Novel Drug Delivery System 1 to 5 Units

CONTENTS

N D D S

(NOVEL DRUG DELIVERY SYSTEMS)

Definition:-

"Novel Drug Delivery System (NDDS) refers to the approaches, formulation, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effects."

-NDDS is a system for delivery of drug other than conventional drug delivery systems.
-NDDS is a combination of advance technique and new dosage forms which are far better than conventional dosage forms.

➢ Advantages of NDDS:-

-Improve therapy by **increasing the duration of action** and **reducing the side-effects**.
-Increase patient compliance through **decrease dosing frequency** and convenient routes of administration.
-Achieve targeting of drugs to a specific site **to reduce unwanted side-effects** and **obtain maximum efficacy.**
-Lead to **reduction in dose** and thus reduction in side effects of drugs.

➢ Challenges of NDDDS:-

-The location of drug targeting changes drug bioactivity and kinetics.
-Every patient has a different metabolism.
-Patient or the drug May respond differently.
-Efficacy is sometimes hard to define.
-Clinical trials are expensive and difficult to conduct

• Types of NDDS

1) Modified drug delivery systems

2) Oral Modified release dosage forms-

a) Matrix tablets
b) Microspheres
c) Hydrogels
d) Osmotic pressure controlled systems
e) Gastro-retentive systems
f) Colon Targeted drug delivery

3) Parenteral drug delivery systems

a) Parenteral suspensions
b) Parenteral emulsions
c) Microspheres
d) Liposomes
e) Niosomes
f) Nanoparticles

4) Transdermal Drug Delivery Systems

5) Site Specific Drug delivery Systems

6) Targeted Drug delivery Systems

7) Trans-mucosal Drug delivery Systems

8) Ocular Drug delivery Systems

•Modified Drug Delivery Systems

-Modified drug delivery systems are sophisticated and take into account pharmacokinetic principles, specific drug characteristics, and variability of response among individuals with different medical conditions.

-These systems are designed to deliver drugs at a specific time or over a period of time after administration, or at a specific location in the body.

➢ Types of Modified Drug Delivery Systems-

(1) Matrix system:-

-Matrix- based oral delivery systems contain **a polymer at is uniformly mixed with the drug** and other formulation excipients.
-The drug becomes distributed and embedded throughout the polymer matrix.
-These matrix can be compressed into tablets, or granules can be put into a capsule.

(2) Reservoir system:-

-These systems usually **contain a rate-controlling polymer membrane surrounding a core that contains the drug.**
-Drug release is facilitated by gradual dissolution and is controlled by the thickness or solubility of the coating.
-A thicker coating will be more resistant to penetration by the aqueous fluids and a coating that is rich in lipophilic polymer will also delay drug release and dissolution.
-In this system water enters the drug reservoir, dissolves or suspends the drug and pushes the drug out through a pre-drilled orifice.
-In reservoir type of system, the drug crystal, pellets, granules may be coated with polymer and then these pellets may either be encapsulated or compressed into tablets.

❖ Estimation of Loading Dose & Maintenance Dose:-

▪ Loading Dose:-

-In pharmacokinetics, **a loading dose is an initial higher dose of a drug that may be given at the beginning of a course of treatment** before dropping down to a lower maintenance dose.

-A loading dose is most useful for drugs that are eliminated from the body relatively slowly, i.e. have a long systemic half-life.
-Such drugs need only a low maintenance dose in order to keep the amount of the drug in the body at the appropriate therapeutic level, but this also means that, without an initial higher dose, it would take a long time for the amount of the drug in the body to reach that level.
- Drugs which may be started with an initial loading dose include digoxin, teicoplanin, voriconazole, procainamide and fulvestrant.
-One or series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly.

-Suppose a patient just started taking 100 mg of drug every day.
-On the first day, they'd have 100 mg in their system; their body would clear 10 mg, leaving 90 mg.
-On the second day, the patient would have 190 mg in total; their body would clear 19 mg, leaving 171 mg.
-On the third day, they'd be up to 271 mg total; their body would clear 27 mg, leaving 244 mg.
-As you can see, it would take many days for the total amount of drug within the body to come close to 1 gram (1000 mg) and achieve its full therapeutic effect.
-For a drug such as this, a doctor might prescribe a loading dose of one gram to be taken on the first day. That immediately gets the drug's concentration in the body up to the therapeutically-useful level.
-First day: 1000 mg; the body clears 100 mg, leaving 900 mg.
-On the second day, the patient takes 100 mg, bringing the level back to 1000 mg; the body clears 100 mg overnight, still leaving 900 mg, and so forth.

-**Calculating the loading dose.**

-Four variables are used to calculate the loading dose:

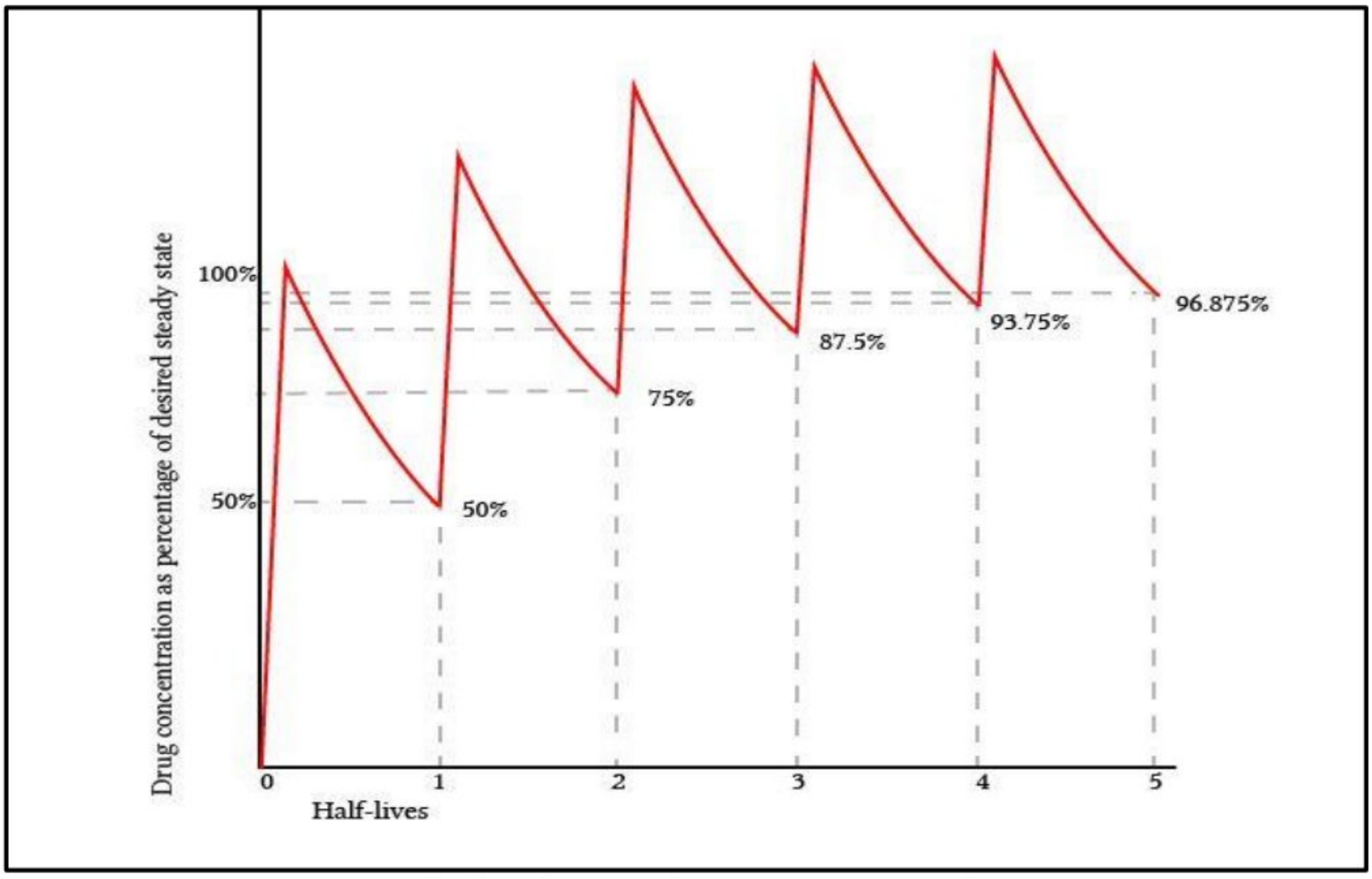
C_p = desired peak concentration of drug
V_d = volume of distribution of drug in body
F = bioavailability
S = fraction of drug salt form, which is active drug

The required loading dose may then be calculated as:-

$$\textbf{Loading Dose} = \frac{C_p . V_d}{F . S}$$

- **Maintenance Dose:-**

-In pharmacokinetics, **a maintenance dose is the maintenance rate [mg/h] of drug administration equal to the rate of elimination at steady state**.
-This is not to be confused with dose regimen, which is a type of drug therapy in which the dose [mg] of a drug is given at a regular dosing interval on a repetitive basis.
-Continuing the maintenance dose for about 4 to 5 half-lives ($t_{1/2}$) of the drug will approximate the steady state level.



Graph showing steady state concentration

-The required maintenance dose may be calculated as:

$$\textbf{Maintenance Dose} = \frac{C_p . CL}{F}$$

-where,

C_p = desired peak concentration of drug [mg/L]
CL = clearance of drug in body [L/h]
F = bioavailability

-For an intravenously administered drug, the bioavailability F will equal 1, since the drug is directly introduced to the bloodstream. If the patient requires an oral dose, bioavailability will be less than 1 (depending upon absorption, first pass metabolism etc.), requiring a larger loading dose.

» Spend some more time to revise and understand the topic more precisely and accurately, Click on the following links-

» Youtube Links:-

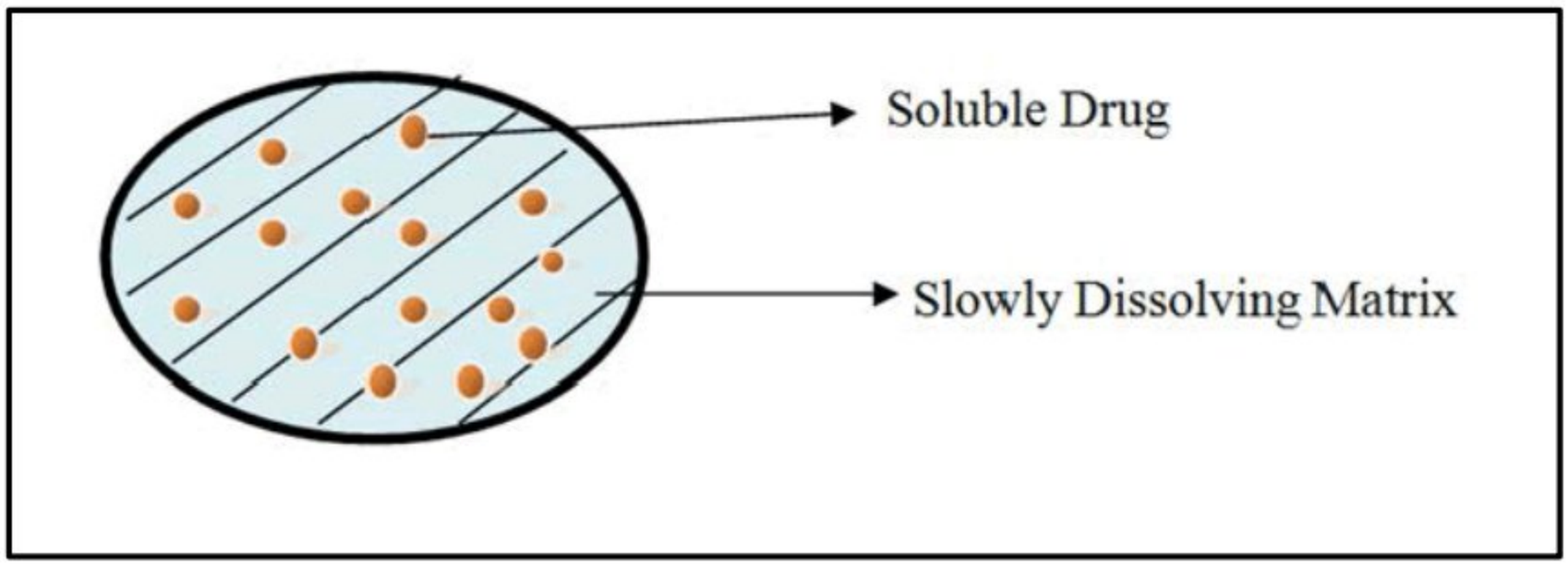
1) https://www.youtube.com/watch?v=57lnnb2yFTE&list=LL_dC_jgRPZYgbmFWVXQVf7w&index=2&t=0s
(animation)

•MATRIX TABLETS

"Matrix tablets refer to dosage forms where the drug is uniformly dissolved or dispersed in a release-retarding material."

-Such devices can be formulated as conventional matrix, or bi- or tri-layered matrix systems.

-These release the drug by both dissolution controlled as well as diffusion controlled mechanisms.



➢ Manufacturing of Matrix tablets-

1) Hydrophilic Matrix-

-The matrix is one where the **release-retarding material is water-swellable or swellable-cum-erodible hydrocolloid** such as high mol. Wt. HPMCs, HPC, HEC, xanthan gum, sodium alginate, guar gum & cross-linked polymers of acrylic acid.

-2 types-

(i) Free-Swelling Matrix- In this matrix, polymer swelling is unhindered.

(ii) Restricted-Swelling Matrix- In this matrix, the surface of the device is partially coated with an impermeable polymer film that restricts the hydration of swellable matrix material.

2) Hydrophobic Matrix-

-In this matrix, the release-retarding material is either-

i) Slowly soluble, erodible, or digestible, ex- Waxes such as glyceryl monostearate, cetyl alcohol, vegetable oil, beeswax, carnauba wax, etc…

ii) Insoluble or non-digestible, ex- Ethylcellulose, polymethacrylates, etc…

-2 types of hydrophobic matrix-

(i) Porous (Heterogeneous) Matrix- This matrix is the one where the drug & release-retarding matrix microparticles are simply mixed with each other and compressed into a tablet.

(ii) Non-porous (Homogenous) Matrix- This matrix is the one in which the release-retarding matrix material is first melted and the drug is then incorporated in it by thorough mixing.

It may be of 2 types-

a) Dissolved Drug Non-porous system

b) Dispersed Drug Non-porous system

➢ Polymers used in Matrix tablets-

The different polymers which can be used are:

1) Hydrogels

i) Poly hydroxyl ethyl methyl acrylate (PHEMA)
ii) Cross –linked polyvinyl alcohol (PVA)
iii) Cross –linked polyvinyl pyrrolidone (PVP)

2) Soluble Polymers

i) Polyethylene glycol (PEG)
ii) Polyvinyl pyrrolidone (PVP)
iii) Hydroxy propyl methyl cellulose (HPMC)

3) Biodegrable Polymers

i) Polylactic acid (PLA)
ii) Polyglycolic acid (PGA)
iii) Polycaprolactone (PCL)

4) Nonbiodegrable Polymers

i) Polyethylene vinyl acetate (PVA)
ii) Poly dimethyl siloxane (PDS)
iii) Polyether urethane (PEU)
iv) Polyvinyl chloride (PVC)
v) Cellulose acetate (CA)
vi) Ethyl cellulose (EC)

5) Mucoadhesive Polymers

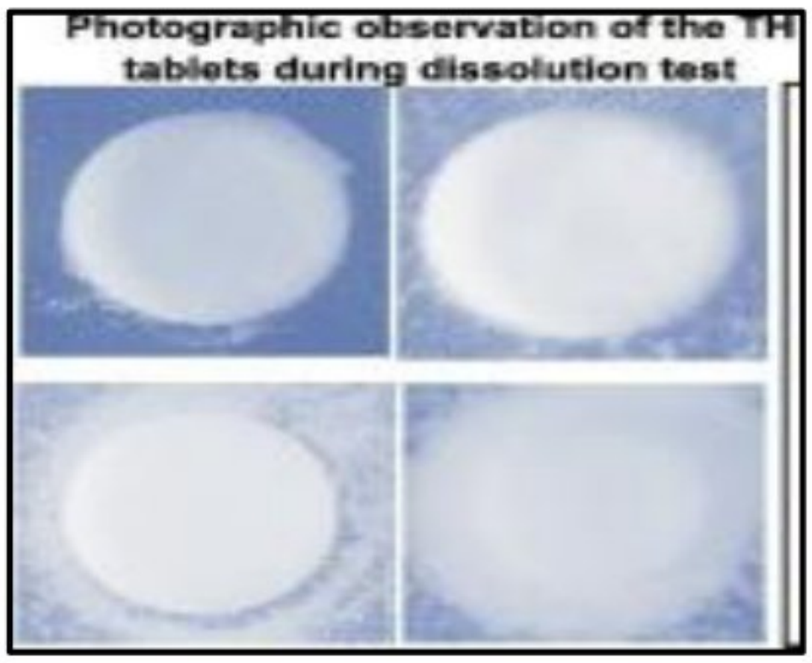
i) Polycarbophil
ii) Sodium carboxymethyl cellulose
iii) Polyacrylic acid
iv) Tragacanth
v) Methyl cellulose
vi) Pectin

6) Natrual Gums

i) Xanthan gum
ii) Guar gum
iii) Karaya gum

➢ Evaluation of Matrix tablets-

- Size & shape
-Content uniformity
-Drug release
-Dissolution test
-Friability
-Weight variation
-Hardness
-DT time
-Swelling studies
-*In-vitro* studies
-Stability study
-Model independent approaches
-Dissolution Efficiency
-Mean Dissolution Time
-Similarity Factor (f2)
-Difference Factor (f1)



Advantages-

-Easy to manufacture.
-Versatile.
-Used for high mol. Wt. compounds.
-Improves Bioavailability.
-Increased stability.
-Reduce the toxicity by slowing drug absorption.

Disadvantages-

-The remaining matrix must be removed after the drug has been released.
-High cost of preparation.

» Spend some more time to revise and understand the topic more precisely and accurately, Click on the following links-

» Youtube Links:-

1) https://www.youtube.com/watch?v=oz170ghdwaw (animation)

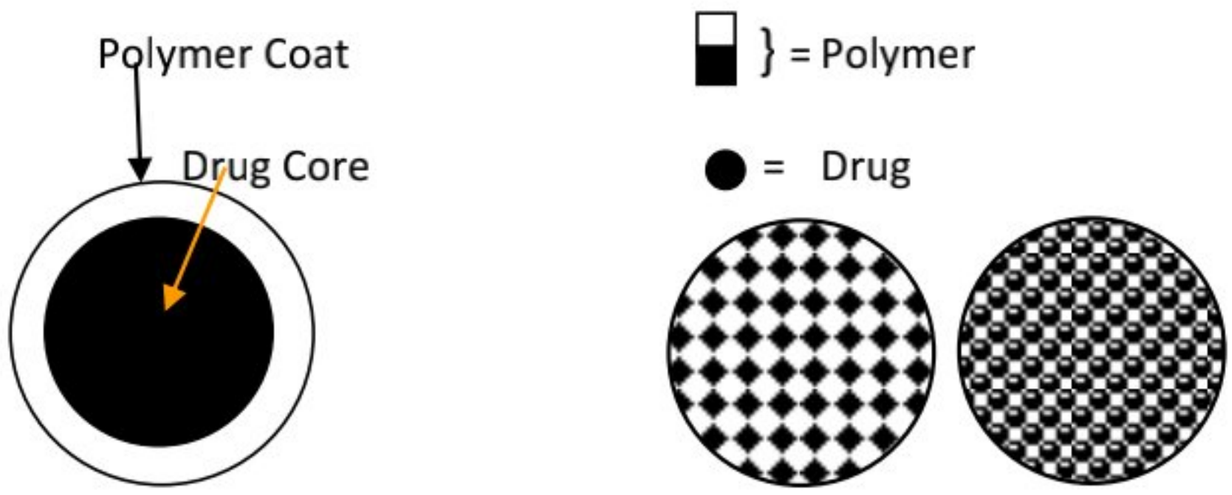
2) https://www.youtube.com/watch?v=b_imMjRtUDw (animation)

•MICROSPHERES

-Micro-particles are the polymeric entities falling in the range of **1-1000µm**.
-Covering two types of the forms as follows:
-Microcapsules:- micrometric **reservoir** systems
-Microspheres:- micrometric **matrix** systems.

-Microspheres are solid, approximately spherical particle ranging 1-1000 µm in size.
-They are made up of polymeric substances, in which the **drug is dispersed throughout the microsphere matrix.**
-Microcapsules are small particles that contain **an active agent or core material surrounded by a shell or coating of polymers.**
-The substances used in the formulation are biodegradable synthetic polymers and natural products such as starches, gums, proteins, fats, and waxes.
-The natural polymers of choice are albumin and gelatin, the synthetic ones are poly lactic acid and polyglycolic acid.
-The Polymers used to manufacture microspheres are chosen according to their solubility, stability profile, process safety, and economic suitability.

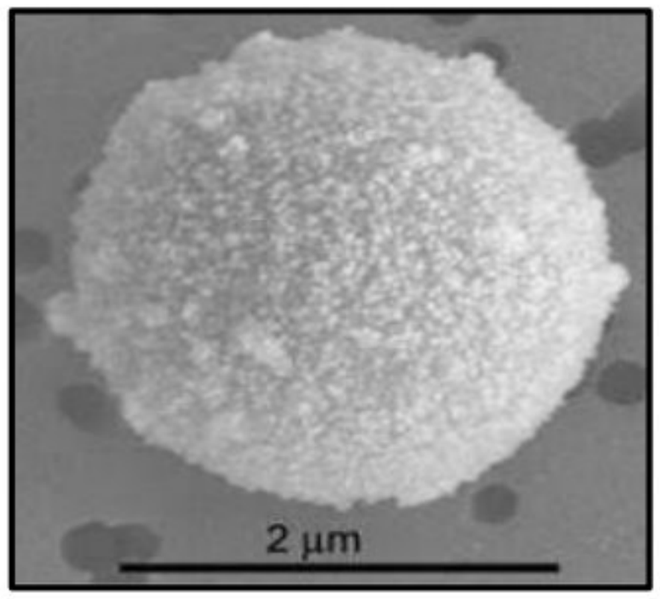
-According to some other authors, microspheres are matrix systems and essentially spherical in shape, whereas microcapsules may be spherical or non-spherical in shape.



➢ Manufacturing of Microspheres –

1) Polymer phase separation
2) Solvent evaporation and solvent extraction
3) Wax coating and hot-melt technique
4) Spray coating and pan coating

5) Coacervation
6) Precipitation
7) Freeze-drying
8) Chemical and thermal cross-linking



1) Polymer phase separation-

-Polymer phase separation in non-aqueous media, by non-solvents or polymer addition, also referred to as 'Coacervation.'

-Method:

-The coacervation of a polymer such as poly-(d,l-lactic acid-co glycolic acid) (PLAGA) dissolved in methylene chloride with a second polymer such as silicone oil allows the formation of matrix systems.

-If crystals of active principles are placed in suspension at the beginning of this process, they will be captured in these matrices after the desolvation of polymer.

2) Solvent evaporation and solvent extraction

-Method:-

-The polymeric supporting material is dissolved in a volatile organic solvent.

-The active medicinal principle to be encapsulated is then dispersed or dissolved in the organic solution to form a suspension, an emulsion or a solution.

-Then, the organic phase is emulsified under agitation in a dispersing phase consisting of a non-solvent of the polymer, which is immiscible with the organic solvent, which contains an appropriate surface-active additive.

-Once the emulsion is stabilized, agitation is maintained and the solvent evaporates after diffusing through the continuous phase.

-The result is the creation of solid microspheres.

-On the completion of the solvent evaporation process, the microspheres held in suspension in the continuous phase are recovered by filtration or centrifugal and are washed and dried.

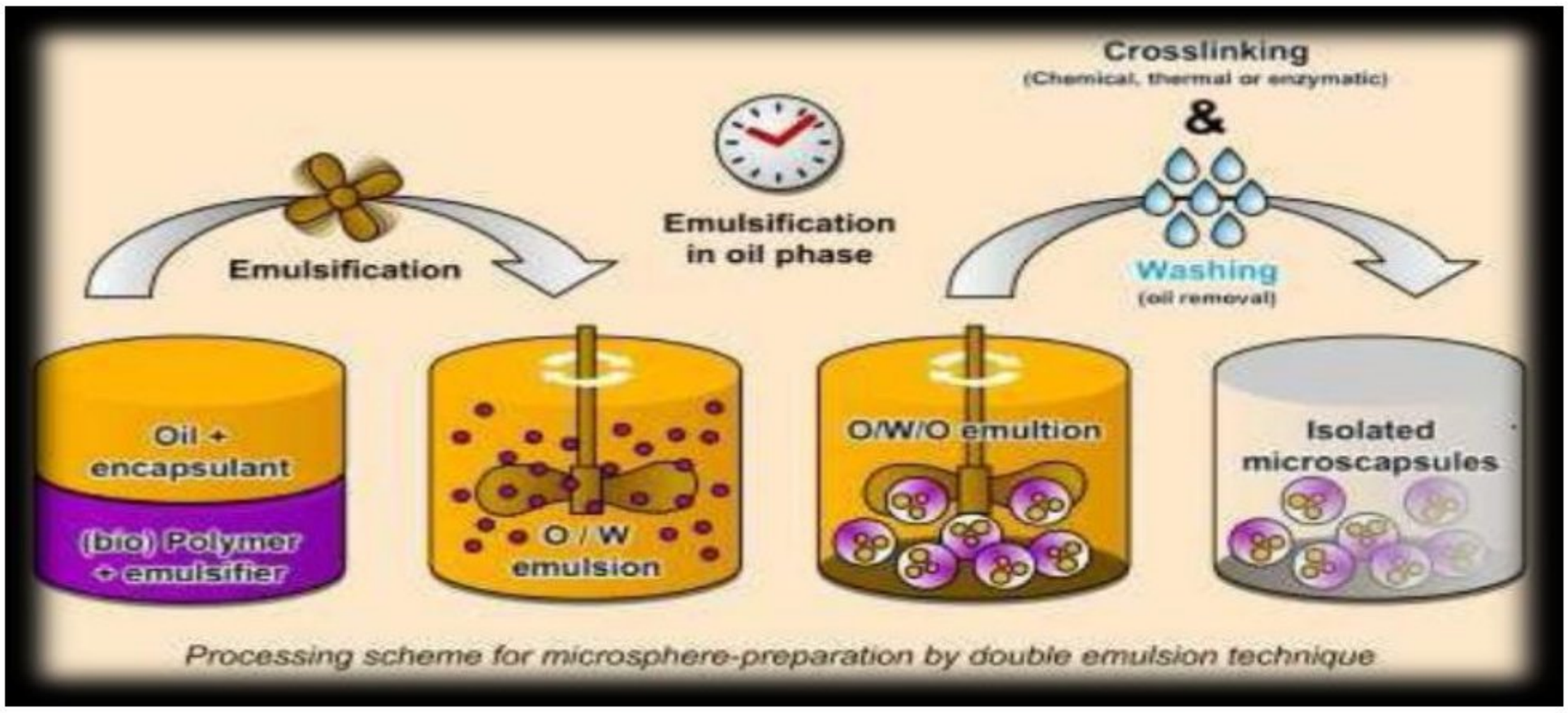
3) Wax coating and hot-melt technique (Double emulsion technique)

-In this method, Wax is used to coat the core particles.

-Method:-

-An aqueous drug solution is dispersed in molten wax to form a water-in-oil emulsion, which is then emulsified in a heated external aqueous phase to form a water-in-oil-in-water emulsion (double emulsion).

-The common external phase is then removed by washing and the microsphere/microcapsule is collected by filtration.



Processing scheme for microsphere-preparation by double emulsion technique

4) Spray coating and pan coating

-Spray coating and pan coating use a heat-jacketed coating pan in which the solid drug core particles are rotated and into which the coating material is sprayed.
-The core particles are in the size range from a micrometer up to a few mL.
-The coating material is usually sprayed at an angle from the side into the pan.
-The process is continued until an even coating is completed.

5) Coacervation

-In the presence of only one macromolecule, this process is referred to as 'Simple Coacervation.'
-When two or more macromolecules of opposite charge are present, it is referred to as 'Complex Coacervation.'
-This process includes separation of a macromolecular solution into two immiscible liquid phases, a dense coacervate phase, which is relatively concentrated in macromolecules and a dilute equilibrium phase.
-It is then cross-linked to form stable microcapsules by the addition of an agent such as gluteraldehyde or by the application of heat.

6) Precipitation

-An emulsion is formed, which consists of polar droplets dispersed in a non-polar medium. Solvent may be removed from the droplets by the use of a co-solvent.
-The resulting increase in the polymer-drug concentration causes a precipitation forming a suspension.

7) Freeze-drying

-This method involves the freezing of emulsion.
-The continuous-phase solvent is usually organic and is removed by sublimation at low temperature and pressure.
-Finally, the dispersed-phase solvent of the droplets is removed by sublimation, leaving polymer-drug particles.

8) Chemical and thermal cross-linking

-Microspheres made from natural polymers, which are prepared by a cross-linking process.
-The polymers include: Gelatin, Albumin, Starch and Dextrin.
-A water-in-oil emulsion is prepared, where the water phase is a solution of the polymer that contains the drug to be incorporated.
-The oil phase is a suitable vegetable oil or oil-organic solvent mixture containing an oil-soluble emulsifier.
-Once the desired w/o emulsion is formed, the water-soluble polymer is solidified by some kind of cross-linking process. This may involve thermal treatment or the addition of a chemical cross-linking agent such as glutaraldehyde to form a stable chemical cross-link as in albumin.

➢ Manufacturing variables in the production of Microspheres-

-The most important physicochemical characteristics that may be controlled in microsphere-manufacture are:-

1) Particle Size and Distribution

2) Molecular Weight of Polymer
3) Ratio of Drug to Polymer
4) Total Mass of Drug and Polymer
5) Ratio of dispersed to continuous phase

➢ Evaluation of Microspheres-

- Electron microscopy, scanning electron microscopy and scanning tunneling microscopy are used for **surface characterization** of microspheres.

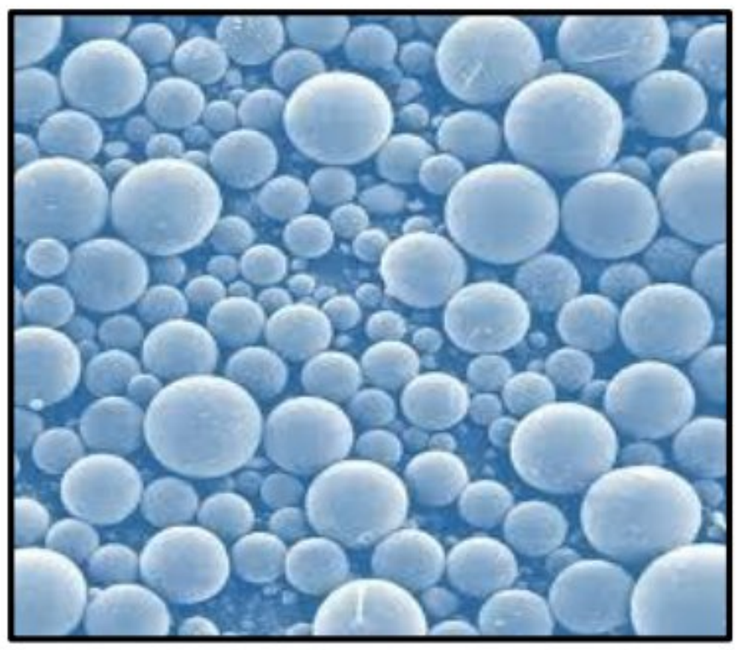
- Fourrier transform Raman spectroscopy or x-ray photoelectron spectroscopy may be used to determine any of the material, which should have been entrapped, is present on the surface and if **any other contaminants are present or not**.

- Other surface characterization techniques include surface charge analysis using micro-electrophoresis. Surface charge can **provide information regarding microsphere aggregation**. Surface charge is an important parameter with respect to the interaction of microspheres within the body. Following an I.V. injection, microspheres can be taken up by the macrophage or monocyte cells present in the plasma; surface charge is one of the parameters, which determines whether this takes place.

- Drug Entrapment Efficiency-
  -It is the measure of **% drug entrapped to how much drug was added in the bulk for entrapment.**

$$\%\ \boldsymbol{Entrapment\ Efficinecy} = \frac{\boldsymbol{Entrapped\ Drug}}{\boldsymbol{Total\ Drug\ Added}} \times \mathbf{100}$$

-The drug entrapment efficiency varies from the technique which the microsphere is made.



Microspheres

Advantages of Microspheres-

-They facilitate acute delivery of small quantities of potent drugs and reduced concentration of the drug at the sites other than the target organ or tissue.

-They provide protection for unstable drugs 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 other cellular interactions of the drug.

-They enable controlled release of drugs.

Disadvantages of Microspheres-

-The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit through gut.

-Differences in the release rate from one dose to another.

-Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the drug release characteristics of the dosage form may lead to potential toxicity.

-Dosage form of this kind should not be crushed or chewed.

Applications of Microspheres-

1) Ophthalmic Drug Delivery- Polymer exhibits favourable biological behaviour such as bioadhesion, permeability enhancing properties, and interesting physico-chemical characteristics, which make it a unique material for design of ocular drug delivery vehicles.
-In addition, its penetration enhancement has more targeted effect and allows lowered uses of the drugs.

2) Gene Delivery- Gene delivery systems include viral vectors, cationic liposomes, polycation complexes, and microencapsulated systems.
-Viral vectors are advantageous for gene delivery because they are highly efficient and have a wide range of cell targets.

3) Intratumoral and Local Drug Delivery- In order to deliver praclitaxel at the tumour site in therapeutically relevant concentrations, polymer films are fabricated.

4) Oral Drug Delivery- The ability of polymer to form films may permit its use in the formulation of film dosage forms, as an alternatives to pharmaceutical tablets.

5) Nasal Drug Delivery -The nasal mucosa present an ideal site for bioadhesive drug delivery systems.
-Drug Delivery Systems, such as microspheres, liposomes and gel have been demonstrated to have good by characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route.

6) Buccal Drug Delivery- Buccal bi-layered devices using a mixture of drugs and chitosan, with or without anionic crosslinking polymers has promising potential for using controlled delivery in the oral cavity.

7) Gastrointestinal Drug Delivery- Floating hollow microcapsules of melatonin showed gastro-retentive controlled release delivery system.
-Release of the drug from these microcapsules is greatly retarded with release lasting for 1.75 to 6.7 hours in simulated gastric fluid.

8) Vaginal Drug Delivery

9) Transdermal Drug Delivery

10) Colonic Drug Delivery

11) Multi-particulate Drug Delivery

» Spend some more time to revise and understand the topic more precisely and accurately, Click on the following links-

» Youtube Links:-

1) https://www.youtube.com/watch?v=67FRYQ7iH90&list=LL_dC_jgRPZYgbmFWVXQVf7w&index=21&t=0s
(animation of preparation of microspheres)

2) https://www.youtube.com/watch?v=Pwn9BwnKyBY (real synthesis of microspheres in lab)

•HYDROGELS

-Hydrogels are **water-swollen polymeric materials** that maintain a distinct three-dimensional structure.

-There is a wide variety of the design options for the preparation of hydrogels of different structures and properties.

-The traditional methods of hydrogel synthesis were limited in the control of their detailed structure, but novel approaches based on genetic engineering and hybrid hydrogels, have considerably enhanced this research.

-As a result, the application potential of hydrogels, in addition to traditional areas such as biomaterials and drug delivery systems, has expanded to other fields, such as microfluidics and nanotechnology.

-In comparison to other synthetic biomaterials, hydrogels resemble living tissues closely in their physical properties because of their relatively high water content , soft and rubbery consistency.

-Hydrogels show minimal tendency to adsorb proteins from body fluids because of their low interfacial tension.

-The term 'hydrogel' implies a material already swollen in water, while in a true sense hydrogel is a cross-linked network of hydrophilic polymers. They possess the ability to absorb large amounts of water and swell, while maintaining their threedimensional (3D) structure.

➢ Types of Hydrogels-

1) *In-situ* gel
2) pH sensitive gel
3) Temperature sensitive gel
4) Ionic sensitive gel
5) Osmotic sensitive gel
6) Homo-polymer gel
7) Co-polymer gel

-There are various types of gel available and formulated according to need.

❖ *In-situ* Gel-

-*In-situ* is Latin phrase which is translated literally as **in position** (at site).
-*In-situ* gel is drug delivery systems that are in solution form before administration in the body, but once administrered, undergo gelation *in situ,* to form a gel.
-The formation of gels depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation, from which the drug gets released in a sustained and controlled manner.

→ Approaches of *in-situ* gelling system:-

i) Stimuli-responsive *in situ* gel system
(Temperature , pH)
ii) Osmotically induced *in situ* gel systems
(Ion-activated systems)
iii) Chemically induced *in situ* gel systems
(Ionic, Enzymatic cross linking, Photo-polymerization.)

➢ Evaluation of *In-situ* Gel-

1) *In-vitro* floating studies- (for gastro-retentive *in-situ* gel)-
-It is the measurement of time required for the gel to float after adding in the solution, known as floating lag time.
-And also the duration of floating, known as total floating time.

2) Viscosity measurement of the *in-situ* gel-
-by Brookfield viscometer

3) Determination of drug content-
-by UV-vis spectroscopy.

4) Swelling Index-

$$\textbf{Swelling Index} = \frac{w2 - w1}{w1} \times 100$$

-where,
w1= Initial wt. of gel
w2= wt. of swollen matrix gel

5) *In-vitro* drug release-

-by IP apparatus-II covered with muslin cloth

6) Stability study-

- By accelerated stability study.

Advantages of *in-situ* gel-

-Ease of administration.
-Improved local bioavailability.
-Reduced dose concentration.
-Reduced dosing frequency.
-Improved patient compliance and comfort.
-Simple formulation and manufacturing so less investment and cost.

Disadvantages of *in-situ* gel-

-Low mechanical strength.
-Hard to handle.
-Difficult to sterilize.
-Non-adherent.

Application of *in-situ* gel-

-New researchers have demonstrated that a gel composed of small, woven protein fragments can successfully carry and release proteins of different sizes to different targets in the body.
-It is enabling the delivery of drugs such as insulin and trastuzumab (A monoclonal antibody) (protein) often used to treat breast and ovarian cancer, hormones, growth factors as well as eye medications.
-Furthermore, one can control the rate of release of active ingredients from hydrogel by changing the density of the gel, allowing for continuous drug delivery over a specific period of time.
-A newly introduced gel, known as a "nanofiber hydrogel scaffold," enables, over hours, days or even months, a gradual release of the proteins from the gel, and the gel itself is eventually broken down into harmless amino acids (the building blocks of proteins).
-Peptide hydrogels are ideally suited for drug delivery as they are pure, easy to design and use, non-toxic, bio-absorbable, and can be locally applied to a particular tissue.
-Depending on the size and density of the mesh, it can carry protein molecules between 14,000 and 1,50,000 daltons .

•OSMOTIC PRESSURE CONTROLLED SYSTEMS

-**Osmotic pressure is a most important colligative property** according to pharmacy point of view. **Colligative property is the concentration of solution independent of solute property**.

-"**Osmotic pressure of a solution is the external pressure that must be applied to the solution in order to prevent it being diluted by the entry of solvent via a process known as Osmosis."**

-Such membrane is only permeable to solvent molecule. Because only solvent can pass through the semi permeable membrane, the driving force for the osmosis arises from the inequity of the chemical potentials of the solvent on opposing side of the membrane.

-**Osmolality** is the number of osmoles per Kg of water.

-Osmolarity is the number of osmoles per liter of solution.

-Iso-osmotic solution is one where two solution are separated by a perfect semi permeable membrane (SPM is membrane which is permeable only to solvent molecule and no net movement of solute occur across the membrane).

-In **Isotonic solution** biological membrane do not always function as perfect SPM and some solute molecule as well as water are able to pass through them.

➢ Objectives of ODDS-

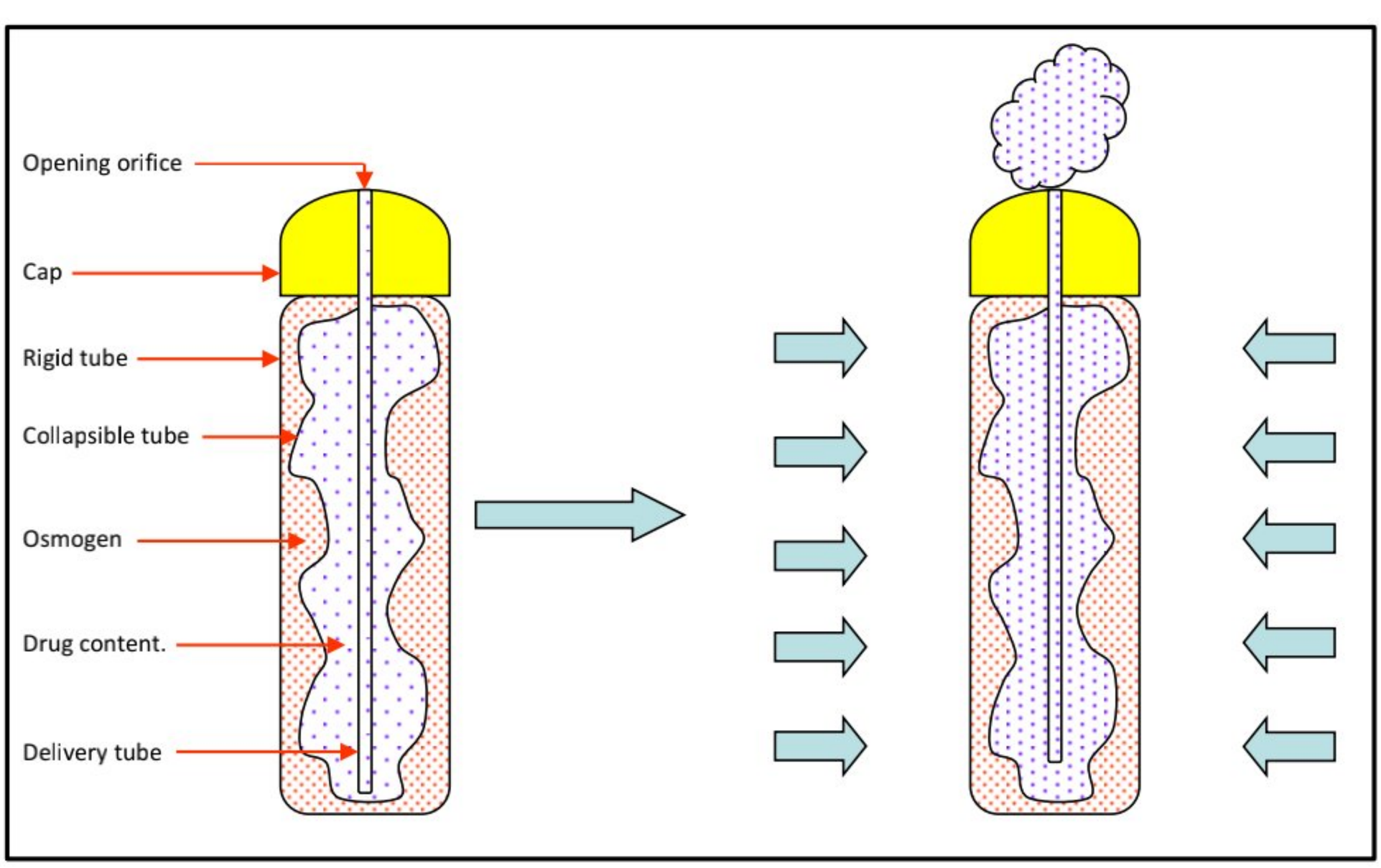
-In order to **reduce the dose**
-To decreases **dose related side effect**
-To minimizes **rate of administration**
-To provide **controlled release**
-To increase **patient compliance**.

➢ Formulation Development of ODDS-

◆ Osmotic Pumps-

-Core contain **water soluble osmotically active agent** and blended with **water soluble or insoluble drug, additives** and coating has been carried out which functions as semi permeable membrane.

-Since barrier is only permeable to water, initial penetration of water dissolves the critical part of the core, resulting in development of an osmotic pressure difference across the membrane.



Osmotic Pump

-When pump placed in an aqueous environment a saturated solution of drug is developed since Semi permeable membrane draws water inside pump which generate osmotic pressure. This pressure is relieved by the flow of saturated solution out of device through the delivery orifice. This process continue at a constant rate until the entire solid drug inside the pump has been dissolved and at last only a solution filled shell remains.

Small osmotic pumps of this form are available under the trade name **Alzet®**.

Delivery of DNA by agarose hydrogel implant facilitates genetic immunization in cattle by using Alzet osmotic pumps.

Osmotic Tablets-

-The development of an **Osmotic Release Oral Systems (OROS) refers to the quality of a therapeutic system designed to control pharmacologic effects through control of plasma concentrations**.

-OROS is a solid, tablet-sized object, it will pass through the GI tract within the transit time of food.
-To reduce drug plasma-concentrations fluctuations on repetitive administration of an OROS system, it is also necessary to consider the half-life associated with the distribution phase.

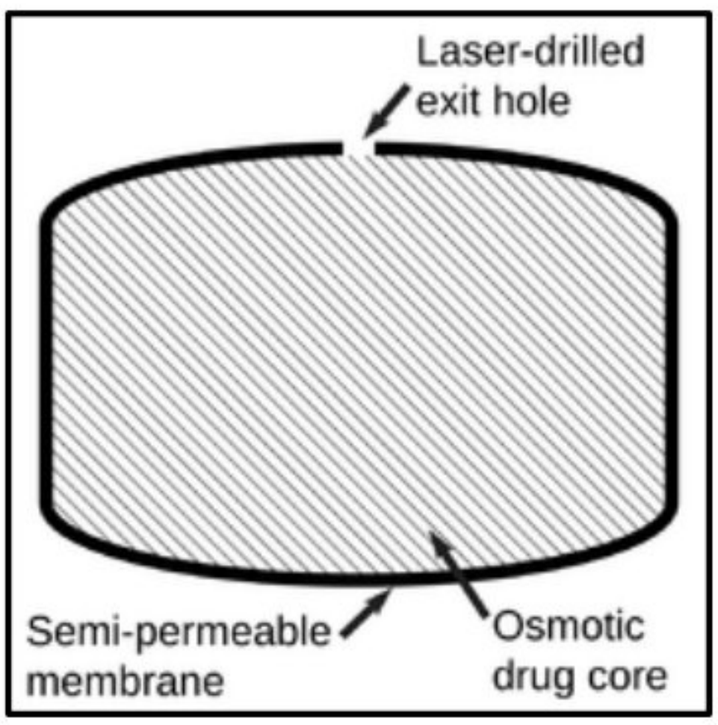
-The Core is made up of Active Drug, Filler, and Viscosity modifier, Solubilizer, Lubricant or Glidant. While coating composed of Polymer, Plasticizer, Membrane modifier, Color and Opacifier.

1) Drug- Drug itself may act as an osmogen and shows good aqueous solubility (e.g., potassium chloride pumps). But if the drug does not possess an osmogenic property, osmogenic salt and other sugars can be incorporated in the formulation.

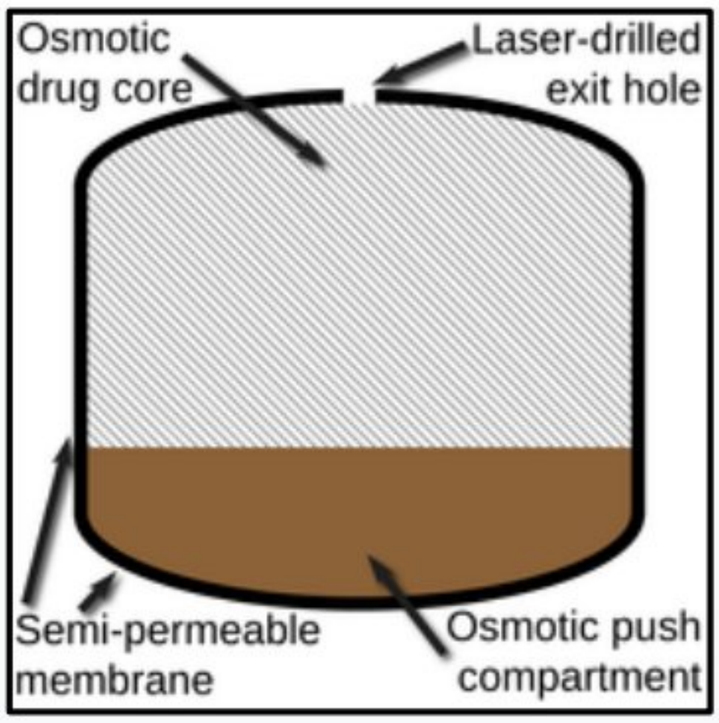
2) Semipermeable membrane- Semipermeable membrane must possess certain performance criteria:
It must have sufficient wet strength and water permeability.
It should be selectively permeable to water and biocompatible.

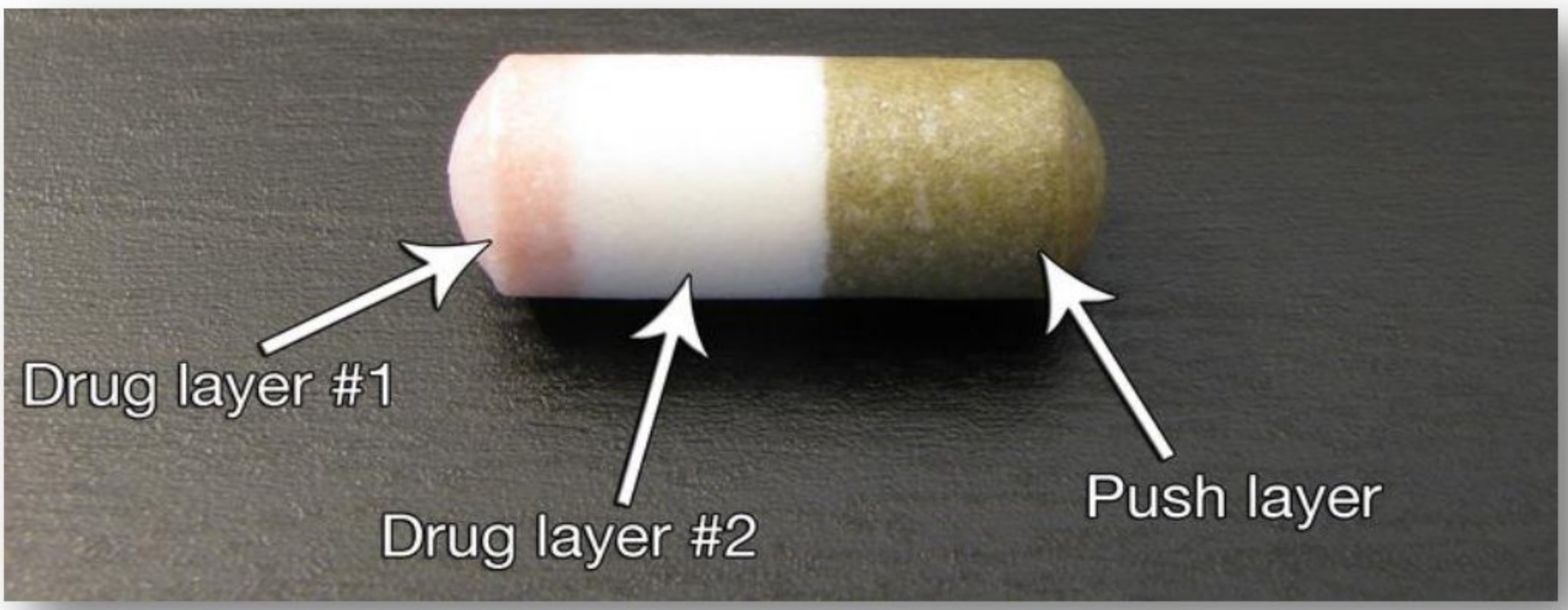
Some other polymers such as agar acetate, amylose triacetate, poly vinylmethyl ether copolymers, poly orthoesters, poly acetals, poly glycolic acid and poly lactic acid derivatives.

→ Single-layer Tablet-



→ Multi-layer Tablet





Multi layer osmotic tablet

➢ Evaluation of ODDS-

-Weight variation
-Hardness
-Friability
-Thickness
-Dissolution
-Pore diameter
-Coating thickness
-*In vitro* evaluation
- *In vivo* evaluation

Advantages of ODDS-

-Zero order release profile after an initial lag.
-Delivery may be delayed or pulsed if desired.
-Drug release is independent of gastric pH and hydrodynamic condition.
-Release mechanism are not dependent on drug
-A high degree of IVIVC.

Disadvantages of ODDS-

-Costly
-Dumping
-Size hole is critical

» Spend some more time to revise and understand the topic more precisely and accurately, Click on the following links-

» Youtube Links:-

1) https://www.youtube.com/watch?v=L7s22Up8N2Y&list=LL_dC_jgRPZYgbmFWVXQVf7w&index=27 (animation of Alzet osmotic pump)

2) https://www.youtube.com/watch?v=uojwMhQpjq8&list=LL_dC_jgRPZYgbmFWVXQVf7w&index=25 (animation of 3-phase osmotic tablet with micro-orifice)

●GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

(GRDDS)

"Gastro-retentive delivery is one of the site specific delivery for the delivery of drugs either at stomach or at intestine."

➢ Rationale of GRDDS-

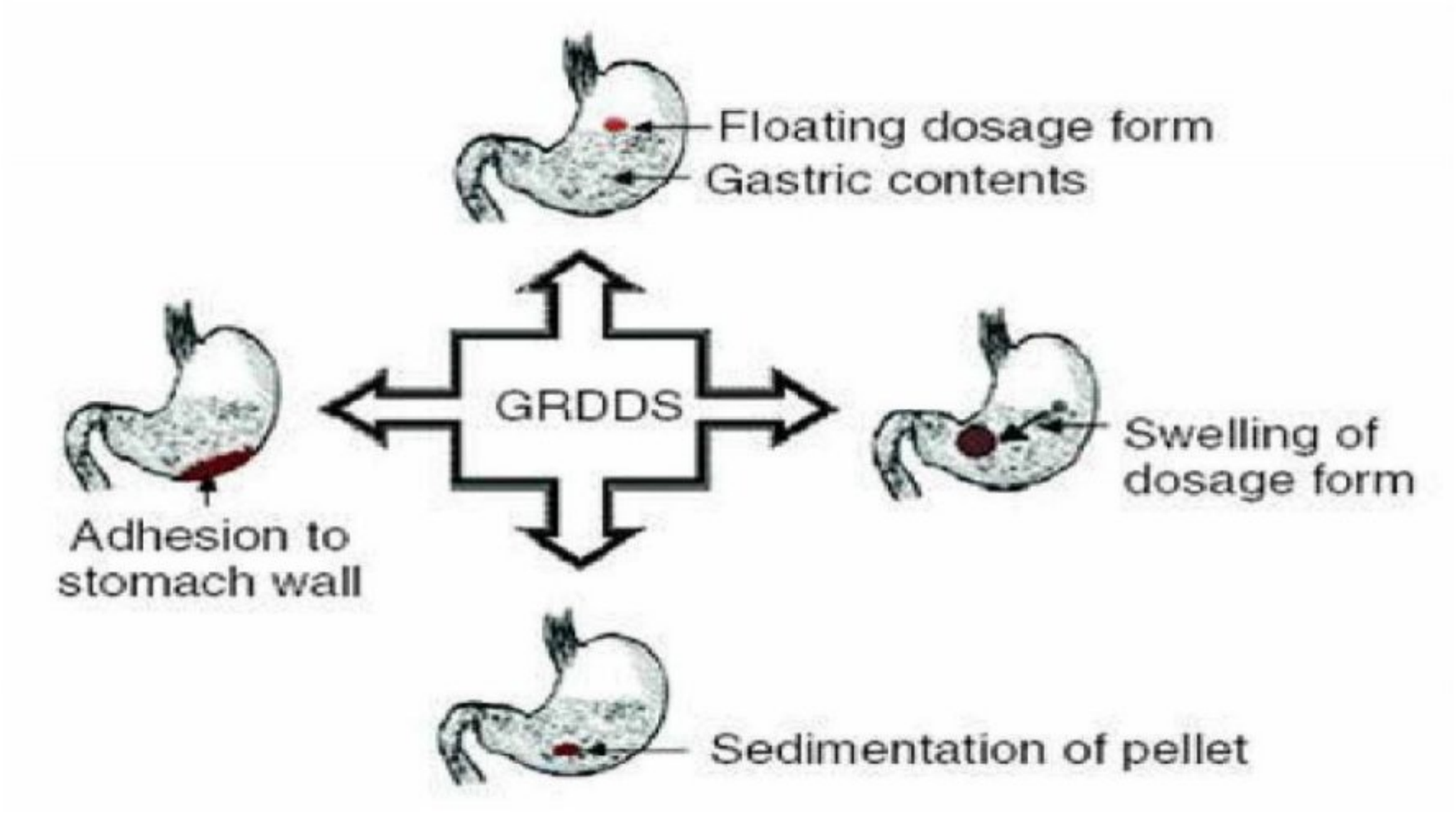
- Delivery of drugs with narrow absorption window in the small intestine region.
-Longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.
-Improved bio-availability is expected for drugs that are absorbed readily upon release in the GI tract such as cyclosporine, ciprofloxacin, ranitidine, amoxycillin, captopril, etc…
-Good patient compliance by making a once a day therapy.
-Improved therapeutic efficacy.

→ Drugs benefited by gastric retention:-

- ✓ Drugs acting locally in the stomach.
  E.g. Antacids and drugs for H. Pylori viz., Misoprostol
- ✓ Drugs that are primarily absorbed in the stomach
  E.g. Amoxycillin
- ✓ Drugs that are poorly soluble at alkaline pH.
  E.g. Furosemide, Diazepam, Verapamil, etc.
- ✓ Drugs with a narrow window of absorption.
  E.g. Cyclosporin, Methotrexate, Levodopa, etc.
- ✓ Drugs which are absorbed rapidly from the GI tract.
  E.g. Metronidazole, tetracycline.
- ✓ Drugs that degrade in the colon.
  E.g. Ranitidine, Metformin HCl.

❖ Approaches for GRDDS:-

(1) Low density systems (Floating drug delivery)
(2) Expandable/Swellable systems
(3) Bio/Muco-adhesive systems
(4) High density systems
(5) Raft forming systems

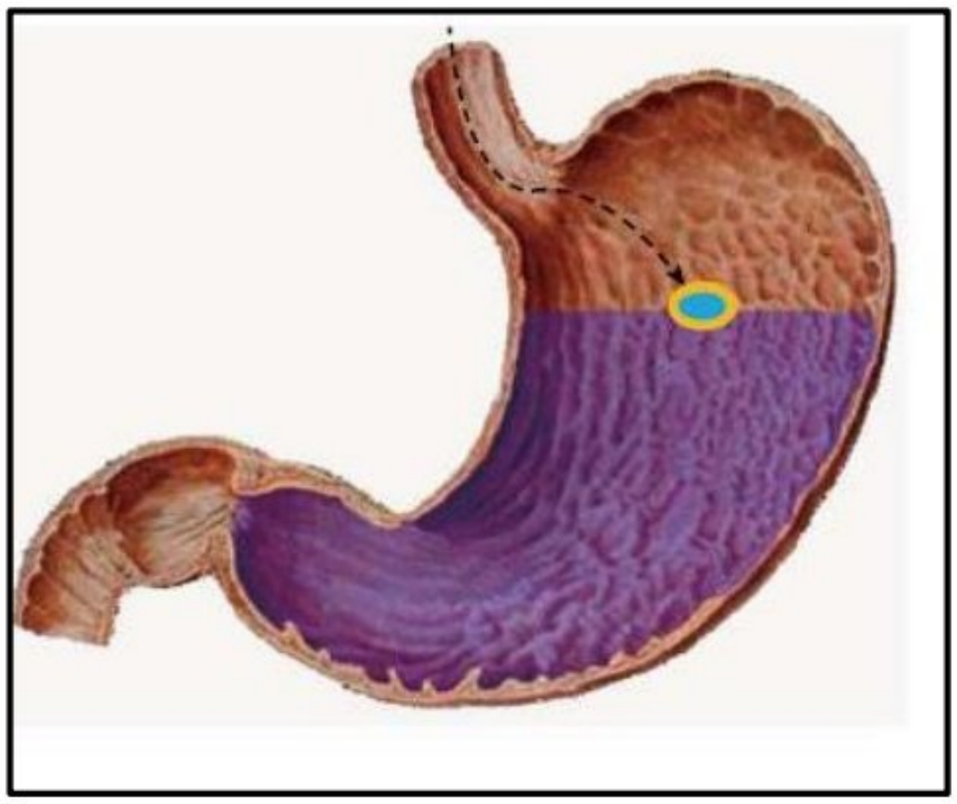


Low Density Approach (Floating drug delivery) / HBS:-

- **Floating drug delivery systems (FDDS) or hydro-dynamically balanced systems (HBS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time**.

-While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the stomach.

- After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the gastric retention time and a better control of fluctuations in the plasma drug concentration in some cases.



Low Density Approach/ Floating systems

CLASSIFICATION OF THE FLOATING SYSTEMS

- Effervescent systems
- Non-Effervescent systems

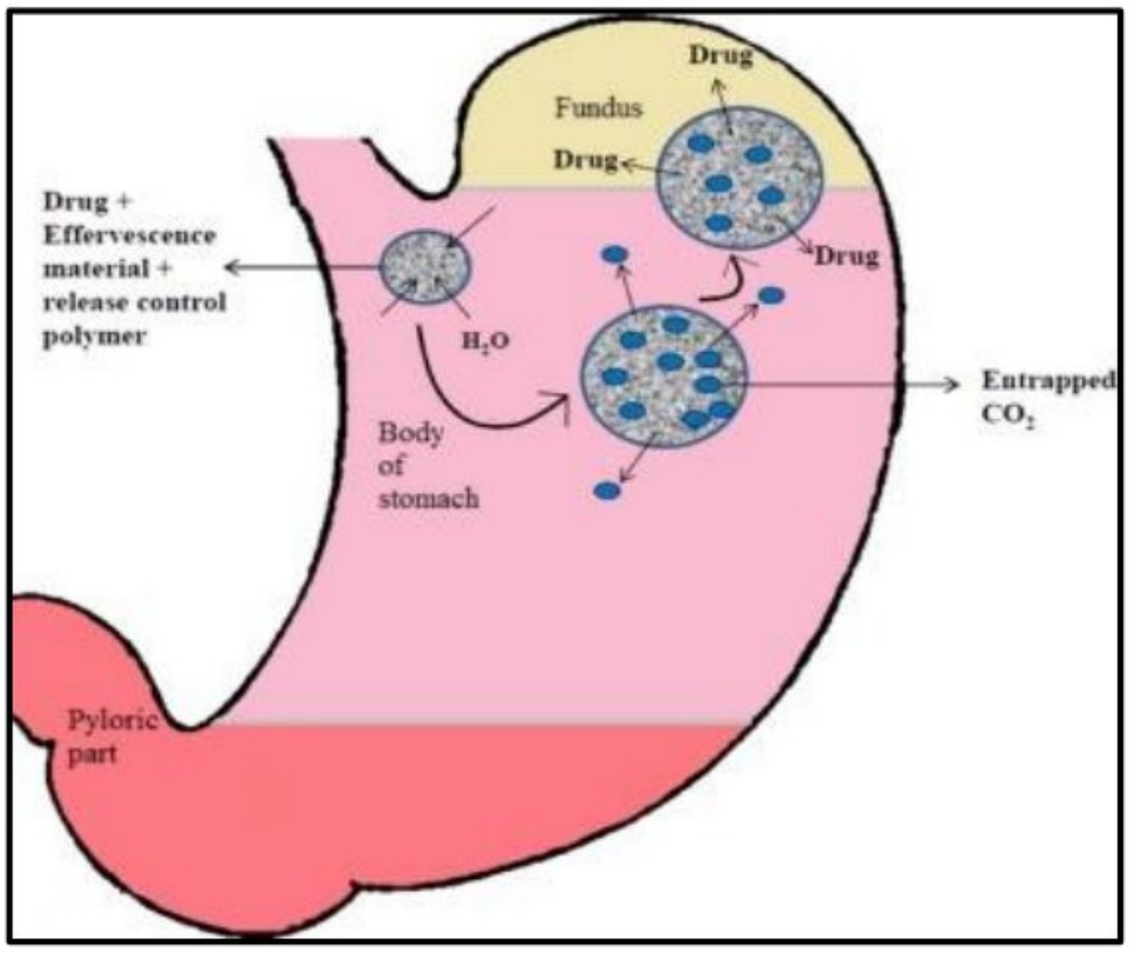
[1] Effervescent systems-

-These are **matrix type** of systems prepared with the help of **swellable polymers** such as Methylcellulose and chitosan and various **effervescent compounds**, e.g. sodium bicarbonate, tartaric acid and citric acid.

- They are formulated in such a way that when in contact with the gastric contents, **CO_2 is liberated and gets entrapped in swollen hydrocolloids**, which provides buoyancy to the dosage forms.

-Tablet is prepared with drug and effervescent material and then coated by polymeric coating of polymer like Eudragit RS with some plasticizer. Coating has higher elongation value and high water and low CO2 gas permeability. So CO2 gas generation makes floating system in gastric fluid.

-By using similar system, pulsatile system is also developed by using semipermeable coat which ruptures after predetermined time and release all drug.



Effervescent systems

[2] Non-Effervescent systems-

-In this type of FDDS, **most commonly used Excipients are gel forming or highly swellable** cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene.

-The approach involves intimate mixing of the drug with gel forming hydrocolloids, which **swell in contact with the gastric fluid after oral administration** and maintains a relative integrity, shape and bulk density of less than GI fluid.

-Within the outer gelatinous barrier, the air entrapped by the swollen polymers confers to the buoyancy of these dosage forms.

➢ Evaluation of FDDS/ HBS/ Low density systems-

a) Floating Lag Time-

-It is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

b) Total Floating Time-

-Test is usually performed in SGF-Simulated Gastric Fluid maintained at 37° C. The time for which the dosage form continuously floats on the dissolution media is termed as floating time.

c) Specific Gravity / Density-

-Density can be determined by the displacement method using Benzene as displacement medium.

d) Resultant Weight-

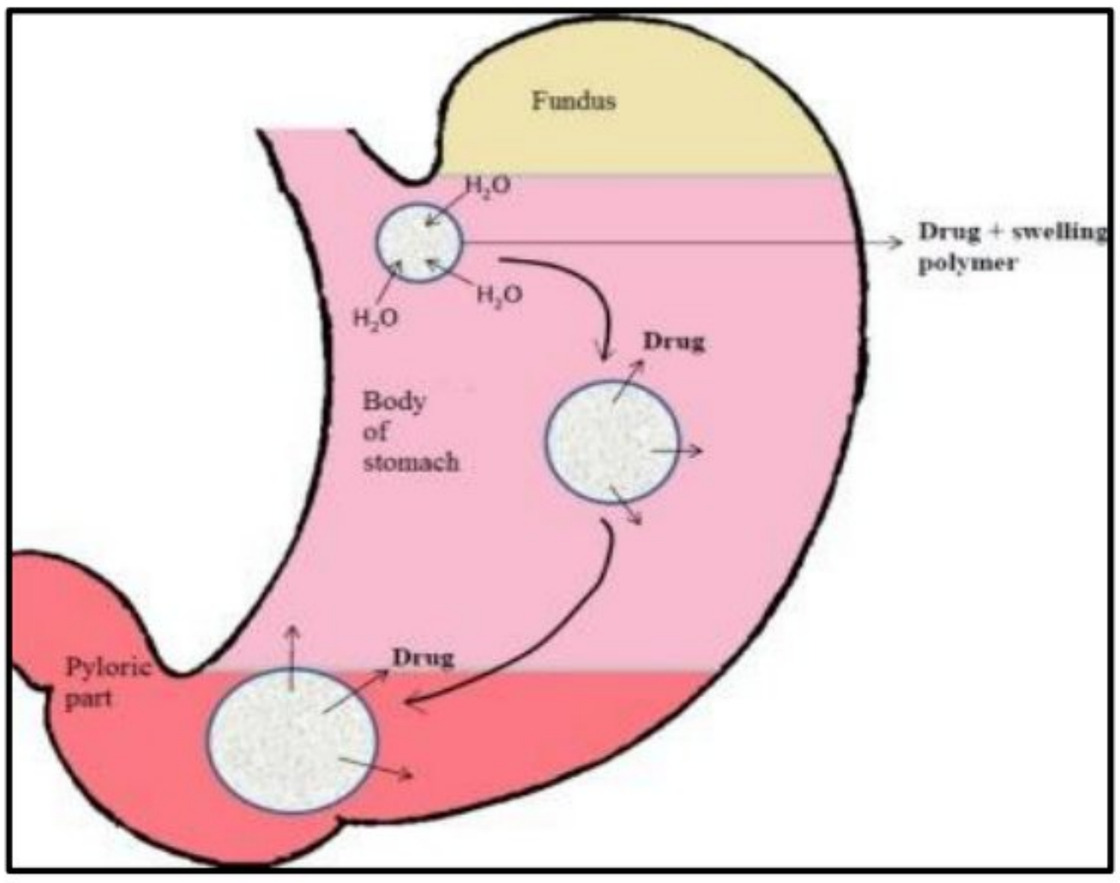
-It is the weight of dosage form after complete swelling and floating.

-Used to determine the final wt. because as the drug release from the intact tablet, the weight decrease leading to entry of GI fluids and sinking of tablet.

e) *In-vivo* test-

Expandable/ Swelleble Approach:-

-**Expandable systems are also called as plug type systems**. They achieve **larger size in stomach and size of whole system goes beyond the size of pyloric sphincter** and thus the system retains in stomach.



Expandable Approach

-Swelling system are generally matrix system containing hydrocolloids which by action of hydration and osmosis get swelled.

-Swelling index means how much fold it can increase in volume and swelling time are the important factor for such systems.

➢ Evaluation of Swelling/ Expandable Systems-

a) Swelling Index-

-After immersion of swelling dosage form into SGF at 37°C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness / diameter with time.

b) Water Uptake-

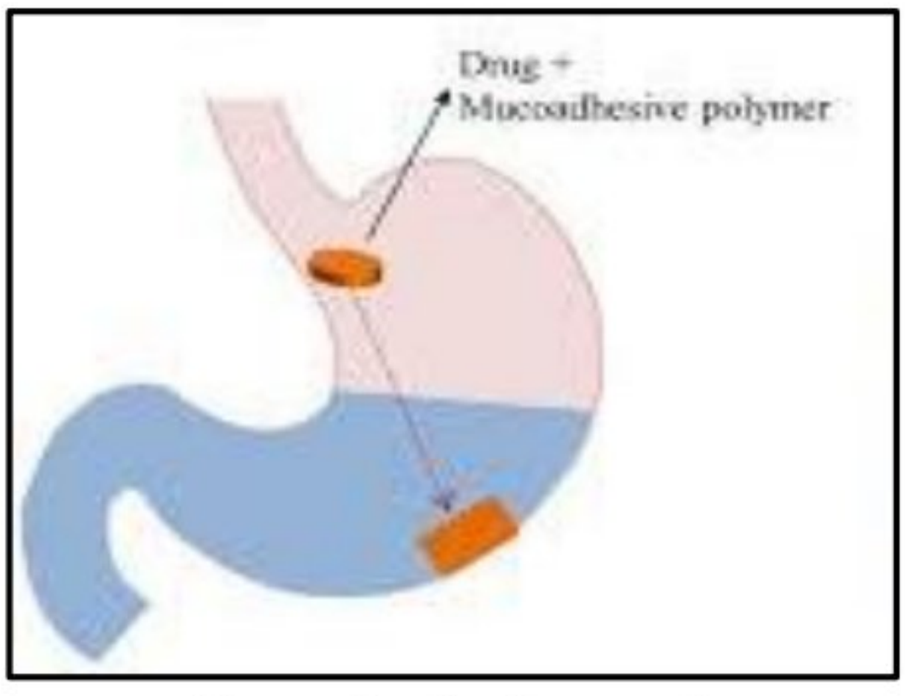
-It is an indirect measurement of swelling property of swellable matrix. Here dosage form is removed out at regular interval and weight changes are determined with respect to time. So it is also termed as Weight Gain.

Mucoadhesive Approach:-

-Adhesive systems may adhere to mucin, which is cytoprotective gel layer on membrane of stomach wall or adhere to epithelial cells.

-And thus due to adhesiveness in stomach wall, retain in stomach.

- The reason why **this approach is less used for GRDDS** can be answered by knowing fact that mucus layer is turning over continuously and mucus is not only at surface of lumen but also found within lumen as soluble mucus. Hence it can show wide variability and unpredictability.



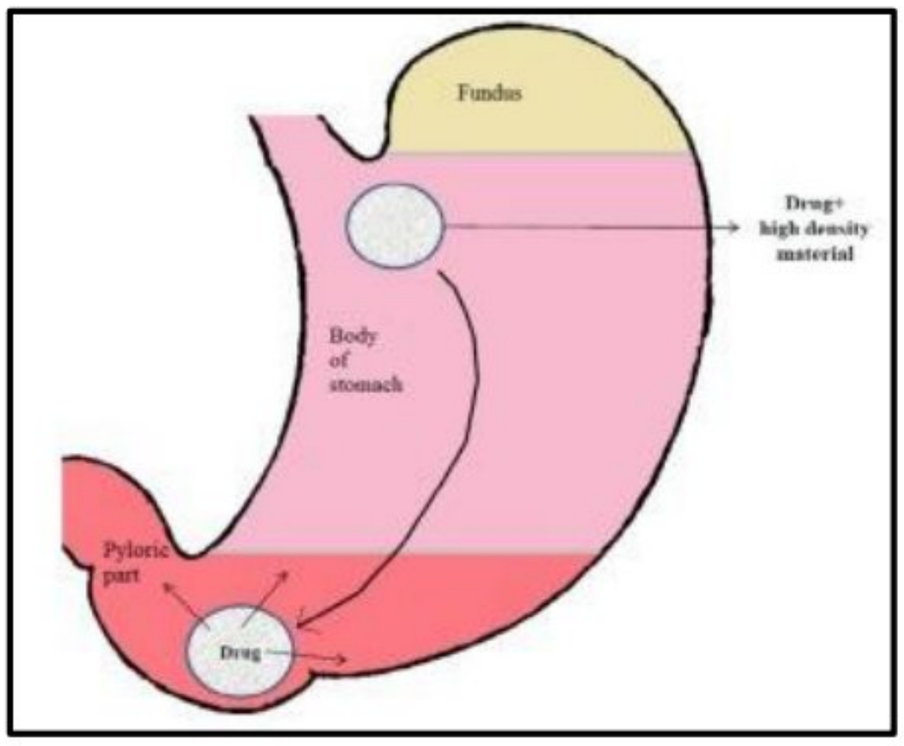
Mucoadhesive Approach

High Density Approach:-

-The bottom part of stomach has curved shape and it is horizontally lower than the position of pyloric sphincter.

-Advantage of such geometry can be taken by preparing dosage form **having higher density around more than 1.004 g/cm3** (density of normal stomach content) and also capable to withstand peristaltic movement of stomach.

-These type of formulations having high density around 2-3 can be prepared by coating drug or mixing drug with heavy inert material like Iron powder, Zinc oxide, TiO_2 or $BaSO_4$ (Density = 4.9).



High Density Approach

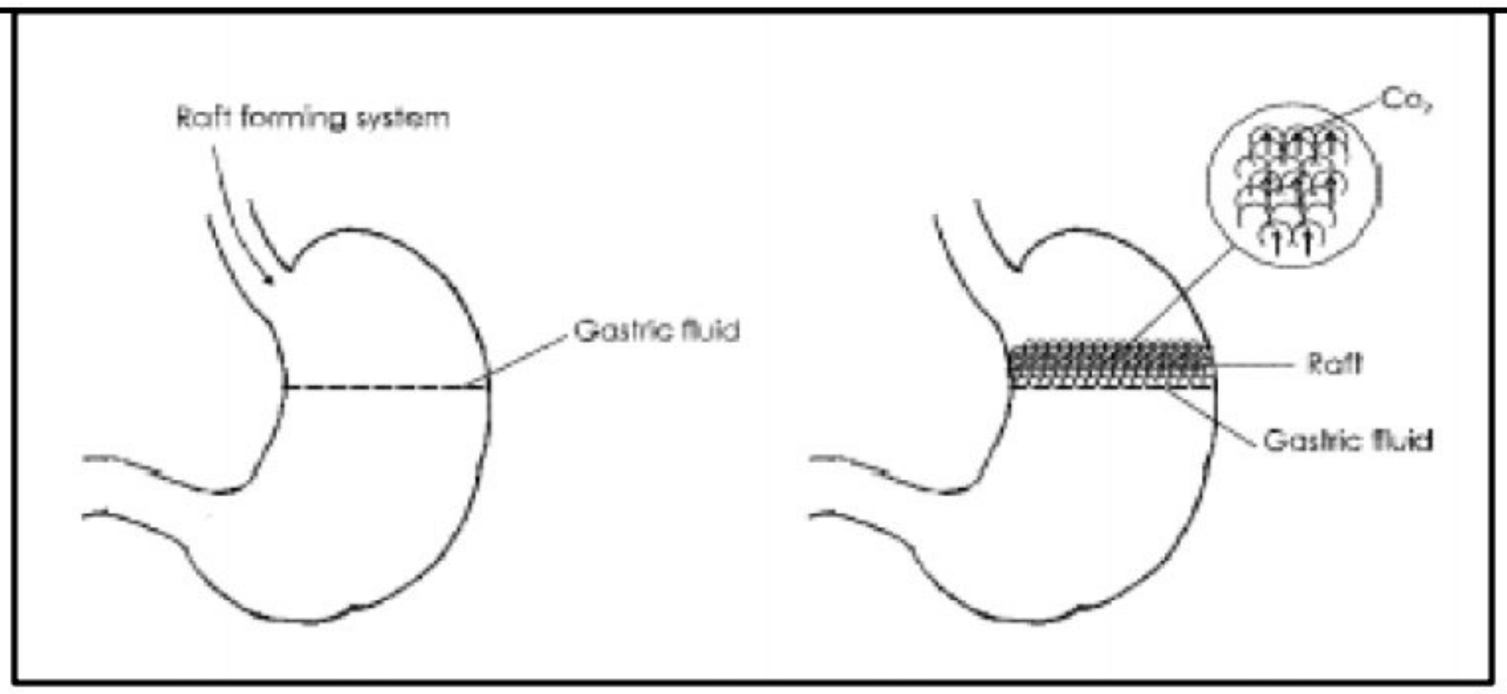
Raft forming systems:-

-Raft forming systems have received much attention for the delivery of antacids and drug delivery for treatment of gastrointestinal infection and disorders.

- The mechanism involved in this system included the **formation of viscous gel** in contact with gastric fluids, wherein each portion of the liquid swells, forming a continuous layer called **RAFT.**

-This raft floats on gastric fluids because of a low density created by the formation of CO_2.

-Usually this contains a gel-forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense to float on the gastric fluids.



Raft forming systems

Advantages of GRDDS-

-Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction in dose.

-Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of anti-biotics.

-Retention of drug delivery systems in the stomach prolongs.

Disdvantages of GRDDS-

-Floating systems has limitation, that they require high level of fluids in stomach for floating and working efficiently. So more water intake is prescribed with such dosage form.

-In supine posture (like sleeping), floating dosage form may swept away (if not of larger size) by contractile waves. So patient should not take floating dosage form just before going to bed.

-Food is also an important factor. Presence of food delays emptying time of food and dosage form. So presence of food is preferable.

-Drugs having stability problem in high acidic environment, having very low solubility in acidic environment and drugs causing irritation to gastric mucosa can not be incorporated into GRDDS.

-Bio/mucoadhesives systems have problem of high turn over rate of mucus layer, thick mucus layer & soluble mucus related limitations.

-Swellable dosage form must be capable to swell fast before its exit from stomach & achieve size larger than pylorus .

» Spend some more time to revise and understand the topic more precisely and accurately, Click on the following links-

» Youtube Links:-

1) https://www.youtube.com/watch?v=MmGCJEqZkOY (animation of Expandable approach)

2) https://www.youtube.com/watch?v=CE7l95BFtTI (Floating lag time- real lab test)

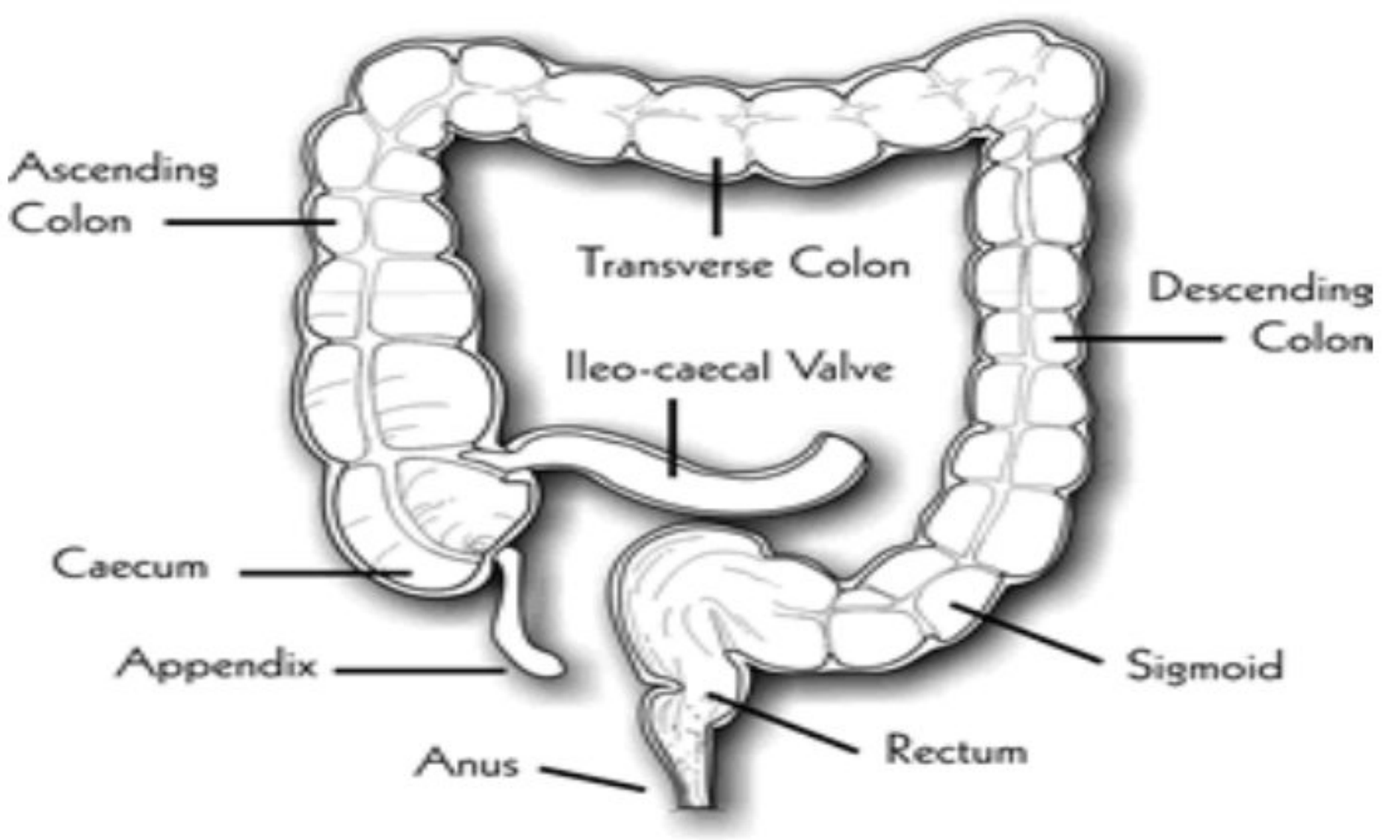
3) https://www.youtube.com/watch?v=gmjMilFJN4Q (Lecture on GRDDS)

•COLON TARGETED DRUG DELIVERY SYSTEMS

(CTDDS)

-Drug delivery to the colon is beneficial not only for the oral delivery of proteins and peptides drugs, but also for the delivery of low mol. Wt. compounds.
-It is used to treat diseases associated with the colon or large intestine such as ulcerative colitis, diarrhoea and colon cancer.
-Also, colon has the longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.
-The colon is a site where both local and systemic delivery of drugs can take place.
-Local delivery allows topical treatment of IBD.
-Specific targeting of drugs to the colon is recognized to have several therapeutic advantages.
-Drugs, which are destroyed by the stomach acid or metabolized by pancreatic enzymes, are slightly affected in the colon & sustained colonic release of drugs can be useful in the treatment of nocturnal asthma, angina and arthritis.
-Treatment of colonic diseases such as ulcerative colitis, colorectal cancer and Crohn's disease is more effective.

Anatomy of Colon



→ Factors affecting colonic drug delivery:-

1) Gastric and intestinal pH.
2) Gastric empting.
3) Colonic microflora.
4) Gastro intestinal disease state.

❖ Approaches for CTDDS:-

(1) Prodrug
(2) pH dependent system
(3) Time dependent system
(4) Microflora activated (triggered) system
(5) Micro particulate system
(6) Pressure controlled system

Prodrug Approach:-

-This approach involves covalent linkage between the drug and its carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine.
-The biotransformation is carried out by a variety of enzymes, mainly of bacterial origin, present in the colon.

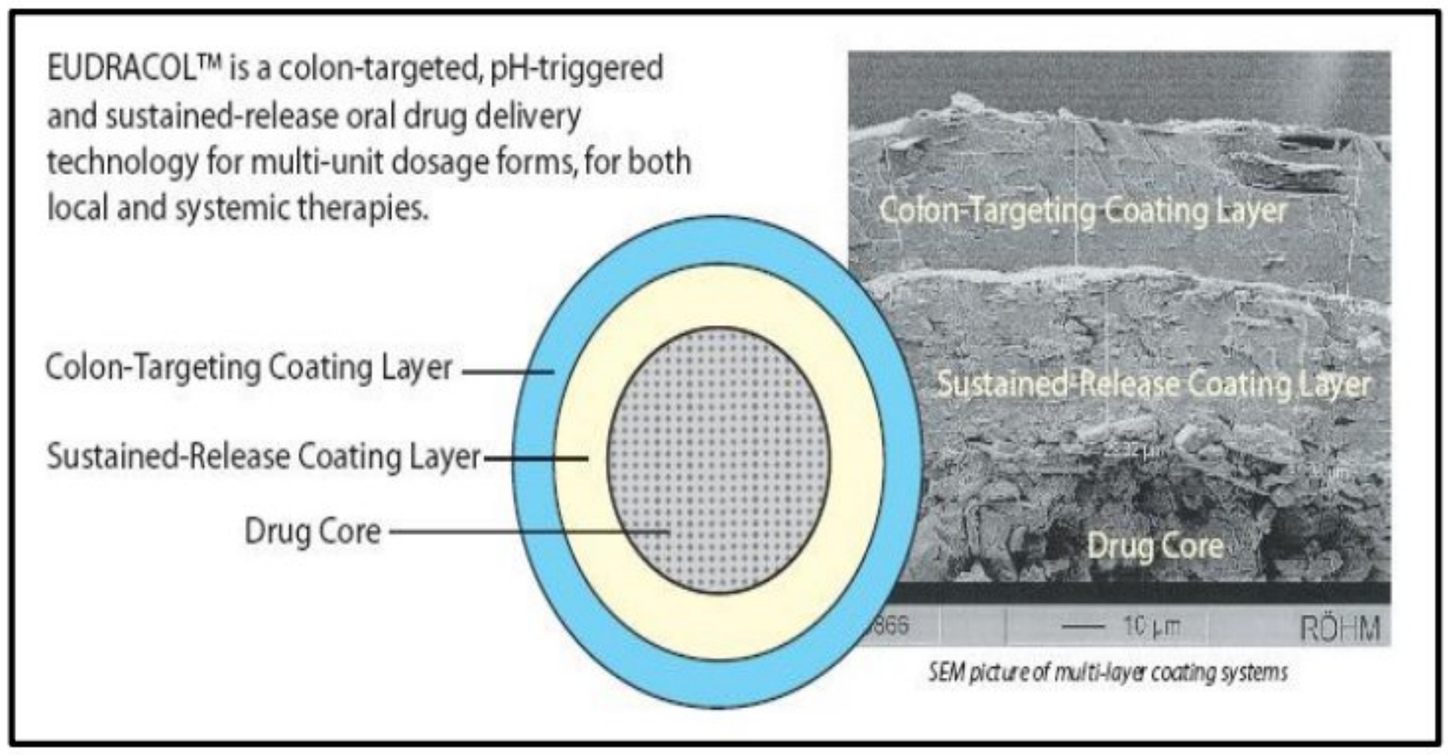
pH dependent systems:-

-pH of the stomach, intestine and colon depends on variety of factors (diet, food intake, intestinal motility, diseases state.).
-This type of dosage form prepare is challenging that with stand variability.
-But this type delivery system is designed based on knowledge of polymers and their solubility.
-Co-polymers of methacrylic acid and methyl methacrylate are widely used.

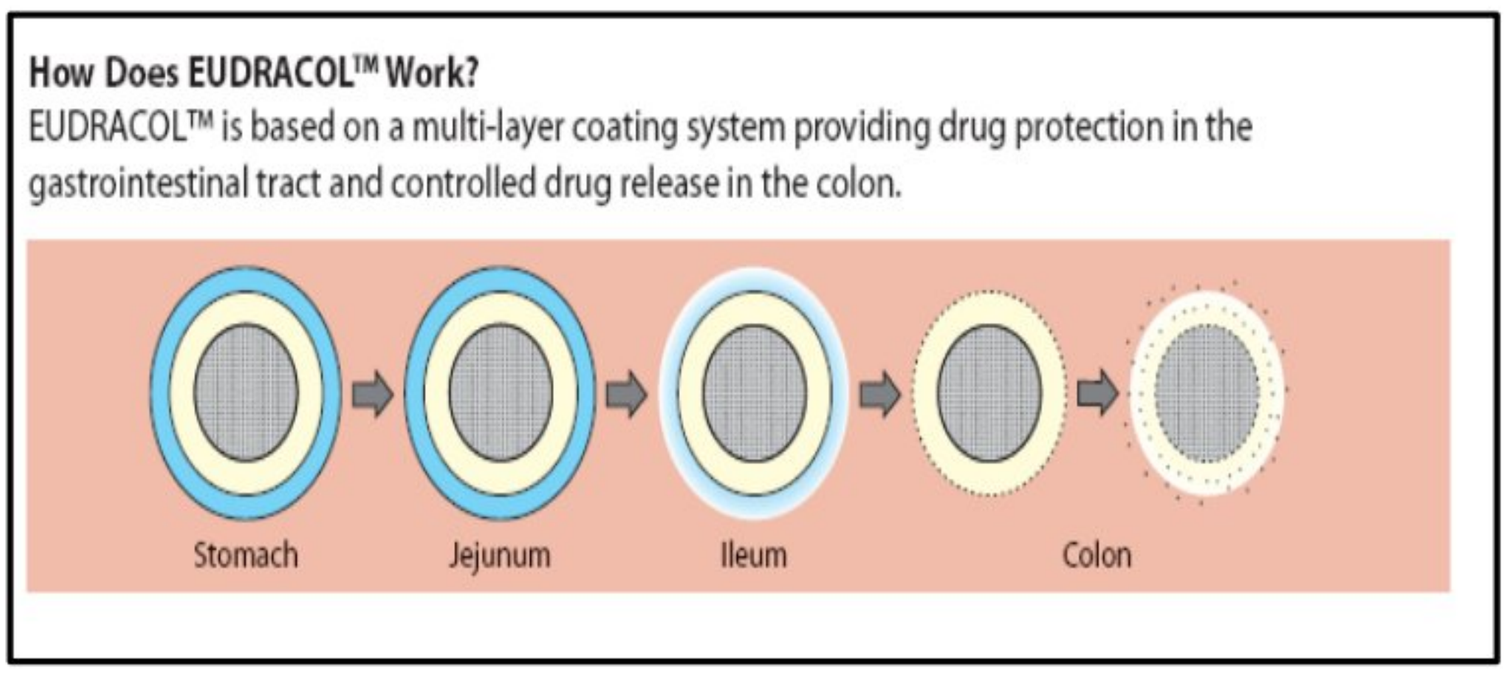
-Eudragit L : pH 6
-Eudragit S : pH 7 } Premature drug release observed.

-To overcome this problem Eudragit FS has been developed.
-Eudragit FS:- pH 7- 7.5 → Slow dissolution rate.

→ Example of pH dependent systems:- **"EUDRACOL™"**



→ Working-



Time dependent systems (Pulsatile Delievry) :-

-The strategy in designing timed-released systems is to resist the acidic environment of the stomach and to undergo a **lag time of predetermined span of time, after which release of drug take place**.

-The lag time in this case is the time requires to transit from the mouth to colon.

-Difficult to predict in advance.
-Lag time of five hours is considered sufficient provided that the intestinal transit time is constant at three to four hours.

TIME DEPENDENT SYSTEM	
Pulsincap	Hydrogel plug gets ejected with extensive swelling from the bottom of capsule & drug release starts in colon.
Time clock	Drug is released after predetermined period because of re-dispersion of polymer
Time controlled explosive system	Extensive swelling breaks Polymeric layer leading to explosive drug release

→ Example of Time dependent systems:-

"PULSINCAP"

-Pulsincap is an earliest example of Time dependent delivery of drug.

-Lag time of five hours is considered sufficient to reach ileo-colic junction & release the drug in colon.

-It Consists of enteric coating capsule containing water soluble cap & water –insoluble body.

-The body is loaded with hydrogel plug & drug layer.

-Enteric coat dissolves in small intestine & water soluble cap dissolves.

-The hydrogel plug absorbs water & swells and release drug at a predetermined lag time of 4 hours.

-The time clock system consists of a solid dosage form coated with lipidic barriers containing carnuba wax & bee's wax along with surfactant, such as polyoxyethylene sorbitan mono oleate.

-This coat erodes or emulsifies in the aqueous environment in a time proportional to the thickness of the film, and the core is then available for dispersion.

-The lag time increase with increasing coating thickness. Such systems are better suited for water soluble drugs.

-Time controlled systems are useful for synchronous delivery of a drug either at pre-selected times such that patient receives the drug when needed or at a pre-selected site of GI tract.

-**Mechanism of drug delivery of Pulsincap-**

Administration of Pulsincap

⬇

Due to outer Enteric coating cap & water insoluble body,

⬇

It is intact & stable in Stomach

⬇

After gastric emptying

⬇

The polymer film of enteric coating cap starts to dissolve,

⬇

After Reaching duodenum (Proximal part of small intestine)

⬇

But we need the drug delivery in Ascending colon (not in small intestine)

⬇

Hence, the coating has a sufficient thickness

⬇

So, that it doesn't dissolve completely OR Not release drug

⬇

It is dissolved as it travels duodenum to jejunum

⬇

After that the hydrogel plug is exposed & starts swelling

⬇

It has enough polymer which swells slowly till it reaches ileo-colic junction

This is termed as **"Lag time to swell "**

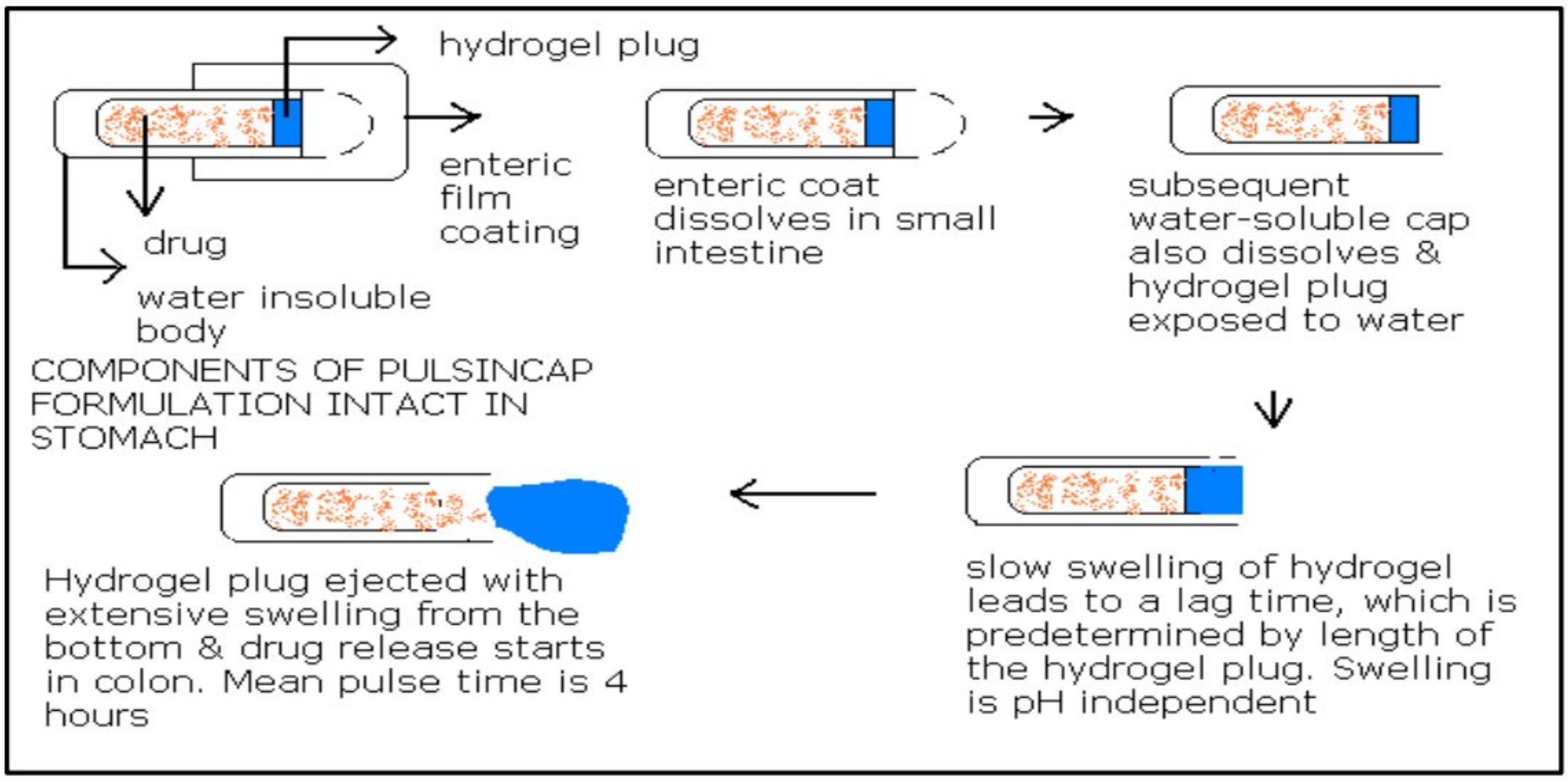
Which is predetermined based on Intestinal transit time (Approx. 4 hrs)

According to that time, the coating thickness of hydrogel is done.

After reaching Ascending colon, Hydrogel is completely swelled

It is ejected with pressure

Drug release starts in colon



Mechanism of drug release in Pulsincap

➢ Evaluation of CTDDS-

-In vitro dissolution study
-In vitro enzymatic degradation test
-Relative colonic tissue exposure
-Relative systemic exposure to drugs
-γ-Scintigraphy
-Magnetic moment imaging study
-Drug delivery index
-High frequency capsule

→In vitro dissolution study

-Invitro test for intactness of coatings and carriers in simulated conditions of stomach and intestine.
-Drug release study in 0.1 N HCl for 2 hours (mean gastric emptying time)
-Drug release study in phosphate buffer for 3 hours (mean small intestine transit time)

Advantages/ Applications of CTDDS-

-In local colonic pathologies.
-Systemic delivery of protein and peptide
-Potential site for the treatment of diseases sensitive to circadian rhythms (asthma, angina and arthritis)
-For the drugs that are absorbed through colon such as steroids
-For the treatment of disorders like IBS, colitis, Crohn's disease

Disadvantages of CTDDS-

-Metabolic degradation by colonic microflora.
-Wide range of pH values throughout the GI tract.
- Lower surface area and relative "tightness" of the tight junctions in the colon restrict drug transport across the mucosa and into the systemic circulation.
-Requires protection against variety of the gastric enzymes

» Spend some more time to revise and understand the topic more precisely and accurately, Click on the following links-

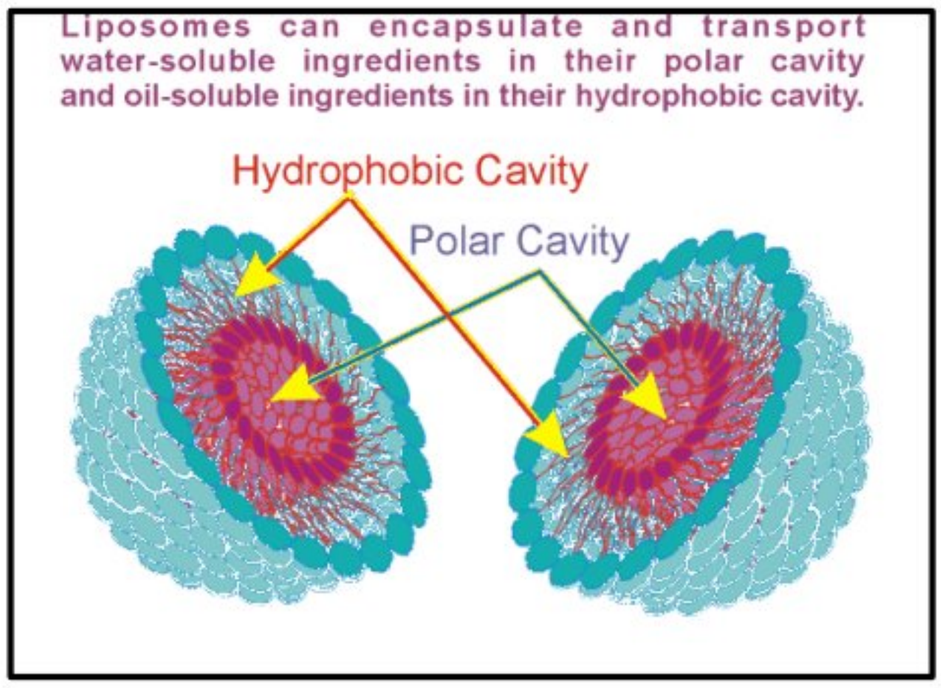
» Youtube Links:-

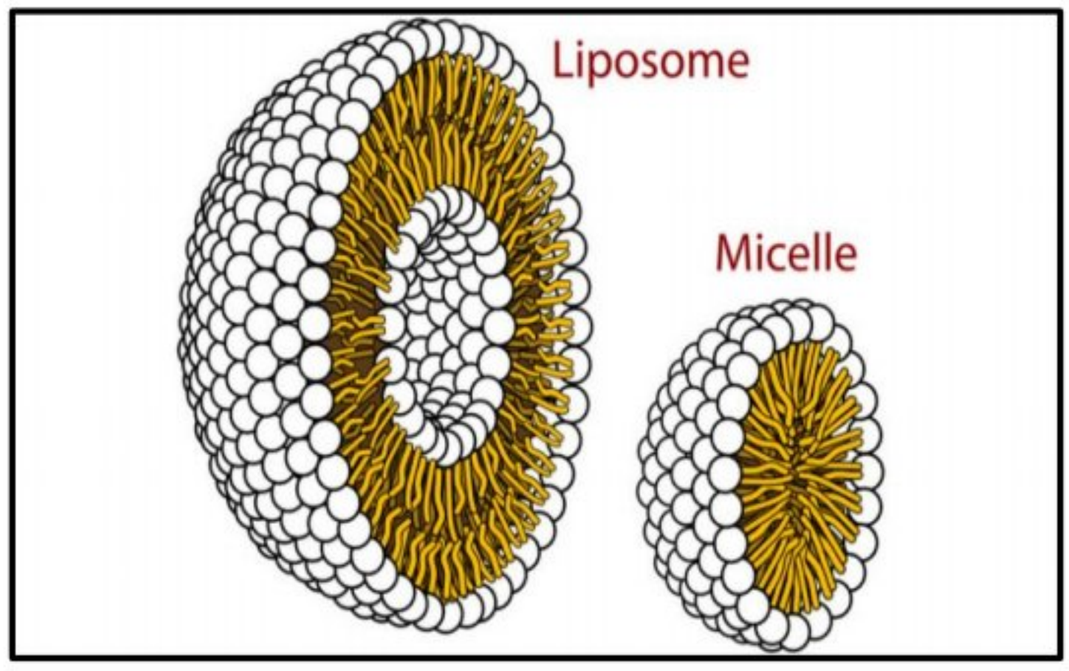
1) https://www.youtube.com/watch?v=uAksSOD-0E8 (animation of pH and microflora triggered drug release)

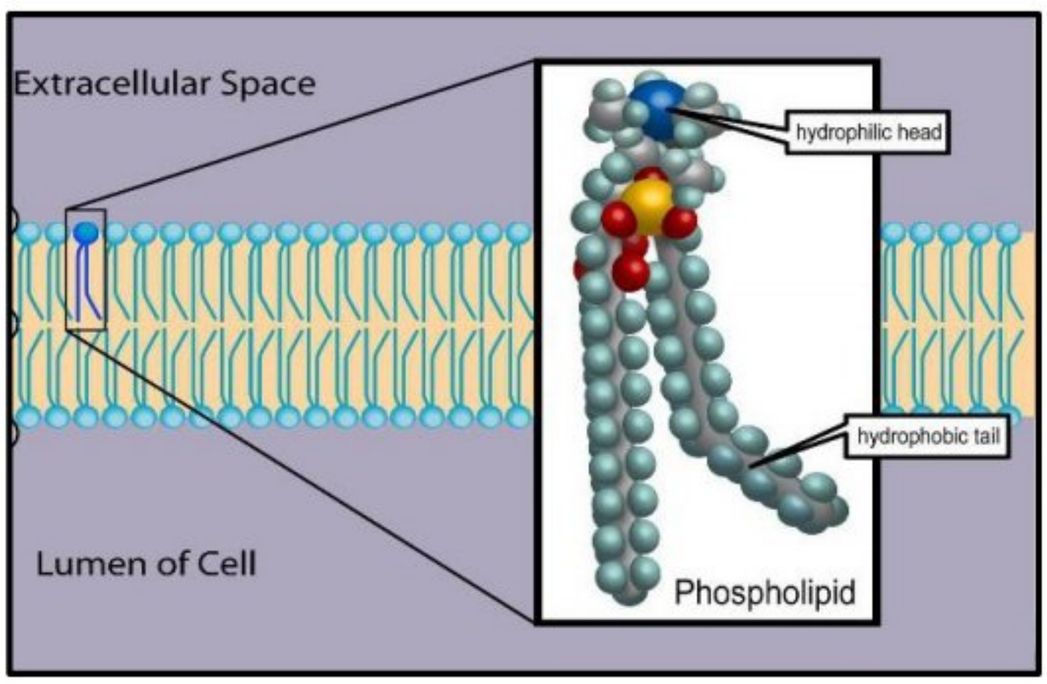
•LIPOSOMES

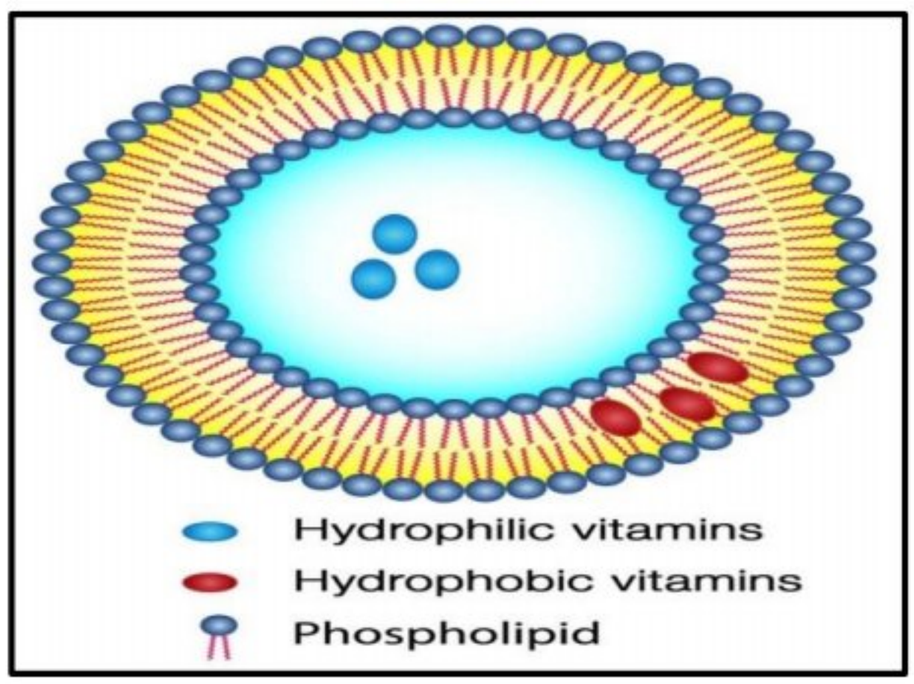
-Liposomes are **microscopic spheres made from fatty materials**, predominantly phospholipids.

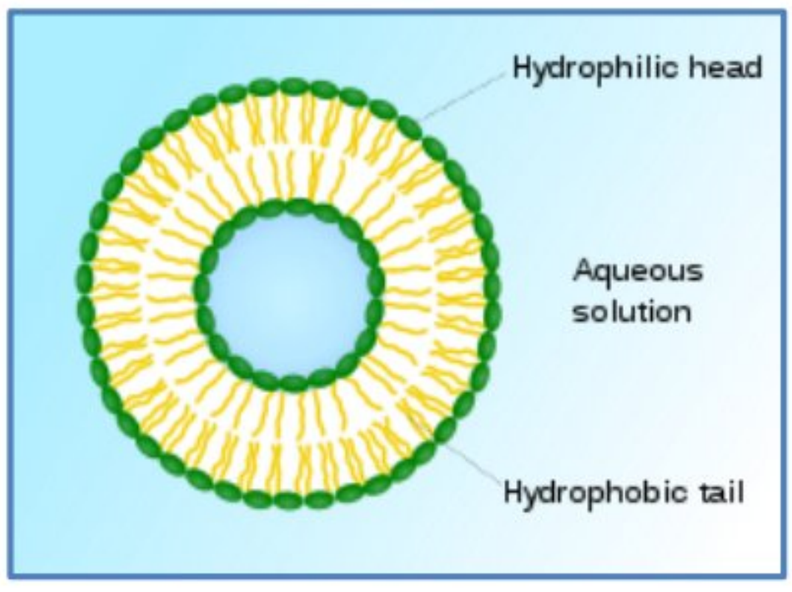
-Liposomes are made of molecules with hydrophilic and hydrophobic ends that form hollow spheres which can encapsulate water-soluble ingredients (drugs) in their inner water space and oil-soluble ingredients (drugs) in their phospholipid membranes that are made up of one or more concentric lipid bilayers, and range in size from 50 nanometers to several micrometers in diameter.











Diagrams and images to understand Liposomes

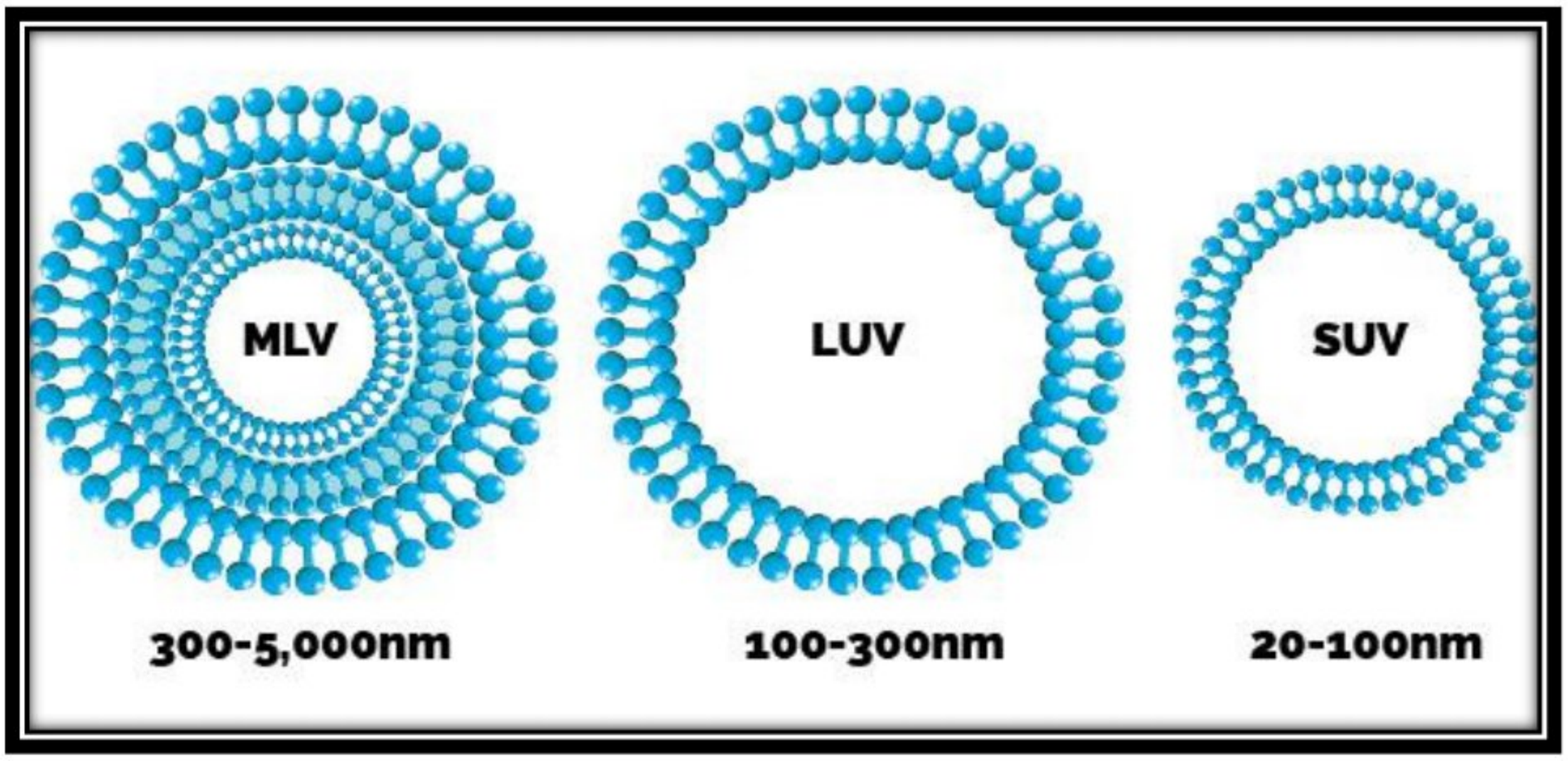
→ Based on their size and number of bilayers liposomes are classified into three basic types:-

1) Multilamellar Vesicles (MLVs)
2) Large Unilamellar Vesicles (SUVs)
3) Small Unilamellar Vesicles (LUVs)

-**Multilamellar Vesicles (MLVs)** are of several lipid bilayers separated one another by aqueous spaces.
-They are heterogenous in size, often ranging from a few hundred to thousands of nanometer in diameter.

-Both **Small Unilamellar Vesicles (SUVs)** and **Large Unilamellar Vesicles (LUVs)** consist of single bilayer surrounding the entrapped aqueous space.

-SUVs are less than 100nm in size whereas LUVs have diameter larger than 100nm.



→ In terms of composition and mechanism of intracellular delivery liposomes are classified into five types:-

(i) Conventional liposomes
(ii) pH sensitive liposomes
(iii)Cationic liposomes
(iv)Immuno liposomes
(v) Long circulating liposomes

Formulation/ Composition of Liposomes-

-Material used in the liposomes formulation depends upon the drug nature.
-The commonly used material includes phospholipids, glycosphingolipids, sterols, cationic lipid, a variety of other lipids and surfactants.

-There are number of structural and nonstructural components of liposomes, major structural components of liposomes are-

1) Phospholipid- It is the major component of the biological membrane; two types of phospholipids are used natural and synthetic phospholipids.
-The most common natural phospholipid is the Phosphatidylcholine (PC).
-It is amphipathic molecule and also known as **lecithin**.
-It is originated from animal (hen egg) and vegetable (soya bean).

2) Cholesterol- Incorporation of cholesterol in liposome bilayer can bring about big changes in the preparation of these membranes.
-It can be incorporated into phospholipids membrane in very high concentration up to 1:1 or 2:1 molar ratios of cholesterol to Phosphatidylcholine.
-Being an amphipathic Molecule, cholesterol insert into the membrane with its hydroxyl group of Cholesterol oriented towards the aqueous surface and aliphatic chain aligned parallel to acyl chains in the centre of the bilayers.

Method of preparation of of liposomes:-

1) Mechanical Dispersion Method
2) Solvent Dispersion Methods
3) Detergent Removal Methods

1) Mechanical dispersion methods- Lipid is solubilized in organic solvent, drug to be entrapped is solubilized in aqueous solvent, the lipid phase is hydrated at high speed stirring.
- Due to affinity of aqueous phase to polar head, it is entrapped in lipid vesicles.

-for example- Lipid film hydration, Micro-emulsification, Sonication, Dried reconstituted vesicle.

2) Solvent dispersion methods- In this method, lipids are first dissolved in organic solvent, which is then brought in to contact with aqueous phase containing material which is to be entrapped in liposome under rapid dilution at rapid evaporation of organic solvent.

-for example- Ethanol injection, Ether injection, De-emulsification.

3) Detergent removal method- In this method, phospholipids are brought into intimate contact with the aqueous phase via detergent which associate with phospholipids molecule and serve to screen the hydrophobic portions of the molecules from water.

➢ Evaluation of Liposomes-

-The characterization parameters for the purpose of evaluation could be classified into three broad categories, which include-

1) Physical Characterization parameter-

- Physical characterization evaluates various parameters, including size, shape, surface features, lamellarity and phase behavior and drug release profile.

2) Chemical characterization parameter-

-This parameter includes those studies which establish the purity and potency of various liposomal constituents.

3) Biological characterization parameter-

- These are helpful in establishing the safety and suitability of the formulations for the *in-vivo* use or the therapeutic application.

4) Drug Entrapment Efficiency-

-It is the measure of % drug entrapped to how much drug was added in the bulk for entrapment.

$$\% \, \boldsymbol{Entrapment\ Efficinecy} = \frac{\boldsymbol{Entrapped\ Drug}}{\boldsymbol{Total\ Drug\ Added}} \times \mathbf{100}$$

5) *In Vitro* Drug release study-

- *In Vitro* diffusion studies are carried out using **Franz diffusion cell.**

Advantages of Liposomes-

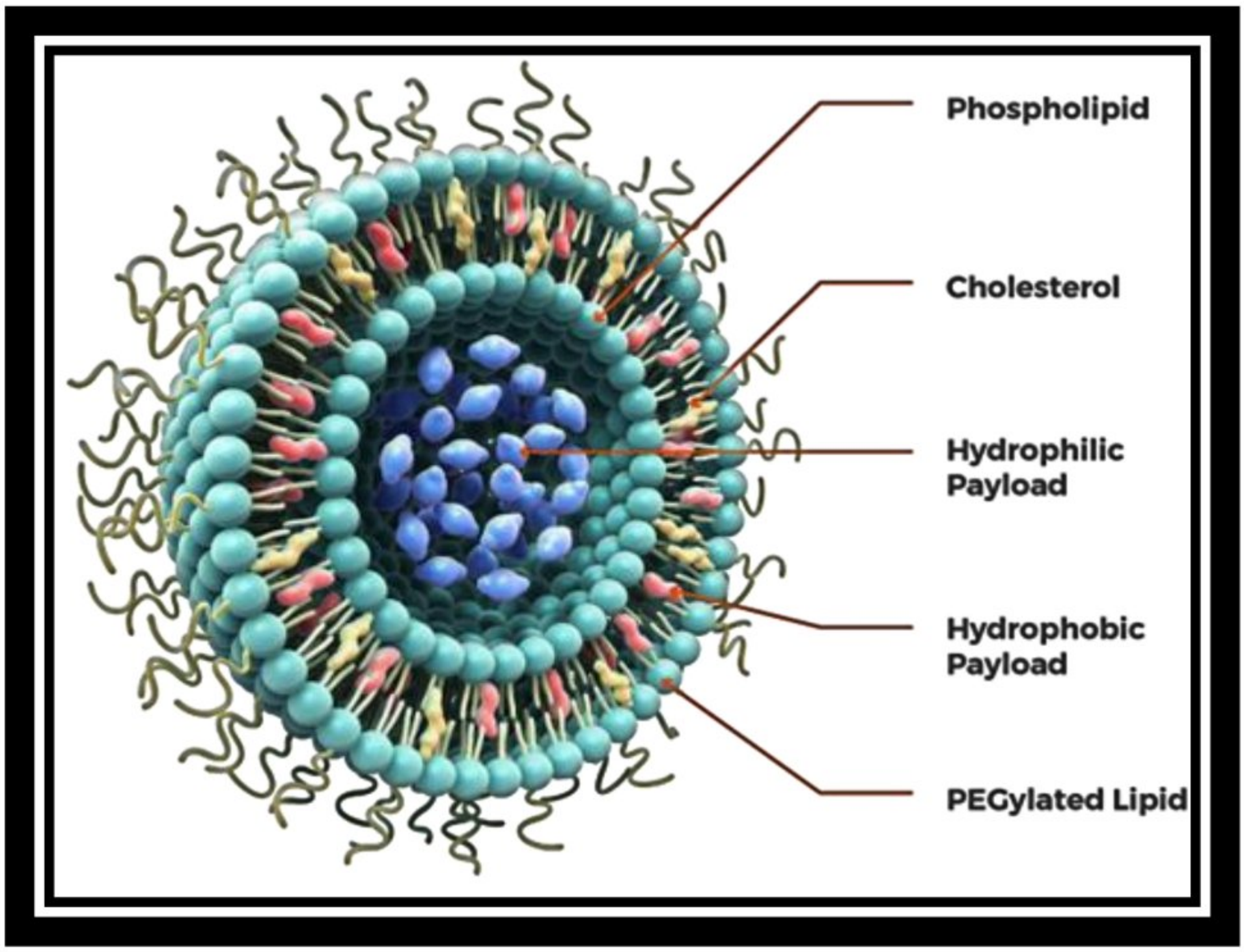
-Liposomes are biocompatible, completely biodegradable, non-toxic, flexible and non-immunogenic for systemic and non-systemic administration.
-Liposomes supply both a lipophilic environment and aqueous in one system and are therefore suitable for delivery of hydrophobic, amphipathic, and hydrophilic drugs and agents.
-Liposomes have ability to protect their encapsulated drug from the external environment and to act as sustained release depots.
-Liposomes can be formulated as a suspension, as an aerosol, or in a semisolid form such as gel, cream and lotion, as a dry vesicular powder (proliposome) for reconstitution or they can be administered through most routes of administration including ocular, pulmonary, nasal, oral, intramuscular, subcutaneous, topical and intravenous.
-Liposomes are increased efficacy and therapeutic index of drug (Actinomycin D)
-Liposomes help to reduce exposure of sensitive tissues to toxic drugs.

Disadvantages of Liposomes-

-Production cost is high.
-Leakage and fusion of encapsulated drug.
-Sometimes phospholipid undergoes oxidation and hydrolysis like reaction.
-Short half-life.
-Low solubility.

Applications of Liposomes-

-Liposomes can target a drug to the intended site of action in the body, thus enhancing its therapeutic efficacy (drug targeting, site-specific delivery).
-Liposomes may also direct a drug away from those body sites that are particularly sensitive to the toxic action of it (site-avoidance delivery).
-Liposomes can act as a depot from which the entrapped compound is slowly released over time. Such a sustained release process can be exploited to maintain therapeutic (but nontoxic) drug levels in the bloodstream or at the local administration site for prolonged periods of time. Thus, an increased duration of action and a decreased frequency of administration are beneficial consequences.
-Drugs incorporated in liposomes, in particular those entrapped in the aqueous interior, are protected against the action of detrimental factors (e.g. degradative enzymes) present in the host. Conversely, the patient can be protected against detrimental toxic effects of drugs.
-Liposomes can interact with target cells in various ways and are therefore able to promote the intracellular delivery of drug molecules that in their 'free' form (i.e. non-encapsulated) would not be able to enter the cellular interior due to unfavorable physicochemical characteristics (e.g. DNA molecules).
-If the drug is an antigen, liposomes can act as immunological adjuvant in vaccine formulations.



3-D image of a Liposome

» Spend some more time to revise and understand the topic more precisely and accurately, Click on the following links-

» Youtube Links:-

1) https://www.youtube.com/watch?v=KQA9YlhgTQc&list=LL_dC_jgRPZYgbmFWVXQVf7w&index=17 (animation of Liposome preparation from **CIPLA**)

2) https://www.youtube.com/watch?v=6oml_EArMo8&list=LL_dC_jgRPZYgbmFWVXQVf7w&index=23 (animation of mechanical method of liposome preparation)

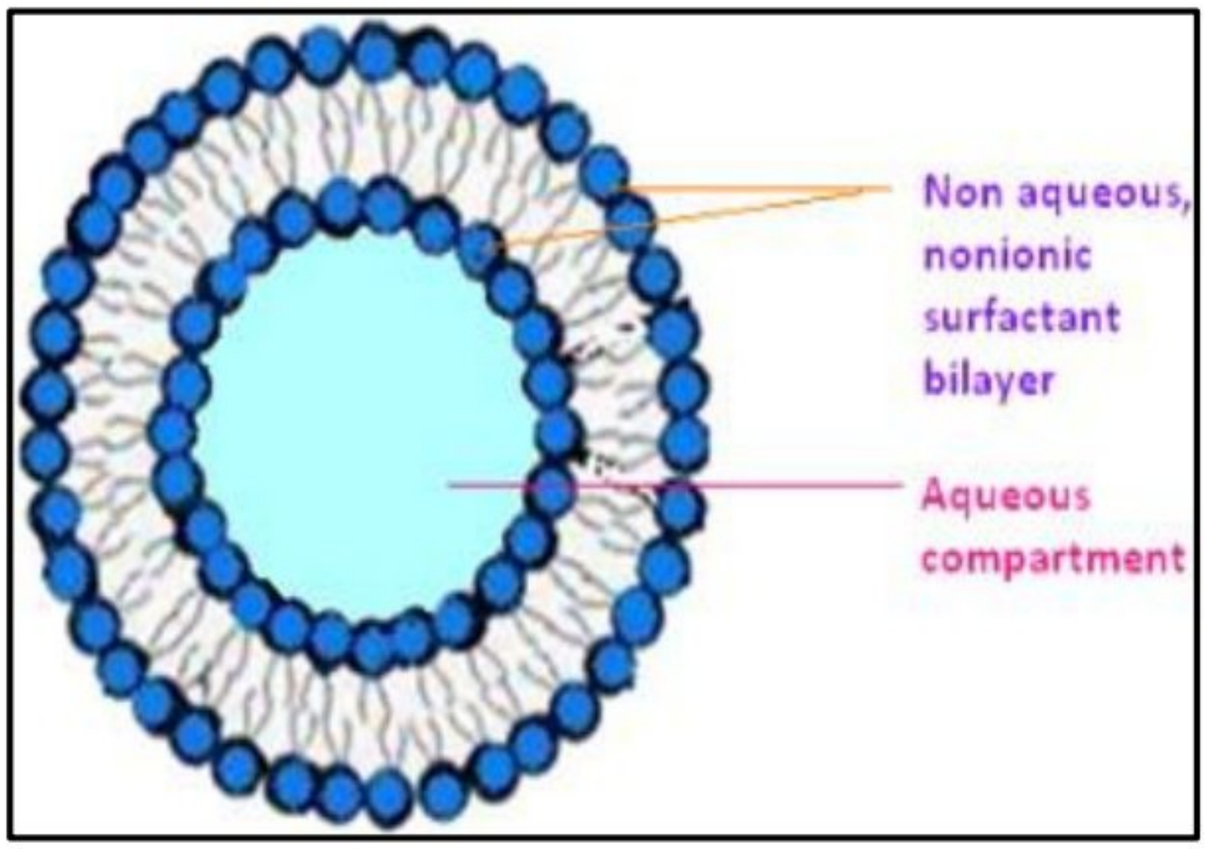
3) https://www.youtube.com/watch?v=7bPc6P7wRP4&list=LL_dC_jgRPZYgbmFWVXQVf7w&index=18 (animation of mechanism of action and drug release in body from a liposome)

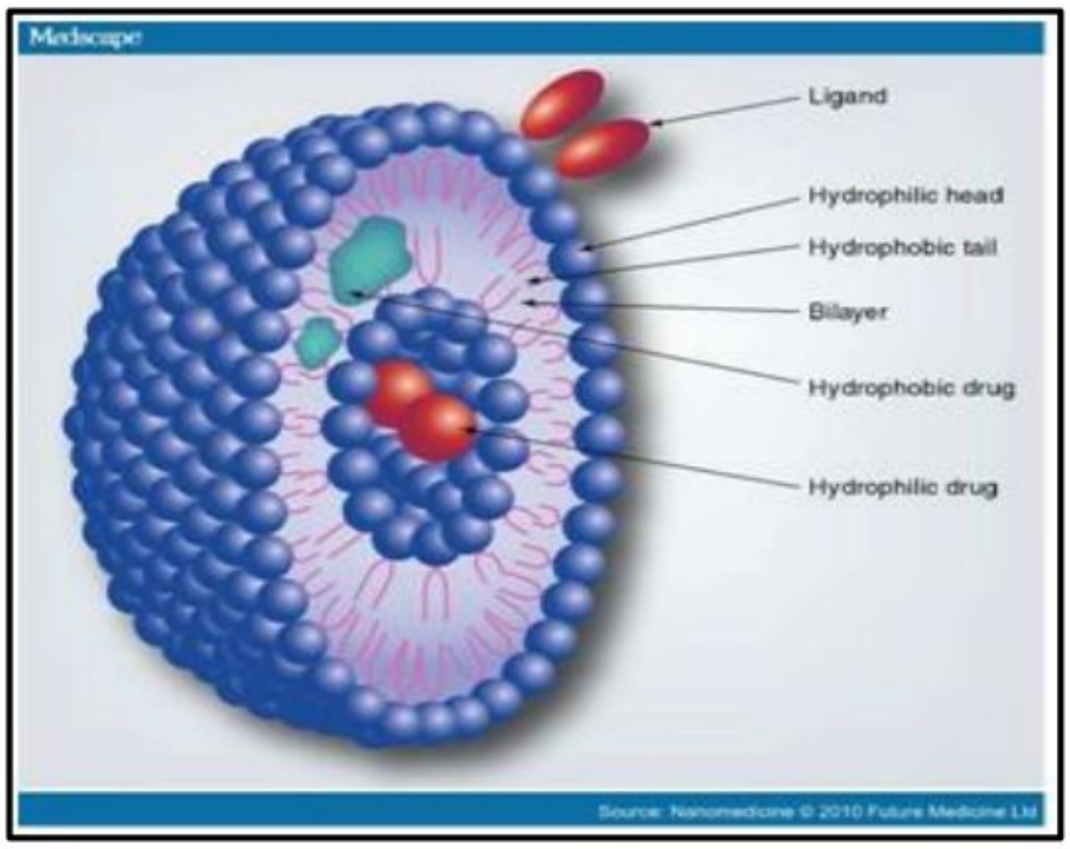
4) https://www.youtube.com/watch?v=vUqwIL5lgS8&list=LL_dC_jgRPZYgbmFWVXQVf7w&index=25 (animation of Liposome preparation of Doxorubicin, an anti-cancer drug marketed by **CIPLA,** from **CIPLA**)

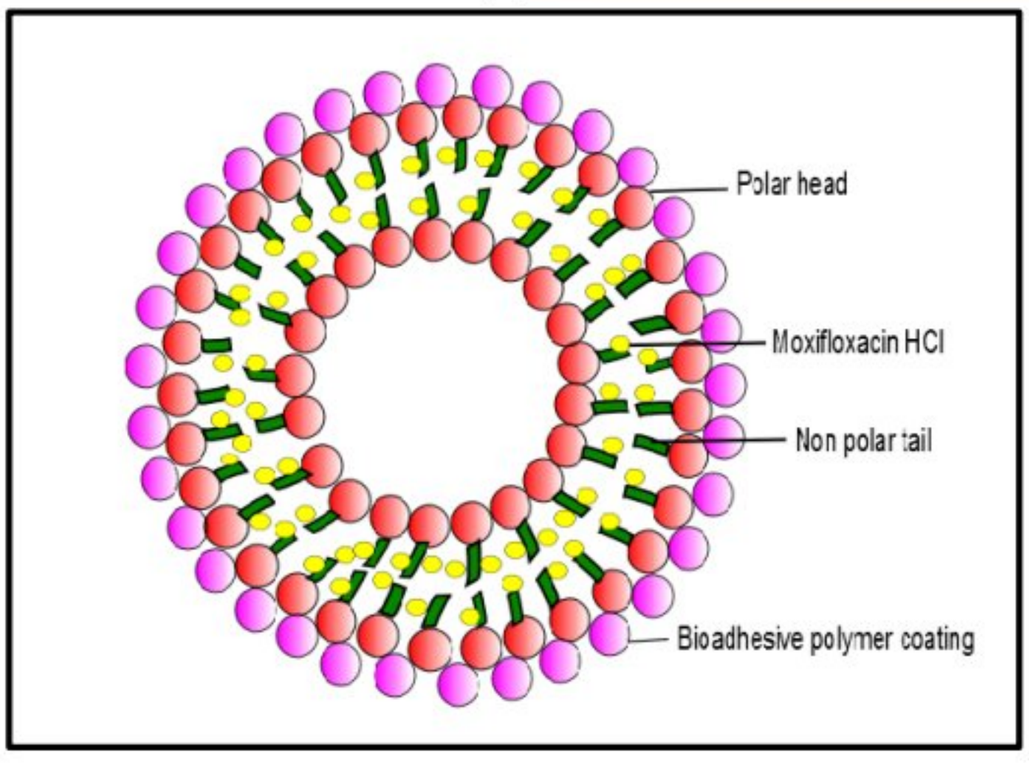
5) https://www.youtube.com/watch?v=oyBUndZ3fbY&list=LL_dC_jgRPZYgbmFWVXQVf7w&index=19 (Lecture on Liposomes)

•NIOSOMES

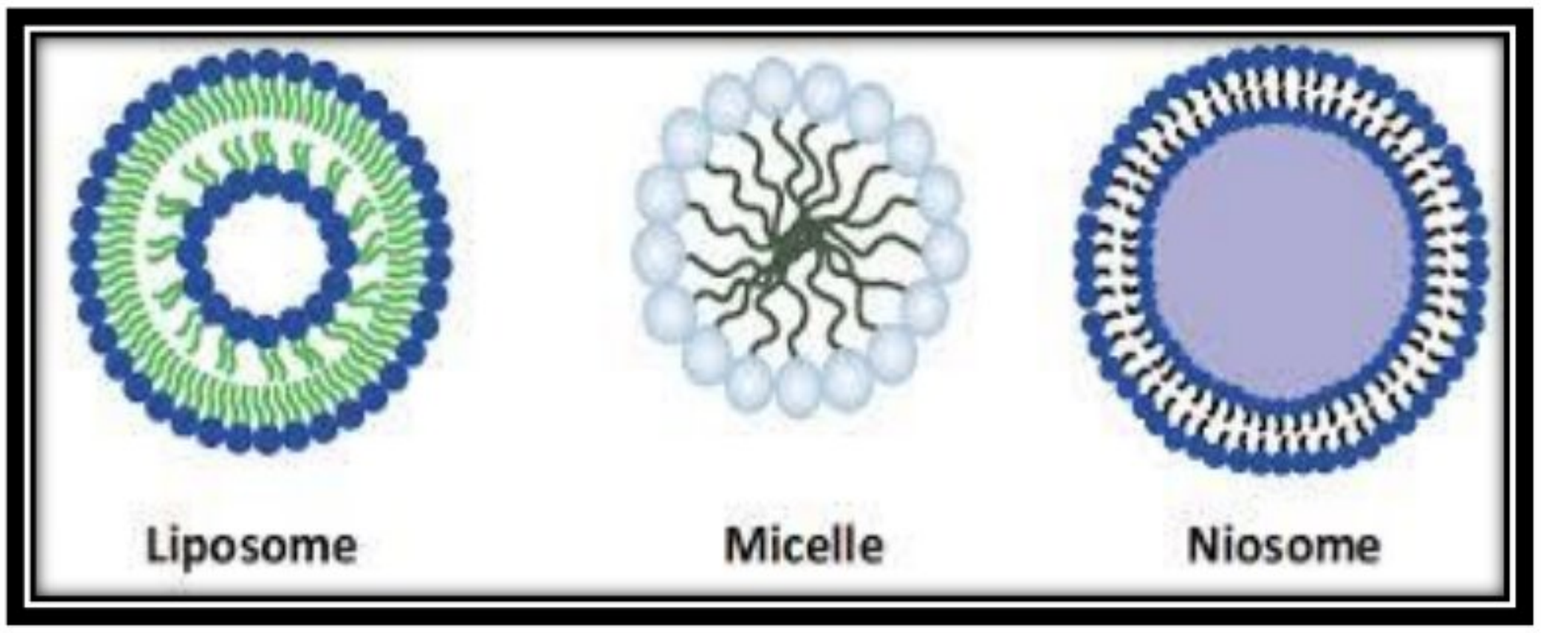
-**Niosomes** (**n**on-**io**nic, **surfactant-based vesicles**) are formed from the self-assembly of non-ionic amphiphiles (surfactant) in aqueous media, resulting in closed bilayer structures.
-The assembly into closed bilayers is rarely spontaneous and usually involves the input of energy such as physical agitation or heat.
-The result is an assembly in which the hydrophobic parts of the molecule are shielded from the aqueous solvent and the hydrophilic head groups have maximum contact with the same.
-This structures are analogous to phospholipid vesicles (liposomes) and can encapsulate aqueous solutes, thereby serving as drug carriers.
-The main advantages such as low cost of production, greater stability, and resultant ease of storage non-ionic surfactants have made this vesicles good alternatives to phospholipids.







Diagrams and images to understand Niosomes



Difference between Liposome and Niosome

➢ Preparation of Niosomes-

-The various used to prepare niosomes are similar to those used to prepare liposomes.

1) Ether Injection Method- The surfactant/cholesterol mixture is dissolved in diethyl ether and injected slowly through a needle into the aqueous phase at 60° C.
-Large unilamellar vesicles (LUVs) are formed during the evaporation of the ether.
-The main disadvantage of this method is that a small amount of ether is often present in the vesicle suspension and is very difficult to remove.

2) Hand Shaking (Film) Method- A surfactant/lipid film is formed by the evaporation of an organic solution of surfactant/lipids.
-This film is then hydrated with a solution of the drug.

3) Sonication- An aqueous pahse is added to the surfactant/cholesterol mixture in a glass vial.
-The mixture is then probe-sonicated for a certain time period.
-Small Unilamellar Veesicles (SUVs) are then formed.

4) Reverse phase evaporation- An oil-in-water (o/w) emulsion is formed from an aqueous solution of the drug.
-The organic solvent is then evaporated to leave niosomes dispersed in the aqueous pahse.
-In certain cases, the resulting gel has to thee further hydrated to yield niosomes.

➢ Evaluation of Niosomes-

-Size, Shape and Morphology
-Entrapment Efficiency
-Osmotic activity
-Vesicle surface charge
- and all other parameters similar to Liposomes.

Advantages of Niosomes-

-The suspension is water based vehicle. This offers high patient compliance in comparison with oily dosage forms.
-They possess an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together and as a result can accommodate drug molecules with a wide range of solubility.
-The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics.
-They are osmotically active and stable, as well as they increase the stability of entrapped drug.
- Handling and storage of surfactants requires no special conditions.
- They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
- They can be made to reach the site of action by oral, parenteral as well as topical routes.
- The surfactants are biodegradable, biocompatible and non-immunogenic.
- They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells.

Disdvantages of Niosomes-

-They have low solubility.
-They have short half-life.
-Production cost is high.
-Fusion.
-Leaking of the entrapped drug.
-Physical instability.

Applications of Niosomes-

1) Anticancer Niosomes- These niosomes, are expected to accumulate within tumours in a similar manner to that of liposomes.
-The niosomal encapsulation of methotrexate and doxorubicin increases drug delivery to the tumour and enables anticancer activity.

2) Niosomes as Vaccines- Niosomal antigens are potent stimulators of cellular and humoral immune response.
-The formulation of antigens as a noisome in a water-in-oil emulsion further increases the activity of antigens.
-The controlled release property of the emulsion formulation is responsible for enhancing immunological response.

3) Niosomes as Topical Delivery- Niosomes are also used for the topical delivery of drugs because of certain advantages such as higher chemical stability, intrinsic skin penetration enhancing properties and lower cost of production.

Difference between Liposomes and Niosomes :-

SR. No.	LIPOSOMES	NIOSOMES
1)	Vesicles are made up of concentric bilayers of Phospholipids.	Vesicles made up of non-ionic surfactants with or without incorporation of cholesterol.
2)	Size range:- 10 to 3000 nm	Size range:- 10 to 100 nm
3)	Comparatively Expensive	Inexpensive
4)	Special storage condition required.	No special requirements
5)	Phospholipids are usually unstable.	Non-ionic surfactants are stable.
6)	Comparatively more toxic.	Comparatively less toxic.
7)	Poor quality and purity.	Good quality and purity.
8)	Liposomes are made up of neutral or charged double-chained phospholipids.	Niosomes are made up of uncharged single-chain surfactant molecules.
9)	Phospholipid:- Phosphatidylcholine	Surfactant- Span- 20, 40, 60, 80 & Tween-20, 40, 60, 80.
10)	Uses- Gene delivery, MDR therapy etc.	Uses- Immunological, Oncology, Transdermal and diagnostics.

» Spend some more time to revise and understand the topic more precisely and accurately, Click on the following links-

» Youtube Links:-

1) https://www.youtube.com/watch?v=gE2TrWUWShw&list=LL_dC_jgRPZYgbmFWVXQVf7w&index=20 (Lecture)

• TRANSDERMAL DRUG DELIVERY SYSTEMS

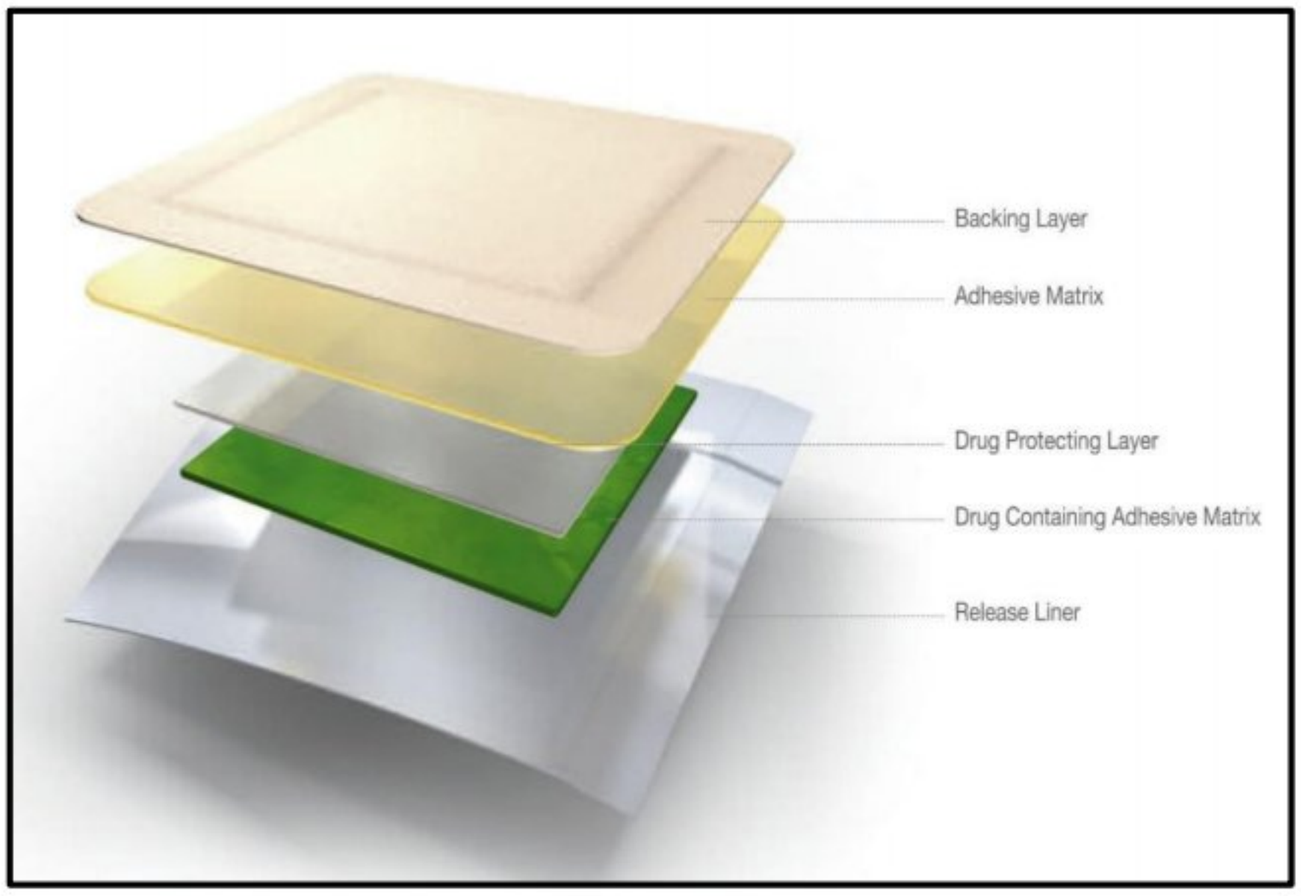
(TDDS)

"Transdermal drug delivery system are formulations that are applied to the body surface and are designed to deliver the active drug across the skin, into the systemic circulation."

Transdermal Patch

➢ Formulation Development of TDDS-

1) Backing films
2) Release liners
3) Pressure –sensitive adhesives
4) Active ingredients
5) Permeation enhancers
6) Microporous or semi-permeable membranes
7) Pouching materials



1) Backing films

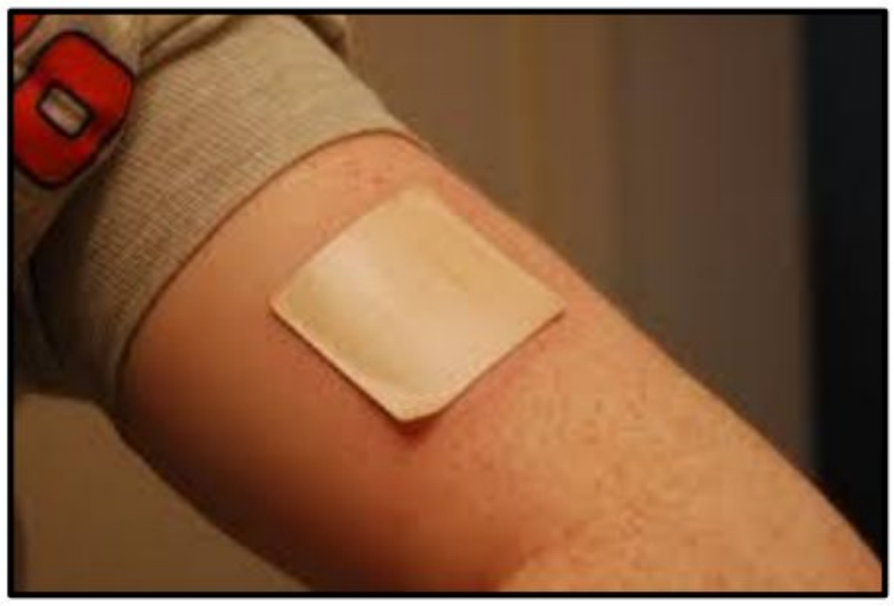
Role of films-

-To protect the active layer & safeguard the stability of the system.

-To affect skin permeation & tolerance, depending on occlusion or breathability.

-It must also be flexible, comfortable & must present good affinity with the adhesive, as well as excellent printability.

Ex. Of materials used-
-Polypropylene
-Poly ethylene
-Saran
-Polyester
-PVC
-Nylon



2) Release liners

Role of films-
-To protect the system as long as it is in the package.
-Play a crucial role in stability of the product.

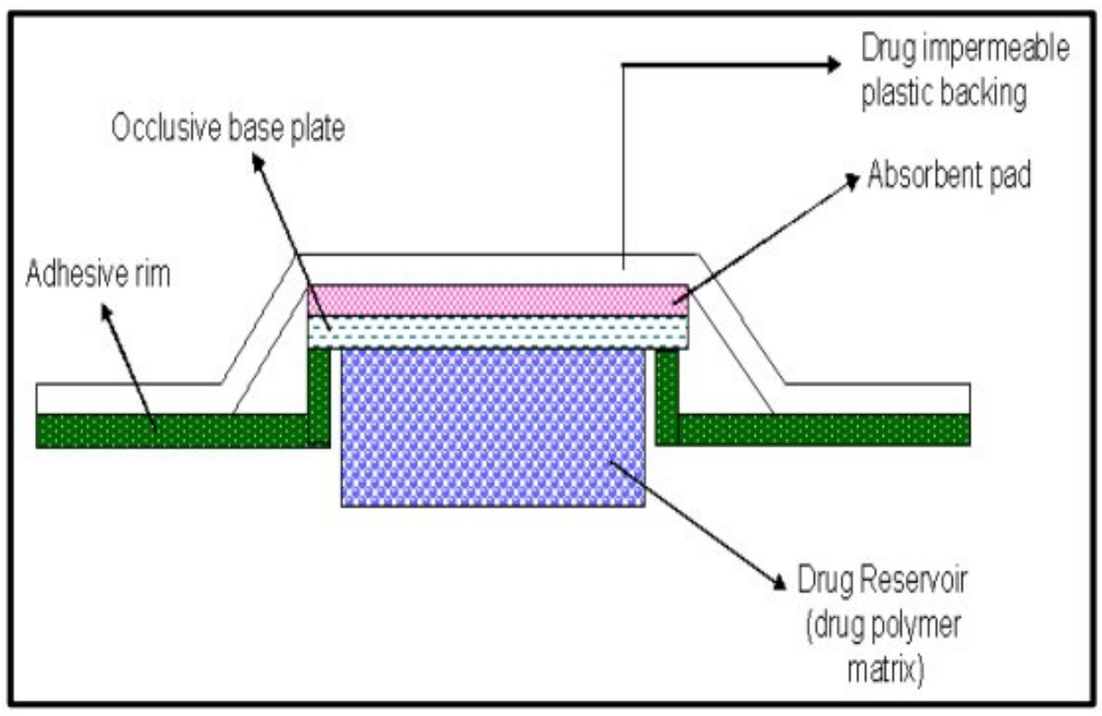
Most common films used-
-Paper based
-Plastic film based
-Composite films

Two major class of anti-adherent coating-
-Silicones
-Fluoro-polymers

3) Pressure-sensitive adhesives (PSAs)

Correct choice for pressure sensitive adhesive-
-A critical effect on the stability of the system.
-Release of the API.
-Dermatotoxicity potential.
-Accurate administration of drug.

Three major families of PSAs-
(i) Rubber based
(ii) Acrylic based
(iii) Emulsion polymers or hot melts



4) API

Properties of the drug to be a candidate for transdermal drug delivery system:-

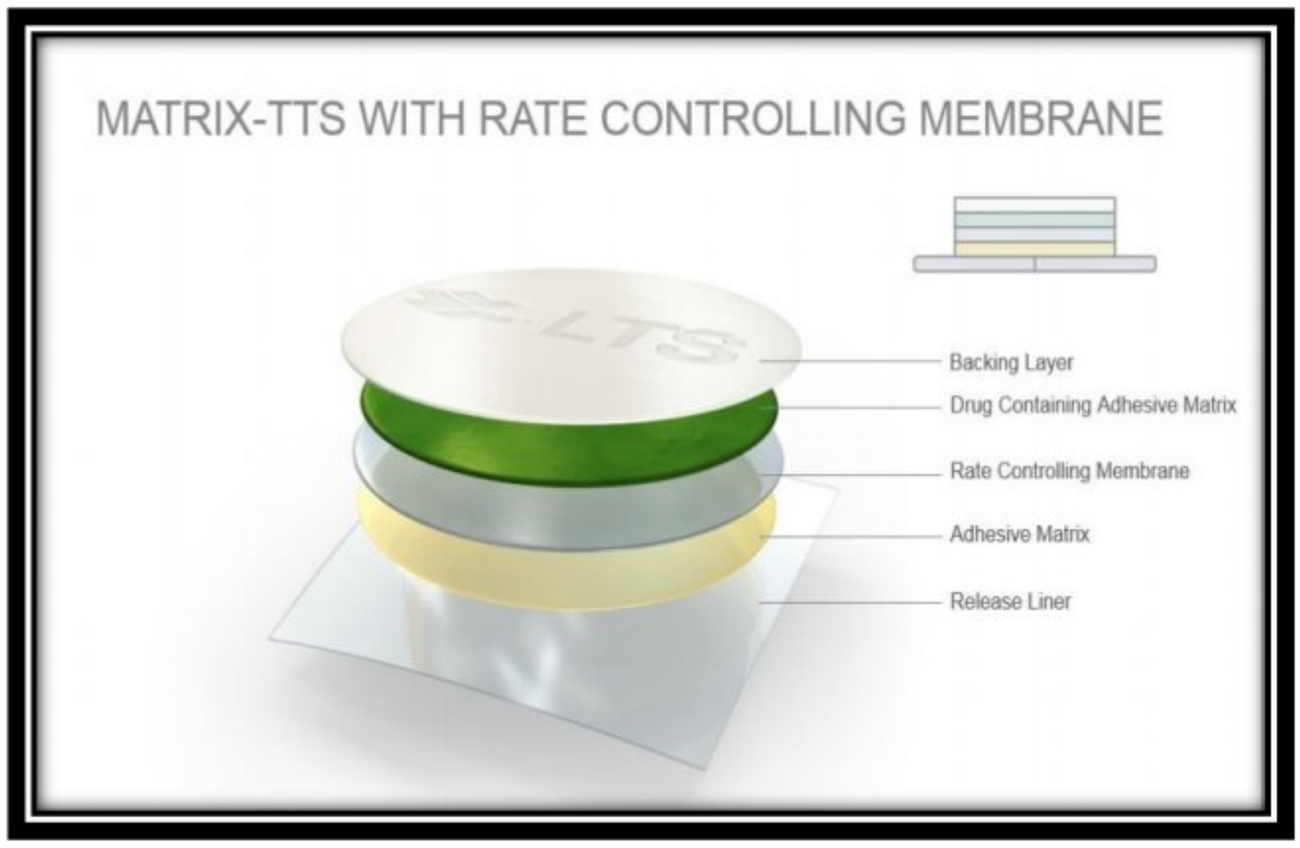
-The drug should have a molecular wt. less than 1000 Dalton.
-The drug should have affinity for both- lipophilic & hydrophilic phases.
-The drug should have low melting point.
-The drug should be potent with a daily dose of order of a few mg/day.
-The half-life of the drug should be short.
-The drug should be non-irritating & non-allergic.

5) Permeation enhancers

Three possible mechanism-

(i) Lipid action
(ii) Protein Modification
(iii) Partitioning promotion

Ex- Fatty acids
-Fatty alcohols
-Terpens
-Sulfoxides
-Surfactants
-Polyols
-Amides
-Ureas
-Lactam
-Sugar



6) Microporous or semi-permeable membranes

-To limit the flow of the semi-solid content from the liquid reservoir, and to act as a rate-limiting membrane for both liquid reservoir & matrix systems.

Two types of porous membranes-
(i) Ethylene vinyl acetate membrane (EVA)
(ii) Microporous polyethylene membranes

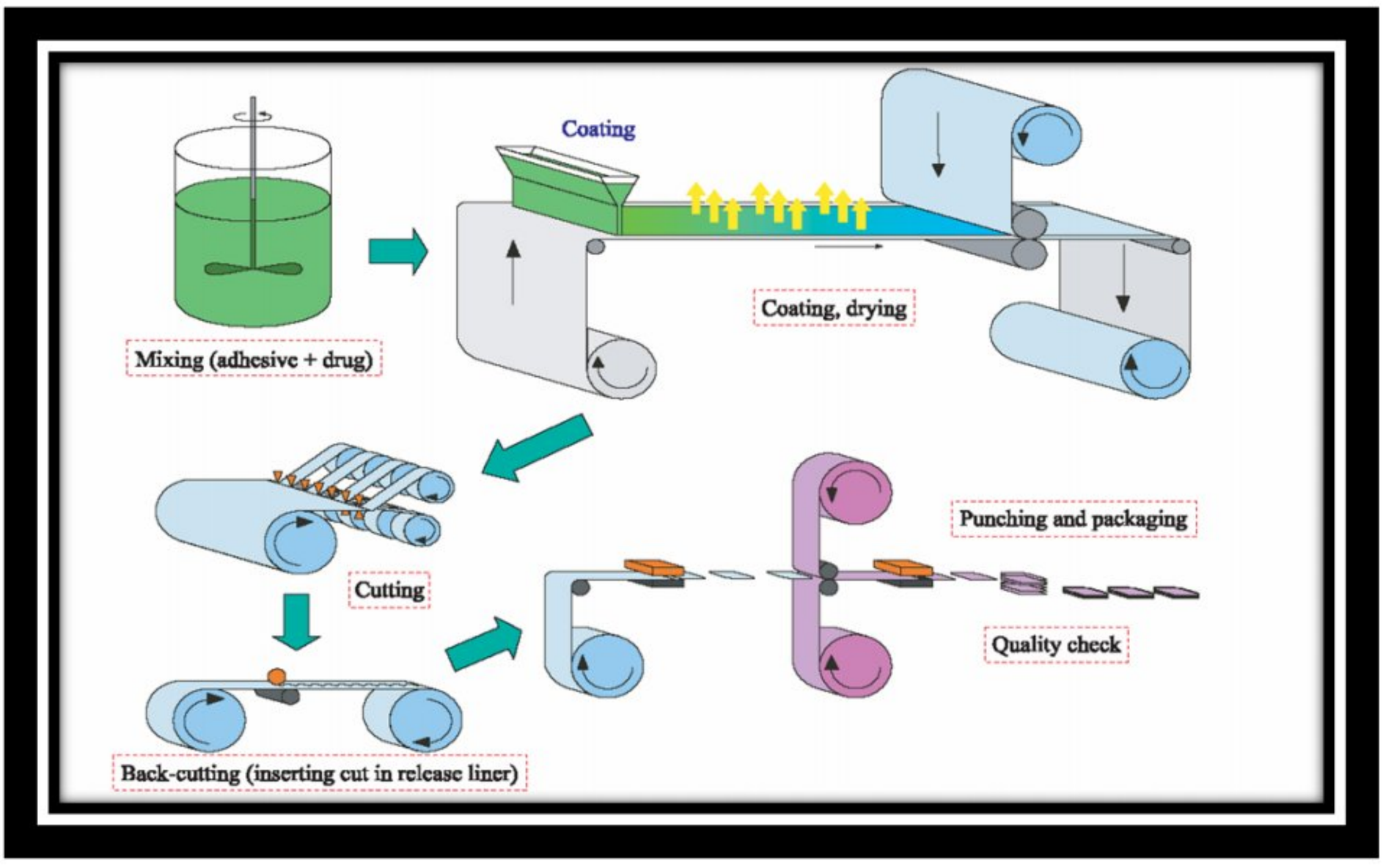
7) Pouching materials

Role- Stability & integrity of the product

Three main layers in the composite materials used for pouches-
(i) Internal plastic heat sealable layer
(ii) Aluminium foil layer
(iii) External printable layer

→ Desinging of TDDS / preparation of transdermal patch from industrial point of view :

Below is the schematic diagram of manufacturing of drug in adhesive system type of TDDS:-



➢ Evaluation of TDDS-

1) Evalution of Adhesives-

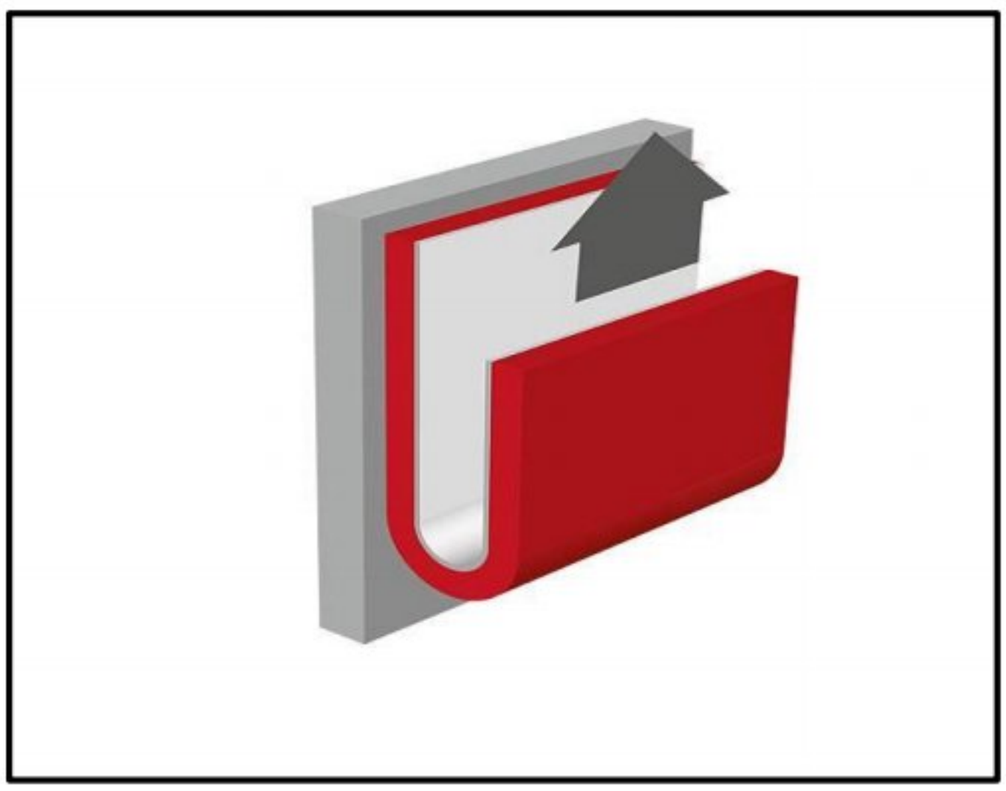
(i) Peel-adhesion properties-

-Peel adhesion is the force required to remove an adhesive coating from a test substrate.

-It is important in TDDS because the adhesive should provide adequate contact of the device with skin and should not damage the skin on removal.

-No residue on the substrate indicates adhesive failure, which is desirable for transdermal devices.

-Remnants on the surface indicates 'cohesive failure' signifying a deficit of cohesive strength in the coating.



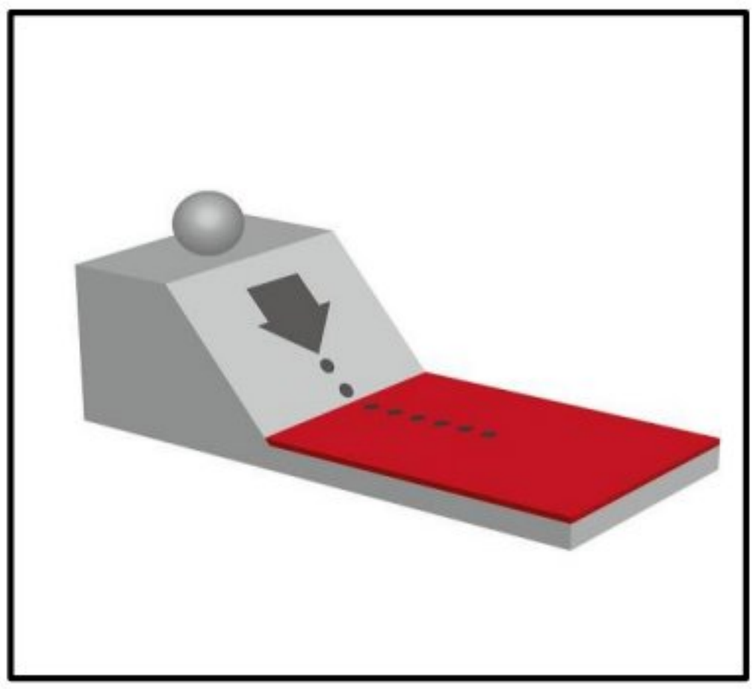
Peel Adhesion test

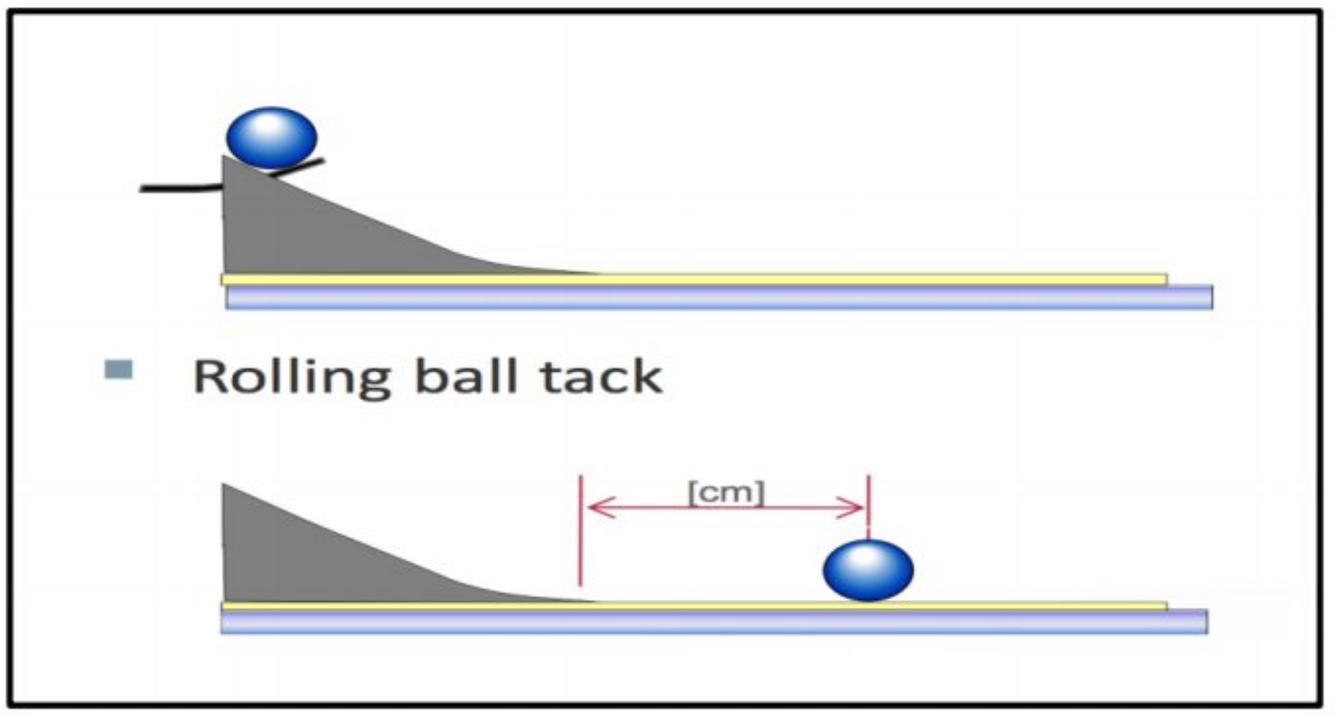
(ii) Tack properties- Tack is the ability of a polymer to adhere to a substrate with little contact pressure.

-Tack properties can be evaluated by three methods-

a) Thumb tack test- This is a subjective test in which evaluation is done by pressing the thumb briefly into the adhesive.

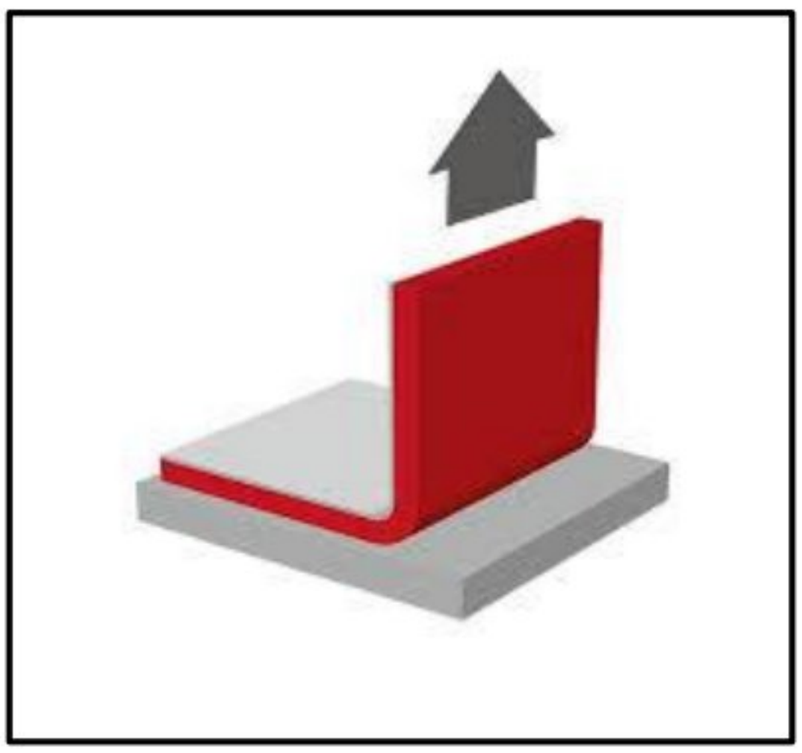
b) Rolling ball tack test- This test involves measurement of the distance that a stainless steel ball travels along an upward facing adhesive.
-The less tacky the adhesive, the farther the ball will travel.

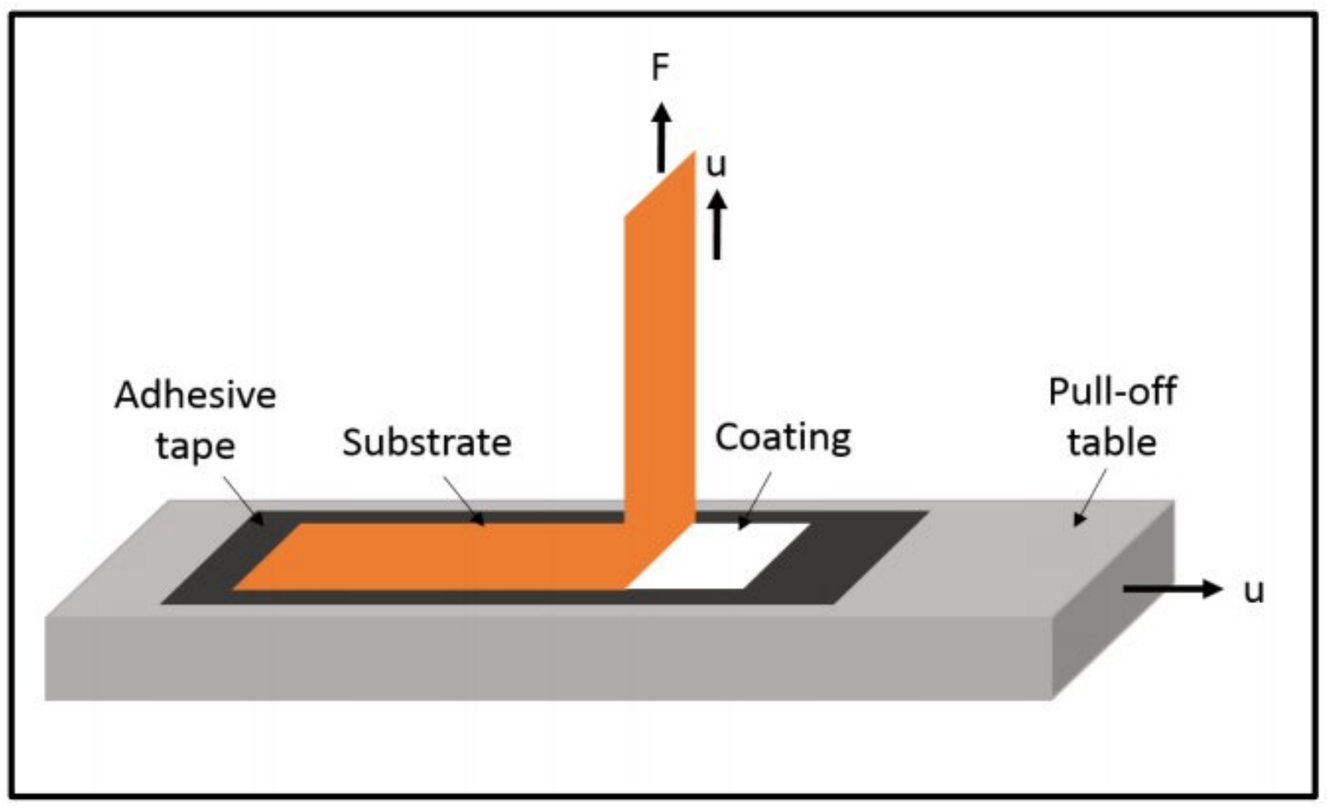




Rolling ball tack test

c) Quick stick Test- The peel force required to break the bond between an adhesive and substrate is measured by pulling the take away from the substrate at 90° at a speed 12inch/min.



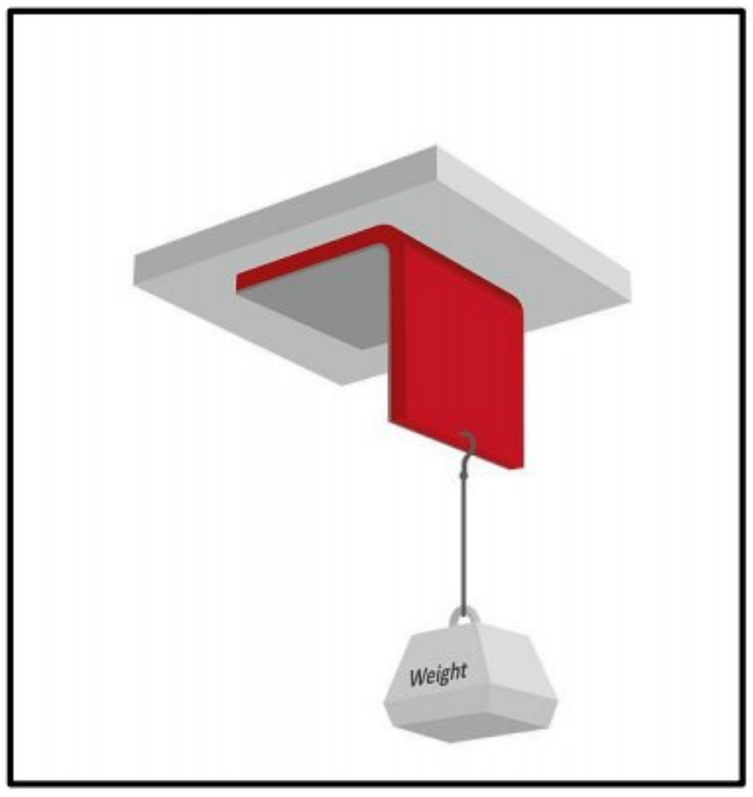


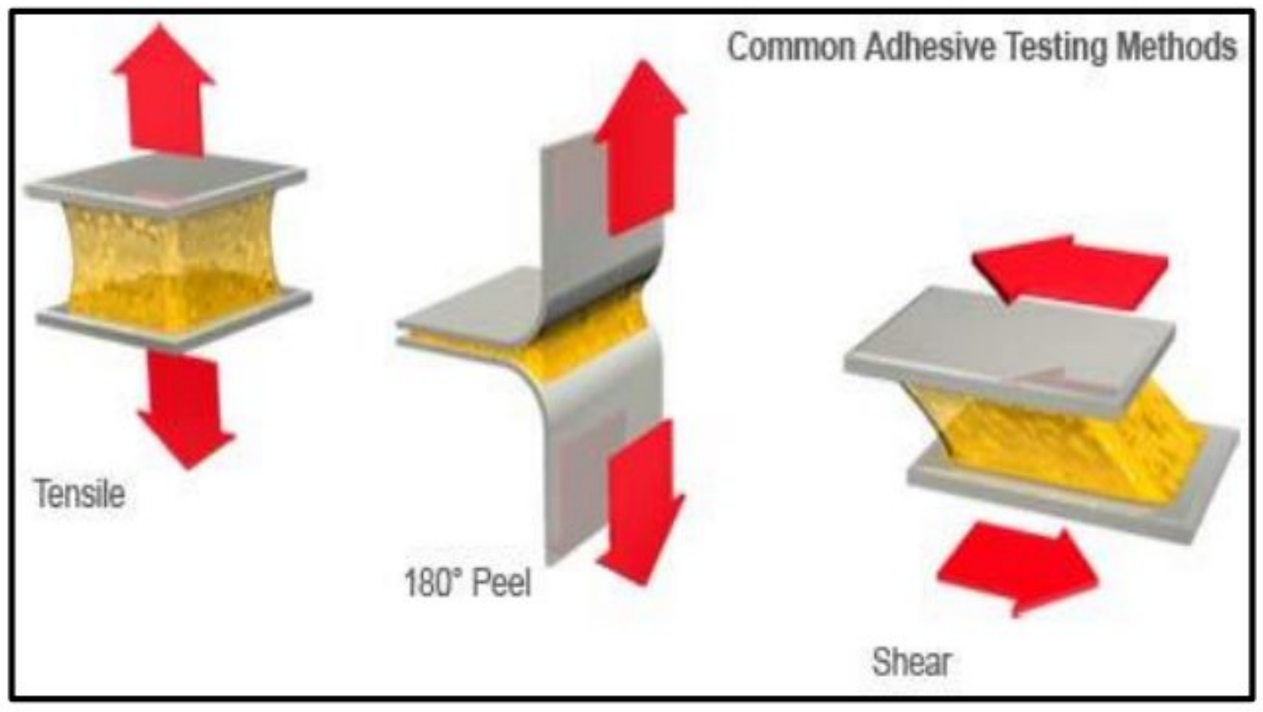
Quick stick test

(iii) Shear strength properties- Shear strength is the measurement of the cohesive strength of an adhesive polymer.

-Adhesive cohesive strength of a device means that device will not slip on application and will leave no residue on removal.

-Shear strength is determined by measuring the time it takes to pull an adhesive-coated tape of a stainless steel plate when a specified weight is hung from the tape, which pulls the tape in a direction parallel to the plate.





Shear Strength Properties

2) *In-vitro* drug release-

-*In-vitro* studies can help in investigating the mechanisms of skin permeation of the drug before it can be developed in a TDDS.

-In *in-vitro* studies, excised skin is mounted on skin permeated cell. The non-availability of human cadaver skin (donated skin), which is the most logical choice for *in-vitro* studies, has led to investigate of other animal skin.

-Various skin permeation systems have been designed and used in *in-vitro* studies.

-These includes **Valia-Chein (V-C) cell, Ghannam-Chein (G-C) cell, Franz diffusion and the Keshary-Chein (K-C) cell.**

-The K-C cell which is modified version of Franz diffusion cell has an effective receptor volume of 12mL and a skin surface area of 3.14cm^2.

-The receptor solution is stirred by a star head magnet rotating at a constant speed of 600rpm.

3) *In-vivo* evaluation-

-This evaluation of the TDDS can be carried out using-

(i) Animal model- *In-vivo* animal models are preferential because considerable time and resources are required to carry-out studies in human.

-Some of the species that have been used both for *in-vivo* & *in-vitro* testing includes mouse, rat, guinea pig, rabbit, etc….

(ii) Human Models- The final stage in the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamics data following application of the device to human volunteers.

Advantages of TDDS-

-Avoid the risk and inconvenience of intravenous therapy (noninvasive).
-Avoidance of first pass hepatic metabolism (avoiding the deactivation by digestive and liver enzymes) thus increasing bioavailability and efficacy of drugs.
-No gastrointenstinal degradation (pH, enzymatic activity, drug interaction with food, drink and other orally administered drugs).
-Substitute for oral administration of medication when that route is unsuitable as with vomiting and diarrohea.
-Extended therapy avoiding frequent dose administration.
-Permit the continuous drug administration and the use of drugs with short biological half life.
-Controlled drug delivery for a longer time.
-Reduces the chance of over and under dosing through the prolonged preprogrammed delivery of drug at the required therapeutic rate.
-Better patient compliance
-Rapidly termination possible when needed simply by removing the patch from the skin surface.
-Relatively large area (1-2m^2) of application in comparison with the buccal or nasal cavity.

Disadvantages of TDDS-

-Limited skin permeability
-Restricted to potent drug
-Cannot use for large molecule (>500 Dalton)
-Significant lag time
-Skin irritation and allergic response

» Spend some more time to revise and understand the topic more precisely and accurately, Click on the following links-

» Youtube Links:-

1) https://www.youtube.com/watch?v=X7Vwj3MsYEU&list=LL_dC_jgRPZYgbmFWVXQVf7w&index=14 (application of Transdermal patch- Real)

2) https://www.youtube.com/watch?v=bukWMyh91IU&list=LL_dC_jgRPZYgbmFWVXQVf7w&index=15 (application of Estrogen Transdermal patch on abdomen- Real)

3) https://www.youtube.com/watch?v=xBUCjnSdfNI&list=LL_dC_jgRPZYgbmFWVXQVf7w&index=13 (animation of Drug release from Transdermal Patch)

•TARGETED DRUG DELIVERY SYSTEMS

-It has been almost 200 years since **Dr. Paul Ehrlich** first put forward the idea of drug targeting. **Dr. Ehrlich** has watched a performance of the opera Der Freischiitz in which Zauberkugeln (magic bullets) play a major role.

-In the opera, these magic bullets could be fired in any direction and still reach their goal.

-Thinking along similar lines, **Dr. Ehrlich** imagined that tiny, drug-loaded, magic bullets could be introduced into human body to target te required site of action, while non-target sites would be largely exempted from the effects of the drug.

-**Dr. Ehrlich** inspired idea led to the development of targeted drug delivery.

➢ Targeted Drug Delivery Requirements-

1) The delivery system should be biochemically inert, non-immunogenic and physically and chemically stable *in vivo* and *in vitro*.
2) The carrier must be biodegradable or readily eliminated without any problems.
3) The delivery system must be reproducible, cost-effective, and simple.

➢ Different Approaches to Drug Targeting-

-There are three approaches of Drug targeting.

- The **first approach** involves the use of biologically active agents that are both potent and selective to a particular site in the body.

-The **second approach** involves the preparation of pharmacologically inert forms of active drugs that, on reaching the active sites, become activated by a chemical or enzymatic reaction (prodrug approach).

-Although these approaches are very successful in some cases, most of the time it is not feasible to synthesize new site-specific drugs for ailments because of the formidable cost and time taken for drug delivery.

-The **third approach-**the delivery of the original drug by specially designed drug delivery systems- is the best and only feasible solution.

-This approach utilizes a biologically inert macromolecules carrier systems that directs a drug to a specific site in the body where it accumulates and produces a response.

-The therapeutic efficacy of a targeted drug delivery system depends on the timely availability of the drug in its active form at the target sites and its intrinsic pharmacological activity.

-The intrinsic pharmacokinetic properties of the free drug should be the same, irrespective of whether or not it is introduced into the body attached to a carrier.

➢ Drug-Carrier Delivery Systems for Drug Targeting-

→ Properties of the drug that can be enhanced by Drug-Carrier Delivery Systems:-

1) **Prolong the drug effect** by ensuring a longer circulation time than free drugs.
2) **Increase the drug concentration at the required site** of action by preferential sequestering of the particles by the tissue of the site.
3) **Reduce drug toxicity** in the tissue.
4) **Protect the drug from metabolism and immune system** recognition until it reaches the desired target site.
5) Confine the **drug delivery system to the chosen anatomical compartment** by selecting an appropriate particle size.
6) Interact **selectively with cells of the target site** if equipped with specific, biological recognition structural units.
7) Retain the drug within the particle while 'in transit' and **release the drug at the target site** at the appropriate rate.
8) **Deliver drugs to the appropriate phagocytic cells** by participating in adsorptive endocytosis.

Spend some more time to revise and understand the topic more precisely and accurately, Click on the following links-

» Youtube Links:-

1) https://www.youtube.com/watch?v=LF-gjSduD7U&list=LL_dC_jgRPZYgbmFWVXQVf7w (Lecture)

•OCULAR DRUG DELIVERY SYSTEMS

-**Except for skin, the eye is the most easily accessible site for topical administration of a medication**.

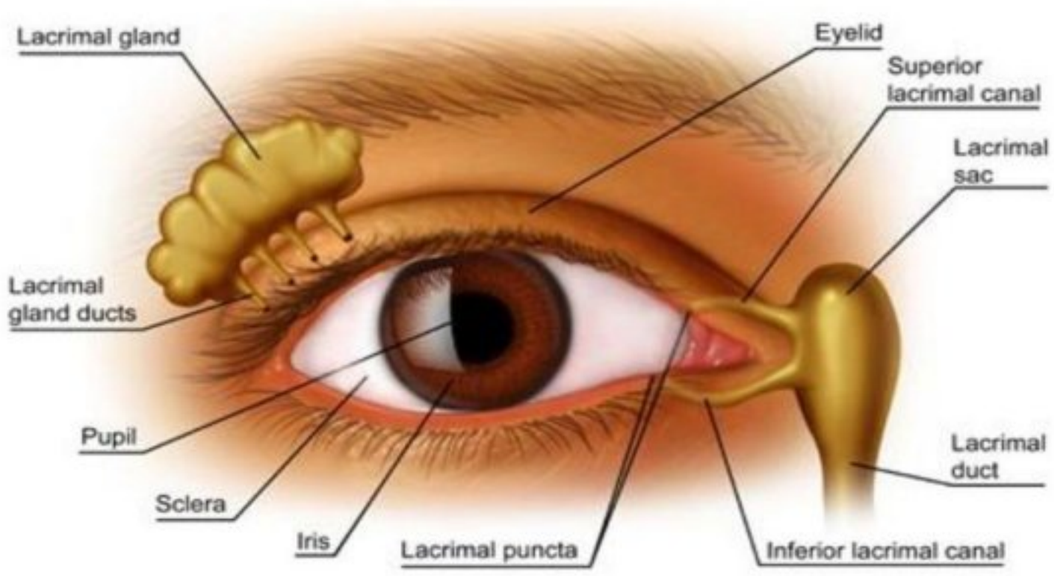
-Drugs are commonly applied to the eye for a localized action, on the surface, or in the interior of the eye.

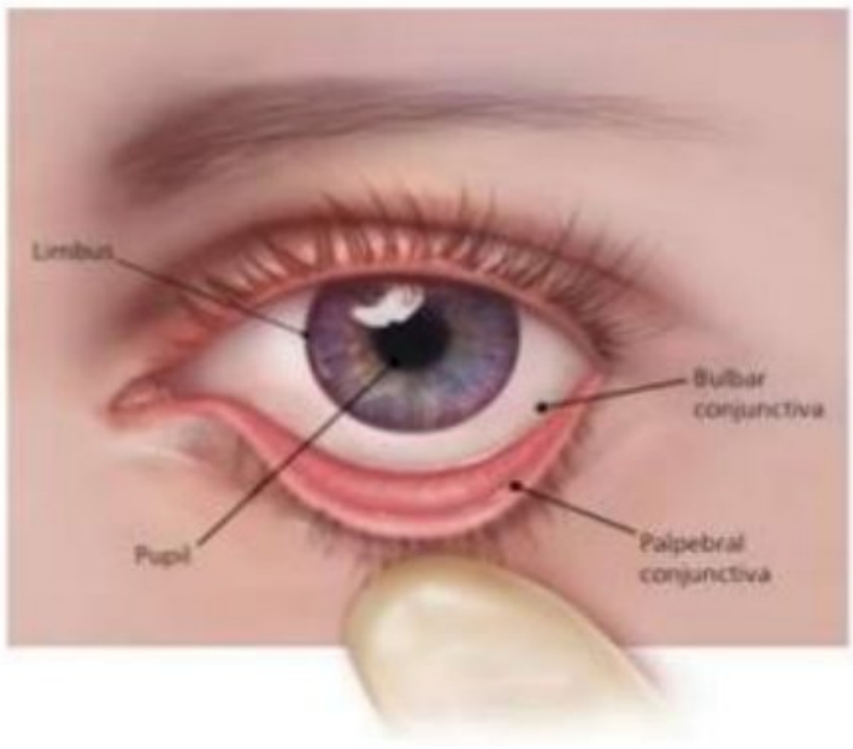
- A major problem in ocular therapeutics is the attainment of an optimal drug concentration at the site of action.

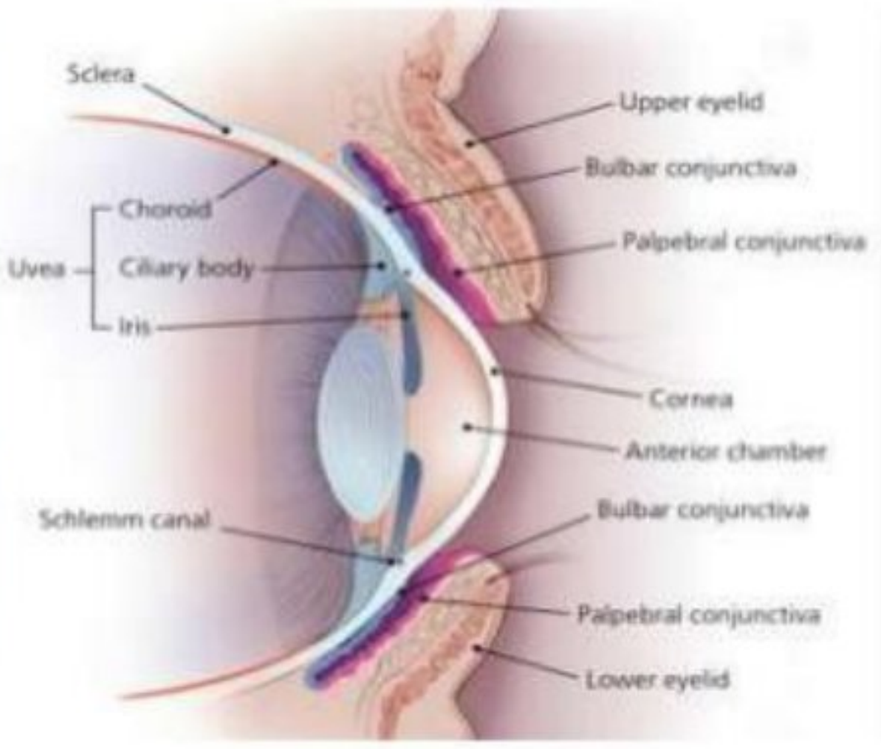
-Poor bioavailability of drugs from ocular dosage forms is mainly due to the pre corneal loss factors which include tear dynamics, non-productive absorption, transient residence time in the cul-de-sac (a region near to palpebral conjunctiva) , and the relative impermeability of the corneal epithelial membrane.

-Due to these physiological and anatomical constraints only a small fraction of the drug, effectively 1% or even less of the instilled dose, is ocularly absorbed.

Anatomy of Human eye





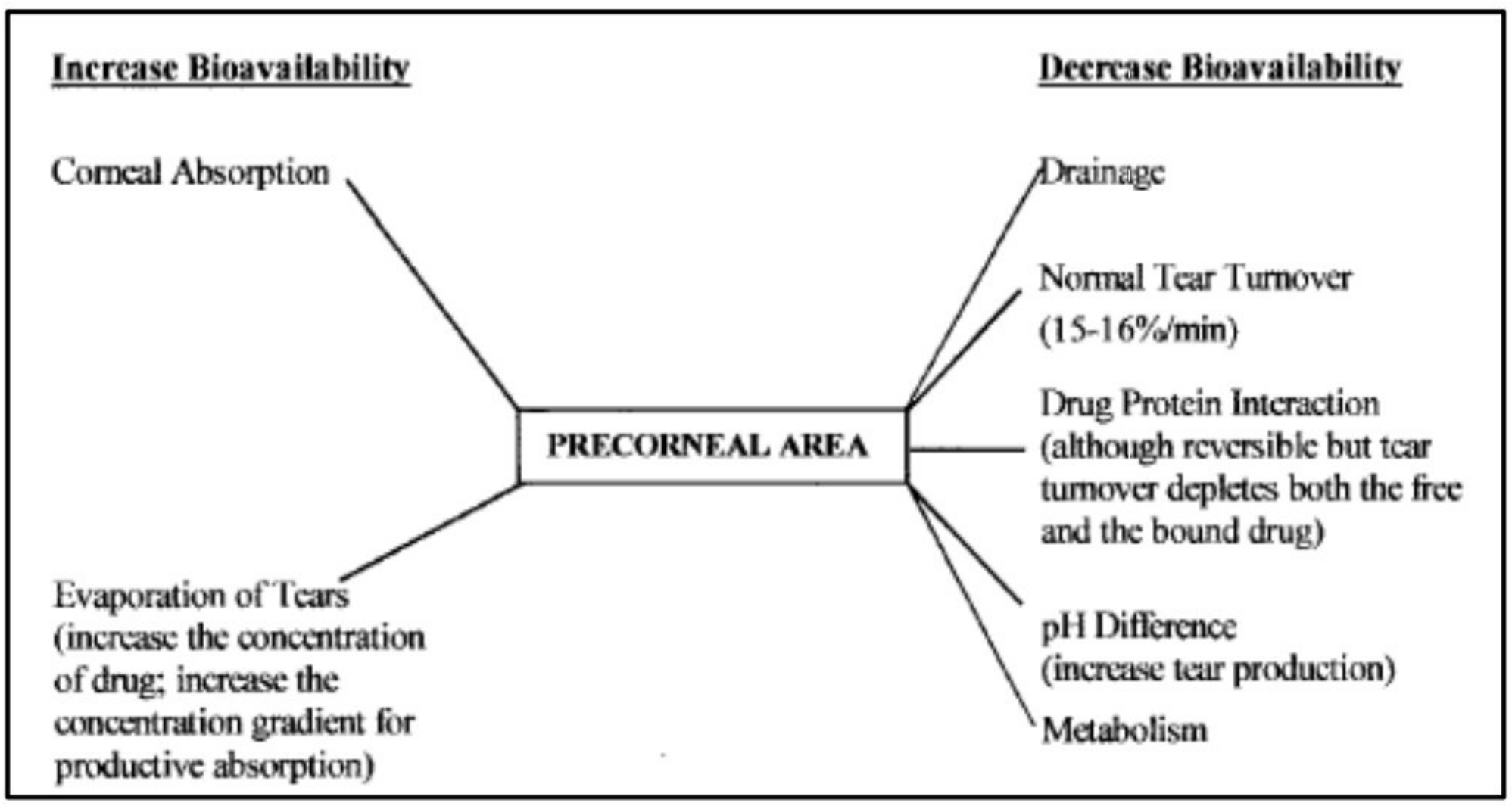


Topical Ocular drug delivery and the challenges to ocular therapy-

-It is common knowledge that the ocular bioavailability of drugs applied topically as eye-drops is very poor. The absorption of drugs in the eye is severely limited by some protective mechanisms that ensure the proper functioning of the eye, and by other concomitant factors.

for example:

- drainage of the instilled solutions;
- lacrimation and tear turnover;
- metabolism;
- tear evaporation;
- non-productive absorption/adsorption;
- limited corneal area and poor corneal permeability; and
- binding by the lacrimal proteins.



-It is now definitively established that the rate at which instilled solutions are removed from the eye varies linearly with instilled volume. In other words, the larger the instilled volume, the more rapidly the instilled solution is drained from the precorneal area.

In sort , we can divide various factors in to two classes :

1. which increases the bioavailability.
2. which decreases the bioavailability.

-So looking to the constraints for ocular drug delivery , we should concentrate on two things:
1) To prolong the contact time of drug with corneal surface.
2) To enhance corneal permeability, either by mild or transient structural alteration of corneal epithelium or by modification of chemical structure of the drug molecules.

➢ Classification of Ocular Drug Delievry System-

→ A multitude of ocular dosage forms are available for delivery of drugs to the eye. These can be classified on the basis of their physical forms as follows:-
1)**LIQUIDS:** Solutions, Suspensions, Sol to gel systems, Sprays
2) **SOLIDS:** Ocular inserts, Contact lenses, Corneal shield, Artificial tear inserts, Filter paper strips
3) **SEMI-SOLIDS:** Ointments, Gels
4) **MISCELLANEOUS:** Ocular iontophoresis, Vesicular systems, Mucoadhesive dosage forms, Particulates, Ocular penetration enhancers:-
Use of Hyaluronic acid, Use of Hydroxy Beta Cyclodextrin.

❖ OCULAR INSERTS (Solids):-

"Ocular inserts are defined as sterile preparations, with a thin, multi-layered, solid or semi-solid consistency devices placed into cul-de-sac or sac of conjunctiva and whose size and shape are especially designed for ophthalmic application."

-They are made-up of polymeric vehicle containing drug and are mainly used for topical therapy.

Advantages:-

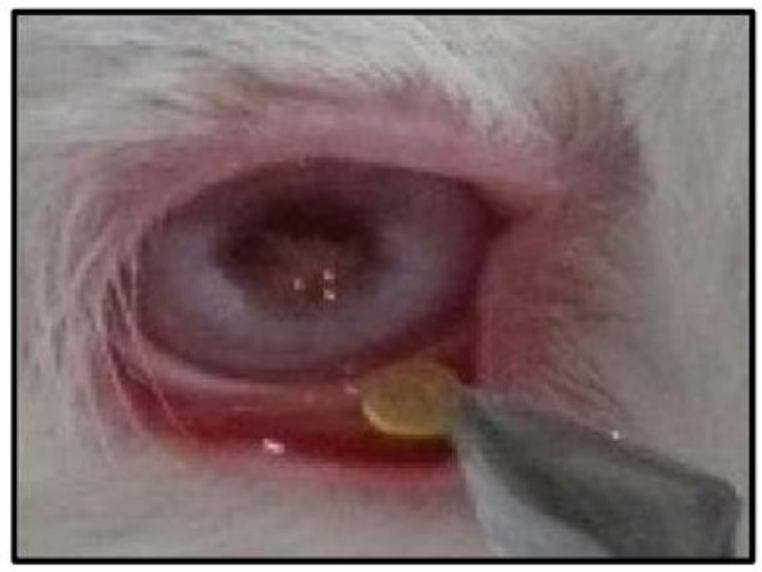
Provide controlled, sustained and continuous drug delivery.
Avoid the side effects of pulsed drug delivery.

-Maintain an effective drug concentration in the target tissues &minimize the number of applications.

-But they are having limited popularity due to unnoticed expulsion from the eye, membrane rupture etc.

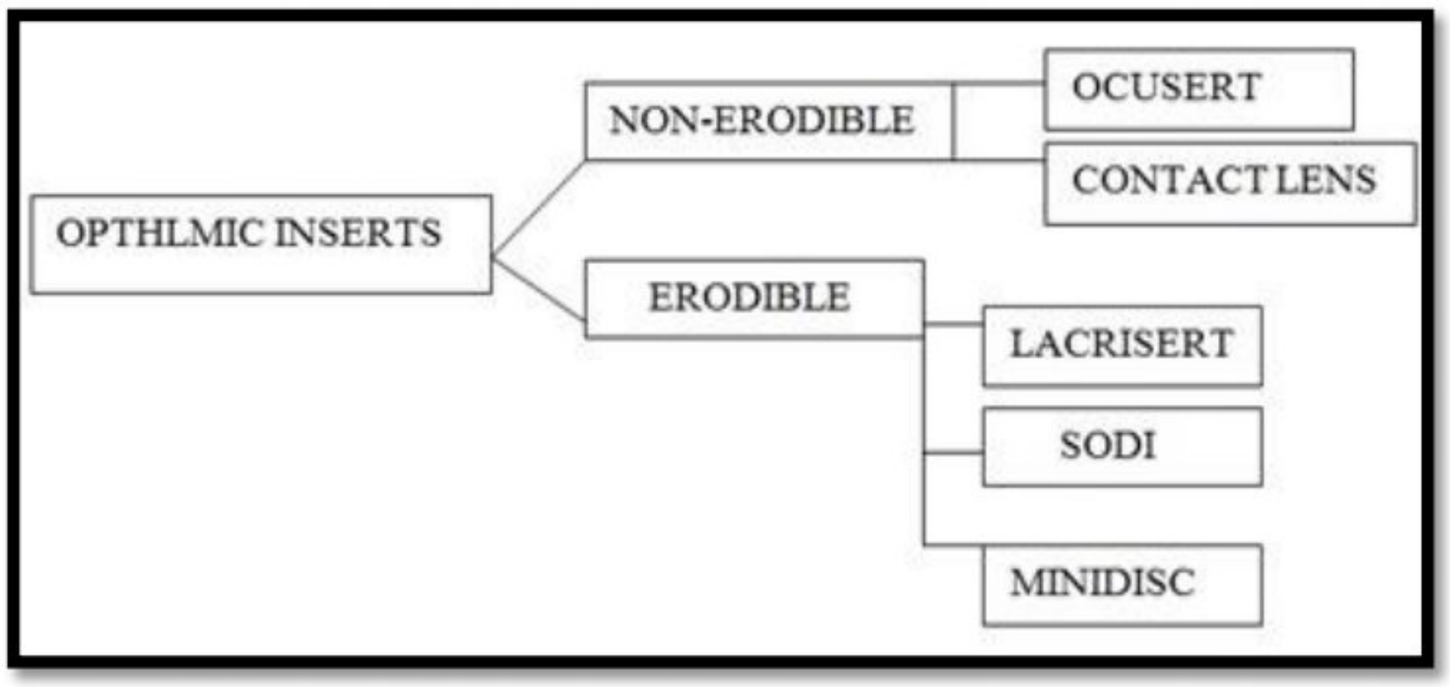
→ Characteristics of Ocular Inserts-

1) Biostable and biocompatible with tissue of eye.
2) Non-toxic and no-carcinogenic.
3) Retrievable and release at a constant rate.
4) Non-immunogenic and non-mutagenic
5) Good mechanical strength.
6) Free from drug leakage.
7) Easily sterilizable.
8) Non-interference with vision and oxygen permeability.



An Ocular Insert

➢ Classification of Ocular Inserts-



1) Non-Erodible-

(i) Contact lens:-

-Currently, approximately 100 million people are estimated to be wearing contact lenses, and the number is increasing exponentially.

-Ocular drug administration is particularly challenging and recent research has been directed towards the design of novel drug delivery systems capable of prolonging the permanence of the drug in the precorneal area and, thus, potentially increasing bioavailability and minimizing adverse effects.

-Conventional hydrogel soft contact lenses have the ability to absorb some drugs and release them into the post-lens lacrimal fluid, minimizing clearance and sorption through the conjunctiva.

-Their ability to be a drug reservoir strongly depends on the water content and thickness of the lens, the molecular weight of the drug, the concentration of the drug loading solution and the time the lens remains in it.

-However, the ability of contact lenses to load drugs and to control their release is in general inadequate and the following approaches,

i) covalent binding of the drug to the lens network via labile bonds
ii) inclusion of the drug in colloidal structures that are dispersed in the lens and are responsible for controlling drug release
iii) functionalization of the network with chemical groups that work as ion-exchange resins

Example:-**Bionite lens** (which was made from hydrophilic polymer:2-hydroxy ethyl methacrylate).

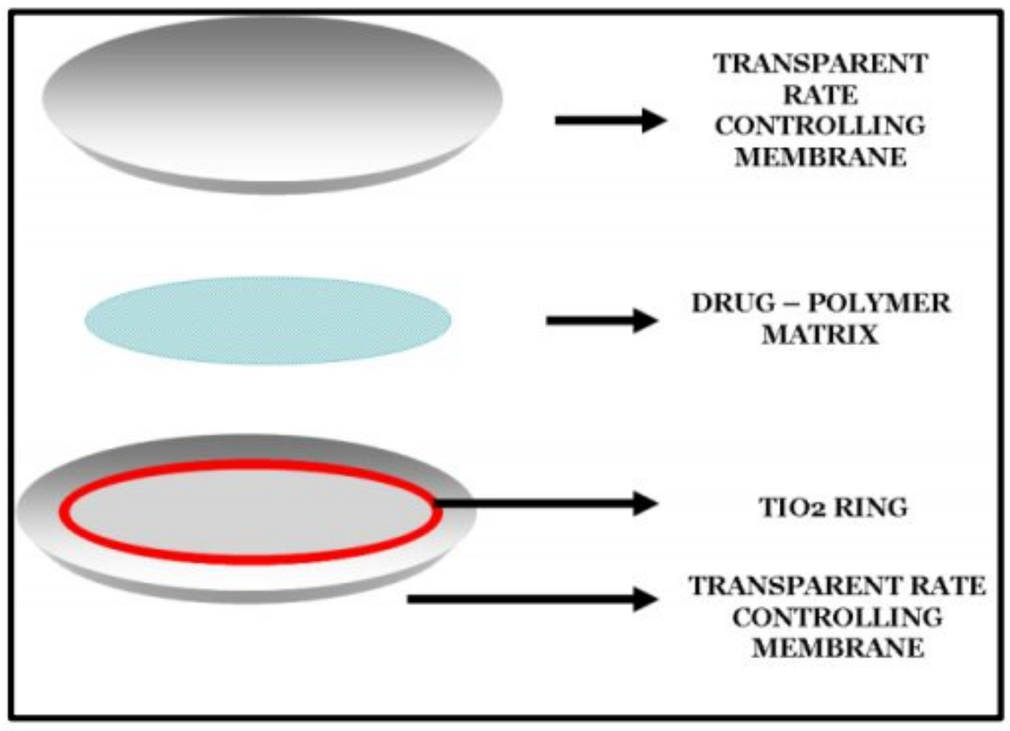
Contact Lens Insertion

(ii) Ocusert® (Osmotic Ocular Insert):-

-A truly continuous controlled release and Zero order kinetic fashion was achieved using ocusert.For hydrophilic Drugs.

-**Pilocarpine ocuserts** (by Alza corporation of California.)

-The system consists of a **Pilocarpine – alginate core (drug) and one osmotic agent in gel form sandwiched between two transparent, rate controlling ethylene-vinyl-acetate copolymer** membranes. Titanium dioxide encloses the drug reservoir circumferentially.



Parts of Ocusert

-The microporous membrane permit the tear fluid to penetrate into the drug reservoir (via osmosis) to dissolve drug from the complex.

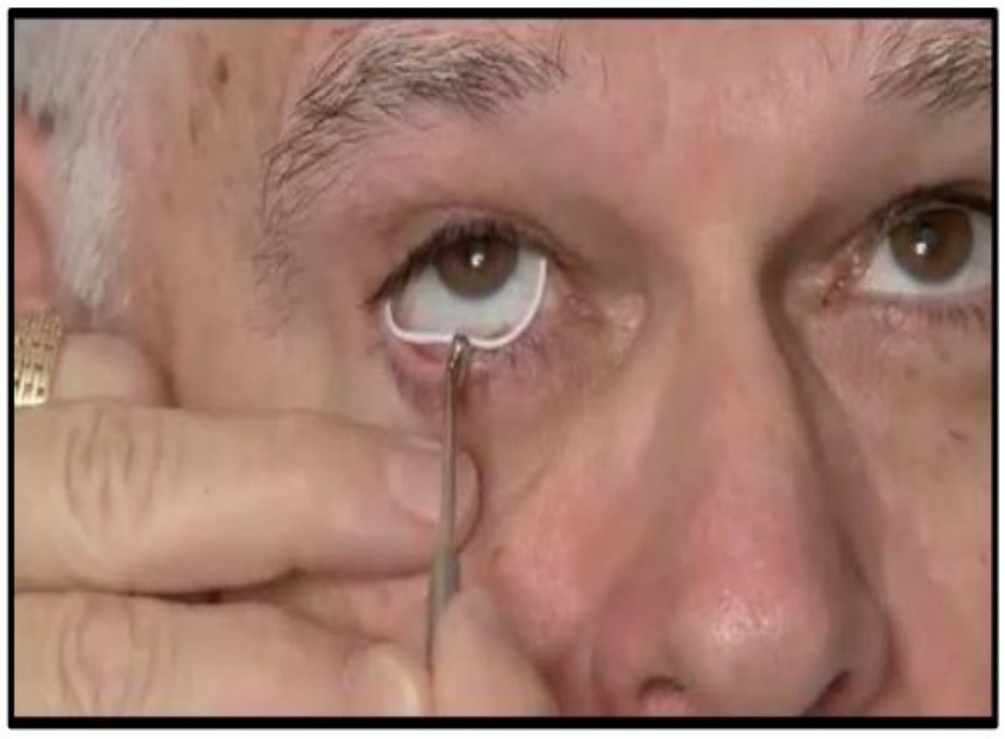
-When this is placed under the upper or lower eyelid, the pilocarpine molecules dissolved in the lacrimal fluid are released through the rate-controlling membranes at predefined rates for a week.

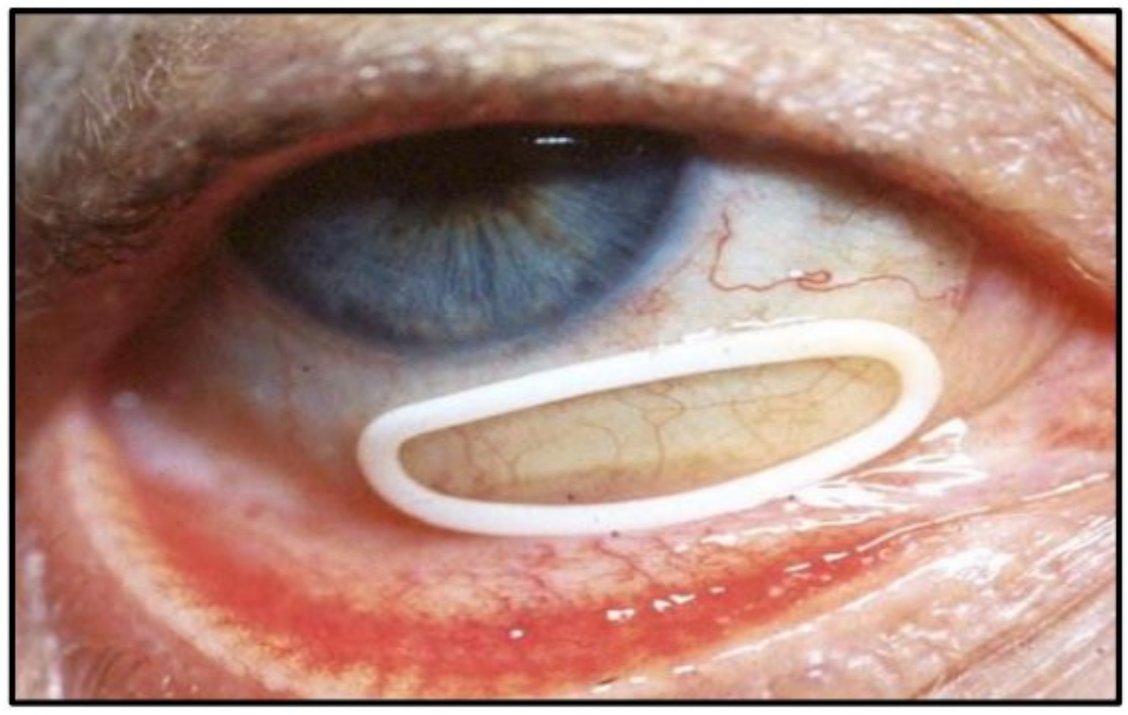
→ Two types of Ocuserts® are available:
1) Ocusert® pilo- 20
2) Ocusert® pilo- 40

This device is more popular among younger patients as compared to elder population who have difficulties in insertion, do not retain device well and often do not notice if it falls out.

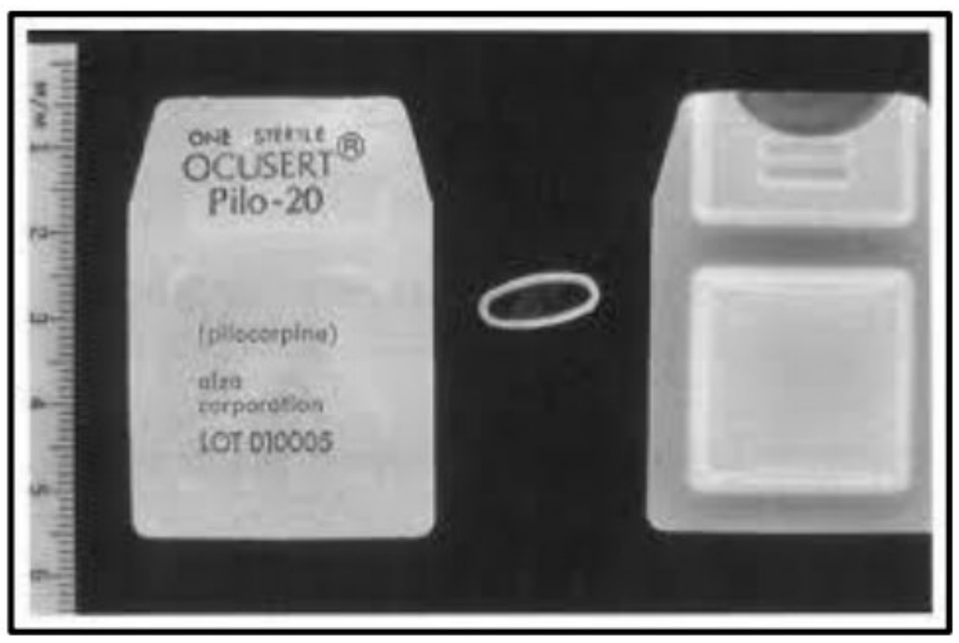
Clinical studies with the pilocarpine Ocusert® demonstrated that slow release of the drug can effectively control the increased intraocular pressure in glaucoma, with a minor incidence of side-effects, such as miosis, myopia, browache, etc.

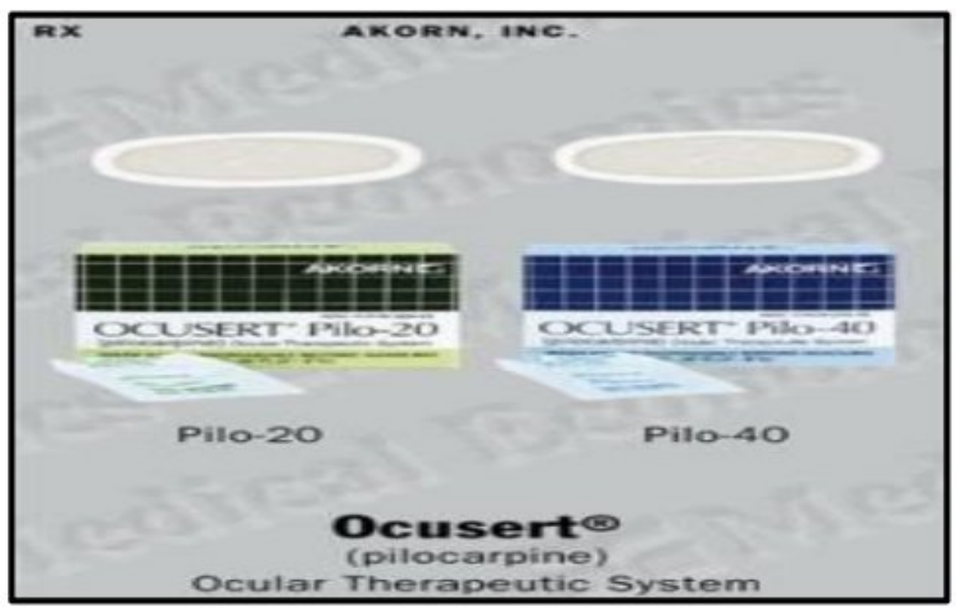
The major drawback for using this therapy is high cost of the device and as this system is not biodegradable, required to be removed and replaced with a fresh one adds to the cost of already expensive therapy.





Pictures showing insertion of Ocusert





Marketed Products of Ocuserts

2) Erodible-

(i) Lacrisert®

-It is **sterile rod shaped device made up of hydroxyl propyl cellulose without any preservative, i.e., used for the treatment of dry eye syndrome**.
-It weighs 5mg and measures 1.27 mm in diameter with a length of 3.5 mm.
-It is inserted into the inferior fornix where it imbibes water from conjunctive and forms a hydrophilic film which stabilizes the tear film and hydrates and lubricates the cornea.
-Daylong relief from dry eye syndrome has been reported from a single insert placed in the eye early in the morning. Learning

Advantages- Replacement of 4 times an hour regimen by once or twice daily regimen is the benefit achieved by this dosage forms.

Pictures showing Insertion of Lacrisert

Marketed Products of Lacriserts

(ii) Soluble Ophthalmic Drug Inserts (SODI):-

-A SODI is a soluble copolymer of acrylamide, N-vinyl pyrrolidone, and ethyl acrylate.
-It is in the form of sterile thin films or wafers of oval shape, weighing 15 to 16 mg.
-After introduction into the upper conjunctival sac, the SODI softens in 10 to 15 sec, conforming to the shape of the eyeball; in the next 10 to 15 min the film turns into a polymeric clot, which gradually dissolves within 1 hr, while releasing the drug.

--The major advantage of these dosage forms is the reduced role of the clinician, since the form is dissolved by total or partial solubilization and there is no need to surgically remove the insert once the drug has been released.

-But they have the drawback that they blur vision while the polymer is dissolving.

-Release of the drug from the SODI is proposed to occur in two stages:
1) hydration of the matrix by penetration of dissolution medium; and
2) diffusion of the medium deep into the matrix and back-diffusion of the dissolved active principle.

(iii) Ocular Therapeutic System (Minidisc):-

-It consists of countered disc with a convex front and concave back surface in contact with eyeball.
-It is like a miniature contact lens with diameter of 4 to 5 mm.
-The major component of it is Silicon based prepolymer.
-The OTS can be hydrophilic or hydrophobic to permit extended release of both water soluble and insoluble drugs.

→ SOME OTHER OCULAR INSERTS:-

VITRASERT®:-

-An ocular implant (Vitrasert) for delivering Ganciclovir (Anti-viral) for the treatment of cytomegalovirus (CMV) has also been developed.

-This implant delivers the drug directly to the retina for over 5 months.

-It is useful for patients with AIDS-associated cytomegalovirus retinitis.

-The pellet was then coated with ethylene vinyl acetate except on its top surface, and again coated with PVA.

The device lasted 4–5 months and all the treated eyes showed resolution of the CMV retinitis.

PROSERT®:-

-PROSERT® is an ophthalmic placebo insert which is insoluble, sterile and biocompatible. This system can contain one or several active components and allow its releasing in a programmed or controlled way.

-PROSERT® is constituted of a matrix able to contain one or several active components, surrounded by a **dyalisantic membrane** of a changeable thickness which allows the releasing controlled by the tears.

-The entirety has the shape of a **small oblong cylinder (reservoir) with rounded forms**.

-When PROSERT® is inserted in the conjonctival cul de sac, the tears enter into the device and saturate the mesh net intended to contain the active component.

-When the osmotic equilibrium is achieved, the active component is released through the dyalisantic membrane and then is spread in the conjonctival bag.

MYDRIASERT®:-

-Mydriasert® is an insoluble ophthalmic insert, gradually releasing two well-known active ingredients: phenylephrine and tropicamide.

- It is indicated in presurgical mydriasis.

-Mydriasert®, a new insoluble ocular insert, ensures a regular and slow *in vivo* release of the drug.

-This release allows the mydriasis to be obtained quickly and to be maintained during surgery.

➢ Evaluation of Ocular Inserts-

1) Uniformity of Thickness-

-Insert thickness should be measured at three different points using Micrometer screw gauge and mean film thickness should be noted.

2) Uniformity of Weight

3) Drug Content Uniformity

4) Percentage Moisture Absorption-

-Individual inserts were weighed and placed in a desiccator maintained at high relative humidity using an excess amount of salt in solution. After three days the inserts were taken out and reweighed. The percentage moisture absorption was calculated using the formula,

$$\% \text{ Moisture Absorption} = \frac{\text{Final Wt. - Initial Wt}}{\text{Initial Wt}} \times 100$$

5) Percentage Moisture Loss-

-Percentage moisture loss is carried out to check the integrity of the film at dry conditions.

-Inserts are weighed individually and kept in a desiccator containing anhydrous calcium chloride.

-After three days, inserts are taken out and reweighed.

-Percentage moisture loss is calculated using the formula,

$$\% \text{ Moisture Loss} = \frac{\text{Initial Wt- Final Wt.}}{\text{Initial Wt}} \times 100$$

6) In vitro Drug Release Study

7) Draize Eye Irritancy Test

-The Draize eye irritancy test is currently the most valuable and reliable method for evaluating hazard or safety of a substance introduced into or around the eye.

-Eye irritancy potential of a substance is determined on the basis of its ability to cause injury to the cornea, iris, and conjunctiva when a substance is applied to the eye.

-Testing is carried out on adult albino rabbits of either sex.

-All rabbits are maintained under 12 h light and dark cycles and are fed with green vegetables throughout the course of study. Food and water is allowed.

-A series of six rabbits are used for testing the eye irritation potential of the polymer. One placebo insert is made up of gelatin sandwiched using films of ethyl cellulose devoid of the drug placed into the cul-de-sac of the rabbit while other eye serve as a control.

Advantages of Ocular Inserts-

-Increasing contact time and thus improving bioavailability.
-Possibility of providing a prolong drug release and thus a better efficacy.
-Reduction of systemic side effects and thus reduced adverse effects.
-Reduction of the number of administrations and thus better patient compliance.
-Reduction in systemic absorption.
-Possibility of targeting inner ocular tissues through non-corneal routes.
-Possibility of incorporation of various novel chemicals and technological approaches of prodrug, mucoadhesives, permeation enhancers, microparticulate, salts acting as buffers.

Disadvantages of Ocular Inserts-

-A Capital disadvantage of ocular inserts recides in their 'solidity' , i.e., in the fact that they are felt by the patients (often oversensitive) as an external body in the eye.
-Their movement around the eyes, in rare instances, the simple removal is made more difficult by unwanted migration of the inserts to upper fornix.
-The occasional inadvertent loss during sleep or while rubbing the eyes.
-The interference with vision.
-Difficult placement of the ocular insert and removal.

Spend some more time to revise and understand the topic more precisely and accurately, Click on the following links-

» Youtube Links:-

1) https://www.youtube.com/watch?v=vnvpiPPGgUo&list=LL_dC_jgRPZYgbmFWVXQVf7w&index=6 (animation of Insertion of Lacrisert)

2) https://www.youtube.com/watch?v=svoPfk9uWgM&list=LL_dC_jgRPZYgbmFWVXQVf7w&index=7 (Insertion of an ocular insert- Real)

3) https://www.youtube.com/watch?v=hQNlPpu31kY&list=LL_dC_jgRPZYgbmFWVXQVf7w&index=8 (Insertion of an Ocusert- Real)

4) https://www.youtube.com/watch?v=HIYYy-hxXc0&t=1s (Lecture on ODDS)

"The Novel Drug Delivery Systems (NDDS) market is projected to witness substantial growth globally between 2020 and 2030 on account of increasing expenditure on healthcare which results in the demand for better and advanced healthcare services."

"TO LIVE A CREATIVE LIFE, WE MUST LOSE OUR FEAR OF BEING WRONG."