UNIT-I

INTRODUCTION TO PHARMACUTICAL CHEMISTRY

What is matter

- Anything that:

–Has mass

–Occupies space (volume).

The trees, the stone, and the buildings in the figure are all examples of matter.

What is chemistry?

- Chemistry is the study of the composition of matter and the changes that matter undergoes.
- Chemistry affects all aspects of life and most natural events because all living and nonliving things are made of matter.

Branches of chemistry

- Inorganic
- Organic
- Analytical
- Physical
- Biochemistry

Inorganic Chemistry

- The study of chemicals that do not contain carbon.
- Many inorganic chemicals are found in nonliving things, such as rocks.

Introduction to pharmaceutical chemistry

Pharmaceutical chemistry is the science that makes use of general laws of chemistry to study drugs

General laws of chemistry include there:

- Preparation
- Chemical nature
- Composition

Prepared By- Sumit Kumar Singh
(Associate Professor)

- Structure
- Influence on an organism
- Studies the physical and chemical properties of drugs and
- The method of quality control and the condition of their usage

In other words: it is the chemistry of drugs

- Is a specialized science which depends on other chemical disciplines such as:

- Inorganic

- Organic

- Analytical

- Physical

- Colloid chemistry and

- Also on medico-biological discipline such as pharmacology, physiology, biological chemistry, etc.

It occupies the most important place among the related sciences such as:

- Drug technology

- Toxicological chemistry

- Pharmacognosy

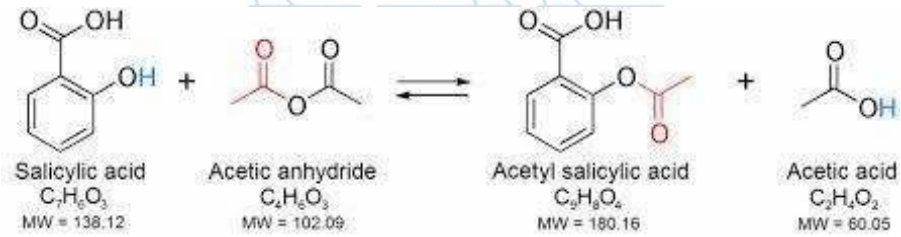
- The economy and organization of the pharmacy

Important aspects of pharmaceutical chemistry:

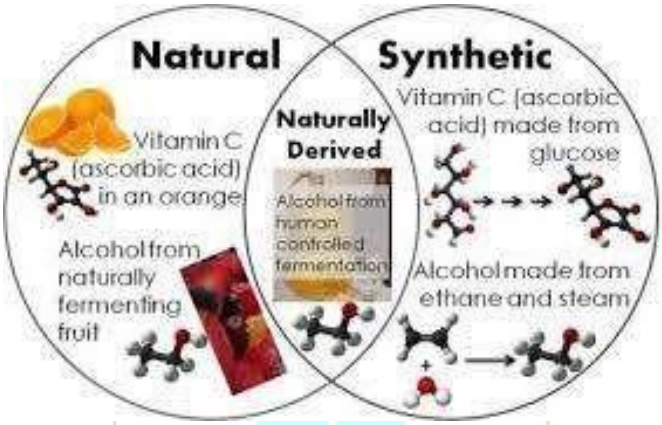
1. Methods for isolation, purification and characterization of medically active agents and materials from natural sources.

Bauxite, a major aluminium ore. The red-brown colour is due to the presence of iron minerals. Opium, dried crudeextract obtained by incising unripe opium poppy capsules

2. The various synthetic route:

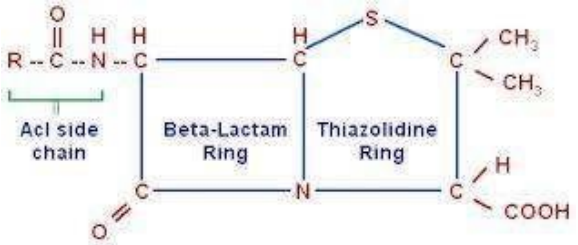


3. Natural substances are converted into products with more favorable therapeutic or pharmaceutical properties



4. Different forms of a medicinal agent which shows optimum medicinal activity and at the same time results in stable formulation and elegant dispensing.

5. Establishment of safe and practical standards with respect to both dosage and quality.



General Structure of Penicillins

6. Search for new therapeutic agents especially when there exists no satisfactory remedy

Newer antibiotics were discovered like semi synthetic penicillin's, Cephalosporin's …etc.

Summary:

- Chemistry is a science which deals with properties matter.
- Pharmaceutical chemistry: Is the chemistry of drugs and pharmaceuticals
- Different branches of chemistry are inorganic, organic, analytical chemistry, physical chemistry and bio chemistry
- Pharmaceutical chemistry covers the aspects of isolation, synthesis, biological activity safety and quality of the drugs and pharmaceuticals

History of Pharmacopoeia

Introduction

Pharmacopoeia: the word derives from the ancient Greek *φαρμακοποιΐα* (*pharmakopoiia*), from *φαρμακο-* (*pharmako-*) ″drug″, followed by the verb-stem *ποι-* (*poi-*) ″make″ and finally the abstract noun ending *-ια* (*-ia*). These three elements together can be rendered as ″drug-mak-ing″ or ″to make a drug″.

A pharmacopoeia, pharmacopeia, or pharmacopoea, in its modern sense, is a legally binding collection, prepared by a national or regional authority, of standards and quality specifications for medicines used in that country or region. A quality specification is composed of a set of appropriate tests that will confirm the identity and purity of the product, ascertain the strength (or amount) of the active substance and, when needed, its performance characteristics. Reference substances, i.e. highly- characterized, physical specimens, are used in testing to help ensure the quality, such as identity, strength and purity, of medicines. The texts cover pharmaceutical starting materials, excipients, intermediates and finished pharmaceutical products (FPPs). General requirements may also be given in the pharmacopoeia on important subjects related to medicines quality, such as analytical methods, microbiological purity, dissolution testing, stability, etc.

The role of a modern pharmacopoeia is to furnish quality specifications for active pharmaceutical ingredients (APIs), FPPs and general requirements, e.g. for dosage forms. The existence of such specifications and requirements is necessary for the proper functioning or regulatory control of medicines. Pharmacopoeial requirements form a base for establishing quality requirements for individual pharmaceutical preparations in their final form. According to the information available to the World Health Organization (WHO), 140 independent countries are at present employing some 30 national as well as the African, European and International Pharmacopoeias. Compared to national and regional pharmacopoeias, *The International Pharmacopoeia* (Ph. Int.) is issued by WHO as a recommendation with the aim to provide international standards – including less technically demanding alternatives where needed - for adoption by Member States and to help achieve a potentially global uniformity of quality specifications for selected pharmaceutical products, excipients and dosage forms.

History and background

The books containing the standards for drugs and other related substances are known as pharmacopoeia and formularies - collectively these books are known as the drug compendia.

The pharmacopoeias or formularies contain a list of drugs and other related substances regarding their source, descriptions, standards, tests, formulae for preparing the same, action and uses, doses, storage conditions etc.

These books are prepared under the authority of the Government of the respective

countries.

CLASSIFICATION

The drug-compendia are classified as:

(i) Official compendia

(ii) Non-official compendia

A. OFFICIAL COMPENDIA

Official compendia are the compilations of drugs and other related substances which are recognized as legal standards of purity, quality and strength by a government agency of respective countries of their origin.

e.g. British Pharmacopoeia (BP)

British Pharmaceutical Codex (BPC)

Indian Pharmacopoeia (IP)

United States Pharmacopoeia (USP)

National Formulary (NF)

The State Pharmacopoeia of USSR and

Pharmacopoeias of other countries

B. NON-OFFICIAL COMPENDIA

The book other than official drug compendia which are used as secondary reference sources for drugs and other related substances are known as non-official drug compendia. e.g.

Merck Index

Extra Pharmacopoeia (Martindale)

United States Dispensatory etc.

Overwhelming empirical knowledge of mankind gained during centuries and constant effort to establish better health care possibilities have led to the creation of a list of origin, preparation and healing properties of medicines.

The term *Pharmacopoeia* first appears as a distinct title in a work published in Basel, Switzerland in 1561

by Dr A. Foes, but does not appear to have come into general use until the beginning of the 17th century. Today's pharmacopoeias focus mainly on assurance of quality of products by various tools of analytical sciences.

The aim to achieve a wide global harmonization of quality specifications for selected pharmaceutical products, excipients and dosage forms came with increased globalization and reciprocal collaboration. History of these approaches goes back to 1902–1925 when agreements established a ″Unified″ Pharmacopoeia. In 1929 the "Brussels Agreement" stipulated the League of Nations to carry out related administrative functions. Eight years later, in 1937, the first meeting of the ″Technical Commission of Pharmaceutical Experts″ was held. An important date in the history of quality assurance of medicines is 1948, when the First World Health Assembly (WHA) approved the Expert Committee on Unification of Pharmacopoeias to continue this work. One year later, the WHA renamed it the Expert Committee on International Pharmacopoeia.

Indian Pharmacopoeia

- First official IP was appeared in 1868 which was edited by Edward John Waring
- In pre-independence days, BP was used in India
- The colonial addendum of BP 1898 was published in 1900 appeared as Government of India edition in 1901
- In 1946 Government of India issued one list known as 'The Indian Pharmacopoeial list'
- Committee under chairmanship of Sir R. N. Chopra along with other 9 members prepared „The Indian Pharmacopeial list"
- It was prepared by Department of Health, Govt. of India, Delhi in 1946.
- In 1948 Government of India appointed an IP committee for preparing „Pharmacopeia of India"
- Tenure of this committee was 05 years.
- Indian Pharmacopeia committee under chairmanship of Dr. B. N. Ghosh Published first edition of IP in 1955
- First edition of IP is written in English & official titles of monographs given in Latin.
- It covers 986 monographs.
- Supplement to this edition was published in 1960.

2 nd edition of IP was published in 1966 under the chairmanship of Dr. B. Mukherjee

- 274 monographs from IP 55 & their supplement were deleted.
- 93 new monographs were added.
- Official titles of monographs given in English
- Dose were expressed in Metric system

 For Tablets and Injections “USUAL STRENGTH” have been given.

 Formulations of the drugs were given immediately after the monograph of drugs.

 Supplement to this edition was published in 1975.

 126 new monographs have been included & 250 monographs amended.

 Cholera vaccine has been deleted.

3 rd edition of IP was published in 1985 with 02 volumes & 09 appendices.

 261 new monographs have been added.

 450 monographs were deleted.

 Addendum I: Published in 1989, 46 new monographs added and 126 amended.

 Addendum II: Published in 1991 were 62 new monographs added and 110 amended.

4 th edition of IP was published in 1996 under the chairmanship of Dr. Nityanand.

 It covered 1149 monographs and 123 appendices.

 It includes 294 new monographs & 110 monographs have been deleted.

Addendum I: Effective from 31st December 2000, 42 new monographs have been added.

Addendum II: Effective from 30th June 2003, 19 new monographs have been added.

The veterinary supplement of IP 1996 contains 208 monographs & 04 appendices.

5 th edition of IP was published in 2007 & addendum to this edition was published in 2008.

IP 2007 is presented in 03 Volumes.

Volume 1: contains general notices & general chapters.

 Volume 2 & 3: Contains general monographs on drug substances, dosage forms & Pharmaceutical aids.

6 th edition of IP is published in 2010 by the Indian Pharmacopoeia Commission (IPC), Ghaziabad

 This edition would be effective from 1 st September, 2010.

 The Indian Pharmacopoeia 2010 is presented in 03 volumes.

 Volume I: contains the Notices, Preface, the Structure of the IPC, Acknowledgements, Introduction, and the General Chapters.

 Volume II: contains the General Notice, General Monographs on Dosage Forms and Monographs on drug substances, dosage forms and pharmaceutical aids (A to M).

 Volume III: contains Monographs on drug substances, dosage forms and pharmaceutical aids (N to Z).

 Monographs on vaccines and immunosera for human use, herbs and herbal products, blood and blood-related products, biotechnology products and veterinary products.

 Products of biotechnology, indigenous herbs and herbal products, veterinary vaccines and additional

antiretroviral drugs and formulations, fixed-dose combinations.

 Standards for new drugs and drugs used under national health programmes are added

 Monographs of excipients, anticancer drugs, herbal products and antiretroviral drugs has been increased in this edition.

 Monographs of vaccines and immunosera are also upgraded in view of development of latest technology in the field.

 A new chapter on liposomal products and a monograph of liposomal Amphotericin B injection is an added advantage in view of latest technology adopted for drug delivery.

 A chapter on NMR is incorporated in Appendices.

 The chapter on microbial contamination is also updated to a great extent to harmonize with prevailing international requirements.

7 th Edition of IP (2014)

 313 New monographs on drug substances, dosage forms & pharmaceutical aids (A to Z)

 43 New drugs substances monographs

 10 Antibiotic monographs

 31 Herbal monographs

 05 Vaccines & immunosera for human use

 06 Insulin products, 07 biotechnology products etc. along with the 19 new general chapters

 19 New radiopharmaceutical monographs & 1 general chapter is first time being included in this edition

8 th Edition of IP (2018)

 04 Volumes

 170 Chemical Monographs

 15 herbal monograph

 10 monograph on blood and related products

 06 monographs on biotechnology derived products

 02 monographs on vaccine and immune sera

 03 monographs of radiopharmaceuticals

 14 monographs of veterinary nonbiologicals

9th edition -Indian Pharmacopoeia 2022

Effective from December 1, 2022

contains:

- 265 chemical monographs,
- 47 vaccine monographs,
- 17 vitamins, minerals, amino acids, fatty acids monographs,
- 7 phytopharmaceutical monographs,
- 43 monographs of herbs and herbal products,
- 14 monographs of blood and blood related products,
- 6 biotechnology derived therapeutic product monographs,
- 14 veterinary monographs.

The IP has omitted general chapters on assay of human anti-D immunoglobulin methods B and C. Monographs of lorcaserin hydrochloride hemihydrate and lorcaserin hydrochloride tablets have been omitted by IPC vide a notification on March 10, 2021.Contains 92 new monographs, 21 vitamins, minerals, amino acids, and fatty acids, as well as 27 active pharmaceutical ingredients (APIs).

Salient Features

New Monographs: 92

- APIs: 27
- Dosage Forms (Chemicals): 33
- Vitamins, Minerals, Amino acids, Fatty Acids etc.: 21
- Biotechnology Derived Therapeutic products: 03
- Herbs & Herbal Products:02
- Blood & Blood RelatedProducts: 02
- Vaccines and Immunosera for human use: 04
- General Chapters: 12
  - 3 new biotechnology derived therapeutic products,
  - 2 herbs & herbal products,
  - 2 blood & blood related products,
  - 33 dosage forms (chemicals),
  - 4 vaccines and immunosera for human use
  - 12 new general chapters.

British Pharmacopoeia

• **First** edition of BP was published in 1864 & consist of two sections

• Part I: Materia Medica

• Part II: Preparation & compounds

• **Second** edition of BP was published in 1867

• **Third** edition of BP was published in 1885

• **Fourth** edition of BP was published in 1898

• **Fifth** edition of BP was published in 1914

• **Eighth** edition of BP was published in 1953:

• Titles of drugs & preparations were in English instead of Latin and metric system.

• It has been published annually.

• In **BP 2007** monographs has been introduced for material specifically used in preparation of Traditional Chinese Medicines.
• Term „Prolonged release" has been replaced the term „Slow" and the term „Gastro-resistant" has been replaced with „Enteric coated" in number of monographs.
• **BP 2008** contains approximately 3100 monographs for substances, preparations and articles used in practice. • It has been made effective from 1 st January 2008.
• **BP 2007-2009** were given in 06 Volumes i.e. Vol. I to Vol. VI.

• Volume I & II: Contains medicinal substances.

• Volume III: Contains formulated preparations, blood related products, immunological products, radiopharmaceutical preparations, surgical materials & homoeopathic preparations.
• Volume IV: Contains supplementary chapters, IR spectra etc.

• Volume V: Contains veterinary products

• Volume VI: Contains CD ROM version.

BP 2010

The Stationery Office, on behalf of BP Secretariat, part of the Medicines and Healthcare products Regulatory Agency (MHRA), has recently published the BP, 2010.
 BP is the official collection of standards for UK medicinal products and pharmaceutical substances.

 Published annually, the BP contains monographs for pharmaceutical substances, formulated preparations and other articles used in the practice of medicine.
 The standards in the BP 2010 are legally effective in the UK from 1 January 2010.

• BP has been providing authoritative, official standards for pharmaceutical substances and medicinal products since 1864.
• It is used in almost 100 countries worldwide and remains an essential reference for any individual or organization working within pharmaceutical research and development, manufacturing and testing across the globe.
• BP 2010 has 40 monographs for formulated preparations, including veterinary medicines and additional

standards for widely used unlicensed formulations.

 All European Pharmacopoeia 6th edition material upto and including Supplement 6.5 is integrated into the text of the BP 2010.

 BP supports regulatory work in the fields of herbal and complementary medicines by providing additional new and revised monographs for herbal medicinal products and for homeopathic stocks and mother tinctures.

 Print edition of BP 2010 comprises 4 volumes of BP 2010 and a single volume of BP (Veterinary) 2010.

27

The BP 2013 package includes:

 06 volume printed edition including the BP (Veterinary) 2013

 41 new BP monographs

 40 new European Pharmacopoeia monographs

 619 amended monographs

 6 new and 1 amended Infrared Reference Spectra BP 2013

 The 2014 edition includes almost 3500 monographs which are legally enforced by the Human Medicines Regulations 2012.

BP 2014

 The BP 2014 package comprises 5 volumes of BP 2014 and a single volume of BP (Veterinary) 2014, along with a fully searchable CD ROM and online access to provide you with flexible resources.

 Legally effective from 1 January 2014

 40 new, 272 amended and 4 new BP (Vet) monographs

 03 new Supplementary Chapters

 01 new BP (Vet) Supplementary Chapter

BP 2018

 35 new monographs

 185 amended BP monographs

 04 new monographs for unlicensed formulations

 04 new monographs for herbal medicines

 06 new monographs for veterinary medicines

United State Pharmacopoeia (USP)

• 1 st edition of USP was published on 15th Dec. 1820 in both Latin & English

• From 1820 to 1942 it was published at 10 years intervals

• From 1942 to 2000 it was published at 05 years intervals

• From 2002 it was published annually

• First National Formulary of the united state appeared in 1888

• USP21-NF16 have 08 supplements

• First appeared in January 1985 & last in November 1988

• USP22-NF17, 1990 is the 3 rd revision that consolidates USP & NF into a single volume

• Electronic version of USP-NF on floppy disks was introduced in 1992

• USP23-NF18, was published in Mumbai at the end of 1994

• USP23 has 10 supplements.

• 1 st supplement was published in January 1995 & Last in May 1999.

• USP24-NF19, appeared from first January 2000

• USP30-NF25, appeared from May 2007.

• It contains scientific standards for drugs, dietary substances, biological products & excipients used in dosage forms.

• It contains 4,100 monographs and 200 general chapters.

• It has been printed in 03 volume set.

• Volume I contains general chapters, while Volume II, III contains monographs.

• 1 st supplement to USP30-NF25, appeared from August 2007 & 2 nd supplement from November 2007 which was official from May 2008.

• From 2006, Spanish edition of USP is also being published. United States Pharmacopoeia 30 – National Formulary 25:

• New heavier paper stock

• Complete table of contents and index in each volume

• Special 'Using the New USP-NF Print' tutorial CD

• Convenient slipcase for easy access and storage (English edition only).

United States Pharmacopoeia 31 - National Formulary 26:

• It is a single-volume combination of two official compendia, the United States Pharmacopeia (USP) and

the National Formulary (NF).

• Monographs for drug substances and preparations are featured in the USP, with monographs for dietary supplements and ingredients appearing in a separate section of the USP.

• Excipients monographs are included in the NF 36

United States Pharmacopoeia 32 - National Formulary 27:

• More than 4,200 monographs

• Includes over 200 general chapters, covering general tests and assays

• Displays helpful guides and charts that make it easy to find focus specific information

• Includes information on emerging areas of science and medicine

• Helps ensure compliance with official standards

• Enables validation of test results against proven benchmarks

• Creates in-house standards for operating procedures and specifications

• Expedites new product development and approvals

United States Pharmacopoeia 33 - National Formulary 28:

• More than 4,400 monographs

• Over 200 general chapters covering general tests and assays

• A new, easy-to-read format and monograph layout

• Helpful guides and charts that make it easy to find focus-specific information

• Ensures compliance with official standards

• Establishes in-house standard operating procedures and specifications

• Facilitates new product development and approval.

United States Pharmacopoeia 34 - National Formulary 29:

• Published in 2011

• USP 34-NF 29 features more than 4,500 monographs for drug substances, dosage forms, excipients, biologics, dietary supplements, and other therapeutics.

• USP 34-NF 29 also offers harmonized material and more than 230 General Chapters with current guidelines for the full range of laboratory tests and established processes for validating methods. **United States Pharmacopoeia 35 - National Formulary 30:**

• USP-NF is a combination of two official compendia: the 'United States Pharmacopeia (USP)' and the 'National Formulary (NF)' and is officially applicable from 1 May, 2012 to 30 April, 2013.

United States Pharmacopoeia 41 - National Formulary 36:

- Published in 2018
- 4900 monographs
- 350 chapters
- Sections of solutions, reagents, indicators
- Section on hazardous drug handling

European Pharmacopeia

- EP commission started working since 1964 to prepare EP
- 1st edition: published 1967
- 2nd edition: published 1980
- 3rd edition: published 1997
- 4th edition: published 2001, valid from 1 January 2002
- 5th edition: published 15 June 2004, valid from 1 January 2005
- 6th edition: published 16 July 2007, valid from 1 January 2008
- 7th edition: published June 2010, valid from 1 January 2011
- 8th edition: published June 2013, valid from 1 January 2014

Impurities in pharmaceutical substances

Impure Chemical Compound:

A compound is said to be impure if it is having foreign matter i.e., Impurities.

Pure Chemical Compound:

Apure chemical compound refers to that compound which is having foreign matter i.e., impurities. Chemical purity means freedom from foreign matter.
Analytically 100 % pure substances are not available and traces of impurities must be present. Normally undesirable foreign materials are presentinthe pharmaceutical substances.
Impurity is any material that affects the purity of thematerial of interest.

Presence of Impurities in the pharmaceutical substances mayproduce toxic effects on the body and may also lower down the active strength of the pharmaceuticalsubstance.

Impurities commonly in chemical substances include smallquantities of Iron, lead, Arsenic,Chloride and sulphate.

Sources of Impurities in Pharmaceuticals

The different sources of impurities in pharmaceuticals are listed below:

1) Raw material used in manufacture

2) Reagents used in manufacturing process

3) Method/ process used in manufacture or method of manufacturing

4) Chemical processes used in themanufacture

5) Atmospheric contamination during the manufacturing process

6) Intermediate products in the manufacturing process

7) Defects in the manufacturing process

8) Manufacturing hazards

9) Inadequate Storage conditions

10) Decomposition of the product duringstorage

11) Accidental substitution or deliberate adulteration with spurious or uselessmaterials

Source of Impurities

Raw Materials

Method of Manufacturing

*Reagents Used

*Intermediate Products

*Reagents used to eliminate impurity

*Solvents Used

*Atmospheric Contamination

Manufacturing Hazards

*Contamination from Matter

*Cross Contamination

*Contamination by Microbes

*Errors in Manufacturing

*Errors in Storage & Packaging

Instability of Products

*Chemical Instabilities

*Physical Instabilities

*Reaction with Container

*Temperature

Impurities & their Sources -Introduction:

 It is virtually impossible to have absolutely pure chemical compounds and even analytically pure chemical compounds contain minute trace of impurities.
 Impurities = a foreign unwanted matter present in a compound which are differ from the actual molecular formula.
 Chemically a compound is impure if it contains undesirable foreign matter i.e. impurities.

Thus, chemical purity is freedom from foreign matter.

Sources of Impurities:

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

1. Raw Materials:

 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.

2. Method of Manufacture:

 The Process or method 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:

 Calcium carbonate contains 'soluble alkali' as impurity

 Anions like Cl- and SO4-2 are common impurities in many substances because of the use of hydrochloric acid and sulphuric acid respectively

 Barium ion may be an impurity in hydrogen peroxide

(B) Regents used to eliminate other impurities:

Barium is used to remove sulphate from potassium bromide, which can be found itself (barium) as impurity at the end of process.

(C) Solvents:

Small amounts of solvents employed in preparation, and purification of the product may also result in the contamination of the pharmaceutical substances.

Water is the cheapest solvent which can be the major source of impurities as it contains different type of impurities like Ca^{2+}, Mg^{2+} ,Na^{+}, Cl^{-}, CO_3^{-2} and SO_4^{-2} in trace amounts.

(D) Intermediates: Sometimes, an intermediate substance produced during the manufacturing process may contaminate the final product

e.g. Sodium bromide is prepared by reaction of sodium hydroxide and bromine in slight excess.

$6\ NaOH + 3\ Br_2 \rightarrow NaBrO_3 + 5\ NaBr + 3\ H_2O$ …

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

$NaBrO_3 + 3\ C \rightarrow NaBr + 3\ CO$ …

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

(E) Atmospheric contamination during the manufacturing process:

Atmosphere may contain dust (aluminium oxide, sulphur, silica, soot etc.) and some gases like carbon dioxide, sulphur dioxide, arsine and hydrogen sulphide. These may contaminate the final product during the manufacturing process.

e.g. sodium hydroxide readily absorbs atmospheric carbon dioxide when exposed to atmosphere.

$2\ NaOH + CO2 \rightarrow Na2CO3 + H2O$

(3) Manufacturing hazards:

If the manufacturer is able to control and check impurities from the all above mentioned sources there exists 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, tabletting and filling machines and the product container.

(B) Cross-contamination of the product:

Cross-contamination of product can occur by air-born dust arising out of handling of powders, granules and tablets in bulk. If 2 or more Products are manufactured in same time this type of contamination is possible.

(C) Contamination by microbes:

 Many products, like liquid preparations and creams intended for topical applications are liable to contamination by microbes from the atmosphere during manufacturing. Microbes like Bacteria, fungi, Algae etc can contaminate the final product.

(D) Errors in the manufacturing process:

 Sometimes in a liquid preparation, there is incomplete solution of the solute.

 A error on the efficiency of mixing, filling, tabletting, sterilization etc arise impurity in final product.

(E) Errors in the packaging:

 Similar looking products, such as tablets of the same size, shape and colour, packed in similar containers can result in mislabeling of either or both of the products.

(4) Instability of the product:

(A) Chemical instability:

 Impurities can also arise during storage because of chemical instability of the pharmaceutical substance.

 Many pharmaceutically important substances undergo chemical decomposition when storage conditions are inadequate.

 This chemical decomposition is often catalyzed by light, traces of acid or alkali, traces of metallic impurities, air oxidation, carbon dioxide and water vapours.

(B) Changes in physical properties:

 Pharmaceuticals may undergo changes in physical properties during storage.

There can be changes in crystal size and shape, sedimentation, agglomeration and caking of the suspended particles.

(C) Reaction with container material:

 The possibility of reaction between the container material and the contents can be possible.

 Preparations susceptible to reaction with metal surfaces

 e.g. salicylic acid ointment must not be packed in metal tubes.

 Plastic containers and closures have tendency to give undesirable additives, such as plasticizers, particularly in the presence of non-aqueous solvents.

(D) Temperature:

 The rate of chemical decomposition and physical changes of stored products depends upon the temperature.

 The susceptible substances may have temperature storage requirements assigned to them in order to protect them against undesirable decomposition.