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SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF BIOMEDICAL ENGINEERING

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UNIT – I - SUSTAINED AND CONTROLLED DRUG DELIVERY– SBM1610

UNIT 1

UNIT 1- SUSTAINED AND CONTROLLED DRUG DELIVERY

SUSTAINED AND CONTROLLED DRUG DELIVERY

Contents:

- Introduction,
- Properties ofdrugs,
- Pharmacokinetic properties of drugs,
- Sustained release formulations –concept,
- Physio-chemical biological properties ofdrugs,
- Advantages anddisadvantages
    - Controlled drug deliverysystems–
    - Automatically controlled drug delivery systems and theirbiomedical applications.

INTRODUCTION

- The ability of a chemical compound to elicit a pharmacological/ therapeutic effect is related to the influence of various physical and chemical (physicochemical) properties of the chemical substance on the bio molecule that it interacts with.

  1)Physical Properties: Physical property of drug is responsible for its action

  2)Chemical Properties: The drug react extracellularly according to simple chemical reactions like neutralization, chelation, oxidation etc.
- Various Physico-Chemical Properties are,
    - Solubility
    - Partition Coefficient
    - Dissociation constant
    - Hydrogen Bonding
    - Ionization of Drug
    - Redox Potential
    - Complexation
    - Surface activity
    - Protein binding
    - Isosterism
- Drug delivery systems refer to the technology utilized to present the drug to the desired body site for drug release and absorption.
- Newer discoveries and advancements in technology has led to various new techniques of delivering the drugs for maximum patient compliance at minimal dose and side effects.

IDEAL DRUG DELIVERY SYSTEM

- First, it should deliver drug at a rate dictated by the needs of the body over the period of the treatment.
- Second it should channel the active entity solely to the site of action.
- This is achieved by development of new various modified drug release dosage forms, like-
    - ✓ Control release dosage forms
    - ✓ Time release dosage forms
    - ✓ Sustained release dosage forms
    - ✓ Site specific or targeted drug delivery systems etc

PROPERTIES OF DRUGS

Physicochemical properties of the drug, which influence drug absorption and various properties, which includes

- Lipid solubility and partition Co-efficient
- pKa
- Molecular weight and volume
- aqueous Solubility
- chemical stability

Lipid Solubility And Partition Co-Efficient

Conventional drug molecules which tend to be Small and lipophilic absorption occurs trans-cellular via passive diffusion across the epithelial cells.For Ex. GI tract (epithelial interface) is assumed to act as a simple lipophilic barrier absorption occurs down a concentration gradient.

1. Absorption Co-efficient
2. Pka: (Degree of Ionization)
3. Molecular Weight and Molecular Conc. Volume:
4. Solubility
5. Stability

1. Absorption Co-efficient

a)Partition Co-efficient

A measure of the lipid solubility of a drug is given by its oil / water equilibrium portion coefficient. This is determined by adding the drug to a mixture of equal volumes of a lipophilic liquid (often Octanol) and H_2O and shaking the mixture vigorously to promote Partitioning of the drug in to each phase.

Absorption Co-efficient

When equilibrium is attained separated and assayed for drug the phases are separated and assayed for drug.

The partition coefficient (P) is given by

$P = C_{oil} / C_{water}$.

Where C_{oil} = Concentration of drug in the oil phase

C_{water}= Concentration of drug in the water phase or water

2) Pka: (Degree of ionization)

(Pka = Constant dissociation of acid)

Mary drugs are weak electrolytes and their degree of ionization depends on both their Pka and the pH of the solution. Example. Assuming for transcellularpassive diffusion that the GI tract is acting as a simple lipophilic barrier, the ionised form of a molecule will be more water soluble and will have negligible lipidsolubilityin the compassion withionized lipid soluble form that is:

- Un-ionized form of the drug = lipophilic.
  Membrane transport
- Ionized form of the drug= hydrophilic
  Minimal membrane transport.

3) Molecular weight and molecular concentration volume:

Drug diffusivity is inversely proportional to molecular volume. This means that drug diffusivityacross membrane is sensitivity to molecular weight, since molecular volume is determined by a number of factors, including the molecular weight of the molecule. Therefore, large molecules will diffuse at a slower rate than Small molecules.
Molecular volume is also determined by:

- The overall confirmation of the molecule.
- The heteroatom content that may be involved in inter and intra molecular hydrogen bonds.

4) Solubility

Drug solubility is also critically dependent on the Pkaof the drug and the prevailing pH of the GI tract. The ionized form of a drug molecules is the more-water soluble form, therefore the dissolution rate of the weak acids increases with increasing pH, whereas the dissolution rate of the weak bases decreases with increasing pH.

Ionised form of a drug that is require for aqueous solubility. Unionised form is required for lipid solubility and passive diffusion. Balance between the lipid and aqueous solubility a drug is required for successful absorption.

Various strategies to increase the stability of the drug are:

- Salt formation
- Polymorphic form- different form of salt
- Amorphous form
- Solvents
- Formulation Factors

5) Stability

The stability of a drug in vitro may be adversely affected by various environmental factors including temperature, Pressure, light moisture and pH.

SUSTAINED RELEASE DRUGS

Any of the dosage form that maintains the therapeutic blood or tissue levels of drug by continuous release of medication for a prolonged period of time, after administration of a single dose.

- The basic goal of therapy is to achieve steady state blood level that is therapeutically effective and nontoxic for an extended period of time.

CONTROLLED RELEASE DRUG DELIVERY

- ✓ Delivery of the drug at a predetermined rate and /or to a location according to the needs of the body and disease states for a definite period of time.
- ✓ Controlled release is perfectly zero order release that is the drug release over time irrespective of concentration.

PHYSIOCHEMICAL PROPERTIES OF DRUGS

Definition pharmacokinetics the quantitative study of drug movement in through and out of the body (or) is the study of how drugs enter the body reach the site of action body that is the and are study of

a) Drug absorption
b) Drug distribution
c) Drug metabolism
d) Drug excretion

These process [ADME) are called pharmacokinetic processes.

Physiochemical Properties of Drugs mainly depends on:

1) Aqueous solubility &PKa:
2) Partition coefficient:
3) Drug stability:
4) Protein binding:
5) Molecular size & diffusivity:
6) Dose size:

1) Aqueous solubility &PKa:

- ✓ **Aqueous solubility**:–
  - A drug with good aqueous solubility, especially if pH independent, serves as a good candidates
  - Drug to be absorbed it first must dissolve in the aqueous phase surrounding the site of administration and then partition into absorbing membrane.

Noyes Whitney Equation is: $\underline{\mathbf{dc = K_D A C_S dt}}$

where ,dc/dt= dissolution rate
K_D = Dissolution rate constant.

A = total surface area of drug.

Cs = aqueous saturation solubility.

- Drugs with low aqueous solubility have low dissolution rate and have oral bioavailability problems. E.g.: Tetracycline.
- Drugs with high aqueous solubility are undesirable to formulate SRDF's. • E.g.: Paracetamol

✓ **pKa (acid dissociation constant)** :–

- The aqueous solubility of weak acids & weak bases is governed by the pKa of the compound and pH of the medium.
- **pH and pKa**
- Once you have pH or pKa values, you know certain things about a solution and how it compares with other solutions:
- The lower the pH, the higher the concentration of hydrogen ions [H^+].
- The lower the pKa, the stronger the acid and the greater its ability to donate protons.
- pH depends on the concentration of the solution. This is important because it means a weak acid could actually have a lower pH than a diluted strong acid. For example, concentrated vinegar (acetic acid, which is a weak acid) could have a lower pH than a dilute solution of hydrochloric acid (a strong acid).
- On the other hand, the pKa value is constant for each type of molecule. It is unaffected by concentration.
- Even a chemical ordinarily considered a base can have a pKa value because the terms "acids" and "bases" simply refer to whether a species will give up protons (acid) or remove them (base). For example, if you have a base Y with a pKa of 13, it will accept protons and form YH, but when the pH exceeds 13, YH will be deprotonated and become Y. Because Y removes protons at a pH greater than the pH of neutral water (7), it is considered a base.

Table. 1: Weak acid and Weak Base

a) FOR WEAK ACID	**b) FOR WEAK BASES**
➢ Weakly acidic drug exist as unionized form in the stomach absorption is favored by acidic medium. **St = So(1+Ka[H]) = So(1+10pH-pKa)** where, St – Total solubility of the weak acid So – Solubility of the un-ionized form Ka – Acid dissociation constant H - Hydrogen ion concentration	➢ Weakly basic drug exists as ionized form in the stomach hence absorption of this type is poor in this medium . **St = So(1+[H] Ka) =So(1+pKa-pH)** Where, St – Total solubility of both conjugate and free base form of weak base. So– Solubility of the free base.

2) Partition coefficient:

Between the time a drug is administered and is eliminated from the body, it must diffuse through a variety of biological membranes.

- Partition coefficient is the fraction of drug in an oil phase to that of an adjacent aqueous phase.

  K=Co/Cs

  where, Co= Equilibrium concentration in organic phase.

Cs= Equilibrium concentration in aqueous phase.

- Drugs with extremely high partition coefficient are very oil soluble and penetrates in to various membranes very easily.
- High partition coefficient compound are predominantly lipid soluble and have very low aqueous solubility and thus these compound persist in the body for long periods.

3) Drug stability:

- Solid state undergoes degradation at much slower rate than in the suspension or solution etc..
- Drugs stable in stomach gets released in stomach and which are unstable gets released in intestine.
- Drugs with stability problems in any particular area of G.I.T are less suitable for the formulation.
- Drugs may be protected from enzymatic degradation by incorporation in to a polymeric matrix

4) Protein binding:

- Drug binding to plasma proteins (albumins) & resulting retention of the drug in the vascular space.
- Drug-protein binding serve as a depot for drug producing a prolonged release profile, especially it is high degree of drug binding occurs.
- Main forces for binding are Vander Waal forces, hydrogen bonding, electrostatic forces.
- Charged compounds has greater tendency to bind proteins than uncharged ones.
- Extensive binding of plasma proteins results in longer half-life of elimination for the drug.
- E.x..95% binding in Amitriptyline , diazepam , diazepoxide.

5) Molecular size & diffusivity:

- The ability of a drug to diffuse through membranes is called diffusivity which is a function of molecular weight.
- In most polymers it is possible to relate log D to some function of molecular size as,
- Log D = - Sv log v + Kv = - SM log M + Km

where, V – Molecular volume.

M – Molecular weight.

Sv, Sm, Kv& Km are constants.

- The drugs with high molecular weight show very slow kinetics.

6) Dose size:

- For those drugs requiring large conventional doses, the volume of sustained dose may be too large to be practical.
- The compounds that require large dose are given in multiple amounts or formulated into liquid systems.
- The greater the dose size, greater the fluctuation.
- So the dose should have proper size.

MERITS OR ADVANTAGES

- Reduction in dosing frequency.
- Enhanced patient convenience and compliance.
- Reduction in adverse effects (both systemic and local), esp. of potent drugs, in sensitive patients.
- Reduction in health care costs.
- Improved efficiency of treatment.
- Reduces nursing and hospitalizing time.
- Maximum bioavailability with a minimum dose.
- Reduction in blood level fluctuations of drug, thus better management of the disease.

DEMERITS OR DISADVANTAGES:

- Probability of dose dumping.
- Reduced potential for dose adjustment.
- Cost of single unit higher than conventional dosage forms.
- Increase potential for first pass metabolism.
- Requirement for additional patient education for proper medication.
- Decreased systemic availability in comparison to immediate release conventional dosage forms.
- Poor *in vitro* and *in vivo* correlations.

PROPERTIES OF DRUG

Biological half life

- The usual goal of sustained release product is to maintain therapeutic blood level over an extended period, to this drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life (t1/2)
- Therapeutic compounds with short half-life are excellent candidates for drug preparation since these can reduce dosing frequency.

Drugs with half-life shorter than 2 hours:

- Drugs like **Furosemide, levodopa** are poor for sustained release formulation because it requires large rates and large dose compounds with long half-life.
- More than 8 hours are also generally not used in sustaining forms, since their effect is already sustained. E.g.; **Digoxin, Warfarin, Phenytoin** etc.

Margin of safety (Therapeutic index):

- In general the larger the volume of therapeutic index safer the drug.

- Drug with very small values of therapeutic index usually are poor candidates for SRDF due to pharmacological limitation of control over release rate .e.g.- induced digtoxin, Phenobarbital, phenotoin.
- Larger the TI ratio the safer is drug. It is imperative that the drug release pattern is precise so that the plasma drug concentration achieved in under therapeutic range.

SUSTAINED RELEASE FORMULATIONS – CONCEPT

Formulations Methods Embedding the drug in matrix:

- Matrix may be defined as uniform dispersion of drug in solid which is less soluble than a drug in the dispersion fluid, & which for the continuous external phase of the dispersion effectively impeder the passage of the drug from the matrix to the dispersion fluid.
- Drug release through-diffusion
- Least complicated approaches to manufacture sustained release dosage form involves the direct compression of drug, materials & additives to form a tablet.

Controlled release formulations – concept

Definition

Controlled release system have become very useful tool in medical practice. Controlled release system maintains of constant therapeutic plasma concentrationof the drug within the therapeutic range of the drug over prolonged periods. These delivery system offers numerous advantages to conventional dosage which include fewer doses per day or week and reduce its adverse effects.

Eg: Polymers used for drug releasein case of controlled drug delivery system

DRUG RELEASE FORMULATION:

Controlled delivery system offer an alternative approach to regulate both the duration and spatial localization of therapeutic agents. In controlled delivery the active agent is combined with other (casually synthetic) components to produce delivery system. Controlled delivery system frequently involve combinationsof active agents with inert polymeric materials for the release of drugs.

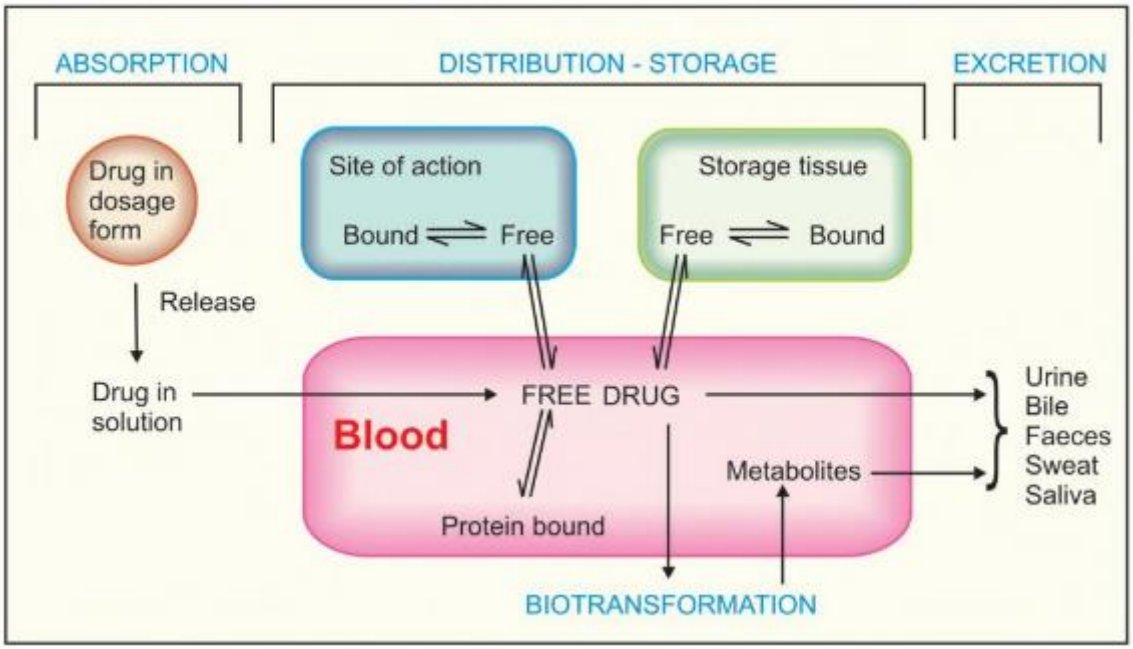

Fig. 1: Pharmacokinetic processes

DISTRIBUTION OF DRUG MOLECULES:

Once a drug has gained access to the blood stream, it gets d distributed to other tissues that initially had no drug, concentration gradient being in the direction of plasma to tissues. The extent of distribution of a drug and its pattern of tissue distribution depends on its:

- Lipid solubility
- Ionization at physiological pH (a function of its pKa)
- Extent of binding to plasma and tissue proteins
- Presence of tissue-specific transporters
- Differences in regional blood flow

Movement of drug proceeds until an equilibrium is established between unbound drug in the plasma and the tissue fluids. Subsequently, there is a parallel decline in both due to elimination.

Apparent volume of distribution {V) Presuming that the body behaves as a single homogeneous compartment with volume V into which the drug gets immediately and uniformly distributed.

$$V = \frac{\text{dose administered i.v.}}{\text{plasma concentration}}$$

Factors governing volume of drug distribution

- Lipid: water partition coefficient of the drug
- pKa value of the drug • Degree of plasma protein binding
- Affinity for different tissues
- Fat: lean body mass ratio, which can vary with age, sex, obesity, etc.
- Diseases like CHF, uraemia, cirrhosis

Lipid-insoluble drugs do not enter cells approximates extracellular fluid volume, e.g. streptomycin, gentamicin 0.25 L/kg.

BIOTRANSFORMATION (Metabolism)

Biotransformation means chemical alteration of the drug in the body. It is needed to render nonpolar (lipid-soluble) compounds polar (lipid-insoluble) so that they are not reabsorbed in the renal tubules and are excreted. In the absence of metabolism, body will not be able to get rid of lipophilic substances, and they will become very long acting. Most hydrophilic drugs, e.g. streptomycin, neostigmine, pancuronium, etc. are little biotransformed and are largely excreted unchanged. The primary site for drug metabolism is liver; others are- kidney, intestine, lungs and plasma.

Biotransformation reactions can be classified into:

(a) Nonsynthetic reactions: a functional group (- OH, -COOH, -CHO, - H2, - SH) is generated or exposed- metabolite may be active or inactive.

(b)Synthetic reactions: Metabolite is mostly inactive; except few drugs, e.g. glucuronide conjugate of morphine and sulfate conjugate of minoxidil are active.

Non synthetic reactions are:

1) Oxidation

2) Reduction

3) Hydrolysis

4) Cyclization (This is formation of ring structure from a straight chain compound, e.g. cycloguanil from proguanil)

5) Decyclization(This implies opening up of ring structure of the cyclic drug molecule, such as barbiturates. phcnytoin. This is generally a minor pathway)

Synthetic Reactions

(i) Glucuronide conjugation

(ii) Acetylation

(iii) Methylation

(iv) Sulphate conjugation

(v) Glycine conjugation

(vi) Glutathione conjugation

(vii) Ribonucleoside/nucleotide synthesis

Only a few drugs are metabolized by enzymes of intermediary metabolism, e.g. alcohol by dehydrogenase. Majority of drugs are acted on by relatively nonspecific enzymes which are directed to types of molecules rather than to specific drugs. The same enzyme can metabolize many drugs. The drug metabolising enzymes are divided into two types:

1) Microsomal enzymes: These are located on smooth endoplasmic reticulum (a system of microtubules inside the cell), primarily in liver, also in kidney, intestinal mucosa and lungs.

2) Nonmicrosomal enzymes: These are present in the cytoplasm and mitochondria of hepatic cells as well as in other tissues including plasma.

Both microsomal and nonmicrosomal enzymes are deficient in the newborn, especially premature, making them more susceptible to many drugs, e.g. chloramphenicol, opioids. This deficit is made up in the first few month s, more quickly in case of oxidation and other phase-I reactions than in case of glucuronide and other conjugations which take J or more months to reach adult levels.

First-pass (Presystemic) Metabolism:

This refers to metabolism of a drug during its passage from the site of absorption into the systemic circulation. A II orally administered drugs arc exposed to drug metaboli zing enzymes in the intestinal wall and liver (where they first reach through the porta l vein).

EXCRETION OF DRUG:

Excretion is the passage out or systemically absorbed drug. Drugs and the ir metabolites are excreted in:

1. Urine:

Drug excretion in urine occurs via the kidney. It is the most important channel of excretion for majority of drugs.

2. Faeces:

Apart from the unabsorbed fraction, most of the drug present in faeces is derived from bile. Liver actively transports into bile organic acids (especially drug glucuronides by OATP and MRP2), organic bases (by OCT), other lipophilic drugs (by P-gp) and steroids by distinct nonspecific active transport mechanisms. Relatively larger molecules (MW > 300) are preferentially eliminated in the bile.

DOSAGE FORMS OF DRUGS:

Dosage form is a product suitable for administrationof a drug to a patient. Every active ingredient(drug) has to be formulated by adding othersubstances (excipients, diluents, preservatives,vehicles, etc.) according to a specific recipe andPackaged into a specific 'dosage form' such astablet, elixir, ointment. Injection vial, etc. whichis then administered to the object. The dosageform provides body to the drug. Demarkets singledoses, protects the active ingredient(s), and makesit suitable for administration in various ways.The important dosage forms are broadly classified into:

1) Solid dosage forms
2) Liquid dosage forms

1) Solid dosage forms

Solid dosage forms are like powders, tablets, pills, capsules, lozenges,suppositories etc.

1. Powders

The drug is in a dry and finelypulverized state. If the drug is for oraladministration, each dose has to be wrappedseparately or packed in sachets; therefore thisdosage form is inconvenient and unpopularexcept when the quantity is several grams.Eg. oral rehydration salts. Powders for topicalapplication (dusting powders) are supplied as:

Bulk powdersin metallic or plastic containerswith holes for sprinkling.

Effervescent powderscontain granulated sodium bicarbonate and citricor tartaric acid. They react when dissolved inwater to liberate CO_2 causing bubbling.

2. Tablets

The drug is powdered or granulated,mixed with binding agents, and othercxcipients, and compressed/moulded intodiscoid, oblong or other shapes suitable forswallowing. Thetablet may be plain or sugarcoated or film coated. Other specialized types of tablets are:

a)Chewable tablets-canbe chewed andswallowed, ingredients must be pleasant tasting.

b) Dispersible tablets- thetable t is dropped ina small quantity of water, wherein it dispersesquickly; the solution is then gulped.

c) Sublingual tablets-put under the tongue, thedrug is rapidly absorbed from the mouth.

d) Enteric coated tablet- thetablet is coated witha material that does not dissolve in the acidicmedium of the stomach; the tablet disintegratesonly on reaching the duodenum.

e) Sustained/Extended release tablets- Thesecontain drug particles which are coated todissolve at different rates. The active ingredientis made available for absorption over a longerperiod of time. The duration of action of shortacting (2-6 hours) drugs can be extended to 12hours or more.

f) Controlled release tablets- Asemipermeablemembrane controls the release of the drug -prolonging its duration of action.

3. Pills

These are archaic dosage forms in whichthe drug powder is mixed with honey/syrupto make a sticky mass. This is then rolled intospherical/oval bodies meant to be swallowed.

The term is often loosely applied to tablets aswell.

4. Capsules

These are water soluble cylindricalcontainers made of gelatin which are filled withpowdered or liquid medicament. The containerdissolves on swallowing so that the drug isreleased in the stomach. Soft gelatin capsulesdissolve very rapidly and generally containliquid medicament.

a) *Enteric coated*capsulesare designed to dissolve only on reaching theileum.

b) *Spansules*are extended release capsuleswhich are packed with granules of the drughaving different coatings to dissolve over arange of time periods.

5. Lozenges

These are tablet-like bodies ofvarious shapes containing the drug along witha suitable gum, sweetening and flavoringagents. They are to be retained in the mouthand allowed to dissolve slowly, providing thedrug for local action in the mouth and throat.

6. Suppositories:

These are conical bullet- shapeddosage forms for insertion into the anal canal,in which the drug is mixed with a mouldablefirm base that melts at body temperature andreleases the contained drug. Oval or suitablyshaped bodies for vaginal insertion are called***'pessaries',***while elongated pencil-like conesmeant for insertion into male or female urethraare called ***bougies.***

2. Liquid dosage forms

Liquid dosage forms are like aqueous solutions, Suspensions, Elixirs, Drops, Lotionsetc.

1. Aqueous solutions

They contain the drugdissolved in water, and may be meant fororal, topical orparenteral administration.Oral drug solutions often contain sweeteningand flavouring agents. Preservatives have tobe mostly added because shelf-life of waterysolutions is short.

2. Suspensions

Theseare dispersion of insolubledrugs in water with the help of a suspendingagent. **Emulsions**are these are uniform mixtures of twoimmiscible liquids (mostly oil and water) inwhich droplets of one (dispersed phase) aresuspended in the other (continuous phase)with the help of an amphiphilic emulsifyingagent. Milk is a naturally occurring emulsion.Both suspensions and emulsions tend to settledown on keeping; should be shaken thoroughlybefore use.

3. Elixirs

These are hydro-alcoholic solutions of drugs,usually sweetened with syrup and flavored byfruit extracts. *Syrups* have higher concentrationof sugar and are thicker in consistency. Drugsthat deteriorate in aqueous medium can bedispensed as *'dry syrups'* which is reconstitutedby adding water and shaking. The reconstitutedsyrup must be used within a few days.

4. Drops

These are relatively more concentratedsolutions of medicaments meant for oralingestion or external application to eye, nose orear canal. Oral drops are the preferred dosageform for infants and young children. Eye/nasal drops should be isotonic. Eye drops needsterilization. Drops are supplied in vials witha nozzle or along with a dropper for accuratedosing.

5. LotionsDrops

These are solutions, suspensions oremulsions meant for external application tothe skin without rubbing. They generally havesoothing, cooling, protective or emollientproperty and are better suited than creamsor ointments for hairy skin.

6.Injections

These are sterile solutions orsuspensions in aqueous or oily medium forsubcutaneous or intramuscular administration.Only aqueous solutions (not suspensions)are suitable for intravenous (i.v.) injection,because particles in suspension and oilsinjected i.v. can cause embolism.

Semisolid dosage forms

1. Ointments

These are greasysemisolidpreparations meant for external application tothe skin, eye, nasal mucosa, ear or anal canal.The drug is incorporated in an oily base, suchas soft or hard paraffin, wool fat, bee's wax,etc. Ointments are not suitable for oozingsurfaces, because they are more occlusive anddo not allow evaporation of water. Rather theyare good for dry, chronic lesions.

2.Creams

These aresimilar to ointment but the base is a water in oilemulsion. The medicament is better absorbedinto the skin from creams than from ointments,and creams are cosmetically more acceptablethan ointments.

3. Pastes

These are nongreasy preparationsof thick consistency containing hydrophilicadhesive powders such as starch, preparedchalk, aluminium/magnesium hydroxide,zinc oxide, carboxy methylcellulose, etc.which swell by absorbing water. Pastes maycontain viscous nonoily liquids like glycerolor propylene glycol. Pastes can be applied toinflamed or excoriated skin, oozing surfacesand mucous membranes. Toothpastes are itemsof personal hygiene, and medicated toothpastesare extensively used in dentistry.

4. Gels

The medicament is incorporated ina viscous colloidal solution of gelatin orsimilar material and is usually dispensed incollapsible tubes. They are meant for externalapplication to the skin or mucosa and providelonger duration contact, but are nongreasyand washable with water. Gels are suitable forapplication to hairy skin, and are commonlyapplied to oral ulcers because they are betterretained than aqueous solutions.

Inhalations:

Drugs which are gases or volatile liquids canbe administered by inhalation carried into air oroxygen with the help ofa mouth piece, face mask,hood or endotracheal tube. Nonvolatile liquidsand fine pa1iicle solids can be aerosolized usinga metered dose inhaler, jet nebulizer, rotahaler orspinhaler for inhalation through the mouth.

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QUESTIONS

1. Write various modified drug release dosage forms
2. Define Biological half-life.
3. Give the importance of dose size
4. What does the term “bioavailability” mean?
5. Which route of drug administration is most likely to lead to the first-pass effect?
6. What is characteristic of the oral route?
7. Explain briefly the Physiochemical properties of drugs
8. Describe briefly the sustained drug delivery mechanism
9. Explain in detail about the various Properties of drugs.
10. Write in detail the drug release formulations

UNIT-II
POLYMERS &TARGETTED DRUG DELIVERY SYSTEMS

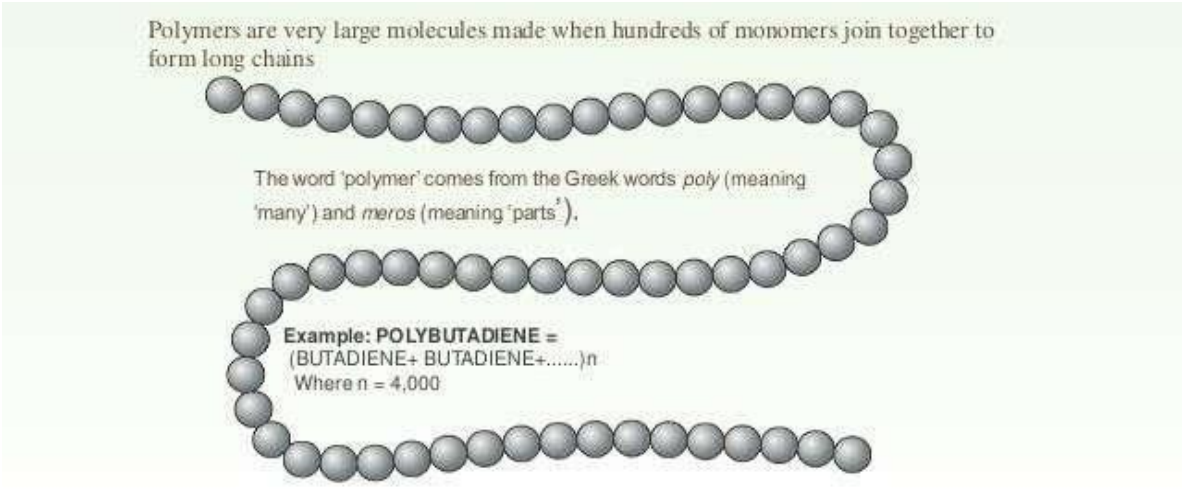
Contents:

Polymers used in drug delivery systems –

- **Modules,**
- **Classification,**
- **Characterization,**
- **Advantages and disadvantages of polymer**
- **Targeted drug delivery systems concepts**
  –Nanoparticles
  –Liposomes,
  –Microspheres
  – Hydrogels

Introduction To Polymers:

- Polymers are complex and giant molecules usually with carbons building the backbone, different from low molecular weight compounds.
- The small individual repeating units/molecules are known as monomers(means single part
- UA polymer with two different monomers is known as a copolymer or homopolymer



1. General characters of Polymers are:-

- Insoluble, inert - polyethylene, polyvinyl chloride, methyl acrilate, ethylcellulose.
- Insoluble, erodible – carnauba wax, stearyl alcohol, castor wax.
- Hydrophilic – methyl cellulose, hydroxyl ethyl cellulose, sodium carboxymethyl cellulose, sodium alginate.
- In a matrix system the drug is dispersed as solid particle within a porous matrix formed of a water insoluble polymer, such as poly-vinyl chloride.

Polymers:- Used in Drug Delivery System

1.Polymers used

- Polyvinyl alcohol
- Polyacrylic acid
- Ethyl cellulose(pH sensitive)
- Polyethylene
- Polymethacrylate
- Poly (ethylene-vinyl acetate)
- Cellulose nitrite
- Silicones
- Poly (lactide-co-glycolide)

Characteristics of Ideal Polymer is:

- Low Density.
- Low coefficient of friction.
- Good corrosion resistance.
- Good mould ability.
- Excellent surface finish can be obtained.
- Can be produced with close dimensional tolerance
- Economical.
- Poor tensile strength
- Low mechanical properties
- Poor temperature resistance.
- Can be produced transparent or in different colours

Classification of Polymers:-

- Based on Source
- Based on Structure
- Based on Polymerization
- Based on Molecular force

Classification based on source:

- Natural polymers - The definition of a natural polymer is a polymer that results from only raw materials that are found in nature. Example - Proteins, Cellulose, Starch, Rubber.
- Semi-synthesis polymers - The polymer can obtained both Natural as well as Synthetic origin is known as Semisynthetic polymer Example Cellulose derivatives - Cellulose acetate (Rayon)
- Synthesis polymers - This are the polymer was prepared by Laboratory is known as Synthetic Polymer Example - Buna-S Buna R. Nylon. Polythene. Polyester

Classification based on structure:

- Linear polymers the smallest repeating unit arrange in straight line path is known as Linear polymer. Example - PVC.

- Branched chain polymers - contain linear chains having some branches. Example - low density polymer.
- Cross linked chain polymers tri-functional monomers and Example bakelite, melamine

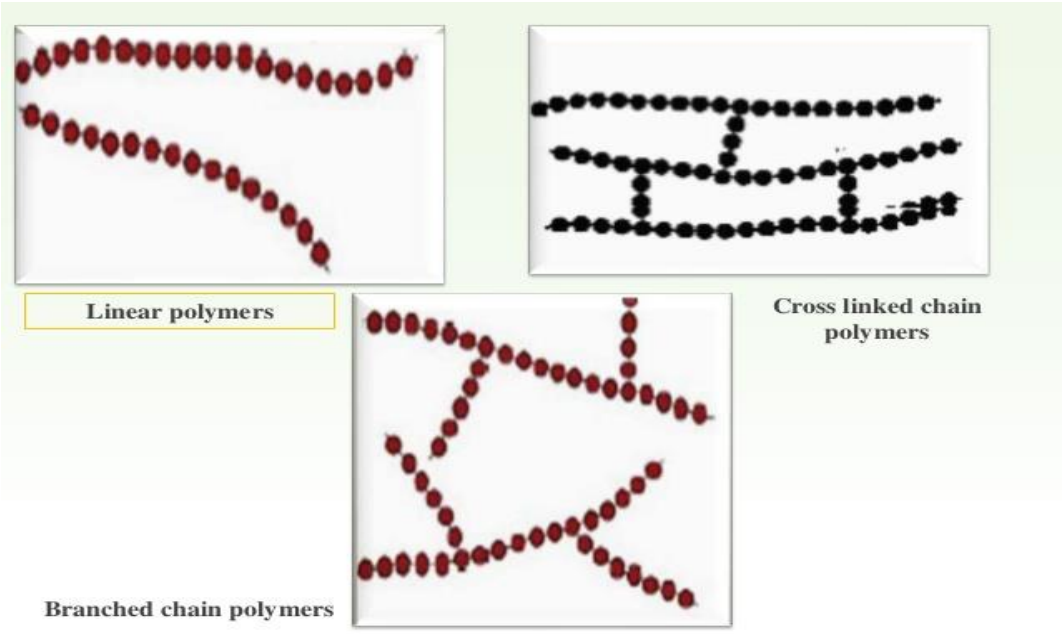


Fig. 1: Polymer Classification

Classification based on polymerization:

There are two type of Polymers:

1. Addition polymers
2. Condensation polymers

1. Addition polymers

- Formed by the repeated addition of monomer molecules possessing double or triple bonds
- One from of polymer is converted into anther from of polymer loss of atoms, ion, from Molecule

  Ex: n(CH=CH2)- Ethylene -(CH-CH2) polyethylene

2.Condensation polymers:

- Formed by repeated condensation reaction between two different bi-functional or iri Junctional monomeric units
- One polymer can converted into another Iron polymer without loss of atoms ion from molecule

  Eg. Terylene (dacron). Nylon 6. 6. Nylon 6

Classification based on molecular force:

Nylon: - Nylon is used as general name for all synthetic fibre forming polyamides,i.e. having a protein like structure. These are the condensation polymers of diamine and dibasic acids A number is usually suffixed with the Nylon which refers to the number of carbon atoms present in the diamine and the dibasic acids respectively.
Example: nylon 6.6, nylon-6,6: Nylon-6,6 is obtained by the polymerization of adipic acid.

Thermoplastic Polymers:

- These are linear or slightly branched long chain polymers, which can be softened on heating & reversibly hardened on cooling repeatedly
- Their hardness is temporary property & varies with temperature.
- The polymer under heating it can convert one stare to another state and after cooling in can again convert its original state.
  Example- polyvinyl chloride

Classification based on molecular force:

Thermosetting polymers:

- Initial Mixture of Reactive, Low Molar Mass
- Compounds Reacts Upon Heating
- In the mold to form an insoluble, infusible network
  Example: Bakelite
- Bakelite: Bakelite Is formed of Phenol and form- aldehyde Polymerization

General Mechanism Of Drug Release From Polymer

Three primary mechanism for drug release, namely:

- Diffusion
- Degradation
- Water penetration (Swelling)

Any of these mechanism can occur in a givenrelease system

Drug release from polymer by diffusion

- Rate limiting step is diffusion of drug through inert water insoluble membrane barrier.

There are two types,

a) Reservoir
b) Matrix

Reservoir diffusion system

- In membrane-controlled reservoir devices, the drug is contained in a core, which is surrounded by a polymer membrane, and it is released by diffusion through this rate controlling membrane
  E.gPoly(N-vinyl pyrrolidone).Polyethylene-co-vinyl acetate).

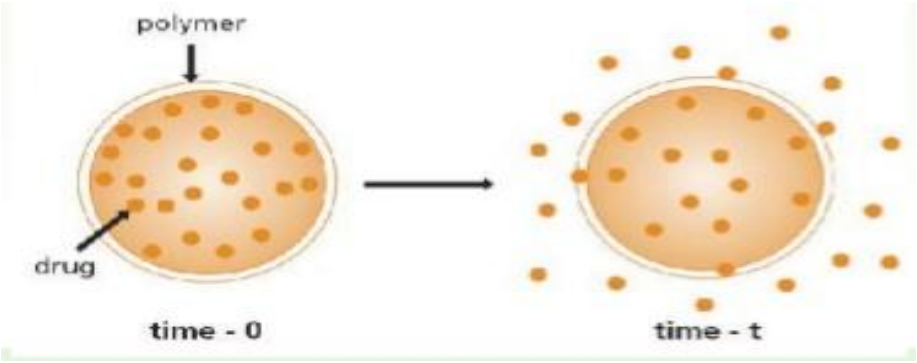


Fig. 2: Reservoir Diffusion System

Matrix diffusion system

In these devices, the drug is released either by passing through the pores or between polymer chains, and these are the processes that control the release rate.

Such as polyethylene, polyvinylacetate

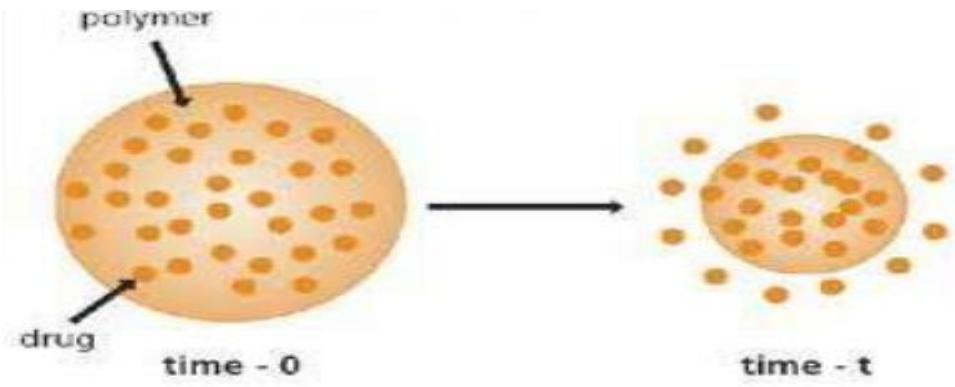


Fig. 3: Matrix Diffusion System

Degradation

- The drug molecules, which are initially dispersed in the polymer, are released as the polymer starts eroding or degrading.
- The four most commonly used biodegradable polymers in drug delivery systems are:
    1. Poly (lactic acid),
    2. Poly(lactic-co-glycolic acid).
    3. Polyanhydrides, poly(ortho esters),
    4. And Poly(phosphoesters).

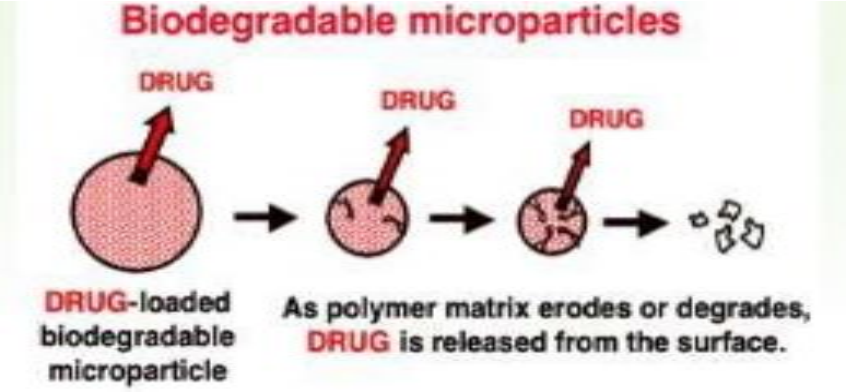


Fig. 4: Degradation

Water penetration (swelling)

- This type of systems are Initially dry and when placed in body, absorb water or other fluid and it swells.
- Swelling increases aq. solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into external environment E.g(N-isopro-pylacrylamide), Ethylene-vinyl alcohol

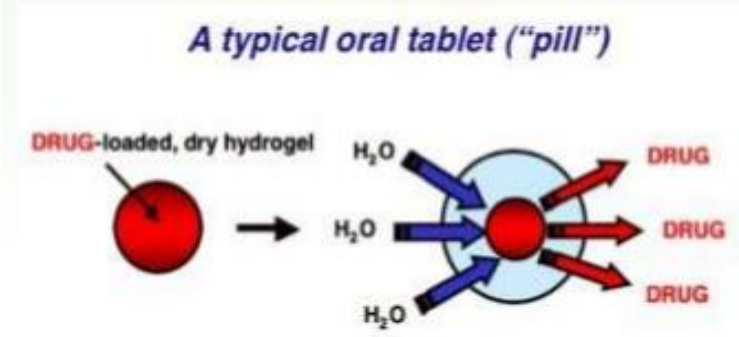


Fig. 5: Water Penetration

<u>Bio degradation of polymers -</u>

- Bio degradation is the chemical chances that alter the nolecular weight of solubility of the polymers
- Bio erosion may refer to as physical process that result in weight loss a polymer device.
- The erosion of polymers basically takes place by two methods:
    1. Hydrolytic mechanism
    2. Enzymatic mechanism

1. Hydrolytic Mechanism

- Hydrolytic degradation of polymers may be defined as the breaking of chemical bonds in the polymer backbone by the attack of water to form oligomers and finally monomers

- This kind of hydrolysis could not require of specific biological compounds as proteases.
- All biodegradable polymer contain hydrolysable bonds Like glycosides, esters, ortho esters, anhydrides, carbonates, amides.
- Rate of hydrolytic degradation is modulated by hydrophilic characteristics.of the polymers

2. Enzymatic mechanism

- Enzymes are biological catalysts
- They accelerate reaction rates in living organisms without undergoing themselves any permanent change.
- Hydrolysis reactions may be catalyzed by enzymes known as hydrolases, which include proteases, esterases, glycosidases, and phos-phatases, among others.
- Enzymatic surface degradation occurs when enzymes cannot penetrate the interior of the polymer, due to high cross-link density or limited access to cleavage points, forcing the surface or exterior bonds to cleave first.

SYNTHESIS OF POLYMER:

INITIATION (Birth):

The first step in chain polymerization initiation involves the formation of a free radical. Each initiating radical has the ability to attack the double bond is a monomer. In this way, the radical is transferred to the monomer and monomerradical is produced. Addition can occur at either end of the monomer.

PROPAGATION (Growth):

The monomer radical is also able to attack another monomer and then another monomer, and so on and so forth. This step is called propagation by which a macro radical is formed. The entire propagation reaction usually takes place within a fraction of a second.

TERMINATION (Death):

Chain termination is the chemical reaction that ceases the formation of reactive intermediates in a chain propagation step in the course of polymerization effectively bringing it to a halt.

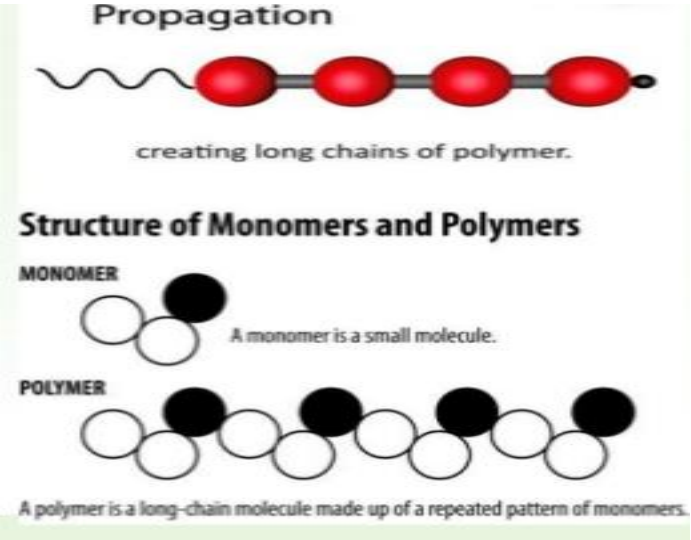


Fig. 6: Synthesis

Biopolymers:

1. Nucleic acid polymers (DNA, RNA)
2. Amino acids polymers (Proteins)
3. Sugar polymers (Carbohydrates)
4. Genetic information for the cell: DNA
5. Structural strength and catalysis: Proteins
6. Energy source: Carbohydrates

Advantages of polymer

- Localised delivery of drug
- Sustained delivery of drug
- Decrease in dosingfrequency
- Reduce side effect
- Improve patient compliance
- Biodegradable and biocompatible

Disadvantages of polymer

- Exhibit dose dumping effect
- High initial drug release after administration
- Low mechanical properties

APPLICATION OF POLYMER

- Application in Drug delivery system
- In modified drug release delivery system
- Controlled release formulation
- Sustained release formulation
- Biomedical applications

- Tissue engineering
- Bone fixation devices
- Vascular graft
- Surgical adhesive

Table. 1: Polymer Applications

Polymer	**Application**
Polyethylene oxide	Cosmetic pharmaceuticals
Polyethylene glycol	Swelling agent
PVP	Tablet granulation
Polyvinyl alcohol	Tablet binder and coating
Ethyl cellulose	Sustained release system
Carboxy methyl cellulose	Super disintegrant
HPMC	Coating and binder

SUSTAINED RELEASE FORMULATIONS – CONCEPT:

1. Ion exchange resins

- Ion exchange resins are polymers that are capable of exchanging particular ions within the polymer with ions in a solution that is passed through them.
- Sustained delivery of ionizing acidic & basic drug can be obtained by complexing them with insoluble non-toxic anion exchanger & cation exchanger resin respectively.
- Release by diffusion.
- The complex can be prepared by incubating the drug-resin solution or passing the drug solution through a column containing ion exchange resin.

2. Micro-encapsulations

- Method for retarding drug release by coating its surface with a material (polymers) that retards penetration by the dispersion fluid.
- It is a mean of applying relatively thin coating to small particles of solid or droplets of liquids and dispersion. Can be done by-
    - spray congealing
    - spray drying
- Examples:
    - Nifedipine sustained-release tablets Treating high blood pressure.
    - Some brands of nifedipine sustained-release tablets may also be used to manage certain kinds of angina (chest pain).

Nifedipine sustained-release tablets are a calcium channel blocking agent. It works by dilating (widening) blood vessels.

1. Paroxetine controlled-release tablets

- Treating depression, panic disorder, or social anxiety disorder. It may also be used to treat premenstrual dysphoric disorder (PMDD), a severe form of premenstrual syndrome. It may also be used for other conditions as determined by your doctor.
- Paroxetine controlled-release tablets are a selective serotonin reuptake inhibitor (SSRI). It works by restoring the balance of serotonin, a natural substance in the brain, which helps to improve certain mood problems.

2. Xiral SR Sustained-Release Tablets

- Relieving congestion, sneezing, runny nose, and itchy, watery eyes due to colds, flu, or hay fever. It may also be used for other conditions as determined by your doctor.
- Xiral SR Sustained-Release Tablets are an antihistamine, decongestant, and anticholinergic combination. It works by blocking histamine, a substance in the body that causes sneezing, runny nose, and watery eyes. It also relieves nasal congestion by shrinking the nasal mucous membranes, which promotes nasal drainage, and dries the chest by decreasing lung secretions.

3. Sustained-release metformin hydrochloride

- Metformin hydrochloride(HCI), the only available biguanide, remains the first-line drug therapy for patients with Type 2 diabetes mellitus (T2DM), acting by decreasing the hepatic glucose output and peripheral insulin resistance. The advantages of metformin are a very low risk of hypoglycemia, weight neutrality and reduced risk of cardiovascular morbidity and mortality.
- It is an oral anti-hyperglycemic agent, shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is 50–60% with a relatively short plasma half-life of 1.5–4.5 h
- An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms such as abdominal discomfort, nausea and diarrhea that especially occur during the initial weeks of treatment.
- Side-effects and the need for administration two or three times per day when larger doses are required can decrease patient compliance.
- A SR formulation that would maintain plasma levels of the drug for 10–16 hours might be sufficient for once-daily dosing of metformin. SR products are needed for metformin to prolong its duration of action and to improve patient compliance.

NANOPARTICLES AS DRUG DELIVERY

1. Nanotechnology Science, engineering, and technology conducted at the nanoscale (1-100nm), where unique phenomena enable novel applications
2. Nanomedicine:
    - The medical application of Nanotechnology
    - Diagnosis, prevention and treatment of diseases

- Usage of nanoparticles to improve the behavior of drugs in different structures of nanoparticles & their approx. sizes
- They are in similar size range as biological nanostructures

3. Nanoparticles act as a vehicle on which the drugs are encapsulated within or chemically bonded
4. Usage of engineered nanoparticles to deliver drugs in a more targeted, efficient way, with less unpleasant side effects to patients
5. Liposome: Most commonly used nanoparticle Nano Drug Delivery System
6. Nano Drug Delivery System – Vehicle & Cargo Liposome as a Nano drug vehicle Specifically targets certain molecules to bind to Nano drugs within are protected during travel
7. Biocompatible as it has similar membrane as human cells
8. Nano drugs of different solubility properties are carried within the Liposome
9. Nanoparticle carrying drug is not able to enter, preventing toxicity to normal tissues
    - Cancerous blood vessels:
    - Cell walls are dilated with large gaps (200-1200nm) & compromised lymphatic drainage
    - Highly permeable for nanoparticles up to dia.400nm to enter and preferentially accumulate at tumor sites Passive Targeting

Nanoparticles As Drug Carriers

- These nanoscale drug carriers coated with nano-sensors
- It recognize diseased tissues and attach to them
- Releasing a drug exactly where needed.
- Nanoparticles could also be used to enter damaged cells and release enzymes that tell the cells to auto-destruct, or they could release enzymes to try to repair the cell and return it to normal functioning.

LIPOSOMES IN DRUG DELIVERY SYSTEM

Introduction

- Liposomes are spherical vesicles having an aqueous core enclosed by one or more phospholipid bilayers.
- Liposome were first produced in England in 1961 by Alec D. Bangham who was studying phospholipids and blood clotting.
- Liposome is derived from Greek
- Lipo- Fatty constitution
- Soma- Structure
- The size of a liposome ranges from some 20 nm up to several micrometers.

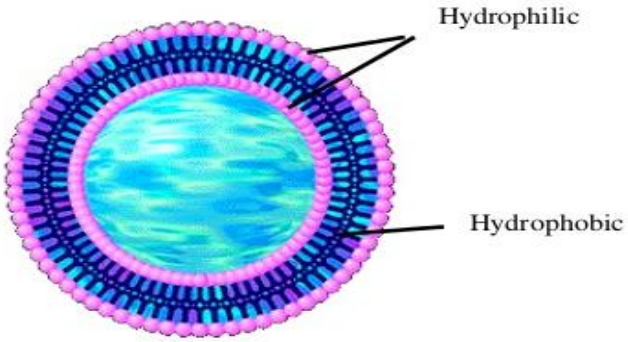


Fig. 7: Liposomes-Spherical vesicles with phospholipid bilayers

Phospholipids

- Phospholipids are the basic molecular building block of the liposome
- Phospholipids is a lipid which is Ampiphilic molecule and consist of
    - Hydrophilic polar head
    - Hydrophobic tails
- Hence have affinity for both hydrophilic drugs can be encapsulated in the aqueous phase and hydrophobic drug molecules can be incorporated in the lipid bilayers.

• Examples

- Dilauryl phosphotidyl choline (DLPCI
- Dimynstoy phosphotidyl choline (DMPC).
- Dipalmitoy phosphotidylcholine (DPPC) • Distearod phosphotidyl chaline (OSPC)
- Deyl phospnotidylcholine OOPC
- Diuril phosphatidyl clvceral DLPG)
- saroylphosphotid serine ESPS

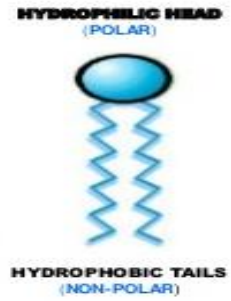


Fig. 8: Structure

Table. 2: Advantages and Disadvantages of Liposomes

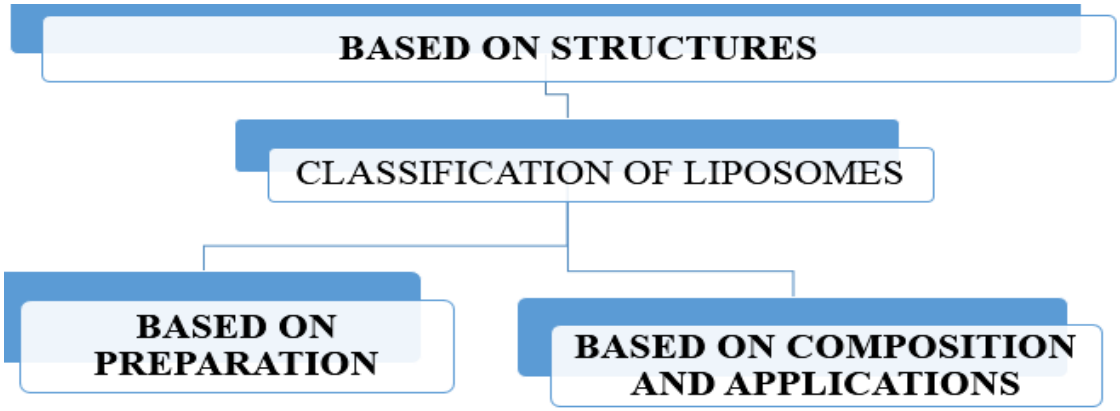
Advantages of Liposomes	Disadvantages of Liposomes
• Can load hydrophilic as well as hydrophobic drug • Increased efficacy & therapeutic index. • Increased stability of encapsulated drug. • Non-toxic. • Biodegradable.	• Long term unstability. • Some times phospholipids undergoes hydrolysis and oxidation reactions. • Sensitive to temperature change. • Leakage of encapsulated drug during storage.

• Non-immunogenic. • Lowers systemic toxicity. • Targeted delivery. • Protection of sensitive drug molecules. • Low Toxicity Due To Reduced Exposure To Sensitive Tissues. • Minimum ADR/No Side Effects. • Possible Formulation- suspension, emulsion, gel, Cream, lotion, Aerosol, reconstituted Vesicles.	• Production cost is high.

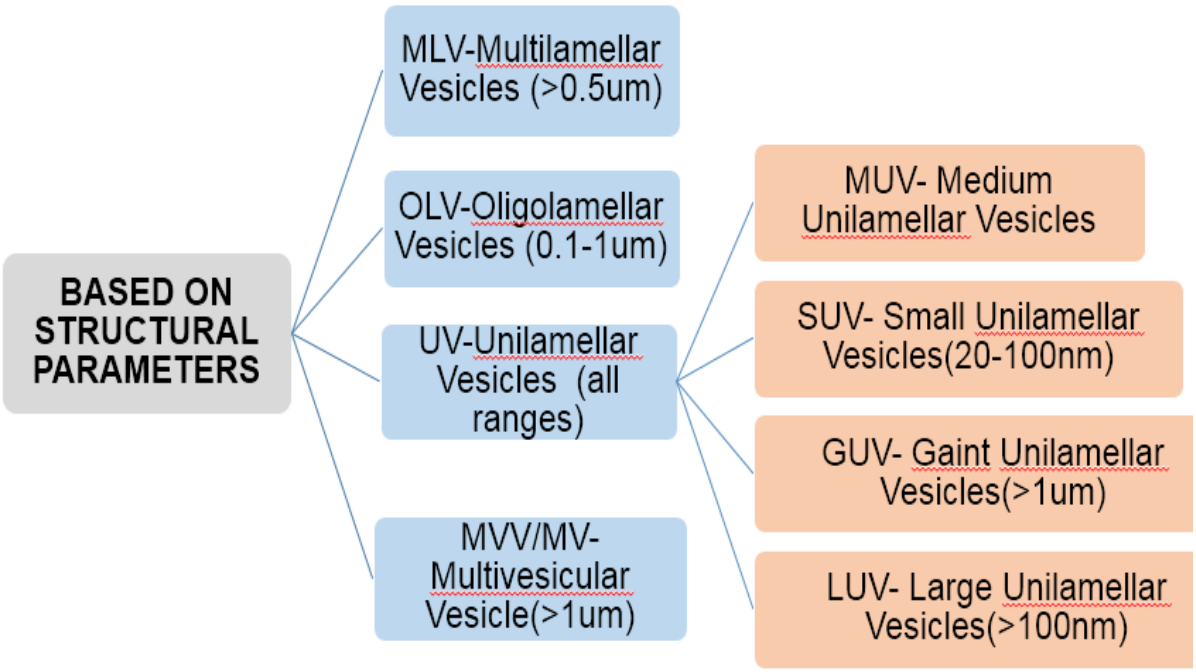
Classification of Liposomes

Liposomes are classified on the basis of:

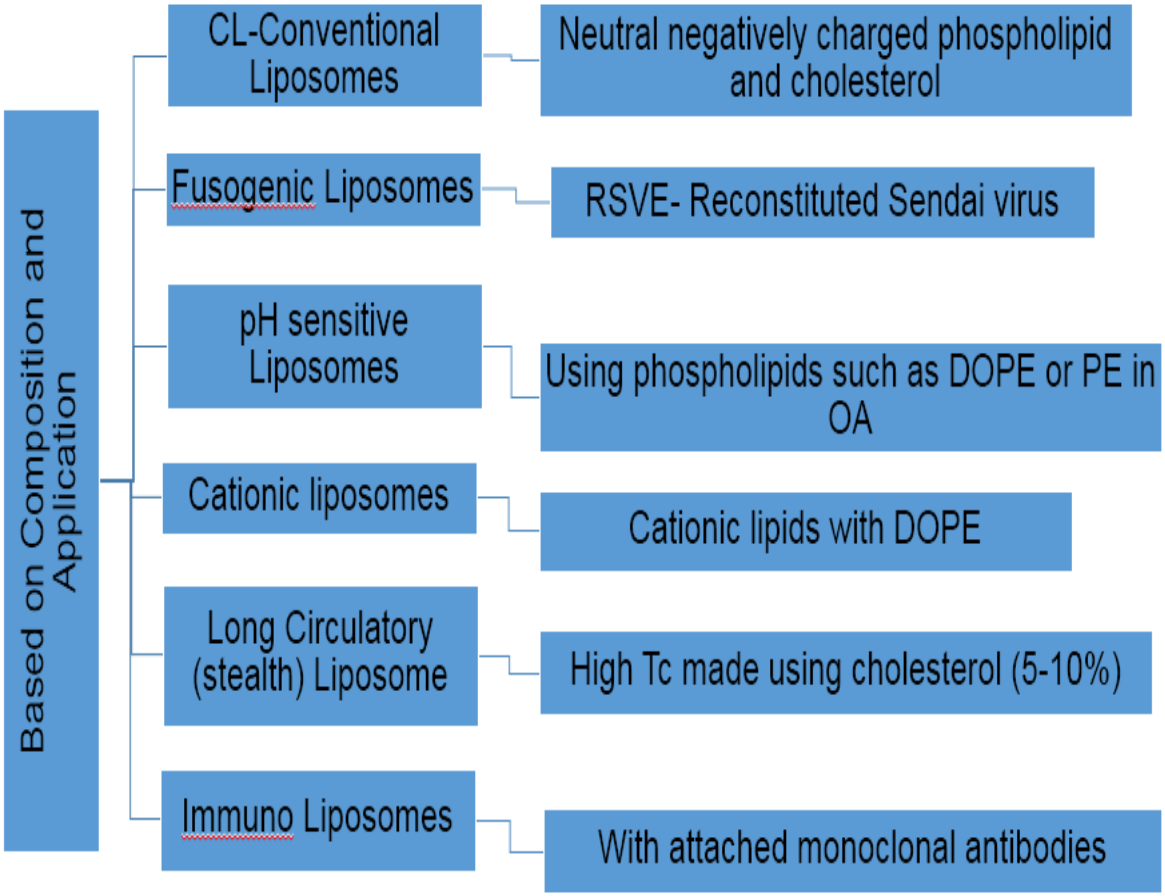
- ✓ Structural parameters
- ✓ Method of preparation
- ✓ Composition and Application



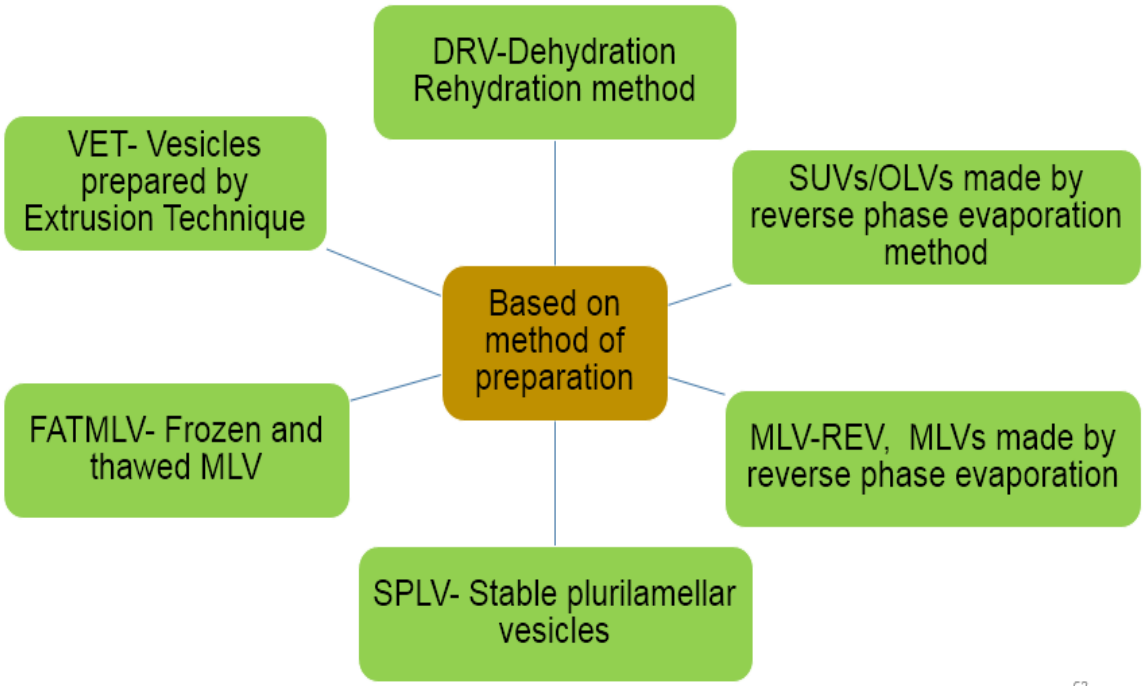
Classification Based on Structural Parameters



Classification Based on Composition and Application



Classification Based on method of preparation



Methods of Liposomes Preparations

The correct choice of liposome preparation method depends on thefollowing parameters:

1) Physicochemical characteristics of the material to be entrapped and those of the liposomal ingredients;
2) The nature of the medium in which the lipid vesicles are dispersed;
3) The effective concentration of the entrapped substance and its potential toxicity;
4) Additional processes involved during application/ delivery of thevesicles;
5) Optimum size, polydispersity and shelf-life of the vesicles for the intended application.
6) Batch-to-Batch reproducibility and possibility of large-scale production of safe and efficient liposomal products.

Therapeutic Application of Liposome

1. **Liposome as drug/protein delivery vehicles**
    - Controlled and sustained drug release.
    - Enhanced drug solubilisation.
    - Altered pharmacokinetics and biodistribution.
    - Enzyme replacement therapy and biodistribution.
    - Enzyme replacement therapy and lysosomal storage disorders.
2. **Liposome in antimicrobial, antifungal and antiviral therapy**
    - Liposomal drugs
    - Liposomal biological response modifiers
3. **Liposome in tumor therapy**
    - Carrier of small cytotoxic molecules.
    - Vehicle for macromolecules as cytokines organeas

4. **Liposome in gene delivery**
    - Gene and antisense therapy.
    - Genetic (DNA) vaccination.
5. **Liposome in immunology**
    - Immunoadjuvant.
    - Immunomodulator.
    - Immunodiagnosis.
6. **Liposome as artificial blood surrogates.**
7. **Liposome as radiopharmaceutical and radio diagnostic carriers.**
8. **Liposome in cosmetics and dermatology.**
9. **Liposome in enzyme immobilization and bioreactor technology.**

MICROSPHERE IN DRUG DELIVERY

- The microsphere are characteristically free flowing powder consisting of proteins or synthetic polymers, which are biodegradable in nature, and ideally having a particle size less than 200 µm.
- Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled released drug.

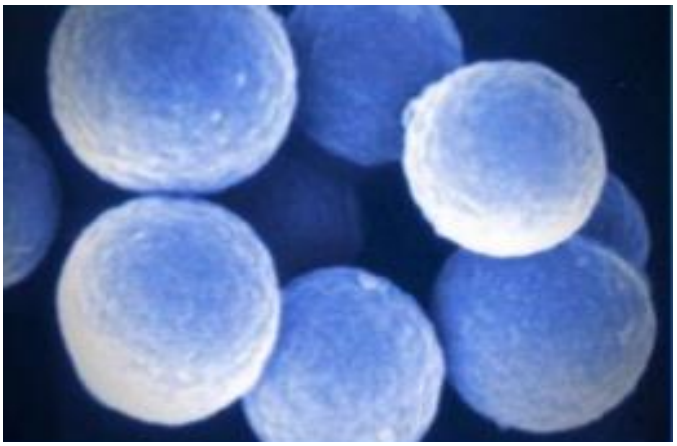
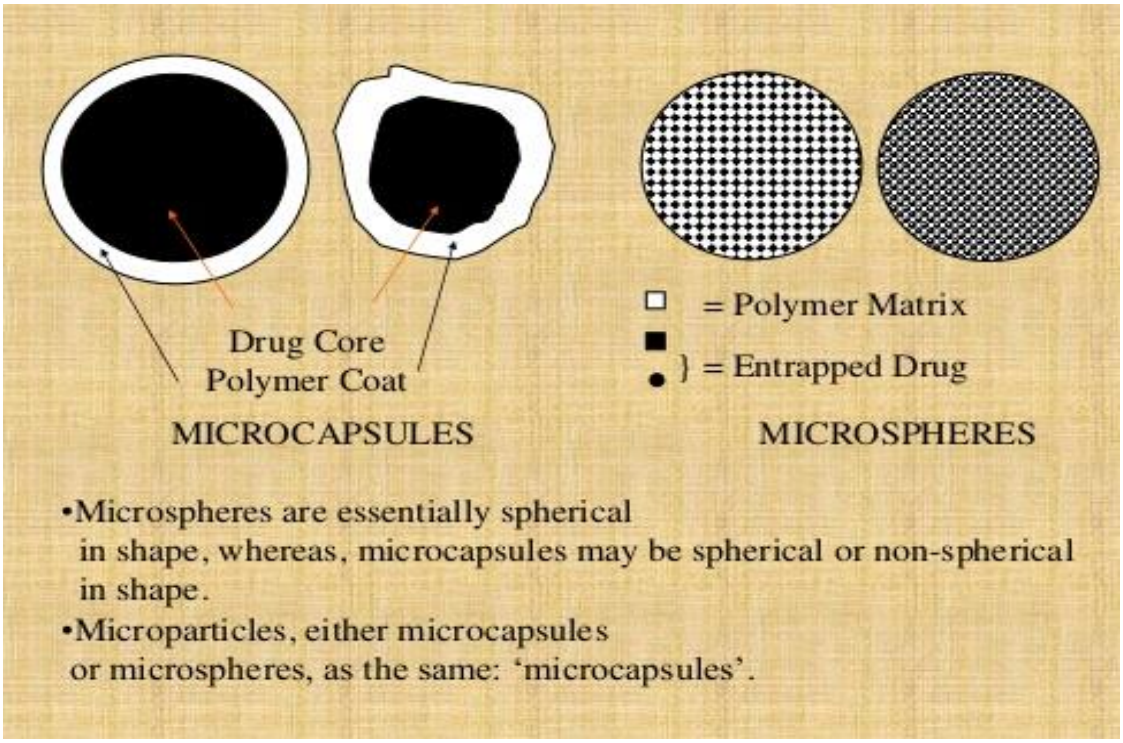


Fig. 9: Microspheres

Table. 3: Differences between Microcapsules, Microspheres&Micro-matrix:

Microcapsules	**Microspheres**	**Micro-matrix:**
• A Microcapsule has a drug located centrally within the particle, where it is encapsulated within a polymeric membrane • Consisting of an encapsulated core particle.	• A Microsphere has its drug dispersed throughout the particle i.e. the internal structure is a matrix of drug and polymer • Entrapped substance completely surrounded by a distinct capsule wall.	• Consisting of homogenous dispersion of active ingredient in particle.



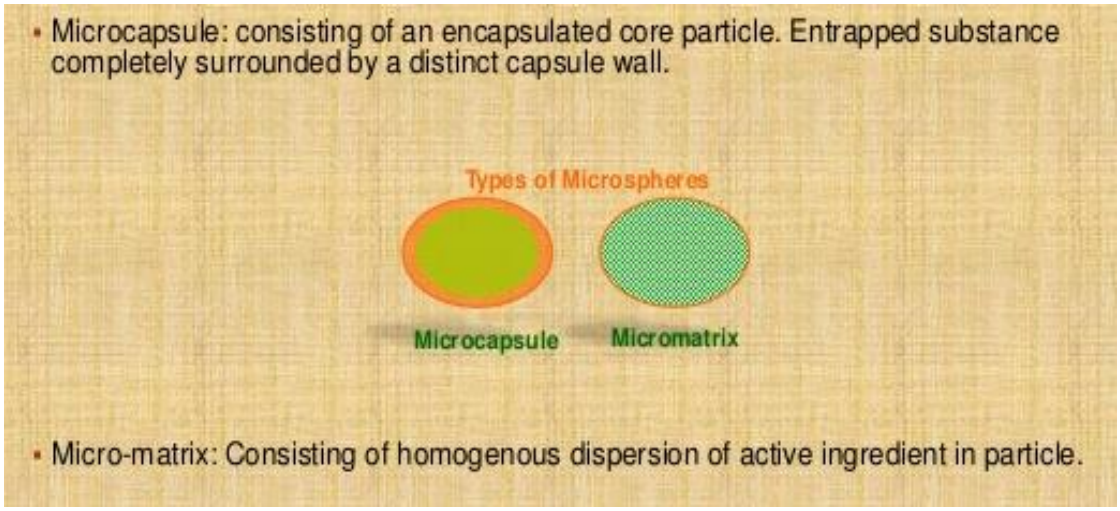


Fig. 10: Microcapsule & Microsphere

- Alternative Terms used in place of microspheres:
  - Microbeads
  - Beads
- They facilitate accurate delivery of small quantities of potent drug and reduced concentration of drug at site other than the target organ or tissue.
- They provide protection for unstable drug before and after administration, prior to their availability at the site of action.
- They provide the ability to manipulate the in vivo action of the drug, pharmacokinetic profile, tissue distribution and cellular interaction of the drug
- They enable controlled release of drug.
  • Ex: narcotic, antagonist, steroid hormones

Characteristics of Microsphere

1. **Biodegradable Non-biodegradable Polymer Used in Microsphere**
    - Lactides& Poly methyl Glycolides and methacrylate their copolymers
    - Acrolein
    - Polyanhydrides
    - Epoxy Polymer
    - Polycynoacrylates
    - Glycidyl methacrylate
2. **Longer duration of action**
3. **Control of content release Increase of therapeutic efficacy**
4. **Protection of drug**
5. **Reduction of toxicity**
6. **Biocompatibility**
7. **Sterilizability**
8. **Relative stability**
9. **Water solubility or dispersibility**
    - Bioresorbability
    - Targetability
    - Polyvalent
10. **Taste and odour masking**
    - Conversion of oil and other liquids, facilitating ease of handling
    - Protection of the drug from the environment
    - Delay of volatilization
11. **Freedom from incompatibilities between drug and excipients, especially the buffers**
    - Improvement of flow properties
    - Dispersion of water insoluble substance in aqueous media
    - Production of sustained release, controlled release and targeted medication
12. **Solvent evaporation method**
    - Single emulsion technique
    - Double emulsion technique
    - Coacervation phase separation method
    - Spray drying and spray congealing method
    - Polymerization method

Polymers used in microsphere

Natural polymer

1. Protein : Albumins, Gelatin, Collagen
2. Carbohydrates : Starch, Agarose, Carrageenan, Chitosan
3. Chemically modified carbohydrates : Poly(acryl)dextran, Poly(acryl)starch
    - Synthetic Polymers

- ✓ Biodegradable Polymer: Lactides&glycolides& their copolymer, Polyalkylcyano acrylates, Polyanhydride.
- ✓ Non-Biodegradable polymers: Acroline, Glycidyl methacrylate, Polyanhydride

Criteria Required For Microsphere

Microspheres should satisfy certain criteria:

- ✓ The ability to incorporate reasonably high concentrations of the drug.
- ✓ Stability of the preparation after synthesis with a clinically acceptable shelf life.
- ✓ Controlled particle size and dispersability in aqueous vehicles for injection.
- ✓ Release of active reagent with a good control over a wide time scale.
- ✓ Biocompatibility.

Susceptibility to chemical modification.

Advantages of Microsphere

1. Reliable means to deliver the drug to the target site with specificity and to maintain the desired concentration at the site of interest without unwanted effects.
2. Microspheres have the potential for the controlled release of drug.
3. Microspheres can achieve not only prolonged release, but also targeting of drugs to the tumor.
4. Studies on the macrophage uptake of microspheres have demonstrated their potential in targeting drugs to pathogens residing intracellularly.
5. Toxic drugs, which can cause side effects when administered in large quantities, or insoluble drugs, which may require large doses to promote absorption, can be administered with a lower frequency and smaller quantity.
6. Sensitive drugs like peptides & proteins are protected against chemical and enzymatic degradation when entrapped in microspheres.
7. The use of microspheres for drug delivery is not limited to any specific illness, rather it can be widely applied to many situations where continuous and controlled drug administration is essential.
8. It provides protection to photosensitive drugs, also to the volatile substances.

Disadvantages of Microsphere/ Limitations:

1. Significant initial burst and unpredictable release in certain cases.
2. The phagocytosis of carriers, rapid clearance are common disadvantages of particulate system.

HYDROGEL IN DRUG DELIVERY

- Hydrogel is a network of polymer chains that are hydrophilic, water insoluble, sometimes found as a colloidal gel in which water is the dispersion medium.
- Hydrogels are highly absorbent natural or synthetic polymers.
- Hydrogels are crosslinked polymer networks that absorb substantial amounts of aqueous solutions.

- These crosslinks provide the network structure and physical integrity. Hydrogels can contain over 99.9% water.
- The high water content of the materials contributes to their biocompatibility.

Table. 4: Classification of Hydrogel in Drug Delivery

Types	**Classification of Hydrogel**
Based on **Structure**	• Amorphous Hydrogels • Semi-crystalline Hydrogels • Hydrogen Bonded Hydrogels
Based on **Charges**	• Neutral Hydrogels • Anionic Hydrogels • Cationic Hydrogels • Ampholytic Hydrogels
Based on **Mechanism of Drug release**	• Diffusion Controlled Release Ssstems • Swelling Controlled Release Systems • Chemically Controlled Release Systems • Environment Responsive Systems
Based on **Methods of Preparation**	• Homopolymer Hydrogel • Co-polymer Hydrogels • Multi Polymer Hydrogels

Advantages of hydrogels :

- ✓ Hydrogels possess a degree of flexibility very similar to natural tissue , due to their significant water content. Entrapment of microbial cells within Hydrogel beads has the advantage of low toxicity.
- ✓ Environmentally sensitive Hydrogels have the ability to sense changes of pH, temperature, or the concentration of metabolite and release their load as result of such a change.
- ✓ Timed release of growth factors and other nutrients to ensure proper tissue growth.
- ✓ Hydrogels have good transport properties
- ✓ Hydrogels are Biocompatible.
- ✓ Hydrogels can be injected. Hydrogels are easy to modify.

Disadvantages of Hydrogels:

- ✓ Hydrogels are expensive. Hydrogels causes sensation felt by movement of the maggots. Hydrogels causes thrombosis.
- ✓ The surgical risk associated with the device implantation and retrieval. Hydrogels are non-adherent ; they may need to be secured by a secondary dressing.
- ✓ Hydrogels used as contact lenses causes lens deposition, hypoxia , dehydration and red eye reactions.
- ✓ Hydrogels have low mechanical strength and Difficulty in handling, loading and Sterilization

- ✓ Low mechanical Strength.
- ✓ Batch variation.
- ✓ Animal derived materials may pass on viruses.

Types of hydrogel in drug delivery:

- ✓ Natural Polymers e.g.: Dextran , Chitosan , Collagen, Dextran Sulfate
- ✓ Synthetic Polymers e.g.:Poly (vinyl alcohol) Disadvantages: Low biodegradability Can include toxic substances

Application Of Hydrogel In Drug Delivery

- Hydrogels can be used in different types of controlled release systems.
- These are classified according to the mechanism controlling the release of drug from the device as
  - Diffusion controlled systems.
  - Swelling controlled system.
  - Chemically controlled system.
  - Environmental responsive systems.

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2. Anya M Hillery et al Drug delivery and targeting CRC press, 2010
3. Robinson R Robinson Conventional drug delivery systems CRC press,2004

QUESTIONS

1. Write five polymers name used in drug and drug delivery system
2. Describe the primary mechanism of drug release
3. Classify hydrogel
4. Compare microcapsule and microsphere
5. Compare microsphere and micromatrix
6. Compare microcapsule and micromatrix
7. Describe about various polymers and their application in DDS
8. Write different types of liposomes and their therapeutic applications
9. Explain in detail about the polymers used in microsphere.
10. Explain in detail about the classification of hydrogel in drug delivery system

UNIT – III - TRANSDERMAL DRUG DELIVERY SYSTEMS – SBM1610

UNIT- 3
TRANSDERMAL DRUG DELIVERY SYSTEMS

Contents:

- **– Transdermal penetration of drugs**
- **– formulation**
- **– addition**
- **– polymers in transdermal drug delivery system**
- **– iontophoresis**
- **– transdermal controlled releaseproducts and devices**

TRANSDERMAL PENETRATION OF DRUGS

- Transdermal therapeutic are defined as self-contained discretedosage form which when applied to the intact skin deliver the drugs,through the skin, at a controlled rate to the systemic circulation.

(or)

- Transdermal drug delivery system (TDDS) are systems that utilizeskin as a site for continuousdrug administration into the systemiccirculation.

Routes of Drug Administration

Most drugs can be administered by a varietyof routes. The choice of appropriate route ina given situation depends both on drug aswell as patient related factors. Mostly commonsense considerations, feasibility and conveniencedictate the route to be used.Routes can be broadly divided into thosefor (a) Local action and (b) Systemic action.

a) Local Routes

These routes can only be used for localizedlesions at accessible sites and for drugs whosesystemic absorption from these sites is minimal or absent.

The local routes are:

1. Topical
2. Deeper tissues
3. Arterial supply

b) Systemic Routes

The drug administered through systemic routesis intended to be absorbed into the blood streamand distributed all over, including the site ofaction, through circulation.

The Systemic routes are:

1. Oral
2. Sublingual or buccal
3. Rectal
4. Cutaneous
5. Inhalation

6. Nasal
7. Parenteral

Drug delivery system under the<u>Cutaneous Root</u>is:

1) **Transdermal therapeutic systems (TTS)**

These are devices in the form of adhesivepatches of various shapes and sizes (5 20 cm2)which deliver the contained drug at a constantrate into systemic circulation via the stratumcorneum. The drug (in solution orbound to a polymer) is held in a reservoirbetween an occlusive backing film and a ratecontrolling micropore membrane, the undersurface of which is smeared with an adhesiveimpregnated with priming dose of the drug. Theadhesive layer is protected by another film thatis to be peeled off just before application. Thedrug is delivered at the skin su1face by diffusionfor percutaneous absorption into circulation.The micropore membrane is such that rate ofdrug delivery to skin surface is less than theslowest rate of absorption from the skin. Thisoffsets any variation in the rate of absorptionaccording tothe properties of different sites. Assuch, the drug is delivered at a constant andpredictable rate irrespective of site of application.Usually chest, abdomen, upper arm, lowerback, buttock or mastoid region are utilized.Transdermal patches of GTN, fentanyl, nicotineand estradiol are available in India, whilethose of isosorbidedinitrate, hyoscine, andclonidine arc marketed elsewhere. For differentdrugs, TTS have been designed to last for1- 3 days. Though more expensive, they providesmooth plasma concentrations of the drugwithout fluctuations; minimize interindividualvariations (drug is subjected to little first passmetabolism) and side effects. They are alsomore convenient- many patients prefer transdermalpatches to oral tablets of the same drug;patient compliance is better. Local irritationand erythema occurs in some subjects, but isgenerally mild: can be minimized by changingthe site of application each time by rotation.

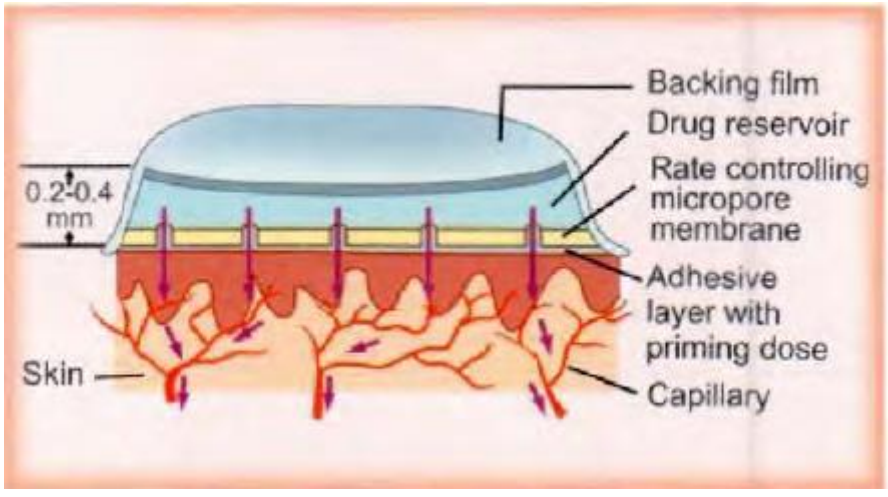

Fig. 1: Transdermal therapeutic systems (TTS)

TOPICAL ADMINISTRATION OF DRUGS

- **Mucosal Membranes:**
  Example: eye drops, antiseptic, sunscreen, nasal, etc.
- **Skin:**
  1.Local action
  2. Systemic action
- **Local Action**
  a. Dermal - rubbing in of oil or ointment
  b. Transdermal - absorption of drug through skin
- **Systemic Action**
  i. Stable blood levels
  ii. No first pass metabolism
  iii. Drug must be potent.

Mechanism of Drug Absorption through Skin

1. Epidermis
   a) Stratum corneum
   b) Stratum lucidum
   c) Stratum granulosum
   d) Stratum spinosum
2. Dermis
3. Subcutaneous

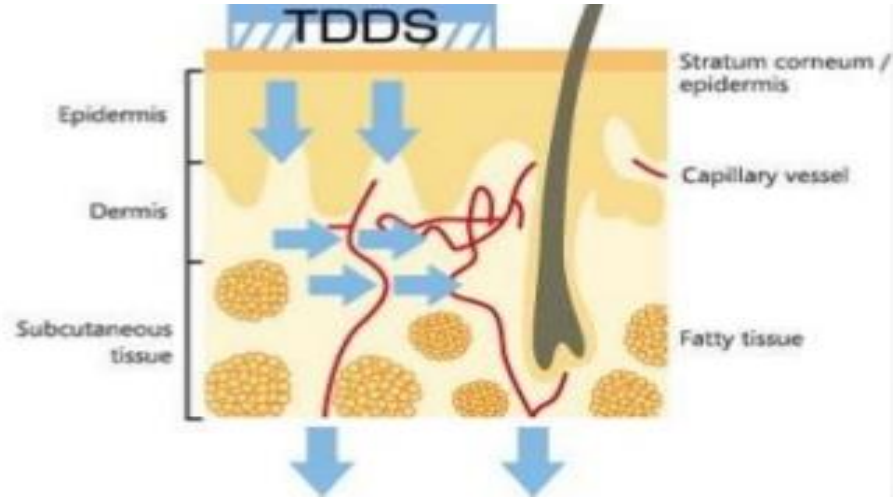

Fig. 2: Drug absorption

Pathway of Drug absorption through skin

a. Transfollicular route:

Transfollicular route is the shortest pathway that drug has to follow to reach the systemic circulation that provides a large area for diffusion of drugs.

b. **Transcellular route**:

Drug delivering through this route passes from corneocytes which has highly hydrated keratin creating hydrophilic pathway. The drug passes through the corneocytes of stratum corneum.

c. **Intercellular route**:

In intercellular pathway the drug diffuses through the continuous lipid matrix present between the cells.

Fundamentals of Skin Permeation:

Rate of permeation, dQ/dt, across a skin can be expressed as

dQ/dt = Ps[cd - cr]

Where, dQ/dt – Rate of permeation

Ps – Permeability coefficient

Cd – Concentration in donor compartment

Cr – Concentration in receptor compartment

Factors affecting Transdermal Permeability

The principle transport mechanism across mammalian skin is by passive diffusion. The factors influencing and having differences in transdermal permeability of the stratum corneum.

a) **Lipid solubility:**At higher concentrations, the rate of penetration of the alcohols is greatly increased, and does not follow the pattern of absorption from weak solution. But, high concentrations may damage the stratum corneum impairing its 'barrier' properties.

b) **Partition coefficient:** Drugs possessing both water and lipid solubility are favorably absorbed through the skin. Transdermal permeability coefficient shows a linear dependency on partition coefficient. A lipid/water partition of 1 or greater is generally required for optimal transdermal permeability.

c) **pH condition:** The extent of dissociation in case of ionic drugs and their transdermal permeability depends on pH condition of the skin surface as well as the drug delivery system. Incase of ephedrine and scopolamine, the transdermal flux of the drug increases with increasing pH upto 1.2 approximately 1.2 higher than their respective pKa values.

Permeation Enhancer:

- These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant.

- These may conveniently be classified as:
    i. Solvents
    ii. Surfactants
    iii. Miscellaneous chemicals

Routes of skin Penetration

There are two diffusional routes to penetrate intact skin:

Include transport via:

1- Hair follicles

2. Sebaceous glands or Sweat glands

These routes avoid penetration through the stratum corneum and therefore known as *shuntroutes* .

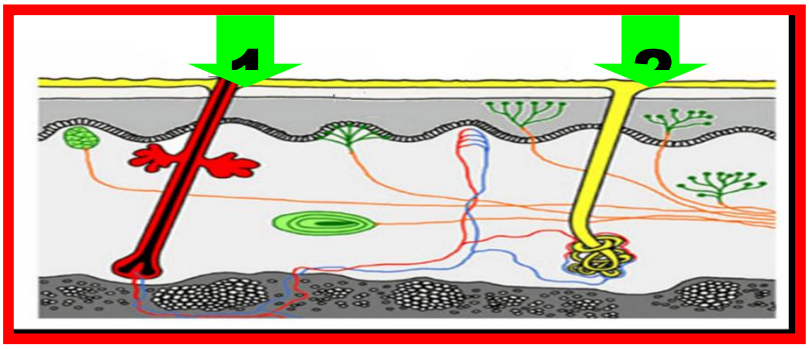

Fig. 3: Routes of skin penetration

Although these routes offer high permeability, they are of minor importance because of their relatively small area, 0.1% of the total skin area. The trans appendagealrouteseems to be most important for ions and large polar molecules which hardly permeate through the stratum corneum

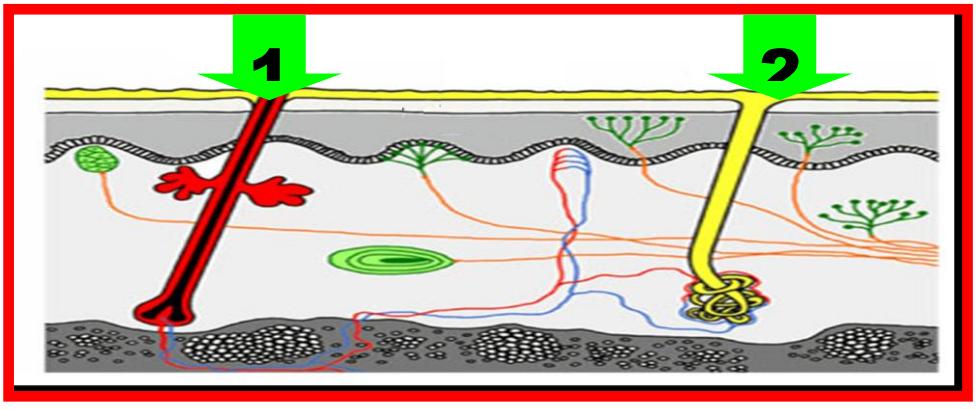

Fig. 4: Routes of skin penetration

The trans-epidermal route:

Trans-epidermal transport means that molecules cross the intact horny layer.

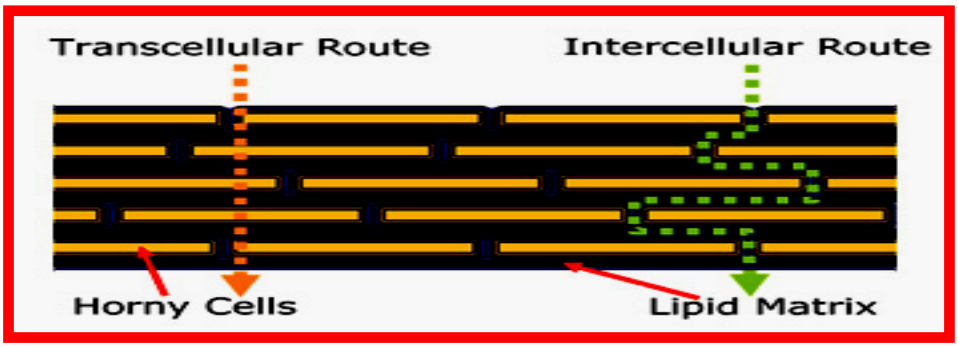

Fig. 5: Routes of skin penetration

Two potential micro-routes are exist

1. *The transcellular (or intracellular) rout.*
2. *The intercellular pathways.*
   - The principal pathway taken by drugs is decided by its partition coefficient.
   - Hydrophilic drugs partition into the intracellular pathways, whereas lipophilic drugs traverse the stratum corneum via the intercellular route.

TYPES OF TDDS

- There are four main types of TDDS
  1) Single-layer Drug-in-Adhesive
  2) Multi-layer Drug-in-Adhesive
  3) Drug Reservoir-in-Adhesive
  4) Drug Matrix-in-Adhesive

1) Single-layer Drug-in-Adhesive

- The Single-layer Drug-in-Adhesive system is characterized by the inclusion of the drug directly within the skin-contacting adhesive.
- In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and all the excipients under a single backing film.
- The rate of release of drug from this type of system is dependent on the diffusion across the skin.

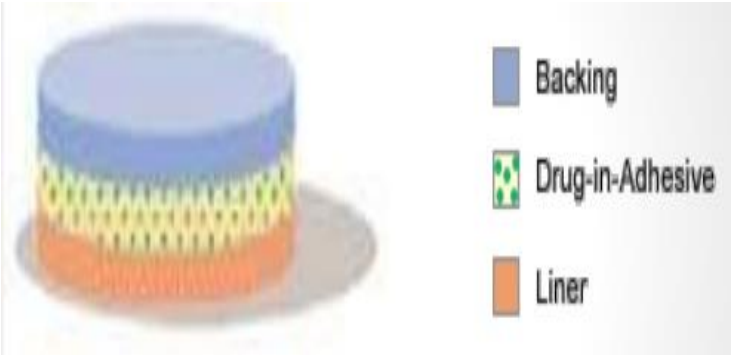

Fig. 6: Single layer

2. Multi-layer Drug-in-Adhesive system

- The Multi-layer Drug-in-Adhesive is similar to the Single- layer Drug-in-Adhesive in that the drug is incorporated directly into the adhesive.
- However, the multi-layer encompasses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film

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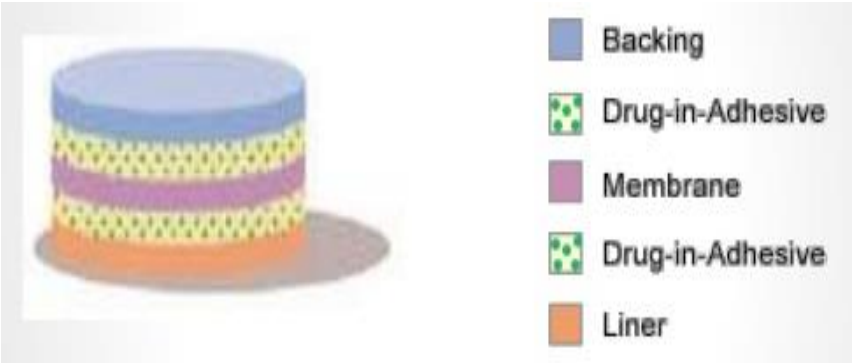


Fig. 7: Multi layer

3. Drug Reservoir-in-Adhesive system

1. The Reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive.
2. The adhesive component of the product responsible for skin adhesion can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane.

Fig. 8: Drug reservoir

4. Drug Matrix-in-Adhesive system

3. The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the release liner.

4. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix

Fig. 9: Drug matrix

Different approaches of TDDS systems

1. Membrane permeation-controlled TDDS
    a. Transderm-Scop, Duragesic, Clonidine-TTS
2. Drug in adhesive-type TDDS -
    a. Daytrana, Climara, Habitrol, Nicoderm, Exelon
3. Matrix diffusion controlled TDDS-
    a. NitroDur
4. Microreservoir dissolution controlled TDDS
    - Androderm

1. Polymer membrane permeation-controlled TDDS

TransdermScop (Scopolamine) for 3 days protection of motion sickness and TransdermNitr (Nitroglycerine) for once a day medication of angina pectoris.

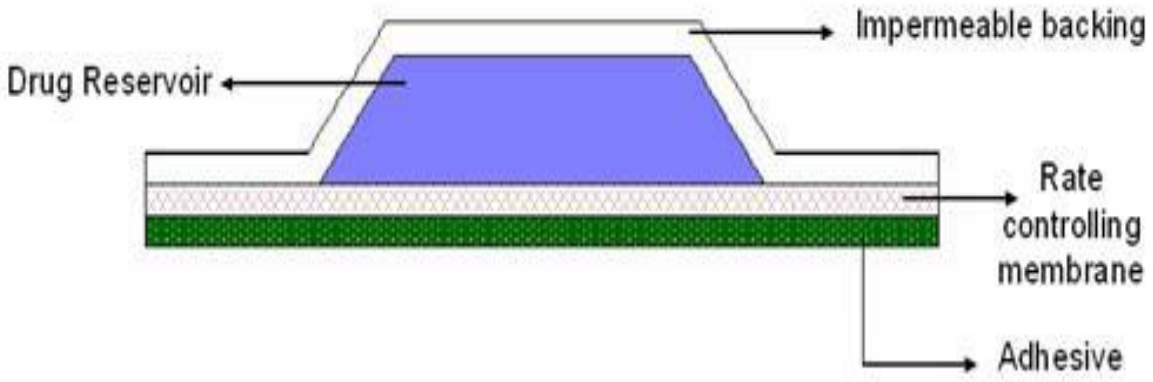


Fig. 10: Polymer membrane permeation-controlled TDDS

1. **Adhesive diffusion controlled - TDDS**

Deponit (Nitroglycerine) for once a day medication of angina pectoris

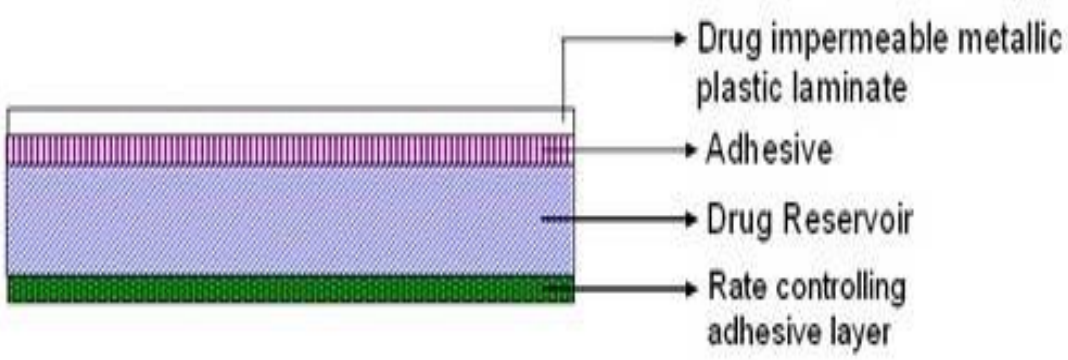


Fig. 11: Adhesive diffusion controlled - TDDS

2. **Matrix diffusion controlled - TDDS**

Nitro Dur (Nitroglycerine) used for once a day medication of angina pectoris

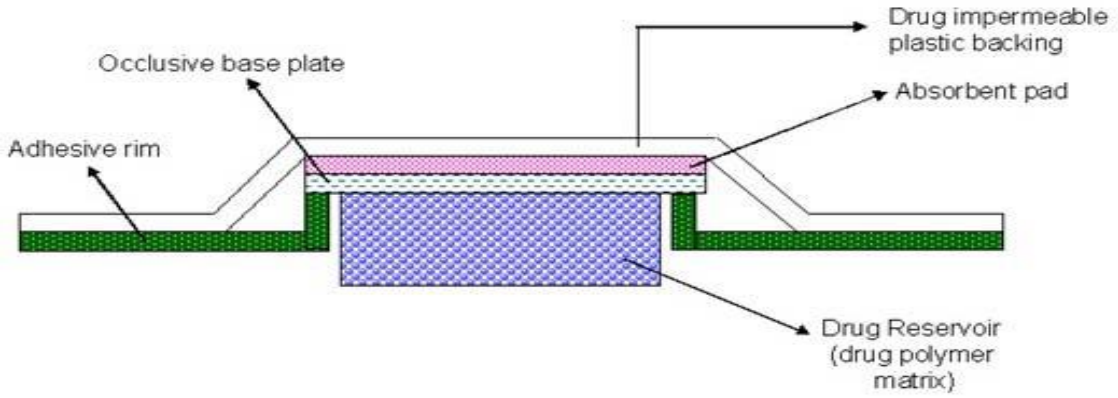


Fig. 12: Matrix diffusion controlled - TDDS

3. **Micro-reservoir controlled - TDDS**

Nitro- dur® System (Nitroglycerin) for once a day treatment of angina pectoris

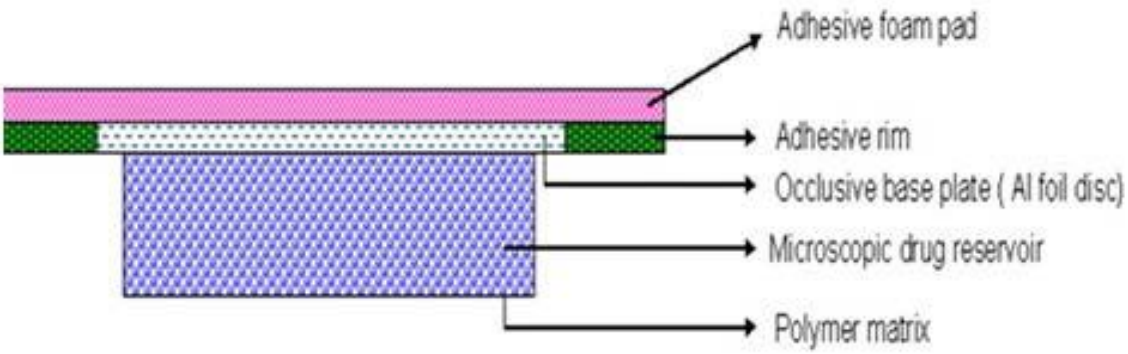


Fig. 13: Micro reservoir controlled - TDDS

Basic Components of - TDDS

Polymer matrix / Drug reservoir

- Drug
- Permeation enhancers
- Pressure sensitive adhesive (PSA)
- Backing laminates
- Release liner
- Other excipients like plasticizers and solvents

Fig. 14: adhesive

Formulation of - TDDS

TRANSDERMAL DOSING SYSTEMS

There are two basic types of transdermal dosing systems:

- Those that control the rate of drug released to the skin.
- Those that allow the skin to control the rate of drug absorption.

Drug delivery systems have been developed to control the rate of drug delivery to the skin over a period of time for subsequent absorption

Technology of Transdermal Delivery Patches

Technically, transdermal drug delivery systems may be categorized into two types:

- *Monolithic systems*
- *membrane-controlled systems*

Fig. 15: Membrane-controlled system

1. Monolithic Transdermal Patches

- Incorporate a drug matrix layer between backing and frontal layers.
- The drug-matrix layer is composed of a polymeric material in which the drug is dispersed.

The polymer matrix controls the rate at which the drug is released for percutaneous absorption.

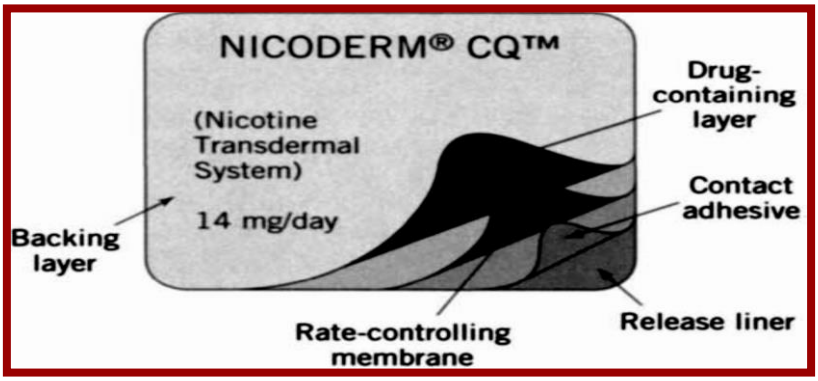


Fig. 16: NicoDerm® CQ® nicotine transdermal system

2. Membrane-controlled Transdermal Patches

- Designed to contain a drug reservoir, usually in liquid or gel form, a rate-controlling membrane, and backing, adhesive, and protecting layers.
- Examples are Transderm-Nitro (Summit) and Transderm-Scop (CIBA)andlevonorgestrel / estradiol for hormonal contraception.

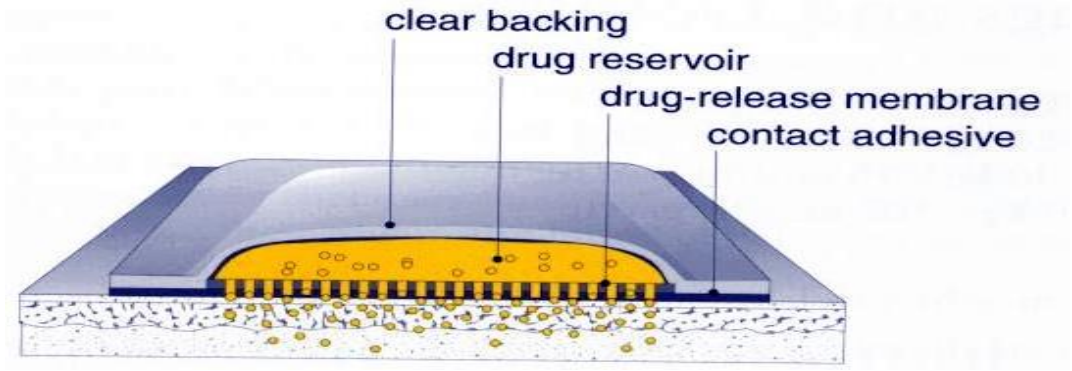


Fig. 17: Membrane-controlled Transdermal patches

Transdermal controlled release products and devices

The matrix may be with or without an excess of drug with regard to its equilibrium solubility and steady-state concentration gradient at the stratum corneum.

- In types having no excess, drug is available to maintain the saturation of the stratum corneum only as long as the level of drug in the device exceeds the solubility limit of the stratum corneum.

As the concentration of drug in the device diminishes below the skin's saturation limit, the transport of drug from device to skin gradually declines.

- In monolithic systems that have an excess amount of drug present in the matrix, a drug reserve is present to assure continued drug saturation at the stratum corneum, this assures continuous drug availability and absorption.

- The rate of drug decline is less than in the type designed with no drug reserve.

Examples of monolithic systems are NitroDur (Key) and Nitrodisc (Searle).

In the preparation of monolithic systems, the drug and the polymer are dissolved or blended together, cast as the matrix, and dried.

The gelled matrix may be produced in sheet or cylindrical form, with individual dosage units cut and assembled between the backing and frontal layers

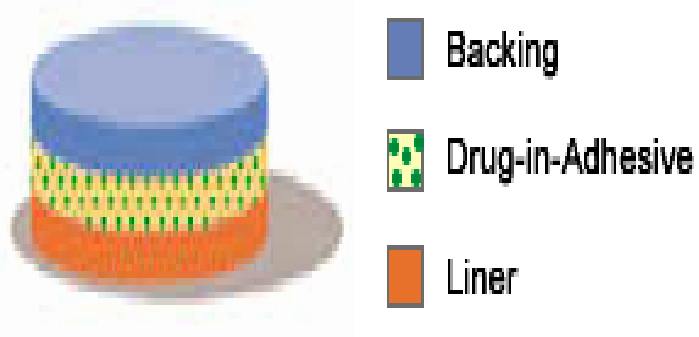


Fig. 18: Drug in adhesive

MEMBRANE-CONTROLLED SYSTEMS:

Membrane-controlled systems have the advantage over monolithic systems:

- As the drug solution in the reservoir remains saturated, the release rate of drug through the controlling membrane remains constant.
- In membrane systems, a small quantity of drug is frequently placed in the adhesive layer to initiate prompt drug absorption and pharmaco-therapeutic effects upon skin placement.
- Membrane controlled systems may be prepared by preconstructing the delivery unit, filling the drug reservoir, and sealing, or by a process of lamination, which involves a continuous process of construction, dosing, and sealing.

USES OF Transdermal Drug Delivery Patches:

General Considerations

1. The site for application should be clean, dry, and hairless (but not shaved).
    - Nitroglycerin patches are generally applied to the chest, estradiol to the abdomen, opolamine behind the ear, nicotine to the upper trunk or upper outer arm for smoking cessation.
    - Because of the possible of skin irritation, the site of application must be rotated, that skin sites must not reused for a week.

2. The transdermal patch should not be applied to skin that is oily, irritated, cut or abraded to assure the intended amount and rate of transdermal drug delivery and absorption.

3. The patch should be removed from its protective package, being careful not to tear or cut it. The patch's protective backing should be removed to expose the adhesive layer, and it should be applied firmly with the palm or heal of the hand until securely in place.

4. The patient should be instructed to cleanse the hands before and after applying the patch.

5. Care should be taken not to rub the eyes or touch the mouth during handling of the patch

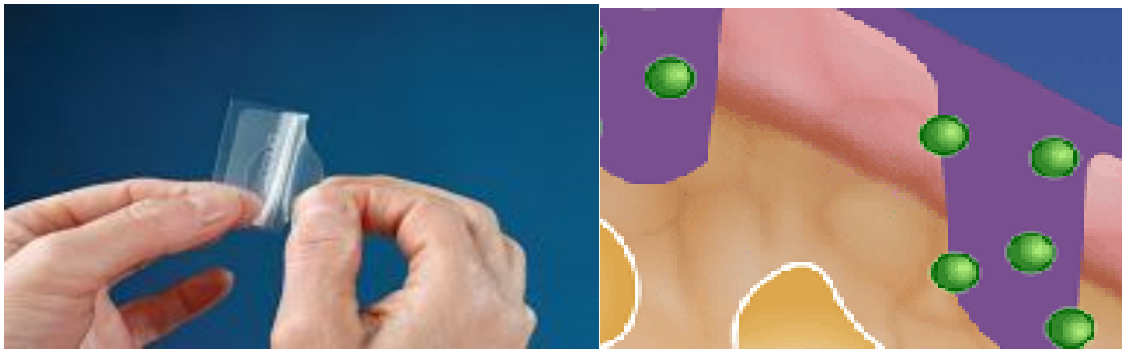


Fig. 19: Uses of Bandage

Polymers in Transdermal Drug Delivery System

- The Polymer controls the release of the drug from the device **.**
- Possible useful polymers for transdermal devices are**:**

A-Natural Polymers :

e.g. Cellulose derivatives, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch.

B-Synthetic Elastomers :

e.g. Polybutadieine, Styrene butadieine, Polysiloxane, Silicone rubber, Acrylonitrile, Butyl rubber, Neoprene**.**

C -Synthetic Polymers :

e.g. Polyvinyl alcohol, Polyvinyl chloride, Polyacrylate, Polyvinylpyrrolidone, Polymethylmethacrylate, Epoxy

Factors Affecting Percutaneous Absorption

Percutaneous absorption is the absorption of substances from outside the skin to positions beneath the skin, including entrance into the blood stream.

1. Factors concerning the nature of the drug
2. Factors concerning the nature of the vehicle
3. Factors concerning the condition of the skin

1. Factors Concerning the Nature of the Drug

- Drug concentration
- Drug partition coefficient (greater attraction to the skin than to the vehicle)
- Molecular weight below 800
- Particle Size
- Solubility in mineral oil and water

2. Factors Concerning the Nature of the Vehicle

- Spreadability of the vehicle
- Mixing with the sebum
- Hydration of the skin

Oleaginous vehicles act as moisture barriers through which the sweat from the skin cannot pass, thus increased hydration of the skin beneath the vehicle and increase Percutaneous absorption

3. Factors Concerning the Condition of the Skin

The Factors Concerning the Condition of the Skin are:

1. The thickness stratum corneum
2. .Multiple application dosing
3. Time of contact with the skin
4. Broken skin permit (remove of the stratum corneum)

This can be achieved by the following mechanisms:

- Alteration of the hydration of the stratum corneum using occlusive formulations.
- Carrier mechanisms in the transport of ionisable drugs.
- Enhance absorption by directly influencing the stratum corneum
  - (CHEMICALLY or PHYSICALLY).

Transdermal absorption follow***Fick's First Law***of Diffusion

$$Js = \frac{Km\ D\ Cs}{E}$$

Js = Flux of solute through the skin

Km = Distribution coefficient of drug between vehicle and stratum corneum

Cs = Concentration difference of solute across the membrane

D = Membrane Diffusion coefficient for drug in stratum corneum

E = Thickness of stratum corneum

Chemical Methods

Chemicals used to enhance absorption by directly influencing the stratum corneum

- Chemicals interact with the keratin structure in the stratum corneum and open the tight protein structure, this leads increase the diffusion coefficient D for substances which use the transcellular route: Surfactants, Dimethylsulfoxide (DMSO) and Urea.
- Solvents extract lipids and making the stratum corneum more permeable: Dimethylsulfoxide (DMSO) and Ethanol.

- Chemical enhancers which intercalate into the structured lipids of the horny layer and disrupt the packing. Thus make the regular structure more fluid and increases the diffusion coefficient of drugs: Azone, Oleic acid, and isopropyl myristate
- Solvents increase solubility and improve partitioning: Alcohol, acetone, polyethylene and propylene glycol
    - **Physical Methods**
- Physical methods can enhance drug flux up to several orders of magnitude above that allowed by passive diffusion (as conventional skin patches).
- The effective delivery range for passive diffusion across the skin is limited to small, hydrophobic agents,
- However, Physical delivery can be used for larger hydrophilic molecules as peptide drug administration

Physical Methods

IONTOPHORESIS

A physical method to enhance transdermal drug delivery and penetration. It involves the delivery of charged chemical compounds across the skin membrane using an applied electrical field.

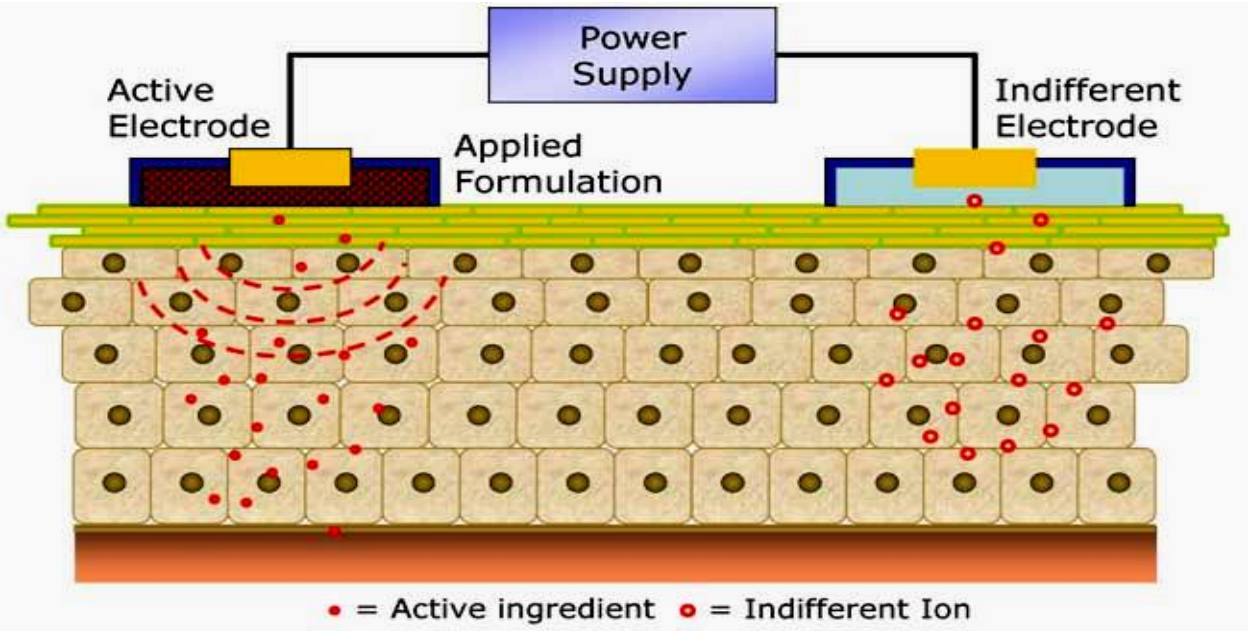


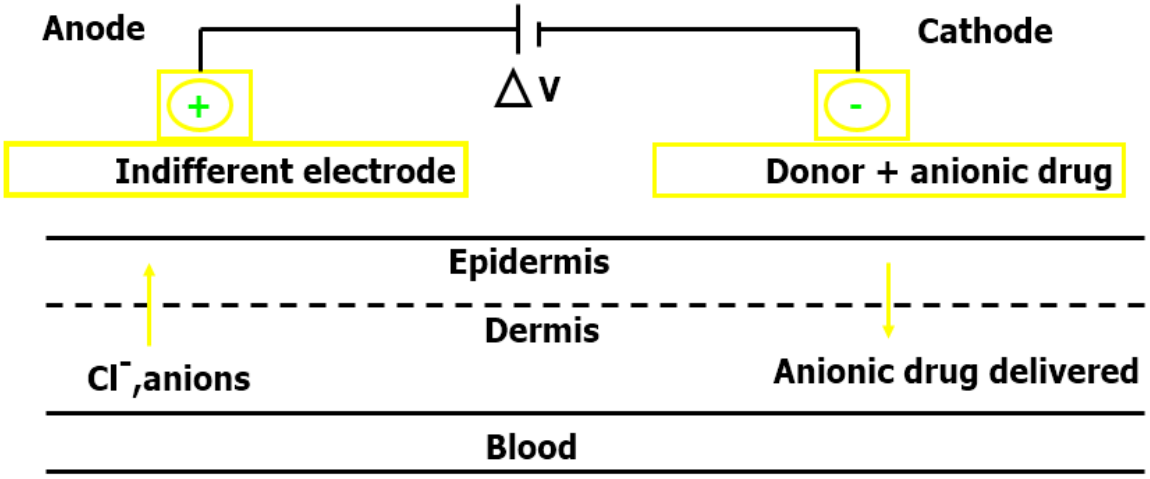
Fig. 20: Iontophoresis

Mechanisms of Transport

- Iontophoresis uses two electrodes, the anode and the cathode, each of which is in contact with a reservoir containing the drug to be delivered as an electrically conductive aqueous solution.

- The reservoir containing the drug is in contact with the electrode of the same charge which is the **(active electrode),** while the other electrode named **(passive electrode).**
- An electrical potential is applied across the electrodes, causing current to flow across the skin and facilitating delivery of the therapeutic agent by repulsion.

Fig. 21: Mechanisms of Transport



- Schematic of iontophoretic drug delivery system shows delivery of an anionic agent from the cathodal reservoir.
- The agent goes through the non-vascularized epidermis and into the dermis, where it can be transported into the blood through the capillary loops

Variables affecting iontophoresis:

1. *The electrical current.*
   - Which may be direct, alternate or pulsed
2. *Biological factors:*
   - Involve the presence of thickness, permeability and porous of the skin.
3. *Physicochemical factors:*
   - Include charge, size, structure and lipophilicity of the drug with small or large molecular size.

The drug should be water soluble, of low dose and ionizable with high charge density

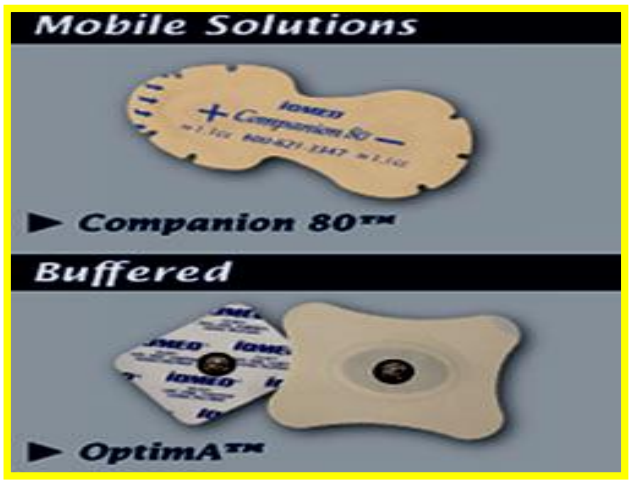


Fig. 22: Mechanism of transport

Formulation factors

- Include drug concentration, pH, ionic strength and viscosity.
- Increasing drug concentration results in greater drug delivery.
- The inclusion of buffer ions in a formula will compete with the drug for the delivery current and decrease the quantity of drug delivered, especially since buffer ions are smaller and more mobile than the large active drug. The pH of the solution can be adjusted and maintained by large molecules as ethanolamine: ethanolamine HCL.
- An increase in the ionic strength of the system will increase the competition for the available current especially when the active drugs are potent and present in small concentration.
- A number of drugs have been used including, lidocaine, amino acids, peptides and insulin.
- These agents are presently delivered by injection, because of their rapid metabolism and poor absorption following oral delivery.
- They are also poorly absorbed from the transdermal route, because of their large molecular size, ionic character, and impenetrability of the skin.

Fig. 23: Formulation factors

SONOPHORESIS

Three effects are results from ultrasound include

1. Cavitation
2. Microstreaming
3. Heat generation

1. Cavitation:

- Involves the formation and collapse of very small air bubbles in a liquid in contact with ultrasound waves.
- These air bubbles can disperse the ultrasound waves resulting in heating at the liquid air interfaces.

2. Micro-streaming:

- Closely associated with cavitation results in efficient mixing by inducing vortexes (currents)in small volume elements of a liquid, this may enhance dissolution of suspended drug particles results in higher concentration of drug near the skin for absorption.

3. Heat generation:

- Heat results from the conversion of ultrasound energy to heat energy and can occur at the surface of the skin and deeper layers of the skin.

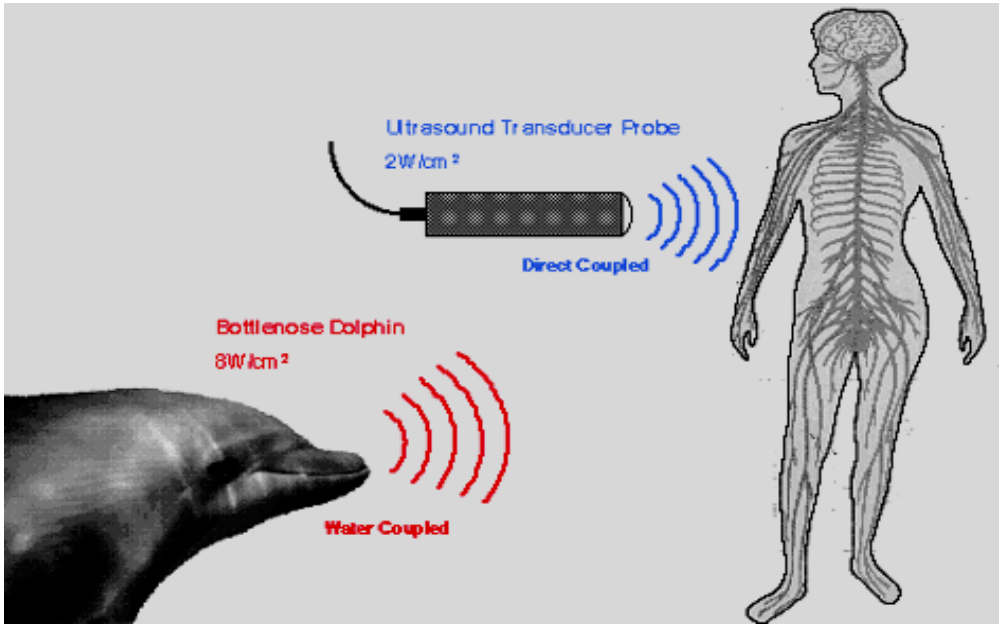


Fig. 24: Sonophoresis

Drug Formulation in Sonophoresis

The vehicle containing the drug must be formulated to provide good conduction of the ultrasonic energy to the skin.

- The product must be smooth and non-gritty as they will be rubbed into the skin by the head of the transducer.
- The product should have low viscosity for easy of application and easy of movement of the transducer (as gels).
- Emulsions can be used but the oil/ water interfaces can disperse the ultrasonic waves, resulting in a reduction of the intensity of the energy reaching the skin. It may case some localized heat

ADVANTAGESOF TDDS

- ✓ Avoidance of significant pre-systemic metabolism and the need therefore a lower daily dose.
- ✓ Recent inter & intra patient variability.
- ✓ Drug input can be terminated simply by removal of patch.
- ✓ Drug levels can be maintained in the systemic circulation, with in the therapeutic window for a prolonged period of time.
- ✓ Self-administration is possible

DISADVANTAGESOF TDDS

- It is limited only to potent drug molecule.
- Drugs must not be locally irritating or sensitizing.
- Drug or drug formulation may cause skin irritation or sensitization.
- Drugs with short biological half-life that are subject to large first pass metabolism.

CONCLUSION

- Transdermal drug delivery technologies are becoming one of the fastest growing sectors within the pharmaceutical industry.
- Advance in drug delivery systems having increasingly brought about rate controlled delivery with fewer side effects as well as increased efficacy and constant drug delivery.

REFERENCES

1. Vyas S.P. Khar RKTargetted and controlled drug delivery Novel Carrier System CBSPD, 2006.
2. Anya M Hillery et al Drug delivery and targeting CRC press, 2010
3. Robinson R Robinson Conventional drug delivery systems CRC press,2004

QUESTIONS

1. Write the pathways of drug absorption through Skin.
2. Write the formula of rate of permeation.
3. What are the factors of percutaneous absorption in the skin?
4. Construct the components of a transdermal patch
5. Express the disadvantages of using a transdermal mode of drug administration
6. Write the factors influencing in transdermal permeability of the stratum corneum.
7. Write the three functional layers of skin.
8. Explain briefly the types of TDDS
9. Design a transdermal patch for the delivery of a drug.
10. With a neat sketch of skin discuss the disposal of drugs from a transdermal patch.

UNIT – IV - IMPLANTABLE DRUG DELIVERY SYSTEMS – SBM1610

UNIT 4

IMPLANTABLE DRUG DELIVERY SYSTEMS

Contents:

- Implantable Micro–Pump Systems
  - Peristaltic Micropump
  - Osmotic Micropump
  - Diaphragm Micropump
  - Fluorocarbon Propellant
- Driven Micro Pump
  - Solenoid Driver Reciprocate Micro Pump
  - Programmable Implanted Drug Administrative Device (DAD)

IMPLANTABLE MICRO–PUMP SYSTEMS

- Micropumps are devices that can control and manipulate small fluid volumes.
- Although any kind of small pump is often referred to as **micropump**, a more accurate definition restricts this term to pumps with functional dimensions in the micrometer range.
- Such pumps are of special interest in microfluidic research, and have become available for industrial product integration in recent years.
- Their miniaturized overall size, potential cost and improved dosing accuracy compared to existing miniature pumps fuel the growing interest for this innovative kind of pump.
- First true micropumps were reported in the mid-1970s but attracted interest only in the 1980s, when Jan Smits and Harald Van Lintel developed MEMS micropumps.
- Most of the fundamental MEMS micropump work was done in the 1990s. More recently, efforts have been made to design non-mechanical micropumps that are functional in remote locations due to their non-dependence on external power.
- **Microelectromechanical systems** (**MEMS**), also called as **micro-electro-mechanical systems** (or microelectronic and microelectromechanical systems)
- It is a microscopic devices, particularly those with moving parts.
- They merge at the nanoscale into nanoelectromechanical systems (NEMS) and nanotechnology.

- MEMS are also referred to as micromachines in Japan and **microsystem technology** (**MST**) in Europe.
- MEMS are made up of components between 1 and 100 micrometers in size (i.e., 0.001 to 0.1 mm), and MEMS devices generally range in size from 20 micrometres to a millimetre (i.e., 0.02 to 1.0 mm)
- Its components are arranged in arrays (e.g., digital micromirror devices) can be more than 1000 mm^2.
- They usually consist of a central unit that processes data (an integrated circuit chip such as microprocessor) and several components that interact with the surroundings (such as microsensors).

Because of the large surface area to volume ratio of MEMS, forces produced by ambient electromagnetism (e.g., electrostatic charges and magnetic moments), and fluid dynamics (e.g., surface tension and viscosity) are more important design considerations than with larger scale mechanical devices

- **Micropumps can be grouped into**
  - Mechanical and
  - Non-mechanical devices.

  Mechanical systemscontain moving parts, which are usually actuation and microvalve membranes or flaps.

  The driving force can be generated by utilizing
    - Piezoelectric,
    - Electrostatic,
    - Thermo-Pneumatic,
    - Pneumatic or Magnetic Effects

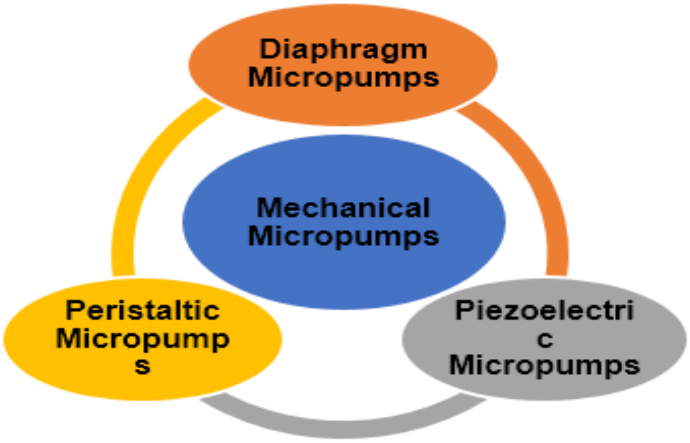


Fig. 1: Mechanical Pump

Non-mechanical pumps function with actuation mechanisms

- Electro-Hydrodynamic,
- Electro-Osmotic,
- Electrochemical
- Ultrasonic Flow Generation

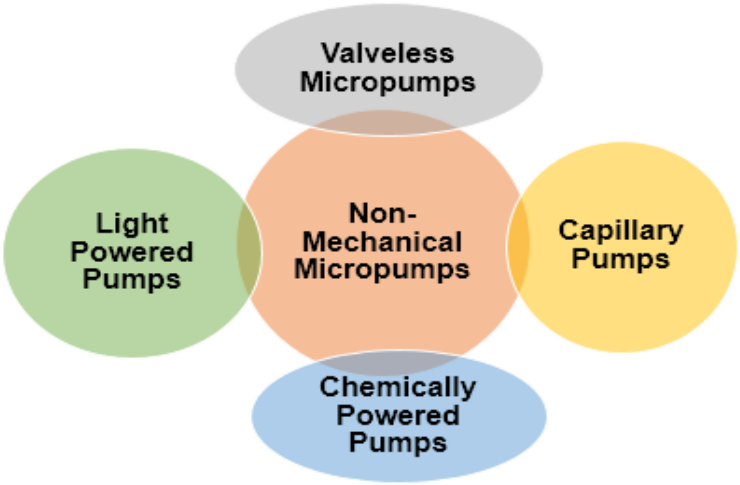


Fig. 2: Non Mechanical Pump

- Micropumps play a significant role in microfludical systems of MEMS.
- Micropumps were started in middle 1980s.
- Before 1990s, mechanical pumps were mainly studied. After 1990s, non-mechanical pumps were introduced.
- Presently most micropumps aim to fluid pumping.

PERISTALTIC PUMP

- A **peristaltic pump**, also commonly known as a roller pump
- It is a type of positive displacement pump used for pumping a variety of fluids.
- The fluid is contained within a flexible tube fitted inside a circular pump casing.
- A rotor with a number of "rollers", "shoes", "wipers", or "lobes" attached to the external circumference of the rotor compresses the flexible tube.
- As the rotor turns, the part of the tube under compression is pinched closed (or "occludes") thus forcing the fluid to be pumped to move through the tube.

- Additionally, as the tube opens to its natural state after the passing of the cam fluid flow is induced to the pump.
- This process is called peristalsis and is used in many biological systems such as the gastrointestinal tract.
- Typically, there will be two or more rollers, or wipers, occluding the tube, trapping between them a body of fluid.
- The body of fluid is then transported, at ambient pressure, toward the pump outlet.
- Peristaltic pumps may run continuously, or they may be indexed through partial revolutions to deliver smaller amounts of fluid.
- The peristaltic pump was first patented in the United States by Rufus Porter and J.D. Bradley in 1855 for blood transfusions.
- It was developed by heart surgeon Dr. Michael DeBakey for blood transfusions while he was a medical student in 1932 and later used by him for cardiopulmonary bypass systems.
- A specialized nonocclusive roller pump using soft flat tubing was developed in 1992 for cardiopulmonary bypass systems.
- The first technically and commercially viable peristaltic pump for use outside the laboratory was developed by Bernard Refson, an inventor who went on to establish Watson-Marlow Fluid Technology Group, a peristaltic pump manufacturer

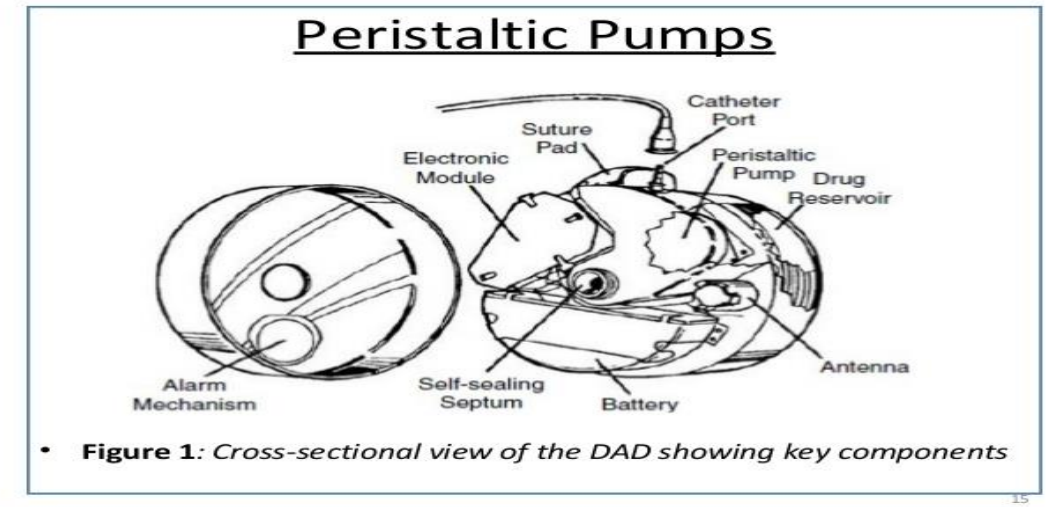


Fig. 3: Peristaltic Pump

APPLICATIONS

- Peristaltic pumps are typically used to pump clean/sterile or aggressive fluids without exposing those fluids to contamination from exposed pump components.
- Some common applications include pumping IV fluids through an infusion device, apheresis, aggressive chemicals, high solids slurries, and other materials where isolation of the product from the environment, and the environment from the product, are critical. It is also used in heart-lung machines to circulate blood during a bypass surgery, and in hemodialysis systems, as the pump does not cause significant hemolysis.

Design Parameters

- The ideal peristaltic pump should have an infinite diameter of the pump head and the largest possible diameter of the rollers.
- Such an ideal peristaltic pump would offer the longest possible tubing lifetime and provide a constant and pulsation-free flow rate.
- Such peristaltic pump cannot be constructed in reality.
- However, peristaltic pumps can be designed to approach these ideal peristaltic pump parameters.
- Careful design can offer constant accurate flow rates for several weeks together with a long tubing lifetime without the risk of tubing rupture.

PERISTALTIC MICROPUMP CHARACTERIZATION

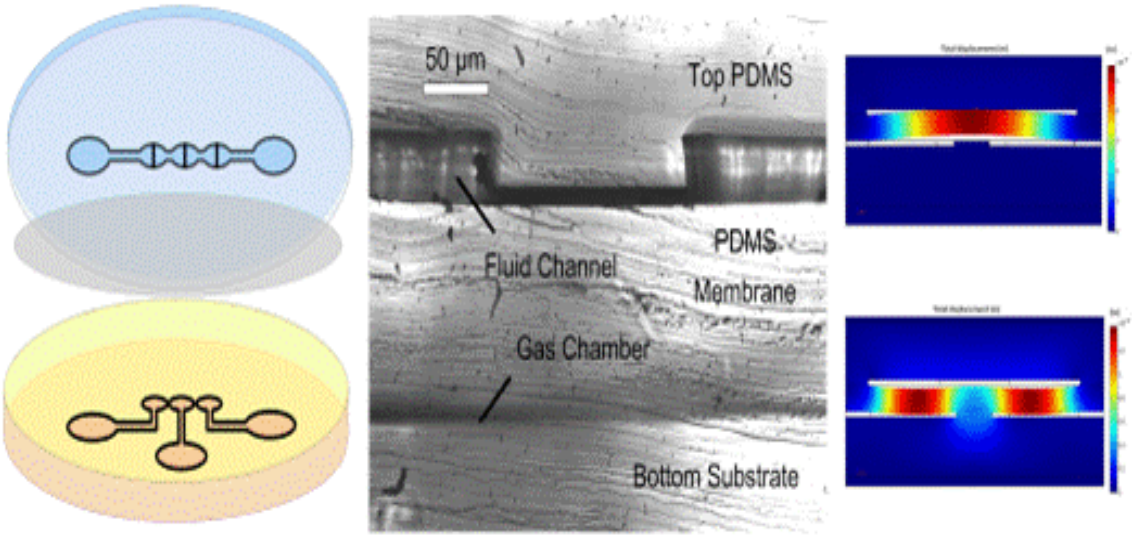


Fig. 4: Stimulation of a complete valve operation (opened and closed).

- The micropumps are composed of three individual microvalves, posing a peristaltic motion for programmable fluid actuation.
- The micropumps are responsible for transporting fluids in a microchip, thus playing a key role in determining the success of the overall assay.

Metering

- The metering is purely a function of frequency and control pressure. Working under the optimal sequence, preliminary calibration curves demonstrate the potential metering capabilities of the current design and setup.

Mechanical Fatigue Test

- To test the reliability of the peristaltic pump under normal operation, a mechanical fatigue test will be individually performed on two identical PDMS valves. Preliminary work indicates the PDMS membrane is able to withstand at least 4 million operational cycles

Optimal Pumping Sequence

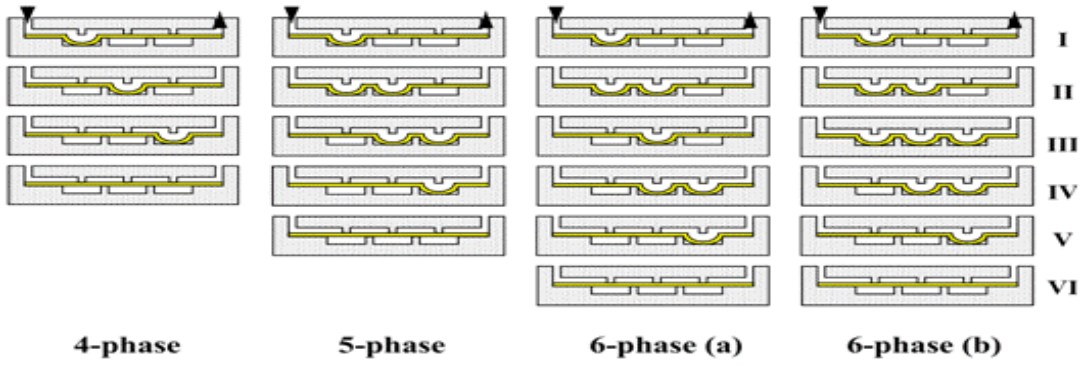


Fig. 5: Optimal pumping sequence

A pumping sequence is the order that how the 3-valve pump is operated. Three dimensionless numbers were used to assess the performance of each sequence.

- **Diodicity (D)** quantifies the relative amounts of forward and backward flow.
- **Discontinuity number (O)** reflects the degree of an oscillation phenomenon.
- **Output efficiency (η)** shows the effective volume ratio that can be generated in each cycle.

Frequency Dependence

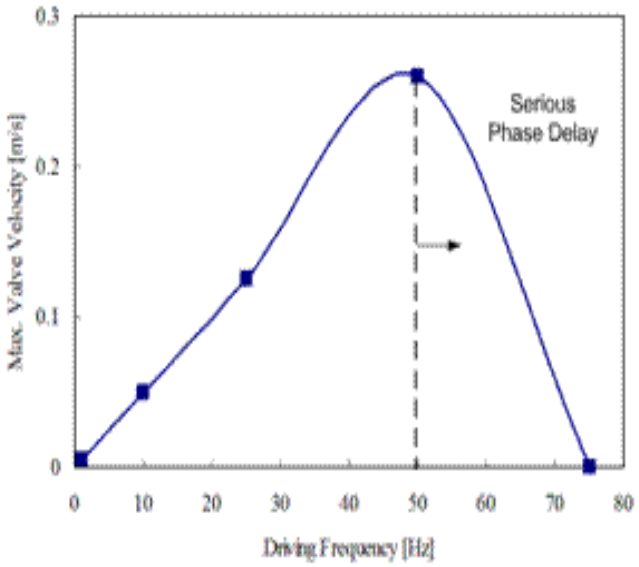


Fig. 6: Frequency dependance

Frequency dependence of the maximum membrane velocity of a microvale. With the applied parameters, the peak frequency corresponding to the maximum membrane velocity of a microvalve is around 50 Hz

A dynamic structure analysis based on a damping model is built to analyze the frequency response of the pump system. The interaction between the membrane and the working fluid is described by Reynolds equation. The membrane of a valve can be treated as a linear spring, thus an equilibrium equation describing the forces acting on the membrane

$$k\delta = F_h + F_c$$

where k is the spring constant of the diaphragm, F_h is a hydrodynamic force, and F_c is the pneumatic force. The frequency response illustrating the motion of a single microvalve

OSMOTIC PUMPS

- **Introduction**

  Osmotic drug delivery uses the osmotic pressure of drug or other solutes (osmogens or osmagents) for controlled delivery of drugs. Osmotic drug delivery has come a long way since Australian physiologists Rose and Nelson developed an implantable pump in 1955.

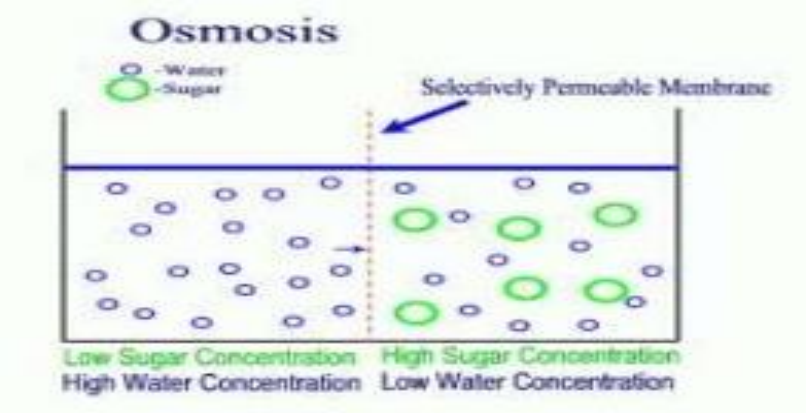


Fig. 7: Osmosis

- **Advantages of osmotic Drug Delivery System**

  The delivery rate of zero-order (which is most desirable) is achievable with osmotic systems. Ease of administration Greater effectiveness in the treatment of chronic conditions Delivery may be delayed or pulsed, if desired. For oral osmotic systems, drug release is independent of gastric pH and hydrodynamic conditions which is mainly attributed to the unique properties of semipermeable membrane (SPM) employed in coating of osmotic formulations. Enhance bioavailability

- **Advantages**

  Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems. The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters. A high degree of in vivo–in vitro correlation (IVIVC) is obtained in osmotic systems because the factors that are responsible for causing differences in release profile in vitro and in vivo (e.g., agitation, variable pH) affect these systems to a much lesser extent. The release from osmotic systems is minimally affected by the presence of food in the gastrointestinal tract (GIT). This advantage is attributed to design of osmotic systems. Environmental contents do not gain access to the drug until the drug has been delivered out of the device. Production scale up is easy.

- **Disadvantages of Osmotic Drug Delivery System**
  - Rapid dExpensive
  - evelopment of tolerance
  - Chance of toxicity due to dose dumping
  - Additional patient education and counseling is required.

- Hypersensitvity reaction may occur after implantation.

Osmotic Pumps are available in three sizes

Design:

- Implantable drug-dispensing osmotic pump, shaped as a small rod with titanium housing.

Mechanism:

- Through osmosis, water from the body is slowly drawn through the semi-permeable membrane into the pump by osmotic agent residing in the engine compartment, which expands the osmotic agent and displaces a piston to dispense small amounts of drug formulation from the drug reservoir through the orifice.
- Application: Systemic or site-specific administration of a drug

Affecting factors

- Compositions of osmotic agent
- Thickness of semipermeable membrane
- Surface area

Implants are designed to bring the benefit of continuous therapy for up to one year. The non-biodegradable, osmotically driven system is intended to enable delivery of small drugs, peptides, proteins, DNA and other bioactive macromolecules for systemic or tissue-specific therapy. (leuprolide acetate implant), the first marketed product to incorporate, is indicated for the palliative treatment of advanced prostate cancer.

ADVANTAGES

- Can deliver highly concentrated and viscous formulations.
- Improved patient compliance
- Titanium protects the drug from enzymatic degradation.
- The system can be engineered to deliver a drug at a desired dosing rate with high degree of precision.

PULSATILE DRUG DELIVERY

Delivering a drug in one or more pulses is sometimes beneficial, from the required pharmacological action point of view.

Mechanical and drug solubility– modifying techniques have been implemented to achieve the pulsed delivery of drugs with an osmotic system.

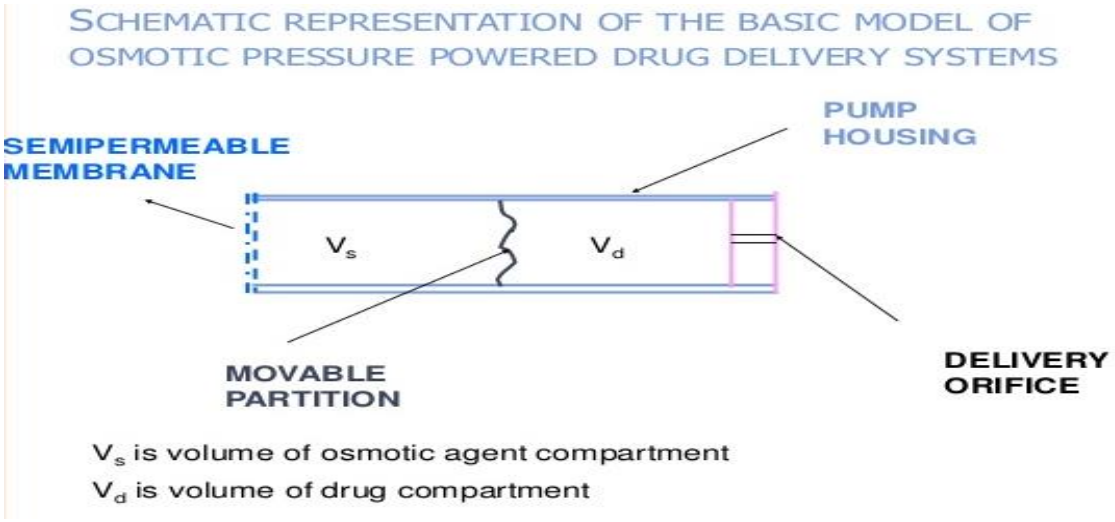


Fig. 8: Osmotic pressure powered DDS

DELAYED-DELIVERY OSMOTIC DEVICES

- Because of their semipermeable walls, osmotic devices inherently show a lag time before drug delivery begins. Although this characteristic is usually cited as a disadvantage, it can be used advantageously.
- The delayed release of certain drugs (e.g., drugs for early morning asthma or arthritis) may be beneficial. The following slides describes other means to further delay drug release.
    - Evaluation of Osmotic tablet
    - Pre-compression parameters
    - Post compression parameters
    - Pore diameter
    - Coating thickness
    - In Vitro drug release
    - Zero order release kinetics
    - First order release kinetics
    - Effect of Osmotic pressure
    - Effect of pH on drug release
    - Effect of agitation

***In vitro* evaluation**

- The in vitro release of drugs from oral osmotic systems has been evaluated by the conventional USP paddle and basket type apparatus.

- The dissolution medium is generally distilled water as well as simulated gastric fluid (for first 2-4 h) and intestinal fluids (for subsequent hours) have been used.
- The standard specifications, which are followed for the oral controlled drug delivery systems are equivalently applicable for oral osmotic pumps.
- In vivo evaluation of oral osmotic systems has been carried out mostly in dogs. Monkeys can also be used but in most of the studies the dogs are preferred.

DIAPHRAGM MICRO PUMP

- A diaphragm micropump uses the repeated actuation of a diaphragm to drive a fluid.
- Adiaphragm pump is a positive displacement pump that uses a combination of reciprocating action and either a flapper valve or a ball valve to transfer liquids.
- The membrane is positioned above a main pump valve, which is centered between inlet and outlet microvalves.
- When the membrane is deflected upwards through some driving force, fluid is pulled into the inlet valve into the main pump valve.
- The membrane is then lowered, expelling the fluid through the outlet valve. This process is repeated to pump fluid continuously.
- This pump is sometimes referred to as a membrane pump. Diaphragm pumps are air rotary vane pumps and are ideal for viscous liquids.
- It is so versatile, they are used in virtually every industry that requires fluid transfer. They are often used for dewatering or water removal across many different industries.

WORKING PRINCIPLE OF DIAPHRAGM PUMP

A diaphragmis a positive displacementpumpwhich utilises two flexible diaphragms that reciprocate back and forth, creating a temporary chamber, which both draws in and expels fluid through thepump.

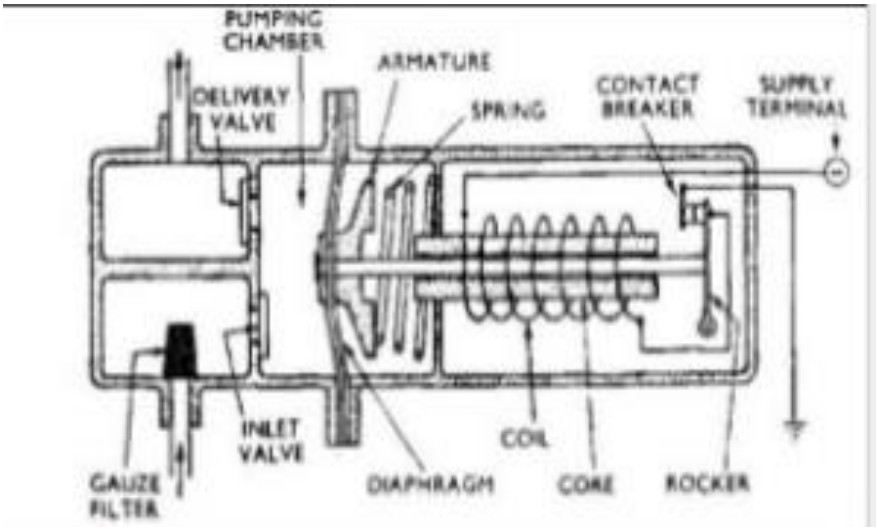


Fig. 9: Diaphragm Pump

TYPES OF DIAPHRAGM PUMPS

- **Air-Operated Pumps:**These pumps can be done by using compressed air
- **Small Air-Operated Pumps**:These pumps are used in low-volume liquid distribute accounts.
- **Small Air-Operated Pumps:** It develop forces to 60 PSI & in some cases 100 PSI

APPLICATIONS OF A DIAPHRAGM PUMP

- **Food & Beverage:**They are perfect for the Food & Beverage Industry.
- **Surface Coating:**Diaphragm Pumps transport chemicals, used for Surface Coating, from storage tanks, containers and baths.
- **Pulp & Paper:**Diaphragm Pumps can transport glue, adhesives and resin solutions, perfect for the Pulp & Paper Industry.
- **Petrochemical:** Diaphragm Pumps can be used for offshore Oil drilling in order to carry oil to the surface and to lubricate the drill.

ADVANTAGES AND DISADVANTAGES OF DIAPHRAGM PUMPS

- Self-priming
- Explosion proof
- Changeable flow rate and expulsion pressure
- Portable
- Easy installation
- They can operate in the long term

FLUOROCARBON PROPELLANTDRIVEN MICRO PUMP

This pumps does not require unique external energy, constant rate, implantable pump has also been used for variable –rate insulin delivery.

Construction:

- Hollow titanium disk, moveable pistons
- 2 chambers—inner-->drug; outer-->fluorocarbon liquid
- Self-sealing silicon rubber & Teflon, bacterial filters,catherter.

Working:

- Vaporization of fluorocarbon
- inner chambercompress
- drug release through catheter
- Adjust flow rate by increasing viscosity

The basic constant rate- pump consist of hollow titanium disc that is divided into two chambers by freely movable titanium bellows. The inner chamber contains the drug solution, while the outer chamber contains a fluorocarbon carbon liquid that exerts a vapor pressure well above atmospheric pressure at 37 ^{o}C. The inner drug chamber is refilled through percutaneous injection by means of a self –sealing withsilicon and Teflon septum. The pressure of the injection causes expansion of the inner chamber and compression of the fluorocarbon. Once filled, the fluorocarbon vaporizes and compresses the inner chamber. The drug solution is then forced to fine – bore Teflon capillary tubing which act as a flow regulator send subsequently through an intra-vascularly located silicon delivery catheter. Flow rate can be modified by changing the length of capillary tubing or by changing the viscosity of drug solution.

The flow through the pump is inversely related to the capillary length of solution viscosity. These pumps can deliver insulin or heparin solution at constant flow rates in the 1 to 5 ml / day range. Drug delivery rate is altered by adjusting drug concentration. The primary advantage of this type of device is the absence of any need for external power. The fluorocarbon driven pump has been modified foe insulin delivery at two infusion by connecting a three way valve to the pump assembly so that a portion of the flow restricting capillary can be bypassed when the valve is opened. A 15 fold increase in flow rate can be obtained and the delivery rate can be maintained between maximum and minimum rates by cycling the valve on and off to provide an intermediate rate determined by placing a small

permanent magnet is held near the valve when the valve is open. In newer design, the valve is housed in module attached to the side of a pump along with the infusion regulator to compensate for the effect of changes in the ambient pressure and temperature. In this design, machine grouped capillaries replace the Teflon tubing restrictor.

The external magnetic controller consists of an electronic timer that rotates a permanent magnet over the pump side to cycle the valve on and off. Without the infusion regulator this pumps are sensitive to charge in ambient temperature and pressure since they are implanted near the skin. The vapour pressure of the fluorocarbon liquid increases and the viscosity of the infused fluid decreases with increasing temperature. This is important in febrile conditions or if there are significant changes in the skin temperature. Similarly the lowering of ambient pressure causes a similar decrease in delivery rate.

Example: In humans the pump has been implanted in a subcutaneous pocket in the abdominal valve for chemo therapy or heparin therapy.

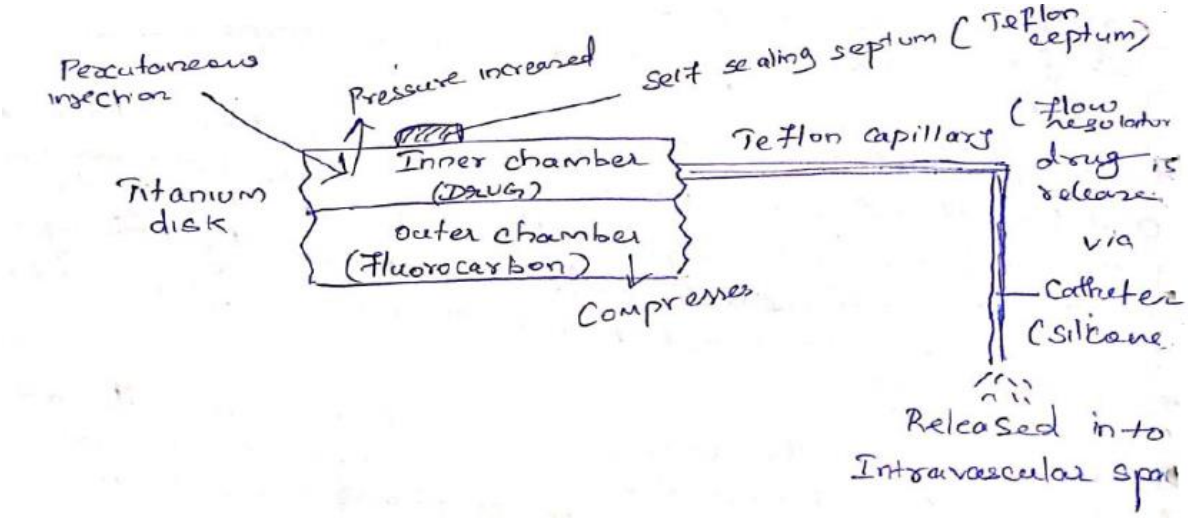


Fig. 10: Fluoro carbon propellent Pump

SOLENOID DRIVER RECIPROCATE MICRO PUMP

Positive displacement pump or Solenoid driven reciprocate Micropump

- An implantable, positive displacement, insulin pump made from piezoelectric disk benders.
- Two 1 in diameter thin wafers of piezoelectric material bonded to brass were glued to a ring of hexan tubing, upon applying a voltage the piezoelectric wafters, unable to

shrink or expand in diameter because of the brass disk bend in the middle to form spherical surfaces (bellows).

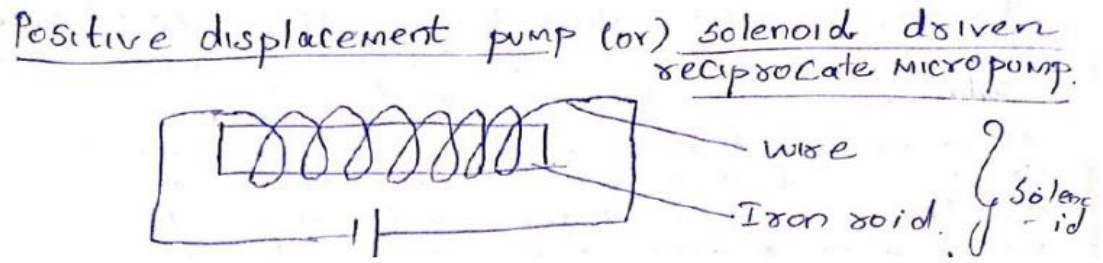
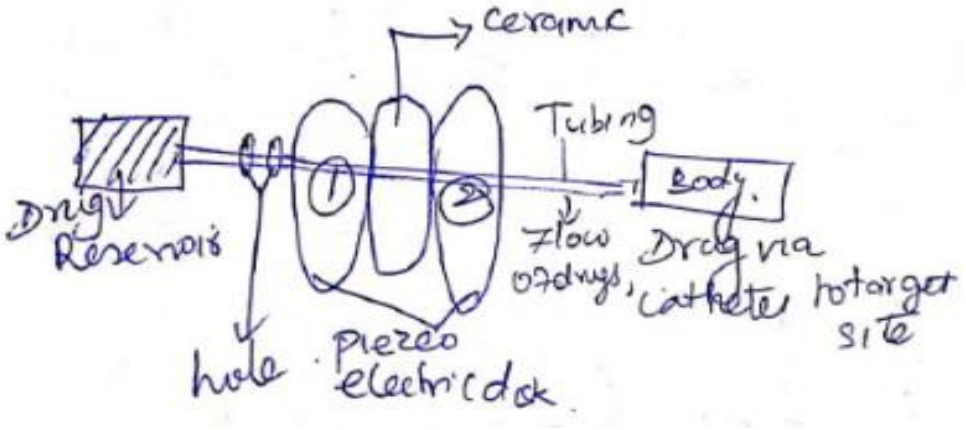


Fig. 11: Solenoid driven pump

- The bender belows are connected by a three way, solenoid driven valve to drug reservoir. Using an appropriately shaped voltage signal, the valve can be opened or closed in sequence with the flexing inward or outward of the disk bender bellows flexing outward causes suction of drug through the valve into the bellows, while a signal of the opposite polarity causes flexing inward, forcing through the valve and delivery to the catheter.
- Another early piezoelectric bellows pump has been prepared with piezoelectric valves. Piezoeletric disks epoxied to two titanium disk are used as bulbs modified diaphragm pump driven by propellent gas.
- The piezoelectric titanium disks lie on either side of a ceramic disk to close off a hole separating a pressurised insulin reservoir from the body.
- Activation of the reservoir-side piezoelectric disk causes fluid to move from the reservoir into the space between the ceramic and piezoelectric disk because of the piezoelectric disk.
- Deactivation of the disk and activation of that disk on the other side of the ceramic disk, draws fluid through the hole in the ceramic disk and into the body.
- A 24-hour clock and control package are designed to operate from a 5-v power supply and are contained along with a refillable reservoir, in a hermatically sealed cane.
- New modified solenoid driven positive displacement diaphragm pump
- When the solenoid is energised -> insulin in the pump chamber pressurised -> by rubber diaphragm driven by the solenoid -> fluid pressure open the multiple outlet valves-> to the delivery catheters-> while an inlet valve prevents backflow in the reservoir-> reservoir is refillable through a self sealing septum.

Diagram:



PROGRAMMABLE IMPLANTED DRUG ADMINISTRATIVE DEVICE(DAD)

Both implantable and external ambulatory infusion devices are currently in use, providing control delivery of insulin and chemotherapeutic agents via various types of catheters.Implanted insulin infusion pumps are widely used. The objective is to establish a safe and effective approach to **"openloop insulin"** insulin delivery from an implanted system. Open loop means that the pump itself does not sense blood glucose rather the patient must monitor blood glucose and the same way, signal the pump with a command describing when and how insulin to insulin to infuse.

Programmable Implantable mediation System (PIMS) was developed

The implanted unit is a disk approximately 3 inches in diameter and 0.78 inches thick, surgically placed beneath the skin in the left side of the abdomen. It delivers pulses of the insulin via catheter the tip of whichis placed deep in the peritoneal cavity. The pump spaces its pulses to deliver a basal release rate which s programmable and recycles every 24 hours. The patient then uses and external transmitting unit(a box about 6x4x2 in) to command the pump to deliver any of a variety of insulin doses. Insulin like other medication can be bound to various polymers and implanted as a pellet and find the way to the blood stream.

This relatively simple approach would be of limited use however because it would require repeated implantations of the pellet and would provide only a continuous infusion of insulin.

DAD:

It has been used clinically in several patients in three primary application areas.

1. Terminal cancer pain management
2. Intractable spasticity management

3. Cancer to chemo therapy

The DAD's longevity is a function of the capacity of the power source and the dispensing rate of the drug.The expected longevity of an implanted pump is 3 to 5 % depending on the application and amount of drug delivered. In cancer patient management –clinically effective relief of implantable cancer pain has been obtained with the DAD using morphine, sulphate Intra therapeutically in those patients for whom oral medication has failed.

In comparison to previous methods of administration the patients were more alert and active and did not experience many of the secondary complications such as lethargy, confusion to constipation and also conveniently accommodates a broad patient range of initial dosage levels.

Spasticity:

- It is caused by spinal cord trauma or multiple sclerosis is often treated with oral baclofer (an analog of the inhibitory neurotransmitter gamma amino butyric acid.
- The goal is to reduce muscle tone to normal levels to suppress spasms.
- The major side effects of the drug are drowsiness and in some causes confusion.
- The DAD has been used to administer baclofer intrathically to patients with severe spasicity who are refractory to oral baclofen
- The drowsiness, confusion or weakness was experienced its dosage levels adequate to supress symptoms.
- The use of the DAD in cancer chemotherapy states the therapeutic effect of implanted programmable drug infusion.

Ex.: In one series of patients with carcinoma of the kindney. Constant rate intravenous infusion of Floxuridine (FUDR) was compared with time modified administration.

Time modified schedule consisted of four dosage intervals-

a) Low level administration in the early morning (quadrants)
b) A step wise dosage increase from late morning into early afternoon (2^o)
c) Peak delivery rate from late afternoon into early evening.
d) A decrease in dosage to second quadrant levels in the final interval

Results of this study were encouraging and support the usefulness of DAD.

- Oncologists currentlys belive that the amount of drug administrated as well as adherence to monthly treatment schedules are important to the altimate success of chemotherapy.
- In the intravenous FUDR group studied 40% of the patients receiving constant rate infusion require treatment delays compared to 6% of the time modified group. Reductions

in dosage were necessary in 60% of the former group, while only 12% of the time-modified patients required reduction because of drug-related symptoms.

- In conclusion, programmable implantable drug delivery is an emerging technology.
- Its clinical benefits include improved drug efficacy dynamic dosing, non-invasive prescription modification reduced side effects, improved quality of life and cost-effectiveness compared to the traditional in hospital therapy.

Drug Administration Device (DAD)Advantages:

- Use of wide variety of drugs.
- Precise delivery of potent & narrow therapeuticsubstances.
- Less risk of infection since it is fully implanted.
- Performed using local anesthesia& onoutpatient basis.
- Presence of alarm system makes the pumpmore safe.

Insulin Pump

INTRODUCTION

- People with diabetes cannot make their own insulin, ahormone that is normally secreted by the pancreas. Insulin is essential to metabolise sugar and hence generate energy
- Currently most diabetics inject insulin 2 or more times per day, with the dose injected based on readings of their blood sugar level
- A personal insulin pump is an external device that mimics the function of the pancreas
- It uses an embedded sensor to measure blood sugar level at periodic intervals and then injects insulin to maintain the blood sugar at a ‘normal’ level
- Designed to transmit drugs and fluids into bloodstream without repeated insertion of needles
- Well suited to the drug delivery requirements of:
  - insulin,
  - steroids,
  - chemotherapeutics,
  - antibiotics,
  - analgesics,
  - and heparin.

Early Insulin Pumps(early 1970s)

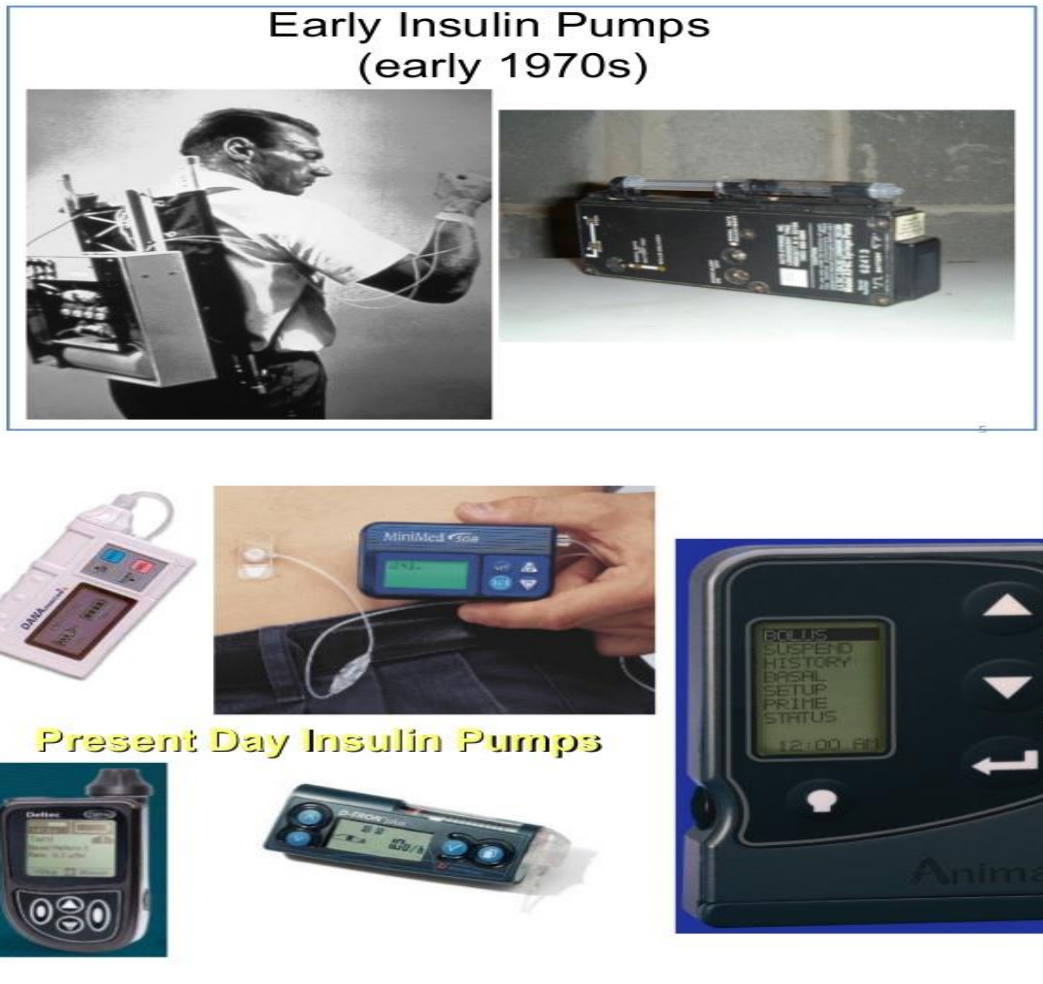


Fig. 12: Present Day Insulin Pumps

Data flow model of software-controlled insulinpump

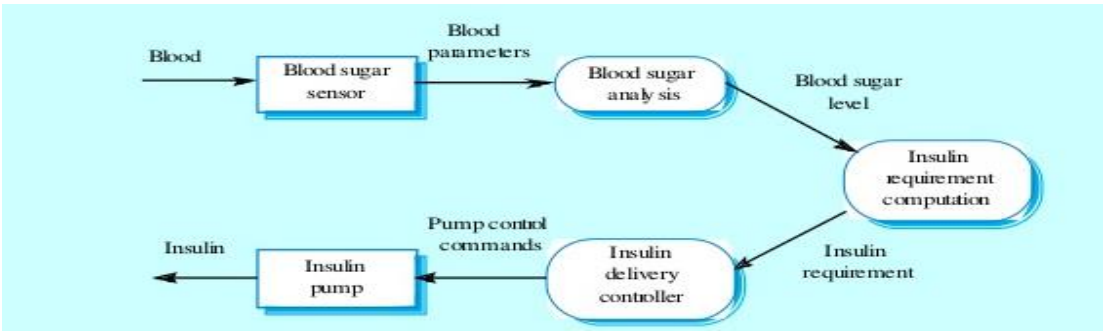


Fig. 13: Data flow of Insulin Pumps

Insulin delivery system•

- Data flow model of software-controlled insulinpump
- InsulinrequirementcomputationBlood sugaranalysisBlood sugarsensorInsulindeliverycontrollerInsulinpump
- Bloodparameterslike Blood sugarlevelInsulinPump controlcommands Insulinrequirement

- Continuous Subcutaneous Insulin InfusionB SL HS BInsulinEffectBolusBasal
- Insulin Delivery as a Model Implant PumpSystem

  • Implantable drug delivery systems are placedcompletely under the skin — usually in aconvenient location.

  • Generally placed in the anterior subcutaneoustissue of chest/abdomen for concealment.

IMPLANTABLE MICRO–PUMP SYSTEMS

- Difference between diffuser pump and membrane pump is that diffuser pump has no check valves. Instead, two diffusers are introduced.
- Diffuser is a channel with a increasing cross sectional area.
- When fluid flows in one way or the other, it will encounter different flow resistances caused by the diffuser.
- Diffuser PumpExcept the difference between diffusers and valves, diffuser pump is similar with membrane pump.
- Many mechanisms can be used to drive a diffuser pump.
- Goodness simple fabrication, free of valve fatigue.
- Weakness sensitive to bubbles, low operating pressure
- Non-Mechanical Pump Without movable parts, non-mechanical pump is often much simpler than mechanical pump.
- Non-mechanical pump includes
    - EHD pump
    - Bubble pump
    - Other pumps
- EHD pump or TheElectrohydrodynamic (EHD) pumps uses applied electric field to induce and drag charges in fluid.
- Goodness is no moving parts, very simple fabrication process
- Weakness is sastainable for conductive fluid

MECHANICAL PUMP

- In general, mechanical pump consists of moveable components, such as moveable valves, moveable membrane, moveable channel, etc.
- Mechanical pump can be categorized into

1. Membrane pump
2. Rotary pump
3. Diffuser pump

MEMBRANE PUMP

- Membrane Pump often consists of two check valves and a chamber with moveable membrane.
- By some mechanisms, membrane can be actuated to change the volume of chamber.
- Because the check valve can be opened only in one direction, for each circle, some fluid will be moved from inlet to outlet.

CONTROLLED RELEASED MICROPUMPS

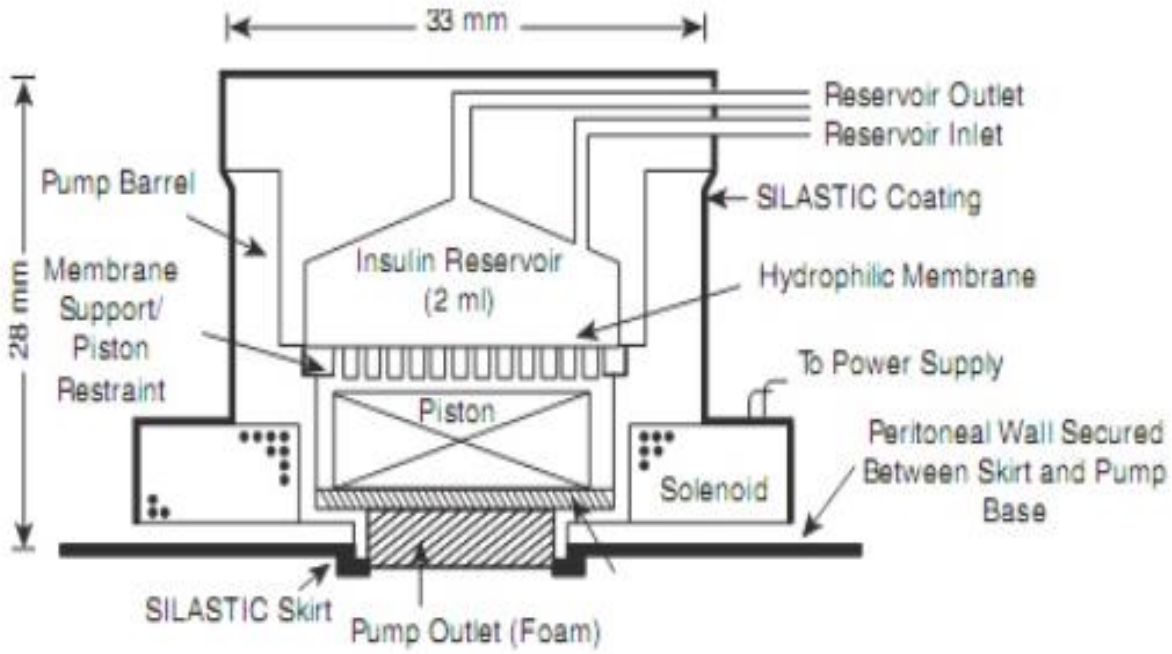


Fig. 14: Controlled relese micropump

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2. Anya M Hillery et al Drug delivery and targeting CRC press, 2010
3. Robinson R Robinson Conventional drug delivery systems CRC press,2004

QUESTIONS

1. Compare the advantages and disadvantage of micro pumps.
2. Write the principle of osmotic micro pumps.
3. Classify the implantable micropump system
4. Classify mechanical micro pumps
5. Give the demerits of osmotic drug delivery system
6. Support with suitable examples the use of micro pump mediated drug delivery for patients.
7. Sketch a peristaltic micro pump and explain
8. Explain in detail about the insulin pump structure and its data flow structure with necessary diagrams
9. With neat sketch explain about fluorocarbon propellent driven micropump in detail
10. Explain about the working principle of diaphragm pump in detail

UNIT – V - SITE SPECIFIC DRUG DELIVERY SYSTEMS– SBM1610

UNIT 5

SITE SPECIFIC DRUG DELIVERY SYSTEMS

Contents:

- **Development in insulin therapy using biomedical controlled drug delivery systems**
- **Drug delivery using monoclonal antibodies**
- **Role of biosensors and transducers in diagnostic**

Development in Insulin Therapy Using Biomedical Controlled Drug Delivery Systems:

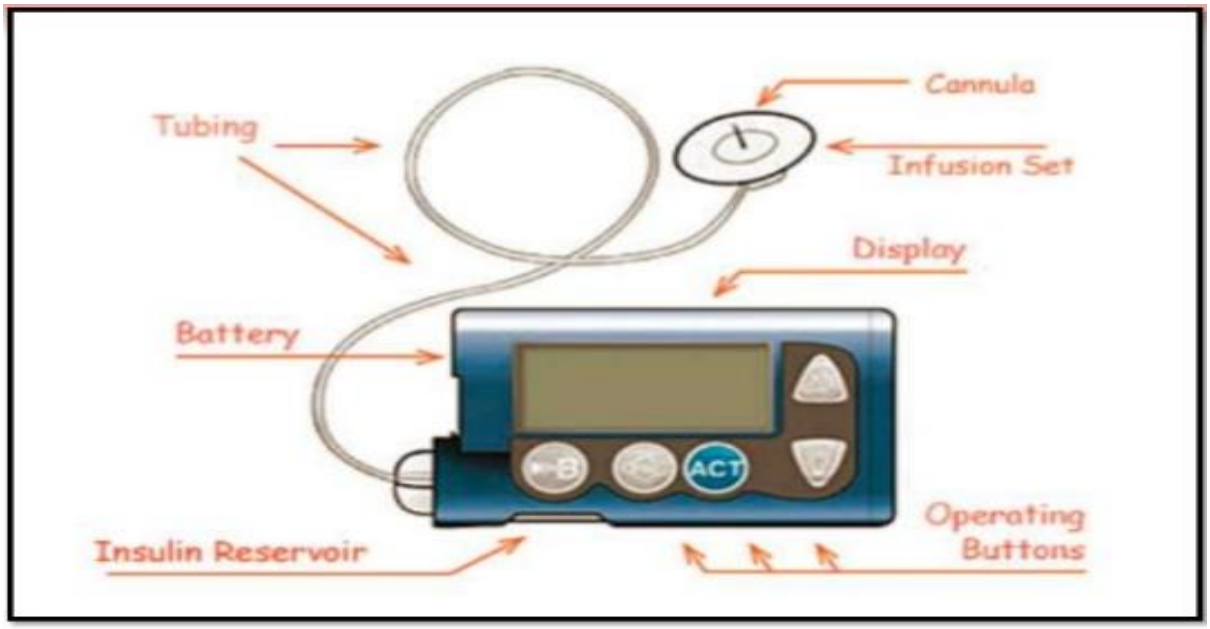
- In case of Diabetes mellitus there is rhythmic increase in the levels of glucose in the body, requiring injection of the insulin at proper time.
- Several systems have been developed which are able to respond to changes in glucose concentration.
- One such system includes pH sensitive hydrogel containing glucose oxidase, immobilized in the hydrogel encapsulating saturated insulin solution.
- When glucose concentration in the blood increases, glucose oxidase converts glucose into gluconic acid which changes the pH of the system.
- This pH change induces swelling of the polymer which results in insulin release.
- Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased.

GLUCOSE-RESPONSIVE INSULIN RELEASE DEVICES

INSULIN PUMP

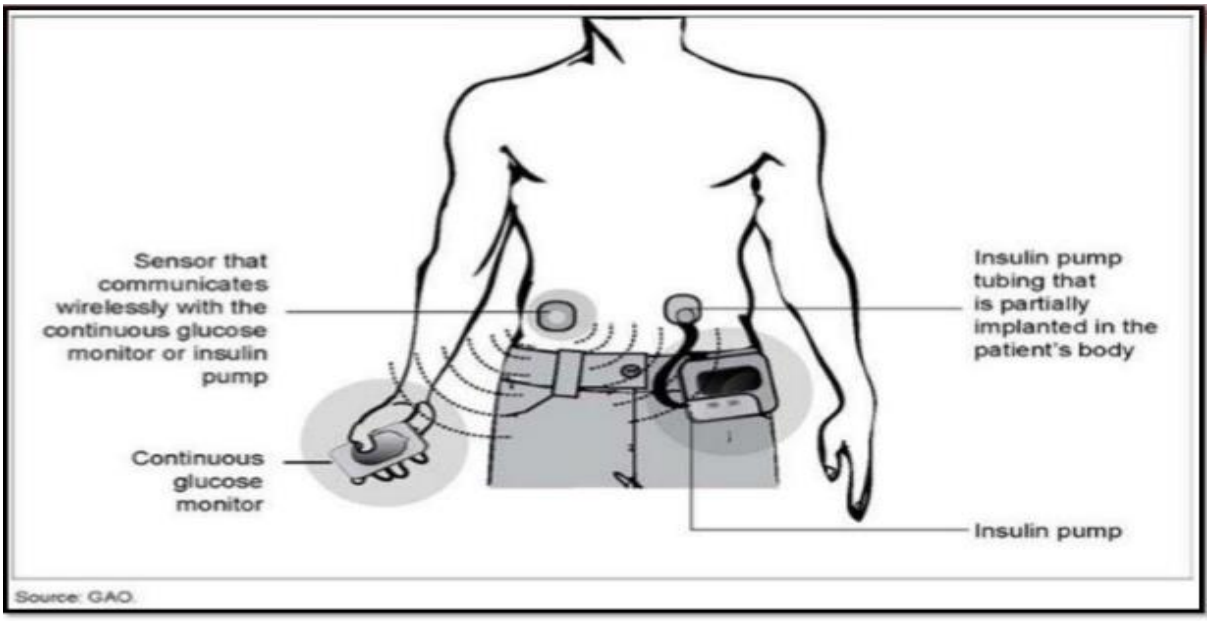
- The ultimate goal of insulin treatment in diabetes mellitus is to control the blood glucose level and prevent or stabilize long - term diabetic complications.
- Administration of insulin through subcutaneous injection is currently the major therapy of diabetes.
- Two or three injections are required a day to maintain the normal blood glucose level. Because this method is burdensome and invasive to living organisms, the patient's situation would not be good regarding the quality of life. Therefore, an insulin pump constructed with polymer materials has been studied.

- Wang developed an insulin reservoir consisting of silicone rubber, which releases insulin stored inside by generation of a pressure gradient by compression.
- Segmented polyurethane (SPU) can be used as an elastic material for preparation of the insulin reservoir.
- The enhancement of insulin permeability and biocompatibility, a novel copolymer composed of 2-methacryloyloxyethyl phosphorylcholine (MPC) and 2-EthylHexyl Methacrylate (EHMA) can be designed.
- Addition of the MPC polymer to other polymers enhances the biocompatibility to the original polymer.
- Two main mechanisms are generally involved in under delivery events:
    1. Insulin aggregation in the pump insulin pathway.
    2. Catheter occlusions.
- Moreover, these aggregates, which are likely to be generated by hydrophobic interactions with the pump circuits, seem to promote an increased production of anti -insulin antibodies in many patients treated by implantable pumps.
- Concomitant improvements of catheter design also contributed to the reduction of under delivery.
- Despite these problems, implantable pumps currently provide the most effective and physiological insulin delivery.



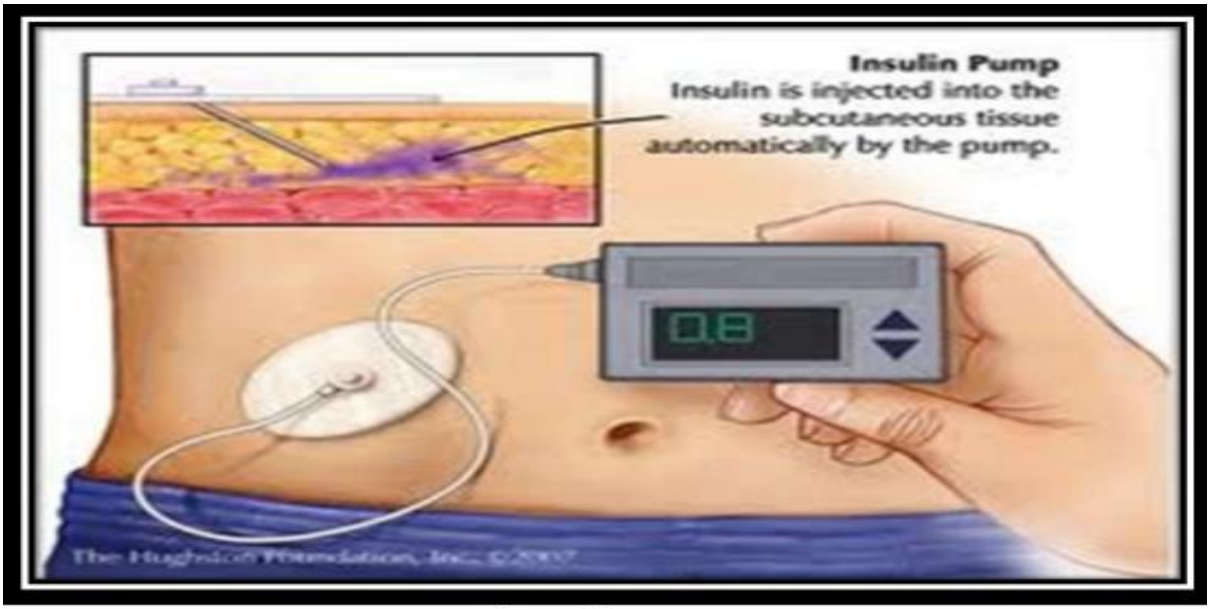
Insulin pump

Fig. 1: Insulin Pump



Insulin pump

Fig. 2: Insulin Pump operating procedure



Insulin pump

Fig. 3: Insulin Injected

2. GLUCO WATCH

- Gluco Watch biographer is non-invasive, watch like device that measures glucose.
- A plastic part of Gluco watch that snaps into the biographer and sticks to the skin.
- Automatic reading every 10 min up to 13 hrs is taken by it.

- Gluco watch presently takes the lead among user-friendly techniques aimed at glucose monitoring.
- This system is based upon the principle of reverse Iontophoresis.
- A low electric current pulls glucose through the skin. Glucose is accumulated in two gel collection discs in the auto sensor. Another electrode in the auto sensor measures the glucose. A signal in proportion to interstitial glucose level can thus be generated.

GLUCO WATCH

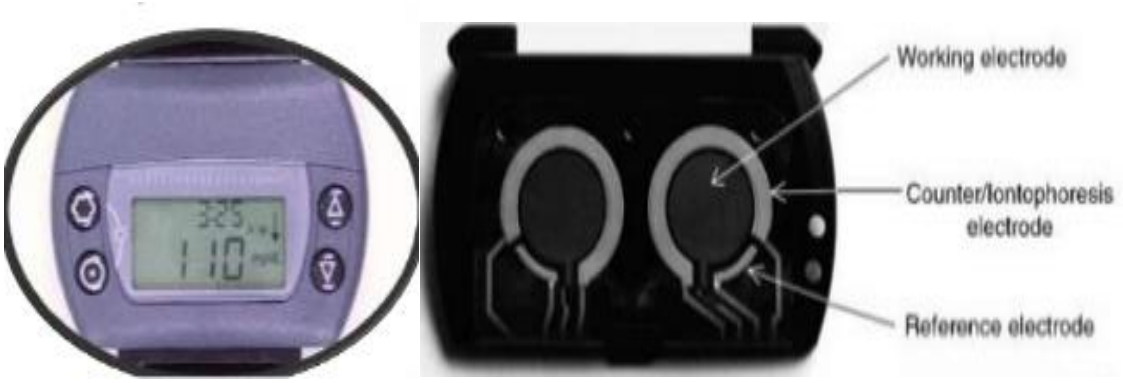


Fig. 4: Gluco watch

3. MICROFABRICATED DRUG DELIVERY SYSTEMS

- Possible applications include micromachined silicon membranes to create implantable bio capsules for the immune isolation of pancreatic islet cells as a possible treatment for diabetes and sustained release of injectable drugs needed over long time periods.
- The development of microneedles for transdermal drug delivery came about as an approach to enhance the poor permeability of the skin by creating microscale conduits for transport across the stratum corneum.
- Microfabrication technology has also created a new class of controlled release systems for drug delivery based on programmable devices called microchips.
- Microchips are particularly intriguing due to their small size, potential for integration with microelectronics and their ability to store and release chemicals on demand.
- The ultimate goal is to develop a microfabricated device devoid of moving parts, but with the ability to store and release multiple chemical substances.
- There are many different types of insulin delivery devices available including syringes, pens, jet injectors, oral insulin and pumps which are detailed below.
- Furthermore, insulin that can be inhaled and other new approached to insulin treatment are at different stages of availability and development throughout the world.
    - Insulin Syringes

- External Insulin Pumps
- Implantable Insulin Pumps
- Insulin Pens
- Insulin Injection Aids
- Insulin Jet Injectors
- Insulin Inhalers

INSULIN SYRINGES

- Direct subcutaneous insulin injection remains the most common form of delivery, using a needle and syringe.
- The capacity of the syringe should be chosen depending on the dosage of insulin.
- Other factors are needle gauge and needle length, both of which should be adjusted for comfort.
- Your diabetes healthcare professional should be able to advise which needle length you need.

EXTERNAL INSULIN PUMPS

- Although external insulin pumps remain hard to access and expensive, many people with diabetes find them to be accurate, precise and flexible as insulin delivery systems providing tight blood glucose control.
- Like most insulin delivery aids, it is important to monitor blood glucose regularly whilst on a pump.

IMPLANTABLE INSULIN PUMPS

- At this stage, implantable insulin pumps are still in development. Research teams across the globe are working to develop implantable insulin pumps to measure blood glucose levels and provide the precise insulin dose needed.
- Those pumps being developed are small, extremely discreet, and weigh very little. This type of pump is implanted surgically, and can deliver a continuous basal dose of insulin and a bolus dose when required.

INSULIN PENS

- Insulin pens are a very useful way to transport insulin in a discreet way, allowing you to administer insulin on the move or whenever suits you.
- Insulin pens are either disposable one-shot devices or they have replaceable cartridges of insulin.
- The tip of insulin pens include a fine, short needle and diabetic patients can turn a dial to select the correct dosage.

DRUG DELIVERY USING MONOCLONAL ANTIBODIES

Introduction

Monoclonal Antibodies used as Drug Targeting Particulate Carrier System

- Antibodies are produced by a specialized group of cells called B-Lymphocytes.

- When an foreign antigen enters the body due immune response B-Lymphocytes develops into plasma cells and liberates antibodies or immunoglobulin's of various types(Ig A, Ig D, Ig E, Ig G, Ig M).
- An antibody is a protein used by the immune system to identify and neutralize foreign objects like bacteria and viruses. Each antibody recognizes a specific antigen unique to its target. Monoclonal antibodies (mAb) are antibodies that are identical because they were produced by one type of immune cell, all clones of a single parent cell. Polyclonal antibodies are antibodies that are derived from different cell lines. They differ in amino acid sequence.

Role of Antibody in Immune System

- Each Antigen has specific antigen determinants (epitopes) located on it. The antibodies have complementary determining regions (CDRs). These are mainly responsible for the antibody specificity.
- Each antigen has several different epitopes on it. They are recognised by many different antibodies. All these antibodies thus produced act on the same antigen. Hence these are designated as polyclonal antibodies.
- In general naturally produced antibodies are non-specific and heterogeneous in nature. Hence there are several limitations in the use of polyclonal antibodies for therapeutic and diagnostic purposes.
- Thus there is a need for producing monoclonal antibodies for different antigens.
- Need to develop antibodies

Advantages of Monoclonal Antibodies in Drug Targeting

- "Targeted drug delivery system is a special form of drug delivery system where the medicament is selectively targeted or delivered only to its site of action and not to the non-target organs or tissues or cells"
- It is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others.
- Targeted drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues.
- This improves efficacy and reduce side effects.
- They are homogenous in nature.
- They are specific to a particular antigen with a particular epitope.
- Ex:Rituximab (Rituxan®, anti-CD20) is a good example – this antibody is used for the treatment of lymphoma.

THE DRUG MAY BE DELIVERD:

- To the capillary bed of the active sites. To the specific type of cell (or) even an intracellular region.

Ex: Tumour cells but not to normal cells.

- To a specific organ (or) tissues by complexion with the carrier that recognizes the target.
- To achieve a desired pharmacological response at a selected sites without undesirable interaction at other sites, there by the drug have a specific action with minimum side effects & better therapeutic index. ´ Ex- In cancer chemotherapy and enzyme replacement therapy.
- Reasons for Drug Targeting is:
    - Drug instability
    - Low absorption
    - Short half-life
    - Large volume of distribution
    - Low specificity
    - Low therapeutic index

Limitations

- As they are specific to a particular antigen, they cannot distinguish molecule as a whole.
- Some times they cannot distinguish groups of different molecules. Ex:- presence of retro viruses as a part of mammalian chromosomes is not distinguished.
- The presence of some of these viruses is detected in hybridomas. This poses a great danger since there is no guarantee for MAb produced is totally virus free.
- For this reason US food and drug administration insists that MAb for human use should be totally free from all pathogenic organisms including viruses.

Monoclonal Antibodies Approved By FDA

- Antibody Target Indication
- Trastuzumab HER2 Breast Cancer
- Bevacizumab VEGF Lung Cancer
- Cetuximab EGFR Colorectal carcinoma
- Panitumumab EGFR Colorectal carcinoma

ROLE OF BIOSENSORS AND TRANSDUCERS IN DIAGNOSTIC

- A sensor that integrates a biological element with a physiochemical transducer to produce an electronic signal proportional to a single analyte which is then conveyed to a detector is called biosensor.

- Father of the Biosensor Professor Leland C Clark Jnr 1918–2005 ′ A device incorporating a biological sensing element either intimately connected to or integrated within a transducer.
- BIO – SENSOR:′ Recognition based on affinity between complementary structures like: enzyme-substrate, antibody-antigen and receptor-hormone complex. ′ Selectivity and specificity depend on biological recognition systems connected to a suitable transducer.
- It is an analytical device which converts a biological response into an electrical signal.
- It detects, records, and transmits information regarding a physiological change or process.
- It determines the presence and concentration of a specific substance in any test solution.

Basic principle of biosensor

Basic principle of biosensor involved in three element:-

- First biological recognition element which highly specific towards the biological material analytes produces.
- Second transducers detect and transduces signal from biological target - receptor molecule to electrical signal which is due to reaction occur.
- Third after transduction signal from biological to electrical signal where its amplification is necessary and takes place and read out in detector after processing the values are displayed for monitor and controlling the system .
- The biological material is immobilized and a contact is made between the immobilized biological material and the transducer
- The analyte binds to the biological material to form a bound analyte which in turn produces the electronic response that can be measured.
- Sometimes the analyte is converted to a product which could be associated with the release of heat, gas (oxygen), electrons or hydrogen ions.
- The transducer then converts the product linked changes into electrical signals which can be amplified and measured

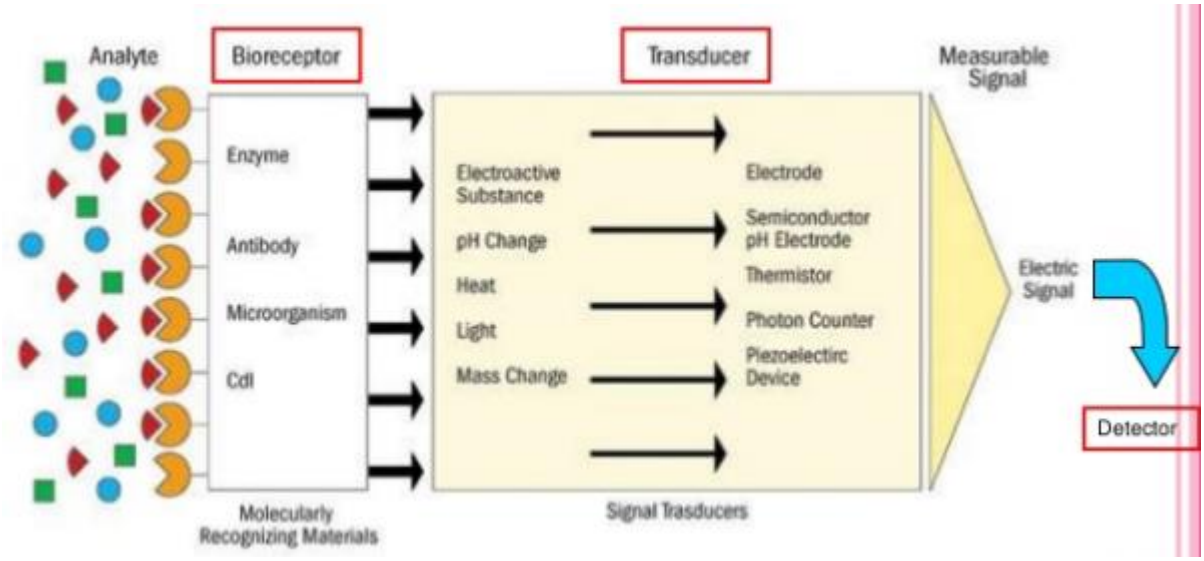


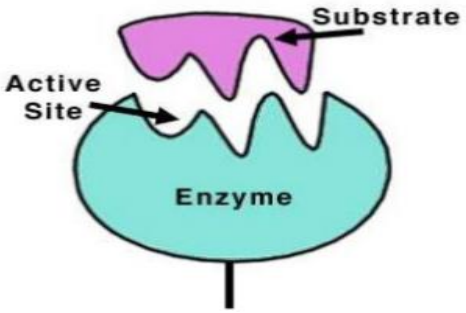
Fig. 5: Components of Biosensor

COMPONENTS OF BIOSENSOR

1st COMPONENT – BIOLOGICAL ELEMENT DETECTOR

The component used to bind the target molecule. Must be highly specific, stable under storage conditions, and immobilized.

- Microorganism
- Tissue
- Cell Organelle
- Nucleic Acid
- Enzyme
- Enzyme Component
- Receptor
- Antibody



Function

- To interact specifically with a target compound i.e. the compound to be detected.
- It must be capable of detecting the presence of a target compound in the test solution.

- The ability of a bio-element to interact specifically with target compound (specificity) is the basis for biosensor.

2nd COMPONENT – PHYSIOCHEMICAL TRANSDUCER

- Acts as an interface, measuring the physical change that occurs with the reaction at the bioreceptor then transforming that energy into measurable electrical output.

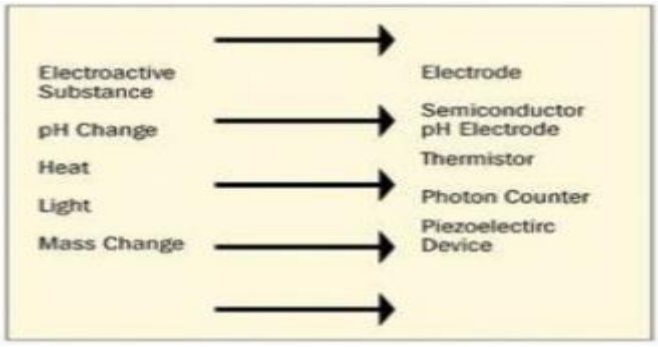


Fig. 6: Procedure

3rd COMPONENT – DETECTOR

- Signals from the transducer are passed to a microprocessor where they are amplified and analyzed.
- The data is then converted to concentration units and transferred to a display or/and data storage device.

Fig. 7: Detector

PRINCIPLE OF DETECTION

PIEZOELECTRIC	Measures change in mass
ELECTRO-MECHANICAL	Measures change in electric distribution
OPTICAL	Measures change in light intensity
CALORIMETRIC	Measures change in heat

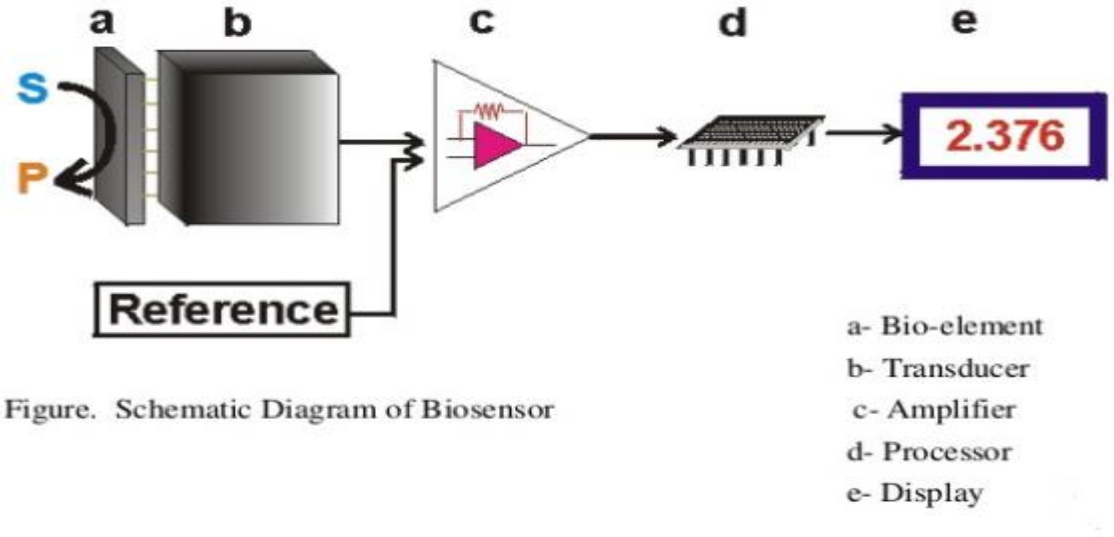


Figure. Schematic Diagram of Biosensor

Fig. 8: Biosensor

- Biosensors basically involve the quantitative analysis of various substances by converting their biological actions into measurable signals.
- Generally the performance of the biosensors is mostly dependent on the specificity and sensitivity of the biological reaction, besides the stability of the enzyme.
- Analyte Sample handling/preparation Detection Signal Analysis Response

IDEAL BIOSENSOR

- The output signal must be relevant to measurement environment.
- The functional surface must be compatible with the transducer.
- High specificity and selectivity (low interference).
- Sufficient sensitivity and resolution.
- Sufficient accuracy and repeatability
- Sufficient speed of response
- Sufficient dynamic range.
- Insensitivity to environmental interference or their effects must be compensated

BASIC CHARACTERISTICS OF BIOSENSOR

a. LINEARITY - Linearity of the sensor should be high for the detection of high substrate concentration.
b. SENSITIVITY - Value of the electrode response per substrate concentration.
c. SELECTIVITY - Chemicals Interference must be minimised for obtaining the correct result.
d. RESPONSE TIME - Time necessary for having 95% of the response.

TYPES OF BIOSENSOR

Based on bioreceptors

- Enzyme biosensor
- Microbial biosensor
- Affinity biosensor

Based on transducer

- Potentiometric
- Amperometric
- Conductometric
- Optical
- Acoustic or piezoelectric etc.

OPTICAL BIOSENSORS

- Colorimetric for color: Measure change in light adsorption as reactants are converted to products.
- Photometric for light intensity: Photon output for a luminescent or fluorescent process can be detected with photomultiplier tubes or photodiode systems.

CALORIMETRIC BIOSENSORS

- If the enzyme catalyzed reaction is exothermic, two thermistors may be used to measure the difference in resistance between reactant and product and hence the analyte concentration.

POTENTIOMETRIC BIOSENSORS

For voltage: Change in distribution of charge is detected using ion-selective electrodes, such as pH- meters.

PIEZO - ELECTRIC BIOSENSORS

- The change in frequency is proportional to the mass of absorbed material.
- Piezo-electric devices use gold to detect the specific angle at which electron waves are emitted when the substance is exposed to laser light or crystals, such as quartz, which vibrate under the influence of an electric field.

ELECTROCHEMICAL BIOSENSORS

Principle Many chemical reactions produce or consume ions or electrons which in turn cause some change in the electrical properties of the solution which can be sensed out and used as measuring parameter.

Classification

(1) Amperometric biosensor

(2) Conductimetric biosensor

(3) Potentiometric biosensor

- Amperometric for applied current: Movement of e- in redox reactions detected when a potential is applied between two electrodes.
- Potentiometric for voltage: Change in distribution of charge is detected using ion-selective electrodes, such as pH-meters.
- Conductimetric for impedance

AMPEROMETRIC BIOSENSORS

- Measuring parameter : Electric current
- Based on oxidase enzymes that generate H2O2 and consume oxygen.
- Formation of H2O2 can be detected by the help of Pt-electrode.

GLUCOSE BIOSENSORS

- Glucose reacts with glucose oxidase(GOD) to form gluconic acid.
- Two electrons & two protons are also produced.
- Glucose mediator reacts with surrounding oxygen to form H2O2 and GOD.
- Now this GOD can reacts with more glucose.
- Higher the glucose content, higher the oxygen consumption.
- Glucose content can be detected by Pt- electrode.

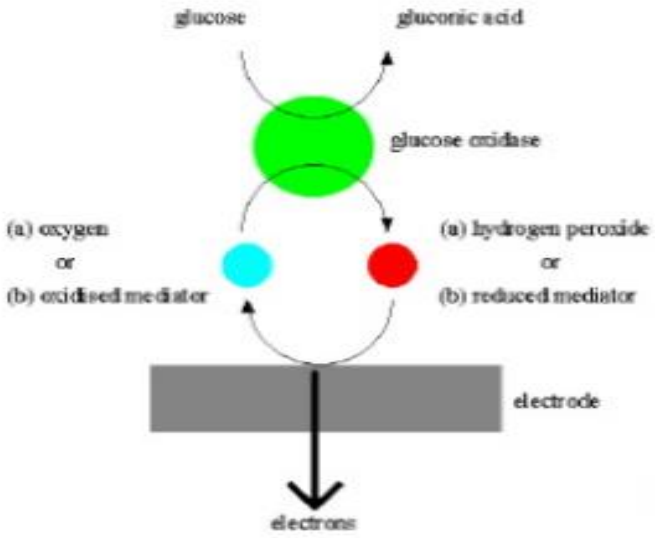
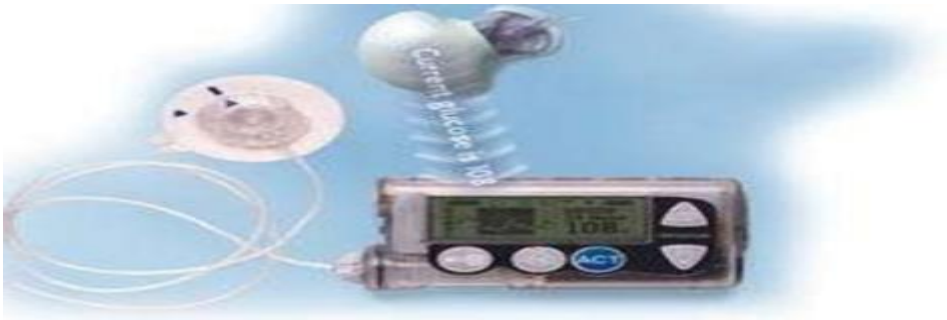


Fig. 9: Glucose Biosensor

Examples of Biosensor



Glucose monitoring device (for diabetes patients)

Monitors the glucose level in the blood.

Fig. 10: Glucose monitoring device

Pregnancy test - Detects the hCG protein in urine.

Fig. 11: Pregnancy test

REFERENCES

1. Vyas S.P. Khar RKTargetted and controlled drug delivery Novel Carrier System CBSPD, 2006.
2. Anya M Hillery et al Drug delivery and targeting CRC press, 2010
3. Robinson R Robinson Conventional drug delivery systems CRC press,2004

QUESTIONS

1. Write notes on insulin syringes
2. Write about insulin pens
3. Give some examples of biosensors
4. Write notes on potentiometric biosensors
5. Give the classification of biosensors
6. Write about optical biosensors

7. Explain in detail about the glucose responsive insulin release concepts with some devices as an example
8. Explain any four biosensors with necessary diagram in detail