

# Textbook of **Pharmaceutical Inorganic Chemistry**

Course Code: BP104T

*for First Semester Bachelor in Pharmacy*

As per the latest syllabus prescribed by the Pharmacy Council of India

Arun Kumar Gupta  
Revathi A Gupta



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Textbook of

# Pharmaceutical Inorganic Chemistry

for Bachelor of Pharmacy (BPharm) Course

As per PCI Syllabus

BPharm (Semester I)

Subject Code: BP 104T

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# Pharmaceutical Inorganic Chemistry

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## Preface

We feel great honor and an immense pleasure in bringing out this book entitled *Textbook of Pharmaceutical Inorganic Chemistry* is written according to the syllabus for Bachelor of Pharmacy (BPharmacy) approved and implemented by the **Pharmacy Council of India**. The major thrust to make the book is, students need a textbook in a comprehensive descriptive manner with updated details of the topic covered in their syllabus. They also expect good quality readable books include basic principles with relevant examples rather than standalone concepts, allowing students to see the relevance of the subject in future professions. The main purpose of writing this book is to provide a qualitative book to pharmacy students and allied health professionals those who are dealing with this subject.

This book covers all the theoretical aspects of the subject BP 104T for BPharmacy first year students. It is a classic common textbook for an undergraduate course in inorganic chemistry. This book is divided into five units. Each unit in the book is self-contained and serves as dual teaching function to highlight the basic concepts. This book not only good introduction of the subject but also tried to describe various inorganic compounds, minimum chemical facts and concepts that are necessary to understand modern inorganic chemistry. Unique very advanced and comprehensive descriptive coverage of all the official compounds included, with a strong focus on preparation, properties, assay and pharmaceutical applications. The book will lay the foundation for students in BPharm first semester regarding the subject knowledge. This book presented in a very systematic way. All the topics in each chapter have been provided with reasonable account, covering the information in easy to understand manner.

In this book we cover basic concepts with respective topic have been discussed which will help to understand the students in a better manner. We also includes revision exercises at the end of the every chapter in the form of multiple choice questions, fill in blanks, short questions and long questions which will help them to prepare better for their exams and self-assess himself/herself. In this book, we also highlights the medical and pharmaceutical terms along with explanation for easy understanding of students. This book will give valuable source of information and appropriate subject knowledge to students, teachers as well as other allied persons.

We are indeed delighted to present the work which will be very fruitful for pharmacy professionals working in different areas of pharmaceutical sector and as well as students at undergraduate and postgraduate levels. We heartily welcome comments along with valuable suggestions from all corners of the profession which will help us in improving the content of the book in ensuing editions of this book and also in other books that are on the anvil. We are gratified to CBS Publishers and his editorial team for their kind assistance in bringing out this book.

Arun Kumar Gupta  
Revathi A Gupta

# Syllabus

Course: BPharm (As per PCI Syllabus)

Semester I

Subject code: BP 104T

UNIT I

10 Hours

- **Impurities in pharmaceutical substances:** History of pharmacopoeia, sources and types of impurities, principle involved in the limit test for chloride, sulphate, iron, arsenic, lead and heavy metals, modified limit test for chloride and sulphate.
- **General methods of preparation,** assay for the compounds superscripted with asterisk (\*), properties and medicinal uses of inorganic compounds belonging to the following classes

UNIT II

10 Hours

- **Acids, bases and buffers:** Buffer equations and buffer capacity in general, buffers in pharmaceutical systems, preparation, stability, buffered isotonic, solutions, measurements of tonicity, calculations and methods of adjusting, isotonicity.
- **Major extra and intracellular electrolytes:** Functions of major, physiological ions, electrolytes used in the replacement therapy: sodium, chloride\*, potassium chloride, calcium gluconate\* and oral rehydration salt (ORS), physiological acid base balance.
- **Dental products:** Dentifrices, role of fluoride in the treatment of dental, caries, desensitizing agents, calcium carbonate, sodium fluoride, and zinc, eugenol cement.

UNIT III

10 Hours

- **Gastrointestinal agents:**

*Acidifiers:* Ammonium chloride\* and Dil. HCl

*Antacid:* Ideal properties of antacids, combinations of antacids, sodium bicarbonate\*, aluminum hydroxide gel, magnesium hydroxide mixture

*Cathartics:* Magnesium sulphate, sodium orthophosphate, kaolin and bentonite

*Antimicrobials:* Mechanism, classification, potassium permanganate, boric acid, hydrogen peroxide\*, chlorinated lime\*, iodine and its preparations

UNIT IV

08 Hours

- **Miscellaneous compounds:**

*Expectorants:* Potassium iodide, ammonium chloride\*.

*Emetics:* Copper sulphate\*, sodium potassium tartarate

*Haematinics:* Ferrous sulphate\*, ferrous gluconate

*Poison and Antidote:* Sodium thiosulphate\*, activated charcoal, sodium nitrite

*Astringents:* Zinc sulphate, potash alum

UNIT V

07 Hours

**Radiopharmaceuticals:** Radio activity, measurement of radioactivity, properties of  $\alpha$ ,  $\beta$ ,  $\gamma$  radiations, half-life, radioisotopes and study of radioisotopes: Sodium iodide  $^{131}\text{I}$ , storage conditions, precautions and pharmaceutical application of radioactive substances.

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# Impurities in Pharmaceutical Substances

- |   |   |
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|---|---|

## INTRODUCTION

Pharmaceutical chemistry is a branch of chemistry that deals with the chemical, biochemical and pharmacological aspects of drugs. It includes synthesis/isolation, identification, structural elucidation, structural modification, Structural Activity Relationship (SAR) studies, study of the chemical characteristics, biochemical changes after drug administration and their pharmacological effects. It is specialized science which depends on other chemical disciplines, such as inorganic, organic, analytical, physical chemistry and also on medicobiological disciplines, such as pharmacology, physiology and biological chemistry, etc.

Inorganic chemistry is the study of all the elements and their compounds except carbon and its compounds (which is studied under organic chemistry). Inorganic chemistry describes the characteristics of substances such as nonliving matter and minerals which are found in the earth except the class of organic compounds. The distinction between the organic and inorganic are not absolute, and there is much overlap, especially in the organometallic chemistry, which has applications in every aspect of the pharmacy, chemical industry including catalysis in drug synthesis, pigments, surfactants and agriculture.

Inorganic pharmaceutical chemistry is a science which makes use of the laws of chemistry to study inorganic substances as drugs. It deals with the study of both non-essential and essential elements about their preparation, chemical nature, structure, standards of purity, test for identification, limit tests, storage, assay methods and uses of inorganic agents used as pharmaceutical aids and as therapeutic and diagnostic agents.

Compounds being synthesized by the geological systems and lack of hydrocarbon (carbon-hydrogen) are known as inorganic compounds while organic compounds are

those found in biological systems. In 19th century, inorganic compounds are inanimate described by Berzelius chemist. The first important synthetic inorganic compound was ammonium nitrate for soil fertilization. Medicinally useful substances are derived from either organic or inorganic sources in which inorganic chemicals contributing significantly in some of the ailments, even after the development of many drugs from synthetic and plant sources. Many of the inorganic salts (antimony, arsenic and mercury) are known to be poison but still they are used in medicine cautiously.

The word 'Pharmaceutical' is used for any chemical substance which is useful in preventive or therapeutic or finds used in the preparation of medicament. Quality of all these pharmaceuticals must be carefully controlled. Hence, specifications of quality are mentioned for each pharmaceutical and their descriptions are reported in the pharmacopeia.

## ■ PHARMACOPEIA

The word pharmacopeia is derived from Greek words '*pharmakon*' means a drug (both remedy and poison) and '*poiein*' means to make or create. Pharmacopeia is a book containing directions for the identification of samples and the preparation of compound medicines and published by the authority of a government or a medical or pharmaceutical society. Pharmacopeia is a legislation of a nation which sets standards and mandatory quality indices for drugs, raw materials used to prepare them and various pharmaceutical preparations. Knowledge of the history of pharmacy would help us better to understand the development of pharmacopeias.

## ■ MONOGRAPH

Monographs are complete descriptions of pharmaceutical preparations which include chemical formulae, atomic and molecular weight, definition, statement of content, category, dose, description, solubility, identification tests, assay, other test, limits for impurities, quantities and conditions for storage. The appendices also include standards for apparatus, reagents and solutions, indicators, reference substances, test animals, calculation of results, other chemicals techniques, processes, etc. of the concerned pharmaceuticals. In another way it is a reference work for pharmaceutical drug specifications. By the direction of the council of the pharmaceutical society of the certain nations, the world's most comprehensive source of drug information in a single volume is published periodically in the society's department of pharmaceutical sciences. It is the traditional activity, to help the practicing pharmacists and physicians aiming to provide unbiased concise reports on the actions and uses of most of the world's drugs and medicines.

By reflecting clinical practice, every publication of pharmacopeia monographs is accurately organized based on the updated needs of today's pharmacist. Details are provided about new compounds in the form of new monographs accompanied by some of the previous monographs are deleted which are not in continued use. The overall effect is to provide an increase in the average of drugs with typographical improvements to assist the reader in locating sections of a monograph.

With the search for an effective treatment of diseases a few of the developing therapeutics are revised continuously in pharmacopeia such as anti-HIV agents. In

pharmacopeia, the drug's distinguished features are updated, renewed and discussed for the treatment of infections and development of antiviral, antiprotozoal and antibacterial therapy. Along with novel approaches in the treatment advances in the cardiovascular group of drugs are included. The other areas like antimalarial drugs, anti-neoplastic agents, anti-parkinsonism drugs, etc. are also included in pharmacopeia.

Pharmacopeia is divided into three different major parts based on the published information. Each part is comprised of several chapters.

**Part I:** Generally, the drugs that have similar use or actions are bringing together by part I of pharmacopeia. The cross references is used to guide reader to find out the drug that may be of interest. Many of the chapters are providing background information with an introduction on that group of drugs having many common actions.

**Part II:** It includes monographs of new drugs, drugs under investigation, drugs which are not easily classified and obsolescent drugs still of interest are presented in this part. It also provides details regarding effects of required drug therapy.

**Part III:** Composition of the proprietary medicines that are advertised to the public in different countries and herbal medicines which have been omitted are included in part III of pharmacopeia.

Only the pharmaceuticals which are commonly and currently in use are included in the pharmacopeia; whereas the substances which are found to be undesirable and are not currently in use are excluded. Moreover part of pharmacopeia may also comprise the pharmaceuticals which are used for application or internal consumption by human beings.

In the pharmacopeia only minimum standards are prescribed for pharmaceuticals, but with more stringent standards the manufacturer may supply these substances. Hence a drug has to obey strictly the standards prescribed by anyone of the pharmacopeias. The medication may be considered as substandard if it does not obey these standards and usually it is not prescribed by medical practitioners.

## HISTORY OF PHARMACOPEIA

Every country has legislation on pharmaceutical preparations which sets a standards and required quality indices for medicament, raw materials and preparations employed in the manufacture of drugs. These regulations are presented in separate articles. General and specific matters relating to individual drugs are published in the form of a book called a Pharmacopeia. On 15th December 1820, the first United State Pharmacopeia (USP) was released. The first British Pharmacopoeia (BP) was published in 1864 with inclusion of monographs on camphor, lactose, sucrose, benzoic acid, gallic acid, tartaric acid, tannic acid and seven alkaloids along with their salts.

### Indian Pharmacopoeia

British Pharmacopoeia was utilised as the official book of standards in India before independence. The government passed Drugs and Cosmetics Act in 1940. The Drugs and Cosmetics Act 1940 stated that the Indian Pharmacopoeia is the book of standards for drugs included therein would be official. If considered necessary, these standards can be amended and the secretary of the Indian Pharmacopoeia Committee is authorized to issue such amendments. The general notices and appendices included

in the Indian Pharmacopoeia and as amended in addendum apply both to the matter contained in the Indian Pharmacopoeia and to the matter contained in this Addendum.

- The actual process of publishing the first Indian Pharmacopoeia started in the year **1944** under the chairmanship of Col. R. N. Chopra.
- The list of drugs was published in the year **1946** and was put forth for approval.
- The government of India constituted a permanent Indian Pharmacopoeia Committee in **1948** for the preparation of the Indian Pharmacopoeia and established a central Indian Pharmacopoeia Laboratory at Ghaziabad, Uttar Pradesh to keep it up to date.
- The first edition of the Indian Pharmacopoeia (IP) was published in the year **1955** under the chairmanship of Dr BN Ghosh. Ministry of Health and Family Welfare, Government of India publishes Indian Pharmacopoeia based on the recommendation of Indian Pharmacopoeia Committee (in accordance with Drugs and Cosmetics Act, 1940, Dangerous Drugs Act, 1930, and Poisons Act, 1919 and the rules framed thereunder).
- Supplement for first edition of Indian Pharmacopoeia was published in the year **1960**. It contained both western and traditional system drugs commonly used in India.
- After eleven years, under the chairmanship of Dr. B. Mukherji the second edition of Indian Pharmacopoeia was released in **1966** with some modification.
- The supplement to the second edition of Indian Pharmacopoeia was published in **1975**.
- There had been a phenomenal growth and development of Indian pharma industry especially from early 1970 both in the range of active pharmaceutical ingredients (APIs) and the dosage forms produced. In view of these rapid advances, it was decided to publish a new edition of the Pharmacopoeia and its addenda at regular and shorter intervals for which the Indian Pharmacopoeia Committee was reconstituted in **1978**.
- Third edition of Indian Pharmacopoeia were in two volumes published in **1985** under the chairmanship of Dr. Nityanand. In this Pharmacopoeia inclusion of traditional system of drugs was limited. However, most of the new drugs manufactured and/or marketed were included while only those herbal drugs which had definite quality control standards had got place in it.
- Addendum/supplement I and II to third edition has been published in **1989** and **1991** respectively.
- Fourth edition of the Indian Pharmacopoeia was published in two volumes under the chairmanship Dr. Nityanand in **1996** which omitted many lesser used and obsolete product monographs and added monographs based on the therapeutic merit, medicinal need and extent of use of such articles in the country.
- Addendum to fourth edition has been published initially in **2000** followed by in **2002**. In addition, supplement for veterinary products are also released.
- Third addendum was published in **2005** which included a large number of antiretroviral drugs, and raw plants commonly used in making medicinal products not covered by any other.
- The Indian Pharmacopoeia Commission (IPC) has been established in the year **2005**.

- It is the 5th edition of IP in 2007. The IPC provided systematic approach and practices for publication of Indian Pharmacopoeia 2007 with focus on those drugs and formulations that cover the National Health Care Programmes and the national essential medicines. It contained monographs on antiretroviral, anticancer, antitubercular and herbal drugs. It also emphasized on biological monographs, such as vaccines, immunosera for human use, blood products, biotechnological and veterinary (biological and non-biological) preparations.
- Addendum 2008 to the IP 2007 was published which had taken care of the amendments to Indian Pharmacopoeia 2007 and also incorporated 72 new monographs.
- Government of India declared Indian Commission, an autonomous institution under the Ministry of Health and Family Welfare by its resolution of 6th May 2008 and declared Central Indian Pharmacopoeia Laboratory, Ghaziabad as subordinate office since 1st Jan 2009.
- The **6th edition** of IP published in 2010. The sixth edition of IP published in accordance with the principles and designed plan decided by the scientific body of the IPC. To establish transparency in setting standards for this edition, the contents of new monographs, revised appendices and other information have been published on the website of IPC.
- The IPC secretariat and Indian Pharmacopoeia laboratory staff, with the support of different advisory expert committee, and expert members of the scientific body have examined the suitability of the standards. In order to make Indian Pharmacopoeia 2010 user friendly, the existing formatting pattern has been suitably revised.
- The Indian Pharmacopoeia 2010 has been considerably revised and improved in respect of the requirements of monographs, appendices and testing protocols by introducing advanced technology. The contents of appendices are by and large revised in consonance with those adopted internationally. The monographs of special relevance disease of this region have been given special attention.
- National Formulary of India 4th edition was published in the same year and it meant for the guidance of the members of the medical profession such as medical students, nurses and pharmacists working in hospitals and other areas.
- The **seventh edition** of the IP 2014 has been published in Nov 2013 by the Indian Pharmacopoeia Commission (IPC). It is presented in four volumes. The scope of the Pharmacopoeia has been extended to include products of biotechnology, indigenous herbs and herbal products, veterinary vaccines and additional antiretroviral drugs and formulations, inclusive of commonly used fixed-dose combinations. Standards for new drugs and drugs used under National Health Programmes are added and the drugs as well as their formulations not in use nowadays are omitted from this edition.
- The IP 2014 incorporates 2548 monographs of drugs out of which 577 are new monographs consisting of APIs, excipients, dosage forms, antibiotic monographs, insulin products and herbal products, etc. 19 New radiopharmaceutical monographs and 1 general chapter is first time being included in this edition.
- First Addendum 2015 of IP 2014 has been released on 2014. It incorporates 82 new monographs consisting of 57 chemical monographs, 13 herbal monographs, 02 human vaccines monographs and 10 radiopharmaceutical monographs, etc.

- Second Addendum 2016 of IP 2014 has been released on 2015. It incorporates 89 new monographs consisting of 64 chemical monographs, 14 herbal monographs, 3 vaccines and immunosera for human use, 3 radiopharmaceuticals monographs, 1 blood related products, 4 biotechnology products monographs and 2 general chapters being included in this addendum.
- The latest edition of the IP 2018 has been published in 29th Sep 2017. IP 2018 has been brought out in 4 volumes incorporating 220 new monographs (chemical monographs (170), herbal monographs (15), blood and blood related products (10), vaccines and immunosera for human use monographs (2), radio-pharmaceutical monographs (3), biotechnology derived therapeutic products (6), veterinary monographs (14)), 366 revised monographs and 7 omissions.

#### ***Salient Features of Indian Pharmacopoeia 2018***

Keeping in view the essential requirement for harmonization of analytical methods with those accepted internationally, steps have been taken for monitoring drug standards.

- It is effective from 1st January, 2018
- Presented in 4 hard bound volumes with DVD
- Total monographs 2761, 220 new monographs included.
- Veterinary product monographs are the integral part of this edition
- Use of chromatographic methods has been greatly extended
- Obsolete monographs have been omitted
- Herbal drug monographs have been added
- General chemical tests and thin layer chromatography (TLC) for identification of an article have been almost eliminated and more specific infrared, ultraviolet spectrophotometer and HPLC tests have been given emphasis. The concept of relying on published infrared spectra as a basis for identification has been continued.
- Most of the existing assays and related substances test methods are upgraded by liquid chromatographic in view to harmonize with other International Pharmacopoeia.
- Pyrogen test has been replaced by bacterial endotoxin test (BET) in parenteral preparations and other monographs.
- For ease of access to make pharmacopoeia more user-friendly, index has been incorporated in volume I along with that already existing in volume IV of IP.
- 53 new fixed dose combination (FDC) monographs have been included, out of which 25 FDC monographs are not available in any pharmacopoeia.
- 10 new general chapters on pharmaceutical, microbiological and biological have been incorporated.
- General chapters on volumetric glassware, conductivity, dissolution test, disintegration test, dimensions of hard gelatin capsule shells, etc. have been revised.
- For controlling the microbial quality of the entire medicinal product, general chapter on maintenance, identification, preservation and disposal of microorganism have been revised.
- IP 2018 has been incorporated with a security feature to avoid counterfeiting.

### **Extra Pharmacopoeia (Martindale)**

Pharmacopoeia possesses wealth of information with no explanation. The person must familiarize himself with the general notices and the various appendices of pharmacopoeia to consult the pharmacopoeia. One can obtain most complete information from Extra Pharmacopoeia (Martindale) on every type of pharmaceutical or drug. A practicing pharmacist William Martindale in the year 1883 published the Extra Pharmacopoeia. This book was rich especially with therapeutic and clinical information of the drugs.

For inorganic pharmaceuticals there are several other useful literature references are included. With an aim to provide practical and up-to-date information concerning drugs and gelenicals included in the British Pharmacopoeia. In the span of three years four editions of Martindale were published. Due to the accumulation of information up to the year 1910 the subject matter to be divided into two volumes in the initial editions of Martindale. The first double volume edition was published in 1912.

In December 1933, the Pharmaceutical Society of Great Britain acquired the copy right of the Extra Pharmacopoeia upon the death of Dr W.H Martindale son of William Martindale. Thereafter the society is continuing to issue it under the editorship of the Director of its Department Pharmaceutical Sciences. 23rd edition of Volume II was published in 1955 and the 24th edition of Volume I was published in 1958. Supplement for 24th edition was published in 1961. In February 1967 the 25th edition was published by the Pharmaceutical Society of Great Britain while 26th edition was released in July 1972. In 30th edition of Martindale contains up-to-date authoritative information on drugs and medicine which are used throughout the world was published in 1993. It is written for all those involve in use of drugs and medicines including practicing pharmacists and physicians.

In order to meet the requirements of today's reader the latest edition of Martindale has been markedly changed. It includes a significant shift to a more clinical emphasis an increase in the number of referenced reviews and massive increase information on proprietary medicines. In addition usual period between editions was shortening to meet the need for up-to-date information.

### **British Pharmacopoeia**

Medical Act, 1858 under Section 54 was stressed the need of publication of a book having a list of medicines and compounds about their manner of preparing them together with true weights and measures by which they are to be prepared and mixed. Hence, the British Pharmacopoeia was decided to publish.

- In the year 1864 the first British Pharmacopoeia was published by combining the three old and reputed Pharmacopoeias, namely Pharmacopoeia Londinensis (1618), Edinburgh Pharmacopoeia (1699) and Dublin Pharmacopoeia (1807). New editions and addendum were released quickly.
- The 2nd edition was released in 1867.
- The 3rd and 4th editions were published in the year 1885 and 1898 respectively.
- Addendum to 2nd and 3rd editions was released in the year 1874 and 1890 respectively.
- Separate parts such as preparation of compounds are included in the year 1864 British Pharmacopoeia. In this edition contents had been arranged alphabetically. A gap in revision belated the next edition of British Pharmacopoeia until 1914.

- Further edition was published in 1928 and 1932.
- A range of diagnostic materials was included in 1932 revision. An important addition was inclusion of standards and tests for antitoxins and insulin.
- Thereafter the commission was recommended to revise the BP every 10 years once.
- Seven addenda covered the interim between 1932 and next edition of 1948.
- In this 1948 edition (7th), for substances newly introduced into medicine, generic names were provided. Methods of analysis such as disintegration tests for tablets and sterilization methods were expanded. Many new monographs related to sex hormones and penicillin's were included.
- Due to the rapid development of pharmaceutical and pharmacological progress at this time it was decided that the normal interval between new editions should be 5 instead of 10 years.
- The next edition was released in the year 1953. It incorporates the titles of drugs and preparations were given in English instead of Latin.
- The 9th edition (1958) contains 160 new monographs. Spectrophotometric analysis and inclusion of tranquilizing drugs are the other features of this edition.
- The next, i.e. tenth edition was published in 1963. The duties of the British Pharmacopoeia Commission were defined clearly in medicines order 1970.

The first edition of British Pharmacopoeia that was prepared strictly under the provisions of Medicines Act was the thirteenth edition which was published in the year 1980. Due to an expansion of drug information latter the British Pharmacopoeia was decided to publish in two volumes.

Authoritative standard for the quality of many substances preparation and articles used in medicine and pharmacy for some 130 years was provided in 1993 edition of British Pharmacopoeia. For the convenience of user this edition consolidates and extends the 1988 edition with its 1989, 1991, and 1992 addenda. Moreover monographs of the European Pharmacopoeia were also included in this particular edition.

The last year edition of the British Pharmacopoeia (BP), i.e. British Pharmacopoeia 2013 comprises six volumes which contain nearly 3,000 monographs for drug substances, excipients and formulated preparation, together with supporting general notices, appendices (test methods, reagents, etc.) and reference spectra used in the practice of medicine. All are comprehensively indexed and cross-referenced for easy reference. Items used exclusively in veterinary medicine in the UK are included in the BP (veterinary).

The volume I and II deals with medicinal substances, whereas volume III describes about formulated preparations, blood related preparations, immunological products, radiopharmaceutical preparations, surgical materials and homeopathic preparations. The volume IV contains appendices, infrared reference spectra and index. The volume V is for veterinary purpose, i.e. British Pharmacopoeia (veterinary). The volume VI is the CD-ROM version of British Pharmacopoeia, British Pharmacopoeia (veterinary) and British approved names. The 2013 edition of British Pharmacopoeia is available as a printed volume and electronically in both on line and CD-ROM versions, the electronic products use sophisticated search techniques to locate information quickly. For example, pharmacists referring to a monograph can immediately link to other related substances and appendices referenced in the content by using 1,30,000 plus hypertext links within the text.

The British Pharmacopoeia 2013 package comprises five volumes and a single volume of the British Pharmacopoeia (veterinary) 2013, along with a fully searchable CD-ROM and online access which provided flexible resources. The British Pharmacopoeia 2013 was legally effective from 1 January 2013 and contains 41 new British Pharmacopoeia monographs, 40 new European Pharmacopoeia monographs, 619 amended monographs, 6 new and 1 amended infrared reference spectra and European Pharmacopoeia 7th edition material up to and including Supplement 7.5. In addition updates in January, April and July to harmonize with the European Pharmacopoeia was also provided. The current edition of the British Pharmacopoeia, i.e. British Pharmacopoeia 2014 comprises five volumes and a single volume of the British Pharmacopoeia (veterinary) 2014, along with a fully searchable CD-ROM and online access to provide with flexible resources. The latest edition was published in 2018 which includes around 4000 monographs spread out in six printed volumes.

### **European Pharmacopoeia**

An official book of standards adopted by Germany, France, Italy, Netherlands, Switzerland and Belgium is European Pharmacopoeia. The council of Europe issued an order to frame out European Pharmacopoeia in July 1964. In 1969 onwards in the respective member countries it was appeared as official standard book for medicinal substances and other drugs. Later on it was revised continuously to keep the information up-to-date.

## **PHARMACOPEIA INTERNATIONALS**

In various countries there are no uniformity in terminology and strengths of pharmaceutical preparations used. In the year 1874, a view had been expressed that uniformity in the standards for potent drugs must necessary to overcome various problems. In 1936, the Health Organization of the League of Nations established a Technical Commission of Pharmacopeial Experts. The work was undertaken by the WHO after the World War II which was ended in 1946. Finally volume I of the long awaited International Pharmacopoeia was published in 1951 by Latin with translation into English and French. This International Pharmacopoeia contains monographs for over 200 drugs and chemicals, with appendices on reagents tests and biological assays. Second volume was published in 1955. In 1967 the second edition followed by a supplement in 1971. Third edition was published in 1979 spread out in several volumes. The pharmacopeial authorities of all countries are expected to give due considerations to its standards so as for achieving uniformity of standards as far as practicable even though the International Pharmacopoeia cannot be imposed legally on any country.

### **United States Pharmacopeia (USP)**

United States Pharmacopeia and the National Formulary (USP-NF) are recognized as official compendia for determining standard of pharmaceutical products. The first USP was published in 1820 with 217 drugs. National formulary was published in 1888 under the authority of American Pharmacists Association. After 1975, USP and NF are published in combined volume as USP-NF by United State Pharmaceutical Convention. It was published at an interval of five years. After 2000, USP-NF has been published annually. The current version of USP-NF standards deemed official by USP

are enforceable by the US Food and Drug Administration for medicines manufactured and marketed in the United States. The USP 42-NF 37 becomes official on 1st May 2019.

## ■ PHARMACOPEIAL DESCRIPTION/PRESENTATION

Most of the pharmacopeias including Indian Pharmacopoeia consist of the three major sections, namely (a) introduction including general notices, (b) monographs of the official drugs, (c) appendices.

### (a) Introduction

It is useful information to pharmaceutical progress since last edition. It summarizes the different changes including additions/deletions in the current edition compared to last edition. To avoid misinterpretation, misunderstanding of later parts of the text, attention should be paid to general notices at the outset.

### (b) Monographs

The general monographs for dosage forms of active pharmaceutical ingredients (APIs) are grouped together at the beginning of volume II of IP 2010. The written study of a subject was implied by the word 'monograph' (mono—single, graph—to write). These are considered as very important because medicinal substances are used for the cure and/or prevention of diseases. Therefore their written studies appear as monographs. Monographs are arranged in the alphabetical order of their names and are somewhat stereotyped in style.

#### *Contents of Individual Monographs*

An official monograph for a drug and pharmaceutical substance generally includes the following.

- Title:** The official name of the compound in English is stated in the title. Sometimes common names or synonyms are also mentioned, e.g. calcium carbonate can also be called precipitated chalk, milk of magnesia can also be called magnesium hydroxide mixture.
- Chemical formulae:** When the chemical structure of an official compound is known, the graphic, molecular formulae and molecular weight are given at the beginning of the monograph.
- Chemical names:** Sometimes the International Union of Pure and Applied Chemists (IUPAC). IUPAC name of the substance is also given in the monograph.
- Atomic and molecular weight:** The atomic and molecular weight is shown, as and when appropriate at the top right hand corner of the monograph.
- Category:** This part of monograph expresses the pharmacological or therapeutic or pharmaceutical application of the compound. Although the compound may have other applications usually this part describes the main application. Analgesics, antibiotic, antacid, laxative, etc. are some of the main categories for inorganic pharmaceuticals in the pharmacopeia.
- Dose:** Dose mentioned in the IP is intended merely for general guidance and represent the average range of quantities regarded as suitable for adults when administered by mouth.

7. **Description:** It illustrates physical and organoleptic properties of the substance such as amorphous nature or crystalline, odor, color and taste, etc. It helps in the preliminary evaluation of the integrity of an article and should not be considered as analytical requirements.
8. **Solubility:** The solubility of the substance given in the monograph is primarily for the information and should not be regarded as standards or test for purity. The term "partly soluble" is used to describe a mixture where only some of the components dissolve. If the exact solubility of the substance is not known, the approximate solubility of the substance is indicated by the descriptive terms. The solubility mentioned in Indian Pharmacopoeia is the approximate solubility at a temperature between 15°C and 30°C.

<i>Descriptive term</i>	<i>Part of solvent required for part of solute to dissolve</i>
Very soluble	Less than 1 part
Freely soluble	From 1 to 10 parts
Soluble	From 10 to 30 parts
Sparingly soluble	From 30 to 40 parts
Slightly soluble	From 100 to 1000 parts
Very slightly soluble	From 1000 to 10000 parts
Insoluble or practically insoluble	More than 10000 parts

9. **Standards:** IP prescribes the standard of purity and strength of all official substances. A substance is not deemed to be of standard quality unless it complies with the requirements stated under this of its monograph.
10. **Identification test:** It is to ensure the correct labelling of substances. Identification tests are specific, but they are not necessarily sufficient in establishing the absolute proof of identity of the substance. This usually involves specific chemical test or tests for identifying the substance. It provides a means of verifying that the identity of the material under examination is in accordance with the label on the container. There is substantial overlap between identification and limit tests. Limit tests are designed to ensure that the undesirable impurities are within the prescribed limits. Identification tests, whether physical or chemical, provided they are sufficiently specific, can be used as the basis of a quantitative estimation. Physical constants, such as boiling point, melting point, solubility, refractive index, viscosity, optical rotation, etc. have characteristic values for a given substance. It can be used in identification, checking quality and maintaining standard of purity.
11. **Tests for purity:** Tests for purity are tests for the presence of impurities in the substance and fix the limits of tolerance for undesirable impurities.
12. **Assay:** Assay is used for the quantitative determination of active ingredients of the official substance and their preparations.
13. **Storage:** It contains information regarding the storage conditions of official substance so they can be protected against possible contamination and deterioration. The precautions need to be taken with the effect of atmosphere, moisture, heat and light are also indicated in the monograph. In case of some drugs or pharmaceutical substances, lower or higher temperatures produce undesirable effects.

The storage conditions are defined by the following terms:

- Store in a dry, well-ventilated place at a temperature not exceeding 30°C
- Store in a refrigerator (2°C to 8°C) and do not freeze
- Store in a freezer (-2°C to -18°C)
- Store in a deep freezer (below -18°C).

The storage conditions not related to temperature are indicated in the following terms:

- Store protected from light
- Store protected from light and moisture

where no specific storage directions or limitations mentioned, it is to be understood that the storage conditions include protection from moisture, freezing and excessive heat (any temperature above 40°C).

**14. Storage containers:** The storage containers in the pharmacopeia are indicated in the following terms:

- Well-closed containers: This implies the substance is stable and gets protected from dust, dirt, insects, etc.
- Tightly closed container: The substances in such cases get affected by atmospheric oxygen or moisture or carbon dioxide. For example, reducing agents, hygroscopic substances, strong bases, etc. must be stored in tightly closed containers. It may also include such compounds are volatile or contain dissolved gases, etc.
- Light resistant container: Substances which are affected by light are stored in amber or dark colored containers.
- Single dose containers: This is generally prescribed for some injectables which once opened should not be used again.

**15. Labeling:** The labeling statements may appear on the container, the package, a leaflet accompanying the package or certificate of analysis associated with the article, as decided by the competent authority.

### (c) Appendices

A comprehensive section of appendices are presented followed by the general notices and monographs.

**Appendix 1:** It describes the apparatus that are needed for various pharmacopeial tests and assays

**Appendix 2:** It describes biological tests and assays

**Appendix 3:** It describes the details of various chemical tests and assays

**Appendix 4:** It describes the details of microbiological tests and assays

**Appendix 5:** It describes some physical tests and determinations like loss on drying, determination of pH, melting range, etc.

**Appendix 6:** It describes includes the useful directions on cleaning glassware.

**Appendix 7:** It describes the reagents and solutions needed for the various tests and assays, their method of preparation, standards, etc.

**Appendix 8:** Describes reference substances

**Appendix 9:** It describes the names, symbols used in the pharmacopeia and their atomic weights.

## IMPURITY

In pharmaceuticals, impurity is defined as any other material besides the drug substance such as intermediates or starting material or by products, interaction products or degradation products due to any side reactions.

Substances which are used in pharmaceutical field must be pure so that they can be used safely. But it is very difficult to obtain an almost pure substance. Impurities defined as a foreign particle that affects the purity of a substance.

An impurity in a drug substance as defined by the International Conference on Harmonisation (ICH) Guidelines is any component of the drug substance that is not the chemical entity defined as the drug substance and affects the purity of active ingredient or drug substances.

### Effect of Impurities

As we know that almost pure substances are difficult to get and some amount of impurity is always present in the material. So, the impurities which are present in the substances may have the following effects:

- Impurities may bring about incompatibility with other substances
- Impurities may lower the shelf life of the substances
- Impurities may cause difficulties during formulations and use of the substances
- Sometimes impurities changes the physical and chemical properties of the substances
- Therapeutic effect can be decreased
- Shows toxic effect after a certain period
- Injurious when present above certain limits
- It may change odor, color, taste of the substance.

### Sources of Impurities

To prevent these impurities many test such as limit test are carried out to lower the impurities to make the pharmaceuticals safer.

A substance having foreign materials is termed to be impure. The cause of impurities in drugs is from various sources and phases of the synthetic process. Many of the impurities may arise from starting materials, by products, synthetic intermediates, synthetic route of manufacturing process and degradation products. The pharmaceutical preparation should be free from toxic and other impurities.

The impurities commonly found in pharmaceutical substances are:

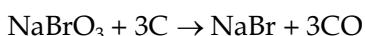
- Raw materials employed in manufacture
- Method or the process used in manufacture
- Chemical processes and the plant materials employed in the processes
- Due to color and flavoring substances
- Incompatibility of active ingredient with other substance
- Storage conditions
- Decomposition
- Impurities due to humidity and temperature.

The various sources of impurities in pharmaceutical substances are as follows:

- 1. Raw materials employed in the pharmaceutical process:** Pharmaceutical substances are either isolated from natural sources or synthesized from chemical starting materials which have impurities. Impurities associated with the raw materials may be carried through the manufacturing process to contaminate the final product, e.g. rock salt used for the preparation of sodium chloride is contaminated with small amounts of calcium and magnesium chlorides, many sulfide ores containing lead and heavy metals as impurities.
- 2. Method or manufacture process:** The process of manufacture may introduce new impurities. Due to impure reagents, catalysts and solvents, reaction vessels and reaction intermediates employed at various stages.
  - a. *Reagents employed in the manufacturing process:* If reagents are employed in the process are not completely removed and these reagents may be present in the final products, e.g. calcium carbonate contains 'soluble alkali' as impurity. Anions like  $\text{Cl}^-$  and  $\text{SO}_4^{2-}$  are common impurities in many substances because of the use of hydrochloric acid and sulfuric acid respectively. Barium ion may be an impurity in hydrogen peroxide.
  - b. *Reagents used to eliminate other impurities:* Barium is used to remove sulfate from potassium bromide, which can be found, itself (barium) as impurity at the end of process.
- 3. Solvents:** In pharmaceutical substances, solvents employed in preparation and purification of the product and it may also contaminate the product. Water is the most commonly used solvent in the pharmaceuticals which can be the major source of impurities. Different types of water are as follows.
  - a. *Distilled water:* It is free from all inorganic and organic impurities and best solvent for pharmaceutical preparation.
  - b. *Demineralized water:* It is free from magnesium, calcium, sodium, sulfates, chlorides, carbonates impurities and prepared by ion exchange method. It contains bacteria, pyrogens and organic impurities.
  - c. *Tap water:* It contains magnesium, calcium, sodium, sulfates, chlorides, carbonates as impurities.
  - d. *Softened water:* It is prepared from tap water and it contains sodium and chloride ions as impurities.
- 4. Intermediates:** An intermediate substance produced during the manufacturing process may contaminate the final product, e.g. sodium bromate is prepared by reaction of sodium hydroxide and bromine in slight excess.

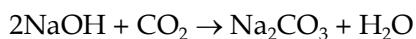


The sodium bromate an intermediate product is reduced to sodium bromide by heating the residue with charcoal.



If sodium bromate is not completely converted to the sodium bromide then it is likely to be present as an impurity.

**5. Atmospheric contamination during the manufacturing process:** Atmosphere may contain dust (aluminium oxide, sulfur, silica, soot, etc.) and some gases like carbon dioxide, sulfur dioxide, arsine and hydrogen sulfide. These may contaminate the final product during the manufacturing process, e.g. sodium hydroxide readily absorbs atmospheric carbon dioxide when exposed to atmosphere.



**6. Chemical process:** Various chemical reactions such as oxidation, reduction, halogenation and hydrolysis are involved in the synthesis of pharmaceuticals. In these reactions chemical and solvents are used which may found in the product as a impurities.

**7. Manufacturing hazards:** Sometimes certain manufacturing hazards which can lead to product contamination.

a. *Contamination from the particulate matter:* The unwanted particulate matter can arise by accidental introduction of dirt or glass, porcelain, plastic or metallic fragments from sieves, granulating, filling machines and the product container.

b. *Cross-contamination of the product:* It can occur by airborne dust arising out of handling of powders, granules and tablets in bulk. If two or more products are manufactured in same time this type of contamination is possible.

c. *Contamination by microbes:* Microbes like bacteria, fungi, algae, etc. can contaminate the final product. Many liquid preparations and creams intended for topical applications are liable to contamination by microbes from the atmosphere during manufacturing.

d. *Errors in the packaging:* Similar looking products such as tablets of the same size, shape and color are packed in similar containers can result in mislabeling of either or both of the products.

**8. Instability of the product:**

a. *Chemical instability:*

- Many pharmaceutically important substances undergo chemical decomposition when storage conditions are inadequate.
- Chemical decomposition is often catalyzed by light, traces of acid or alkali, traces of metallic impurities, air oxidation, carbon dioxide and water vapors.
- Impurities can also arise during storage because of chemical instability.

b. *Reaction with container material:* The reaction between the container material and the contents can affect the stability. Preparations susceptible to reaction with metal surfaces, e.g. salicylic acid ointment must not be packed in metal tubes.

c. *Temperature:* The rate of chemical decomposition and physical changes of stored products depends upon the temperature.

To minimize and prevent impurities many test such as limit test carried out to diminish the impurities and make the pharmaceuticals safer.

## LIMIT TEST

**Limit test** is defined as **quantitative or semiquantitative** test designed to identify and control small quantities of impurity which is likely to be present in the substance.

Limit test for chlorides, sulfates, iron, lead and heavy metal are carried out in Nessler cylinders (Fig. 1.1). It is made up of borosilicate glass having fixed diameter and length as per IP. Two similar kinds of cylinders are required for test and standard to make the comparison in identical manner. No numerical values for the limits in these tests are prescribed in pharmacopeia as it is not practicable. The sample quantity may vary according to the limits while standard remains constant.

In these tests, the **test opalescence/turbidity/color/stain** produced by the reaction of specified amount of impurity in the test sample with the reagent is compared with the **standard opalescence/turbidity/color/stain** produced by the reaction of known amount of impurity [standard] with the reagent. It is generally carried out to determine the inorganic impurities present in compound.

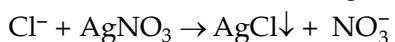
Importance of limit tests:

- To find out the harmful amount of impurities
- To find out the avoidable/unavoidable amount of impurities.

### Limit Test for Chloride

#### Principle

Limit test of chloride is based on the simple reaction between silver nitrate and soluble chlorides in presence of dilute nitric acid to give opalescence of silver chloride.



A comparison **Limit Test** is made of the opalescent solution so obtained with the standard opalescence containing a known amount of chloride ions.

#### Preparation of Solutions

**Chloride standard solution (25 ppm Cl):** Dilute 5 ml of 0.0824% w/v solution of sodium chloride in 100 ml of water.

**Silver nitrate solution (0.1 M):** 0.1 M silver nitrate was prepared by dissolving 17 g of silver nitrate in sufficient water to produce 1000 ml.

**Nitric acid, dilute:** Contains approximately 10% w/w of  $\text{HNO}_3$ . Dilute 106 ml of nitric acid to 1000 ml with water.

#### Procedure

Take two (50 ml) Nessler cylinders and label it one as 'Standard' and other as 'Test'.

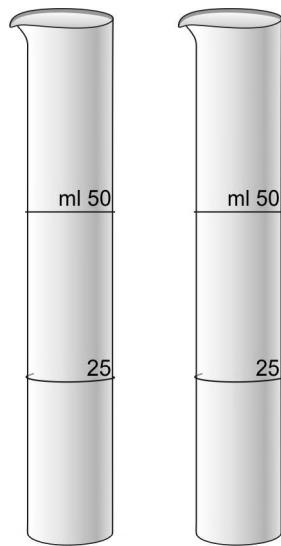


Fig. 1.1: Nessler cylinders

<i>Test solution</i>	<i>Standard solution</i>
Dissolve the specified quantity of the substance under examination in water and transfer to a Nessler cylinder	Take 1 ml of chloride standard solution (25 ppm Cl <sup>-</sup> ) in a Nessler cylinder
Add 10 ml of dilute nitric acid	Add 10 ml of dilute nitric acid
Dilute to 50 ml with distilled water	Dilute to 50 ml with distilled water
Add 1 ml of 0.1 M silver nitrate	Add 1 ml of 0.1 M silver nitrate
Stir immediately with a glass rod and keep aside for 5 minutes protected from light	Stir immediately with a glass rod and keep aside for 5 minutes protected from light
Observe the opalescence/turbidity	Observe the opalescence/turbidity

### **Comparison of Opalescence**

Both the Nessler cylinder viewed transversely against a black background for comparison of opalescence (Fig. 1.2).

**Observation:** The opalescence produced in test solution should not be greater than standard solution. If opalescence produces in test solution is less than the standard solution, the sample will pass the limit test of chloride and *vice versa*.

#### **Reason for adding nitric acid:**

- It extracts a common ion effect by furnishing nitrate ions and thereby suppression of dissociation of silver chloride.
- Dilute nitric acid is used to dissolve other impurities if present and helps silver chloride precipitate to make solution turbid at the end of process.

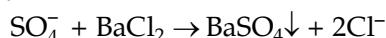
#### **Precautions:**

- Distilled water must be used because chloride present in the tap water will interfere the result
- Same glass rod should not be used because it will affect your observation.
- Silver nitrate is photosensitive store it in amber color bottle.

### **Limit Test for Sulfate**

#### **Principle**

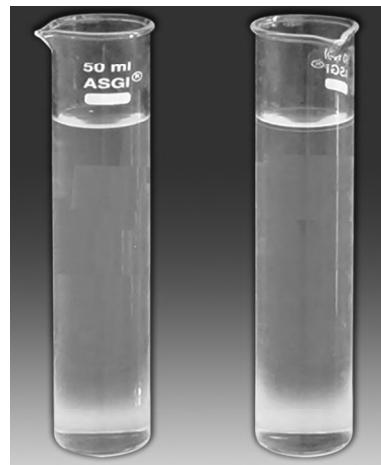
Limit test of sulfate is based on the reaction of soluble sulfate with barium chloride in presence of dilute hydrochloric acid to form barium sulfate which appears as solid particles (turbidity) in the solution.



A comparison is made of the turbid solution so obtained with the standard turbidity containing a known amount of sulfate ions.

#### **Preparation of Solutions**

**Barium chloride solution (25% w/v):** It is prepared by dissolving 25 gm of barium chloride in sufficient quantity of water and volume was adjusted to 100 ml.



**Fig. 1.2:** Comparison of limit test for chloride

**Acetic acid solution (5M):** 5M acetic acid solution prepared by diluting 185 ml of glacial acetic acid with sufficient water to produce 1000 ml.

**Ethanolic sulfate standard solution (10 ppm):** Dilute 1 volume of 0.181% w/v solution of potassium sulfate in ethanol (30%) to 100 volume with ethanol (30%).

**Sulfate standard solution (10 ppm SO<sub>4</sub>):** Dilute 1 volume of a 0.181% w/v solution of potassium sulfate in distilled water to 100 volumes with the same solvent.

### Procedure

Test solution	Standard solution
To 1 ml of a 25% w/v solution of barium chloride chloride in a Nessler cylinder add 1.5 ml of ethanolic sulfate standard solution (10 ppm SO <sub>4</sub> ), mix and allow to stand for 1 minute	To 1 ml of a 25% w/v solution of barium chloride in a Nessler cylinder, add 1.5 ml of ethanolic sulfate standard solution (10 ppm SO <sub>4</sub> ), mix and allow to stand for 1 minute
Dissolve the given sample in 15 ml of water and 0.15 ml of 5M acetic acid	Add 15 ml of sulfate standard solution (10 ppm SO <sub>4</sub> ) and 0.15 ml of 5M acetic acid
Add sufficient water to produce 50 ml	Add sufficient water to produce 50 ml
Stir immediately with a glass rod and keep aside for 5 minutes	Stir immediately with a glass rod and keep aside for 5 minutes.
Observe the opalescence/turbidity	Observe the opalescence/turbidity

**Observation:** The opalescence/turbidity produced in test solution should not be greater than standard solution. If opalescence/turbidity produces in test solution is less than the standard solution, the sample will pass the limit test of chloride and *vice versa*.

#### Reason for adding:

- Hydrochloric acid helps to make solution acidic
- Potassium sulfate is used to increase the sensitivity of the test by giving ionic concentration in the reagent.

### Modified Limit Test for Chloride

In modified limit test for chloride, as KMnO<sub>4</sub> gives purple color in aqueous solution that interferes in the comparison of opalescence and turbidity, so the aqueous solution first be decolorized. KMnO<sub>4</sub> is an oxidizing agent and ethanol is reducing agent. When KMnO<sub>4</sub> is treated with ethanol in presence of heat, redox reaction will takes place which reduces KMnO<sub>4</sub> to manganese dioxide (precipitate) and the filtrate is colorless to proceed the limit chloride.

**Method:** Weighed amount of test substance after treated with suitable reducing agent dissolve it in water. Transfer the solution to Nessler cylinder and add 10 ml dilute of nitric acid, except when nitric acid is used in the preparation of solution and make up the volume to 50 ml with water. Then add 0.1 ml of silver nitrate, mix well and allow it stand for 5 minutes protected from light. On viewing transversely against a black background, any opalescence produced in the test solution should not be greater than that formed by treating a mixture of 10 ml of standard chloride solution (25 ppm Cl) and 5 ml of water in the similar manner.

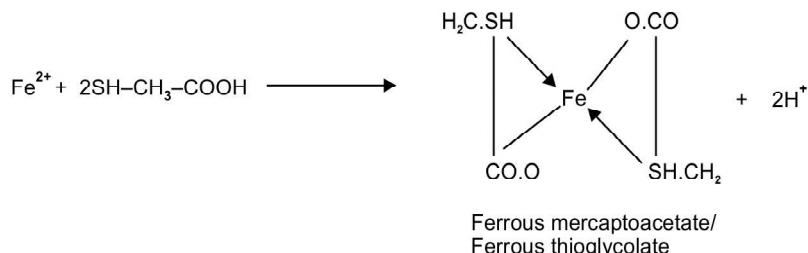
### Modified Limit Test for Sulfate

**Method:** Take 1 ml of 25% w/v barium chloride solution in a Nessler cylinder; add 1.5 ml of standard ethanolic sulfate solution (10 ppm), mix well and allowed to stand for 1 minute. Then add 15 ml of the test solution prepared as specified in monograph and 0.15 ml of 5 M acetic acid after treatment with suitable reducing agent. Dilute the solution up to the mark (50 ml) with water, stir well immediately with a glass rod and allowed to stand for 5 minutes. On viewing transversely against a black background, any opalescence produced in the test solution should not be greater than that formed by treating a mixture of 15 ml of standard sulfate solution (10 ppm SO<sub>4</sub>) in the similar manner.

### Limit Test for Iron

#### Principle

Limit test of iron is based on the reaction of iron impurities with thioglycolic acid to form ferrous thioglycolate which produce purple color in the solution.



A comparison is made of the color solution so obtained with the standard color containing a known amount of iron.

#### Preparation of Solutions

**Iron-free citric acid solution (20% w/v):** It is prepared by dissolving 20 gm of iron free citric acid in sufficient quantity of water and volume was adjusted to 100 ml.

**Iron-free ammonia solution:** Contains approximately 10% w/w of NH<sub>3</sub>. Dilute 425 ml of strong ammonia solution to 1000 ml.

**0.05 M sulfuric acid:** It is prepared by careful adding 2.7 ml sulfuric acid to equal volume of water and further diluting 1000 ml with water.

**Iron standard solution (20 ppm Fe):** Dilute 1 volume of a 0.1726% w/v solution of ferric ammonium sulfate in 0.05 M sulfuric acid to 10 volumes with water. Contains iron in ferric state.

#### Procedure

Test solution	Standard solution
Dissolve the specified quantity of the substance in water and then volume is made up to 40 ml	Take 2 ml of iron standard solution (20 ppm Fe) diluted with water up to 40 ml
Add 2 ml of a 20% w/v solution of citric acid (iron-free)	Add 2 ml of a 20 % w/v solution of citric acid (iron-free)

(Contd.)

<i>Test solution</i>	<i>Standard solution</i>
Add 0.1 ml of thioglycolic acid	Add 0.1 ml of thioglycolic acid
Add ammonia to make the solution alkaline	Add ammonia to make the solution alkaline
Adjust the volume to 50 ml	Adjust the volume to 50 ml
Keep aside for 5 minutes	Keep aside for 5 minutes
Color developed is viewed vertically and compared with standard solution	Color developed is viewed vertically and compared with standard solution

**Observation:** The purple color produced in sample solution should not be greater than standard solution. If purple color produced in sample solution is less than the standard solution, the sample will pass the limit test of iron and *vice versa*.

#### **Reason for adding:**

- Citric acid (iron free) is used to complex metal cations other than iron if present
- Thioglycolic acid helps to oxidize iron (II) to iron (III)
- Ammonia to make solution alkaline.

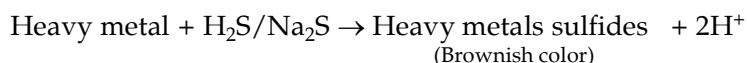
#### **Precautions**

- Distilled water must be used during preparation of all the solution if required.
- Same glass rod should not be used because it will affect your observation.
- Iron free ammonia and citric acid are used during preparation of reagents.

### **Limit Test for Heavy Metals**

#### **Principle**

Limit test of heavy metals is based on the reaction of heavy metals impurities with saturated solution of hydrogen sulfide to form sulfides, which produce color (brownish) in the solution. A comparison is made of the color solution so obtained with the standard color (reaction of known amount of lead with saturated solution of hydrogen sulfide).



Metals that respond to this test are lead, mercury, bismuth, arsenic, antimony, tin, cadmium, silver, copper, and molybdenum. The metallic impurities in substances are expressed as parts of lead per million parts of the substance. The usual limit as per Indian Pharmacopoeia is 20 ppm.

#### **Preparation of Solutions**

**Dilute acetic acid solution (approx. 6% w/w):** It is prepared by diluting 57 ml of glacial acetic acid to 1000 ml with water.

**Dilute ammonia solution (approx. 10% w/w):** It is prepared by diluting 425 ml of strong ammonia solution to 1000 ml with water.

**Lead standard solution (0.1% Pb):** Dissolve 0.400 gm of lead nitrate in water containing 2 ml nitric acid and add sufficient quantity of water to produce 250 ml.

**Lead standard solution (100 ppm):** Dilute 1 volume lead standard solution (0.1 % Pb) to 10 volumes with water.

**Lead standard solution (20 ppm):** Dilute 1 volume lead standard solution (100 ppm Pb) to 5 volumes with water.

### Procedure

Indian Pharmacopoeia provided four methods depending on resulting solution substance (i.e. based on solubility, color, etc.)

**Method A:** It is used for the substance which gives clear colorless solution under the specific condition.

Test solution	Standard solution
Solution is prepared as per the monograph and 25 ml is transferred in Nessler's cylinder	Take 2 ml of standard lead solution (20 ppm Pb) and dilute to 25 ml with water
Adjust the pH between 3 to 4 by adding dilute acetic acid or dilute ammonia solution	Adjust the pH between 3 to 4 by adding dilute acetic acid or dilute ammonia solution
Dilute with water to 35 ml	Dilute with water to 35 ml
Add freshly prepared 10 ml of hydrogen sulfide solution	Add freshly prepared 10 ml of hydrogen sulfide solution
Dilute with water to 50 ml	Dilute with water to 50 ml
Allow to stand for 5 minutes	Allow to stand for 5 minutes
View downwards over a white surface	View downwards over a white surface

**Observation:** The color produced in sample solution should not be greater than standard solution. If color produced in sample solution is less than the standard solution, the sample will pass the limit test of heavy metals and *vice versa*.

**Method B:** It is used for the substance which does not give clear colorless solution under the specific condition. In this method hydrogen sulfide is used after igniting the substance.

Test solution	Standard solution
Weigh in a suitable crucible the quantity of the substance specified in the individual monograph, add sufficient sulfuric acid to wet the sample, ignite carefully at a low temperature until thoroughly charred. Add to the charred mass 2 ml of nitric acid and 5 drops of sulfuric acid and heat cautiously until white fumes are no longer evolved. Ignite, preferably in a muffle furnace at 500 to 600°C, until the carbon is completely burnt off. Cool and add 4 ml of hydrochloric acid cover, digest on a water bath for 15 minutes, uncover and slowly evaporate to dryness on a water bath. Moisten the residue with 1 drop of hydrochloric acid, add 10 ml of hot water and digest for 2 minutes	Take 2 ml of standard lead solution (20 ppm Pb) and dilute to 25 ml with water
Add ammonia solution dropwise until the solution is just alkaline to litmus paper, dilute to 25 ml with water and adjust with dilute acetic acid to a pH between 3.0 and 4.0. Filter, if necessary dilute with water to 35 ml	Adjust the pH between 3 to 4 by adding dilute acetic acid or dilute ammonia solution
Add freshly prepared 10 ml of hydrogen sulfide solution	Dilute with water to 35 ml
Dilute with water to 50 ml	Add freshly prepared 10 ml of hydrogen sulfide solution
Allow to stand for 5 minutes	Dilute with water to 50 ml
View downwards over a white surface	Allow to stand for 5 minutes
	View downwards over a white surface

**Observation:** The color produced in sample solution should not be greater than standard solution. If color produced in sample solution is less than the standard solution, the sample will pass the limit test of heavy metals and *vice versa*.

**Method C:** Use for the substance which gives clear colorless solution and used sodium sulfide solution after treating the substance with sodium hydroxide solution.

Test solution	Standard solution
Dissolve the specified quantity of the substance under examination in a mixture of 20 ml of water and add 5 ml of dilute sodium hydroxide solution	Take 2 ml of standard lead solution (20 ppm Pb)
Make up the volume to 50 ml with water	Add 5 ml of dilute sodium hydroxide solution and make up the volume to 50 ml and mix
Add 5 drops of sodium sulfide solution	Add 5 drops of sodium sulfide solution
Mix and allow to stand for 5 minutes	Mix and allow to stand for 5 minutes
View downwards over a white surface	View downwards over a white surface

**Observation:** The color produced in sample solution should not be greater than standard solution. If color produced in sample solution is less than the standard solution, the sample will pass the limit test of heavy metals and *vice versa*.

#### Method D:

Test solution	Standard solution
Prepare as directed in the individual monograph and pipette 12 ml into a small Nessler cylinder	Pipette 10.0 ml of either lead standard solution (1 ppm Pb) or lead standard solution (2 ppm Pb) and add 2.0 ml of the test solution
Add 2 ml of acetate buffer pH 3.5	Add 2 ml of acetate buffer pH 3.5
Add 1.2 ml of thioacetamide reagent	Add 1.2 ml of thioacetamide reagent
Allow to stand for 2 minutes	Allow to stand for 2 minutes
View downwards over a white surface	View downwards over a white surface

**Observation:** The color produced in test solution is not more intense than standard solution. If color produced in test solution is less than the standard solution, the sample will pass the limit test of heavy metals and *vice versa*.

**Reasons for adding:** Dilute acetic acid and ammonia solution is added to maintain the pH between 3.0 to 4.0 so that precipitate formed is colloidal and uniform.

#### Precautions

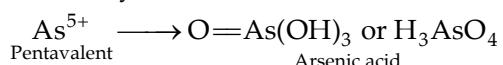
- Distilled water must be used during preparation of all the solution if required.
- Same glass rod should not be used because it will affect your observation.

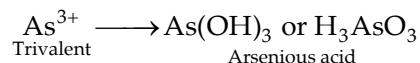
#### Limit Test for Arsenic

##### Principle

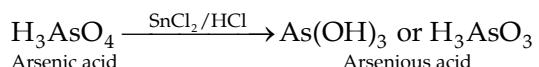
The principle is based on converting any arsenic impurity present in the sample to arsine gas by a series of reaction. The arsine gas is made to come in contact with mercuric chloride test paper when it produces a yellow or brown stain due to the formation of mercuric arsenide. It is also called Gutzeit test and requires special apparatus.

The arsenic impurity is converted in acidic medium into arsenious acid or arsenic acid depending upon the valency state of arsenic.

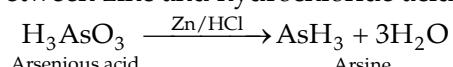




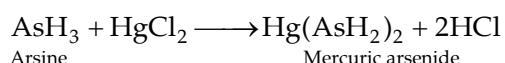
Any arsenic acid formed is converted into arsenious acid by reduction with stannous chloride and hydrochloric acid



The arsenic acid is further reduced to arsine gas with the help of nascent hydrogen obtained in the reaction between zinc and hydrochloride acid



Arsenic gas reacts with mercuric chloride test paper to produce yellow to brown stain due to formation of mercuric arsenide



The stain (yellow or brown) produced by the sample is compared to a standard stain produced by standard.

### Preparation of Solutions

**Potassium iodide, 1 M:** Dissolve 166 g of potassium iodide in sufficient water to produce 1000 ml.

**Sodium hydroxide, 2 M:** Dissolve 80 g of sodium hydroxide in sufficient water to produce 1000 ml.

**Arsenic standard solution (10 ppm As):** Dissolve 0.330 g of arsenic trioxide in 5 ml of 2M sodium hydroxide and dilute to 250.0 ml with water. Dilute 1 volume of this solution to 100 volumes with water.

**Lead acetate solution:** A 10% w/v solution of lead acetate in carbon dioxide-free water.

**Stannous chloride solution:** May be prepared by either of the following two methods.

1. Dissolve 330 g of stannous chloride in 100 ml of hydrochloric acid and add sufficient water to produce 1000 ml.
2. Dilute 60 ml of hydrochloric acid with 20 ml of water, add 20 g of tin, heat gently until no more gas is evolved and add sufficient water to produce 100 ml. Store over a little of the undissolved tin remaining in the solution and protected from air.

### Procedure

**Test solution:** The test solution is prepared by dissolving specific amount in water and stannated HCl (arsenic-free) and kept in a wide mouthed bottle.

To this solution 1 gm of KI, 5 ml of stannous chloride acid solution and 10 gm of zinc is added (all these reagents must be arsenic-free). Keep the solution aside for 40 min and stain obtained on mercuric chloride paper is compared with standard solution.

**Standard solution:** Transfer 1 ml of arsenic standard solution (10 ppm As) diluted to 50 ml with water. Add 10 ml of stannated hydrochloric acid, 5 ml of 1 M potassium iodide and 10 g of zinc AsT. Immediately assemble the apparatus and immerse the

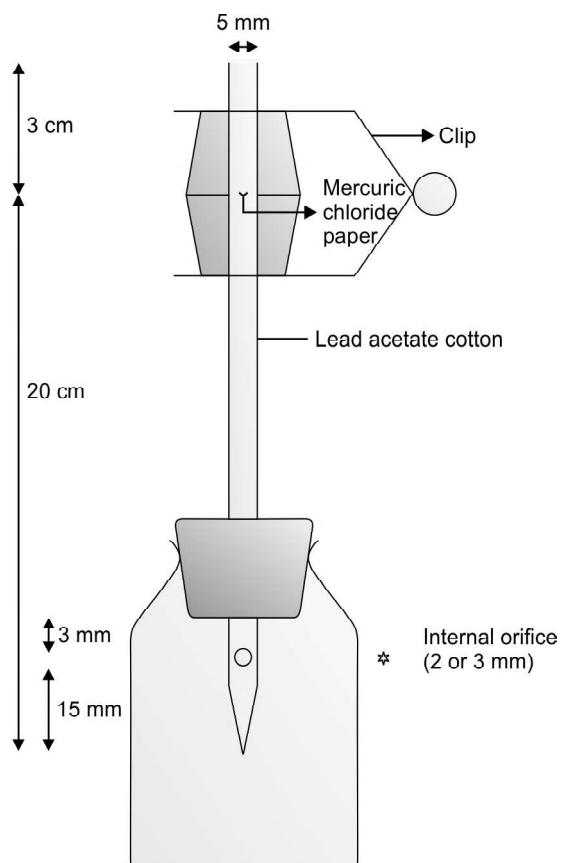
flask in a water bath at a temperature such that a uniform evolution of gas is maintained. Keep aside for 40 minutes observe the stain produced on the mercuric chloride paper.

**Observation:** Stain produced by test sample is not more intense than that obtained by standard sample or equals to the standard one, passes the limit test. If stain produced by test sample is more intense than that obtained by standard sample which fails the limit test for arsenic as per IP.

**Arsenic apparatus:** This apparatus details are as follows:

- It consists of a 100 ml bottle or conical flask closed with a rubber or ground glass stopper through which passes a glass tube (about 20 cm × 5 mm).
- The lower part of the tube is drawn to an internal diameter of 1.0 mm, and 15 mm from its tip is a lateral orifice 2 to 3 mm in diameter.
- When the tube is in position in the stopper the lateral orifice should be at least 3 mm below the lower surface of the stopper.
- A second glass tube of the same internal diameter and 30 mm long is placed in contact with the first and held in position by two spiral springs or clips.
- Into the lower tube insert 50 to 60 mg of *lead acetate cotton, loosely packed*.
- Between the flat surfaces of the tubes place a disc or a small square of *mercuric chloride paper* large enough to cover the orifice of the tube.

The arsenic apparatus is shown in Fig. 1.3.



**Fig. 1.3: Arsenic apparatus**

**Reason for adding:**

- Lead acetate papers are used to trap any hydrogen sulphide which may be evolved together with arsine
- Stannous chloride is used for complete evolution of arsine
- HCl is used to make the solution acidic
- Zinc, potassium iodide and stannous chloride is used as a reducing agent.

#### **Precautions**

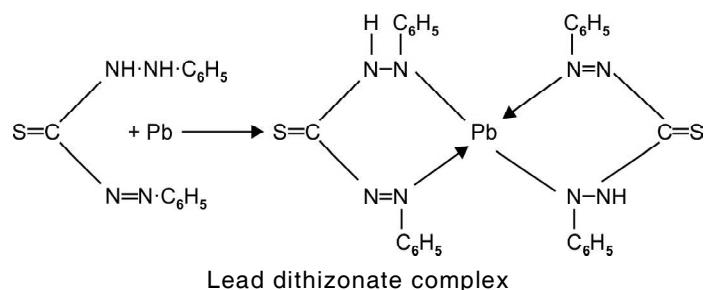
- The most suitable temperature for carry out this test is 40°C.
- Care must be taken that the filter paper remains quite dry during the reaction.

- During the succeeding tests the tube must be washed with HCl AsT rinsed with water and dried.
- All the reagents used for this test should be free from arsenic and mentioned as AsT.

### Limit Test for Lead

#### **Principle**

It is based on the violet color produced in chloroform due to the reaction between lead impurity and dithizone (diphenyl thiocarbazone) which results in the formation of lead dithizonate. The intensity of final violet color produced in the chloroform medium is compared with standard.



#### **Preparation of Solutions**

**Preparation of standard lead solution (1 ppm Pb):** Dissolve 0.4 g of lead nitrate in water containing 2 ml of dilute nitric acid and add sufficient water to produce 250 ml. This gives standard lead solution (1% Pb). Standard lead solution (1 ppm Pb) is prepared by diluting 1 volume of standard lead solution (1% Pb) to 1000 volumes with water.

**Preparation of dithizone extraction solution:** Dissolve 30 mg of dithizone in 1000 ml of chloroform and add 5 ml of ethanol (95%). The solution is stored in refrigerator. Before use, the solution is shaken with about half of its volume of 1% v/v nitric acid solution and acid is discarded.

**Preparation of dithizone standard solution:** Dissolve 10 mg of dithizone in 1000 ml of chloroform.

#### **Procedure**

<i>Test solution</i>	<i>Standard solution</i>
A known quantity of sample solution is transferred in a separating funnel	A standard lead solution is prepared equivalent to the amount of lead permitted in the sample under examination
Add 6 ml of ammonium citrate	Add 6 ml of ammonium citrate
Add 2 ml of potassium cyanide and 2 ml of hydroxylamine hydrochloride	Add 2 ml of potassium cyanide and 2 ml of hydroxylamine hydrochloride
Add 2 drops of phenol red	Add 2 drops of phenol red
Make solution alkaline by adding ammonia solution	Make solution alkaline by adding ammonia solution
Extract with 5 ml of dithizone until it becomes green	Extract with 5 ml of dithizone until it becomes green

(Contd.)

<i>Test solution</i>	<i>Standard solution</i>
Combine dithizone extracts are shaken for 30 mins with 30 ml of nitric acid and the chloroform layer is discarded	Combine dithizone extracts are shaken for 30 mins with 30 ml of nitric acid and the chloroform layer is discarded
To the acid solution add 5 ml of standard dithizone solution	To the acid solution add 5 ml of standard dithizone solution
Add 4 ml of ammonium cyanide	Add 4 ml of ammonium cyanide
Shake for 30 mins	Shake for 30 mins
Observe the color	Observe the color

**Comparison of stain:** Compare the violet color of the chloroform layer.

**Observation:** The intensity of the color of complex is depends on the amount of lead in the solution. The color produce in sample solution should not be greater than standard solution. If color produces in sample solution is less than the standard solution, the sample will pass the limit test of lead and *vice versa*.

#### Reason for adding:

- The interference by other metal ions is eliminated by adjusting the optimum pH for the extraction by using reagents like ammonium citrate, potassium cyanide and hydroxylamine hydrochloride.
- Lead present as an impurities in the substance, gets separated by extracting an alkaline solution with a dithizone extraction solution.
- Phenol red is used as indicator to develop the color at the end of process.

#### Precautions

- All reagents used for the test should have as low a content of lead as practicable.
- All reagent solutions should be stored in containers of borosilicate glass.
- Glassware should be rinsed thoroughly with warm dilute nitric acid followed by water.

### IMPORTANT QUESTIONS/ANSWERS

#### I. Multiple Choice Questions

- Indian Pharmacopoeia is published by:
  - Indian Pharma Commission
  - Indian Pharmacopoeia Commission
  - Indian Patent Commission
  - None of the above
- Impurities may be present in pharmaceutical substances because of:
  - Raw material
  - Chemical instability
  - Manufacturing process
  - All of the above
- Why HCl is used in the limit test of sulfate?
  - Forms precipitate
  - Clear the solution
  - Remove the impurities of sulfate
  - All of the above
- Limit test is performed in:
  - Round bottom flask
  - Nessler cylinder
  - Volumetric flask
  - Conical flask
- ..... is also called Gutzeit test.
  - Limit test of sulfate
  - Limit test of chloride
  - Limit test of lead
  - Limit test of arsenic

6. In pharmacopeia, directions and specifications of drugs mentioned which are intended for medicinal use is known as:
  - a. Test for impurity
  - b. Monograph
  - c. Limit test
  - d. Quality parameters
7. Indian Pharmacopoeia update frequency of addendum is once in every ..... years.
  - a. Two
  - b. Four
  - c. Three
  - d. Five
8. Which reagent is added to prevent supersaturation of barium sulfate in the limit test of sulfate?
  - a. Ethanol
  - b. HCl
  - c. Methanol
  - d. Butanol
9. In limit test of heavy metals, the metal sulfides formed are in ..... color.
  - a. Orange
  - b. Yellow
  - c. Brownish
  - d. Green
10. Limit test for iron, formation of ..... produce purple color.
  - a. Citric acid
  - b. Thioglycolic acid
  - c. Arsine
  - d. Nitric acid
11. Limit test for lead is based on the reaction between lead and ..... in an alkaline medium.
  - a. Diphenylamine
  - b. Aluminum chloride
  - c. Methanol
  - d. Diphenylthiocarbazone
12. The limit test for lead is based upon reaction of lead with ..... in an alkaline media.
  - a. Ethanol
  - b. HCl
  - c. Methanol
  - d. Butanol

### Answers

1. b    2. d    3. c    4. b    5. d    6. b    7. b    8. a    9. c    10. b    11. d  
12. a

### II. Fill in the Blanks

1. The standard and test solution used for limit test are prepared in .....
2. The limit test for arsenic is based upon ..... test.
3. In limit test for arsenic ..... is converted into arsenous acid/arsine gas.
4. Arsine gas is carried and comes into contact with ..... in produces a yellow or brown stain.
5. The function of granulated Zn in limit test for arsenic is .....
6. Limit test for sulfate has been based upon the precipitate of sulfate with ..... in the presence of .....
7. In limit test for sulfate to prevent the supersaturation of  $\text{BaSO}_4$  a small amount of ..... has been added in the reagent.
8. Limit test for iron is based upon reaction of Fe with ..... in presence of a ..... solution buffered with ammonium citrate.
9. Limit test for iron purple color is due to formation of .....
10. In limit test for iron ..... prevent the precipitate of iron as  $\text{Fe(OH)}$  solution.
11. In limit test for iron ferrous thioglycolate has stable pink to reddish purple colour in ..... medium.

12. Limit test is ..... test designed to identify and control small quantities of impurities.
13. Limit test for chloride has been based open reaction between ..... and ..... to obtain silver chloride.
14. Limit test for Pb has been based upon reaction between ..... and ..... to form complex.
15. Ppm is ..... and one ppm is .....

### Answers

1. Distilled water
2. Gutzeit test
3. Arsenious acid
4. Mercuric chloride
5. Slow and prolonged evolution of nascent H<sub>2</sub> gas
6. Barium chloride, dilute hydrochloric acid
7. Alcohol
8. Thioglycolic acid, citric acid
9. Iron thioglycolate
10. Citric acid
11. Alkaline
12. Quantitative
13. Silver nitrate and soluble chloride
14. Lead and diphenyl thiocarbazone
15. Parts per million, 1 mg in 1 kg

### III. Short Answer Questions

1. Define pharmaceutical inorganic chemistry.
2. Write a note on sources of impurities in pharmaceutical preparation.
3. Explain the importance of inorganic chemistry in pharmacy.
4. Write the salient features of recent edition of Indian Pharmacopoeia.
5. What is the role of citric acid, thioglycolic acid and ammonia in the limit test of iron?
6. What is the use of stannous chloride in limit test of arsenic?

### IV. Long Answer Questions

1. Briefly explain the history of Indian Pharmacopoeia.
2. Discuss about various pharmacopeias.
3. Define the term monograph and explain with any one official drug.
4. Explain the development of pharmacopeias.
5. Discuss limit test of iron.
6. Explain the principle and procedure for the limit test of sulfate.
7. Discuss in detail about the apparatus used in limit test of arsenic.
8. Discuss the principle of limit test of sulfate, arsenic and chloride.
9. Give complete principle and method as per IP of limit test of lead.
10. Explain the limit test of heavy metals.

# Acids, Bases and Buffers

<ul style="list-style-type: none"> <li>• Introduction</li> <li>• Acids and Bases           <ul style="list-style-type: none"> <li>Henderson-Hasselbalch Equation</li> <li>Theories of Acids and Bases</li> </ul> </li> <li>• Buffers           <ul style="list-style-type: none"> <li>Mechanism of Buffer Action</li> <li>Types of Buffers</li> <li>Buffer Action</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Buffer Capacity</li> <li>Buffers in Pharmaceutical System</li> <li>Buffer Solutions</li> <li>Buffered Isotonic Solution</li> <li>• Tonicity           <ul style="list-style-type: none"> <li>Methods used for the Measurement of Tonicity</li> <li>Methods of Adjustment of Tonicity</li> </ul> </li> <li>• Important Questions/Answers</li> </ul>
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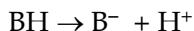
## INTRODUCTION

Electrolytes are dissolved in water which is split up into two or more electrically charged particles. The most of living creatures comprises about 70% of water. Water is a polar solvent which dissolves most charged or polar molecules and most salts by hydrating them (forming hydrogen bond) and after stabilizing the cations and anions by weakening their electrostatic interactions between them.

## ACIDS AND BASES

An acid may be defined as a substance which is able to donate protons which has sour taste and its aqueous solution turns blue to red. It reacts with bases to form ionic compounds called salts and water.

A base may be defined as a substance which accepts protons. It has bitter taste and its aqueous solution turns red to blue.

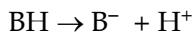


In the above example, BH is an acid because it donates proton and B is an anion liberated by the deprotonation of the acid. B<sup>-</sup> behaves like a base, so it is called conjugate base.

Acids can be classified into strong acids and weak acids.

1. **Strong acids** get dissociated almost completely, e.g. hydrochloric acid, sulfuric acid. This is because the conjugate bases of these acids are very weak (have less affinity for the proton).
2. **Weak acids** get dissociated partially, e.g. acetic acid, carbonic acid. This happens because the conjugate bases of these acids are strong (have greater affinity for proton).

**Henderson-Hasselbalch equation:** Since the dissociation of the weak acids is partial, the equilibrium constant for the dissociation reaction of the weak acid (BH) can be written as follows:



By applying the law of mass action at equilibrium:

$$K_a = \frac{[\text{B}^-][\text{H}^+]}{[\text{BH}]}$$

K<sub>a</sub> is dissociation constant.

The equilibrium constants for ionization reactions are commonly called ionization or dissociation constant (K<sub>a</sub>). The above equation can be rearranged as:

$$[\text{H}^+] = \frac{K_a \times [\text{BH}]}{[\text{B}^-]}$$

By multiplying the above equation by -1 and taking logarithm of both sides, the following expression can be derived

$$-[\text{H}^+] = -\left[ \frac{K_a \times [\text{BH}]}{[\text{B}^-]} \right]$$

$$-\log_{10} [\text{H}^+] = -\log_{10} K_a - \log_{10} [\text{BH}]/[\text{B}^-] - \log_{10} [\text{H}^+] \text{ is pH}$$

As the hydrogen ion concentration increases, the pH of the solution decreases. As the hydrogen ion concentration decreases, pH will increase. Hydrogen ion concentration and pH are reciprocally related.

$$\begin{aligned} \text{pH} &= \text{pKa} + \log_{10} [\text{B}^-]/[\text{BH}] \\ &= \text{pKa} + \log_{10} \frac{[\text{Conjugate base}]}{[\text{Acid}]} \end{aligned}$$

This expression is called **Henderson-Hasselbalch equation**. If the conjugate base and acid concentration is the same, then **pH = pKa**. The value of pKa is lower for strong acids and higher for weak acids.

### Theories of Acids and Bases

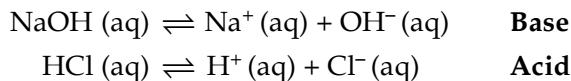
Like many other chemical theories, the three main theories of acids and bases have been widely used today. They are:

1. Arrhenius theory
2. Bronsted-Lowry theory or proton transfer theory
3. Lewis theory or electronic theory

**Arrhenius theory:** In 1887, Arrhenius explained this property of electrolytes and hence it is known as **Arrhenius theory of electrolyte dissociation**. Water molecules are produces H<sup>+</sup> and OH<sup>-</sup> ions through ionization.

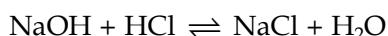
The charged particles, which are formed when the electrolyte is dissolved in water, are called ions, and this process is called ionization. The process of ionization is reversible. These ions may have positive or negative charge. Since they are charged, they are responsible for carrying the electric current through the solution.

According to the Arrhenius model, “**Acids are substances that dissociate in water to produce H<sup>+</sup> ions and bases are substances that dissociate in water to produce OH<sup>-</sup> ions”**



The extent of ionization is given by the ratio of the total number of dissociated molecules to the number of molecules dissolved. The degree of ionization can be increased by diluting the solution in case of weak electrolytes.

According to neutralization reaction, these two ions combine to form salt and water.



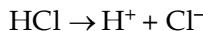
### **Limitations**

1. It is simple, limited only to aqueous solution and not to substance.
2. It could not explain the acidic character of the substances.
3. The neutralization of acid and base in absence of solvent could not be explained.
4. It could not explain the basic character of the substances such as NH<sub>3</sub> which do not contain OH<sup>-</sup> ions.

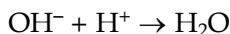
**Bronsted-Lowry theory or proton transfer theory:** In 1923, Bronsted-Lowry theory was proposed by Danish chemist J. N. Bronsted and British chemist J.M. Lowry. It is also called proton transfer theory of acids and bases.

According to him, “**An acid is any substance (molecular or ionic) which is able to donate protons (proton donor) to any other substance, whereas base is any substance which accepts protons (proton acceptor)”**.

Examples of acids are as follows:

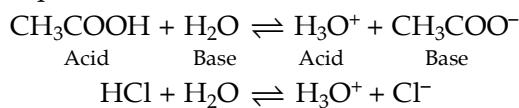


For base



**Conjugate acid-base pair:** Acid-base pair is a substance which can be formed from each other mutually by the gain or loss of a proton is called conjugate acid-base pair. Thus, conjugate of an acid is a substance formed by the loss of proton while conjugate of an base is a substance formed by the gain of proton.

Some examples, a reaction of acetic acid in water:

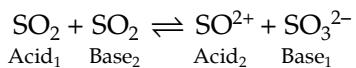


In the above reaction, acetic acid donates proton to water therefore an acid. Water accepts proton and therefore acts as base. In the reverse reaction hydronium ions donate proton to acetate ions and acetate ions accept protons.

### **Limitations**

1. This concept lays emphasis on the proton transfer. Although it is true that most common acids are protonic in nature, yet there are many which are not.

2. A large number of acid-base reactions are known in which no proton transfer takes place, e.g.

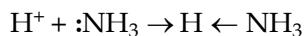


Thus, the protonic definition cannot be used to explain the reactions occurring in non-protonic solvents such as  $\text{COCl}_2$ ,  $\text{SO}_2$ ,  $\text{N}_2\text{O}_4$ , etc.

**Lewis theory or electronic theory:** In 1923, An American chemist Lewis introduced another concept of acid and base along with the formation of coordinate bond.

According to Lewis, “**An acid may be defined as any species (molecule, ion or radical) that can accept an electron pair to form coordinate bond while base may be defined as any species that can donate an electron pair to form coordinate bond. In Lewis system, an acid is electron pair acceptor and base is an electron pair donor**”.

The reaction between Lewis acid and base results in a product which is described as adduct, e.g.



Here ( $\text{H}^+$ ) accepts one electron pair from  $\text{NH}_3$  molecule and is therefore a Lewis acid, whereas  $\text{NH}_3$  molecule donates one electron pair is a base. The adduct is  $\text{NH}_4^+$  ion.

**Lewis acid:**  $\text{NH}_4^+$ ,  $\text{H}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cu}^{2+}$ ,  $\text{Al}^{3+}$ , etc.

**Lewis base:**  $\text{OH}^-$ ,  $\text{H}_2\text{O}$ ,  $\text{NH}_3$ ,  $\text{Cl}^-$ ,  $\text{CN}^-$ ,  $\text{S}^{2-}$ , etc.

### Limitations

1. The relative strength of an acid and bases depend on the type of reaction and cannot be explained on the basis of Lewis theory.
2. A Lewis acid-base reactions involve electrons therefore it is expected to be very fast reaction, however many Lewis acid-base reactions which are slow.

## BUFFERS

Buffers are solutions that **resist changes in the pH** when an acid or alkali is added. The buffer system has an acid component and salt component. Buffers are prepared by mixing a weak acid and its salt with a strong base or by mixing weak base and its salt with a strong acid.

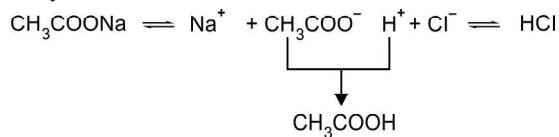
### Mechanism of Buffer Action

When a strong acid is added, protons are scavenged by the salt component of the buffer system. Similarly, when an alkali is added, acid component will get deprotonated and the alkali combines with the proton to form water.

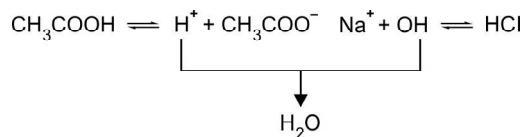
Acetate buffer is made up of acetic acid ( $\text{CH}_3\text{COOH}$ ) and sodium acetate ( $\text{CH}_3\text{COONa}$ ).

- i. When acid like  $\text{HCl}$  is added to the acetate buffer system,  $\text{CH}_3\text{COONa}$  (sodium acetate) gets converted to  $\text{CH}_3\text{COO}^-$  (acetate). Acetate combines with the protons

released by the strong acid to give acetic acid, which is a weak acid, and the change in pH is very small.



ii. When a strong alkali like NaOH is added, OH<sup>-</sup> combines with H<sup>+</sup> released by the CH<sub>3</sub>COOH to form water. Na<sup>+</sup> combines with acetate to form sodium acetate.



According to Henderson-Hasselbalch equation, when the concentration of the salt component and the acid component of the buffer system is equal, pH of the solution equals pKa. At this pH, buffer can respond equally to both added acid as well as the alkali.

### Types of Buffers

Generally, buffers are classified into three categories.

1. Acidic buffers
2. Basic buffers
3. Phosphate buffers (double salt buffers).

**Acidic buffers:** An acidic buffer is a combination of weak acid and its salt with a strong base, i.e. Weak acid and salt with strong base (conjugate base).

*Examples:* Mixture of acetic acid and sodium acetate (CH<sub>3</sub>COOH/CH<sub>3</sub>COONa), H<sub>2</sub>CO<sub>3</sub>/NaHCO<sub>3</sub>, H<sub>3</sub>PO<sub>4</sub>/NaH<sub>2</sub>PO<sub>4</sub>, HCOOH/HCOONa.

The pH of acid buffer can be calculated from the dissociation constant, K<sub>a</sub> of the weak acid and the concentrations of the acid and salt used.

$$\begin{aligned} \text{HA} &\leftrightarrow \text{H}^+ + \text{A}^- \\ \text{pOH} &= \text{pK}_b - \log [\text{base}]/[\text{salt}] \\ \text{or} \quad \text{pOH} &= \text{pK}_b + \log [\text{salt}]/[\text{base}] \end{aligned} \quad (2.3)$$

Equation (2.3) is called Henderson-Hasselbalch equation for base. It helps in calculating the pOH value of buffer solution, if the concentrations of base as well as that of the salt are known.

**Basic buffers:** A basic buffer is a combination of weak base and its salt with a strong acid, i.e. weak base and salt with strong acid (conjugate acid).

*Examples:* Mixture of ammonium hydroxide and ammonium chloride (NH<sub>4</sub>OH/NH<sub>4</sub>Cl), NH<sub>3</sub>/NH<sub>4</sub>Cl, NH<sub>3</sub>/(NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub>.

The pH of basic buffer can be calculated from the dissociation constant, K<sub>b</sub> of the weak base and the concentrations of the base and salt used.

$$\begin{aligned} \text{BOH} &\leftrightarrow \text{B}^+ + \text{OH}^- \\ \text{pOH} &= \text{pK}_b - \log [\text{base}]/[\text{salt}] \\ \text{or} \quad \text{pOH} &= \text{pK}_b + \log [\text{salt}]/[\text{base}] \end{aligned} \quad (2.4)$$

Equation (2.4) is called Henderson-Hasselbalch equation for base. It helps in calculating the pOH value of buffer solution, if the concentrations of base as well as that of the salt are known.

$$\begin{aligned} \text{pK}_w &= \text{pH} + \text{pOH} \\ \text{pOH} &= 14 - \text{pH} \end{aligned}$$

Equation (2.4) can be rewrite as

$$\begin{aligned} 14 - \text{pH} &= \text{pK}_b - \log [\text{base}]/[\text{salt}] \\ -\text{pH} &= \text{pK}_b - 14 - \log [\text{base}]/[\text{salt}] \\ \text{pH} &= 14 - \text{pK}_b + \log [\text{salt}]/[\text{base}] \end{aligned} \quad (2.5)$$

**Phosphate buffers (double salt buffers):** Besides the two general types of buffers (i.e. acidic and basic), a third appears to exist.

This is buffer system composed of two salts: Monobasic potassium phosphate ( $\text{KH}_2\text{PO}_4$ ), dibasic potassium phosphate ( $\text{K}_2\text{HPO}_4$ ).

**Neutral buffer solution:** It is having mixture of weak acid and weak base.

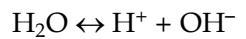
*Example:* Mixture of acetic acid and ammonium hydroxide.

### Buffer Action

The resistance of a buffer solution to a change in pH is known as buffer action even when small amount of acid or base is added to its solution.

Pure water is considered to ionize into a small degree and represented by following equation.

Hydrogen ion concentration



$$K_w = \frac{[\text{H}^+][\text{OH}^-]}{[\text{H}_2\text{O}]}$$

$$K_w [\text{H}_2\text{O}] = [\text{H}^+] [\text{OH}^-]$$

$$K_w = [\text{H}^+] [\text{OH}^-]$$

where  $K_w$  is an ion product constant. It is expressed by only the concentration of ionic substances on the right hand side of the reaction. It has a constant value at  $25^\circ\text{C}$  of  $1 \times 10^{-14}$ . So

$$[\text{H}^+] [\text{OH}^-] = 1 \times 10^{-14}$$

In pure water both the concentrations of ions are equal such as value of  $1 \times 10^{-7} \text{ M}$

$$[\text{H}^+] = [\text{OH}^-] = 1 \times 10^{-7}$$

If acid or base is added to the water, hydrogen ion concentration is greater than hydroxide ion concentration. So, the value of hydrogen ion concentration (pH) is  $10^{-7}$  gm ion per liter.

**pH of the buffer:** Sorenson introduced the practical concept of expressing acidity that is pH scale. Negative logarithm (to the base 10) of hydrogen ion concentration is called pH. It is expressed as gram equivalent per liter or mole per liter.

pOH term is defined as negative logarithm of hydroxyl ion concentration.

$$\begin{aligned} \text{pH} &= -\log [\text{H}^+] \\ &= -\log 1/[\text{H}^+] \end{aligned}$$

In pure water

$$\begin{aligned} \text{H}^+ &= [\text{OH}^-] = 1 \times 10^{-7} \\ \text{pH} &= -\log [1 \times 10^{-7}] = -\log 1 + \log 10^7 \\ &= 7 \end{aligned}$$

Hence, the pH scale range from 0–14.

In Neutral solution  $[\text{H}^+] = [\text{OH}^-]$  ions are equal.

$[\text{H}^+]$  ions are high then the solution is acidic

$$[\text{H}^+] > [\text{OH}^-] \text{ (pH is } < 7)$$

$[\text{H}^+]$  ions are low then the solution is basic

$$[\text{H}^+] < [\text{OH}^-] \text{ (pH is } > 7)$$

Relationship between pH and pOH.

Ionic product of water is given by

$$K_w = [\text{H}_3\text{O}^+] [\text{OH}^-]$$

Take a log on both sides

$$\log K_w = \log [\text{H}_3\text{O}^+] [\text{OH}^-]$$

$$\log K_w = \log [\text{H}_3\text{O}^+] + \log [\text{OH}^-]$$

By multiplying by  $-1$  by both sides

$$-\log K_w = -\log [\text{H}_3\text{O}^+] - \log [\text{OH}^-]$$

Considered

$$\text{pH} = -\log [\text{H}_3\text{O}^+]$$

and

$$\text{pOH} = -\log [\text{OH}^-]$$

$$\text{pK}_w = \text{pH} + \text{pOH}$$

$$= -\log K_w \quad [K_w = 10^{-14}]$$

so

$$-\log K_w = -\log (10^{-14})$$

$$\text{pK}_w = (-14) \log 10 \quad [\log 10 = 1]$$

$$= 14 \log 10$$

$$= 14$$

By this equation, the pH of a buffer solution can be calculated from the initial concentrations of the weak acid and the salt provided when  $K_a$  is given. However, the Henderson equation for a basic buffer will give pOH, and so pH can be calculated as;

$$\text{pK}_w = \text{pH} + \text{pOH}$$

or

$$\text{pH} = \text{pK}_w - \text{pOH}$$

$$= 14 - \text{pOH} \text{ or } \text{pOH} = 14 - \text{pH}$$

Also, the dissociation constant of a weak acid ( $\text{pK}_a$ ) or a weak base ( $\text{pK}_b$ ) can be calculated by measuring the pH of a buffer solution containing equimolar concentrations of the acid (or base) and the salt.

### Examples

- Calculate the pH of a buffer solution containing 0.03 moles/liter of acetic acid and 0.1 moles/liter of sodium acetate.  $\text{pK}_a$  for  $\text{CH}_3\text{COOH}$  is 4.57.

**Solution:**

Conc. of acid = 0.03 M

Conc. of salt = 0.1 M

so,

$$\begin{aligned} \text{pH} &= \text{pK}_a + \log [\text{salt}]/[\text{acid}] \\ &= 4.57 + \log 0.1/0.03 \\ &= 4.57 + 0.52 \\ &= 5.09 \end{aligned}$$

**Result:** The pH of the buffer solution containing 0.03 M of acetic acid and 0.1 M of sodium acetate is 5.09.

2. Calculate the pH of a buffer solution containing 0.25 moles/liter of formic acid (HCOOH) and 0.10 moles/liter of sodium formate (HCOONa).  $K_a$  for formic acid is  $1.8 \times 10^{-4}$ .

**Solution:**

$$\text{Conc. of acid} = 0.25 \text{ M}$$

$$\text{Conc. of salt} = 0.10 \text{ M}$$

$$K_a = 1.8 \times 10^{-4}$$

and

$$\begin{aligned} \text{pK}_a &= -\log K_a = -\log 1.8 \times 10^{-4} \\ &= -(log 1.8 \times 10^{-4}) = -(log 1.8 + log 10^{-4}) \\ &= -[0.25 + (-4)] = -(-3.75) = 3.75 \end{aligned}$$

so,

$$\begin{aligned} \text{pH} &= \text{pK}_a + \log [\text{salt}]/[\text{acid}] \\ &= 3.75 + \log 0.10/0.25 \\ &= 3.75 - 0.397 \\ &= 3.34 \end{aligned}$$

**Result:** The pH of a buffer solution containing 0.25 M of formic acid and 0.10 M of sodium formate is 3.34.

### Buffer Capacity

The buffer capacity of a buffer solution is “a measure of its magnitude of its resistance to change in the pH on an addition of an acid or a base.” Buffer capacity is also referred as *buffer index*, *buffer value*, *buffer efficiency* or *buffer coefficient* or capacity of the buffer to resist the change in the pH of a solution when an acid or alkali is added is called buffering capacity. It is estimated by calculating the **amount of acid or alkali required to change the pH of 1 L of buffer by 1 unit**.

Buffering capacity depends upon the following factors:

- The concentration of the acid and base component of the buffer:** As the concentration of acid and base component of the buffer increases, buffering capacity of the buffer also increases.
- The pH of the buffer:** Buffer can act best at  $\text{pH} = \text{pK}_a$  and its buffering range is about one pH unit above or below the  $\text{pK}_a$  value.

The buffer capacity represented by  $\beta$  may also be defined as the ratio of the increment (amount added) of strong acid or base to the small change in pH ( $\Delta\text{pH}$ ) brought about by this addition.

$$\beta = \Delta A \text{ or } \Delta B / \Delta \text{pH}$$

where,  $\Delta A$  or  $\Delta B$  represents the small increment (in gram equivalents/liter of strong acid or base added) to the buffer to bring about a pH change of  $\Delta\text{pH}$ .

According to the above equation, a solution has a buffer capacity of 1 when 1 L of it requires 1 gm equivalent of a strong acid or base to change the pH by 1 unit. So,

smaller the pH change in a solution upon the addition of an acid or base, greater is the buffer capacity and *vice versa*.

### Example

Prepare a buffer solution of pH 5 from acetic acid ( $\text{CH}_3\text{COOH}$ ) and  $\text{CH}_3\text{COONa}$ .

Required:

- $\text{pH} = 5$
- $\text{pK}_a = 4.7$
- Molar concentration of acid = 1 M
- Molar concentration of base =  $x$  M = ?

So, by putting above information in equation, we get:

$$\text{pH} = \text{pka} + \log [\text{salt}]/[\text{acid}]$$

$$5 = 4.7 + \log [x]/[1]$$

$$5 - 4.7 = \log x - \log 1$$

$$\log 1 = 0,$$

$$0.3 = \log x$$

$$x = \text{log} - 0.3 \text{ ('log -' means antilog)}$$

$$= 2$$

**Result:** In order to prepare buffer solution of pH 5, acetic acid  $\text{CH}_3\text{COOH}$  and sodium acetate  $\text{CH}_3\text{COONa}$  must be mixed in a ratio of 1 M : 2 M.

### Buffers in Pharmaceutical System

**In biological systems:** The pH of blood is maintained at about 7.4 by two buffer systems. That are:

- a. **Primary buffers:** These are present in plasma. The plasma contains carbonic acid / carbonate and acid / alkali sodium salt of phosphoric acid.
- b. **Secondary buffers:** These are present in erythrocytes which are oxyhemoglobin / hemoglobin and acid / alkali potassium salts of phosphoric acid.

**In pharmaceutical systems:** Buffers are widely used in the field of pharmacy as ingredients in most of the pharmaceutical formulations in order to adjust the pH of the product to that required for maximum stability. It also plays vital role in ensure the solubility of the system:

- a. **Solubility:** Buffers control the solubility of the medicinal compound by providing a suitable and stable pH media. Many inorganic salts like phosphates, borates are soluble in acid media but precipitate out in basic media. Organic compounds with acidic functional groups are soluble in basic media.
- b. **Stability:** Certain compounds when exposed to redox conditions undergo decomposition due to auto-oxidation, e.g. ascorbic acid and penicillin is unstable in basic pH, nitrite becomes brown in acidic media due to formation of nitrogen oxides.
- c. **Solid dosage form:** Buffers have been widely for controlling the pH of the environment around the solid particles. This has practical application for the drugs that have dissolution rate limited absorption from unbuffered solutions. Gastric irritation caused by acidic drugs is reduced with application of buffers, e.g. antacids are used for the purpose of reducing toxicity.

- d. **Semi-solid dosage form:** Buffers are used to maintain their stability in semi-solid preparations. Due to long storage time, they undergo pH changes, resulting in its reduced stability. Citric acid, sodium citrate or phosphoric acid/sodium phosphate is used.
- e. **In parenteral preparations (i.e. injections):** In case of parenteral preparations, pH should be considered carefully as large deviations of pH may lead to serious consequences. The ideal pH of a parenteral product is 7.4, which is pH of blood. The most commonly used buffers in parenteral products (injections) are *acetate, phosphate, citrate and glutamate*.
- f. **In ophthalmic preparations:** Buffers are generally used in ophthalmic preparations to maintain the pH within the physiological pH range of lacrimal fluid (i.e. eye fluid). The lacrimal fluid has a pH in range 7–8, but it has good buffering capacity and can tolerate preparations having pH values between 3.5 and 10.5 with little discomfort. Outside this range (i.e. 3.5–10.5), increase lacrimation may occur with other complications. The buffering agents most commonly used in ophthalmic preparations include *borate, carbonate and phosphates*.
- g. **In ointments and creams:** Topical products (which are used on skin) such as ointments and creams are also buffered to ensure stability of the formulation. The most commonly used buffers in ointments and creams are citric acid/its salts and phosphoric acid/its salts.

### Buffer Solutions

Buffer solutions are mentioned in the pharmacopoeia under appendix for solutions and reagents. There are two kinds of buffer solutions.

1. Standard buffer solutions
2. Other buffer solutions

**Standard buffer solutions:** These are solutions which have standard pH which is used to fulfil many pharmacopeial tests that require adjustments or maintenance of a specific pH and for reference purposes in pH measurements. Appropriate combinations of 0.2 M HCl or 0.2 M NaOH is required for preparation of standard buffer solutions for various ranges of pH values between 1.2 and 10.

#### Composition of standard buffer solutions:

Name of buffer	pH	Method of preparation
Hydrochloric acid buffer	1.2–2.2	Measure and transfer 50 ml of the 0.2 M KCl and add specified quantity of 0.2 M HCl and then dilute the solution with water up to 200 ml
Acid phthalate buffer	2.2–4.0	Measure and transfer 50 ml of the 0.2 M potassium hydrogen phthalate and add specified quantity of 0.2 M HCl and then dilute the solution with water up to 200 ml
Neutralized phosphate buffer	4.2–5.8	Measure and transfer 50 ml of the 0.2 M potassium hydrogen phthalate and add specified quantity of 0.2 M NaOH and then dilute the solution with water up to 200 ml
Phosphate buffer	5.8–8.0	Measure and transfer 50 ml of the 0.2 M potassium dihydrogen phosphate and add specified quantity of 0.2 M NaOH and then dilute the solution with water up to 200 ml
Alkaline borate buffer	8.0–10.0	Measure and transfer 50 ml of the 0.2 M boric acid and KCl and add specified quantity of 0.2 M NaOH and then dilute the solution with water up to 200 ml

**Other buffer solutions:** A large number of various buffer solutions are mentioned in the Appendix of Indian Pharmacopoeia along with the method of preparation, e.g. acetate buffer solutions in various pH, ammonia buffer solution and phosphate buffer solution.

### Buffered Isotonic Solutions

**Isoelectric point:** The isoelectric point of the protein is the pH at which any given protein has no charge or zero charge due to an equal number of positive and negative charges. In protein purification and electrophoresis, this property has important biochemical implications.

Pharmaceutical preparations which are meant for application to delicate membranes of the body should adjust to some osmotic pressure as that of body fluids.

**Osmosis:** It is the process in which solvent molecules cross the semipermeable membrane from lower to higher concentration to establish concentration equilibrium.

**Osmotic pressure:** The pressure driving osmosis is called osmotic pressure and it is colligative property governed by the number of "particles" of solute in solution.

## TONICITY

It is a measure of the osmotic pressure of two solutions separated by a semipermeable membrane. Tonicity of the solution mainly depends on the number of particles present in the solution.

**Isosmotic solutions:** Solutions that have the same osmotic pressure. An isosmotic solution containing specific amount of drug is isotonic to blood only when blood cells are impermeable to the solute (drug) molecules and permeable to solvent molecules.

**Osmolality and osmolarity** are the two colligative properties which measure the concentration of solutes independently of their ability to cross the membrane. Osmolality means amount of osmotically active particles present in the solution. It is denoted by milliosmole or osmole.

**Isotonic solution:** Two solutions having the same osmotic pressure as a specific body fluid.

Isotonic solutions should not cause no swelling or no contraction when in contact with tissues and produce no discomfort when used with nasal tract, blood, eye and other body tissues.

### Types of Tonicity

Based on solute concentration, there are three types of solutions in our body.

1. **Isotonic solution:** In this type of solution concentration of solute is same in both inside and outside of the cell, e.g. a small quantity of blood is mixed with a solution containing 0.9% NaCl, the cell retain their normal size.
2. **Hypotonic solution:** The concentration of solute is greater in inside of the cell than outside, e.g. the blood is mixed with a 0.2% NaCl solution causing them to swell and finally burst.
3. **Hypertonic solution:** The concentration of solute is greater in outside of the cell than inside of it, e.g. red blood cells are suspended in a 2% NaCl solution causes shrinkage.

Hypertonic	Isotonic	Hypotonic
NaCl 2%	NaCl 0.9%	NaCl 0.2%
Solute < solute	Solute = solute	Solute > solute
Inside outside	Inside outside	Inside outside
Shrinkage	Equilibrium	Swelling

### Reasons for maintenance of isotonicity:

1. The formulations of the parenteral product should be isotonic with *in vivo* body fluids.
2. If any isotonicity and pH differences may cause irritation, hemolysis, necrosis and tissue toxicity.
3. Ophthalmic solutions should be isotonic with lacrimal fluid (tears) to prevent irritation and pain.
4. Similarly, injectable solutions should be isotonic with blood plasma.

On injecting the **hypotonic solution** into bloodstream.

- It may enter the red blood cells in an attempt to produce equilibrium
- The cells swell rapidly until they burst leading to hemolysis
- As this damage is irreversible may lead to serious danger to red blood cells.

When **hypertonic solution** is injected into the bloodstream:

- The water comes out of the membrane of red blood cells in order to reach the equilibrium
- The cells shrink leading to crenulations which is only a temporary damage
- When the osmotic pressure of two solutions becomes equal, the shrinking cells will come to its original position.

### Methods Used for the Measurement of Tonicity

In various pharmaceutical preparations, many drugs and chemicals are used and these substances contribute to maintain the tonicity of the solution. Therefore, various methods are used to measure and adjust the tonicity. There are two methods are used to measure the tonicity of the solution.

1. **Hemolytic method:** In this method, to examine the effect of various solutions of the drug is observed on the appearance of red blood cells in the solution. The appearance of red blood cells is observed for swelling, shrinking, wrinkling and bursting of the blood cells. A quantitative method developed by hunter, based on the concept of that hypotonic solution liberates oxyhemoglobin released is proportional to the number of cells hemolyzed. In hypertonic solutions, the cells shrink and become wrinkled, whereas in case of isotonic solutions the cells do not undergo any change. Van't Hoff 'i' factor of drug solution can be determined.
2. **Determination of slight temperature difference:** Isotonicity values are determined by slight temperature difference is measured from difference in the vapor pressure of thermally insulated samples present in the humidity chamber, e.g. freezing point of blood and tears and it was necessary to make solutions isotonic with these fluids. Freezing point of both was found to be  $-0.52^{\circ}\text{C}$ . This temperature is analogous to the freezing point of a 0.9% NaCl solution, therefore which is considered to be isotonic with blood and lacrimal fluid.

3. **Using  $L_{iso}$  values:** Isotonicity is also measured from colligative properties of the solutions. Freezing point depression ( $\Delta T_f$ ) property is most widely used.

$$\Delta T_f = L_c$$

$L$  value can be find out from the freezing point depression of solutions of a given ionic type at a concentration of  $c$ .  $L$  is denoted as  $L_{iso}$ .

### Methods of Adjustment of Tonicity

There are several methods used to adjust the isotonicity of the pharmaceutical substances by which amount of NaCl, dextrose and other substances can be calculated to include them to solutions of drugs to make them isotonic. The amount of adjusting agents to be added is easy to determine by using the appropriate calculations based on colligative properties of the solutions. It helps to overcome the side effects due to drug administration which containing adjusting agents.

The methods are divided into two classes.

**Class I methods:** Add a material to a hypotonic solution to adjust the freezing point depression (FPD) to  $-0.52^\circ\text{C}$ .

- a. **Cryoscopic method:** Calculate how much sodium chloride required to further drop FPD by  $X^\circ\text{C}$ .

Freezing point depression (FPD)

$$w\% = \frac{0.52 - a}{b}$$

where  $w\%$  is conc. gm/100 ml of adjusting substance

$a$  is FPD of 1% of unadjusted substance (table)  $\times$  percentage strength

$b$  is FPD of 1% of adjusting substance, i.e. NaCl

#### Example I

How much NaCl is required to render 100 ml of a 1% soln. of apomorphin HCl isotonic?

FPD of 1% NaCl =  $0.58^\circ$

FPD of 1% drug =  $0.08^\circ$

$$\begin{aligned} w\% &= \frac{0.52^\circ - a}{b} \\ &= \frac{0.52^\circ - 0.08^\circ}{0.58^\circ} \\ &= 0.76\% \end{aligned}$$

1% drug  $\rightarrow 0.08^\circ$  ( $0.52^\circ - 0.08^\circ = 0.44^\circ\text{C}$ )

1% NaCl  $\rightarrow 0.58^\circ$

$w\%$  NaCl  $\leftarrow 0.44^\circ$

$W\% = 0.76\%$

Thus, 0.76% NaCl will lower the freezing point by  $0.44^\circ\text{C}$  and will render the solution isotonic.

#### Example II

Adjust isotonicity of procaine HCl 3% using NaCl?

FPD of 1% NaCl =  $0.57^\circ$

FPD of 1% drug =  $0.112^\circ$

$$\begin{aligned} w\% &= \frac{0.52 - a}{b} \\ &= \frac{0.52 - (0.112 * 3)}{0.576} \\ &= 0.32 \text{ gm/100 ml} \rightarrow \text{NaCl} \end{aligned}$$

b. **Sodium chloride equivalence:** Calculate contribution of drug in terms of sodium chloride equivalent and make up to 0.9% with addition of NaCl. NaCl equivalent is denoted by "E".

Amount of NaCl that is equivalent to [i.e. has the same osmotic effect (same FPD) as] 1 gm of drug. First calculate  $E_{\text{NaCl}}$  and second add NaCl to reach 0.9%

To calculate amount of NaCl by

$$w\% = 0.9 - (\text{drug}\% \times E_{\text{NaCl}})$$

w% = weight of NaCl in gm per 100 ml (to make solution isotonic)

drug% = weight of drug in gm per 100 ml

$E_{\text{NaCl}}$  = NaCl equivalent weight to 1 gm of drug

0.9 = Isotonic solution of NaCl

### Example III

Calculate  $E_{\text{NaCl}}$  of drug ( $M \cdot \text{wt} = 187$ ,  $L_{\text{iso}} = 3.4$ )?

$$E_{\text{NaCl}} = \frac{17L_{\text{iso}}(\text{drug})}{M \cdot \text{wt}_{\text{drug}}}$$

$$= 0.31 \text{ gm}$$

$$(0.31 \text{ g (NaCl)}) = 1 \text{ gm (drug)}$$

$$(0.62 \text{ g (NaCl)}) = 2 \text{ gm (drug)}$$

$$0.9 - 0.62 = 0.28 \text{ gm (NaCl)}$$

→ 2 gm drug, 0.28 gm NaCl complete with water to 100 ml

### Example IV

Calculate amount of NaCl needed to adjust 1.5% atropine SO<sub>4</sub>.

$$\begin{aligned} E_{\text{NaCl}} &= 0.12 \text{ g} \\ &= 0.9 - (W \times E) \\ &= 0.9 - (1.5 \times 0.12) \\ &= 0.72 \text{ gm of NaCl should be added} \end{aligned}$$

Thus, it require 1.5 gm of drug and 0.72 gm of NaCl.

**Class II methods:** Start with drug powder, make an isotonic drug solution, then make up to final volume with isotonic salt solution or isotonic buffer: a. White-Vincent method, b. Sprowls method.

a. **White-Vincent method:** The class II methods of calculating tonicity involve the addition of water to the drugs to make an isotonic solution than add isotonic vehicle to bring solution to final volume.

White-Vincent introduces simplified equation for calculating the volume of isotonic solution prepared by mixing drug with water.

$$v = w \times E_{\text{NaCl}} \times 111.1$$

where  $v$  = Volume of  $\text{H}_2\text{O}$

$w$  = Weight of drug

$$111.1 = 100/0.9$$

### Example I

Suppose preparing 30 ml of 1% drug isotonic with body fluid ( $E_{\text{NaCl}} = 0.16 \text{ gm}$ )

$$\begin{aligned} 1 \text{ gm} &\rightarrow 100 \text{ ml} \\ ? &\rightarrow 30 \text{ ml} = 0.3 \text{ gm} \end{aligned}$$

Amount of NaCl eq. to 0.3 drug

$$= 0.3 \times 0.16 = 0.048 \text{ gm}$$

- $0.9 \text{ gm} \rightarrow 100 \text{ ml}$
- $0.048 \text{ gm} \rightarrow ? \text{ ml} = 5.3 \text{ ml}$

$$V = 0.3 \times 0.16 \times 111.1 = 5.3 \text{ ml}$$

### Example II

Add volume of  $\text{H}_2\text{O}$  and then complete with isotonic solution

- Phenacaine HCl 0.06 gm ( $E_{\text{NaCl}} = 0.16$ )
- Boric acid 0.3 gm ( $E_{\text{NaCl}} = 0.5$ )
- Sterile distilled  $\text{H}_2\text{O}$  up to 100 ml

$$\begin{aligned} V &= 111.1 \times (\text{weight} \times E_{\text{NaCl}}) \\ V &= 111.1 \times [(0.06 \times 0.16) + (0.3 - 0.5)] \\ &= 17.7 \text{ ml } \text{H}_2\text{O} \end{aligned}$$

- b. **Sprowls method:** The equation  $V = 0.3 \times 0.21 \times 111.1$ , could be used to construct a value of  $V$ , when the weight of drug  $W$  is fixed. Sprowls choose the weight of drug is 0.3 gm, the quantity for 1 fluid ounce of 1% solution. Compute the volume  $V$  of isotonic solution of 0.3 gm drug with sufficient water, for drugs commonly used in parenteral and ophthalmic preparations.

## Isotonic Buffers

The addition of any compound to a solution will affect the isotonicity since isotonicity is a property of the number of particles in solution. So, the osmotic pressure of a solution will be affected not only by the drug but also by any buffer compounds that are included in the formulation. But after these compounds have been added, it is still possible that the solution will not be isotonic. It may be necessary to add additional sodium chloride to bring the solution to isotonicity.

## IMPORTANT QUESTIONS/ANSWERS

### I. Multiple Choice Questions

1. Acid is a:
  - a. Proton donor
  - b. Ligand donor
  - c. Proton acceptor
  - d. All of the above

2. When acid and base is mixed:
  - a. New acid formed
  - b. No reaction occurs
  - c. Salt and water formed
  - d. New base formed
3. ..... is also known as slaked lime.
  - a. Calcium chloride
  - b. Calcium hydroxide
  - c. Calcium carbonate
  - d. Calcium fluoride
4. Which one of the following buffer is used to maintain acid-base balance in blood?
  - a. Acidic buffer
  - b. Phosphate buffer
  - c. Carbonic acid and bicarbonate
  - d. Acetic acid and sodium carbonate
5. ..... methods are used to adjust the tonicity.
  - a. White-Vincent
  - b. Sprowls
  - c. Both a and b
  - d. None of the above
6. Commonly used biological buffer for pharmaceutical formulation is .....
  - a. Acidic buffer
  - b. Phosphate buffer
  - c. Basic buffer
  - d. None of the above
7. Which one is the conjugate acid-base pair?
  - a. HCl and OH<sup>-</sup>
  - b. CH<sub>3</sub>COOH and OH<sup>-</sup>
  - c. HCN and CN<sup>-</sup>
  - d. None of the above
8. Sodium hydroxide is known as .....
  - a. Baking soda
  - b. Slaked lime
  - c. Quick lime
  - d. Spirit of salt
9. ..... is prepared by Haber's process.
  - a. Caustic soda
  - b. Strong ammonium chloride
  - c. Strong ammonium hydroxide
  - d. None of the above
10. The value of hydrogen ion concentration is .....
  - a.  $1 \times 10^{-7}$
  - b.  $1 \times 10^7$
  - c.  $1 \times 10^8$
  - d.  $1 \times 10^{-8}$

### Answers

1. a    2. c    3. b    4. c    5. c    6. b    7. c    8. d    9. c    10. a

### II. Fill in the Blanks

1. Base has ..... taste.
2. Acid turns ..... litmus .....
3. pH can be measured by .....
4. pH = pKa + .....
5. pH of blood in human body is .....
6. Buffers are solutions that resist changes in the .....
7. ..... is a measure of the osmotic pressure of two solutions separated by a semi-permeable membrane.
8. The concentration of solute is greater in outside of the cell than inside of it is known as .....
9. ..... means amount of osmotically active particles present in the solution.
10. The ..... of the protein is the pH at which any given protein has no charge or zero charge due to an equal number of positive and negative charges.

**Answers**

1. Bitter
2. Blue, red
3. pH meter
4. [Conjugate base]/[Weak acid]
5. 7.3–7.4
6. pH
7. Tonicity
8. Hypertonic solutions
9. Osmolality
10. Isoelectric point.

**III. Short and Long Answer Questions**

1. Define buffers with examples.
2. Explain the type of buffer solution.
3. Write any three pharmaceutical applications of buffers.
4. Describe the mechanism of action of buffer.
5. What is isoelectric point?
6. What do you understand the term buffer capacity? Give a note on factors affecting buffer capacity.
7. Discuss the method of preparation of some standard buffer solutions.
8. Enumerate the buffered isotonic solutions.
9. Define isotonic solutions.
10. Differentiate buffer system and buffer capacity. Explain how buffer system resists small changes in pH.
11. Discuss the various acid-base theories in detail.
12. What do you understand the term conjugate acid-base pairs?
13. Discuss the different methods for adjustment of tonicity.
14. Explain methods used for the measurement of tonicity.

## Major Extracellular and Intracellular Electrolytes

- |  |  |
|--|--|
| <ul style="list-style-type: none"> <li>• Introduction</li> <li>• Major Physiological Ions</li> <li>• Electrolyte Replacement Therapy</li> <li>• Sodium Chloride</li> <li>• Potassium Chloride</li> </ul> | <ul style="list-style-type: none"> <li>• Calcium Gluconate</li> <li>• Oral Rehydration Salt (ORS)</li> <li>• Physiological Acid–Base Balance</li> <li>• Important Questions/Answers</li> </ul> |
|--|--|

### INTRODUCTION

Body fluids are mainly consist of inorganic and organic substances. In cell and tissues, these components should be in balance to maintain the constant environment. Despite of various changes in life, stress introduced by diseases, the volume and composition of the body fluids are continued to be remarkably constant by considerably varying from one compartment to another. The electrolyte concentration in various body fluids is maintained constant in healthy person.

Electrolytes are minerals that carry an electric charge when they are dissolved in a fluid (suitable ionizing solvents). It is a substance when dissolved in solution separates into ions and is able to carry an electrical current. This includes most soluble acids, bases and gases. It dissociates into cations (positively charged electrolyte) and anions (negatively charged electrolyte). The internal homeostasis is preserved by various regulatory mechanisms operating in the body which are capable to control pH, ionic balances, osmotic balance, etc. which in turn maintain the concentration of solutes in various fluids.

Electrolytes are used in replacement therapy and for correction of ionic balance in various body fluids. The electrolyte concentration will vary with a particular fluid compartment. The total body fluids are divided into three compartments. The various body fluids are:

1. **Intracellular fluid:** It is present inside the cell, e.g. cytoplasm, fluid within the cell constitutes 45–50% of body weight and its volume in 30 liters.
2. **Extracellular fluid (ECF):** The fluid present in the interstitial and vascular compartments are referred to collectively known as extracellular fluid.
3. **Interstitial fluid:** This is the fluid which is present between the cells. This constitutes 12–15% of body weight and its volume in 10 liters.
4. **Plasma or vascular fluid:** This is the fluid which is present within the blood vascular system. This constitutes 4–5% of body weight and its volume in 3–5 liters. (of body weight).

**5. Transcellular fluid:** Fluids inside the GIT, humor of eye, excretory system, glands, cerebrospinal, pericardial and synovial fluid.

All the body fluids are composed of electrolytes (solutions of inorganic and organic solutes). All these fluids have different concentration of electrolytes and all the fluid compartments are separated from each other by membranes that are permeable to water and many organic and inorganic solutes. They are nearly impermeable to macromolecules such as proteins and are selectively permeable to certain ions such as  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Mg}^{2+}$ . Each fluid compartment has a distinct solute pattern [sodium and chloride are found in the plasma and interstitial fluids while potassium and phosphate ( $\text{HPO}_4^{2-}$ ) are found in intracellular fluid]. The solution in each compartment is ionically balanced.

The major electrolytes found in the body are sodium, potassium, calcium, magnesium, chloride, bicarbonate, phosphate and sulfate.

### Fluid Electrolyte Concentrations

Ions	Plasma (mEq/L)	Interstitial fluid (mEq/L)	Intracellular fluid (mEq/L)
<b>Cations</b>			
$\text{Na}^+$	142	145	10
$\text{K}^+$	4	4	160
$\text{Mg}^{2+}$	5	3	–
$\text{Ca}^{2+}$	3	2	35
<b>Totals</b>	<b>154</b>	<b>154</b>	<b>205</b>
<b>Anions</b>			
$\text{HCO}_3^-$	27	30	8
$\text{Cl}^-$	103	115	2
$\text{HPO}_4^{2-}$	2	2	140
$\text{SO}_4^{2-}$	1	1	–
<b>Organic</b>			
Acids	5	5	–
Protein	16	1	55
<b>Totals</b>	<b>154</b>	<b>154</b>	<b>205</b>

### Fluid Balance

The amount intake and output of water maintain the electrolyte balance in the body. The average daily intake is 2500 ml [intake by fluids, food and metabolic water] and average daily output is 2500 ml [excreted by urine, feces, perspiration, insensible perspiration].

The concentrations of individual ions are expressed by mEq/L (milliequivalents/liter) rather than weight/volume (w/v). Dosages of individual ions are expressed in mEq/L. Equivalent weight is obtained by dividing the atomic or molecular weight by the valence.

$$\begin{aligned}\text{mEq/L} &= \text{mg of substance/L} \div \text{Eq. wt} \\ &= \text{mg of substance/L} \div (\text{Mol. wt/valence})\end{aligned}$$

### Role of Electrolyte in Body

Mineral salts (inorganic compounds) are necessary within the body for carrying out all body processes. Important functions served by electrolytes in general, are as muscle contraction, nerve impulses, cellular signaling, cellular transport, waste excretion, maintaining pH balance, physiological function and osmotic balance.

### MAJOR PHYSIOLOGICAL IONS

#### Sodium (Na)

It is the principal cation in the extracellular fluid. More than adequate amounts of sodium are contained in the daily diet with nearly complete absorption from the intestinal tract. Excess sodium is excreted by the kidneys which make them the ultimate regulator of the sodium content of the body. 80–85% of the sodium in the glomerular filtrate is reabsorbed and this reabsorption is under hormonal control. The main source of sodium required for our body is table salt which is used for cooking. Normal concentration of sodium is 135–145 mEq/L.

#### *Functions*

It plays an important role in:

1. Transmission and conduction of nerve impulses
2. Many processes in the body, especially in the brain, nervous system, and muscles
3. Responsible for osmolarity of vascular fluids
4. Responsible for charge balance in body fluid
5. Regulation of body fluid levels
6. Assists with regulation of acid–base balance by combining with  $\text{Cl}^-$  or  $\text{HCO}_3^-$  to regulate the balance.

**Hyponatremia:** Deficiency of sodium (<135 mEq/L) due to:

- a. Extreme urine loss in diabetes insipidus (a disease of pituitary gland that secretes less antidiuretic hormone ADH that causes decreased water permeability of the collecting duct of nephrons and thus causes large amounts of urine to be produced).
- b. Metabolic acidosis in which the sodium is excreted.
- c. Addison's disease with decreased excretion of ADH hormone, aldosterone.
- d. Diarrhea and vomiting.
- e. Kidney damage.

Symptoms of hyponatremia are muscle weakness, respiratory depression, headache and faintness.

**Hypernatremia:** Increase of sodium (145 mEq/L) is caused by:

- a. Hyperadrenalinism (Cushing's syndrome) with increased aldosterone production.
- b. Severe dehydration.
- c. Certain types of brain injury.
- d. Excess treatment with sodium salts.

Symptoms of hypernatremia are thirst, flushed skin, dry mucus membranes, low urinary output, tachycardia, seizures and hyperactive deep tendon reflexes.

## Potassium (K)

It is the major intracellular cation, present in a concentration approximately 23 times higher than the concentration of potassium in the extracellular fluid compartments. This concentration differential is maintained by an active transport mechanism. This active transport mechanism has been called the sodium-potassium pump. Normal concentration of potassium is 3.5–5.0 mEq/L (in ECF). The main source of potassium in food includes milk, meat, some vegetables and whole grains. Human body has about 2 to 6 per kg weight of potassium.

### Functions

- It maintains the electrolyte balance in body's cells
- Manages blood pressure and keeps heart functioning properly
- It involves transmission of nerve impulses
- It helps the muscles contract
- Enhances muscle control, the growth and health of cells
- Promotes efficient cognitive functioning by helping to deliver oxygen to the brain.

**Hypokalemia:** Decrease of potassium (<3.5 mEq/L) is caused by:

- Inadequate intake (malnutrition)
- Excessive use of diuretics—thiazides, loop diuretics, amphotericin, cisplatin and mineral/glucocorticoids
- Illness in which postoperative treatment includes IV administration of solutions (deficient of potassium) for long-time
- While treatment of dehydration or alkalosis with sodium and water, there occurs depletion of potassium
- GI losses.

Signs and symptoms of hypokalemia are anorexia, nausea, vomiting, drowsiness, lethargy, confusion, leg cramps, muscle weakness, hyper-reflexia (overactive or over-responsive reflexes), hypotension, cardiac dysrhythmias and polyuria.

**Hyperkalemia:** Increase of potassium (>5 mEq/L) is caused by:

- Excessive intake
- Excessive release from cells due to burns, rhabdomyolysis, tumor lysis syndrome and acidosis
- Decreased excretion due to acute or chronic kidney disease.

Signs and symptoms of hyperkalemia are apathy, confusion, numbness/paresthesia of extremities, abdominal cramps, nausea, flaccid muscles, diarrhea, oliguria, bradycardia and cardiac arrest.

## Calcium (Ca)

In our body 99% of calcium is found in bones. The remaining Ca is found largely in extracellular fluid. Ca is absorbed from the upper part of the small intestine where the intestinal contents are still acidic. As the intestinal contents remain neutral to basic, Ca is precipitate as the  $\text{CaHPO}_4$ , carbonate, oxalate and sulfate salts. Actual absorption is controlled by parathyroid hormone and metabolite of vitamin D. it is an important constituent for teeth and bones. The main sources of calcium include milk, cheese,

green vegetables, fish and egg. Normal concentration of calcium in extracellular fluid is 4–5 mEq/L. Daily requirement of phosphate is 400 mg/day and greater amount is needed in children and during pregnancy and lactation.

### **Functions**

1. Usually combined with phosphorus to form the mineral salts of bones and teeth. Functionally, 99% of all body Ca is supportive, being found in bone as hydroxyapatite.
2. Ionic Ca involved in blood clotting, muscle contraction, nerve signaling (important in the transmission of nerve impulses across synapses).
3. In CVS Ca is essential for contraction in cardiac muscles and for the conduction of electric impulse in certain regions of heart.
4. It plays role in maintaining the integrity of mucosal membrane, cell adhesion and function of the individual cell membrane.

Calcium regulated by the parathyroid gland. In parathyroid hormone it helps with calcium retention and phosphate excretion through the kidneys, promotes calcium absorption in the intestines and helps mobilize calcium from the bone.

**Hypocalcemia:** Decrease of calcium (<4 mEq/L) is caused by:

- a. Hypoparathyroidism
- b. Vitamin D deficiency
- c. Osteoblastic metastasis
- d. Acute pancreatitis
- e. Hyperphosphatemia
- f. Bone is the dynamic tissue involving constant exchange of calcium and phosphate ions with the body fluids. Much of this exchange is under hormonal control.

Signs and symptoms of hypocalcemia are muscle cramps, hyperactive deep tendon, reflexes, paresthesia of fingers, toes and face, tetany, laryngeal spasms, confusion, memory loss and cardiac dysrhythmias.

**Hypercalcemia:** Increase of calcium (>5 mEq/L) is caused by:

- a. Excessive intake
- b. Excessive use of antacids with phosphate-binding
- c. Prolonged immobility
- d. Excessive vitamin D intake
- e. Thiazide diuretics
- f. Cancer
- g. Thyrotoxicosis.

Signs and symptoms of hypercalcemia include muscle weakness, personality changes, nausea and vomiting, extreme thirst, anorexia, constipation, polyuria, pathological fractures, calcifications in the skin and cornea and cardiac arrest.

### **Magnesium (Mg)**

It is the second most plentiful cation in the intracellular fluid compartment. Most of the absorption takes place in the acid medium of the duodenum. Approximately 54% in bone while approximately 45% in intracellular fluid. Normal concentration of

magnesium is 1.5–2.4 mEq/L. Daily requirement of magnesium is 350 mg. Dietary source of magnesium is nuts, soybeans, whole grains and sea foods.

### **Functions**

- Magnesium cation has a definite pharmacological action
- Role in protein synthesis and carbohydrate metabolism
- Helps in cardiovascular system function (vasodilation)
- Regulates muscle contractions
- Helps in  $\text{Na}^+/\text{K}^+$  ATPase pump
- Controls blood sugar level and helps support the body's defense (immune) system.

**Hypomagnesemia:** Serum  $\text{Mg}^{2+}$  level <1.5 mEq/L is caused by:

- Poor dietary intake
- Poor GI absorption
- Excessive dietary intake of  $\text{Ca}^{2+}$  or vitamin D
- Excessive GI/urinary losses
- Chronic alcoholism
- Excessive diuretic therapy.

Signs and symptoms of hypomagnesemia include muscle weakness, cardiac arrhythmias, nausea, confusion and anorexia.

**Hypermagnesemia:** Serum  $\text{Mg}^{2+}$  level >3.0 mEq/L is caused by:

- Usually results from renal failure
- Excessive intake
- Untreated diabetic ketoacidosis
- Hypoadrenalinism.

Signs and symptoms of hypermagnesemia include lethargy and drowsiness, depress neuromuscular activity, hypotension, bradycardia and cardiac arrest.

### **Chloride ( $\text{Cl}^-$ )**

It is the major extracellular anion. Chloride ions principally responsible for maintaining proper hydration, osmotic pressure and normal cation-anion balance in the extracellular fluid. Food is the main source of chloride with the anion being almost completely absorbed from the intestinal tract. Chloride is removed from the blood by glomerular filtration and possibly is reabsorbed by the kidney tubules. The extracellular fluid contains 100 to 106 mEq/L chloride. The total chloride ion present in the body is about 50 mEq per body weight and body daily requirement is 5–10 gm as sodium chloride. The main source of chloride is table salt which is used for cooking.

### **Functions**

1. Chloride travels primarily with sodium and water and helps generate the osmotic pressure of body fluids.
2. It is an important constituent of stomach hydrochloric acid (HCl), the key digestive acid.
3. Chloride is also needed to maintain the body's acid-base balance. Chloride may also be helpful in allowing the liver to clear waste products.

**Hypochloremia:** Deficiency of chloride ion concentration is caused by:

- Salt-losing nephritis (inflammation of the kidney) associated with chronic pyelonephritis (inflammation of the kidney and its pelvis) leading to a lack of tubular reabsorption of chloride.
- Metabolic acidosis such as found in diabetes mellitus and renal failure, causing either excessive production or diminished excretion of acids leading to the replacement of chloride by acetoacetate and phosphate.
- Prolonged vomiting with loss of chloride as gastric hydrochloric acid.

Symptoms of hypochloremia are alkalosis, respiratory depression and muscle spasm.

**Hyperchloremia:** Increase of chloride ion concentration is caused by:

- Dehydration
- Decreased renal blood flow found in congestive heart failure
- Severe renal damage
- Excessive chloride intake
- Excess loss of bicarbonate ions.

### Bicarbonate ( $\text{HCO}_3^-$ )

It is the second most prevalent anion in ECF. Bicarbonate levels are measured to monitor the acidity of the blood and body fluids. The acidity is affected by foods or medications that we ingest and the function of the kidneys and lungs. Disruptions in the normal bicarbonate level may be due to diseases that interfere with respiratory function, kidney diseases and metabolic conditions. Normal arterial bicarbonate is 22–26 mEq/L while normal venous bicarbonate is 26–30 mEq/L (in venous blood, bicarbonate is measured as carbon dioxide content).

Each day kidney filters about 4320 milliequivalents of bicarbonate and under normal conditions all of this is reabsorbed from the tubules, thereby conserving the primary buffer system of the extracellular fluid. When there is reduction in the ECF hydrogen ion concentration (alkalosis) the kidneys fail to reabsorb all the filtered bicarbonate thereby increasing the excretion of bicarbonate.

Because bicarbonate ions normally buffer hydrogen in the extracellular fluid, this loss of bicarbonate is as good as adding a hydrogen ion to the extracellular fluid. Therefore, in alkalosis, the removal of bicarbonate ions raises the ECF hydrogen ion concentration back towards normal. In acidosis, the kidneys reabsorb all the filtered bicarbonate and produces new bicarbonate which is added back to the ECF. This reduces the ECF  $\text{H}^+$  concentration back towards normal, i.e. reverse of acidosis since  $(\text{HPO}_3^-)$  is alkaline.

### Functions

- The bicarbonate ion acts as a buffer to maintain the normal levels of acidity (pH) in blood and other fluids in the body.
- It is the major form in which  $\text{CO}_2$  is transported.
- It acts as a base (alkaline substance).

### Phosphate ( $\text{PO}_4^{3-}$ )

It is principal anion of ICF compartment. Inorganic phosphate in the plasma is mainly in two forms hydrogen phosphate ( $\text{HPO}_4^{2-}$ ) and dihydrogen phosphate ( $\text{H}_2\text{PO}_4^-$ ). Only

the dihydrogen phosphate anion will be absorbed from the intestines. When pH of the ECF becomes more acidic there is relative increase in  $\text{H}_2\text{PO}_4^-$  and decrease in  $\text{HPO}_4^{2-}$  and *vice versa*. Normal concentration of phosphate is 2.5–4.5 mEq/L (in ECF). Daily requirement of phosphate is 400 mg/day and greater amount is needed in children and during pregnancy and lactation. Dietary source of phosphate is milk, milk products, legumes, whole grains and nuts, etc.

### Functions

1.  $\text{HPO}_4^{2-}$  and  $\text{H}_2\text{PO}_4^-$  make an important buffer system of body.
2. Phosphorus is essential for proper metabolism of calcium, normal bone and tooth development.
3. The phosphoric acid anhydride linkage is the body's means of storing potential chemical energy as adenosine triphosphate (ATP).
4. Hexoses are metabolized as phosphate esters.

**Hyperphosphatemia:** Increase of phosphate is caused by:

- a. Renal failure due to the inability to excrete phosphate into the urine
- b. Hypoparathyroidism (lack of parathyroid hormone) permits renal tubular reabsorption of phosphate which results in decreased urinary phosphate and a rise in serum phosphate
- c. Hypervitaminosis D which increases intestinal phosphate absorption along with calcium.

**Hypophosphatemia:** Decrease of phosphate is caused by:

- a. Vitamin D deficiency (rickets)
- b. Decreased intestinal calcium absorption
- c. Hyperparathyroidism
- d. Long-term aluminum hydroxide gel antacid therapy.

### Iron

It is an important component of hemoglobin which carries oxygen in blood. Dietary sources of iron include green leafy vegetables, millets like *bajra* and *ragi*. It is necessary for growing children and pregnant women. The deficiency of iron causes anemia and goiter.

## ELECTROLYTE REPLACEMENT THERAPY

Under normal physiological condition, the body is able to adjust the electrolyte balance while in some conditions such as prolonged fever, severe diarrhea and vomiting, there occurs heavy loss of water and electrolyte. So, there is a need to administration of lost electrolyte in appropriate concentration of tonicity is essential. These products include electrolytes, acids and bases, blood products, carbohydrates, amino acids and proteins. There are some electrolytes which are used in replacement therapy are sodium chloride and its salts, such as sodium chloride injection, hypertonic solution, sodium lactate, potassium chloride and its salts.

There are two types of supply of electrolytes

1. **Rapid initial replacement:** Solution contains electrolytes with concentration resemble with the electrolytes concentration found in extracellular fluids.
2. **Subsequent replacement:** Solution containing lower concentration of electrolytes.

## SODIUM CHLORIDE

**Molecular formula:** NaCl

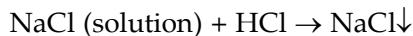
**Molecular weight:** 58.44

**Category:** Pharmaceutical aid (tonicity agent)—fluid and electrolyte replenisher.

**IP limit:** Sodium chloride contains not <99.0% and not >100.5% of NaCl, calculated with reference to the dried substance.

### Preparation

1. **From sea water:** It is prepared by evaporation of sea water.
2. **From common salt:** Common salt was dissolved in water and subsequently HCl gas passing through the solution. Crystal of sodium chloride precipitated out.



**Properties:** It occurs as colorless cubic crystals or as white crystalline powder having saline taste.

**Solubility:** It is freely soluble in water, and slightly more soluble in boiling water, soluble in glycerine and slightly soluble in alcohol.

**Storage:** Stored in tightly-closed containers.

**Acidity or alkalinity:** To 20 ml of 20% w/v solution and add 0.1 ml of *bromothymol blue solution*; not >0.5 ml of 0.01 M *hydrochloric acid* or of 0.01 M *sodium hydroxide* is required to change the colour of the solution.

**Clarity and color of solution:** 20% w/v solution is *clear and colorless*.

### Test for Purity

**Arsenic:** Dissolve 10 gm in 50 ml of *water* and 12 ml of *stannated hydrochloric acid AsT*. The resulting solution complies with the *limit test for arsenic* (1 ppm).

**Heavy metals:** Not >5 ppm, determined by Method A on a solution of 4 gm in 2 ml of *dilute acetic acid* and sufficient *water* to produce 25 ml.

**Iron:** 2 gm dissolved in 20 ml of *water* complies with the *limit test for iron* (20 ppm).

**Loss on drying:** Not >1%, determined on 1 gm by drying in an oven at 105°C for 3 hours.

### Assay

Weigh accurately about 0.1 gm and dissolve in 50 ml of water in a glass-stoppered flask. Add 50 ml of 0.1 M silver nitrate, 5 ml of 2 M nitric acid and 2 ml of dibutyl phthalate, shake well and titrate with 0.1 M ammonium thiocyanate using 2 ml of ferric ammonium sulfate solution as indicator, until the color becomes reddish yellow. Each ml of 0.1 M silver nitrate is equivalent to 0.005844 gm of NaCl.

**Uses:** Used as fluid and electrolyte replenisher, manufacture of isotonic solution, flavor enhancer.

### Official Preparations of Sodium Chloride

1. **Sodium chloride injection:** It is a sterile isotonic solution of sodium chloride in water for injection. It contains not <0.85% and not >0.95% w/v of sodium chloride. It contains no antimicrobial agents. It is a clear, colorless solution with pH between 4.5 and 7.

2. **Sodium chloride hypertonic injection (hypertonic saline):** It is a sterile solution of sodium chloride in water for injection. It contains not <1.52% and not >1.68% w/v of sodium chloride. It contains no antimicrobial agents. It is a clear, colorless solution with pH between 5.0–7.5.
3. **Compound sodium chloride injection (Ringer injection):** It contains not <0.82% and not >0.9% w/v of sodium chloride, not <0.0285%, not >0.0315% w/v of potassium chloride and not <0.03% and not >0.036% w/v of calcium chloride in water for injection. It contains no antimicrobial agents. It is a clear, colorless solution with pH between 5 and 7.5.
4. **Sodium chloride and dextrose injection:** It is a sterile solution of sodium chloride and dextrose in water for injection. It is clear colorless or faintly straw colored solution with pH between 3.5 and 6.5. It contains not <95% and not >105% w/v of the stated amount of sodium chloride and dextrose.

## POTASSIUM CHLORIDE

*Molecular formula:* KCl

*Molecular weight:* 74.56

**Category:** Electrolyte replenisher.

**IP limit:** Potassium chloride contains not <99% and not >100.5% of KCl, calculated with reference to the dried substance.

### Preparation

It is prepared by the reaction of hydrochloric acid with potassium carbonate or bicarbonate



**Properties:** It occurs as colorless crystals or white, crystalline powder and odorless. It is having saline taste.

**Solubility:** Freely soluble in water—practically insoluble in ethanol and in ether.

**Storage:** Stored in tightly-closed containers.

**Acidity or alkalinity:** 5 gm dissolved in 50 ml of carbon dioxide-free water requires not >0.5 ml of 0.01 M sodium hydroxide or 0.01 M hydrochloric acid for neutralization to bromothymol blue solution.

**Clarity and color of solution:** 10% w/v solution is *clear* and *colorless*.

### Test for Purity

**Arsenic:** Dissolve 10 gm in 50 ml of water and add 10 ml of stannated hydrochloric acid AsT. The resulting solution complies with the limit test for arsenic (1 ppm).

**Heavy metals:** Not >10 ppm, determined by Method A on 2 g dissolved in 10 ml of water to which are added 2 ml of dilute acetic acid and 13 ml of water.

**Iron:** 20 ml of solution A complies with the limit test for iron (20 ppm).

**Loss on drying:** Not >1%, determined on 1 gm by drying in an oven at 105°C.

**Assay**

Weigh accurately about 0.15 gm, dissolve in 50 ml of water and titrate with 0.1 M silver nitrate using potassium chromate solution as indicator. Each ml of 0.1 M silver nitrate is equivalent to 0.007455 gm of KCl.

**Uses:** Electrolyte replenisher in potassium deficiency, familial periodic paralysis, myasthenia gravis.

**CALCIUM GLUCONATE**

*Molecular formula:*  $C_{12}H_{22}CaO_{14}\cdot H_2O$

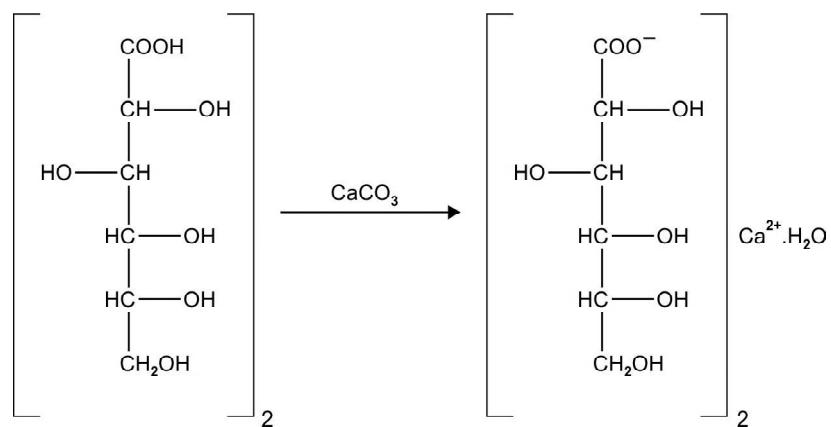
*Molecular weight:* 448.40

**Category:** Calcium replenisher.

**IP limit:** Calcium gluconate contains not <98.55 and not >102% of  $C_{12}H_{22}CaO_{14}\cdot H_2O$ .

**Preparation**

It is prepared by boiling the solution of gluconic acid with calcium carbonate.



**Properties:** It occurs as white, crystalline powder or granules, odorless and tasteless.

**Solubility:** Sparingly soluble in water but freely soluble in boiling water; insoluble in ethanol (95%).

**Storage:** Store in well-closed containers.

**Acidity or alkalinity:** Dissolve 0.5 gm in 20 ml of *water*, add 0.1 ml of 0.01 M *hydrochloric acid* and 0.1 ml of *phenolphthalein solution*; no color is produced. Add 0.3 ml of 0.01 M *sodium hydroxide*; a pink color is produced.

**Clarity and color of solution:** A 2% w/v solution at 60° is not more intensely colored than *reference solution YS6*, on cooling to room temperature the solution is not more opalescent than *opalescence standard OS<sub>2</sub>*.

**Arsenic:** Dissolve 5 gm in 50 ml of *water* and 12 ml of *stannated hydrochloric acid*. The resulting solution complies with the *limit test for arsenic* (2 ppm).

**Heavy metals:** Not >20 ppm, determined by Method A on 1 gm dissolved in 4 ml of *dilute hydrochloric acid* and sufficient *water* to produce 25 ml.

**Chloride:** 1 gm complies with the limit test for 250 ppm of chloride.

**Sulfate:** 1 gm complies with the limit test for sulfates (150 ppm).

### Assay

Weigh accurately about 0.5 gm and dissolve in 50 ml of warm *water*; cool, add 5 ml of 0.05 M magnesium sulfate and 10 ml of *strong ammonia solution* and titrate with 0.05 M disodium edetate using *mordant black II mixture* as indicator. From the volume of 0.05 M disodium edetate required subtract the volume of the magnesium sulfate solution added. Each ml of the remainder of 0.05 M disodium edetate is equivalent to 0.02242 gm of  $C_{12}H_{22}CaO_{14}\cdot H_2O$ .

**Uses:** An excellent source of calcium in oral treatment of calcium deficiency.

### Official Preparations of Calcium Gluconate

1. **Calcium gluconate injection:** Calcium gluconate injection is a sterile solution of calcium gluconate in water for injection. Not >5% of the calcium gluconate may be replaced with a suitable calcium salt as a stabilizing agent.

**Usual strengths:** The equivalent of 500 mg and 1 gm of calcium gluconate in 5 ml; the equivalent of 1 gm of calcium gluconate in 10 ml. (A 10% w/v solution of calcium gluconate contains approximately 0.45 mmol of  $Ca^{++}$  per ml).

2. **Calcium gluconate tablets:**

**Standards:** Calcium gluconate tablets contain not <95% and not >105% of the stated amount of calcium gluconate,  $C_{12}H_{22}O_{14}Ca\cdot H_2O$ .

**Usual strengths:** 325 mg, 500 mg, 650 mg, 1 gm.

**Storage:** Stored in well-closed containers.

### ORAL REHYDRATION SALT (ORS)

Oral rehydration salts are dry, homogeneously mixed powders containing dextrose, sodium chloride, potassium chloride and either sodium bicarbonate or sodium citrate for use in oral rehydration therapy after being dissolved in the requisite amount of water. Composition of the formulation in terms of the amount (in gm) is to be dissolved in sufficient water to produce 1000 ml in ancient times home-made ORS is used which contains 1 tablespoonful of salt and 2 tablespoonful of sugar in 1000 ml of water.

### Composition of the Formulation

S. no.	Salt name	Gram	Electrolytes	mmol/L
1	Sodium chloride	2.6	Sodium	75
2	Dextrose (anhydrous)	13.5	Potassium	20
3	Dextrose monohydrate	14.85	Chloride	65
4	Potassium chloride	1.5	Citrate	10
5	Sodium citrate	2.9	Dextrose	75

#### Role of each ingredient:

- Water:** Water is the essential ingredient to a rehydration solution, as a solvent.
- Sodium chloride:** Sodium and chloride is a replenisher.
- Glucose (dextrose):** It provides energy to the cells.

**4. Potassium chloride:** Potassium also acts as a replenisher.

**5. Trisodium citrate dihydrate:** Buffering agent.

**Properties:** A white to creamy-white, amorphous or crystalline powder, odorless. The total osmolar concentration of the solution in terms of mOsm per liter is 245.

**Storage:** Store protected from moisture in sachets, preferably made of aluminum foil, containing sufficient powder for a single dose or for a day's treatment or for use in hospitals, in bulk containers containing sufficient quantity to produce a volume of solution appropriate to the daily requirements of the hospital concerned.

**Uses:** It is used as an excellent source of electrolytes like sodium potassium and chloride. It is used for the treatment of dehydration in heavy water loss and electrolyte replacement therapy. It is also used as energy source. It is used in cases of severe vomiting, diarrhea and prolonged fever.

## ■ PHYSIOLOGICAL ACID-BASE BALANCE

Body fluids are having balanced quantity of acids and bases and this is maintained by intricate mechanism. Balance depends on regulation of free hydrogen ions and concentration of hydrogen ions is measured in pH. The maintenance of this balance quantity is essential for biochemical reactions taking place in the body and are very sensitive even a small changes in acidity or alkalinity. Arterial blood gases are the major diagnostic tool for evaluating acid-base balance. The pH values of certain body fluids are given as follows:

Body fluid	pH value
Gastric juice	1.5–3.5
Saliva	5.4–7.5
Bile	6.0–8.5
Blood	7.4–7.5
Semen	7.2–7.6
Urine	4.5–8

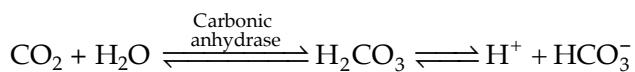
Acidosis and alkalosis conditions are generated due to change in body pH. Acidosis ( $\text{pH} < 7.35$ ) caused by accumulation of acids or by a loss of bases and alkalosis ( $\text{pH} > 7.45$ ) occurs when bases accumulate or acids are lost.

Acids are continuously being produced during metabolism. Since most metabolic reaction occurs only within a very narrow pH range, the body utilizes several buffer systems. Three of the major buffer systems in the body are:

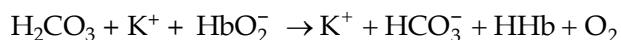
1. Bicarbonate/carbonic acid found in plasma and kidneys.
2. Phosphate/dihydrogen phosphate found in the cells and kidney.
3. Hemoglobin buffer system which is the most effective single system for buffering carbonic acid produced during metabolic processes.

Carbon dioxide is continuously produced in the cells. It diffuses from the cells into the plasma where a small portion is dissolved and another small portion reacts with the water to form carbonic acid. The increased carbonic acid is buffered by plasma protein. Most  $\text{CO}_2$  enters the erythrocytes where it either rapidly forms carbonic acid by the action of carbonic anhydrase or combines with hemoglobin.

The tendency to lower the pH of the electrolyte due to increased concentration of carbonic acid is compensated by hemoglobin.



Bicarbonate anion then diffuses out of the erythrocyte and chloride anion diffuses in this has been named chloride shift. The bicarbonate in plasma along with the plasma carbonic acid, now acts as an efficient buffer system.

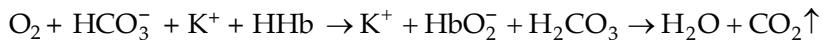


Most metabolic reactions take place only within a very narrow pH range; homeostasis of H<sup>+</sup> concentration becomes essential for survival and is done by involving the following three major mechanisms:

1. Respiratory system
2. Chemical buffer system
3. Kidneys.

### 1. Respiratory System

The above process is reversible in lungs due to large amounts of oxygen present where oxygen combines with the deoxyhemoglobin, releasing protons. These further combine with the bicarbonate, forming carbonic acid, which then dissociates to carbon dioxide and water. The carbon dioxide is exhaled by the lungs.



### 2. Chemical Buffer System

It acts immediately. It is combining with offending acid or base to neutralize harmful effects until another system takes over.

- **Bicarbonate buffer:** Mainly responsible for buffering blood and interstitial fluid
- **Phosphate buffer:** Effective in renal tubules
- **Protein buffers:** Most plentiful like hemoglobin in body cells and plasma.

### 3. Kidneys

The third mechanism is via reabsorb or excretes excess acids or bases into urine. Absorption of certain ions and elimination of others are able to maintain the acid-base balance in body fluids.

Acid excretion in the kidneys occurs as follows:

1. Sodium salts of mineral and organic acids are removed from the plasma by glomerular filtration.
2. Sodium is preferentially removed from the renal filtrate or tubular fluid and in the tubule cells, reacts with carbonic acid formed by the carbonic anhydrase catalyzed reaction of carbon dioxide and water. This is sometimes called the Na<sup>+</sup>-H<sup>+</sup> exchange.
3. The sodium bicarbonate returns to the plasma and the proton enter the tubular fluid, forming acids of the anions that originally were sodium salts.

Acid excretion in the kidneys occur by three ways:

1. Bicarbonate reabsorption
2. New bicarbonate production (connected with  $H^+$  excretion)
3. Ammonium ion excretion.

### IMPORTANT QUESTIONS/ANSWERS

#### I. Multiple Choice Questions

1. Electrolytes are:
  - a. Minerals
  - b. Amino acids
  - c. Vitamins
  - d. None of the above
2. The body fluids found inside the cell is called:
  - a. Interstitial fluid
  - b. Intracellular fluid
  - c. Plasma
  - d. Extracellular fluid
3. Sodium chloride is used as:
  - a. Fluid and electrolyte replenisher
  - b. Toxic agent
  - c. Pharmaceutical aid
  - d. All of the above
4. Potassium chloride used for the treatment of:
  - a. Myasthenia gravis
  - b. Antidote in digitalis detoxification
  - c. Menieres syndrome
  - d. All of the above
5. Replacement therapy is required in the condition of:
  - a. Heavy loss of water
  - b. Diarrhea
  - c. Both a and b
  - d. None of the above
6. Water lost occurs through:
  - a. Kidney and lungs
  - b. GI tract
  - c. Skin
  - d. All of the above
7. Total output of the body fluid under normal conditions:
  - a. 1500 ml/day
  - b. 250 ml/day
  - c. 2500 ml/day
  - d. 4500 ml/day
8. .... ions easily diffuses between intra- and extra-cellular compartments.
  - a. Chloride
  - b. Potassium
  - c. Sodium
  - d. Magnesium
9. In metabolic acidosis, .... occurs.
  - a. Excess  $HCO_3^-$
  - b. Deficit  $HCO_3^-$
  - c. Excess  $Cl^-$
  - d. Deficit  $CO_2$
10. Calcium chloride is used as:
  - a. Electrolyte replenisher
  - b. Toxic agent
  - c. Antacid
  - d. All of the above
11. .... is used as urinary acidifier:
  - a.  $NaHPO_4$
  - b. Sodium carbonate
  - c. Calcium chloride
  - d. All of the above

## Answers

1. a    2. b    3. d    4. d    5. c    6. d    7. c    8. a    9. b    10. a    11. a  
12. c    13. b    14. c    15. b

## **II. Fill in the Blanks**

1. Electrolyte solution can be given by ..... and .....
  2. Magnesium chloride lies in the category of .....
  3. Excessive loss of CO<sub>2</sub> can cause .....
  4. ORS stands for .....
  5. .... is absorbed from upper part of small intestine.
  6. Home-made ORS constitutes of .....
  7. .... therapy is not recommended in patients having impaired renal function and acute dehydration.
  8. Calcium gluconate is prepared from ..... and .....
  9. The concentration of electrolytes expressed in .....
  10. .... are found in intracellular fluid.

## Answers

1. Oral and IV
  2. Magnesium replenisher
  3. Acidosis
  4. Oral rehydration salt
  5. Calcium
  6. One teaspoonful of salt, eight teaspoonful of sugar in one liter of water
  7. Potassium
  8. Gluconic acid  $\text{CaCO}_3$
  9. Milliequivalents per liter
  10. Potassium, magnesium and phosphate

### **III. Short Answer Questions**

1. Define major intra- and extracellular electrolytes.
  2. Discuss physiological acid-base balance.

3. Define acidosis and alkalosis.
4. What do you understand the term replacement therapy?
5. What is the concentration of sodium, potassium, magnesium and calcium ion in our body?
6. Write any two functions of sodium and potassium in our body.
7. Differentiate hypernatremia and hyponatremia.
8. Write the dietary sources of calcium and magnesium.

#### IV. Long Answer Questions

1. What are major intra- and extracellular electrolytes? Discuss the physiological role of sodium.
2. Give the method of preparation, properties and uses of potassium chloride.
3. Write a detail note on physiological role of bicarbonate and chloride ions.
4. Write a short note on ORS.
5. Define replacement therapy. Explain any two ions used in replacement therapy.
6. Describe the preparation and uses of calcium gluconate.
7. Give the detail account of iron and phosphate ions.

# Dental Products

- Introduction
- Anatomy of Tooth
- Anticaries Agent
- Role of Fluoride
- Role of Phosphate
- Sodium Fluoride
- Dentrifrices

- Calcium Carbonate
- Desensitizing Agents
- Zinc Chloride
- Polishing Agents
- Zinc Oxide Eugenol Cement
- Important Questions/Answers

## INTRODUCTION

Dental hygiene is important to maintain oral hygiene on regular basis to prevent oneself from oral diseases or dental disorders and other oral problems. The most common dental disorders include tooth decay (cavities, caries) and gum disease (gingivitis, periodontitis). One can keep the mouth clean and free from diseases by routinely brushing the teeth twice a day and cleaning the teeth. A good dental health means to maintain a healthy mouth, teeth, gums which in turn improve the quality of life and appearance. Vitamin A and C are necessary for proper teeth formation. Deficiency of these vitamins can affect the teeth.

The teeth are accessory organ of digestive system. It also called dentes. It is located in oral or buccal of the mouth. Teeth are mainly used to bite and chew the food that is also called mastication. Teeth cut, tear up the food with the help of long, sharp canine teeth while grind and mash up the food by wide, flat molar teeth. Then mixed with saliva effectively and swallowed more easily. Teeth performed all actions mechanically (as opposed to chemical).

## ANATOMY OF TOOTH

Tooth consists of three major external regions: The crown, root and neck, and calcified layers of tissue, namely:

1. **Enamel:** Crystalline calcium salts cover the crown to protect the tooth.
2. **Dentin:** Largest part of the tooth beneath the enamel and protect pulp.
3. **Pulp:** It consists of free nerve endings.
4. **Cementum:** Bone-like structure, cover the root and provide the attachment of the tooth with periodontal ligaments.

## Dental Products

Dental products are the substance which used to produce effect on teeth and in dental cavity is called dental products. It is used to maintain dental hygiene.

In order to prevent tooth decay, varieties of dental products are available in the market. A large number of inorganic compounds are used to overcome the problems associated with dental disorders. These dental products include:

- Anticaries agents
- Cleansing agents or dentifrices
- Desensitizing agent
- Polishing agents
- Oral antiseptic
- Mouthwashes
- Cements and fillers.

### **ANTICARIES AGENT**

Dental caries or tooth decay involves demineralization (softening) of enamel and dentin. It is caused by acid produced by the action of microorganisms or carbohydrates. It is also called dental plaque. It is a biofilm or mass of bacteria that grows on surfaces within the mouth. Initially, it is sticky colorless deposit then it changes into brown or pale yellow. It is characterized by decalcification of tooth by foul odor. If it is not treated then microorganisms may invade the pulp which causes inflammation and infection.

Dental caries or cavities are formed by the growth and implantation of microorganism in teeth. The microbial flora present in the mouth act on carbohydrates which produce acids especially lactic acid. Calcium salts are dissolved in acidic media (demineralize the enamel) and the remaining organic matter digested by proteolytic enzymes and cavities are formed. Initially, the demineralized enamel appears as chalky white area and eventually becomes brown or yellow.

Dental caries can be prevented by dentifrices which help to maintain oral and dental hygiene. Dentifrices are the products which enhance the removal of stain and tooth decay by toothbrush. The most accepted approach to prevent caries includes flossing and brushing accompanied by administration fluoride either internally or topically to the teeth. Deprived nutrition of the mother during pregnancy may cause poor architecture of the teeth that become susceptible to the development of caries in the early age. Nowadays, dentist using newer devices to detect tooth decay in early stage by laser technique which actually can be reversed most commonly used dental caries is a liquid dye or stain. Dentist can spread the nontoxic dye into the teeth and rinse it off. After rinsing, the healthy areas of teeth are free from stain but it sticks to the decayed areas.

An agents or substances which are used to prevent dental caries are called anticaries agents.

Example of anticaries agent: Sodium fluoride, stannous fluoride, sodium monofluorophosphate.

### **ROLE OF FLUORIDE**

Fluoride ion is a trace element in the body. It is acquired from food and water in adequate quantity. Fluoride is able to help in reducing and preventing dental caries.

An administration of small quantity (1 ppm) of fluoride containing salts or their use in topical formulation on teeth to prevent caries. In some parts of the world, ground water is completely lacking fluoride. In such cases, addition of fluoride to the municipal water supply known as *fluoridation* and topical fluoride can also provide antimicrobial action. However, excessive fluoride (more 2–3 ppm) intake during the period of tooth development can cause dental *fluorosis*.

### **Mode of Action**

When a fluoride having salt or solution is taken internally, it is readily absorbed, transported and deposited in the bone or developing teeth and remained get excreted by kidneys. The deposited fluoride on the surface of teeth does not allow the action of acids or enzymes that produce lesions. Fluoride is anticariogenic as it replaces the hydroxyl ion in hydroxyapatite with the fluoride ion to form fluoroapatite in the outer surface of the enamel. Fluoroapatite hardens the enamel and makes it more acid resistant. It is also possible the fluorides may possess some antimicrobial activity and help in remineralization of enamel.

It can be administered by two routes: (i) Orally and (ii) topically. Public water supply containing 0.5–1 ppm (should not >1 ppm) which is sufficient and for topical application 2% solution is generally used on teeth.

### **ROLE OF PHOSPHATE**

Inorganic phosphate salts are also been found to useful in reducing the dental caries. Generally phosphate ions are required for stronger bone as well as healthy teeth. Both soluble and insoluble salts of phosphate ions are obtained from normal diets. It also acts as a cleansing agent. Soluble inorganic salts phosphate ions such as 1% mixture of sodium dihydrogen phosphate and disodium hydrogen phosphate is used to prevent caries.

### **SODIUM FLUORIDE**

*Molecular formula:* NaF

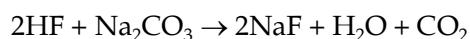
*Molecular weight:* 41.99

**Category:** Preventive for dental caries.

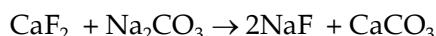
**IP limit:** Sodium fluoride contains not <98.5% and not >100.5% of NaF, calculated with reference to the dried substance.

#### **Preparation**

- Neutralizing hydrofluoric acid with sod. carbonate



- Double decomposition of calcium fluoride with sod. carbonate



**Properties:** A white powder or colorless crystals.

**Solubility:** Soluble in water practically, insoluble in ethanol (95%).

**Storage:** Store in tightly-closed containers.

**Identification:** Dissolve 2.5 gm in sufficient *carbon dioxide-free water* without heating to produce 100 ml (solution A). To 2 ml of solution add 0.5 ml of *calcium chloride solution*;

a gelatinous white precipitate is produced which dissolves on adding 5 ml of *ferric chloride solution*.

**Acidity or alkalinity:** Dissolve 2.5 gm of *potassium nitrate* in 40 ml of 2.5% w/v solution, dilute to 50 ml with *carbon dioxide-free water*, cool to 0°C and add 0.2 ml of *dilute phenolphthalein solution*. If the solution is colorless, not >1 ml of 0.1 M *sodium hydroxide* is required to produce a red color that persists for not <15 seconds. If the solution is red, not >0.25 ml of 0.1 M *hydrochloric acid* is required to change the color of the solution. Reserve the neutralized solution for the test for fluorosilicate.

**Clarity and color of solution:** **Solution A** is *clear and colorless*.

**Chloride:** 40 ml of solution A complies with the *limit test for chlorides* (250 ppm).

**Fluorosilicate:** Heat to boiling the solution reserved in the test for **acidity or alkalinity** and titrate while hot with 0.1 M *sodium hydroxide* until a red color is produced. Not >1.5 ml of 0.1 M *sodium hydroxide* is required.

**Sulfate:** Dissolve 0.25 gm in 10 ml of a saturated solution of *boric acid* in *distilled water* and add 5 ml of *distilled water* and 0.6 ml of 7 M *hydrochloric acid*. The solution complies with the *limit test for sulfates*. Prepare the standard by mixing together 0.6 ml of 7 M *hydrochloric acid*, 5 ml of *sulfate standard solution* (10 ppm  $\text{SO}_4^{2-}$ ) and 10 ml of a saturated solution of *boric acid* in *distilled water* (200 ppm).

**Loss on drying:** Not >0.5%, determined on 1 gm by drying in an oven at 130° for 3 hours.

### Assay

Weigh accurately about 80 mg, add a mixture of 5 ml of *acetic anhydride* and 20 ml of *anhydrous glacial acetic acid* and heat to dissolve. Cool, add 20 ml of *dioxan* and carry out *non-aqueous titration*, using *crystal violet solution* as indicator, until a green color is produced. Perform a blank determination and make any necessary correction. Each ml of 0.1 M *perchloric acid* is equivalent to 0.004199 gm of NaF.

**Action and uses:** Sodium fluoride due to its fluoride ion is an important agent in dental practice for retarding or preventing dental caries. Fluoridized teeth have been resistant to microorganisms causing dental caries. It also decreases microbial acid production.

Sodium fluoride in 2% aqueous solution is widely used topically; occasionally the solution is applied to the surface of dry teeth periodically over several times in a year.

**Application:** 1.5–3 ppm (equivalent to 0.7–1.3 ppm of fluoride ion) in drinking water; topically as a 2% solution to the teeth.

## DENTIFRICES OR CLEANSING AGENTS

"A dentifrice is a substance used with a toothbrush for the purpose of cleaning the accessible surface of the teeth".

### Types of Dentifrices

1. **Cosmetic dentifrices:** These must clean and polish teeth.
2. **Therapeutic dentifrices:** These must reduce disease process caries and sensitivity.

Dentifrices are products that enhance the removal of stains and dental plaque by the toothbrush. They are:

- Toothpastes
- Antiplaque agents
- Anticalculus agents
- Mouthwashes
- Cosmetic whiteners
- Desensitizing agents
- Disclosing agents.

### **Ideal Properties of a Dentifrice**

1. It should not be harmful to the oral tissue and fluid.
2. It should not stain teeth.
3. It should not be scratching to the enamel surface of tooth.
4. If it is ingested it should not be harmful to the GIT.
5. It should have pleasant odor and taste.

Commercial dentifrices are available in the form of pastes, tooth powder and gels. The main functions of dentifrices are removing stains; act as anticaries, minimizing plaque build-up and as mouth freshener.

### **Toothpaste**

Dentifrices or toothpastes are responsible for decrease the incidence of dental caries, reduce mouth odors and enhance personal appearance. The main ingredients of toothpaste are:

1. **Abrasives:** Abrasives are responsible for physically removing plaque and debris, e.g. silicates, sodium bicarbonate, dicalcium phosphate, sodium metaphosphate, calcium pyrophosphate, calcium carbonate and aluminum oxides.
2. **Surfactants/foaming agents:** It is used due to their detergent action which helps in removing debris, e.g. sodium lauryl sulfate, sodium dodecyl benzene sulfonate.
3. **Humectants:** Humectants are incorporated into toothpastes to prevent loss of water and subsequent hardening of the preparation upon exposure to air, e.g. sorbitol, glycerin, propylene glycol.
4. **Suspending agents:** Suspending agents will add thickness to the product, e.g. methylcellulose, tragacanth, karaya gum.
5. **Therapeutic agent:** The majority of dentifrices contain therapeutic agents such as fluoride salts. Fluoride salts inhibit caries. Common fluoride salt, which are used in the paste are sodium monofluoride phosphate (SMFP), monofluorophosphate (MFP), stannous fluoride, triclosan.
6. **Pyrophosphates:** Pyrophosphates are found in tartar control toothpastes. They prevent tartar formation. They are water softening agents that remove calcium from saliva thus preventing their deposition on teeth to form tartar.
7. **Flavoring agent:** Flavoring agent provide a smooth pleasant flavor both during brushing and as aftertaste, e.g. spearmint, peppermint, wintergreen or cinnamon-mint.
8. **Sweetening agents:** Most frequently used synthetic sweetener is saccharin.

9. **Preservatives:** Preservatives are used to inhibit bacterial proliferation in the preparation, e.g. benzoic acid, esters of p-hydroxybenzoic acid.
10. **Coloring agent:** Red, green or blue coloring agents are used.
11. **Water.**

## **CALCIUM CARBONATE**

*Molecular formula:*  $\text{CaCO}_3$

*Molecular weight:* 100.086

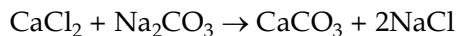
**Synonym:** Precipitated chalk, precipitated calcium carbonate.

It is used as an ingredient in our toothpaste since 1975. It is a common substance found in rocks. Its most common natural forms are chalk, limestone, and marble. It is also a component of harder organic materials like the shells of clams and eggshells.

Calcium carbonate is a mild abrasive which helps to safely remove plaque when brushing and gently polishes away surface stains. Some alternatives include hydrated silica gels, hydrated aluminum oxides, magnesium carbonate, phosphate salts and silicates. While excess calcium from supplements, fortified food and high-calcium diets, is known to cause milk-alkali syndrome under certain circumstances. There is no known toxicity or associated risk in using calcium carbonate toothpaste.

### **Preparation**

Calcium carbonate is obtained by mixing the boiling solutions of calcium chloride and sodium carbonate and allowing the resulting precipitate to settle down.



The precipitate is collected on calico filter, and washed with boiling water, until it becomes free from chloride ions. Finally, the precipitate is dried.

**Properties:** It is a white, odorless powder or colorless crystals.

**Solubility:** Practically insoluble in water. Slightly soluble in carbonated water, soluble in dil. hydrochloric acid.

### **Assay**

Weigh accurately about 0.1 gm and dissolve in 3 ml of *dilute hydrochloric acid* and 10 ml of *water*. Boil for 10 minutes, cool, dilute to 50 ml with *water*. Titrate with 0.05 M *disodium edetate* to within a few ml of the expected endpoint, add 8 ml of *sodium hydroxide solution* and 0.1 gm of *calcon mixture* and continue the titration until the color of the solution changes from pink to a full blue color. Each ml of 0.05 M *disodium edetate* is equivalent to 0.005004 gm of  $\text{CaCO}_3$ .

### **Uses**

Precipitated chalk, which is having a fine powdery texture, is used in dentifrice, both powders and pastes. It furnishes both abrasive and antacid effect in the mouth. It forms a common ingredients of tooth powder and toothpaste. It is having a tendency to cause constipation and hence it is usually administered alternatively or along with magnesium salts. It is rapidly acting non-systemic antacid. It neutralizes gastric acid and forms calcium chloride.

## DESENSITIZING AGENTS

Teeth are somewhat sensitive to hot and cold especially during teeth decay or in toothache. Therefore, some desensitizing agents are used in dental preparations so as to reduce sensitivity of teeth to hot and cold.

### Mechanism of Action

Exact mechanism of action of desensitizing agent is not known with certainty. However, they act probably like local anesthetic, e.g. strontium chloride and zinc chloride.

### Mechanism of Action of Strontium Chloride ( $\text{SrCl}_2$ )

Strontium chloride forms a barrier and blocks the openings of dentinal tubules, thus not allowing fluid movement within the tubules.

### Dental Floss

Dental floss, or tooth floss, is a cord of thin filaments used to remove food and dental plaque from spaces between teeth where a toothbrush is unable to reach.

## ZINC CHLORIDE

*Molecular formula:*  $\text{ZnCl}_2$

*Molecular weight:* 136.29

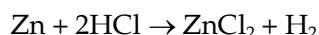
**Synonym:** Butter of zinc.

**Category:** Desensitizing agent

**IP limit:** It contains not <95% and not >100.5% of  $\text{ZnCl}_2$ , calculated with reference to the dried substance.

### Preparation

1. It is prepared by heating metallic or granulated zinc with hydrochloric acid. When evolution of hydrogen ceases, the solution is filtered and evaporated to dryness.



2. It can also be prepared by treating zinc carbonates or zinc oxide with HCl.



### Properties

It occurs as white crystalline granules or powder. It is odorless and deliquescent. It is soluble in water, freely soluble in alcohol and glycerine.

### Storage

As it is deliquescent and absorbs carbon dioxide, it should be stored in tightly closed container.

### Uses

It is used as desensitizer in dental preparations and also acts as powerful astringent and mild antiseptic.

## POLISHING AGENTS

One of the important constituents of good dentifrice is good abrasive or polishing agent to have polish effect on teeth which is achieved by abrasive action. It provides whiteness of teeth. Besides that some desensitizing agents are added to the dentifrices for reducing sensitivity of teeth in hot and cold condition. The numbing effect is of short duration like that local anesthetic. Astringent type of compounds shown this property so it can be incorporated in dental products.

### Oral Antiseptics

There are some inorganic substances which can be safely used as antiseptics in oral cavity. For oral hygiene purpose some products having inorganic chemicals may be used due to their antiseptic and astringent action, e.g. hydrogen peroxide, magnesium peroxide and sodium perborate.

### Mouthwashes

There are very few inorganic substances are used in mouthwashes. Zinc sulfate used due to its mild antiseptic and astringent action or zinc chloride due to its deodorant and desensitizing action or  $\text{KMnO}_4$  for its anti-infective and astringent action or sodium bicarbonate due to its antacid property or sodium chloride for irrigation.

### Cements and Fillers

Dental cements are used to cover protect areas temporarily and then undergo operation as in dental surgery. The cementing material is applied as paste which gets hardened in a short duration and forming a protective layer. After healing, dentist removed the hardened cement. The temporary cement is also medicated, usually with eugenol, which is antiseptic and local anesthetic. Additives are used controlled the consistency of the cement. A cement of suitable consistency finds uses temporary filler for cavities. More often metal and their alloys used as permanent filling materials for cavities. Gold and silver find used as permanent filling materials, e.g. zinc oxide.

### Ideal Properties of Dental Cements

- It should be strong and hard
- It is able to protect pulp
- It should be insoluble in saliva and liquids taken in mouth
- It should be dimensionally stable
- It should be adhesive
- It should be non-porous
- It should be biocompatible and non-irritant
- Co-efficient of thermal expansion should be equal to the tooth structure
- It should not be affected by thermal changes and moisture
- It should be easy to manipulate.

### Classification

Cements are classified into four types:

- Type I: Used for temporary cementation
- Type II: Used for long-term cementation of fixed prosthesis

- Type III: Used for temporary filling/thermal insulating base
- Type IV: Intermediate restorations and cavity liners.

## ZINC OXIDE EUGENOL CEMENT

It is compatible with the hard and soft tissues of the mouth and extensively used in dentistry since 1890s. It is a least irritant of all the dental materials. It has poor strength when compared to zinc phosphate. It has sedative effect on exposed dentin.

### Composition of Zinc Oxide Eugenol

<i>Powder</i>	<i>Nature</i>	<i>Quantity in %</i>	<i>Liquid</i>	<i>Nature</i>	<i>Quantity in %</i>
ZnO	Principal ingredient	69	Eugenol	Reacts with ZnO	85
White resin	Brittleness of set cement	29.3	Olive oil	Plasticizer	15
Zn acetate	Accelerator, improve strength	up to 1	Acetic acid/ alcohol	To accelerate setting	up to 1
MgO	Modifier	Traces	Water	Initiator	Traces
Zn stearate	Plasticizer	0.7	-	-	-

**Properties:** It has low strength, low abrasive resistance and low flow after setting. So, it is used for temporary filling not more than few days. It has adhesive effect on exposed dentin.

### Resin Reinforced Zinc Oxide Eugenol Cement

#### Composition

##### In powder:

1. Zinc powder 80%
2. Poly methyl-methacrylate 20% (bond to other components)
3. Zinc stearate-traces (accelerator)
4. Zinc acetate
5. Thymol and hydroxyquinoline—traces (antimicrobial agent).

##### In liquid:

1. Eugenol 85%
2. Olive oil 15% (as plasticizer, masks irritating effect of eugenol).

### EBA and Other Chelate Cements

#### Composition

##### In powder:

1. ZnO
2. Aluminum oxide/other mineral fillers 20–30%
3. Polymeric reinforcing agent (polymethyl methacrylate)
4. Barium sulfate—radiopacity.

**In liquid**

1. O-ethoxybenzoic acid 50–60%
2. Eugenol 40–50%

**Uses**

It is used as protective, sedative lining in deep cavities, used in temporary filling. It is also used for temporary cementing, pulp capping and root canal filling.

**IMPORTANT QUESTIONS/ANSWERS****I. Multiple Choice Questions**

1. Dentifrices are used for:
  - a. Cleaning of teeth and gums
  - b. To control caries
  - c. Reduce hypersensitivity
  - d. All of the above
2. Precipitated chalk is:
  - a. Sodium carbonate
  - b. Sodium fluoride
  - c. Calcium carbonate
  - d. Zinc chloride
3. Vitamin which is essential for tooth formation:
  - a. Vitamin C
  - b. Vitamin A
  - c. Vitamin D
  - d. All of the above
4. Commonly used desensitizing agents are:
  - a.  $ZnCl_2$
  - b.  $SrCl_2$
  - c. Both a and b
  - d. None of the above
5. Dental caries is defined as:
  - a. Tooth decay
  - b. Cleaning agent
  - c. Removing stains
  - d. Polishing action
6. Phosphate is used as:
  - a. Anticaries agent
  - b. Cleansing agent
  - c. Removing stains
  - d. Polishing action
7. Which one in anticaries agents:
  - a. Stannous fluoride
  - b. Both a and b
  - c. Sodium fluoride
  - d. None of the above
8. Ideal properties of dental cement is:
  - a. It should be insoluble in saliva and other oral fluids
  - b. It should be adhesive
  - c. It should be non-porous
  - d. All of the above
9. Fluoride inhibits the caries formation by:
  - a. Antimicrobial action
  - b. Remineralization of enamel
  - c. Downward acid solubility of tooth enamel
  - d. All of the above
10. Zinc oxide eugenol cement used for:
  - a. Bacterial inhibition
  - b. Cavity lining, pulp capping and root canal filling
  - c. Sensitivity
  - d. All of the above

**Answers**

1. d    2. c    3. d    4. c    5. a    6. b    7. c    8. d    9. d    10. b

**II. Fill in the Blanks**

1. Toothpaste containing ..... should be used to prevent dental caries.
2. ..... is a substance used with brush for cleaning purpose.
3. Dental plaque is due to combined action of ..... and .....
4. The polishing effect is achieved by its .....
5. Basically setting is a ..... reaction.
6. Soluble salts of phosphate are .....
7. Calcium carbonate is prepared by using ..... and .....
8. ..... are used in treating dental caries.
9. Setting time of zinc eugenol cement is .....
10. Agents which are used to reduce sensitivity of teeth to heat and cold is known as .....

**Answers**

1. Sodium fluoride
2. Dentifrices
3. Periodontal disease, *Streptococcus mutans*
4. Abrasive
5. Acid-base
6.  $\text{NaHPO}_4$ ,  $\text{NaH}_2\text{PO}_4$
7. Slaked lime and  $\text{CO}_2$
8. Fluorides
9. 4–10 minutes
10. Desensitizing.

**III. Short Answer Questions**

1. What are anticaries? Discuss anyone of its official compound.
2. Discuss the role of fluoride with mechanism of action.
3. Name any two inorganic compounds as dental products.
4. Define dentifrices.
5. How is stannous fluoride prepared?

**IV. Long Answer Questions**

1. Discuss the preparation and uses of sodium fluoride.
2. Write a detail note on preparation, assay and uses of calcium carbonate.
3. Describe the composition of toothpaste.
4. What are the ideal requirements of dental cement?
5. Define polishing agents and desensitizing agents with examples.
6. Explain in detail about zinc oxide eugenol cement.

# Gastrointestinal Agents

- Introduction
- Stomach

- Secretion of Gastric Juice/HCl

## INTRODUCTION

Digestive tract or gastrointestinal tract consists of group of organs. GI tract includes the stomach, small intestine, large intestine (colon), rectum and terminates at the anus. GI tract consists of structures that aid in the ingestion and digestion of food by means of enzymatic breakdown/biochemical process. Ingestion is the process of consuming something and taking it into the body, whereas digestion is a mechanical and chemical breaking down of food into smaller components to a form that can be absorbed. Disfunctioning of anyone of the GIT compartments may lead to human illness and discomfort.

### Stomach

It is made-up of 5 layers of smooth muscles. The mucus lining of the stomach protects the stomach walls from the action of stomach acid. The walls of the stomach are lined with parietal cells that secrete mucus, gastric juice [pepsin (an enzyme) or pepsinogen and HCl]. The digestion of protein takes place in acidic medium. Pepsin is most effective in the very acidic condition of the stomach (pH 2). It became inactive at higher pH. Thus, HCl present in the gastric juice [secreted by the oxyntic (or parietal) cells of the stomach] is acidifies the food, kills many microbes which may be harmful to the body, and provides the acid environment needed for effective digestion by pepsin.

### Secretion of Gastric Juice/HCl

Hydrochloric acid secretion is under the control of bases, i.e. acetylcholine, histamine, and gastrin (a 17 amino acids substance heptadecapeptide) through an interlinked mechanism and by respective receptor sites. The release of gastric acid (i.e. intracellular hydrogen ions) occurs through  $H^+ - K^+$  ATPase pump. Inadequate secretion of HCl causes achlorhydria or hypochlorhydria. Excessive secretion of HCl takes place in the stomach causes the imbalance of acid-enzyme in stomach it leads to hyperacidity and ulcers. In large intestine, insufficient absorption of fluids causes diarrhea and insufficient peristaltic movement causes constipation.

Agents or substances which are used to treat gastrointestinal disorders are known as gastrointestinal agents. Various inorganic agents used to treat GIT disorders include:

- Acidifying agents
- Antacids
- Protectives and adsorbents
- Saline cathartics or laxatives.

# Acidifiers

- |  |  |
|--|--|
| <ul style="list-style-type: none"> <li>• Introduction</li> <li>• Dilute Hydrochloric Acid</li> </ul> | <ul style="list-style-type: none"> <li>• Ammonium Chloride</li> <li>• Important Questions/Answers</li> </ul> |
|--|--|

## INTRODUCTION

Acidifiers are inorganic chemicals that either produce or become acid. These chemicals increase the level of gastric acid in the stomach when ingested, thus decreasing the stomach pH. The pH of stomach is 1.5–2 when empty and rises to pH 5–6 when food is ingested.

These are many types of acidifiers but the main four types are:

- i. Gastric acidifiers, used in controlling pH in stomach.
- ii. Urinary acidifiers, used in controlling pH in urine.
- iii. Systemic acidifiers, used in controlling pH in all the parts of body.
- iv. Acids.

### Gastric Acidifiers

Drugs which are used to increase the acidity of the stomach in patients suffering from achlorhydria or hypochlorhydria.

### Achlorhydria

In patients suffering from achlorhydria, there is deficient secretion of HCl in stomach. The pH of stomach is so low because of the secretion of HCl. Gastric HCl act by destroying the bacteria in the ingested food and drinks. It softens the fibrous food and promotes the formation of the proteolytic enzyme pepsin. This enzyme is formed from pepsinogen at acidic pH (>6). Pepsin helps in the metabolism of proteins in the ingested food. Therefore lack of HCl in the stomach can cause achlorhydria.

Two types of achlorhydria are known:

1. Where the gastric secretion is devoid of HCl, even after stimulation with histamine phosphate.
2. Where gastric secretion is devoid of HCl, but secreted upon stimulation with histamine phosphate.

The cause of achlorhydria initially may be subtotal gastrectomy, atrophic gastritis, carcinoma, gastric polyp, etc. while in later case it may be chronic nephritis, tuberculosis, hyperthyroidism, chronic alcoholism, sprue, pellagra, etc. The symptoms

vary with associated disease but they generally include mild diarrhea or frequent bowel movement, epigastric pain and sensitivity to spicy food. It can be treated by various acidifying agents like ammonium chloride, dilute HCl, calcium chloride, etc.

### **Urinary Acidifiers**

Drugs that are used to remove acidic urine from the body or in controlling pH in urine, e.g. many bacteria grow badly in acidic urine as far as concerned. When the urine is acidic, hexamine only act as antiseptic. However, hexamine itself break-up into ammonia and formaldehyde in acidic media.

### **Systemic Acidifiers**

Systemic acidifiers are those which act by reducing the alkali reserve in the body especially blood or to maintain pH of all parts of the body and are also useful in reducing metabolic alkaloids. It is used to treat systemic alkalosis and given usually by injection.

### **Acids**

It is used in the preparation of medicaments as pharmaceutical aids.

## **DILUTE HYDROCHLORIC ACID**

*Molecular formula:* HCl

*Molecular weight:* 36.5

**IP limit:** It contains not <9.5% and not >10.5% w/w of HCl.

The acid should be diluted with 25–50 volumes with water or juice and sipped through a glass tube to prevent reaction upon dental enamel. It is taken during or after meals given in conjunction with iron therapy in hyperchromic anemia.

### **Preparation**

It is prepared by mixing 274 gm of HCl and 726 gm of purified water.

### **Properties**

1. It possesses pungent odor.
2. It is colorless liquid.

### **Test for Identification**

1. When added to KMnO<sub>4</sub> with dilute nitric acid, chlorine is evolved.



2. To acidified solution add silver nitrate solution, shake and allow to stand, curdy white precipitate is formed, which is insoluble in HNO<sub>3</sub> but soluble after being washed with water in ammonium hydroxide from which it is re-precipitated by the addition of HNO<sub>3</sub>.

### **Assay**

Weigh accurately 6 gm, add 30 ml of distilled water mix and titrate with 1N NaOH using methyl red as indicator. Each ml of 1N NaOH is equivalent to 0.03646 gm of HCl.

**Storage**

It is stored in well-closed glass container at room temperature.

**Use**

Used as pharmaceutical aid.

**AMMONIUM CHLORIDE**

*Molecular formula:* NH<sub>4</sub>Cl

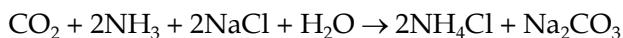
*Molecular weight:* 53.49

**Synonym:** Sal ammoniac, solutions of ammonium chloride are mildly acidic.

**Physical properties:** White solid, hygroscopic, odorless, free soluble in water and glycerol, sparingly soluble in alcohol.

**Preparation**

1. Ammonium chloride prepared through the Solvay process



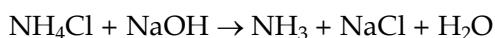
2. Ammonium chloride is prepared commercially by combining ammonia (NH<sub>3</sub>) with either hydrogen chloride (gas) or hydrochloric acid (water solution)

**Reactions**

Ammonium chloride appears to sublime upon heating but actually decomposes into ammonia and hydrogen chloride gas



Ammonium chloride reacts with a sodium hydroxide (strong base) and release ammonia gas.



Similarly, ammonium chloride also reacts with alkali metal carbonates at elevated temperatures giving ammonia and alkali metal chloride

**Assay**

Dissolve 1 gm of ammonium chloride in 20 ml of water and add a mixture of 5 ml of formaldehyde solution with few drops of phenolphthalein solution. After 1–2 minutes, titrate slowly with 1 M sodium hydroxide. 1 ml of 1 M sodium hydroxide is equivalent to 53.49 mg of NH<sub>4</sub>Cl.

In this ammonium chloride undergoes hydrolysis and yield ammonium hydroxide and HCl. This reaction is facilitated by formaldehyde by fixing ammonia as hexamine. Indicator is colorless in acid and pink in alkaline medium.

**Dose**

1 to 2 gm (as systemic acidifier), 0.3–0.5 gm (expectorant)

**Storage**

Store in highly closed container.

**Uses**

1. It is used as an expectorant in cough medicine.
2. It is used as a systemic acidifying agent in treatment of severe metabolic alkalosis.
3. The main application of ammonium chloride is as a nitrogen source in fertilizers.
4. It is used as a flux in preparing metals to be tin coated, galvanized or soldered.

**IMPORTANT QUESTIONS/ANSWERS****I. Multiple Choice Questions**

1. Hydrochloric acid is also known as:
 

a. Spirit of salt	b. Muriatic acid
c. Epsom salt	d. Both a and b
2. Which one is the symptom of achlorhydria:
 

a. Pain in stomach	b. Frequent bowel moment
c. Diarrhea	d. All of the above
3. Inorganic compounds, used to increase or produce acid in GI tract, are called:
 

a. Antacid	b. Absorbents
c. Acidifier	d. None of the above
4. .... in the stomach can cause achlorhydria.
 

a. Lack of HCl	b. Presence of $H_2SO_4$
c. Presence of HCl	d. All of the above
5. Drugs which are used to neutralize the alkaline body fluids are known as:
 

a. Systemic acidifies	b. Acids
c. Urinary acidifier	d. Gastric acidifier

**Answers**

1. d    2. d    3. c    4. a    5. a

**II. Short and Long Answer Questions**

1. Define acidifiers or acidifying agents. Write the classification of acidifies.
2. What do you understand by the term systemic acidifier?
3. Differentiate systemic and urinary acidifier.
4. What is achlorhydria?
5. Describe the preparation, properties and uses of ammonium chloride.
6. Give the methods of preparation and assay of dil. HCl.

# Antacid

- |   |   |
|---|---|
| <ul style="list-style-type: none"><li>• Introduction</li><li>• Ideal Properties of Antacids</li><li>• Combination of Antacids</li><li>• Sodium Bicarbonate</li><li>• Aluminum Hydroxide Gel</li></ul> | <ul style="list-style-type: none"><li>• Magnesium Oxide</li><li>• Calcium Carbonate</li><li>• Magnesium Hydroxide</li><li>• Important Questions/Answers</li></ul> |
|---|---|

## INTRODUCTION

Antacids are the substances which reduce gastric acidity resulting in an increase in the pH of stomach. Antacids are alkaline bases used to neutralize the excess gastric HCl associated with gastritis or peptic ulcer. Gastric acidity occurs due to excessive secretion of HCl in stomach due to various reasons.

When hyperacidity occurs the outcome can range from:

1. Gastric ulcer (stomach)
2. Peptic ulcer or esophageal ulcer (lower end of esophagus)
3. Gastritis (a general inflammation of gastric mucosa)
4. Duodenum ulcers.

Peptic ulcers occur due to defective esophageal sphincter as in hiatal hernia. Gastric ulcers occur in lesser curvature and are found in first portion of duodenum.

## IDEAL PROPERTIES OF ANTACIDS

- The antacid should buffer in the range of pH 4–6
- The antacid should not be absorber/or cause systemic alkalosis
- It should not be a laxative or constipative
- It should exert effect rapidly and over a long period of time
- The reaction of antacid with gastric HCl should not cause large evolution of gas
- It should probably inhibit pepsin.

### Side Effects of Long-term Antacid Therapy

- Sodium containing antacids are problem for patients on sodium restricted diet
- Some antacids cause constipation while others have laxative effect
- If pH raises too high rebound acidity to neutralize the alkali occurs
- Antacids which absorbed systemically exert alkaline effect on body's buffer system.



### Systemic Antacids

Systemic antacids are antacids which get systemically absorbed, e.g. sodium carbonate is water soluble and potent neutralizer, but it is not suitable for the treatment of peptic ulcer because of risk of ulcer perforation due to production of carbon dioxide in the stomach.

### Non-systemic Antacids

They are insoluble and poorly absorbed systemically, e.g. magnesium carbonate, magnesium hydroxide, aluminum hydroxide, calcium carbonate.

## COMBINATION OF ANTACIDS

Among various antacids every single compound has some side effect especially when used for longer period or in elderly patients. Combinations of antacids are used to avoid certain side effects associated with antacids such as:

- i. Magnesium and calcium containing preparation where one is laxative and the another is constipative in nature
- ii. Magnesium and aluminum containing preparation, e.g. magnesium hydroxide a fast-acting antacid with aluminum hydroxide which is a slow-acting antacid.

## SODIUM BICARBONATE

*Molecular formula:* NaHCO<sub>3</sub>

*Molecular weight:* 84.01

**Synonym:** Baking soda, sodium hydrogen carbonate.

**IP limit:** It contains not <99% and not >101% of NaHCO<sub>3</sub>

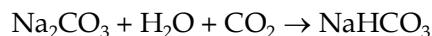
**Properties:** White crystalline powder, odorless, slight alkaline taste, stable in dry air, freely soluble in water, insoluble in alcohol.

### Preparation

1. **Solvay process:** By passing strong brine (NaCl) containing high concentrations of ammonia through a carbonating tower where it is saturated with carbon dioxide under pressure. The ammonia and carbon dioxide reacts to form ammonia bicarbonate which is allowed to react with NaCl to precipitate NaHCO<sub>3</sub> and separated by filtration.



2. It can also be prepared by covering sodium carbonate crystals with water and passing carbon dioxide to saturation.



### Test for Identification

To 5 ml of 5% w/v solution in carbon dioxide free water add 0.1 ml phenolphthalein solution a pale pink color is obtained. On heating a gas is evolved and the solution turns red.

**For sodium:** To sample solution add 15% w/v potassium carbonate, heat, no precipitate is obtained add potassium antimonite solution heat to boiling, cool and if



necessary scratch the inside of test tube with a glass rod, a dense white precipitate is produced.

**For bicarbonate:** To sample add magnesium sulfate no precipitate is produced. On boiling a white colored precipitate is formed.

### Assay

Weigh accurately 1 gm and dissolve in 20 ml of water, titrate with 0.5 N sulfuric acid using methyl orange as indicator. Each ml of 0.5 N sulfuric acid is equivalent to 0.0425 gm of  $\text{NaHCO}_3$ .

### Use

It is used as antacid and electrolyte replacement.

## ALUMINUM HYDROXIDE GEL

*Molecular formula:*  $\text{Al}(\text{OH})_3$

*Molecular weight:* 78.0

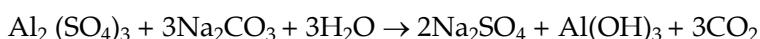
**Synonym:** Aluminum hydroxide powder.

Aluminum hydroxide is a white, light odorless, tasteless amorphous powder. It is an aqueous suspension of hydrated aluminum oxide with different amounts of basic aluminum carbonate and bicarbonate. It is soluble in dilute mineral acids but practically insoluble in water. It forms gel on prolonged contact with water at pH 5.5–8. The aluminum hydroxide gels are ideal buffers in the pH 3–5 range due to its amphoteric nature.

**IP limit:** It contains not <3.5% and not >4.4% of  $\text{Al}_2\text{O}_3$ .

### Preparation

It is prepared by dissolve sodium carbonate in hot water and filters the solution. Add clear solution of alum (aluminum salt, chloride or sulfate) to the filtrate in water with constant stirring. Add more of water and remove all gas. The aluminum hydroxide precipitate out, collect the precipitate, wash and suspend in sufficient purified water flavored with 0.01% peppermint oil to strengthen aluminum hydroxide gel and preserve with 0.1% sodium benzoate.



Aluminum hydroxide is a weak and slow reacting antacid. The aluminum ions relax smooth muscles and cause constipation. It absorbs pepsin at pH >3 and releases it at lower pH. It also prevents phosphate absorption. Major disadvantage of this gel is that losses antacid properties on aging.

### Storage

It should be stored in an airtight container.

### Assay

Accurately weigh 5 gm and dissolve in 3 ml HCl by warming on water bath, cool to below 20°C and dilute to 100 ml with water. To 20 ml of this solution add 40 ml of 0.05 M disodium EDTA, 80 ml water, 0.15 ml methyl orange/red and neutralize by



the dropwise addition of 1 M sodium hydroxide. Again warm on water bath for 30 minutes, add 3 gm hexamine and titrate with 0.05 M lead nitrate using 0.5 ml xylenol orange as indicator. Each ml of 0.05 M disodium EDTA = 0.002549 gm of  $\text{Al}_2\text{O}_3$ .

### **Uses**

It is used as antacid in the management of peptic ulcer, gastritis, gastric hyperacidity. It is also used as skin protectant and mild astringent.

## **MAGNESIUM OXIDE**

*Molecular formula:*  $\text{MgO}$

*Molecular weight:* 40.3

**Synonym:** Magnesia

**IP limit:** It contains not >98% of magnesium oxide

It occurs in nature as mineral periclase. There are two varieties; heavy magnesium oxide and light magnesium oxide.

### **Preparation**

It can be prepared by heating gently magnesium carbonate to redness.



### **Properties**

Both heavy and light magnesium oxides are odorless, slightly alkaline taste, practically insoluble in water yield a solution which is alkaline. It readily dissolves in dilute acids with slight effervescence. In presence of acid, the oxide forms the magnesium hydroxide.

### **Test for Identification**

To the sample solution of sample add dilute nitric acid solution a white precipitate is produced which is re-dissolved by adding 1 ml of 2 M ammonium chloride, add 0.25 M disodium hydrogen phosphate, a white crystalline precipitate is produced, shows presence of magnesium.

### **Uses**

It is used as antacid and laxative. It is ingredient of universal antidote along with tannic acid and charcoal. It is used for compounding and preserving fluid extract because of its absorptive power.

## **CALCIUM CARBONATE**

*Molecular formula:*  $\text{CaCO}_3$

*Molecular weight:* 100.09

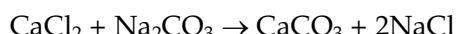
**Synonym:** Precipitated chalk

It is found in nature as limestone, marble, calcite, vaterite, aragonite and shell of sea animals. Precipitated chalk is prepared as a fine precipitate by adding a solution of ammonium carbonate and ammonia or sodium carbonate to a solution of calcium nitrate.



### **Preparation**

1. It can be prepared by mixing and boiling calcium and sodium carbonate solution and allowing the resulting precipitate to settle. The precipitate is collected, washed with boiling water until free from chloride and dried.



2. By passing carbon dioxide through lime water



### **Properties**

It occurs as a white, odorless tasteless microcrystalline powder which is stable in air. It is practically soluble in air. It exists in two crystal form and both are commercial importance, one aragonite and other is calcite.

### **Test for Identification**

Dissolve substance in 5 M acetic acid and add 0.5 ml of potassium ferrocyanide solution. The solution remains clear. Add ammonium chloride white crystalline precipitate is formed. It shows the presence of calcium.

**For carbonate:** Suspend sample in 2 ml water in a test tube, add 2 M acetic acid close the tube immediately with a stopper fitted with a glass tube bent at two right angles, heat gently and collect the gas in 5 ml of 0.1 M barium hydroxide a white precipitate is formed which is dissolves on addition of excess of dilute HCl.

### **Uses**

It is a potent antacid with rapid acid neutralizing capacity, but on long-term use, it can cause hypercalcemia, hypercalciuria and formation of calcium stone in kidney. It is used in calcium deficiency, dentifrices and in combination with magnesium containing antacids due to its constipative properties.

## **MAGNESIUM HYDROXIDE**

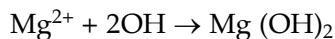
*Molecular formula:* Mg(OH)<sub>2</sub>

*Molecular weight:* 58.31

**Synonym:** Milk of magnesia

### **Preparation**

It can be prepared by combining a solution of magnesium salts with basic water induces precipitation of solid magnesium hydroxide.



### **Properties**

It occurs as a white powder and odorless. It is insoluble in water, ethanol and soluble in dilute mineral acids.

### **Uses**

It is used as laxative and also used to treat gastrointestinal ailments such as heartburn, stomach upset and indigestion.



## IMPORTANT QUESTIONS/ANSWERS

### I. Multiple Choice Questions

1. Antacids are used:
  - a. To maintain gastric pH 3.5–7
  - b. Increase the concentration acid
  - c. Decrease the concentration acid
  - d. Both a and c
2. Dried aluminum hydroxide gel consists of:
  - a. Hydrated aluminum oxide
  - b. Basic aluminum carbonate and bicarbonate
  - c. Both a and b
  - d. None of the above
3. Simethicone is used as:
  - a. Astringent
  - b. Antacid
  - c. Antiseptic
  - d. Both a and c
4. Aluminum hydroxide gel is used as:
  - a. Astringent
  - b. Gastritis
  - c. Peptic ulcer
  - d. All of the above
5. Ideal properties of antacids are:
  - a. Should probably inhibit pepsin
  - b. Should not cause systemic alkalosis
  - c. Should exert effect rapidly and over a long period of time
  - d. All of the above
6. Antacid acts by which of the following mechanisms:
  - a. Increase the volume of gastric HCl contents
  - b. Neutralizing the gastric HCl contents
  - c. Inhibit Na/K ion exchange
  - d. All of the above
7. Side effects of antacid therapy:
  - a. Constipation
  - b. Systemic alkalosis
  - c. Both a and b
  - d. None of the above
8. Antiflatulents are used to:
  - a. Decrease the volume of gastric HCl contents
  - b. Prevent the formation of HCl
  - c. Synergistic effect
  - d. Decrease the surface tension of bubbles in the stomach
9. Which one is the example of systemic antacid.
  - a. Sodium bicarbonate
  - b. Magnesium hydroxide
  - c. Calcium carbonate
  - d. Magnesium carbonate
10. Combinations of antacids are used to:
  - a. Avoid absorption of antacid
  - b. Counteract the constipative effect
  - c. Synergistic effect
  - d. All of the above

### Answers

1. d    2. c    3. b    4. d    5. d    6. b    7. c    8. d    9. a    10. b



**II. Fill in the Blanks**

1. .... are the substances which reduce gastric acidity.
2. Gastric acid is secreted from ..... in the stomach
3. Systemic antacids are systemically ..... while a non-systemic antacid does not exert any .....
4. Sodium bicarbonate is also known as .....
5. Antacids are administered to ..... excess HCl.
6. .... is a systemic antacid.
7. Magnesium oxide is also known as .....
8. Antacid neutralizing capacity expressed as .....
9. .... containing aluminum salt as antacid.
10. .... can be prepared by heating gently magnesium carbonate to redness.

**Answers**

1. Antacids
2. Parietal cell
3. Absorbed, systemic effect
4. Baking soda
5. Neutralize
6. Sodium bicarbonate
7. Magnesia
8. Milliequivalents of HCl
9. Aluminum hydroxide gel
10. Magnesium oxide.

**III. Short Answer Questions**

1. What are antacids? Discuss anyone of its official compound?
2. Classify antacids. Write the ideal requirements of an antacid.
3. Discuss the preparation, properties and uses of calcium bicarbonate.
4. How would you prepare magnesium oxide?
5. Explain neutralizing capacity of antacid.

**IV. Long Answer Questions**

1. Discuss the preparation, assay and uses of aluminum hydroxide gel.
2. Write a detail note on magnesium containing salt as antacids.
3. Discuss the preparation, properties and uses of sodium bicarbonate.



# Cathartics

- Introduction
- Saline Cathartics
- Magnesium Sulfate
- Sodium Orthophosphate
- Sodium Potassium Tartrate
- Bentonite

- Protectives and Adsorbents
- Bismuth Subcarbonate
- Bismuth Subgallate
- Kaolin
- Activated Charcoal
- Important Questions/Answers

## INTRODUCTION

Constipation is generally defined as infrequent and /or unsatisfactory defecation fewer than 3 times per week. Patients may define constipation as passing hard stools or straining, incomplete or painful defecation.

Drugs that relieve constipation and promote defecation, i.e. empty stomach (push out the excreta from the body through the anus). **Laxatives** are called aperients. These **laxative** drugs produce peristalsis (movement of the intestines) and promote evacuation of the bowel to relieve constipation. More powerful **laxatives** are called **purgatives**. Even more powerful **purgatives** are called **cathartics**.

The order of effectiveness is described as follows:

- Aperients—to smooth and soft
- Evacuant—to empty
- Purgative—to clean
- Cathartic—to completely clean

Laxative should only be used for short-term therapy as prolonged use may lead to loss of spontaneous bowel rhythm upon which normal evacuation depends, causing patient to become dependent on laxatives, the so-called laxative effect. It could not be used on a regular basis because it may cause imbalance of water and electrolytes of our body.

Constipation is the infrequent or difficult evacuation of the feces. It may be due to a person resisting the natural urge to defecate, causing the fecal material which remains in the colon to lose fluid and to become relatively dry and hard. Constipation can also be due to intestinal atony, intestinal spasm, emotions, drugs and diet. Many a time constipation can be helped by eating food such as natural laxatives or food with large roughages. Cathartics or purgatives generally act by four different mechanisms which are described as various types of laxatives.



### Stimulants

Stimulants are drugs or substances which act by local irritation on the intestinal tract which increase peristaltic activity. They include phenolphthalein, aloin, cascara extract, rhubarb extract, senna extract, podophyllin, castor oil, bisacodyl, calomel, etc.

### Bulk Forming Cathartics

These are substances which are used to increase the bulk of intestinal contents, i.e. increased bulk provides stimulation of bowels (peristalsis). They are made from cellulose, sodium carboxyl methyl cellulose and karaya gum.

### Lubricants (Stool Softener) Cathartics

The emollient laxatives act either as lubricants facilitating the passage of compacted fecal material or as stool softeners, e.g. d-octyl sodium sulfosuccinate, an anionic surface active agent.

Substances such as liquid paraffin, glycerin, mineral oil, etc. act as lubricants which cause smooth clearance of fecal stool. It increases the fluid level in the small intestine by coating of lubricants which in turn decreases the absorption of water and enhances the water level in small intestine. This effect could increase the flow of stool by lubricants from intestine and help to clearing the bowels.

### Osmotic (Saline) Cathartics

Saline cathartics or purgatives are agents that quicken and increase evacuation from the bowel. Laxatives are mild cathartics. Cathartics are used:

- To ease defecation in patients with painful hemorrhoids or other rectal disorders and to avoid excessive straining and concurrent increase in abdominal pressure in patients with hernias
- To relieve acute constipation
- To remove solid material from intestinal tract prior to certain roentgenographic studies
- To avoid potentially hazardous rise in BP during defecation in patients with hypertension, cerebral coronary or other arterial disease.

### SALINE CATHARTICS

These substances act by increasing the osmotic load of the GIT by absorbing large quantity of water and stimulating peristalsis. They are salts of poorly absorbable anions  $-H_2PO_4^-$  (biphosphate),  $-H_2PO_4^{2-}$  (phosphate), sulfates, tartrates and soluble magnesium salt.

Saline cathartics are water soluble and are taken with large quantities of water. This prevents excessive loss of water from body fluids and reduces nausea and vomiting if a too hypertonic solution should reach the stomach. They act in the intestine and a full cathartic dose produces a water evacuation within 3–6 hours. Because of their quick onset of action they are given early in the morning before breakfast. They are used for bowel evacuation before radiological, endoscopic and surgical procedures and also to expel parasite and toxic materials.



Small amounts of these drugs may be absorbed in the systemic circulation (blood) causing occasional toxicity. The absorption of magnesium may cause marked CNS depression while that of sodium worsens the existing congestive cardiac failure (CCF). Following compounds are used as saline cathartics.

## MAGNESIUM SULFATE

*Molecular formula:* MgSO<sub>4</sub>·7H<sub>2</sub>O

*Molecular weight:* 246.47

**Synonym:** Epsom salt, bitter salt.

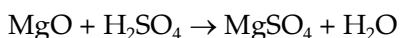
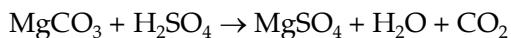
**IP limit:** It contains not <99% and not >100.5% of magnesium sulfate, calculated with reference to dried substance.

**Properties:** It forms colorless prismatic crystals. It dissolves in water, is practically insoluble in alcohol. It has cooling saline bitter taste. It is soluble in water and sparingly soluble in alcohol. It efflorescences in warm dry air.

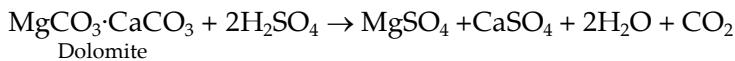
It forms double salt of ammonium and magnesium phosphate when preparation is reacted with disodium hydrogen phosphate in presence of ammonium chloride.

### Method of Preparation

1. It can be prepared by neutralizing hot dilute sulfuric acid with magnesium or its oxides or carbonate. The solution is filtered; the filtrate is concentrated and recrystallized.



2. On commercial scale it is manufactured by reacting sulfuric acid with dolomite. Magnesium sulfate so formed is dissolved in the solution and the sparingly soluble calcium sulfate is deposited. The liquid is filtered, the filtrate is concentrated and crystallized.



### Test for Identification

**For magnesium:** To solution of sample add dilute nitric acid solution a white precipitate is produced that is re-dissolved by adding 1 ml of 2 M ammonium chloride, add 0.25 M disodium hydrogen phosphate, a white crystalline precipitate is produced.

**For sulfate:** To 5 ml of sample solution add 1 ml of dilute HCl and 1 ml barium chloride solution white precipitate. Add 1 ml of iodine solution to the suspension, the suspension remains yellow (distinction from sulfites and dithionites) but decolorize on adding stannous chloride (distinction from iodates).

### Assay

Weigh accurately about 6.3 gm of sample dissolve in 50 ml of water, add 10 ml of strong ammonia ammonium chloride solution and titrate with 0.05 M disodium EDTA using 0.1 gm of moderate black II mixture as indicator until blue color is obtained. Each ml of 0.05 M disodium EDTA = 0.00602 gm of MgSO<sub>4</sub>.

**Uses**

It is used as osmotic (saline) laxative, in treatment of electrolyte deficiency, in wet dressing in boils, treatment of cholecystitis (inflammation of gallbladder), sea sickness, hypertension, etc.

Its excessive use may cause hypermagnesemia, gastrointestinal irritation and watery diarrhea.

**SODIUM ORTHOPHOSPHATE**

*Molecular formula:*  $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$

*Molecular weight:* 358.14

**Synonym:** Disodium hydrogen phosphate, phosphor soda

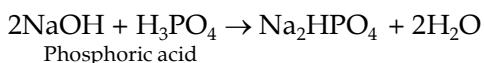
**IP limit:** It contains 98–101% of  $\text{Na}_2\text{HPO}_4$  calculated with reference to the dried substance.

**Properties**

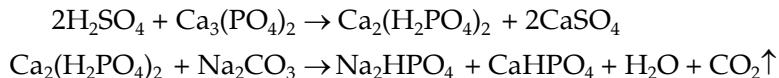
It occurs as colorless, odorless, crystalline powder and very efflorescent. It is readily soluble in water and insoluble in alcohol.

**Method of Preparation**

1. It is prepared by reaction of orthophosphoric acid calculated quantity of sodium hydroxide.



2. From bone ashes or mineral phosphorite, which is treated with sulfuric acid.
3. It is also obtained from calcium phosphate treated with calculated quantity of sulfuric acid yields mono basic calcium phosphate. Then the mixture is filtered and the filtrate is treated with sodium bicarbonate when dibasic calcium phosphate gets deposited leaving sodium phosphate in solution.

**Assay**

Weigh accurately 4 gm of substance and dissolve in 25 ml of water add 25 ml 1 N HCl and titrate potentiometrically with 1 M NaOH to first inflection point of the pH curve ( $n_1$ ) continue titration until second modulation of curve is reached. The total volume of NaOH required is  $n_2$  ml and calculate percent content from the expression.

$1420(25 - n_1)/w(100 - d)$  where  $d$  is percentage of water content.

**Use**

Widely used as saline cathartic and orally as antihypercalcemic. It is used as pharmaceutical aid and buffering agent.

**SODIUM POTASSIUM TARTRATE**

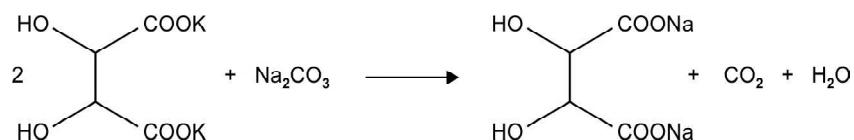
*Molecular formula:*  $\text{COONaCH(OH)} \cdot \text{CH(OH)COOK} \cdot 4\text{H}_2\text{O}$     *Molecular weight:* 282.22

**Synonym:** Potassium sodium tartrate, Seignette's salt, Rochelle's salt.

**IP limit:** It contains not <99% and not >102% of  $C_4H_4KNa$  calculated on the anhydrous basis.

### Preparation

It is prepared by boiling a solution of sodium carbonate and potassium bitartrate for some time and allowing the reaction mixture to stand at 60°C. The solution is filtered, concentrated and crystallized.



### Properties

It occurs as colorless, odorless, white crystalline powder. It is soluble in water and practically insoluble in alcohol. It is having a cooling saline taste.

### Test for Identification

**For potassium:** To 1 ml of solution add 1 ml dilute acetic acid and 1 ml of 10% w/v sodium cobalt nitrite a yellow color produced.

**For sodium:** To 2 ml of solution of 2 ml of 15% w/v of  $K_2CO_3$  heat to boil, no precipitate is produced. Add 3 ml of potassium antimonite solution and heat to boil. Allow to cool in ice and if necessary scratch the inside of the test tube with glass rod white precipitate is produced.

#### For tartrate:

1. Warm the substance with sulfuric acid charring occurs and carbon monoxide which burns with blue flame is evolved.
2. To 5 ml of sample solution add 1% w/v solution of ferrous solution and 0.05 ml of hydrogen peroxide (10 vols) a transient yellow color is produced. After color disappears add 2 M NaOH intense blue color is produced.

### Assay

Accurately weighed quantity 2 g of substance is heated in a silica crucible until carbonized, cool and boil the residue with 50 ml of water and 0.5 N sulfuric acid (15 ml). It is filtered and the residue washed with water. The filtrate and washing are titrated with 0.5 N NaOH using methyl orange as indicator. Each ml of 0.5 N  $H_2SO_4$  = 0.07056 gm of  $NaKC_4H_4O_6 \cdot 4H_2O$ .

### Uses

It is used as laxative, food additive, as stabilizer in cheese and meat products.

## BENTONITE

Molecular formula:  $Al_2O_3 \cdot 4SiO_2 \cdot H_2O$

Molecular weight: 422.29

#### Synonym: Clay

It is a natural, colloidal and is an absorbent aluminum phyllosilicate clay consisting mostly of montmorillonite. It may also contain magnesium, calcium and iron. It is prepared by removing grit and non-swelling content of the ore. The most common

type is volclay bentonite, composed of about 90% montmorillonite ( $\text{Al}_2\text{Si}_4\text{O}_{10}(\text{OH})_2 \cdot n\text{H}_2\text{O}$ ) and feldspar ( $\text{K}_2\text{O} \cdot \text{Al}_2\text{O}_3 \cdot 6\text{SiO}_2$ ) and aluminosilicate containing  $\text{SiO}_2$ ,  $\text{Al}_2\text{O}_3$ ,  $\text{Fe}_2\text{O}_3$ ,  $\text{CaO}$ ,  $\text{MgO}$  and some Na and K.

### **Properties**

It occurs as very fine odorless, cream colored to greyish white powder. It is insoluble in water and soluble in organic solvents. It is slightly earth in taste. The special properties of bentonite are an ability to form thixotropic gels with water, an ability to absorb large quantities of water with an accompanying increase in volume of as much as 12–15 times its dry bulk, and a high cation exchange capacity. It is stored in tightly closed containers.

### **Uses**

It is used as filler in pharmaceuticals, and due to its absorption/adsorption functions, it allows paste formation. Such applications include industrial protective creams, calamine lotion, wet compresses and anti-irritants for eczema. In medicine, bentonite is used as an antidote in heavy metal poisoning. Personal care products such as mud packs, sunburn paint, baby and face powders and face creams may all contain bentonite.

## **PROTECTIVES AND ADSORBENTS**

These are chemically inert substances which are used in the treatment of mild diarrhea or dysentery. Diarrhea is defined as the frequent passage of watery stools as liquid feces due to improper absorption of food or by bacterial infections and chemical toxins. As a result increased motility in colon, the stool may contain blood, pus, mucus or excess quantity of fats. It may be mild or chronic diarrhea while chronic diarrhea is due to GI disturbance, absorption and inflammation. This also results in electrolyte imbalance or dehydration due to excessive discharge of fluid. Dysentery is a frequent elimination of watery fluid with or without mucus or blood due to infection of small protozoa like ameba.

Many chemical agents are used to treat diarrhea and their main action is protection and adsorbent in nature. They are:

- i. Bismuth subcarbonate
- ii. Bismuth subgallate
- iii. Kaolin, activated charcoal
- iv. Bentonite.

Following compounds are used as protectives and adsorbents.

## **BISMUTH SUBCARBONATE**

*Molecular formula:  $(\text{BiO})_2\text{CO}_3\text{H}_2\text{O}$*

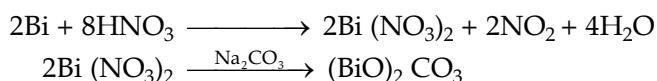
*Molecular weight: 518.98*

**IP limit:** It contains 90–92% of bismuth calculated with reference to dried substance.

### **Preparation**

To a solution of bismuth nitrate an excess of 20% sodium carbonate solution is added with constant stirring and the solution is allowed to stand for some time. Filter the

solution and wash the residue till washings are neutral. The solid is collected and dried at about 50°C



### **Properties**

It occurs as white or pale yellowish and tasteless powder. It should be stored in air-tight container when ignited it gets decomposed into bismuth trioxide. It is insoluble in water and soluble in hydrochloric acid and nitric acid.

### **Test for Identification**

**For bismuth:** To 0.5 gm sample add 10 ml 2 N HCl and heat to boiling for 1 minute, cool and filter, if necessary. To 1 ml add 20 ml of water a white or slightly yellow precipitate is formed which on addition of 0.05–0.1 ml of sodium sulfate solution turns brown.

**For carbonate:** Suspend sample in 2 ml water in a test tube, add 2 M acetic acid close the tube immediately with a stopper fitted with a glass tube bent at two right angles, heat gently and collect the gas in 5 ml of 0.1 M barium hydroxide, a white precipitate is formed, which is dissolves on addition of excess of dilute HCl.

### **Assay**

Weigh accurately 0.5 gm of sample and dissolve in 3 ml HNO<sub>3</sub> and dilute with 250 ml of H<sub>2</sub>O. Add strong ammonia solution until cloudiness is first observed; add 0.5 ml of HNO<sub>3</sub> and heat to 70°C maintain the solution at this temperature till it becomes clear. Add about 50 mg of xylanol orange mixture and titrate with 0.1 M disodium EDTA until color changes from pinkish violet to lemon yellow. Each ml of 0.1 M disodium EDTA = 0.02090 gm of bismuth.

### **Uses**

Topically as protective in lotions and ointments, internally as astringent and absorbent. It is also used as adsorbent in enteritis, diarrhea, dysentery, ulcerative colitis, in wound dressing.

## **BISMUTH SUBGALLATE**

*Molecular formula:* Bi(OH)<sub>2</sub>C<sub>7</sub>H<sub>5</sub>O<sub>5</sub>

*Molecular weight:* 412.13

**Synonym:** Bismuth oxygallate

**IP limit:** It contains not <52% and not >57% of bismuth trioxide calculated with reference to the substance dried to constant weight at 105°C.

### **Preparation**

It is prepared from bismuth nitrate and gallic acid in acetic acid medium. The acetic acid can be replaced by mannitol or glycol.

### **Properties**

Bismuth subgallate is a basic salt of bismuth. It is amorphous, bright yellow powder, odorless, tasteless. Practically insoluble in water, ether, ethanol but readily dissolves in hot mineral acids with decomposition and in solution of alkali hydroxides.

### **Test for Identification**

To 0.5 gm sample add 10 ml 2 N HCl and heat to boiling for 1 minute, cool and filter, if necessary. To 1 ml add 20 ml of water a white or slightly yellow precipitate is formed which on addition of 0.05–0.1 ml of sodium sulfate solution turns brown.

### **Assay**

Dry about 1 gm at 105°C to constant weight, add nitric acid dropwise with stirring and warm until solution is complete. Evaporate the solution to dryness and carefully ignite the residue to constant weight. The residue represents the quantity of  $\text{Bi}_2\text{O}_3$  in the weight of substance taken.

### **Use**

It is used as astringent, antacid and protective.

### **Milk of Bismuth**

It is a suspension which is prepared by using bismuth hydroxide and bismuth subcarbonate in water. It is also known as 'Bismuth magma' or 'Bismuth cream'. Milk of bismuth mainly used as astringent and antacid rather than protective adsorbent. It is usually given in 4–5 ml dose.

## **KAOLIN**

*Molecular formula:*  $\text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot 2\text{H}_2\text{O}$

*Molecular weight:* 258.16

**Synonym:** China clay, porcelain clay, white bole.

Heavy kaolin is purified natural hydrated aluminum silicate of variable composition. Light kaolin is native hydrated aluminum silicate free from most of its impurities by elutriation and dried. It may contain a suitable dispersing agent.

### **Preparation**

Kaolin is widely distributed in nature contaminated with ferric oxides. It is prepared when the rock is mined, evacuated and the impurities are washed with water and then powdered. The rock is elutriated with water and large sized particles are separated. The turbid liquid is allowed to settle; heavy kaolin containing large particles and colloidal kaolin containing particles of small size are separated and dried. For pharmaceutical use it is purified by treatment with HCl and  $\text{H}_2\text{SO}_4$  or both and then washed with water.

### **Test for Identification**

Fuse 2 gm of substance with 4 gm anhydrous sodium carbonate. Warm residue with water and filter, acidify the filtrate with HCl evaporate to dryness and warm the residue with dilute HCl, residue of silica is obtained and the acid solution after neutralization gives reaction for aluminum.

**For aluminum:** To 0.5 gm in a metal crucible add 1 gm  $\text{HNO}_3$  and 3 gm anhydrous sodium carbonate, heat to melt and allow cool, adding 20 ml of boiling water to this residue and filtering. To filtrate add 1 ml of 10 M NaOH and filter. To filtrate add 3 ml of ammonium chloride solution a gelatinous white precipitate is obtained.

**For silicate:** Fuse 1 gm of substance with 2 g anhydrous sodium carbonate and warm the residue with 10 ml of water, filter, wash with water and reserve the residue. To combined filtrate and washings add 3 ml of HCl a gelatinous precipitate is obtained.

#### **Use**

It is used as adsorbent in diarrhea caused by agents capable of being absorbed, e.g. due to food poisoning and also used in chronic ulcerative colitis. As poultice, dusting powder, clarifying and decolorizing medium, as filtering medium, as tablet diluent.

### **ACTIVATED CHARCOAL**

Absorbing power should not be <40% of weight of phenazone calculated with reference to the dried substance.

#### **Preparation**

Decolorizing charcoal is obtained from magnesium matter by suitable carbonization process intended to confer a high absorbing power.

#### **Test for Identification**

When heated to redness burns slowly without flame.

#### **Assay**

To 0.3 gm of substance add 25 ml of freshly prepared 1% w/v solution of phenazone, shake thoroughly for 15 minutes filter the solution and discard the first 5 ml of the filtrate. To 10 ml of the filtrate add 1 gm potassium bromide, 20 ml of 2 M HCl and titrate with 0.0167 M potassium borate using 0.1 ml of ethoxychrysoidine HCl solution as indicator. The endpoint is change of color from reddish pink to yellow pink. Repeat the titration with phenazone only using 10 ml of phenazone. Calculate the % of phenazone absorbed using expression

$$2.353 (a - b)/w$$

where w = weight in gm of sample

- a = volume consumed during first titration
- b = volume consumed by phenazone only

### **IMPORTANT QUESTIONS/ANSWERS**

#### **I. Multiple Choice Questions**

1. Laxatives are called:
  - a. Mild cathartics
  - b. Protective
  - c. Stimulants
  - d. All of the above
2. Magnesium sulfate is known as:
  - a. Blue vitriol
  - b. Epsom salt
  - c. Clay
  - d. None of the above
3. Cathartics are used to .....
  - a. Reduce GI irritation
  - b. Induce vomiting
  - c. Evacuation of bowel
  - d. All of the above

4. Mild diarrhea caused due to:
  - a. Hypersensitivity
  - b. Intentional poisoning
  - c. Accidental poisoning
  - d. All of the above
5. When the rock is mined ..... is prepared.
  - a. Mild cathartics
  - b. Bentonite
  - c. Kaolin
  - d. Ammonium chloride
6. ..... are chemically inert substances which are used in the treatment of mild diarrhea or dysentery.
  - a. Mild cathartics
  - b. Protectives and absorbents
  - c. Antacids
  - d. None of the above
7. Purgatives are .....
  - a. Mild cathartics
  - b. Protective
  - c. Strong cathartics
  - d. All of the above
8. ..... is defined as the frequent passage of watery stools as liquid feces.
  - a. Mild cathartics
  - b. Diarrhea
  - c. Stimulants
  - d. All of the above
9. Milk of bismuth is also known as:
  - a. Bismuth magma
  - b. Bismuth cream
  - c. Both a and b
  - d. None of the above
10. ..... is used as food additive.
  - a. Bentonite
  - b. Sodium potassium tartrate
  - c. Kaolin
  - d. Ammonium chloride

### Answers

1. a    2. b    3. c    4. d    5. b    6. b    7. c    8. b    9. c    10. b

### II. Fill in the Blanks

1. Molecular formula of kaolin .....
2. Saline cathartics should not be used in patients' with .....
3. Major side effect of saline cathartics is .....
4. Emollient laxatives act either as ..... or .....
5. Kaolin is used as .....
6. Sodium potassium tartrate is also known as .....
7. Kaolin is .....
8. ..... can be prepared by neutralizing hot dilute sulfuric acid with magnesium or its oxides or carbonate.
9. Mineral oil is ..... laxative.
10. ..... can be prepared from solution of bismuth nitrate an excess of 20% sodium carbonate solution.

### Answers

1.  $\text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot 2\text{H}_2\text{O}$
2. Low sodium diet
3. Excessive loss of body fluids as watery stools

4. Lubricants, stool softeners
5. Adsorbents
6. Rochelle's salt
7. Natural hydrated aluminum silicate
8. Magnesium sulfate
9. Lubricant
10. Bismuth subcarbonate.

### III. Short Answer Questions

1. Define the following terms.
  - a. Purgative
  - b. Laxative
  - c. Cathartics
2. Discuss various types of laxatives.
3. Write the method of preparation of magnesium sulfate.
4. How would you prepare bismuth subcarbonate?
5. Define diarrhea. What are the causes of diarrhea?
6. Differentiate light and heavy kaolin.
7. What is milk of magnesia?
8. What are protectives and adsorbents?
9. What are side effects of  $MgSO_4$  when excessive amount consumed?
10. Write the method of preparation of bismuth subcarbonate.

### IV. Long Answer Questions

1. Write a note on saline cathartics.
2. Briefly discuss the preparation, properties, assay and uses of magnesium sulfate.
3. Describe in detail about the method of preparation, properties and uses of sodium potassium tartrate.
4. Discuss in detail about the method of preparation, properties and uses of bismuth subcarbonate.
5. Briefly discuss the kaolin.
6. Explain in detail about the bentonite.
7. Write a short note on bismuth subgallate.
8. Give a detailed note on official compound sodium orthophosphate.

# Antimicrobials

- |   |   |
|---|---|
| <ul style="list-style-type: none"> <li>• Introduction</li> <li>• Mechanism of Action           <ul style="list-style-type: none"> <li>– Classification</li> </ul> </li> <li>• Boric Acid</li> <li>• Potassium Permanganate</li> </ul> | <ul style="list-style-type: none"> <li>• Hydrogen Peroxide</li> <li>• Chlorinated Lime</li> <li>• Iodine and its Preparation</li> <li>• Povidone-Iodine</li> <li>• Important Questions/Answers</li> </ul> |
|---|---|

## INTRODUCTION

An antimicrobial is an agent that kills or stops the growth of microorganisms. The word antimicrobial was derived from the Greek words '*anti*'—against, '*mikros*'—little and *bios*—life. Antimicrobial substances are either destroying (microbiocidal) or inhibiting the growth of microorganisms (microbiostatic) especially pathogenic organism such as bacteria, fungi or protozoans. The most common targets for antimicrobial drug actions are fall into five basic categories:

- i. Inhibition of cell wall synthesis
- ii. Inhibition of nucleic acid synthesis
- iii. Inhibition of protein synthesis
- iv. Inhibition of unique metabolic steps
- v. Effects on cell membrane sterols (antifungal agents).

These are mainly classified into antiseptics, disinfectants, germicides, bacteriostatics and sanitizers.

1. **Antiseptics:** Antiseptic(s) (from Greek *anti*: 'against' and *septikos*: 'putrefactive') are antimicrobial substances which are applied to living tissue/skin to reduce or arrests the possibility of infection, sepsis, or putrefaction. These are the chemical substances used in destroying disease causing microorganism (also called pathogens) externally on wound or taken internally to treat infection. All antiseptics or protein denaturants and act on enzymes in the bacteria. They can be applied to all tissues of the body and may be use in the form of mouthwashes, soaps, deodorants, throat and nasal spray, e.g. Dettol, tincture of iodine, boric acid, cetrimide.
2. **Disinfectants:** These are the drugs or substances which are applied to the surface of non-living objects to destroy microorganisms that are living on the objects. Disinfection does not necessarily kill all microorganisms, especially resistant bacterial spores; it is less effective than sterilization. These are commonly used in houses, disinfection of surgical instruments, hospital sanitation and sputum

containers on floor. They are bactericidal and rapidly produce irreversible lethal effects. Some chemical disinfectants are too irritant to the skin, e.g. cresol and phenol.

3. **Germicides:** These are substances which kill microorganisms. More specific terminology like 'bactericide' (against bacteria) 'fungicide' (against fungi), 'viricide' (against virus), etc. signifies exact action. Potency of germicide is expressed by phenol coefficient. It mainly acts by denaturation of bacterial enzymes and proteins, by oxidation of bacterial protoplasm and by increasing bacterial cell membrane permeability.
4. **Bacteriostatics:** These are substances which primarily function by inhibiting the growth of bacteria. Thus, bacteriostatic drugs or agents do not kill but inhibit the growth of bacteria.
5. **Sanitizers:** It is the process of rendering sanitary by decreasing the number of bacterial contaminants. Disinfectants that are used to maintain general public health standards, are termed sanitizers. Sanitizers are mainly concerned with cleaning or washing away the organic matter.

## MECHANISM OF ACTION

Based upon the mechanism of action inorganic antimicrobial agents can be divided into three general categories:

1. Oxidation
2. Halogenation
3. Protein precipitation.

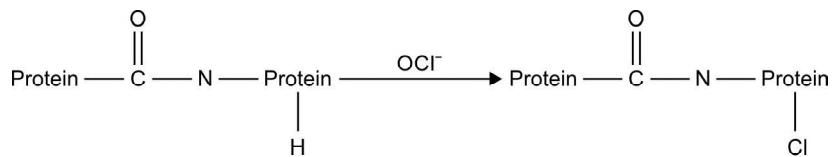
### Oxidation

Convert sulphhydryl into a disulfide bridge, thus altering the conformation of the protein and thereby alter its function. Nonmetals and certain types of anions function through oxidative mechanisms, e.g.  $\text{H}_2\text{O}_2$ ,  $\text{KMnO}_4$ , iodine solution, povidone-iodine.

### Halogenation

Hypohalides can react with amide hydrogen to form N-chloro derivatives. This is a reaction occurring with antiseptics of the hypohalite type, e.g. sodium hypochlorite.

Since these types of compounds can serve as reagents in the chlorination of primary and secondary amides, e.g.



It is expected that a similar reaction can take place under appropriate conditions with the peptide linkage between the amino acid groups comprising the protein molecule.

### Protein Precipitation

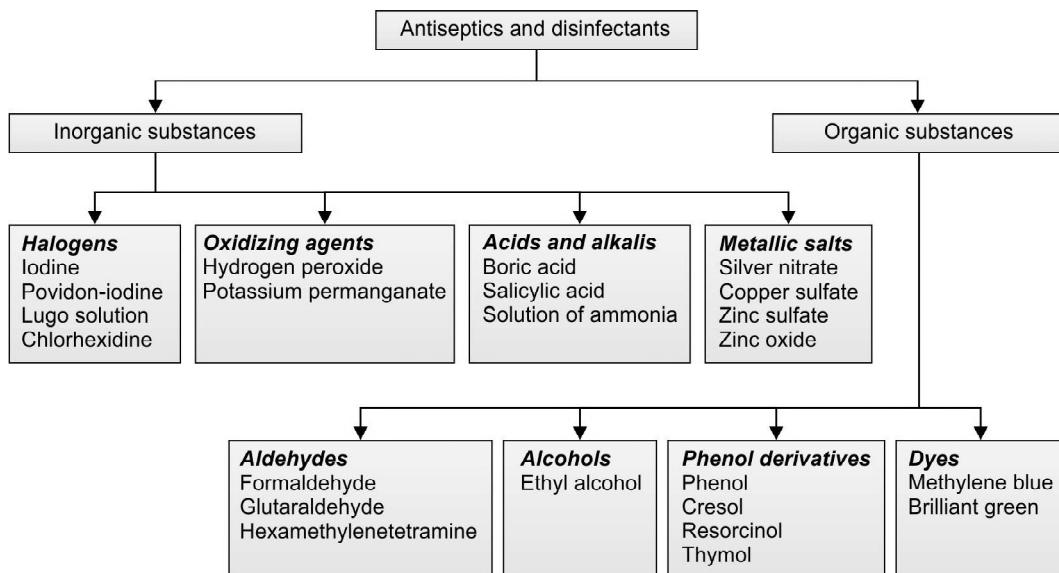
The complex of protein precipitants results in a radical change in the properties of the proteins and them 'tie-up' important functional groups at the active site of enzymes resulting in antimicrobial activity, e.g.  $\text{AgNO}_3$ , mild silver protein, mercury, yellow mercuric oxide, ammoniated mercury.

A non-selective antimicrobial agent causes most destructive effect on the majority of microorganisms (antiseptics and disinfectants). The chemical agents must possess following properties to treat as antiseptics and disinfectants:

- Must have a broad-spectrum and rapid onset of action
- Should have a small latency period and high activity
- Must be chemically resistant and low toxicity
- High availability and low cost
- Lack of local irritant or allergic effects on tissues
- Minimal absorption from the place of their application.

### Classification

**Classification of antiseptics and disinfectants (according to chemical structure):** Antimicrobial agents are classified according to their chemical structure.



### BORIC ACID

*Molecular formula:  $\text{H}_3\text{BO}_3$*

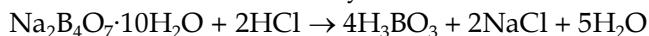
*Molecular weight: 61.83*

**Synonym:** Ortho boric acid, hydrogen borate, acidum boricum, boracic acid.

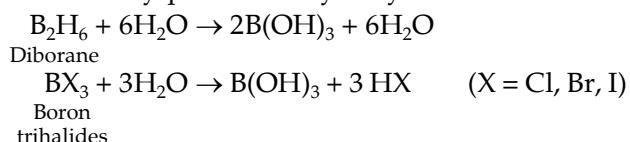
Boric acid widely distributed in sea water, plants, fruits and also available in combined form as its largest natural resource. As per IP boric acid contains 99.5–100.5% of  $\text{H}_3\text{BO}_3$  on the dry basis.

### Method of Preparation

1. Boric acid may be prepared by reacting borax (sodium tetraborate decahydrate) with a mineral acid, such as hydrochloric acid or sulfuric acid.

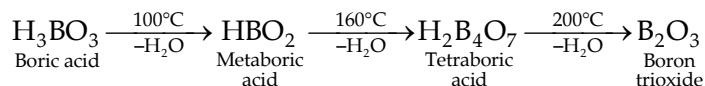


2. It is also formed as a by-product of hydrolysis of boron trihalides and diborane.

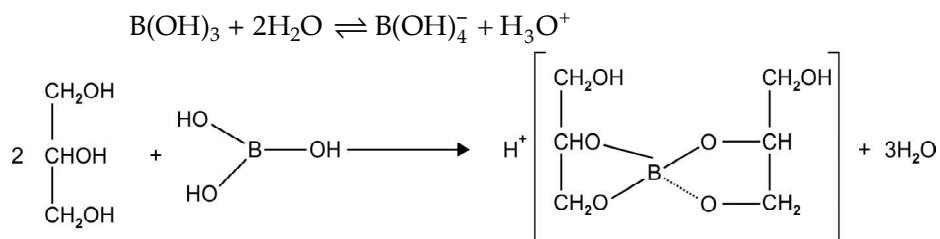


### Properties

It occurs as white crystalline solid or granular, odorless, sparingly soluble in water and slightly soluble in alcohol. When heated above 100°C, it dehydrates, forming metaboric acid ( $\text{HBO}_2$ ) and when metaboric acid heated at 160°C it converted into tetraboric acid or pyroboric acid ( $\text{H}_2\text{B}_4\text{O}_7$ ) and when pyroboric acid is heated above 200°C it decompose into boron trioxide ( $\text{B}_2\text{O}_3$ ).



Boric acid is weak acid but when boric acid dissolve in glycerin it gives glyceroboric acid and has ionization constant is 10,000 times greater than that of boric acid.



Boric acid reacts with alcohols to form borate esters  $[\text{B(OR)}_3]$  where R is alkyl or aryl.



### Uses

- Boric acid can be used as an antiseptic for minor burns or cuts. It is also used as weak bacteriostatic, fungistatic and astringents.
- It is also used in preservation of grains such as rice and wheat.
- Boric acid is applied in a very dilute solution as an eyewash.
- Dilute boric acid can be used as a vaginal douche to treat bacterial vaginosis due to excessive alkalinity.
- It is also used as mouthwashes, skin lotion for local anti-infective action.
- It also used as an insecticide.
- The boric acid-borate system can be useful as a primary buffer system.
- Boric acid is used in some nuclear power plants as a neutron poison.

It should be stored in well-closed container and kept in a cool place. Adverse effects on ingestion are vomiting, abdominal cramps, etc.

## POTASSIUM PERMANGANATE

*Molecular formula:*  $\text{KMnO}_4$

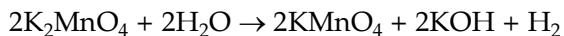
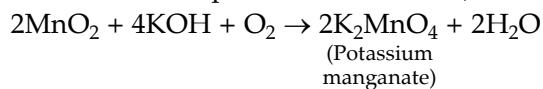
*Molecular weight:* 158.03

**Synonym:** Condy's crystals, permanganate of potash, hypermangan

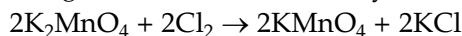
**IP limit:** As per IP, it contains 99–100.5% w/w of  $\text{KMnO}_4$ .

### Method of Preparation

It is prepared by heating potassium hydroxide with manganese dioxide in presence of air or potassium nitrate/potassium chlorate (oxidizing agent).



Potassium manganate can be oxidized by chlorine, it gets converted into  $\text{KMnO}_4$



Potassium manganate when treated with hydrochloric acid



Potassium manganate when treated with carbon dioxide

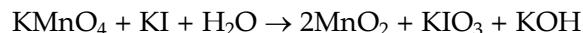


The above solution is filtered to separate the precipitated  $\text{KMnO}_4$  from  $\text{MnO}_2$  and then concentrated and cooled to crystallize potassium permanganate.

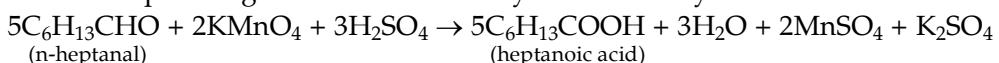
### Properties

It occurs as dark purplish or brownish black crystals or granular powder. It is odorless, has metallic lusture. It is sweet with astringent taste and freely soluble in water and alcohol. As it is strong oxidizing agent, it decomposes with a high-risk of explosion in contact with certain organic substances. It is stable in air when it is heated it decomposes at about  $240^\circ\text{C}$  with evolution of oxygen.

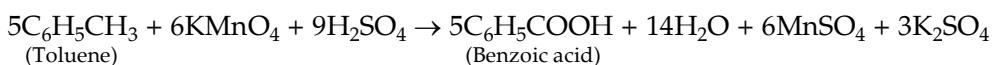
Potassium permanganate acts as strong oxidizing agents. Iodides are oxidized to iodate by alkaline or neutral solution.



Potassium permanganate oxidizes aldehydes to carboxylic acids



Even an alkyl group (with benzylic hydrogen) on an aromatic ring is oxidized, e.g. toluene to benzoic acid.



When heated solid potassium permanganate decomposes.



### Uses

1. It possesses strong oxidizing properties and oxidizes proteins and other bioorganic substances so it is used as disinfectant and deodorant.
2. It is also used as astringents, anti-infective and bactericidal.
3. It was used as a bleaching agent and extensively used in the water treatment.
4. It finds used in the treatment of urethritis. Its solutions are used to clean the ulcer or abscesses as wet dressing and in baths in eczematous conditions and acute dermatitis.
5. It finds use as an antidote for poisoning by barbiturates, chloral hydrate and many alkaloids.

### Storage

Store in well-closed container and kept in a cool place.

## HYDROGEN PEROXIDE

*Molecular formula:* H<sub>2</sub>O<sub>2</sub>

*Molecular weight:* 34.01

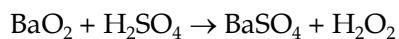
**Synonym:** Dioxidane, oxidanyl, perhydroxic acid.

It is a nonplanar molecule with twisted symmetry. Although the O—O bond is a single bond, the molecule has a relatively high rotational barrier. The molecular structures of gaseous and crystalline H<sub>2</sub>O<sub>2</sub> are significantly different. This difference is attributed to the effects of hydrogen bonding, which is absent in the gaseous state.

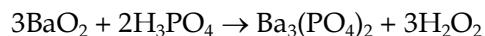
**IP limit:** As per IP, hydrogen peroxide solution (20 vol/100 vol) is an aqueous solution of H<sub>2</sub>O<sub>2</sub>. It contains a suitable stabilizing agent. Hydrogen peroxide solution (20 vol) contains 5–7% of H<sub>2</sub>O<sub>2</sub> which corresponds to about 20 times its volume of available oxygen while hydrogen peroxide solution (100 vol) contains 26–28% of H<sub>2</sub>O<sub>2</sub> which corresponds to about 100 times its volume of available oxygen.

### Preparation

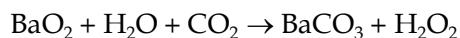
1. *From barium peroxide:* When aqueous cream of barium peroxide treated with cold dilute sulfuric acid forms hydrogen peroxide.



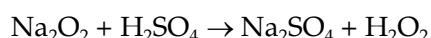
It is also obtained by decomposing barium peroxide treated with phosphoric acid forms hydrogen peroxide.



2. When carbon dioxide is passed slowly through ice-cold paste of barium peroxide, then hydrogen peroxide produced:



3. *From sodium peroxide:* In laboratory it is prepared by Merck's process. Sodium peroxide decomposed by addition of cold dilute (20%) solution of sulfuric acid forms hydrogen peroxide.



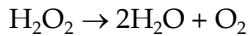
## Properties

It is a clear, colorless and odorless liquid or may have an odor related to that of ozone unstable liquid. It is bitter in taste, caustic to skin, acidic to litmus. It is miscible with water, dissolves in ether, immiscible in pet ether. It rapidly decomposes in contact with oxidizable matter and metals. It is a good oxidizing agent.

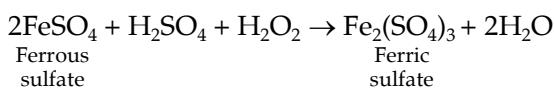
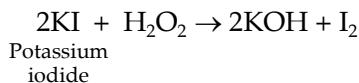
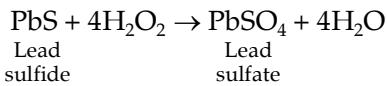
It should be stored in a paraffin wax coated with glass, plastic or Teflon bottles partially filled container having stabilizing agent and small vent in a closure at 8–15°C. It should be protected from light. It should not be stored in glass containers due to metal oxides present in the containers catalyzes its decomposition. A small quantity of acid, alcohol, glycerol and phosphoric acid is often used as a stabilizing agent to check its decomposition.

## ***Chemical Properties***

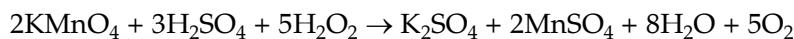
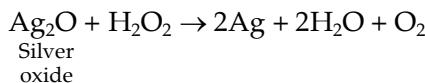
1. **Decomposition:** Pure hydrogen peroxide decomposes slowly, but when heated at 100°C it liberates oxygen.



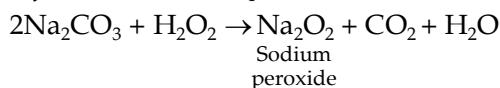
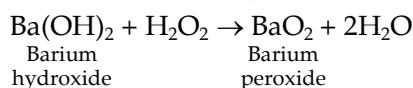
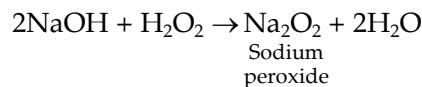
2. Oxidation properties: Hydrogen peroxide is a strong oxidizing agent and reacts with many organic materials.



3. Reduction properties: Hydrogen peroxide behaves as reducing agents towards other oxidizing agents.



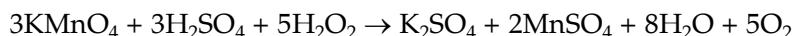
4. Acidic in nature: Hydrogen peroxide is slightly acidic in nature through in dilute solution it is neutral towards litmus.



## Assay

Assay of hydrogen peroxide based on the oxidation-reduction (redox) titration. 10 ml of  $\text{H}_2\text{O}_2$  is diluted with 10 ml distilled water, then add 10 ml of 5 N sulfuric acid and

then titrated with 0.1 N potassium permanganate solution, until a faint pink color is obtained. Each ml of 0.1 N  $\text{KMnO}_4$  = 0.001701 gm of  $\text{H}_2\text{O}_2$ .



### Uses

#### 1. In Medical:

- Used as an antiseptic, germicidal and disinfectant.
- Can be used for the sterilization of various surfaces, including surgical tools and may be deployed as a vapor (VHP) for room sterilization.
- Demonstrates broad-spectrum efficacy against viruses, bacteria, yeasts, and bacterial spores. In general, greater activity is seen against gram-positive than gram-negative bacteria.
- Was used for disinfecting wounds.
- Effective antidote for phosphorus and cyanide poisoning.

#### 2. Cosmetic applications:

- Diluted  $\text{H}_2\text{O}$  (between 1.9% and 12%) mixed with ammonium hydroxide is used to bleach human hair, wool, feather, ivory, etc.
- Also used for tooth whitening. It can be found in most whitening toothpastes
- May be used to treat acne
- It finds use in deodorants.

**3. Propellant:** High-concentration  $\text{H}_2\text{O}$  is referred to as "high-test peroxide" (HTP). It can be used either as a monopropellant (not mixed with fuel) or as the oxidizer component of a bipropellant rocket.

**4. Explosives:** Used for creating organic peroxide-based explosives, such as acetone peroxide, for improvised explosive devices.

#### 5. Industrial:

- Used for pulp and paper-bleaching
- Manufacture of sodium percarbonate and sodium perborate which are used as mild bleaches in laundry detergents
- Used as an antichlor
- Aerating agents in production of sponge rubber.

### Storage

Store in cool and dark place and light resistant container.

## CHLORINATED LIME

*Molecular formula:  $\text{Ca(ClO)}_2$*

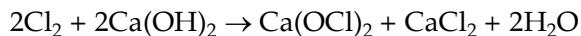
*Molecular weight: 142.98*

**Synonym:** Hypochlorous acid, bleaching powder, calcium oxychloride, calcium hypochlorite.

Bleaching powder is not a simple mixture of calcium hypochlorite, calcium chloride, and calcium hydroxide. Instead, it is a mixture consisting principally of calcium hypochlorite [ $\text{Ca(OCl)}_2$ ], dibasic calcium hypochlorite [ $\text{Ca}_3(\text{OCl})_2(\text{OH})_4$ ], and dibasic calcium chloride [ $\text{Ca}_3\text{Cl}_2(\text{OH})_4$ ]. It is made from slightly moist slaked lime.

### Preparation

Calcium hypochlorite is produced industrially by treating slaked lime  $[\text{Ca}(\text{OH})_2]$  with chlorine gas.

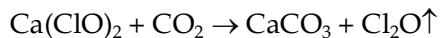


### Properties

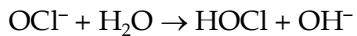
It is a dull, dry, white powder, contains not <30% w/w of chlorine. It is slightly soluble in water and alcohol. It has strong odor of chlorine. On exposure to air, it becomes moist and rapidly decomposes to release hypochlorous acid. Carbon dioxide being absorbed and chlorine gas is evolved. Its aqueous solution is strongly alkaline. It is stored in well-closed containers at dry, cool place and away from organic materials and metals. The hydrated form is safer to handle.

### Chemical Reactions

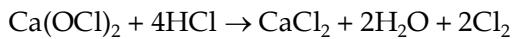
1. Calcium hypochlorite reacts with carbon dioxide to form calcium carbonate and release dichlorine monoxide



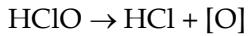
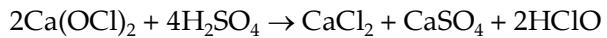
2. A calcium hypochlorite solution is basic. This basicity is due to the hydrolysis performed by the hypochlorite ion, as hypochlorous acid is weak, but calcium hydroxide is a strong base. As a result, the hypochlorite ion is a strong conjugate base, and the calcium ion is a weak conjugate acid:



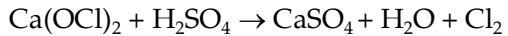
Similarly, calcium hypochlorite reacts with hydrochloric acid to form calcium chloride, water and chlorine.



3. Treatment of chlorinated lime with dilute sulfuric acids liberates hypochlorous acid which behaves as oxidizing and bleaching agents.



4. On treatment with excess of dilute acid or  $\text{CO}_2$ , the whole of chlorine is liberated.



### Uses

It has rapid bactericidal action. It kills most of bacteria, some fungi, yeast, algae, viruses and protozoa. It is commonly used to sanitize swimming pools in combination with cyanuric acid stabilizer which reduces the loss of chlorine due to UV radiation and disinfect drinking water. It is also used for sugar industry for bleaching sugar cane juice before its crystallization. It is a general oxidizing agent. It is used for bleaching cotton and linen. In the preparation of surgical chlorinated soda solution (Dakin's solution) it is employed as a wound disinfectant. A mixture of chlorinated lime and boric acid solution (Eusol) is used as a disinfectant lotion and wet dressing.

## IODINE

*Molecular formula:* I<sub>2</sub>

*Molecular weight:* 253.8

It is a dark violet non-metallic halogen element.

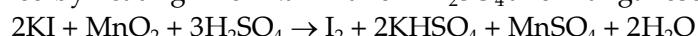
**IP limit:** As per IP, it contains 99.5–100.5% w/w of iodine.

### Method of Preparation

- From seaweeds: By reacting seaweed ash with water, sulfuric acid and hydrogen peroxide



- It is prepared by heating KI or NaI with dil. H<sub>2</sub>SO<sub>4</sub> and manganese dioxide.



### Properties

It occurs as grayish violet colored crystalline powder with irritant odor. It has pungent taste. It is sparingly soluble in water, soluble in ethanol and freely soluble in ether. It is volatile in nature.

### Storage

It should be stored in well-closed amber colored container with a glass stopper at a cool place.

### Incompatibility

It is incompatible with hypophosphite, sulfate, some metal, reducing agent, alkalis and alkali carbonates.

### Uses

It is used as topical agent, antimicrobial agent and the solution used as germicide and fungicide. It is used in the treatment of thyrotoxicosis and antidote for alkaloidal poisoning. It is also used as counterirritant. It is used in the manufacture of dye stuffs and drugs.

### Preparation

It is mainly of three types:

#### 1. Aqueous Iodine Solution (Strong Iodine Solution)

It contains 5% w/v of iodine and 10% w/v of potassium iodide in water. It is a transparent brown colored liquid and has a smell of iodine.

#### Composition:

Sr. no.	Ingredient	Qty.
1.	Iodine	50 gm
2.	Potassium iodide	100 gm
3.	Purified water	1000 ml qs

**2. Weak Iodine Solution (*Iodine Tinctures*)**

It contains 2% w/v of iodine and 2.5% w/v of potassium iodide in water. The required volume is made by adding sufficient alcohol (90%). Its alcoholic content is 45–48% v/v as per IP. It is a transparent brown colored liquid and has smell of alcohol.

**Composition:**

Sr. no.	Ingredient	Qty.
1.	Iodine	20 gm
2.	Potassium iodide	25 gm
3.	Alcohol 50% (qs)	1000 ml

**3. Phenolated Iodine Solution (*Binton's Solution or Carbolised Iodine Solution*)**

It consists of 15 ml strong iodine solution, 6 ml purified phenol, 165 ml of glycerin and sufficient water to make up the volume up to 1000 ml.

**Uses**

It is used as topical antimicrobial agent and used for disinfection of skin before surgery. Dilute solution used to apply on wounds and cuts also used as amebicidal agent.

**POVIDONE-IODINE**

Povidone-iodine is an iodophor, i.e. complex of iodine with povidone (a polymer/polyvinyl pyrrolidone). Iodophors class of compounds is complexes of iodine with carrier organic molecules serving as a solubilizing agent. These complexes slowly liberate iodine in solution. It is less irritating iodine product without losing antibacterial effectiveness.

Povidone-iodine (PVP I) is a stable chemical complex of polyvinyl pyrrolidone (povidone, PVP) and elemental iodine. It contains from 9–12% available iodine, calculated on a dry basis.

**Properties**

It is a yellowish brown colored amorphous powder and having slight characteristic odor. It is soluble in water and ethanol. Its aqueous solution is acidic in nature.

**Storage**

It should be stored in well-closed airtight container at a cool place.

**Advantages of Povidone-Iodine Complex over Elemental Iodine Solutions**

It is having non-irritating effect on tissues and comparatively low oral toxicity. It is soluble in water. Low iodine vapor pressure making it stable to possible iodine loss. It is non-staining and can be washed clear from skin and clothing.

**Uses**

It is used as a topical agent as a broad-spectrum antiseptic. It is also used as gargles and mouthwashes (to treat oral cavity infection). It is used as a disinfectant.

**IMPORTANT QUESTIONS/ANSWERS****I. Multiple Choice Questions**

1. .... is an agent that kills or stops the growth of microorganisms.
  - a. Antimicrobials
  - b. Antacids
  - c. Protectives
  - d. All of the above
2. Antimicrobial agents act by ..... mechanism.
  - a. Oxidation
  - b. Protein precipitation
  - c. Halogenation
  - d. All of the above
3. .... is an effective antidote for phosphorus and cyanide poisoning.
  - a.  $\text{KMnO}_4$
  - b.  $\text{H}_2\text{O}_2$
  - c. Borax
  - d. Calcium chloride
4. Chlorinated lime is also known as .....
  - a. Clay
  - b. Dioxidane
  - c. Bleaching powder
  - d. Calcium chloride
5. .... is a dark violet non-metallic halogen element.
  - a. Hypochlorite
  - b. Iodine
  - c. Zinc sulfate
  - d. Mercury
6. Strong iodine solution is also known as:
  - a. Aqueous iodine solution
  - b. Lugol's solution
  - c. Both a and b
  - d. None of the above
7. Povidone iodine is an:
  - a. Oxadione
  - b. Pyrazine
  - c. Both a and b
  - d. Polyvinyl pyrrolidone
8. .... is produced industrially by treating slaked lime with chlorine gas.
  - a. Calcium hypochlorite
  - b. Calcium carbonate
  - c.  $\text{KMnO}_4$
  - d. Polyvinyl pyrrolidone
9. Hydrogen peroxide should be stored in a paraffin wax coated with ..... bottles.
  - a. Glass
  - b. Plastic
  - c. Teflon
  - d. All of the above
10. .... acts as strong oxidizing agents.
  - a. Titanium dioxide
  - b. Potassium permanganate
  - c. Magnesium sulfate
  - d. All of the above

**Answers**

1. a    2. d    3. b    4. c    5. b    6. c    7. d    8. d    9. d    10. b

**II. Fill in the Blanks**

1. .... are the substances which are applied to the surface of non-living objects to destroy microorganisms.
2. .... is the process of rendering sanitary by decreasing the number of bacterial contaminants.
3. .... are substances which kill microorganisms.
4. Molecular formula of borax .....

5. Boric acid is a ..... acid.
6. ..... is used as astringents, anti-infective and bactericidal.
7. Hydrogen peroxide is used as .....
8. ..... is used as an anti-hyperthyroid.
9. ..... and ..... are examples of disinfectants.
10. Povidone iodine is an .....

### **Answers**

1. Disinfectants
2. Sanitization
3. Germicides
4.  $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$
5. Weak
6.  $\text{KMnO}_4$
7. Antiseptics
8. Iodine
9. Cresol, phenol
10. Iodophor

### **III. Short Answer Questions**

1. Write the method of preparation of iodine in laboratory.
2. Define antimicrobials. Discuss the mechanism of action of antimicrobial.
3. Classify antimicrobials on the basis of mode of action with examples.
4. Classify antimicrobials on the basis of chemical structure with examples.
5. Define the following terms:
  - a. Germicide
  - b. Bacteriostatic
  - c. Sanitizers
6. Differentiate antiseptics and disinfectants.
7. Discuss the method of preparation and properties of boric acid.
8. What are the pharmaceutical uses of boric acid.

### **IV. Long Answer Questions**

1. Explain the method of preparation, properties and uses of hydrogen peroxide.
2. Discuss in detail about the method of preparation, properties and uses of potassium permanganate.
3. Describe in detail about the method of preparation, properties and uses of chlorinated lime.
4. Give a detail note on iodine and its preparations.

# MISCELLANEOUS COMPOUNDS

## UNIT 4.1

### Expectorants

- Introduction
- Classification of Expectorants
- Potassium Iodide

- Ammonium Chloride
- Important Questions/Answers

#### INTRODUCTION

A cough is a sudden expulsion of air through the large breathing passages that can help clear them of fluids, irritants, foreign particles and microbes. Cough due to irritation from lack of sufficient demulcent respiratory tract fluid below the epiglottis. As a protective reflex, coughing can be repetitive with the cough reflex following three phases: an inhalation, a forced exhalation against a closed glottis, and a violent release of air from the lungs. Cough can be the irritant and productive. Irritative cough is a dry cough which may be produced by cold or inhalation of irritant foreign particles or gases and produce no sputum. Whereas productive cough produces a phlegm or sputum (mucus) and producing cough which is associated with asthma and bronchitis. It should not be suppressed and clears mucus from the lungs.

Expectorants are drugs that help in removing sputum from the respiratory tract either by increasing the fluidity (or reducing the viscosity) of sputum or increasing the volume of fluids that have to be expelled from the respiratory tract by coughing. Expectorants derived from the latin word '*Expectorate*' means 'to drive from the chest'.

These are medicinal substances which enhance the secretion of the sputum by the air passages so that it is easier to remove the phlegm through coughing. They are used in cough mixtures for this purpose they act either by increasing the bronchiole secretion or by making it less viscous (mucolytic agents). In case of dry cough, many of the expectorants act reflexly irritate the lining of the stomach which stimulates the production of sputum by the glands in the bronchial mucous membrane.

Commonly used expectorants are Guafensin is commonly available in many cough syrups. Drugs such as ipecacuanha in small doses act as stimulant expectorants. Volatile oils are direct expectorants. Potassium iodide stimulates the gastric mucosa which increases the bronchiole secretion and liquify mucus. Ammonium chloride acts like potassium iodide but it is less potent. Antimony potassium tartrate also used as expectorant.

## CLASSIFICATION OF EXPECTORANTS

According to their mechanism of action it is classified into two categories.

### 1. Sedative Expectorants

These are stomach irritant expectorants which are able to produce their effect through stimulation of gastric reflexes, e.g. bitter drugs—ipecac, senega, Indian squill and inorganic compounds such as antimony potassium tartrate, ammonium chloride, sodium citrate, potassium iodide, etc.

### 2. Stimulant Expectorants

These are the expectorants which bring about a stimulation of the secretory cells of the respiratory tract directly or indirectly. Since these drugs stimulate secretion, more fluid produced in respiratory tract and sputum is diluted, e.g. eucalyptus, lemon, anise.

## POTASSIUM IODIDE

*Molecular formula:* KI

*Molecular weight:* 166.0

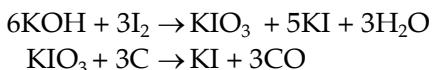
**Synonym:** Kalii iodidum, potide.

**IP limit:** As per IP it contains 99–101.5% of potassium iodide with reference to a dried basis.

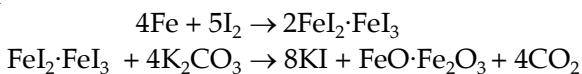
**Category:** Antithyroid, antifungal, expectorant.

### Method of Preparation

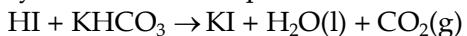
1. In laboratory, it is prepared by treating a hot aqueous solution of potassium hydroxide with iodine in slight excess to form a mixture of potassium iodide and iodate. The obtained pale yellow solution is evaporated and the residue (iodate) is heated with charcoal to reduce iodate to iodine.



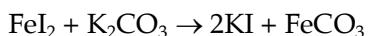
2. On large scale, it is prepared by treating iron fillings with potassium carbonate. Iron fillings are agitated in the iodine solution to form ferro ferric iodide ( $\text{FeI}_2 \cdot \text{FeI}_3$ ) solution of which is further boiling with concentrate potassium carbonate gives potassium iodide.



3. It is prepared by the reaction of a potassium base with hydroiodic acid, e.g.:



4. Alternatively iron (II) iodide, prepared using scrap iron and iodine (made from iodide rich brines or from Chile saltpeter), can be treated with potassium carbonate:



### Properties

It occurs as cubic crystals, white granular powder. It is soluble in water, alcohol and freely soluble in glycerine. Its taste is saline and slightly bitter. It is slightly hygroscopic.

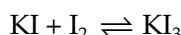
in nature, on exposure to air; it becomes yellow due to liberation of iodine. It should be stored in airtight container protected from light and moisture.

### Dose

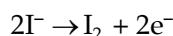
As expectorant, 250–500 mg.

### Chemical Properties

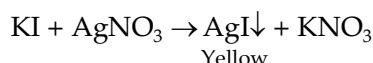
- Iodine gets readily dissolved in aqueous solution of KI, forming a dark brown solution of potassium triiodide.



- It reacts with silver nitrate gives yellow precipitate of silver iodide.

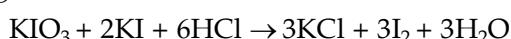


- Iodine ion readily gets oxidized by treating with oxidizing agents like nitric acid, copper, chlorine, etc.



### Assay

It is based upon oxidation-reduction method using iodometric method. Dissolve accurately weighed 350 mg of potassium iodide in about 10 ml of water, and add 35 ml of hydrochloric acid and 5 ml of chloroform. Titrate with 0.05 M potassium iodate until purple color of iodine disappears from the chloroform. The last portion of the iodate solution is added dropwise and the solution is agitated continuously and vigorously. It is then allowed for 5 minutes; if any color develops in the chloroform layer then the titration is continued. Each ml of 0.05 M potassium iodate is equivalent to 16.60 mg of KI.

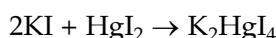
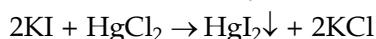


### Identification

A 10% w/v solution in carbon dioxide-free water (solution A) gives the reactions of potassium salts, and of iodides.

### Identification Test

Add mercuric chloride solution to 1 ml of sample solution a dark red precipitate is obtained which is slightly soluble in excess of this reagent and completely soluble in excess of potassium iodide solution by forming potassium mercuri iodide precipitate.



### Alkalinity

To 10 ml of solution A add 0.2 ml of 0.01 M sulfuric acid; no color is produced on addition of a drop of phenolphthalein solution.

### Clarity and Color of Solution

Solution A is clear and colorless.

### Test of Purity

1. **Arsenic:** Dissolve 5 gm in 50 ml of water and 12 ml of stannated hydrochloric acid AsT. The resulting solution complies with the limit test for arsenic (2 ppm).
2. **Heavy metals:** Not >10 ppm, determined on 2 gm by Method A.
3. **Iron:** Solution A complies with the limit test for iron (20 ppm).
4. **Cyanide:** Warm 5 ml of solution A, add one drop of ferrous sulfate solution and 0.5 ml of sodium hydroxide solution and acidify with hydrochloric acid; no blue color is produced.
5. **Iodate:** Dissolve 0.5 gm in 10 ml of carbon dioxide-free water and add 0.15 ml of dilute sulfuric acid and a drop of iodide-free starch solution; no blue color is produced within 2 minutes.
6. **Sulfate:** 1 gm dissolved in 15 ml of water complies with the limit test for sulfates (150 ppm).
7. **Loss on drying:** Not >1%, determined on 1 gm of the powdered substance by drying in an oven at 105°C for 3 hours.

### Incompatibility

Incompatible with salts of mercury, bismuth, lead, iron, potassium chlorate, chloral hydrate, other oxidizing agent and dilute hydrochloric acid.

### Uses

It is used as mild expectorants (dose of 300 mg in 4 times a day), treatment of hypothyroidism, used as a source of iodine, in cough preparation, to stabilize in preparation of solutions of iodine. It is also used as antifungal in veterinary practices.

## AMMONIUM CHLORIDE

*Molecular formula:* NH<sub>4</sub>Cl

*Molecular weight:* 53.49

**Synonym:** Salmiac, amchlor, ammonium muriate.

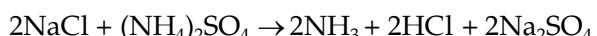
**IP limit:** As per IP it contains not <99.5% of ammonium chloride with reference to a dried basis.

### Method of Preparation

1. Ammonium chloride is made by reacting hydrochloric acid with ammonia and the resulting solution is evaporated to dryness. The product is purified by recrystallization or by sublimation.



2. It is also prepared by treating ammonium sulfate with sodium chloride.

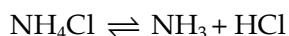


### Properties

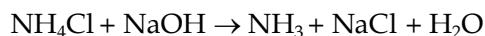
It is a white crystalline salt, odorless and has cooling saline taste. It is freely soluble in water but slightly soluble in alcohol. It is hygroscopic. On heating it sublimes without melting. It should be stored in tightly closed containers.

### Chemical Properties

1. In its vapor form, it dissociates in ammonia and hydrochloric acid.



2. It reacts with strong base such as sodium hydroxide to release ammonia gas.

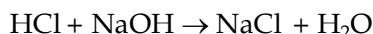


3. It also reacts with alkali metal carbonates at elevated temperatures to give alkali metal chlorides and ammonia gas.



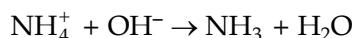
### Assay

It is assayed by acid–base titration method. Formaldehyde, previously neutralized is added to the solution of the substance. It fixes the ammonia in ammonium chloride as hexamine. The liberated hydrochloric acid is titrated against 0.1 M sodium hydroxide, using phenolphthalein as indicator. Each 1 ml of 0.1 N sodium hydroxide is equivalent to 0.005439 gm of ammonium chloride.



### Identification Test

It gives reactions with ammonium salts and chlorides. It is heated with sodium hydroxide solution releases ammonia gas which is recognized by its odor and its action on moist litmus paper.



### Test of Purity

It is tested for the following impurities.

1. Arsenic should not be >2 ppm.
2. Heavy metals should not be >10 ppm.
3. Iron should not be >20 ppm.
4. Sulfate should not be >150 ppm and calcium not >200 ppm.
5. Loss on drying should not be >1%.

**pH:** Between 4.5 and 6, determined in a 5% w/v solution.

### Clarity and Color of Solution

A 10% w/v solution is clear and colorless.

### Incompatibility

Incompatible with alkalies, alkali metal carbonates, lead and silver salts.

### Uses

It is used as expectorant, diuretic and systemic acidifiers in treatment of severe metabolic alkalosis. It is used as a thickening agent in shampoos and also used as flavoring agent. It is used in textile and leather industry in dying, tanning and textile printing. In fertilizers, it is a nitrogen source.

**IMPORTANT QUESTIONS/ANSWERS****I. Multiple Choice Questions**

1. Ammonium chloride is also known as:
  - a. Ammonium murriate
  - b. Ammonical oxide
  - c. Amalgam
  - d. Blue vitriol
2. Potassium iodide is used for:
  - a. Emetics
  - b. Expectorant
  - c. Analgesic
  - d. Antithyroid agent
3. Productive cough produces:
  - a. Amalgam
  - b. Vomiting
  - c. Dehydration
  - d. Mucus
4. Cough is a physiological protective reflex occurs due to:
  - a. Inhalation of foreign particles
  - b. Cold and infection
  - c. Chemical irritant
  - d. All of the above
5. Which cough does not produce mucus?
  - a. Productive cough
  - b. Non-productive cough
  - c. Both a and C
  - d. None of the above

**Answers**

1. a
2. b
3. d
4. d
5. b

**II. Fill in the Blanks**

1. Ammonium chloride is prepared by .....
2. Molecular formula for potassium iodide .....
3. Expectorants are mainly used for .....
4. The latin word 'expectorate' means .....
5. Ammonium chloride is ..... in nature.
6. Cough is a ..... reflex.
7. ..... is used as nitrogen source in fertilizers.
8. Ammonium chloride solutions are highly .....
9. Inorganic sedative expectorant is .....
10. Potassium iodide is prepared by treating ..... and .....

**Answers**

1. Solvay process
2. KI
3. Removal of secretions
4. To drive from the chest
5. Hygroscopic
6. Protective
7. Ammonium chloride
8. Soluble in water
9. Ammonium chloride
10. Iron fillings and iodine

**III. Short and Long Answer Questions**

1. Discuss in detail about cough.
2. How does expectorant acts on the respiratory tract?
3. Define expectorant. Classify the expectorants.
4. Discuss in detail about preparation, properties and uses of ammonium chloride.
5. Give a note on official compound potassium iodide.

# Emetics

- |  |  |
|--|--|
| <ul style="list-style-type: none"> <li>• Introduction</li> <li>• Mechanism of Action</li> <li>• Sodium Potassium Tartrate</li> </ul> | <ul style="list-style-type: none"> <li>• Antimony Potassium Tartrate</li> <li>• Copper Sulfate</li> <li>• Important Questions/Answers</li> </ul> |
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## INTRODUCTION

Emetic is derived from the word emesis it means vomiting. Vomiting is defined as involuntary, forceful expansion of the contents in the stomach through mouth sometimes nose. Emetics are the drugs which give rise to forced regurgitation (emesis) by which the contents of the stomach get expelled through the oral cavity. Vomiting center is situated in medulla oblongata which is known as area postrema. It is administered orally or injection to induce vomiting.

## MECHANISM OF ACTION

The emetics act by two types:

### 1. Locally Acting Emetics

By local irritation of gastric mucosa, e.g. ammonium bicarbonate, ipecacuanha.

### 2. Centrally Acting Emetics

Directly on the chemoreceptor trigger zone (CTZ) in the floor of IVth ventricle in medulla, e.g. apomorphine and morphine.

In ancient times, salt water and mustard water used as emetic. It is added in cough preparation in small dose to stimulate the flow of respiratory tract secretion. They are very important in cases of poisoning as antidotes that are given before absorption of poison into intestines so it may help to expel out the toxic substance from the body. Strong coffee is one of the best domestic stimulants, especially after a narcotic poison. Emetics should not be given to children, in the early pregnant women, corrosive poisoning, in conditions like CNS depressions, unconscious or coma.

Inorganic substances include antimony potassium tartrate, zinc sulfate, copper sulfate and sodium chloride. The most common side effects of emetics are dehydration so the person must be kept hydrates by continuous administration of fluid and electrolytes.

## SODIUM POTASSIUM TARTRATE

*Molecular formula:* C<sub>4</sub>H<sub>4</sub>KNaO<sub>6</sub>

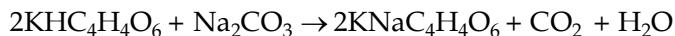
*Molecular weight:* 210.16

**Synonym:** Rochelle salt, seignette salt.

It is the double salt of sodium and potassium of tartaric acid.

### Preparation

It is prepared by boiling the solution of potassium bitartrate and sodium carbonate and allowed the reaction mixture to remain at 60°C for some time.



### Properties

It is a colorless to white crystalline powder with a cool and saline taste. It has a pH value of 6.5–8.5. It has a large piezometric effect which makes it widely useful in sensitive vibrational and acoustic devices. It is soluble in hot water and insoluble in alcohol. It should be stored in airtight containers.

### Uses

It is used as an emetic because of its irritant action on GI mucosa. It is used as a laxative and food additive in the form of stabilizer in cheese and meat products. It is used in the silvering of mirrors. It is one of the ingredients in Fehling's solution and used in the electroplating process. It is used in cigarette paper. It is one of the ingredients in biuret reagent to measure the concentration of protein. It is used as a common precipitant in protein crystallography.

## ANTIMONY POTASSIUM TARTRATE

*Molecular formula:* C<sub>4</sub>H<sub>4</sub>KO<sub>7</sub>Sb

*Molecular weight:* 333.93



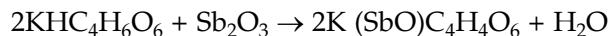
**Synonym:** Emetic tartar, tartarised antimony.

It is the double salt of potassium and antimony of tartaric acid.

**Category:** Expectorant, diuretic, systemic acidifier.

### Preparation

It is obtained by mixing 5 parts of antimony trioxide (Sb<sub>2</sub>O<sub>3</sub>) with 6 parts of potassium acid tartrate in a fine paste. Keep this paste aside for a day. Boil it with water for 15 minutes with constant stirring. The liquid is then filtered and left for crystallization.



### Properties

It occurs as colorless transparent crystals, odorless having a sweetish taste. On exposure to air crystals are efflorescence. It is soluble in water, glycerol but insoluble in alcohol. It should be stored in well-closed container at a cool place.

**Dose**

40–140 mg daily.

**Uses**

Initially, it is used as an emetic due to its irritant action on mucosa. It is administered by IV and should never be given by IM or subcutaneous because it causes severe pain and necrosis. It is also used in the treatment of schistosomiasis and leishmaniasis.

## COPPER SULFATE

*Molecular formula:* CuSO<sub>4</sub>. 5H<sub>2</sub>O

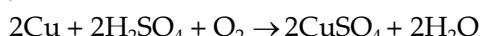
*Molecular weight:* 249.7

**Synonym:** Blue vitriol, cupric sulfate.

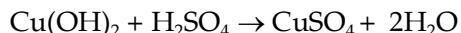
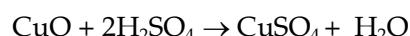
**IP limit:** As per IP it contains 98.5–101% of copper sulfate.

**Method of Preparation**

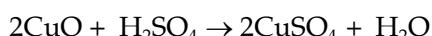
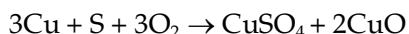
- It is prepared by treating granulated copper in presence of air with sulfuric acid. The oxygen of air assists the reaction.



- In laboratory, it is also prepared by dissolving cupric oxide or cupric carbonate or cupric hydroxide in dil. H<sub>2</sub>SO<sub>4</sub>



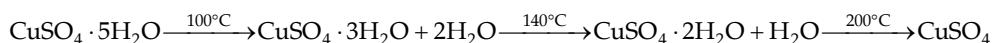
- Copper granules are heated with sulfur a mixture of copper sulfate and cupric oxide is obtained. The residue of CuO is again treated with dil. H<sub>2</sub>SO<sub>4</sub> to convert it to copper sulfate.

**Properties**

It is a hydrated salt exist in the form of deep blue crystals. It shows effervescence in dry air slowly. It is soluble in water but insoluble in alcohol. It is acidic in nature. It should be protected from air, moisture and heat.

**Chemical Properties**

- On heating at 100°C it loses two molecule of water, at 140°C it loses one molecule of water and at 200°C, white anhydrous salt is formed.

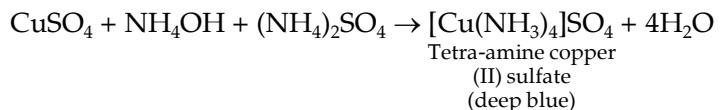
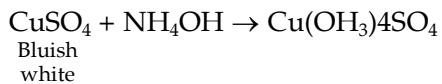


- On further heating at high temperature it decomposes into cupric oxide and sulfur dioxide gas.

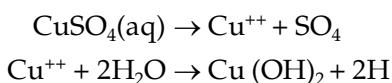


- Reaction with KI: KI reduces CuSO<sub>4</sub> to cuprous iodide which appears as white ppt while KI is oxidized to I<sub>2</sub>.

4. Reaction with  $\text{NH}_3$ : When  $\text{NH}_3$  is added to  $\text{CuSO}_4$  solution, a bluish white ppt of  $\text{Cu}(\text{OH})_2$  is formed which dissolves in excess ammonia forming tetra-amine copper (II) sulfate which is commonly known as Schweizer's reagent.

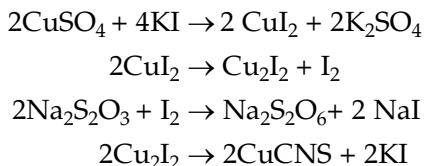


5. Action of water:  $\text{CuSO}_4$  gives acidic salt solution due to hydrolysis of  $\text{Cu}^{++}$  ion as it is salt of weak base and strong acid.



### Assay

It is assayed by the principle of oxidation-reduction reaction of iodine/thiosulfate. A solution of copper sulfate is first treated with potassium iodide and acetic acid. Cuprous iodide ( $\text{CuI}$ ) is formed with iodine and the liberated iodine is titrated with 0.1 N sodium thiosulfate using starch as an indicator. The titration is continued until blue color persists. Each ml of 0.1 N sodium thiosulfate is equivalent to 0.02497 gm of copper sulfate.



**Uses:** It is used as an emetic in a dose of 300 mg in 30 ml water. It is used as a germicide and insecticide in agriculture. A mixture of copper sulfate and lime, commonly known as Bordeaux mixture, is used as fungicide. It is used as electrolyte in purification of copper and electroplating of Cu. It is used in making Schweizer's reagent used for manufacturing of paper. It is an ingredient for Fehling's and Benedict's solution. It is considered to be chemical antidote for phosphorus poisoning.

### IMPORTANT QUESTIONS/ANSWERS

#### I. Multiple Choice Questions

1. Emetics are used to produce:
  - a. Dehydration
  - b. Vomiting
  - c. Alkalosis
  - d. All of the above
2. ..... is used as emetic in ancient times.
  - a. Salt water
  - b. Sugar solution
  - c. KI
  - d. None of these
3. Which official compound is used as emetic?
  - a. KI
  - b.  $\text{NH}_4\text{Cl}$
  - c. Potassium antimony tartrate
  - d. Potassium chloride

4. Emetics acts by:
  - a. On lungs
  - b. Decrease fluid viscosity
  - c. Decrease bronchial secretion
  - d. Stimulate the chemoreceptor trigger zone
5. Copper sulfate is also called .....
 

a. Blue vitriol	b. Yellow vitriol
c. Green vitriol	d. None of the above

**Answers**

1. b    2. a    3. c    4. d    5. a

**II. Fill in the Blanks**

1. Copper sulfate is used as antidote for ..... poisoning.
2. Sodium potassium tartrate is also known as .....
3. Antimony potassium tartrate is also known as .....
4. ..... is used as emetic in veterinary practices.
5. Sodium potassium tartrate acts an emetic due to .....

**Answers**

1. Phosphorus
2. Rochelle
3. Emetic tartrate
4. Hydrogen peroxide
5. Irritant action GI mucosa.

**III. Short and Long Answer Questions**

1. Define emetics. How they are useful in poisoning?
2. Differentiate vomiting and emetic.
3. Write a detail note on sodium potassium tartrate.
4. Discuss the preparation, properties, assay and uses of copper sulfate.
5. Write a note on antimony potassium tartrate.

# Hematinics

- Introduction
- Iron
- Ferrous Sulfate

- Ferrous Gluconate
- Important Questions/Answers

## INTRODUCTION

Hematinics are the substances which are required in the formation of blood and also used in the treatment of anemias. A hematinic is a nutrient required for the formation of blood cells in the process of hematopoiesis. The main hematinics are iron, vitamin B<sub>12</sub> and folate ions. These agents increase the number of erythrocytes or hemoglobin content in the blood. Anemia is a condition in which there is a deficiency of red cells or of hemoglobin in the blood, resulting in pallor and weariness.

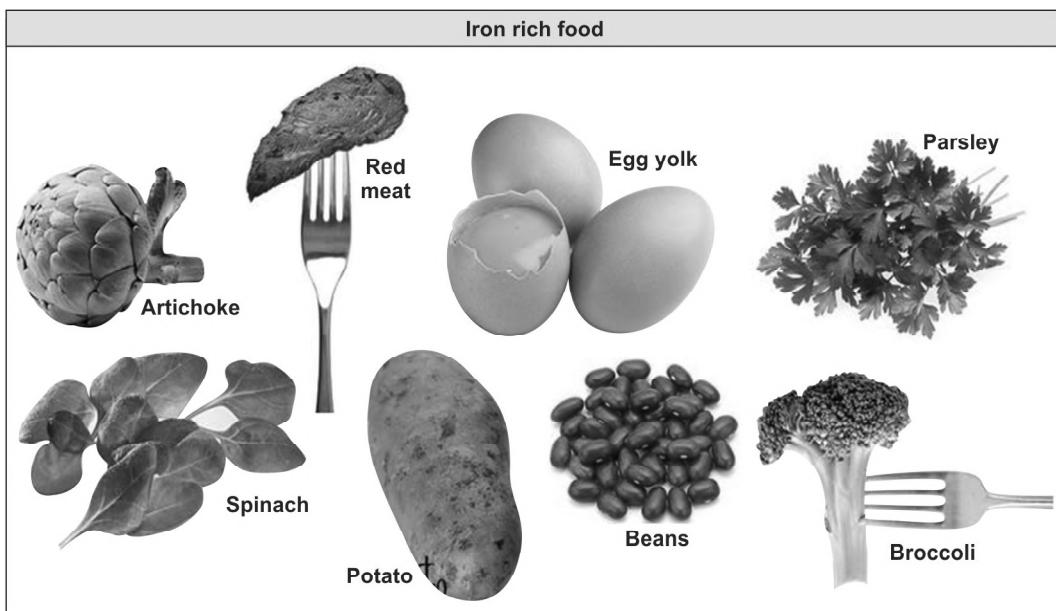
Anemia occurs when balance between production and destruction of RBCs are disturbed by blood loss (acute or chronic), impaired cell formation due to deficiency of essential factors, such as iron, vitamin B<sub>12</sub> and folic acid, bone marrow depression (hypoplastic), erythropoietin deficiency and increased cell destruction (hemolytic).

## IRON

Iron is one of the essential elements for the body. Total body iron content in an adult is 3.5 gm (average) which is found 50 mg/kg in men and 38 mg/kg in women. Iron is distributed in the body in form of 66% hemoglobin, 25% of ferritin and hemosiderin, 3% of myoglobin and 6% in parenchymal iron (in enzymes-cytochromes, peroxidases, catalases).

Hemoglobin is a protoporphyrin molecule which consists of four iron containing haeme residues as prosthetic group and four globin chain as apoprotein. It has 0.33% of iron, thus loss of 100 ml of blood means loss of 50 mg elemental iron. To raise 1 gm/dl about 200 mg elemental iron is required. It is stored only in ferric form (Fe<sup>3+</sup>) and in combination with apoferritin. The daily iron requirement of an adult is 0.5–1 mg for men and 1.5–2 mg/day for women.

Iron is very important component of metabolic processes which is responsible for the transport of molecular oxygen from respiratory chain. It is an essential constituent of blood cells and tissues. It is associated with types of proteins, such as hemoprotein, iron storage and transport proteins. Iron forms the nucleus of iron-porphyrin haem ring, which together with globin chains forms hemoglobin. Hemoglobin binds oxygen, transporting it from lungs to tissues.



### Physiological Functions of Iron

1. The primary function of iron is to form hemoglobin.
2. It is necessary for the formation and maturation of RBC.
3. It is responsible for the transport of oxygen in the form of oxyhemoglobin.
4. Cytochrome is an iron containing enzyme. It is concerned with the oxidation of metabolites in the cell.
5. Myoglobin of muscle is an iron containing chromoprotein. It combines with  $O_2$  and acts as an oxygen store for muscle.
6. The chromatin of the nucleus contains iron and thus helps in the functioning of nuclei.

Dietary sources of iron are wheat, vegetables, fruits, dry fruits, dry beans, egg yolk, liver and oyster. Medium sources of iron are meat, chicken, fish, spinach and apple. Poor sources of iron are milk and milk products. Iron deficiency occurs due to malnutrition, congenital atransferrinemia (inability to release iron from transferrin).

### Absorption of Iron

Iron absorption occurs mainly in the duodenum and upper jejunum and is influenced by many factors. Dietary iron must first be released from protein complexes by acid and proteases in the stomach. Solubilizing agents such as sugars and ascorbic acid enhance absorption, and phosphates and phytates in cereals form insoluble complexes with iron which inhibit its absorption. Iron that is of animal origin (haem iron) is more readily absorbed than non-haem iron found in cereals, and the ferrous ( $Fe^{2+}$ ) form is more soluble than the ferric ( $Fe^{3+}$ ) form. Iron uptake occurs both by active transport and passive diffusion and can be increased to 20–30% in iron deficiency or pregnancy. Iron overload decreases absorption by an unknown mechanism.

### Mechanism of Absorption

For absorption, iron is converted into ferrous form in presence of ferroreductase. Absorbed by two mechanisms:

1. On luminal surface of intestinal epithelial cells, divalent metal transporter 1 (DMT 1) is present, through which ferrous form of iron is actively transported. This new iron along with that splits from haem, are transported to blood across basolateral membrane by ferroprotein (ferriportin 1). It is then oxidized to ferric form by ferro-oxidase.
2. Haem iron (present in meat) is absorbed without conversion to elemental form.

### Regulation of Storage

If body requirements are low, iron is stored inside intestinal mucosal cells in form of ferritin. Ferritin is water-soluble complex consisting of a core of ferric hydroxide covered with a shell of specialized storage protein, apoferritin. If body requirements are high, more iron is transported across basolateral membrane to blood. In plasma, it binds transferrin, a globulin which binds to ferric iron. Transferrin-iron complex is carried to different organs including spleen, liver, and bone marrow. Transferrin acceptors (TFA) are present in these organs and as a result iron is internalized by these organs, and transferrin receptor complex are recycled to plasma.

### Factors Affecting Iron Absorption

Factors facilitating iron absorption

1. **Acid:** Acid enhances dissolution and reduction of ferric iron.
2. **Reducing substances:** Ascorbic acid reduces ferric iron and forms absorbable complexes.
3. **Meat:** Meat also facilitates iron absorption by increasing HCl secretion.
4. **Pregnancy/menstruation:** Due to increased iron requirement.

### Factors Impeding Iron Absorption

1. **Phosphates:** Phosphates are present in egg yolk.
2. **Phytates:** Phytates occur in wheat and maize.
3. **Alkalies:** Alkalies form non-absorbable complexes as well and oppose the reduction.
4. **Tetracyclines:** Tetracyclines impede absorption.
5. Presence of other foods in stomach.

### Transport of Iron

Transport occurs by transferrin, a  $\beta$ -globulin that binds two molecules of ferric iron, forming transferrin-iron complex. This complex binds transferrin receptors present in large number of erythroid cells. They bind and internalize the complex by receptor mediated endocytosis. In endosomes, ferric iron is released, and is reduced to ferrous form. It is then transported by DMT 1 into cells, used:

1. For Hb synthesis
2. Stored as ferritin

Transferrin-transferrin receptor (TfR) complex is recycled to cell membrane. Transferrin dissociates and returns to plasma. Increased erythropoiesis leads to increased number of transferrin receptors on cells. Iron deficiency leads to increased concentration of serum transferrin (Tf).

### **Utilization and Storage**

The released iron is utilized for hemoglobin synthesis or other purposes. Tf and TfR are returned to the cell surface to carry fresh loads.

It is stored into reticuloendothelial cell in liver, spleen, bone marrow, hepatocytes and myocytes.

### **Elimination**

Trace amounts of iron are lost in feces, urine, bile and sweat. Less than 1 mg/day of iron is lost.

### **Iron Deficiency Anemias**

Iron deficiency anemia manifests as hypochromic, microcytic anemia, in which:

1. Erythrocyte mean cells volume is low (MCV <80 fl).
2. Mean cell Hb concentration is low (MCHC <30%).

Infants, children during rapid growth, pregnant and lactating women and patients of chronic kidney disease (due to increased loss during hemodialysis) required increased iron requirements. Inadequate iron absorption has seen in gastrectomy.

### **Treatment of Iron Deficiency**

Oral and parenteral preparations can be used. Oral preparation is present in the form of salts like:

- Ferrous gluconate
- Ferrous sulfate
- Ferrous fumarate.

Both are equally effective but oral therapy is preferred. Parenteral preparations are given only in:

- Chronic anemia
- Impaired GI absorption
- Patients of chronic kidney disease undergoing dialysis
- Patients who cannot tolerate oral iron.

### **Oral Iron therapy**

Only ferrous salts are used because iron is absorbed only in ferrous form.

### **Preparations**

Iron salts	Tablet size	Iron in tablet	Adult (dose/day)	Iron salts
Ferrous sulfate (hydrated chocolate colored)	325 mg	65 mg	3–4	Ferrous sulfate (hydrated chocolate colored)
Ferrous sulfate (desiccated)	200 mg	65 mg	3–4	Ferrous sulfate (desiccated)
Ferrous gluconate	325 mg	36 mg	3–4	Ferrous gluconate
Ferrous fumarate	100 mg	33 mg	6–8	Ferrous fumarate

### Dose

50–100 mg iron can be incorporated into Hb daily. 25% of oral iron as ferrous salt can be absorbed. So, 200–400 mg/day elemental iron should be given.

Adverse effects of oral administration: Mainly GIT—nausea, gastric irritation, abdominal discomfort, altered bowel habits, black staining of stools (can mask GIT bleeding).

### Parenteral Iron Therapy

A colloid containing particle is made with a core of iron oxyhydroxide surrounded by a shell of carbohydrate (e.g. dextran polymers). In this way, bioactive iron is released slowly from stable colloid particles.

### Drawback

Parenteral administration of free inorganic ferric iron produces serious dose-dependent toxicity which limits the dose of iron.

### Forms of Parenteral Therapy

**Iron dextran:** Iron dextran can be given IM or IV. It is a stable combination of ferric hydroxide with low molecular weight dextran containing 50 mg elemental iron/ml of solution.

**Iron sucrose and sodium ferric gluconate complex:** Iron sucrose and iron sodium gluconate complex are two compounds given IV, however, they are less antigenic and allergic manifestations are less commonly encountered.

### Formula for Calculating Total Dose of Iron in Grams

$$\text{Dose of iron in grams} = 0.25 \times (\text{normal Hb} - \text{patients Hb})$$

$$\text{Iron requirement (mg)} = 4.4 \times \text{body weight (kg)} \times \text{Hb deficit (g/dl)}$$

[Hb = hemoglobin]

Iron levels should be monitored in parenteral therapy as it is not subjected to normal regulatory mechanism (as in oral therapy).

### Adverse Effects of Parenteral Route

Painful (especially IM injection of dextran), abdominal discomfort, nausea, vomiting, allergic manifestations, dizziness, headache, fever, arthralgia, urticarial and bronchospasm.

### Uses

It is used in:

1. Iron deficiency anemia: Nutritional deficiency, chronic blood loss (GIT—ulcers and hookworm).
2. Megaloblastic anemia.
3. As astringent: Ferric chloride.

Iron poisoning can be generally treated by gastric lavage, followed by giving sodium bicarbonate and sodium dihydrogen phosphate which are able to convert iron into insoluble iron salts.

### Types of Anemia

There are several types and classifications of anemia. The occurrence of anemia is due to the various red cell defects such as:

- Production defect (aplastic anemia)
- Maturation defect (megaloblastic anemia)
- Defects in hemoglobin synthesis (iron deficiency anemia)
- Genetic defects of hemoglobin maturation (thalassemia)
- Due to the synthesis of abnormal hemoglobin (hemoglobinopathies, sickle cell anemia and thalassemia)
- Physical loss of red cells (hemolytic anemias)
- The size of red blood cells is smaller than normal size (microcytic)
- Size of red blood cells larger than normal (macrocytic).

## FERROUS SULFATE

*Molecular formula:*  $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$

*Molecular weight:* 278.01

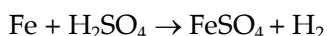
**Synonym:** Green vitriol

**IP limit:** As per IP it contains 98–105% of ferrous sulfate.

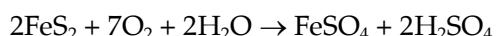
Pernicious anemia occurs in old people for lack of intrinsic factor which is essential for absorption of vitamin  $\text{B}_{12}$ .

### Method of Preparation

1. It is obtained from the reaction between elemental iron and sulfuric acid, to yield ferrous sulfate and hydrogen gas.



2. The commercial grade of this salt is made by piling in pyrites ( $\text{FeS}_2$ ) in heaps and exposing it to atmospheric oxidation. The mass is leached with water and the dilute solution of ferrous sulfate is run into large vats. The liquid is concentrated by crystallization.

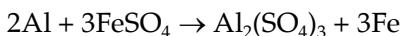


### Properties

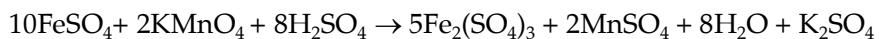
It is a bluish green crystalline powder, odorless and metallic in taste. On exposure to moist air, the crystals rapidly oxidize and become brown. It shows effloresces in dry air. It is soluble in water but insoluble in alcohol. It should be stored in airtight containers.

### Chemical Properties

1. Ferrous sulfate reacts with aluminum under displacement reaction forming aluminum sulfate and metallic iron.



2. Ferrous sulfate reacts with potassium permanganate in the presence of sulfuric acid forms ferric sulfate, manganese sulfate, potassium sulfate, and water.



3. When it is treated with ceric ammonium sulfate in acidic medium, it reduces ceric ion.

### **Identification**

Gives reaction of ferrous salts and the reaction of sulfates.

### **pH**

Between 3 and 4, determined in a 5% w/v solution.

### **Clarity of Solution**

Dissolve 2.5 gm in carbon dioxide-free water, add 0.5 ml of 1 M sulfuric acid and dilute to 50 ml with water. The solution is not more opalescent than opalescence standard.

### **Arsenic**

Dissolve 5 gm in 10 ml of water, add 15 ml of stannated hydrochloric acid and distil 20 ml. To the distillate add a few drops of bromine solution, remove the excess of bromine with a few drops of stannous chloride solution AsT and add 40 ml of water. The resulting solution complies with the limit test for arsenic (2 ppm).

### **Lead**

Make 25 ml of solution B alkaline with dilute ammonia solution, add 1 ml of potassium cyanide solution and sufficient water to produce 50 ml. Add 0.1 ml of sodium sulfide solution; the solution is not more intensely colored than a mixture of 10 ml of hydrochloric acid, 0.5 ml of nitric acid, 5 ml of lead standard solution (20 ppm Pb), 0.1 ml of sodium sulfide solution and sufficient water to produce 50 ml (50 ppm).

### **Chloride**

Dissolve 2.5 gm in carbon dioxide-free water, add 0.5 ml of 1 M sulfuric acid and dilute to 50 ml with water. Take 20 ml of solution complies with the limit test for chlorides (250 ppm).

### **Assay**

The assay is based on redox titration method. Dissolve 2.5 gm of sodium bicarbonate in a mixture of 150 ml of water and 10 ml of sulfuric acid. When effervescence ceases, add 0.5 gm of the substance being examined, accurately weighed, shake gently to dissolve and titrate with 0.1 M ceric ammonium nitrate using 0.1 ml of ferroin solution as indicator, until the red color disappears. Each ml of 0.1 M ceric ammonium nitrate is equivalent to 0.02780 gm of  $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ .

### Uses

It is used as hematinic agent in the treatment of anemia. It is also used to dye fabrics and in tanning leather.

### FERROUS GLUCONATE

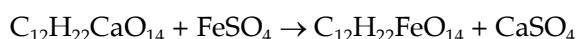
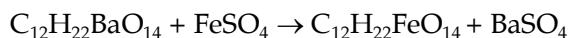
*Molecular formula:*  $C_{12}H_{22}FeO_{14} \cdot H_2O$       *Molecular weight:* 446.14 (anhydrous)

**Synonym:** Ferrous di (D-Gluconate), iron (II) gluconate

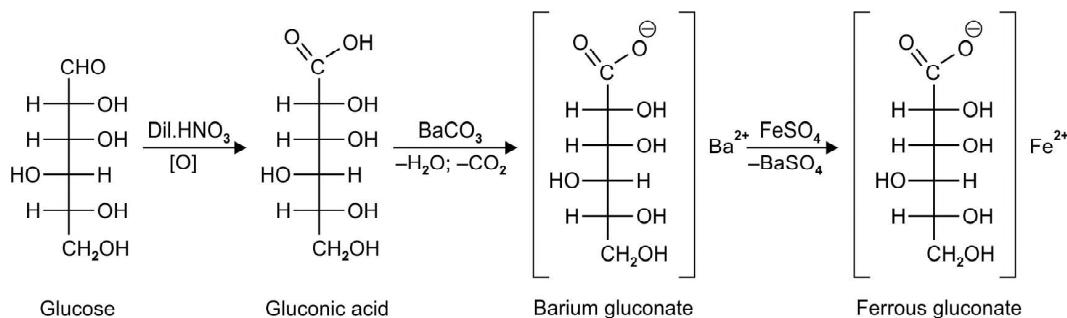
**IP limit:** As per IP it contains 95–102% of ferrous gluconate.

### Method of Preparation

1. It is prepared by double decomposition reactions between barium gluconate / calcium gluconate and ferrous sulfate.



2. The gluconate solution is first produced by the fermentative oxidation of glucose. The solution of gluconic acid is then treated with barium carbonate. The barium gluconate treated with ferrous sulfate and filtered. From the filtrate, the ferrous gluconate is crystallized. The salt contains one molecule of water of crystallization.



### Properties

It occurs as yellowish grey or pale greenish yellow fine powder or granules, odor, similar to burnt sugar. It is soluble in water but insoluble in alcohol. It should be stored in airtight containers and protected from light.

### Dose

Prophylactic, 600 mg daily; therapeutic, 1.2 to 1.8 gm daily, in divided doses (300 mg of ferrous gluconate is approximately equivalent to 35 mg of ferrous iron).

### pH

Between 4 and 5.5, determined in a solution prepared by dissolving 5 gm in carbon dioxide-free water at 60°, cooling and diluting to 50 ml with the same solvent (solution A), and measured 3–4 hours after preparation.

### **Clarity of Solution**

Dilute 2 ml of solution A to 10 ml with water. When examined against the light, the resulting solution is clear.

### **Arsenic**

To 5 gm add 15 ml of water and 15 ml of stannated hydrochloric acid, distil 22 ml and add to the distillate 40 ml of water and 0.2 ml of stannous chloride solution AsT. The resulting solution complies with the limit test for arsenic (2 ppm).

### **Heavy Metals**

Not >20 ppm, determined by method A, on a solution prepared in the following manner. Warm 2 gm gently with 10 ml of nitric acid until reaction begins and allows to stand until the evolution of nitrous fumes subsides. Boil gently to complete oxidation, adding a further 5 ml of nitric acid, if necessary, and continue boiling until the volume is reduced to about 5 ml. Add 20 ml of hydrochloric acid, boil gently for 1 minute, cool and extract with three quantities, each of 20 ml, of ether. If the acid solution is still more than faintly yellow, extract with a fourth quantity of 20 ml of ether and discard the ether extracts. Transfer the acid solution to a narrow-necked flask, rinse the separator with 5 ml of water, and add the rinsing's to the flask. Heat the solution to remove the dissolved ether and part of the hydrochloric acid. Cool and dilute to 50 ml with water. Use 25 ml for the test.

### **Chloride**

0.4 gm complies with the limit test for chlorides (625 ppm).

### **Sulfate**

0.3 gm complies with the limit test for sulfates (500 ppm).

### **Loss on Drying**

Between 5% and 10%, determined on 1 gm by drying in an oven at 105°.

### **Uses**

It is used as iron source for treatment of various anemias.

## **IMPORTANT QUESTIONS/ANSWERS**

### **I. Multiple Choice Questions**

1. Absorption of iron is inhibited by:
  - a. Antacids
  - b. Phosphates and tetracycline
  - c. Bicarbonates
  - d. All of the above
  
2. On which condition iron requirement increases:
 

a. Growth	b. Lactation
c. Pregnancy	d. All of the above

3. Ferrous sulfate is incompatible with:
 

a. Silver salts	b. Carbonates
c. Alkalies	d. All of the above
4. Ferrous sulfate crystals are ..... in color:
 

a. Blue	b. Red
c. Green	d. White
5. Which of the following enzymes having iron:
 

a. Catalase	b. Peroxidase
c. Both a and b	d. None of the above
6. Iron poisoning can be treated by:
 

a. Gastric lavage	b. Deferroxamine
c. Both a and b	d. None of the above
7. In adult, total iron content in our body:
 

a. 2.5–5 gm	b. 6–7 gm
c. 1–2 gm	d. 8–10 gm
8. Iron preparation can cause:
 

a. Nausea, vomiting	b. Staining of teeth
c. Constipation	d. All of the above
9. ..... is a condition in which there is a deficiency of red cells or of hemoglobin in the blood.
 

a. Emetic	b. Anemia
c. Abdominal irritation	d. None of the above
10. Ferrous sulfate is also known as:
 

a. Blue vitriol	b. Green vitriol
c. Yellow vitriol	d. White vitriol

**Answers**

1. d    2. d    3. d    4. c    5. c    6. c    7. a    8. d    9. d    10. b

**II. Fill in the Blanks**

1. ..... are the substances which are required in the formation of blood and also used in the treatment of anemias.
2. For absorption, iron is converted into ..... form in presence of .....
3. Iron absorption occurs mainly in the ..... and .....
4. ..... of iron can be incorporated into Hb daily.
5. Dietary sources of iron are ....., ..... and .....

**Answers**

1. Hematinics
2. Ferrous, ferroreductase
3. Duodenum, upper jejunum
4. 50–100 mg
5. Wheat, vegetables, fruits.

**III. Short and Long Answer Questions**

1. Define hematinics. Discuss the compounds used in hematinics.
2. What do you understand the term anemia? Classify various types of anemia.
3. Discuss the absorption and transportation of iron in our body.
4. Describe the preparation, properties, assay and uses of ferrous sulfate.
5. Write a detail note on iron.
6. Explain the factors affecting absorption of iron and storage regulation of iron.
7. Write a detail note on preparation, properties and uses of ferrous gluconate.

# Poison and Antidote

- Introduction
- Sodium Thiosulfate
- Sodium Nitrite

- Activated Charcoal
- Important Questions/Answers

## INTRODUCTION

A poison may be defined as any substance that when introduced into or absorbed by a living organism causes illness or death. The diagnosis of poisoning is often difficult. Poisoning occurs in many ways, such as occupational, accidental, criminal or suicidal, using recreational substances (cannabis, opiates, etc.) and intentional behavior.

The poisoning may be either accidental or intentional requires immediate support and symptomatic management. It means removal of poison from the body by emesis induction. The perfect support management and treatment mainly depends upon the identification of ingested poison or corrosive substance so that exact antidote can be used to counteract the poison.

Poisoning may be classified into:

1. **Intentional poisoning:** A person consumes the substance with intention of causing harm to that person, e.g. suicide.
2. **Unintentional poisoning:** If the person consumes the substance without knowing its toxic effects, e.g. accidental.
3. **Undetermined:** When the circumstances is not clear whether it is intentional or unintentional, e.g. poisoning due to pesticides or insecticides.

Other common causes are:

1. Due to overdose of drug.
2. Intentionally cyanide poisoning.
3. Poisoning of heavy metals which may occur metallic contamination of food and water by leaching process.

## Sign and Symptoms of Poisoning

Nausea, vomiting, diarrhea, muscle cramps, increased or decreased heart rate, decreased breath rate, partial consciousness and dilated pupils.

## ANTIDOTES

"Antidote is a chemical especially a drug that limits the effects of a poison", or "A way of preventing or acting against something bad".

It is an agent which counteracts as poisons. The term antidote is a Greek word 'Antididonai' meaning 'given against'.

According to WHO, "Antidote was defined as a therapeutic substance used to counteract the toxic action(s) of a specified xenobiotic." It reduces the overall burden of health service in managing of poisoning cases:



### Mechanism of Action of Antidotes

Antidotes act by different mechanism. The mechanisms of action of antidotes are given below:

1. Complex formation.
2. Metabolic conversion.
3. Prevention of toxic metabolite formation.
4. By changing the physiochemical nature of toxicant.
5. Antidote returns to normal function by repairing a defect.

### Classification of Antidotes

Antidotes are classified into three types according to mode of action.

#### **1. Physiological**

Producing opposite effects to that poison. They are also called antagonists, e.g. sodium nitrite in cyanide poisoning, which converts hemoglobin into methemoglobin in order to bind cyanide.

#### **2. Mechanical**

Prevent absorption of poison into the body or expel out the poison from the body by emesis or eliminate through urine, e.g. activated charcoal absorbs the poison prior to the absorption of intestinal wall.

#### **3. Chemical**

Change chemical nature of poison by converting the poison into inactive or harmless substance, e.g. sodium thiosulfate in cyanide poisoning which converts the toxic cyanide into nontoxic thiocyanate, EDTA (chelating agent for heavy metal poisoning).

### Inorganic Antidotes

1. In **cyanide poisoning**: Sodium nitrite and sodium thiosulfate
2. In **lead poisoning**: Sodium calcium edetate and dimercaprol.

### Cyanide Poisoning

Cyanide is a rapidly acting lethal agent. Its effects are very fast and can cause death within a few minutes. Hydrogen cyanide (formonitrile) is a gas. Hydrocyanic acid (liquid form) is a colorless or pale blue at the normal room temperature. It is volatile and flammable, diffuse either by air and explosives, very easy to mix with water. Other forms are sodium cyanide and potassium cyanide.

It takes place intentionally or accidentally to commit suicide. It may occur by inhalation of fumes of hydrocyanic acid, ingestion of cyanide inorganic salt or cyanide

releasing substances like cyanide, cyanogen, bitter almond, peach or apricot, photographic chemical and silver polishes. Consumption of 300 mg of potassium cyanide may cause death.

Cyanide is hazardous by:

- **Inhalation:** Rapid onset of action (seconds to minutes)
- **Ingestion:** Delayed onset (15–30 minutes)
- **Skin contact:** Delayed onset (15–30 minutes)

**Death occurs in 6–8 minutes after inhalation of a high concentration (2–5 mg/kg of it is lethal).**

### **Sources of Cyanide**

It is available in

- Low-dose in nature and in every product that we usually eat or use
- Cyanide can be produced by bacteria, fungi and algae
- Cyanide is found in cigarettes, motor vehicle fumes, food and the synthetic product
- Cyanide in seed plants, especially grains (cassava wild, wild tubers, intersection buffoonery, wild cherry, plum, apricot, wild amigdaline, jetberry bush, etc.).

### **Mechanism of Toxicity**

1. It produces cellular hypoxia by binding to ferric iron specially that present in cytochrome oxidase system. When it binds to this enzyme complex electron transport is inhibited (ATP will not produce) this is result in decrease cellular utilization of oxygen (hypoxia).
2. It inhibits cellular respiration (cytochrome a-a3).
3. Tissues cannot utilize oxygen.
4. Arterialization of venous blood.

### **Clinical Effects of Cyanide**

- **In CNS:** Headache, dizziness, seizures, coma
- **In cardiovascular:** Hypertension, bradycardia, hypotension, later in course, cardiovascular collapse
- **In pulmonary (lung):** Dyspnea, tachypnea, pulmonary edema, apnea
- **In gastrointestinal:** Nausea, vomiting, caustic effects.

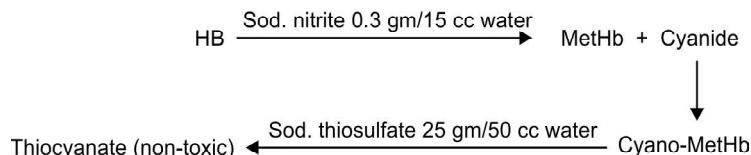
### **Treatment**

Sodium nitrite and sodium thiosulfate injections both antidotes one by one are administered to counteract this poisoning.

Sodium nitrite is used for this purpose because it has very weak vasodilator action. Nitrite generates ferrous ion of hemoglobin to the ferric ion of methemoglobin that has high affinity to cyanide radicals to form cyanomethemoglobin. This may again dissociates to release cyanide. Then sodium thiosulfate is administered to form sodium thiocyanate which is poorly dissociable and excreted through urine.

### Cyanide Antidote Kit

- Sodium nitrite (300 mg IV)  
–0.33 ml/kg of 10% solution
- Sodium thiosulfate (12.5 gm IV)  
–1.65 ml/kg of 25% solution



### Heavy Metal Poisoning

Poisoning of the body is due to various reasons. Heavy metal poisoning occurs due to intake of salts of arsenic, lead, mercury, iron and cadmium. It occurs because of overdose intake or incomplete metabolism in the body. Depending upon the content and type of heavy metal and the toxic effects can be seen in the patients. Most widely heavy metal antagonist used which will be able to form chelate or complex with the substance.

#### *Treatment*

Initially activated charcoal is given for absorbing heavy metals or poison followed by administration of compounds which are able to produce emesis to eliminate any poison left in the stomach or being absorbed in the circulation. Some inorganic compounds precipitate the heavy metals and prevent the absorption in blood circulation, e.g. activated charcoal, light kaolin, copper sulfate, magnesium sulfate and sodium phosphate.

### Lead Poisoning

Lead is a health hazard for all humans and important toxic heavy element in the environment. Especially children under the age of six are most at risk for lead poisoning. Lead toxicity causes hematological, gastrointestinal and neurological dysfunction. Lead inhibits some enzymes, alters cellular calcium metabolism. It stimulates synthesis of binding proteins in kidney, brain, bone and slows down nerve conduction. Acute lead poisoning is relatively infrequent and results from ingestion of acid soluble lead compounds or inhalation of lead vapors but chronic exposure to low levels of the metal is still a public health issue. Both occupational and environmental exposures to lead remain a serious problem in many developing and industrializing countries and a public health problem of global dimensions.

Lead is considered as a potent occupational toxin and toxicological manifestations are well known. In case of severe lead poisoning, dimercaprol, sodium calcium edetate are widely used and chelation therapy has also been used.

#### *Treatment*

Firstly remove the source of the lead. In more severe cases, chelation therapy can be used. This treatment binds to lead that has accumulated in the body. The lead is then

excreted through urine. Dimercaprol is more effective than sodium calcium edetate as chelating which lead from the soft tissues. Sodium calcium edetate leads from the bone and extracellular space and then expel out from the urine.

### **Universal Antidote**

It is used as an antidote when the exact cause of poisoning is unknown. It is a mixture of compounds. A mixture contains two parts of activated charcoal, one part tannic acid and one part magnesium oxide intended to be administered to the person who consumed poison. The mixture is ineffective and no longer used but activated charcoal is used as universal antidote for many poisons.

## **SODIUM THIOSULFATE**

*Molecular formula:*  $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$

*Molecular weight:* 248.17

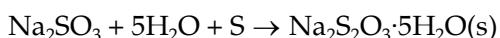
**Synonym:** Sodium hyposulfite

**Category:** Antidote to cyanide poisoning.

**IP limit:** As per IP, sodium thiosulfate contains 99–101% w/w of  $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ .

### **Preparation**

1. The solution of sodium sulfite treated with powdered sulfur wetted with small amount of ethanol and gently boiled under reflux for an hour. The obtained solution is filtered. The filtrate is evaporated to concentrate and cooled to 30°C and if any unchanged sodium sulfite is left it will separate as a crystal meal which is to be filtered off. The solution is left at room temperature in a crystallizing dish until an abundant crop of crystals is obtained.



2. It can be obtained by mixing sulfide liquors with sodium carbonate by passing  $\text{SO}_2$  gas.



### **Properties**

It occurs as large colorless crystals or coarse crystalline powder, odorless, having alkaline taste, deliquescent in moist air and effloresces in dry air at temperature above 33°. It dissolves in its water of crystallization at about 49°.

### **Solubility**

Very soluble in water; practically insoluble in ethanol (95%).

### **Storage**

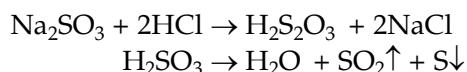
It should be stored in tightly-closed containers.

### **pH**

Between 6 and 8.4 of 10% w/v solution in carbon dioxide-free water.

### Chemical Properties

When sodium thiosulfate acidified with HCl, it decomposes to give sulfur dioxide, water and sulfur.



### Clarity and Color of Solution

10% w/v solution in carbon dioxide-free water is clear, and colorless.

### Arsenic

Dissolve 5 gm in 50 ml of water and add 10 ml of stannated hydrochloric acid AsT. The resulting solution complies with the limit test for arsenic (2 ppm).

### Heavy Metals

Not >20 ppm, determined by method A.

### Chloride

To 12.5 ml of 10% w/v solution in carbon dioxide-free water add 15 ml of 2 M nitric acid, boil gently for 3–4 minutes, cool and filter. The filtrate complies with the limit test for chlorides (200 ppm).

### Sulfide

To 10 ml of 10% w/v solution in carbon dioxide-free water add 0.05 ml of a freshly prepared 5% w/v solution of sodium nitroprusside; the solution does not become violet.

### Sulfate and Sulfite

Dilute 2.5 ml of 10% w/v solution in carbon dioxide-free water to 10 ml with distilled water. To 3 ml of this solution add 2 ml of iodine solution and gradually add more iodine solution and dilute to 15 ml with distilled water. The resulting solution complies with the limit test for sulfates (0.2%).

### Assay

Weigh accurately about 0.5 gm, dissolve in 20 ml of water and titrate with 0.05 M iodine using starch solution, added towards the end of the titration, as indicator. Each ml of 0.05 M iodine is equivalent to 0.02482 gm of  $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ .

### Uses

It is used as antidote for cyanide poisoning and titrant for titrimetry. It is also used to treat parasitic skin diseases. It is used as a fixer in photographic work as hypo solution.

## SODIUM NITRITE

*Molecular formula:*  $\text{NaNO}_2$

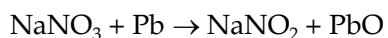
*Molecular weight:* 68.99

**Synonym:** Nitrous acid sodium salt.

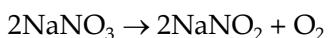
**Category:** Antidote to cyanide poisoning.

### Preparation

1. Sodium nitrate and elemental lead are heated with constant stirring using an iron spatula. After the reaction is complete, the mass is cooled. The sodium nitrite is extracted with hot water. To precipitate the lead which has gone into the solution, carbon dioxide is passed for a few minutes. The solution is filtered and neutralized cautiously with a very little dilute nitric acid. The solution is evaporated to a small volume to obtain crystals, filtered, washed with alcohol.



2. It is prepared by strongly heating sodium nitrite.



### Properties

It is an odorless, colorless to yellowish white crystalline solid. Its taste is saline.

### Solubility

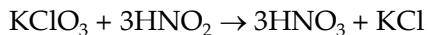
Soluble in water; practically insoluble in ethanol (95%).

### Storage

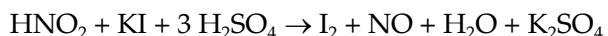
Store in tightly-closed containers.

### Chemical Properties

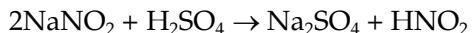
1. Sodium nitrite acts as a reducing and oxidizing agent. It is readily oxidized by  $\text{KMnO}_4$  or  $\text{KClO}_3$ .



When nitrites react as oxidizing agents, the reduced product will be nitric oxide.



2. It is easily decomposed by acidification with dil.  $\text{H}_2\text{SO}_4$ .



### Uses

It is used as an

- Antidote to cyanide poisoning
- Food additive
- Inhibition of lipid oxidation
- Inhibition of microbial growth.

## ACTIVATED CHARCOAL

Charcoal is a dark grey residue. It consists of carbon and any remaining ash obtained by removing water and other volatile constituent from animal and vegetable substances.

## Preparation

1. Activated charcoal is simply burnt wood that has had all the oxygen removed through controlled oxidation and or processing by steam. The obtained residue consists of nearly pure carbon.
2. It is prepared from vegetable matter by suitable carbonization processes.
3. Activation of charcoal: It is having high adsorption power. Due to its absorptive power, it could be extremely increased by treating it with various substances, such as air, steam, CO<sub>2</sub>, oxygen, sulfuric acid, zinc chloride, phosphoric acid or combination of these substances at 500–900°C. In this process, the activating substance presumably removes previously absorbed substances on charcoal and breaking down the granules of carbon into smaller ones.

## Properties

It occurs as a light black powder, free from grittiness and odorless. It should be stored in airtight container and protected from moisture.

## Mechanism of Charcoal

Internally as an antidote and remedy, charcoal works by binding drugs and poisons within the gastrointestinal tract. This allows their transfer out of the body in a harmless form. Charcoal absorbs like a sponge, and renders poisons harmless. It can do varied tasks because of its amazing ability to attract other substances to its surface and hold onto them until they exit the body.

Charcoal used as an antidote however how charcoal work with drug or aspirin poisoning.

- The most common drug poisoning is from aspirin. Charcoal should be given within the first 30 minutes of an overdose.
- Powdered charcoal reaches its maximum rate of absorption rapidly, within 1 minute. The sooner it is given the better the chances of successful treatment.
- Charcoal given after 1 hour of fast absorbing drugs, like aspirin, is usually only about 10% effective.

Common side effects of charcoal antidotes are: Black stools (severe), diarrhea (less severe), throwing up (less severe).

Rare side effects of charcoal antidotes are: Stomach cramps (severe), swelling of the abdomen (less severe).

## Uses

1. As an antidote, activated charcoal is mainly known both for its use in drug overdoses and chemical poisonings.
2. Charcoal acts to purify and cleanse the body due to its amazing ability to attract poisons to itself.
3. Charcoal has a wide range of absorption. Heavy metals, viruses, bacterial and fungal toxins, etc. are all absorbed effectively.
4. Activated charcoal often absorbs more than its own weight of injurious materials.
5. It is used in overdose of aspirin.
6. It is used as protective and adsorbent.

7. It is used to filter toxin from blood and kidney diseases.
8. It is also used as burning fuel.

## IMPORTANT QUESTIONS/ANSWERS

### I. Multiple Choice Questions

1. An antidote is used to:
  - a. Absorb the poison
  - b. To counteract the poison
  - c. Reduce hypersensitivity
  - d. All of the above
2. Poisoning occurs in:
  - a. Accidental
  - b. Insecticides
  - c. Recreational substances
  - d. All of the above
3. Cyanide poisoning is treated by combine use of:
  - a. Sodium nitrite, sodium thiosulfate
  - b. Sodium nitrite, sodium bicarbonate
  - c. Sodium nitrite, sodium carbonate
  - d. Sodium nitrite, sodium chloride
4. Which therapy is used for lead poisoning?
  - a. Occupational therapy
  - b. Inhalation therapy
  - c. Chelation therapy
  - d. None the above
5. Which one is the physiological antidote?
  - a. Sodium chloride
  - b. Sodium bicarbonate
  - c. Zinc chloride
  - d. Sodium nitrite
6. ..... is used to absorb the poison.
  - a. Activated charcoal
  - b. Potassium iodide
  - c. Zinc sulfate
  - d. None of the above
7. Mechanism of antidotes is:
  - a. Neutralize the effect of poison
  - b. It inhibits cellular respiration
  - c. Tissues cannot utilize oxygen
  - d. All of the above
8. Symptoms of poisoning are include:
  - a. Trouble in breathing
  - b. Paralysis
  - c. Confusion
  - d. All of the above
9. Heavy metal poisoning is treated by:
  - a. Administration of compounds which are able to produce emesis
  - b. Activated charcoal
  - c. Both a and b
  - d. None of the above
10. Sodium thiosulfate is also known as:
  - a. Sodium hyposulfite
  - b. Sodium monosulfite
  - c. Sodium hyposulfite
  - d. None of the above
11. Which one is the mechanical antidote:
  - a. Magnesium sulfate
  - b. Copper sulfate
  - c. Activated charcoal
  - d. All of the above

12. Antidote for lead poisoning:

  - a. Dimercaprol
  - b. Atropine
  - c. Ethanol
  - d. All of the above

13. Cyanide poisoning has a characteristic odor of .....

  - a. Fruit
  - b. Bitter almonds
  - c. Lemon
  - d. Wheat

14. ..... is prepared from vegetable matter by suitable carbonization processes.

  - a. Sodium nitrite
  - b. Activated charcoal
  - c. Sodium sulfate
  - d. Magnesium sulfate

15. Which type of antidote reduces the poison across the intestine?

  - a. Physiological antidote
  - b. Mechanical antidote
  - c. Chemical antidote
  - d. None of the above

## Answers

1. b    2. d    3. a    4. c    5. d    6. a    7. d    8. d    9. c    10. a    11. d  
12. a    13. b    14. b    15. b

## **II. Fill in the Blanks**

1. The poisoning may be either accidental or intentional requires immediate ..... and .....  
.....
  2. Molecular formula for sodium thiosulfate .....
  3. Assay of sodium thiosulfate is based on ..... titration method.
  4. ..... is used as a fixer in photographic work as hyposolution.
  5. ..... is the first choice of antidote when the cause of poisoning is unknown.
  6. Cyanide poisoning kit contains ..... and .....
  7. Sodium nitrite acts as a ..... and ..... agent.
  8. ..... antidotes act by producing opposite effects to that poison.
  9. ..... is used as a food additive.
  10. ..... is a substance that when introduce into or absorbed by a living organism causes illness.

## Answers

1. Supportive therapy, symptomatic management
  2.  $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$
  3. Iodimetry
  4. Sodium thiosulfate
  5. Activated charcoal
  6. Sodium nitrite, sodium thiosulfate
  7. Oxidizing and reducing
  8. Physiological
  9. Sodium nitrite
  10. Poison.

**III. Short Answer Questions**

1. What are antidotes? Classify antidotes with examples.
2. Differentiate poison and antidote.
3. Differentiate between mechanical and physiological antidote.
4. Which antidote is used for cyanide poisoning? Explain with its mechanism of action.
5. Explain universal antidote.
6. Discuss the role of activated charcoal in poisoning.

**IV. Long Answer Questions**

1. Define antidotes and discuss its mechanism of action.
2. Give a detail note on heavy metal poisoning and its treatment.
3. Discuss the preparation, properties, assay and uses of sodium nitrite.
4. Explain the preparation and uses of sodium thiosulfate.
5. Write a note on lead poisoning and its treatment.

# Astringents

- Introduction
- Zinc Sulfate

- Potash Alum
- Important Questions/Answers

## INTRODUCTION

Astringent is substance that causes the contraction or shrinkage of tissue that dry up secretions. Astringent acts as protein precipitant and arrest discharge by causing shrinkage of tissue. It forms protective layer on the surface and stops bleeding by constricting the blood vessels. Astringent is applied to skin, mucous membrane and does not destruct the tissue. The word ‘astringent’ is derived from Latin word ‘*adstringere*’ means ‘to bind fast’. A small quantity of astringent applied to wound to stimulate the growth of new tissues while in larger quantity produces irritation.

Zinc oxide and calamine are astringents used in lotions, powders and ointments.

It is used in much diluted form and is used topically.

1. If suffer from oily skin, astringent can help improve your skin’s appearance by minimizing pores and drying up oily skin.
2. Astringent is usually applied after cleansing, but before moisturizing.
3. The alcohol based product can also help remove bacteria and leftover traces of cleanser or make-up.
4. An astringent is also used to improve blood circulation and tighten the skin besides. One such example is the Stolin Gum Astringent aimed at total oral hygiene.
5. Used to treat hemorrhoids.

## Mechanism of Protein Precipitation

Skin made up of lipids and proteins which contain peptides. Transition metal cations have protein precipitation action. If very dilute solution of this cation is used over a tissue, it causes shrinkage on surface of the skin this is known as astringent action. It means atoms which are capable to form metallic bonds, i.e. chelation of metal with protein. The complexation of important functional groups at the protein site of action causes a drastic change in the properties of proteins. It hardens the epidermis of the skin and makes barrier against infection.

Inorganic astringents are salt of iron, zinc, manganese, iron and bismuth, aluminum sulfate, alum, zinc chloride, zinc sulfate, zirconium oxide and zirconium silicate.

### Uses of Astringents

- Styptic to arrest minor bleeding by coagulation of blood
- Anti-perspirant to reduce perspiration by constricting pores of skin
- Anti-inflammatory action
- At high concentration to remove unwanted tissue growth
- Internally they can use in diarrhea
- As cosmetic as skin tone and bring out the hardening effect
- In dental products it can promotes hardening the gums
- It reduces the cell permeability.

### ZINC SULFATE

*Molecular formula:*  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$

*Molecular weight:* 287.54

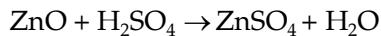
**Synonym:** White vitriol.

**Category:** Astringent

**IP limit:** As per IP, zinc sulfate contains not <99% and not >104% of  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ .

### Preparation

1. By the reaction of zinc oxide with sulfuric acid



2. Small quantity of zinc carbonate adds to the sulfuric acid at a time, stirring between additions and allowing any effervescence to die away before adding more. Filter the solution into an evaporating basin. Slowly evaporate the solution until it is about one-fifth of its original volume. Allow the concentrated solution to cool until crystals form. Filter off the crystals and put the filter paper and crystals on a watch glass and dab dry with another piece of filter paper. Cover them with a piece of clean filter paper and leave them to dry at room temperature.



### Properties

It occurs as colorless, transparent crystals or white, crystalline powder, odorless, efflorescent and astringent taste.

### Solubility

Very soluble in water; practically insoluble in ethanol (95%).

### Storage

Store in tightly-closed, non-metallic containers.

### pH

Between 4.4 and 5.6, determined in 5% w/v solution.

### Clarity and Color of Solution

5% w/v solution is clear, and colorless.

### Arsenic

Dissolve 1 gm in 50 ml of water and add 10 ml of stannated hydrochloric acid AsT. The resulting solution complies with the limit test for arsenic (10 ppm).

### Iron

2 ml of 5% w/v solution diluted to 10 ml with water complies with the limit test for iron (100 ppm). Use 0.5 ml of thioglycolic acid in the test.

### Chloride

20 ml of 5% w/v solution complies with the limit test for chlorides (250 ppm).

### Incompatibility

It is incompatible with carbonates, hydroxides and with astringent infusions and decoctions.

### Assay

Weigh accurately about 0.5 gm and dissolve in 5 ml of 2 M acetic acid and dilute to 50 ml with water. To the resulting solution add about 50 mg of xylenol orange triturate and sufficient hexamine to produce violet-pink color. Add a further 2 gm of hexamine and titrate with 0.1 M disodium edetate until the color changes to yellow. Each ml of 0.1 M disodium edetate is equivalent to 0.02875 gm of  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ .

### Uses

It is widely used as an astringent and emetic. Water-soluble zinc is used as supplements for zinc deficiency. It is also used as topical agent and mild germicidal. It is used in preparation of bandages and adhesive tapes. It also has local styptic action. It is also used as ophthalmic astringents (0.25% aqueous solution). It is used in narcotic poisoning as a reflex emetic.

## POTASH ALUM

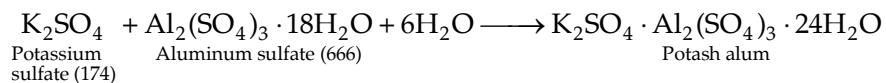
*Molecular formula:*  $\text{KAlSO}_4 \cdot 12\text{H}_2\text{O}$

*Molecular weight:* 474.37

**Category:** Astringent.

### Preparation

Potash alum is prepared by dissolving an equimolar mixture of hydrated aluminum sulfate and potassium sulfate in minimum amount of water containing a little of sulfuric acid and then subjecting the resulting solution to crystallization, when octahedral crystals of potash alum separate out.



### Properties

It occurs as colorless granular crystalline powder, odorless and sweet astringent taste.

**Solubility**

Soluble in water, soluble in glycerin, insoluble in alcohol.

**Storage**

It should be stored in well-closed container at a cool place.

**Uses**

Alum precipitates proteins and is most powerful topical astringent. It also has local styptic action. It is used as antiseptics and preparation of toxoids.

**IMPORTANT QUESTIONS/ANSWERS****I. Multiple Choice Questions**

1. Astringent acts by:
  - a. Protein precipitation
  - b. Constriction of capillaries
  - c. Harden the skin
  - d. All of the above
2. Astringent causes ..... on surface of the skin.
  - a. Shrinkage
  - b. Elongation
  - c. Harden the skin
  - d. All of the above
3. Zinc sulfate is also known as .....
  - a. Blue vitriol
  - b. White vitriol
  - c. Green vitriol
  - d. Yellow vitriol
4. Potash alum is used as:
  - a. Antidote
  - b. Antacid
  - c. Topical astringent
  - d. All of the above
5. Topical astringents are used to .....
  - a. Firm up the skin
  - b. Skin irritation
  - c. Skin permeation
  - d. All of the above
6. Zinc sulfate is prepared by the action of ..... with sulfuric acid.
  - a. Zinc carbonate
  - b. Zinc oxide
  - c. Aluminum sulfate
  - d. All of the above
7. ..... astringent is used in the treatment of narcotic poisoning.
  - a. Zinc chloride
  - b. Zinc oxide
  - c. Zinc sulfate
  - d. All of the above
8. Zinc sulfate is stored in ..... containers.
  - a. Metallic
  - b. Glass
  - c. Plastic
  - d. Non-metallic

**Answers**

1. d
2. a
3. b
4. c
5. a
6. b
7. c
8. d

**II. Fill in the Blanks**

1. Disodium edetate is a ..... agent.
2. In assay of zinc sulfate ..... is added to maintain the pH 5–6.

3. ..... and ..... are astringents used in lotions, powders and ointments.
4. ..... used as topical agent and mild germicidal.
5. Potash alum is prepared by dissolving an equimolar mixture of hydrated ..... and .....
6. Taste of alum is .....

**Answers**

1. Complexing agent
2. Hexamine
3. Zinc oxide, calamine
4. Zinc sulfate
5. Aluminum sulfate and potassium sulfate
6. Sweet astringent taste.

**III. Short and Long Answer Questions**

1. Define astringent. Discuss the mechanism of astringents.
2. Write any two pharmaceutical uses of alum.
3. Write down the incompatibility of zinc sulfate.
4. Explain preparation, properties, assay and uses of zinc sulfate.
5. Describe the preparation and uses of potash alum.
6. Explain in detail about uses of astringent.

# Radiopharmaceuticals

- |   |   |
|---|---|
| <ul style="list-style-type: none"> <li>• Introduction</li> <li>• Radioactivity and Rays</li> <li>• Isotopes</li> <li>• Radioactive Decay</li> <li>• Units of Radioactivity</li> <li>• Radioactive Dosimetry</li> <li>• Half-life</li> <li>• Detection Methods of Radioactivity</li> <li>• Measurement of Radioactivity</li> </ul> | <ul style="list-style-type: none"> <li>• Storage, Handling and Precautions of Radioactive Material</li> <li>• Radiopaque Contrast Media</li> <li>• Barium Sulfate</li> <li>• Sodium Iodide (<math>^{131}\text{I}</math>)</li> <li>• Pharmaceutical Applications of Radioactive Substances</li> <li>• Important Questions/Answers</li> </ul> |
|---|---|

## INTRODUCTION

An atom is the smallest particle of the substance which can be identified from the element. An atom consists of central nucleus surrounded by electrons. Group of atom joined together are called molecules. The nucleus containing positively charged protons and neutrons (no charge).

Radiopharmaceutical is a branch of science that deals with the study of the radioactive compounds which are used for the diagnosis and therapeutic treatment of human diseases. It is used to treat tumors, diagnose thyroid and other metabolic disorders including brain function. Radioactive substances are those substances which emit continuous radiation spontaneously by itself, to decompose to stable nuclei. The emission of radiation is not depending by pressure, temperature and catalyst.

### Discovery of Radioactivity

In 1895, Wilhelm Roentgen discovered that invisible rays were emitted when electrons bombarded the surface of certain materials and can darken photographic plates and the invisible high-energy emissions named X-rays. In 1896, the French scientist Henry Becquerel accidentally discovered that certain minerals were constantly producing energy rays that could penetrate matter. Becquerel determined that:

1. All the minerals that produced these rays contained uranium
2. The rays were produced even though the mineral was not exposed to outside energy.

He called them uranic rays because they were emitted from minerals that contained uranium (like X-rays) but not related to phosphorescence. Then Marie Curie discovered few more radioactive elements like polonium and radium.

Isotopes are atoms of the same element that have different numbers of neutrons. Isotopes of atoms with unstable nuclei are called radioisotopes. Radioisotopes showed

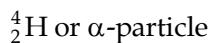
radioactive phenomena, i.e. radioactivity. The phenomenon of spontaneous emission of certain kind of invisible radiation by certain substances is called radioactivity. Substances which contain radioisotopes and emit such radiation are called radioactive substance. It is a natural and spontaneous process by which the unstable atom of one element emits or radiates excess energy in the form of particles or waves. The emitted particles or waves are called ionizing radiations due to their ability to remove electrons from the atom of any matter they interact with.

## RADIOACTIVE RAYS

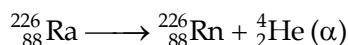
Radioactive radiations are composed of three different rays which differ very much in their nature and properties. The most common form of radiations emitted has been traditionally classified as  $\alpha$ -rays,  $\beta$ -rays,  $\gamma$ -rays.

### Alpha Rays

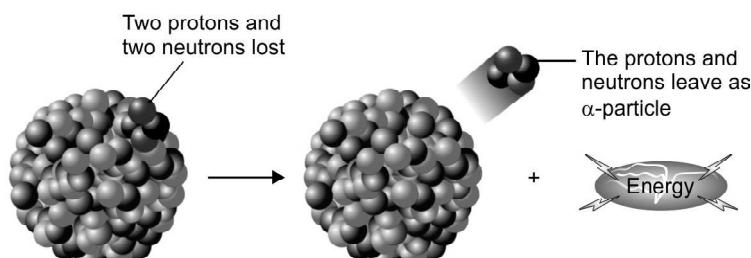
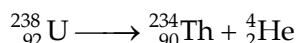
1. These  $\alpha$ -rays are the positively charged particles as they are produced when the heaviest element decay.
2. As a particle contains two protons and two neutrons, having a mass of 4 amu and these are similar to helium atom.



3. These particles are large and heavy in nature, so cannot penetrate but easily get absorbed.
4. Due to less penetration of  $\alpha$ -particles, elements which emit them do not find any use in biological application as they cannot penetrate tissues.
5. When a radioactive element emits  $\alpha$ -particles, the resulting nucleus will have its atomic number <2 and mass number will be <4 units as compared to the original.

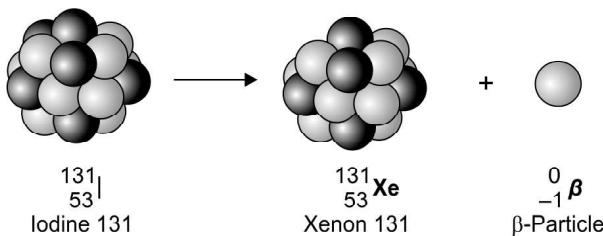
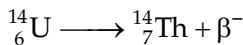


6. It travels 2.5 cm in air and penetrate skin only 0.3 mm.
7. They get deflected in electric and magnetic field and they produce fluorescence and phosphorescence in some materials such as zinc sulfide.
8. Their energy is about 6 MeV.
9. They ionize the gas through which they pass, e.g. isotope of thorium 234 from uranium 238. Here two protons and two neutrons lost from uranium 238 and these protons and neutrons are leave as an  $\alpha$ -particle.



### $\beta$ -Rays

- These rays or particles are negatively charged, much lighter energy particles and have less ionizing power than  $\alpha$ -particles.
- During the emission of  $\beta$ -particles from element does not alter the atomic mass and atomic number increases by one unit, e.g. isotope of carbon 14 and iodine 131.



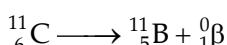
The  $\beta$ -particle that is emitted during  $\beta$  decay has high energy and can penetrate human skin and damage cells.

- $\beta$ -Particles are smaller (8000 times) than the  $\alpha$ -particles, having negligible masses, higher speed and thus these particles are much more penetrating than  $\alpha$ -particle.
- They have less ionizing power than  $\alpha$ -particle
- Their energy ranges from 2–3 MeV.
- It travels 4.5 m in air and penetrates skin only 4 mm.

$\beta$ -Particles can be classified into two types.

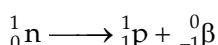
#### 1. Positron Emission

Positron is a type of  $\beta$ -particle, in which a proton inside a radionuclide nucleus is converted into a neutron and as they are short lived. Positron has a charge of +1 e and negligible mass (anti-electron) and similar to  $\beta$ -particles in their ionizing and penetrating ability. When an atom loses a positron from the nucleus, its mass number remains the same and atomic number decreases by 1 unit. Positrons result from a proton changing into a neutron. Isotopes which undergo this decay and thereby emit positrons are include iodine 121, nitrogen 13, oxygen 15, carbon 11, aluminum 26, sodium 22 and fluorine 18.



#### 2. Electron Emission or Negatrons

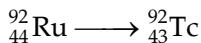
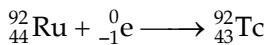
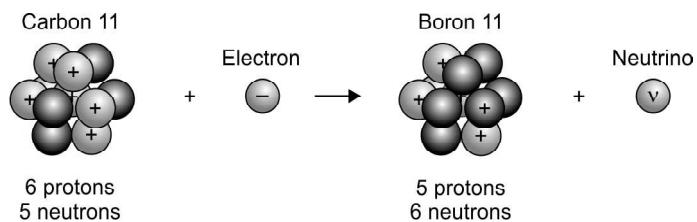
These are emitted by unstable nuclei in which neutrons are transformed into protons with  $\beta$  emission.



where the released proton particle has the same mass as that of original atom while the  $\beta$ -particle has charge as an electron.

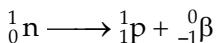
### Electron Capture

It occurs when an inner orbital electron is pulled into the nucleus and there is no particle emission. But it changes atom and same result as positron emission. Proton combines with the electron to make a neutron, its mass number stays the same and atomic number decreases by one.

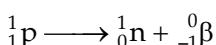


### Particle Changes

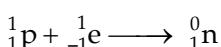
$\beta$  Emission—neutron changing into a proton



Positron emission—proton changing into neutron

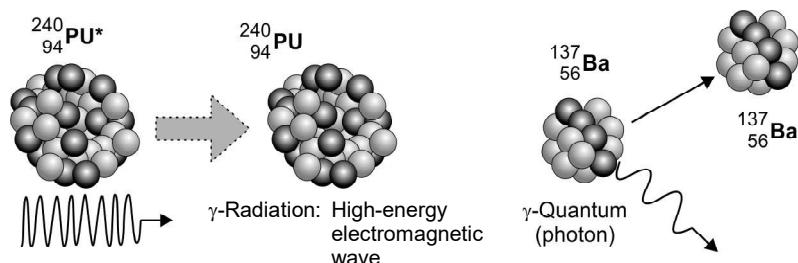


Electron capture—proton changing into neutron



### $\gamma$ -Rays

$\gamma$ -Rays are high energy photons of light. They do not have any charge or mass on them. It travels with the same velocity of light. It has shorter wavelength than the visible light. Like X-rays. It has least ionizing, but most penetrating power. When  $\gamma$ -rays are emitted from a radioactive element, no change or loss of atomic mass or number takes place, only there is lowering of nuclear energy. It produces heat on the surface on which they fall and knock out electrons from it. So, they can produce nuclear reaction (Table 5.1).



**Table 5.1:** Properties of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -radiations

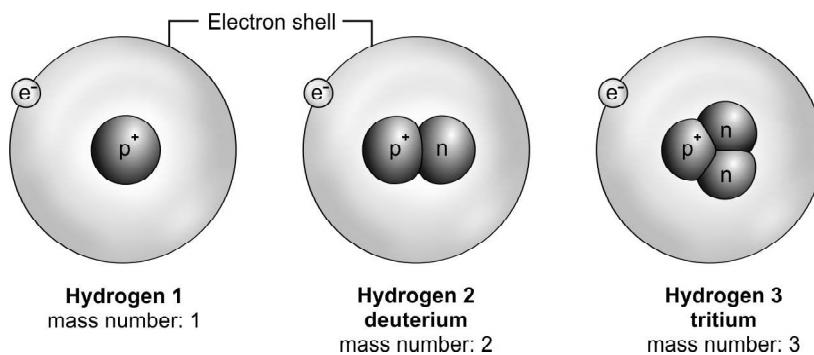
Property	Type of radiation		
	$\alpha$	$\beta$	$\gamma$
Charge	Positive (+1)	Carry 1 unit of negative (-1)	They are neutral (no charge - 0)
Mass (each particle has)	$4 \text{ amu}$ ( $6.64 \times 10^{-24} \text{ g}$ )	$5.5 \times 10^{-4} \text{ amu}$	Negligible mass
Relative penetrating power	Small	100 times that of $\alpha$ -rays	10000 times that of $\alpha$ -rays
Nature of radiation	${}_2^4\text{He}$ nuclei	Electron	High-energy photons
Velocity	$3 \times 10^7 \text{ ms}^{-1}$	$2.97 \times 10^8 \text{ ms}^{-1}$	$3 \times 10^8 \text{ ms}^{-1}$

## ISOTOPES

Nucleus contains protons and neutrons and electron circles the nucleus in orbits. Protons are having +1 charge with mass number (MN) of 1 and neutrons do not carry charge (0) with MN of 1, whereas electrons carry negative (-1) charge with MN nearly zero.

**Isotopes** are having same number of protons but different number of neutrons; or **Isotopes** are having same atomic number but different mass numbers.

The nucleus of an isotope is called nuclides. Nuclides have same number of protons but different number of neutrons. They are chemically same but have physical properties are different due to different number of neutrons, e.g. hydrogen has three isotopes which are shown below.



Isotopes are classified into two types.

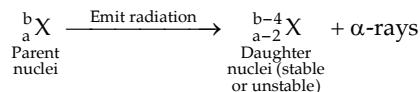
### 1. Stable Isotopes

Isotopes which are stable in nature and do not emit any kind of radiation. e.g.  $^{13}\text{C}$ ,  $^{35}\text{Cl}$ ,  $^1\text{H}$  (protium),  $^2\text{H}$  (deuterium).

### 2. Radioactive Isotopes

Radioactive isotopes are also called radioisotopes. These are naturally occurring or artificially created radioactive isotope of a chemical element. A version of a chemical element that has an unstable nucleus and emits radiation during its decay to a stable form reached. The original nuclide is called the parent (undergoes decay) and the

product is termed daughter nuclide. The stable end product is a non-radioactive isotope of another element. This phenomenon of nuclear changes is termed disintegration or radioactive decay, e.g.



Radioactive isotopes are of two types:

1. **Naturally occurring:** It occurs in nature.

*Examples:* U<sup>235</sup> (uranium), Ra<sup>226</sup> (radium), Rb<sup>87</sup> (rubidium), K<sup>40</sup> (potassium)

2. **Artificial radionuclides:** These radionuclides are produced in nuclear reactions.

It is created by bombardment of atoms of specific element with radiation particles, e.g. bombarding aluminum with  $\alpha$ -particles to produce radioactive isotope of phosphorus



### Stability of Isotopes

The naturally occurring nuclides have a particular ratio of protons and neutrons in most of the elements. If more neutrons are added to the nucleus and the ratio will get disturbed so the nuclide becomes unstable. Any deviation in this ratio alters the atomic number and causes instability of nucleus.

An isotope can be unstable if:

- It is too heavy ( $>83$  protons).
- Its  $n^0$  (N) to  $p^+$  (Z) ratio is too high.
- Its  $n^0$  (N) to  $p^+$  (Z) ratio is too low.

## RADIOACTIVE DECAY

Radioactivity describes an atom which undergoes radioactive decay. It releases radiation from the nuclei of radioactive isotopes. Radioactive decay is when an unstable atom of an element emits radiations in the form of electromagnetic waves or subatomic particles; to stabilize it.

According to the law of radioactive decay, the quantity of radioelement which disappears in unit time is directly proportional to the amount present. It is independent of temperature so its activation energy is zero. Each radionuclide, whether natural or artificial get disintegrated by the emission of energy.

Carbon 12 and carbon 13 are stable, but carbon 14 is radioactive.



Identification of radioactive element depends upon disintegration rate, decay constant, half-life and type of radiation emitted.

### Decay Constant

Various forms of equation for radioactive decay are

$$\text{Rate of disintegration} = -dN/dt \propto N$$

or

$$-dN/dt = KN$$

where  $K$  is amount of proportionality which is called disintegration or decay constant

$$-\frac{dN}{N} = K \cdot dt \quad (i)$$

Integrating equation (i) over limit  $5A_0$  and  $N$  (for the left hand side) and 0 and  $t$  (for the right hand side), we get:

$$\int_{N_0}^N \frac{dN}{N} = - \int_0^t K dt$$

$$\ln N/N_0 = -Kt \quad (ii)$$

On simplification of equation (ii)

$$\begin{aligned} N/N_0 &= e^{-Kt} \\ N &= N_0 e^{-Kt} \end{aligned} \quad (iii)$$

where  $K$  = Disintegration or decay constant

$N_0$  = Initial number of atoms of the nuclei at time 0

$(N_0 - N)$  = the amount of substance that gets disintegrated into another after time  $t$ .

## ■ UNITS OF RADIOACTIVITY

The standard unit of radioactivity is Curie (Ci) or (C).

### Curie (Ci)

It defined as mass of radioactive elements that produces  $3.7 \times 10^{10}$  disintegration per second. This is approximately the amount of radioactivity emitted by 1 gram (1 gm) of radium = 226.

$1\text{Ci} = 3.7 \times 10^{10}$  disintegrations or nuclear transformations per second

But nowadays, the unit curie is replaced by Rutherford.

### Becquerel (Bq)

The quantity of a radioactive material that have one transformation per second or one decay per second

$\text{Bq} = \text{one transformation per second}$

or  $1\text{Ci} = 3.7 \times 10^{10} \text{ Bq} = 37 \text{ GBq}$

or  $1\text{Bq} \approx 2.703 \times 10^{-11}\text{Ci}$

$= 27 \text{ pCi}$

### Rutherford (Rd)

It is a non-SI unit of radioactive decay. It is defined as the activity of a quantity of radioactive material in which one million nuclei decay per second.

$1\text{Rd} = 10^6 \text{ decay/second}$

or  $1\text{Rd} = 10^6 \text{ Bq}$

or  $1\text{Rd} = 2.703 \times 10^{-5}\text{Ci}$

### Radiation Absorbed Dose (RAD)

Original measuring unit for expressing the absorption of all types of ionizing radiation ( $\alpha$ ,  $\beta$ ,  $\gamma$ , neutrons, etc. into any medium. One rad is equivalent to the absorption of 100 ergs of energy per gram of absorbing tissue. Pharmaceutical dosage forms are described in terms of rad units.

$$1 \text{ rad} = 10^{-2} \text{ J/kg (SI system)}$$

Pharmaceutical dosage forms are described in terms of rad units.

### Roentgen (R)

It is the measurement of energy produced by  $\gamma$  or X-ray radiation in a cubic centimeter of air.

$$1\text{R} = 2.58 \times 10^{-4} \text{ C kg}^{-1} \quad (\text{C} = \text{Coulomb})$$

### Roentgen Equivalent Man (REM)

It is a measurement that correlates the dose of any radiation to the biological effect of that radiation. This expresses the relative effects of radiations ( $\alpha$ ,  $\beta$  and  $\gamma$ ) on the biological system.

## RADIOACTIVE DOSIMETRY

Dosimetry is the measurement of radiation dose. It can be calculated only if bio-distribution and clearance rate are known. Bio-distribution is the amount of activity within the organ, while the clearance rate is the rate at which the drug is eliminated from the body with respect to time.

### Absorbed Dose (D)

**Gray (Gy):** It is a derived unit of ionizing radiation dose in the International Standard (SI) of Units. One gray is the absorption of one joule of energy, in the form of ionizing radiation, per kilogram of matter.

$$1 \text{ Gy} = 100 \text{ rad}$$

**Sievert (Sv):** It is a measure of the health effect of low levels of ionizing radiation on the human body. The Sievert is of importance in dosimetry and radiation protection, and is named after Rolf Maximilian Sievert, a Swedish medical physicist renowned for work on radiation dose measurement and research into the biological effects of radiation.

$$1 \text{ Sv} = 100 \text{ rem}$$

Radiopharmaceuticals used in majority of diagnostic studies in adults ordinary result in organ dose of <5 rad, within dose to the whole body of <0.2 rad. Radiation dose below 1 rad is considered to be in 'low dose' range.

Radiation dose level is estimated using average activities administered to adults (Table 5.2).

**Table 5.2:** Radiation dose level

<i>Radiation dose</i>	<i>Diagnostic use</i>
High dose (>5 rads)	$^{131}\text{I}$ - Sodium iodide for thyroid imaging $^{99\text{m}}\text{Tc}$ -DMSA (dimercaptosuccinic acid) for renal imaging $^{\text{m}}\text{I}$ -iodocholesterol for adrenal imaging
Medium dose (1–5 rads)	$^{201}\text{Tl}$ -chloride for heart imaging $^{67}\text{Ga}$ -citrate for tumor and abscess imaging $^{99\text{m}}\text{Tc}$ -pertechnetate for brain imaging $^{99\text{m}}\text{Tc}$ -gluceptate for brain and kidney imaging
Low dose (<1 rad)	$^{99\text{m}}\text{Tc}$ (Technetium)-red blood cells for blood pool imaging $^{131}\text{I}$ -hippuran for kidney function studies

**HALF-LIFE ( $t_{1/2}$ )**

The half-life of a radioactive nuclide is the time taken for half the nuclei present to disintegrate or it is the time required for a radioactive isotope to decay to one half of its original value at any given point of time.

If the half-life is represented by  $T_{1/2}$ , then when  $t = T_{1/2}$ ,  $N = N_0/2$ , and therefore by equation

$$\begin{aligned}N &= N_0 e^{-Kt} \\N_0/2 &= N_0 e^{-Kt^{1/2}} \\t_{1/2} &= 0.693/K\end{aligned}$$

where  $K$  = disintegration constant

Each radioactive isotope has its own characteristic half-life ( $t_{1/2}$ ). The half-life period for any given radioelement remains unchanged under varying conditions of temperature, pressure and chemical environment. This is because radioactivity is a nuclear property and remains unaffected by changes in the outer electron arrangement. An element having shorter half-life, greater is the number of disintegrating atoms hence greater its radioactivity. It is widely varied from fraction of seconds to millions of years.

For example, initially 64 micro curies of radioactivity occur in a given sample of ferric citrate ( $^{59}\text{Fe}$ ) solution on a particular date. It was observed that radioactivity is reduced to 4 micro curies (1/6th of its original) value after 4th half-life.

The reciprocal of the radioactive constant or decay constant is called average half-life period. It is denoted by  $\tau$  (tau).

$$\tau = 1/K$$

In calculating the dose of any radiopharmaceutical, i.e.  $t_{1/2}$  calculation needs to be considered (Table 5.3).

**Table 5.3:** Application of radioisotopes with half-life

<i>Name</i>	<i>Half-life</i>	<i>Application</i>
Sodium iodide ( $^{131}\text{I}$ )	8.06 days	Thyroid scanning and study of thyroid uptake
Sodium phosphate ( $^{32}\text{P}$ ) injection	14.2 days	Treatment of polycythemia (overproduction of RBCs)
Ferric citrate ( $^{59}\text{Fe}$ ) solution	45 days	Study of iron metabolism and RBC formation
Calcium chloride ( $^{45}\text{Ca}$ )	160 days	Study of calcium metabolism disorder, bone cancer

## ■ DETECTION METHODS OF RADIOACTIVITY

Radioactivity was discovered by Becquerel because it left marks on photographic film. The equipment used for detection or measurement of radiation generally utilizes some type of material or substance which responds to the radiation. Various detection methods are as follows.

### Film

A photographic film when knocked with radiation gave picture. The more radiation exposure, the more blackening of the film.

### Thermoluminescence Dosimetry (TLD)

A crystal such as LiF containing Mn as an impurity is used. The impurity causes traps in the crystalline lattice where, following irradiation, electrons are held. When the crystal is warmed, the trapped electrons are released and light is emitted. The amount of light is related to the dose of radiation received by the crystal.

### Ionization

Radiation results in the formation of positive and negative ions in a gas as well as in all other materials. Ionization can be used both for Bq measurements as well as for dose measurement.

### Scintillation

A number of compounds have the property that they will emit light when exposed to radiation. The intensity of the emitted light depends on the radiation exposure and the light intensity is easily measured.

### Semiconductors

Radiation produces an electric current in semiconductors that can be measured.

### Free Radicals

Radiation produces a class of chemical species known as free radicals. Although they are very reactive, they can trap in some solid materials. The number of trapped free radicals is a measure of the radiation dose.

### Redox Products

Radiation either reduces (by electron addition) or oxidizes (by electron abstraction) the absorbing molecules. Although these changes are initially in the form of unstable free radicals, chemical reactions occur which ultimately result in stable reduction and oxidation products.

There are three types of commonly used radiation detectors are electroscope, cloud chamber and ionization chamber.

## ■ MEASUREMENT OF RADIOACTIVITY

Radiations interact with matter, i.e. charged particles, electrons and photons which can directly ionize or excite the atoms. Therefore, measurement of radiation and

detection is an important aspect in the identification of type of radiations (a, b, g). Emitted radiations are identified on the basis of their properties. Suitable detectors are also needed to assay the radioisotope emitting the radiation.

Ionization effect is measured in ionization chamber, proportional counter and Geiger-Müller counter. The scintillation effect of radiation is measured using scintillation detector and the photographic effect is measured by autoradiography.

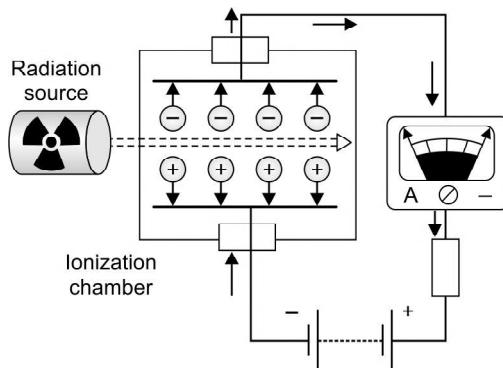
### Types of Detectors

#### *Detectors Based on Ionization*

All the detectors are based on the principle that the radiation deposits its energy through the formation of charge carriers, either directly or indirectly in the detector which results in the flow of current or a voltage pulse. The ions created in the detector can be collected by applying the electric field within the detector and the current flowing through the detector can be measured using an electrometer.

#### *Gas Filled Detectors*

1. **Ionization chamber** (Fig 5.1): An ionization chamber consists of a chamber filled with gas volume (like argon, helium or air, etc.) and fitted in an electric field between two electrodes kept at different electric potential (50–100 V) and a measuring device to indicate the flow of current. Radiation entering this volume results in the formation of ions. The positive ions will be attracted to the negative electrode, and negative ions will be attracted to the positive electrode. It works on the principle which is based on the collection of all the charges created by direct ionization of the gas molecules through the application of electric field.



**Fig. 5.1:** Ionization chamber

2. **Proportional counters:** It is the modified form of ionization chamber. In this instrument the voltage across the electrodes is adjusted to let the number of ions that reach the electrodes be equal or proportional to the number of ions induced by the radiation. Thus, the pulse size reflects the energy deposited by the incident radiation in the detector gas.

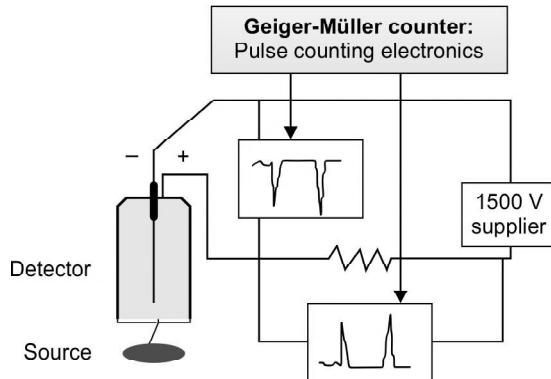
If the electric field gradient between the cathode and anode is increased by increasing applied voltage, the electron produced in primary ionization further ionize the gas molecule and number of ion pairs is multiplied. For each primary

electron liberated, larger numbers of additional electrons are liberated and the current pulse gets amplified. The voltage range over which ionization occurs is called proportional region and counters working in this region is called proportional counter.

The gas used in the counters is usually a noble gas (mainly argon). For special purposes other mixtures of gases have been used, such as a tissue equivalent gas mixture consisting of 64.4% methane, 32.4% carbon dioxide and 3.2% nitrogen. For neutron detection He3 and BF3 (boron trifluoride) are the most commonly employed gases.

### 3. Geiger-Müller counter (Fig. 5.2):

In 1928, Geiger and Müller developed GM counter in Germany. It is the oldest radiation detector due to its low cost, simplicity; it is the best detector among all. It does not require use of any high gain amplifier and easily can detect  $\alpha$ -,  $\beta$ -,  $\gamma$ -radiations.



**Fig. 5.2:** Geiger-Müller counter

### Principle

The counter consists of a GM tube having sensing element which detects the radiation and processing electronics which shows the result. The GM tube is filled with an inert gas at low pressure, to which a high voltage (450–500 V) is applied. The tube conducts electrical charge when a particle or photon of incident radiation makes the gas conductive by ionization. The ionization considerably amplified within the tube to produce easily measured detection pulse, which is fed to processing electronics and display the result.

### Construction and Working

It consists of a cylinder made-up of stainless steel or glass coated with silver on inner side which acts as cathode. A tungsten wire is suspended internally which is mounted at one end with a glass bead, act as anode. Cylinder is filled mixture of gas (argon or neon and helium generally used) which also contain a small amount of quenching vapors.

Quenching vapors are used to prevent the false pulse and to absorb photons emitted by exciting atoms and molecules returning to their ground state. Chlorine, bromine, ethanol are commonly used as quenching agents. The counter consists of a gas volume with two electrodes that have a high voltage between them. Very often the detector element is cylindrical in shape with the cylinder wall serving as the negatively charged (ground) electrode and a thin metal rod running along the middle axis serving as the positively charged electrode.

Ionizing radiation passing through the gas volume produces ions in the gas. The voltage is high enough for each electron attracted to the central electrode to make a cascade of new ions. This results in a pulse which is detected by a counter system.

Different counters are used depending on purpose such as:

1. In order to count the radioactive solid source, the end window type GM counter has been used and window has been made-up of aluminum alloy or mica.
2. For counting radioactive liquids, the counter having 3% solution of uranium salt is used and the capacity of  $10\text{ cm}^3$ .
3. To count radioactive gases, counter having lead or copper cathode have been used.
4. For counting  $\beta$ - and  $\gamma$ -particles, thin glass walled counters may be used and tube is coated on inside with graphite to form cathode.

### **Disadvantages**

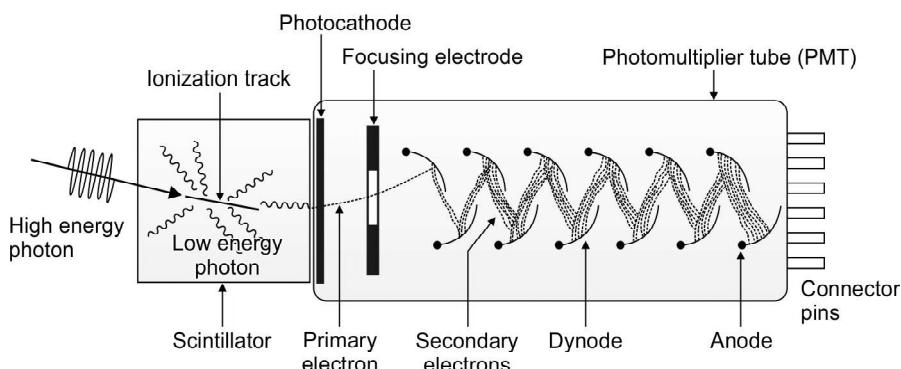
A GM counter cannot differentiate between different types of radiation and their energy. However, the multiplication factor is a big advantage in simple radioactive counting.

### **Scintillation Detector (Fig. 5.3)**

The scintillation counter is based on the principle that light is emitted when a scintillator is exposed to radiation. When high energy radiation or photons is incident on certain substance, a flash of light is emitted by the phenomenon called fluorescence or phosphorescence.

Several organic compounds, such as benzene and anthracene can be used. Crystals of certain substances, e.g. cesium fluoride, cadmium tungstate, anthracene and sodium iodide emit small flashes of light when bombarded by  $\gamma$ -rays. The most commonly used phosphor in scintillation counters is NaI with a minute quantity of thallium added. The light pulse produced when radiation interacts with the scintillators is recorded by a photomultiplier tube. It multiplies and amplifies even a small signal so it becomes possible to measure  $\alpha$ -,  $\beta$ - or  $\gamma$ -radiation.

The light emitted when the crystal is irradiated is proportional to the  $\alpha$ -energy deposited. Consequently these counters are suited to measure the energy of  $\alpha$ -radiation and, therefore, can be used to identify  $\gamma$ -emitting isotopes.



**Fig. 5.3: Scintillation detector**

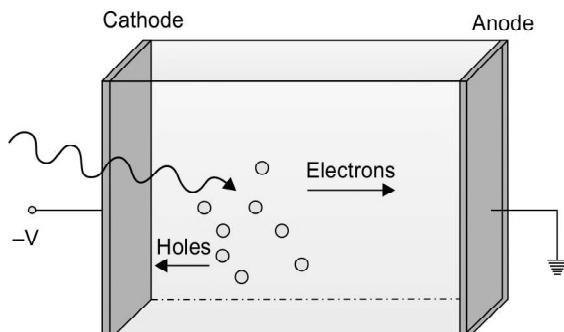
Both organic and inorganic scintillations can be used as detector. The incident light should be proportional to light produced on detectors. It has high scintillation efficiency. Inorganic scintillation detectors like alkyl halides are most common

compounds, e.g. sodium iodide, cesium iodide, lithium iodide. Organic scintillators like plastic scintillators have good scintillation property but stilbene have low scintillation property. Short decay time of the induced fluorescence can be increased by dynodes which are made-up of phosphor or fluor which multiplies the electrons when strike to them. Hence, various inorganic and organic scintillation detectors can be used to measure the incident radiation.

### Semiconductor Detector

A large, clean and almost perfect semiconductor is ideal as a counter for radioactivity. The released electric charge is closely related to the radiation energy. These counters are employed to measure the energy of the radiation and for identification. The crystals are made of silicon or germanium. However, it is difficult to make large crystals with sufficient purity. The semiconductor counters have, therefore, low efficiency, but they do give a very precise measure of the energy. In order to achieve maximum efficiency the counters must operate at the very low temperatures of liquid nitrogen ( $-196^{\circ}\text{C}$ ).

It is a diode of  $n$  (electron rich) and  $p$  (electron deficient) semiconductors. In a semiconductor the band gap is very small and large numbers of electron hole pairs are formed. The absorption of incident radiations results in the formation of electron and hole pairs which move under the influence of applied electric field. The collection of electrons at the electrode produces a voltage pulse, which is proportional to the intensity of the incident radiation.



**Fig. 5.4:** Semiconductor detector

### STORAGE, HANDLING AND PRECAUTIONS OF RADIOACTIVE MATERIAL

A care should be taken to protect the people and personal from its harmful effects during in handling and storage of radioactive materials.

1. The radioactive materials are stored in remote areas and it should be away from exposure to human beings.
2. The area of radioactive material should be tested for intensity of radioactivity.
3.  $\alpha$ - and  $\beta$ -emitters are stored in thick glass such that shielding effect is provided, while  $\gamma$ -emitters are stored in lead containers.
4. Lead shielding is required while handling with radioactive substances.
5. Exposure to radioactive radiation can cause blood cancer to persons.

The following precautions are taken while working with radioassays, radio-detectors, radioelements, radioisotopes and other radioactive materials.

1. These materials should be handled by means of forceps and never be touched with hands.
2. Area of where these materials stored and used should be monitored properly.
3. Sufficient protective clothing or shielding must be used while handling the material.
4. Food contaminated with radioactive material which can cause serious injury to internal organs, so avoid any food intake, drinking and smoking within the laboratory.
5. Radioactive material should be kept in labeled containers and must be shielded by lead bricks.
6. Final disposal of radioactive material should be done with great care.

### **Labeling on Radioactive Preparations**

The label of radiopharmaceutical preparations should be appropriate and the following details are to be mentioned on the label:

- Name of radionuclide
- Route of administration
- Date of manufacture
- Date of expiry
- Date of calibration
- A statement 'caution-radioactive material'
- Dosage calculation
- Correction to be made for radioactive decay
- The half-life of radioactive nuclei.

### **Radiopharmaceuticals**

Radiopaque agents such as iodine or barium compounds are used for X-ray examinations of kidney, liver, heart, brain and blood vessels.

### **RADIOPAQUE CONTRAST MEDIA**

Radiopaque contrast media are the chemical compounds having the capacity to absorb and block the passage of X-rays and they are used as a diagnostic aid in radiology which emits X-rays. X-rays are capable of passing through most of the tissues. When a photographic film is placed opposite to the X-rays through patient's body organ, the film is darkened in the amount of X-rays that have been passed. All radiopaque materials are not radiopharmaceuticals. Various radiopaque contrast media are used in X-ray examination of GIT, gallbladder, bile duct, kidney, ureter, fallopian tubes, liver, heart and brain. Radiopaque contrast media do not produce any pharmacological effect.

### **BARIUM SULFATE**

*Molecular formula:* BaSO<sub>4</sub>

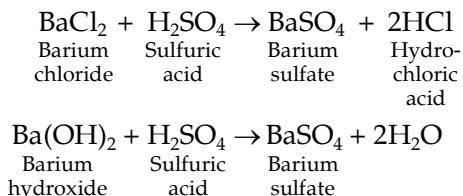
*Molecular weight:* 233.39

**Synonyms:** Barium meal, shadow meal

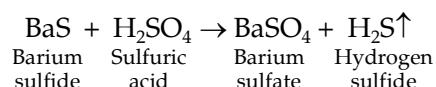
**IP limit:** It contains not <90% and not >110% of the labeled amount of barium sulfate.

### Methods of Preparation

- It is prepared from barium hydroxide and barium chloride by the action of sulfuric acid and the precipitates formed are filtered and dried.

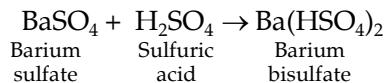


- It can also be prepared by the action of sulfuric acid on barium sulfide.



### Properties

It is a fine, heavy, white, odorless, bulky powder which is free from grittiness. It is insoluble in water and organic solvents but soluble in hydrochloric acid and nitric acid. Suspension of barium sulfate is susceptible to barium emitting microorganisms so in suspension is permitted to contain suitable preservatives. It is also soluble in sulfuric acid by forming bisulfate salt.



### Dose

Oral dose: 60–450 gm in suspension, rectal dose: 150–750 gm in suspension.

### Identification Test

- 0.5 gm of barium sulfate is mixed with 2 gm each of anhydrous sodium carbonate and potassium carbonate. The mixture is heated in a crucible until fusion is completed; the fused mass is treated with hot water and filtered. The filtrate is acidified with  $\text{H}_2\text{SO}_4$  to meet the requirement of test for sulfates.
- Dissolve a portion of well-washed residue from the above identification test in 6 N acetic acid; the solution meets the requirement for the test of barium.

### Test of Purity

The following tests are carried out to test the purity of sample:

- pH 3.5–10 in 60% w/v aqueous suspension.
- Loss on drying at 105°C for 4 hours: it should not lose >1% of its weight.

### Assay

Take a mixture sodium carbonate and potassium carbonate (0.6 gm) and heat it at 1000°C for 15 minutes. It is cooled, water is added, filtered by decantation and residue is washed with sodium carbonate solution. Then dil. HCl, ammonium acetate,

potassium dichromate and urea are added to the residue, heated in an oven at 80–85°C for 16 hours, filtered, the precipitates are washed with potassium dichromate and finally with water and dried at 105°C.

$$1 \text{ gm of the residue} \equiv 0.213 \text{ gm of BaSO}_4$$

### Uses

It is used as radiopaque contrast media for X-ray examination and diagnosis for GI tract. It is used primarily as a whitening agent in industrial applications. Barium ion stimulates smooth muscles causing vomiting, severe cramps, hemorrhage and diarrhea.

## SODIUM IODIDE ( $^{131}\text{I}$ )

*Molecular formula:* NaI

*Molecular weight:* 153.90

**Synonym:** Radioactive iodine, natrii radioiodidum.

Among all radioactive isotopes of iodine,  $^{131}\text{I}$  is most frequently used. It is used as an aqueous solution of sodium iodide having sodium thiosulfate as a reducing agent.

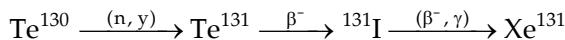
### Standards

It should not contain <90% and not >110% of labeled amount of Iodine-131 as iodide which is expressed in microcuries or millicuries at the time indicating in the labeling.

### Method of Preparation

In 1949, the first production of Iodine-131 took place in France at the Fort de Chatillon, the site of the first Zoe atomic reactor. Since 1942, the isotope has been used in the treatment of thyroid cancer.

Most  $^{131}\text{I}$  is prepared in nuclear reactor by neutron-irradiation of a natural tellurium target. Irradiation of natural tellurium produces almost entirely  $^{131}\text{I}$  as the only radionuclide with a half-life longer than hours. Finally in 8.02 days it gets converted into Xenon-131 (stable isotope).



### Properties

It is a clear and colorless solution.  $^{131}\text{I}$  undergoes decay by emitting  $\beta$ - and  $\gamma$ -radiations with a half-life of 8.02 days. Its solution is having pH range of 7.5–9. It easily solubilizes in water and alcohol.

### Treatment of Hyperthyroidism by $^{131}\text{I}$

Iodide inhibits the release of thyroid hormone and it is used in hyperthyroidism. All the isotopes of iodine are rapidly taken up by thyroid follicles. Radioactive iodine, i.e.  $^{131}\text{I}$  is available as  $\text{Na}^{131}\text{I}$  solution and is administered orally.

The absorption of  $^{131}\text{I}$  leads to highly localized destruction of thyroid follicles due to  $\alpha$ -particles emission. This property has promoted radioactive iodine as a therapeutic

alternative in surgical removal of the gland. The radioiodine therapy is considered advantageous over surgery because of the simplicity of its procedure, its applicability to patients, avoidance of surgical risks and complications.

### Solution and Capsule

Sodium iodide ( $^{131}\text{I}$ ) is suitable for both oral and IV administration. The solution is clear and colorless, but during the time passes both the solution and glass may get darken due to the effect of radiation.

For injection, a suitable preservative such as benzyl alcohol and reducing agent such as sodium thiosulfate is also added to the solution, to prevent the oxidation of sodium iodide in aqueous solutions. Potassium salt, iodide and iodate have been acting as a carrier for iodide ions and for iodate ions present in the  $^{131}\text{I}$  solution.

Sodium iodide ( $^{131}\text{I}$ ) capsules are prepared by evaporating an alcoholic solution of sodium radioiodide directly on the walls of the capsule or on inert capsule filling material.

### Radioactive Identification

The spectrum of  $^{131}\text{I}$  has been complex but the most abundant type of photon is having energy of 0.364 MeV. The  $\gamma$ -ray scintillation spectrum of  $^{131}\text{I}$  solution has been found to be identical to that of specimen of  $^{131}\text{I}$  of known purity, which exhibits major photoelectric peak, having energy of 0.365 MeV.

### Packaging and Storage

It should be stored in single or multiple dose containers that have been treated previously to prevent absorption.

$^{131}\text{I}$  solution should be first of all rinsed with a solution having approximately 0.8% of sodium bisulfate and 0.25% of sodium iodide and then water until the last rinsing has been neutral to litmus.

### Assay

It is possible to determine its activity, using suitable counting equipment by comparison with a standardized  $^{131}\text{I}$  solution or by measurement of an instrument calibrated with the aid of such solutions. Iodine-131 has been emitting both  $\beta$ - and  $\gamma$ -particles in its decay process. Radioactivity has to be recorded on a counting assembly which is having either a Geiger-Müller counter or a scintillation detector used as a sensing unit and an electronic sealing device.

### Uses

Radioactive iodine is mainly used for the diagnosis of disorders of thyroid function. It is mainly used in the treatment of hyperthyroidism. It is also used in the treatment of thyrotoxicosis and radiotherapy of thyroid cancer. Radioactive iodine is also used in the treatment of Graves' disease (toxic diffused goiter).

## PHARMACEUTICAL APPLICATIONS OF RADIOACTIVE SUBSTANCES

Nowadays, radiation and radioactive substances have been widely used in medicine, mainly for diagnosis and treatment of various health ailments.

**In diagnosis:**

1. Sodium iodide ( $^{131}\text{I}$ ) injection is used to study the functioning of thyroid gland.
2. Iodinated ( $^{131}\text{I}$ ) human serum albumin injection finds the use to investigate cardiovascular functions.
3. Chromium in the form of sodium chromate attaches strongly to the hemoglobin of red blood cells. Chromium-151 isotope is also useful for determining the lifetime of RBC, which can be of great importance in the diagnosis of anemia.
4. Colloidal gold ( $^{198}\text{Au}$ ) has been used in studying the blood circulation in liver.
5. Radioactive cobalt (Cobalt-59 or Cobalt-60) is used to study defects in vitamin  $\text{B}_{12}$  absorption.
6. Cyanocobalamin ( $^{57}\text{Co}$ ) is used for measuring glomerular filtration rate.
7. Ferric citrate ( $^{59}\text{Fe}$ ) injection finds the use in hematological disorders.

**In treatment:** The therapeutic use of radioisotopes depends on the ability of their ionization. These are useful to destroy or weaken malfunctioning cells. It is  $\beta$ -radiation that causes the destruction of damaged cells. An ideal therapeutic radioisotope should be a strong  $\beta$ -emitter with just enough  $\gamma$  to enable imaging, e.g.

1. Iodine-131 is used to treat the thyroid for cancers and abnormal conditions such as hyperthyroidism.
2. Yttrium-90 is used for the treatment of cancer particularly liver cancer and it is being used more widely including for arthritis.
3. Lead-212 can be attached to monoclonal antibodies for cancer treatment.

**In research:** Excellent biological and medicinal study can be carried out with radioactive isotopes as radiotracers. Generally carbon-14 and tritium are most commonly used.

**In sterilization:** Thermolabile substances like vitamins, hormones, antibiotics can be safely sterilized by strong radiation sources, e.g. cobalt-60 or cesium-137 may be used for sterilizing surgical instrument. In agriculture,  $\gamma$ -rays are used to kill pests and induce genetic mutations in a plant. Californium-252 is used for neutron activation analysis, to inspect airline luggage for hidden explosives. It is also used for various analytical purposes such as radioimmunoassay (RIA) and solubility determination.

**Table 5.4:** Some commonly used radioisotopes for various therapeutic and diagnostic applications

Radioisotope	Applications/Uses
Iodine-123 ( $\gamma$ -emitter)	Diagnose thyroid imaging
Iodine-125	Used in diagnosis of clotting by fibrinogen scan
Iodine-131	Used to treat thyroid disorders
Calcium-44, 45 (Ca-44, 45)	Study of bone structure and bone cancer
Cesium 147	Used to treat cancerous tumors
Sodium-22,24 (Na-22, Na-24)	Used in estimation of extracellular fluid, body circulation rate, excretion and distribution of water
Xenon-133	Used in nuclear medicine for lung ventilation and blood flow studies

(Contd.)

<i>Radioisotope</i>	<i>Applications/Uses</i>
Carbon-14 (C-14)	Used in medical and pharmaceutical research
Strontrium-90 (Sr-90)	Used in radiotherapy of superficial carcinoma
Cobalt-60 (Co-60)	radiotherapy, sterilization of heat labile substances, study of vitamin B <sub>12</sub>
Cobalt-57 (Co-57)	Used in diagnosis of pernicious anemia
Hydrogen- <sup>2</sup> H, <sup>3</sup> H	Used to determine total body water content
Iron-59 (Fe-59)	Used to study iron absorption, lifespan of red blood cells
Phosphorus-32	In the treatment of polycythemia and related disorders
Radium-223 ( $\alpha$ -emitter)	In the treatment of metastatic cancer in bone
Selenium-75 ( $\gamma$ -emitter)	Investigation of adrenal gland imaging and bile salt absorption
Fluorine-18	Used in investigation of tumor imaging, bone imaging, myocardial imaging
Nitrogen-13, 15 (N-13, N-15)	Used in investigation of amino acid and protein metabolism
Oxygen-17, 18 (O-17, O-18)	To study organic reactions and photosynthesis
Oxygen-15 (O-15)	Cerebral and myocardial blood flow imaging
Gallium-67 ( $\gamma$ -emitter)	Tumor imaging and inflammation/infections imaging
Gallium-68	Prostate cancer imaging
Sodium chromate (Cr-51)	It finds use in measuring red cell volume and its survival time
Cr-51 EDTA	For glomerular filtration rate estimation
Dysprosium-165 ( <sup>165</sup> Dy)	In arthritis treatment

## IMPORTANT QUESTIONS/ANSWERS

### I. Multiple Choice Questions

1. Radioactivity was discovered by:
  - a. Louis Pasteur
  - b. Becquerel
  - c. William Crookes
  - d. Benjamin Franklin
2. 1 curie is equivalent to:
  - a.  $3.7 \times 10^8$  Becquerel
  - b.  $3.7 \times 10^{12}$  Becquerel
  - c.  $3.7 \times 10^{-8}$  Becquerel
  - d.  $3.7 \times 10^{10}$  Becquerel
3. Radioactive decay undergoes ..... order of reaction.
  - a. Second
  - b. Zero
  - c. First
  - d. Third
4. Positron emission results in:
  - a.  $\alpha$ -Decay
  - b.  $\beta^+$ -Decay
  - c.  $\beta$ -Decay
  - d.  $\gamma$ -Decay
5. ..... is used as quencher in Geiger-Müller counter.
  - a. CCl<sub>4</sub>
  - b. Chloroform
  - c. Methanol
  - d. Ethanol
6. ..... device used for the measurement of radioactivity.
  - a. Geiger-Müller counter
  - b. NMR spectroscopy
  - c. Cyclotron
  - d. Nuclear reactor

7. Iodine  $^{131}\text{I}$  is produced from the neutron bombardment of .....
- Indium-111
  - Xenon-133
  - Tellurium-132
  - Tellurium-130
8. Gamma rays are:
- No charge
  - No penetrating power
  - High penetrating power than  $\alpha$  and  $\beta$
  - Less penetrating power than  $\alpha$  and  $\beta$
9. .... is gas filled detector.
- Ionization chamber
  - GM counter
  - Both a and b
  - None of the above
10. Beta rays are:
- Negatively charged
  - Positively charged
  - Neutral
  - None of the above
11. Isotopes are having:
- Same atomic number and same mass number
  - Same atomic number but different mass number
  - Sum of number of protons and neutrons
  - None of the above
12. Alpha rays are:
- Negatively charged
  - Positively charged
  - Neutral
  - None of the above
13. Radioactivity undergoes ..... reaction.
- Spontaneous reaction
  - Statistical process
  - Chemical reaction
  - None of the above
14. Radioactivity is due to:
- Stable nucleus
  - Electronic configuration
  - Cosmogenic
  - Unstable nucleus
15. In PET ..... is used as a tracer.
- Sodium-24
  - Fluorine-18
  - Phosphorus-32
  - Tellurium-132
16. The units of ..... are the Sievert (Sv) and the roentgen equivalent man (rem).
- Dose equivalent
  - Half-life
  - $\alpha$ -Emitted
  - None of the above
17. Atomic number is equivalent to:
- Number of electrons
  - Number of neutrons
  - Number of protons
  - None of the above
18. .... is the commonly used quenching agent.
- Argon
  - Methane
  - Hydrogen
  - Bromine and chlorine
19. Which of the following detectors is not used in medicine?
- $\alpha$ -Particle emitters
  - $\gamma$ -Particle emitters
  - $\beta$ -Particle emitters
  - All of the above

20. The standard unit of radioactivity is:  
 a.  $\Omega$   
 b. Ci  
 c.  $\delta$   
 d. All of the above

**Answers**

1. b    2. d    3. c    4. b    5. d    6. a    7. b    8. c    9. c    10. a    11. b  
 12. b    13. a    14. d    15. b    16. a    17. c    18. d    19. a    20. b

**II. Fill in the Blanks**

1. Dynodes are used in ..... detectors.
2. Half-life period of radioactive is calculated by .....
3. The function of quenching vapor is .....
4. P-10 gas is a mixture of ..... and .....
5. Proportional counter has a basic cylindrical geometry with a central wire made up of tungsten acting as .....
6. ..... is the measurement of radiation dose.
7. ..... is the time required for a radioactive isotope to decay to one half of its original value at any given point of time.

**Answers**

1. Scintillation counter
2.  $t_{1/2} = 0.693/K$
3. To prevent false pulses
4. 90% argon and 10% methane
5. Anode
6. Dosimetry
7. Half-life

**III. Short Answer Questions**

1. Define radioactivity. Discuss about radioactive rays.
2. Differentiate  $\alpha$ -,  $\beta$ - and  $\gamma$ -rays.
3. Define the following terms:
  - a. Half-life
  - b. Isotope
  - c. Units of radioactivity
4. How to label radioactive material?
5. What are the uses of radiopaque contrast media?
6. List any two radioisotopes with their applications.
7. Write a note on storage conditions and precautions of radioactive substance.

**IV. Long Answer Questions**

1. Discuss the construction, working and principle of Geiger-Müller counter with a neat and labeled diagram.
2. Discuss the preparation, properties and uses of  $^{131}\text{I}$  and barium sulfate.

3. What are the different modes of decay of a radioisotope, also discuss in detail of the half-life.
4. Explain the properties of  $\alpha$ -,  $\beta$ - and  $\gamma$ -particles and also write the applications of radioisotopes.
5. Give a detail note on scintillation counter.
6. Describe methods of measurement of radioactivity. What are the standards and units of radioactivity?
7. Discuss the diagnostic and therapeutic applications of radioisotopes in detail.

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# Textbook of Pharmaceutical Inorganic Chemistry

for First Semester Bachelor in Pharmacy

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