UNIT-III

PRINCIPLES OF PHARMACOKINETICS, PHARMACODYNAMICS & DRUG DELIVERY

DEFINITIONS: -

DISEASES: - A simple definition of disease is an "illness (or) sickness characterized by specific signs (or) symptoms".

- Disease is an abnormal condition of an organism which interrupts the normal bodily functions that offen leads to feeling of pain and weakness and usually associated with symptoms and Signs.

DRUG:- A drug may be defined as an chemical substance which is used in the prevention (or) diagnosis (or) treatment of disease (or) chemical used to modify a physiological process (or) broadly drug is define as a chemical substance that produce a biological effect in biological system.

CHARACTERISTICS OF IDEAL DRUG: -

An ideal drug most processes the following characteristics.

1. An ideal drug works an a specified system in the body but not on other systems.
2. It should work effectively, safety and for considerable period of time.
3. It should possess minimum side effects and should be non-toxic to the body. That means a should neither distribute the normal physiological activity of the body nor damage the cells.
4. Its cost should be within the rich of common man.
5. It shouldn't leads to drug resistance (or) drug addiction.

BASIC PRINCIPLES OF PHARMACOLOGY:-

Pharmacology is a branch of medical science which deals with the study of biological active substance especially drugs.

(PHARMACON = DRUG, LOGUS = STUDY).

- Therefore Pharmacology means the study of drugs (or) science of drugs.
- It is broadly divided into 2 sub-branches.

1. **PHARMACOKINETICS: -** Pharmacokinetics is a branch of pharmacology that describes the process of absorption, distribution, metabolism and excretion of a drug by the body as a mathematical function of time and concentration. It describes how to concentration of a dose drug and its metabolites in the body fluids and tissues change with time.

2. **PHARMACODYNAMICS: -** Pharmacodynamics is defined as the response of the body to the drug. It is the study of relationship between the concentration of drug at the site of action and the biochemical and physiological effect. Thus it deals with the mechanism of drug action and generally describes what a drug does to the body.

PHARMACOKINETICS

- ❖ It deals with the routes of administration, absorption, distribution, metabolism and excretion of drugs (ADME)

1. **METHODS OF ADMINISTRATION**: - The drug can be administrated by following methods.
   a. Oral method
   b. Sub lingual method
   c. Inhalation method
   d. External application method
   e. Injection method.

a. ORAL METHOD: -

In this method, drug is taken by the mouth.

ADVANTAGES: -

It is preferred route for the most of the patients. In this method certain precautions should be observed.

PRECAUTIONS:-

1. Drug which reacts with food & interfere with its absorption should not be taken along with food.
   E.g.:- Tetracycline strongly reacts with calcium & Hence their absorption decrease when taken along with milk.
2. Certain drugs are destroyed by gastric juice in stomach hence such drugs should not be taken by mouth.
   E.g.:- Penicillin-G.
3. This route is not highly suitable for many children.
4. This method is not suitable for patients suffering from vomiting.
5. Drug which causes gastric irritations cannot be given by this method.

b. SUB LINGUAL METHOD: -

In this method the drug is taken under tongue.

ADVANTAGES:-

1. In this method prevents the interaction of the drug with gastric juice in the stomach and also interaction with bile secreted by the liver.
2. In this method the drug is directly absorbed into the blood stream.
   E.g:- Anti Anginal drugs such as Isosorbid di Nitrate (or) glyceryl trinitrate are taken by this method.

c. INHALATION METHOD:-

In this method, certain Volatile drugs are taken through a nose (or) by the mouth through inhalation.

Eg: - Solbutamol, a bronchiodilator drug is generally taken in by Inhalation by the Asthma patients.

d. EXTERNAL APPLICATION METHOD:-

In this method, the drugs are applied externally on the skin in the form of creams and lotions ointments gels and powder etc.

Eg: - Soframycin ointment (or) Nebasulf powder for wounds (or) Abscesses and cotrimoxazole ointment (or) powder for fungal infection is used externally.

e. INJECTION METHOD:-

In this method, the drug is administrated into the body with the help of injection needle. The most important type of this method is given below.

1. Intradermal /Subcutaneous Injection method
2. Intramuscular Injection method
3. Intraveneous Injection method

1. INTRADERMAL /SUBCUTANEOUS INJECTION METHOD

In this method the drug is administered in the form of a solution inside the skin.

E.g.:- B.C.G Vaccine, hepatic vaccine, Insulin, hormone…. etc are administered by this method .

ADVANTAGES: - The drug action is slow and prolonged.

DISADVANTAGES: - Irritation and Necrosis may occur at the site of the injection.

2. INTRA-MUSCULAR INJECTION METHOD

In this method, the drug in the form of a solution, emulsion (or) suspension is given into the muscle of upper arm (or) thigh.

ADVANTAGES: - The drug action is moderately rapid & less prolonged

DISADVANTAGES: - Irritation and Slight pain may be felt at the site of injection.

3. INTRA-VENEOUS INJECTION METHOD

In this method, the drug is given into the large vein at the forearm in the form of a solution.

ADVANTAGES: - The drug action is rapid, large quantity of the drug can be given slowly (or) rapidly

DISADVANTAGES: -

1. Self – medication is not possible
2. Treatment is costly
3. Aseptic conditions must be maintained

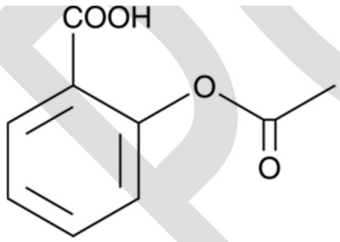
E.g.:- Normal saline solution, glucose solution, a blood transfusion are given by this method.

DRUG ABSORPTION

"Absorption" is a process in which the drug enters the bloodstream from the site of administration. The drug molecules pass into the body through the intercellular gaps (or) Phospholipids gaps. The absorption of the drug into the bloodstream takes place in the stomach, small intestine (or) large intestine.

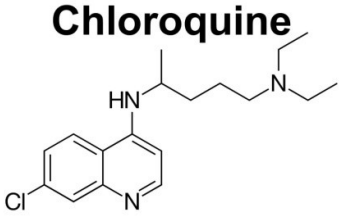
- If the PH of the drug is very low, it absorbs from the stomach.
- If it is very high it is absorbed from the large intestine.
- if the PH is moderate if it absorbed from the small intestine
- That means highly acidic drug are absorbed from the stomach
- Basic drugs are absorbed from the large intestine and slightly acidic (or) neutral drug are absorbed from small intestine.

E.g.:- Aspirin – Acetyl Salicylic acid, Diclofenac, Penicillin's etc are acidic drugs and are mainly absorbed from stomach.



ASPIRIN

1. Chloroquine is a basic anti malarial drug and it is mainly absorbed from large intestine.



2. The griseofulvin is a neutral drug and it is absorbed in small intestine.

DRUG DISTRIBUATION:-

The transfer of the drug from the blood to the intra & extra cellular fluids of all parts of body is called "distributio". The time taken for complete distribution throughout the body depends upon the following factors.

a. **MOLECULAR SIZE OF A DRUG, THE DEGREE OF IONISATION**

The smaller the size and greater the degree of Ionisation, the more rapidly the drug is distributed throughout the body.

b. **BINDING NATURE OF THE DRUG**

If the drug is strongly bonded to the proteins, it will be distributed slowly from the site of action and it will be eliminated slowly from the body.

c. **CONCENTRATION OF DRUG**

In general, the greater the concentration of a drug, the more rapid will be distribution of the drug.

DRUG METABOLISM (BIO-TRANSFORMATION)

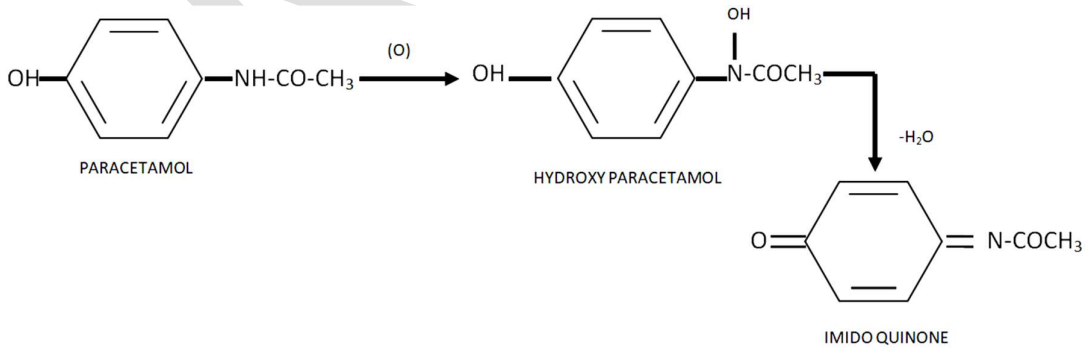
The drug after absorption and distribution passes into the liver, kidneys, etc and undergoes biochemical changes. The process in which the drug undergoes biochemical changes is called "Metabolism" (or) "Bio-Transformation". The metabolism changes are oxidation, reduction, hydrolysis (PHASE I REACTIONS), Conjugation reactions such as alkylation, acylation, acid derivative formation etc. The metabolic changes are discussed below.

PHASE I METABOLIC CHANGES

1. **OXIDATIVE METABOLISM**: - The Drug reacts with O_2 (or) some other oxidative reagents and gets oxidized to different forms.

E.g.:-

a) Dapsone, Which is the most common "Anti leprosy drug", is oxidized to N- hydroxy dapsone.
b) Ibuprofen (BRUFEN) the most commonly used "Anti-Inflammatory drug" for the joint pains is oxidized to hydroxyl Ibuprofen.
c) Paracetamol, the most commonly used for "Anti-fever drug" is oxidized to ImidoQuinone.

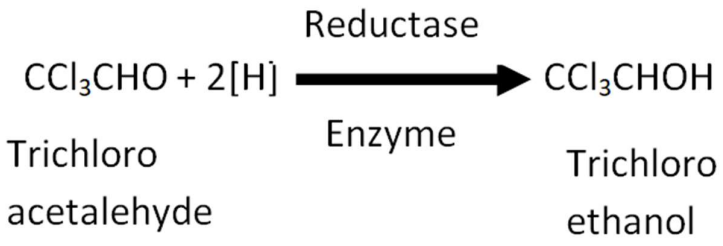


PARACETAMOL — HYDROXY PARACETAMOL — IMIDO QUINONE

2. **REDUCTIVE METABOLISM: -** Drug containing carbonyl groups are reduced to alcohols, Nitro compounds are reduced to amines etc.

E.g.:-

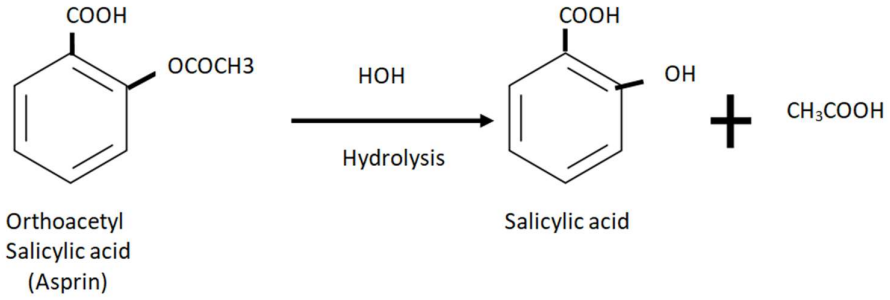
Chloral hydrate, a hypnotic is reduced to trichloroethanol.



3. **HYDROLYTIC METABOLISM** :- Certain drugs undergo hydrolysis & form acidic (or) basic compounds.

   E.g.:-

   Asprin is hydrolysed to Salicylic acid



PHASE-II

BIO TRANSFORMATIONS.

- Phase-II metabolic reactions involve conjugation reactions which increase polarity and hence water solubility of the drugs.
  So that drugs are eliminated more easily from the kidneys the most common Phase-II metabolic reactions are

1. Acylation
2. Glycine conjugation
3. Glucuronic Acid Conjugation

1. **ACYLATION:-** In the body, certain drugs are converted to N-Acetyl derivatives

   E.g.:-

   Isoniazid, a common “Anti T.B. Drug" is converted to N-Acetyl Isonioazid.

2. **GLYCINE CONJUGATION:-** The phase-I metabolite of the procainamide i.e. P-amino benzoic acid reacts with glycine in the cell and forms hippuric acid derivatives which is more easily eliminated by the kidney.

3. GLUCURONIC ACID CONJUGATION (GLUCURONIDATION)

Glucuronic Acid is mainly formed from D- Glucose present in the body. This glucuronic acid is converted into Co- Enzyme called "UDPGA" (Uridine diphosphate glucuronic acid)

- ❖ This Co-enzyme readily supplies glucuronic acid for the conjugation reactions.
- ❖ Glucuronic acid reacts with hydroxyl, carboxyl (or) amino group in the drug and form glucuronide derivatives which are normally non toxic, more water soluble and hence they are easily excreted by the kidney.

E.g.:-

Glucuronic acid reacts with Salicylic acid & forms an Ester.

DRUG EXCRETION:- The drug after undergoing metabolic changes and after performing its medicinal activity is thrown out of the body mainly by the kidney. This process is called "Excretion."

- ❖ Most of the drugs are converted into their suitable metabolic products and these are eliminated. Certain drugs are excreted without undergoing any biochemical changes.

a. **ELIMINATION BY THE KIDNEY:-** Drugs whose molecular weight is less than 500 units are generally excreted by the kidney.

E.g.:-

Aspirin, paracetamol etc.

b. **ELIMINATION BY THE LIVER:-** Drugs whose molecular weight is greater than 500 units are excreted by the liver into the bloodstream along with the bile.

E.g.:-

Streptomycin, rifampicin,mebendazole etc

c. **ELIMINATION THROUGH LUNGS:-** Highly volatile drugs (or) their metabolites are eliminated from the lungs.

E.g.:-

Alcohol, ether, chloroform, acetone etc.

d. **ELIMINATION THROUGH THE SKIN:-** The skin eliminates some inorganic toxins such as lead, arsenic etc

PHARMACODYNAMICS

- Pharmacodynamics deals with the mechanism by which a disease (or) a disorder is cured (or) controlled by the drugs.
- It is also deals with the theories of drug mechanism.

NATURE OF DRUG RECEPTOR INTERACTIONS

In general, drugs act on 4 main types of proteins these proteins are called "regulatory proteins".

- This four types of drug targets are

1. Carrier molecules which transport glucose (or) move Na^+ and K^+ ions out of the cells are drug targets.
2. Enzymes are biological catalysis that controls the biochemical reactions of the cell. A drug can inhibit the action of a specific enzyme & so alter a Pharmacological response.
3. Ion channels
4. Receptors.

RECEPTORS THEORY OF DRUG ACTION: - These are 2 theories about drug receptor interactions.

1. Occupancy Theory
2. Rate theory

- The receptor theory of drug action insists that a drug works only when it is bound to its target receptor.
- A drug receptor is complex is formed readily

$$\text{Drug + receptor} \longleftrightarrow \text{Drug-receptor complex}$$

$$D + R \underset{K2}{\overset{K1}{\longleftrightarrow}} DR \quad \text{---------- 1}$$

Where K_1 & K_2 are rate constants for association and dissociation respectively for the drug receptor complex.

- According to the law of mass action, the rate of forward reaction is given by K_1 [D] [R]and the rate of backward reaction is K_2 [DR] at equilibrium, the rate of association and the rate of dissociation of the complex are equal

$$K_1 [D] [R] = K_2 [DR] \text{ ---------- 2}$$

$$\frac{K2}{K1} = K_D = \frac{[D][R]}{[DR]} \text{ ---------- 3}$$

Where K_D is the dissociation constant. K_D is also the concentration of the drug associated with 50% occupance.

OCCUPANCY THEORY

- According to the Clark's occupancy theory, the biological response to the drug is directly proportional to the number of receptors occupied by the drug.
- The second assumption is that the maximum response occurs when all of the receptors have drug molecules attached.
- Thus when 50% of the receptors are occupied there is 50% the possible response, when the response is maximal all the receptors are occupied.
- Ariens proposed a modified occupancy theory. It is based on 2 assumptions. First, different drugs have different affinity for receptor sites.
- Drugs with high affinity are strongly attracted to the receptor.
- The second assumption is that drugs, once attached to a receptor, have different abilities to simulate the receptor.
- A drugs ability to stimulate the receptor is called its "**Intrinsic activity**".

RATE THEORY:-

- Rate theory was developed by "**W.D.M Paton**"
- He postulated that the biological response is proportional to the rate at which the drug combines with the receptor.

INDUCED FIT THEORY

- This theory is an extension of rate theory
- This theory is mainly due to koshland & his co-workers.
- According to this theory,
    1. The active site in enzyme (or) the binding sites in receptors are not rigid, but highly flexible. The drug molecule induce suitable structural & conformational changes in active site of enzyme (or) the binding site of receptor such that the drug molecule exactly fit into the active site (or) binding sites & thus they stimulate the receptor (or) Inhibits the action of enzymes in a proper way.
    2. Similarly the structures of molecules are not rigid but flexible. As the drug molecule approaches the active site (or) binding sites, the sites also induce suitable conformation changes in drug molecules. So that drug molecules exactly fit into the sites & effectively stimulate the receptor (or) inhibit the action of enzymes.
    3. Thus the structure of the drug molecules, the binding sites of the receptor (or) the active sites of enzymes are flexible & they undergo suitable deformation/ modifications when required and they have the ability to return to the original form after being deformed.

DRUG SYNERGISM AND ANTAGONISM

DRUG SYNERGISM:- These are some substances which increase the efficiency of a drug and this phenomenon is called 'drug synergism. The substance is called the 'synergic drug. Most common examples are given below

1. **Sulphamethoxazole** is a bactereostatic drug. Its antibiotic action is due to the inhibition of the utilization of PABA by the bacteria (inhibition of cell wall synthesis).
2. **Trimethoprim** also exhibits antibacterial activity by inhibiting the bacterial cell wall synthesis (at different stage). The combination of these drugs is found to be more powerful than the individual drugs. Thus trimethoprin has a synergic action on sulphamethoxyzole. The combination of sulphamethoxazole and trimethoprim (5: 1) is known as contrimoxazole. It is sold in the market as **sepmax, septran tablets**.
3. **Chavulamic Acid**: It inhibits the activity of the enzyme -B- lactamase and hance increases the the action of the B-lactam group of drugs such as penicillins and cephalosporins.
4. **Metaclopramide**: It increases the gastric motility and helps in the faster absorption of analgesics and faster relief from pain. Hence it is used along with the painkillers used for migraine.

DRUG ANTAGONISM

There are certain drugs or substances which diminish the efficiency of a drug and this phenomenon is called the drug antagonism. This type of drugs are called antagonist drugs. Some of the most common antagonist drugs are discussed below-

1. **Ranitidine** is one of the most commonly used drug for the treatment of gastric ulcer or duodenal ulcer. But its efficiency is decreased by antacids.
2. **Diazepam** is one of the most commonly used drug to relieve anxiety. But its action is inhibited by ranitidine.

CLINICAL TRAILS

Clinical trials are research studies designed to test new medical treatments interventions or therapies in Romans. These Wials are essential for developing new drugs, medical devices, diagnostic tests, and tabinet protocols, as well as improving existing ones. Clinical trials follow a structured process to ensure patient safety therein of results, and adherence to ethical guidelines. Here's an overview of kly aspects related to clinical trials

1. **Phases of Clinical Trials**

   Phase I. The initial phase where a new drug or therapy is tested for safety in a small group of healthy volunteers 06-100 participarms. It aims to determine dosage, side effects, and how the body processes the treatment.

   Phase II Conducted on a larger group (100-300 people who have the condition the drug is Intended to treat. This phase evaluates the treatment's effectiveness and further investigates safety.

   Phase III Involves even larger groups (1.000-3.000 people) to confirm the treatment's effectiveness monitor side effects, and compare it to existing standard treatments. This phase is crucial for regulatory approval

   Phase IV Post-markating phase where the treatment is monitored in a larger population over the long term It helps detect any rare or long-terrn side effects and gathers additional data on the Deatment's effectiveness

2. **Types of Clinical Trials**
   - Interventional Trials Participants receive a specific intervention, such as a drug therapy, or procedure
   - **Observational Trials:** Researchers observe and collect data without providing any interventions. These studies help understand health trends, risk factors, and the effectiveness of treatments already in use
   - **Prevention Trials:** Designed to test methods for preventing diseases, such as vaccines or lifestyle changes
   - **Diagnostic Trials**: Evaluate new tests or procedures for diagnosing diseases.
   - **Quality of Life Trials:** Focus on improving the well-being and comfort of individuals with chronic diseases or conditions.
   - **Diagnostic Trials:** Evaluate new tests or procedures for diagnosing diseases
   - **Quality of Life Trials:** Focus on improving the well-being and comfort of individuals with chronic diseases or conditions.

3. **Key Components**

- **Informed Consent:** Participants must be fully informed about the trial's purpose, potential risks, and benefits, and they must voluntarily agree to participate.
- **Randomization:** Many clinical trials randomly assign participants to different treatment groups to reduce bias and ensure that the results are due to the treatment itself and not other factors.
- **Blinding:** In double-blind trials, neither the participants nor the researchers know which treatment is being administered to avoid bias in the results.
- **Placebo Control:** In some trials participants receive a placebo (an inactive substance) to compare the effects of the active treatment with no treatment.

4. **Ethical Considerations**
    - **Safety Monitoring:** Clinical trials are closely monitored by independent boards (Data Safety Monitoring Boards) to ensure patient safety and to stop the trial if there are significant risks
    - **Ethical Approval:** All clinical trials must be reviewed and approved by an Institutional Review Board (IRB) or ethics committee, ensuring that they comply with ethical standards
    - **Participant Rights:** Participants have the right to withdraw from a trial at any time without penalty.
5. **Finding Clinical Trials**

Clinical trials are registered in databases such as

- **Clinical Trials.gov:** A U.S.-based registry that provides detailed information about ongoing and completed trials worldwide
- **World Health Organization's International Clinical Trials Registry Platform (ICTRP):** A global initiative to make clinical trial information more accessible.

Clinical trials are essential for advancing medical knowledge and improving patient care. Participation in a clinical trial may offer access to new therapies, but it also carries risks. It's important for participants to carefully consider the potential benefits and risks before joining a trial.

CONCEPT OF DRUG DELIVERY

Concepts of Drug Delivery

Drug delivery refers to the methods, formulations, or systems used to administer therapeutic agents to the body in a controlled, targeted, and effective manner. The goal is to maximize the therapeutic effect while minimizing side effects. Several key concepts underpin drug delivery systems (DDS). These include:

1. **Pharmacokinetics and Pharmacodynamics**
   - Pharmacokinetics: Describes how the body absorbs, distributes, metabolizes, and excretes drugs (ADME). It helps determine the appropriate drug delivery strategy to ensure the drug reaches the site of action in the right concentration.
   - Pharmacodynamics: Refers to how the drug affects the body, including its mechanism of action, therapeutic effects, and potential side effects.
2. **Routes of Drug Administration**

Drug delivery can occur via various routes, depending on the drug and desired effect

- **Oral:** Tablets, capsules, liquids.
- **Intravenous (IV):** Direct delivery into the bloodstream, fast action.
- **Topical**: Application on the skin or mucosal surfaces
- **Inhalation**: Used for respiratory drugs (eg, asthma medications).
- **Transdermal**: Delivered through the skin (eg. patches).
- **Subcutaneous, Intramuscular, and Intradermal:** For sustained or controlled release.

3. **Controlled Release**
   This refers to the release of a drug over an extended period, maintaining a therapeutic level without frequent dosing. It aims to enhance patient compliance and improve drug efficacy. Examples
   - Sustained-release: Delivers a drug at a steady rate.
   - Extended-release: Prolongs the drug's action for longer periods.
   - Delayed-release: The drug is released after a set time, such as after passing through the stomach.
4. **Targeted Drug Delivery**
   Involves directing the drug to a specific site of action, minimizing exposure to healthy tissues, and reducing side effects. This can be achieved through:
   Nanotechnology: Nanoparticles can be engineered to carry drugs directly to diseased cells (e.g. cancerous tumors)
   Ligand targeting: Drugs are linked to molecules that target specific receptors on diseased cells.
   Biodegradable polymers: Used for controlled release and tissue-specific targeting.

5. **Nanomedicine**
   The application of nanotechnology in drug delivery involves using nanoparticles, liposomes, micelles, and other nanostructures to carry drugs in the body. These systems can provide targeted drug delivery. increase bioavailability, and improve drug solubility.
6. **Biodegradable Drug Delivery Systems**
   These systems degrade within the body, eliminating the need for surgical removal. They are typically made of biocompatible materials, such as biodegradable polymers, and are used for controlled or sustained drug release.
7. **Smart Drug Delivery Systems**
   Smart systems respond to specific stimuli, such as changes in pH, temperature, or enzymes, to release the drug at the desired location and time. Examples include: Release the drug in response to changes in the pH at different parts of the gastrointestinal tract
   Thermosensitive systems: Release drugs in response to temperature variations, often used for localized delivery
   Enzyme-responsive systems: Release drugs upon encountering specific enzymes at the target site.
8. **Gene Delivery**
   Gene therapy involves delivering DNA or RNA to cells to treat genetic disorders. Delivery systems, such as viral vectors or lipid nanoparticles, are used to introduce the genetic material into the target cells.
9. **Liposomes and Lipid-Based Systems**
   Liposomes are spherical vesicles composed of lipid bilayers that can encapsulate drugs. Lipid-based drug delivery systems are widely used due to their abi to improve the solubility, stability, and bioavailability of poorly soluble drugs.
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10. **Microencapsulation**
    This involves encasing a drug in a polymeric or lipid material to protect it from degradation and control its release. Microencapsulation can also be used to mask the taste of certain drugs.
11. **Tissue Engineering and Implantable Systems**
    These systems focus on creating structures or scaffolds that deliver drugs or biomolecules to specific tissues, such as in wound healing.bone regeneration, or tissue repair

12. **Nanoparticles and Nanocarriers**

    Nanopartides are engineered to carry drugs and can be modified to target specific tissues. These camiers can increase drug solubility control release, and enable targeted delivery. Examples include

    - Gold nanoparticles
    - Polymeric nanoparticles
    - Liposomes
    - Dendrimers

13. **Pharmacogenomics and Personalized Medicine**

    This concept focuses on talloning drug delivery systems based on individual genetic profites, which can influenice drug metabolism and response. Pharmacogenomic approaches help in predicting how a patient will respond to a particular drug, improving the effectiveness of drug delivery systems.

14. **Bioavailability and Drug Solubility**

    Ensuring that the drug reaches the bloodstream in an effective concentration is crucial. Drug solubility is an important factor, and many drug delivery systems are designed to improve the solubility of poorly water-soluble drugs, thus enhancing their bioavailability

15. **Microspheres**

    Small spherical particles that can encapsulate a drug and release it over time. They are commonly used in controlled-wase drug delivery systems and can be made of various biodegradable materials

16. **Exosomes and Vesicles**

    These are small vesicles secreted by cells that can be used as natural carriers for drug delivery. Exosomes have potential in gene and drug delivery systems because they can cross biological barriers.

17. **Drug-Polymer Conjugates**

    Drug are chemically linked to polymers to improve their pharmacokinetic properties, such as solubility and half-life. These conjugates can also allow for controlled release and targeted delivery.

Conclusion

The development of effective drug delivery systems is essential to modem medicine, as it can significantly improve the therapeutic efficacy of drugs, minimize side effects, and improve patient compliance. With advancements in nanotechnology, biotechnology, and materials science, the field of drug delivery is rapidly evolving, offering new possibilities for treating a wide range of diseases.