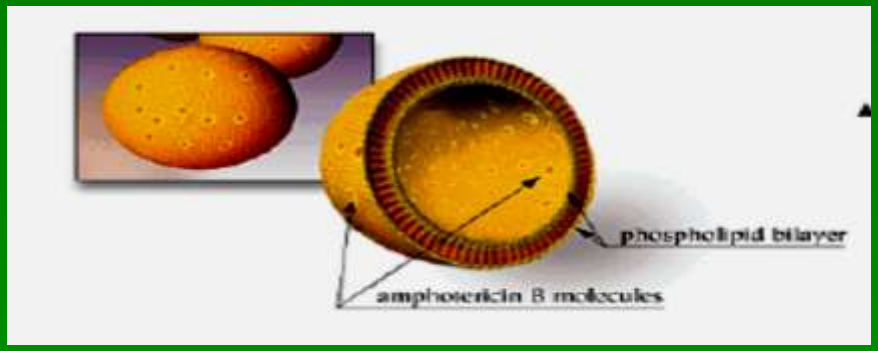
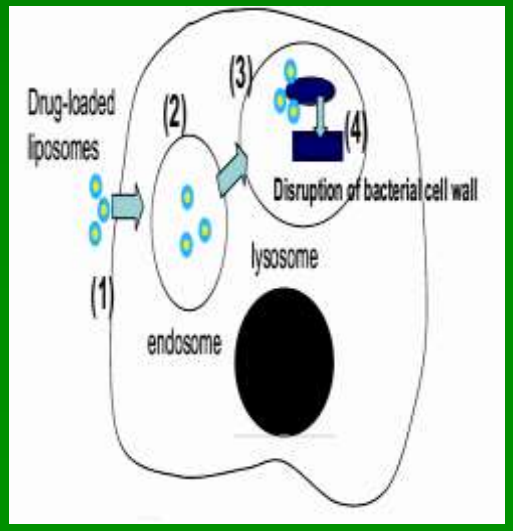
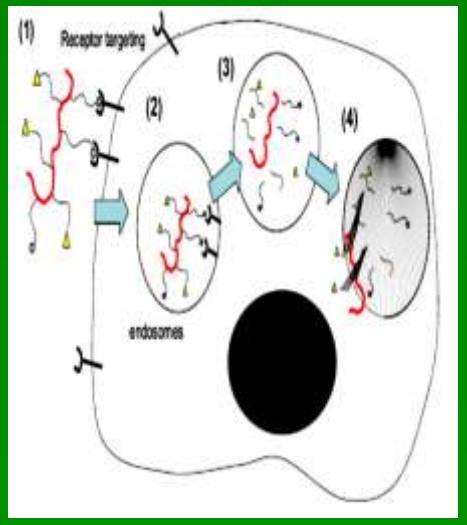


Sustained Release Dosage Forms



DR
Abbas Azzawi



The Sustained Release Concept

- **Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot, and repository (storage area) dosage forms**

  are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing therapeutic agents over an extended period of time after administration of a single dose.

- Products of this type have been formulated for oral, injectable, and topical use, and include inserts for placement in body cavities as well.

- In the case of injectable dosage forms, the prolonged period may vary from days to months.

- In the case of orally administered forms, the period is measured in hours and critically depends on the residence time of the dosage form in the gastrointestinal (GI) tract.

Advantages of sustained release system

- **Avoid problems of drugs have a narrow therapeutic index (small difference between toxic level and therapeutic level)**
  - **Requires multiple injections**
  - **Poor patient compliance**
  - **Increased incidence of infection and hemorrhages**

- **Avoid danger of systemic toxicity with more potent drugs.**

- **Improves availability of drugs with short half lives *in vivo***
  - **Some peptides have half-lives of a few minutes or even seconds**

- Targeted delivery is possible

- The variable drug-blood level of multiple dosing of conventional dosage forms is reduced, because a more even drug-blood level is maintained. So improve efficacy of the treatment which result in :
  - cure or control condition more promptly
  - Improve bioavailability

- The total amount of drug administered can be reduced, thus maximizing availability with a minimum dose.
  - Minimize or eliminate local side effect
  - Minimize or eliminate systematic side effect
  - Minimize drug accumulation
  - Economy for the patient

The disadvantages of sustained release formulations:

1. Administration of sustained release medication does not permit the prompt termination of therapy.
2. The physician has less flexibility in adjusting dosage regimens. This is fixed by the dosage form design.
3. Not all drugs are suitable candidates for formulation as prolonged action medication.

4. Sustained release forms are designed for the normal population, i.e., on the basis of average drug biologic half-lives. Consequently, disease states that alter drug disposition as significant patient variation, are not accommodated.

5. Economic factors must also be assessed, since more costly processes and equipment are involved in manufacturing many sustained release forms.

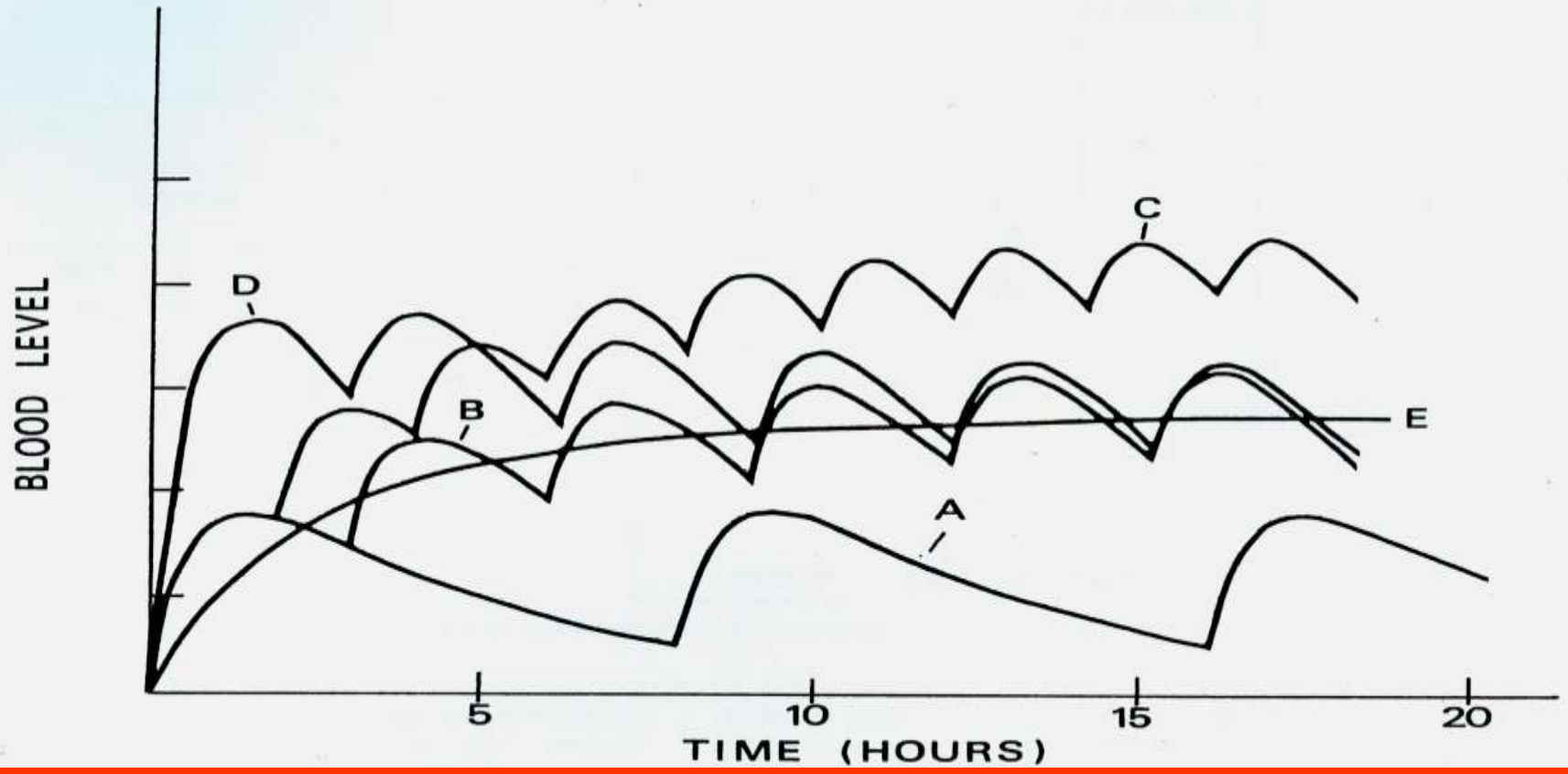
Characteristics of Drugs suitable for oral Sustained Release Forms

Characteristics		Drugs
Not effectively absorbed in the lower intestine		Riboflavin, ferrous salts
Absorbed and excreted rapidly; short biologic halflives (<1 hr)		Penicillin G, furosemide
Long biologic half-lives (> 12 hr)		Diazepam, phenytoin
Large doses required (>1 g)		Sulfonamides
Cumulative action and undesirable side effects; drugs with low therapeutic index.		Phenobarbital, digitoxin
Precise dosage titrated to individual is required		Anticoagulants, cardiac glycosides
No clear advantage for sustained release formulation		Griseofulvin

Design (Theory)

- The basic goal of therapy with any drugs is to achieve a steady-state blood or tissue level that is therapeutically effective and nontoxic for an extended period of time.
- This is usually accomplished by maximizing drug availability to attain a maximum rate and extent of drug absorption or to controlling bioavailability to reduce drug absorption rates.

characteristic of multiple dosing therapy of immediate release forms (conventional drug therapy).



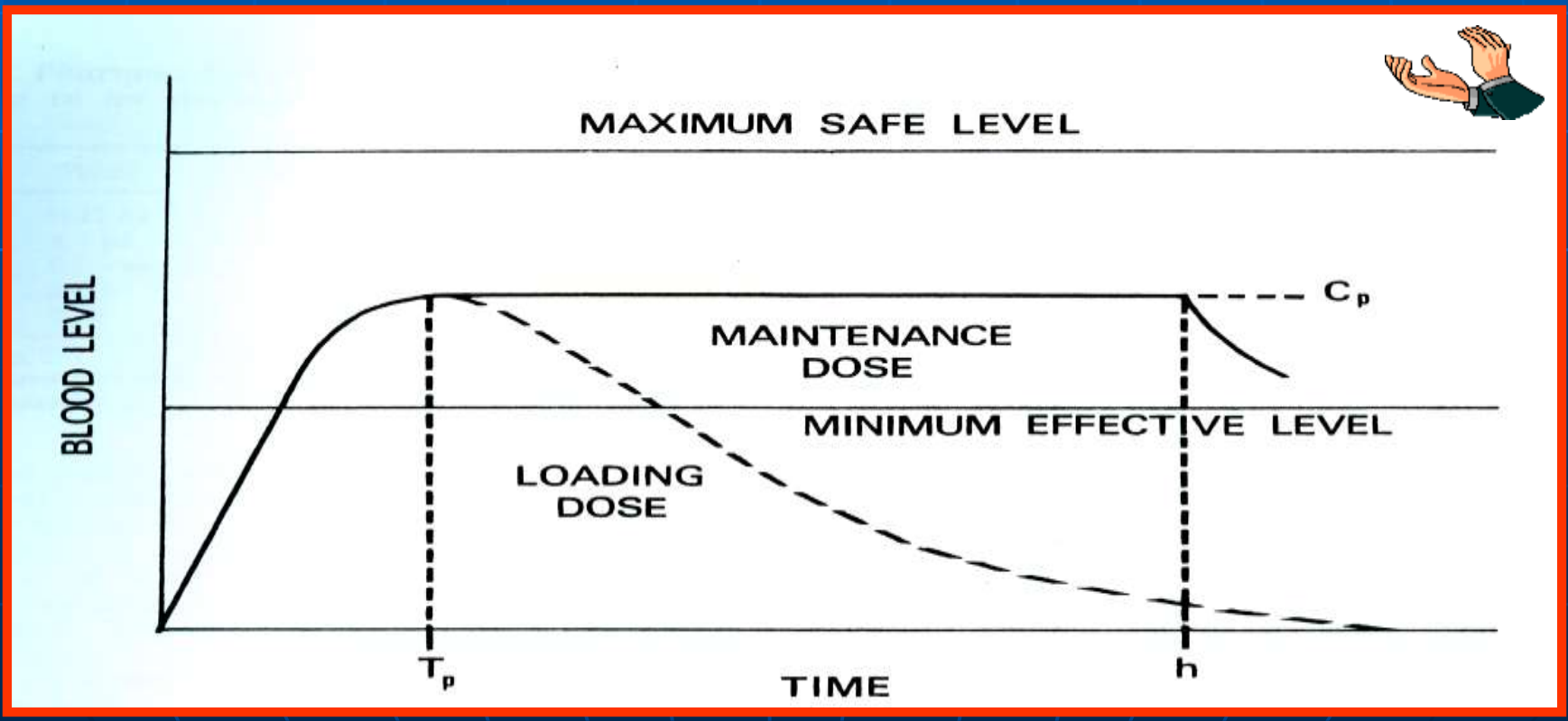
Multiple patterns profiles after non-sustained peroral administration of equal doses of a drug using different dosage intervals are: every 8 hours (A), every 3 hours (B), and every 2 hours (C) every 3 hr (loading dose is twice the maintenance dose) (D) Constant rate intravenous infusion (E).

- Selection of the proper dose and dosage interval is a prerequisite to obtaining a blood - drug level pattern that will remain in the therapeutic range.

- Drug must be provided by the dosage form at a rate that keep drug concentration constant at the absorption site (To obtain a constant drug level, the rate of drug absorption must be equal to its rate of elimination)

- Drug-blood level fluctuation can be avoided either by:
- administration of drugs repetitively using constant dose interval (A,B,C) (Non acceptable Multiple-dose therapy).
- administration of drug through constant-rate intravenous infusion (E). (Non acceptable)

- The objective in formulating a sustained release dosage form is to be able to provide a similar blood level pattern for up to 12 hours after administration of the drug.
- body drug level - time profile characterizes an ideal peroral sustained release dosage form after a single administration.



Terms used to describe Drug Release

1- Delayed release (DR):

Indicates that the drug is not being released immediately following administration but at later time,

e.g, enteric-coated tablets, pulsatile-release capsules.

2- Repeated action (RA):

Indicates that individual dose is released moderately soon after administration, and second or third doses are subsequently released at regular intervals thus provide frequent drug release for drugs having low dosage with short half lives.

3- Extended Release (XR):

Dosage forms release slowly, so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time.

4- Modified Release (MR):

Modified Release Dosage forms are those whose drug release characteristics of time and / or location are chosen to accomplish therapeutic objectives not offered by conventional forms.

5- Controlled Release (CR):

Systems provide some actual therapeutic control, whether temporal or prolonged.

6- Sustained Release (SR):

Systems provide medication over an extended period. With the goal of maintaining therapeutic blood levels.

SUSTAINED RELEASED

Formulation

Components of a sustained- release delivery systems

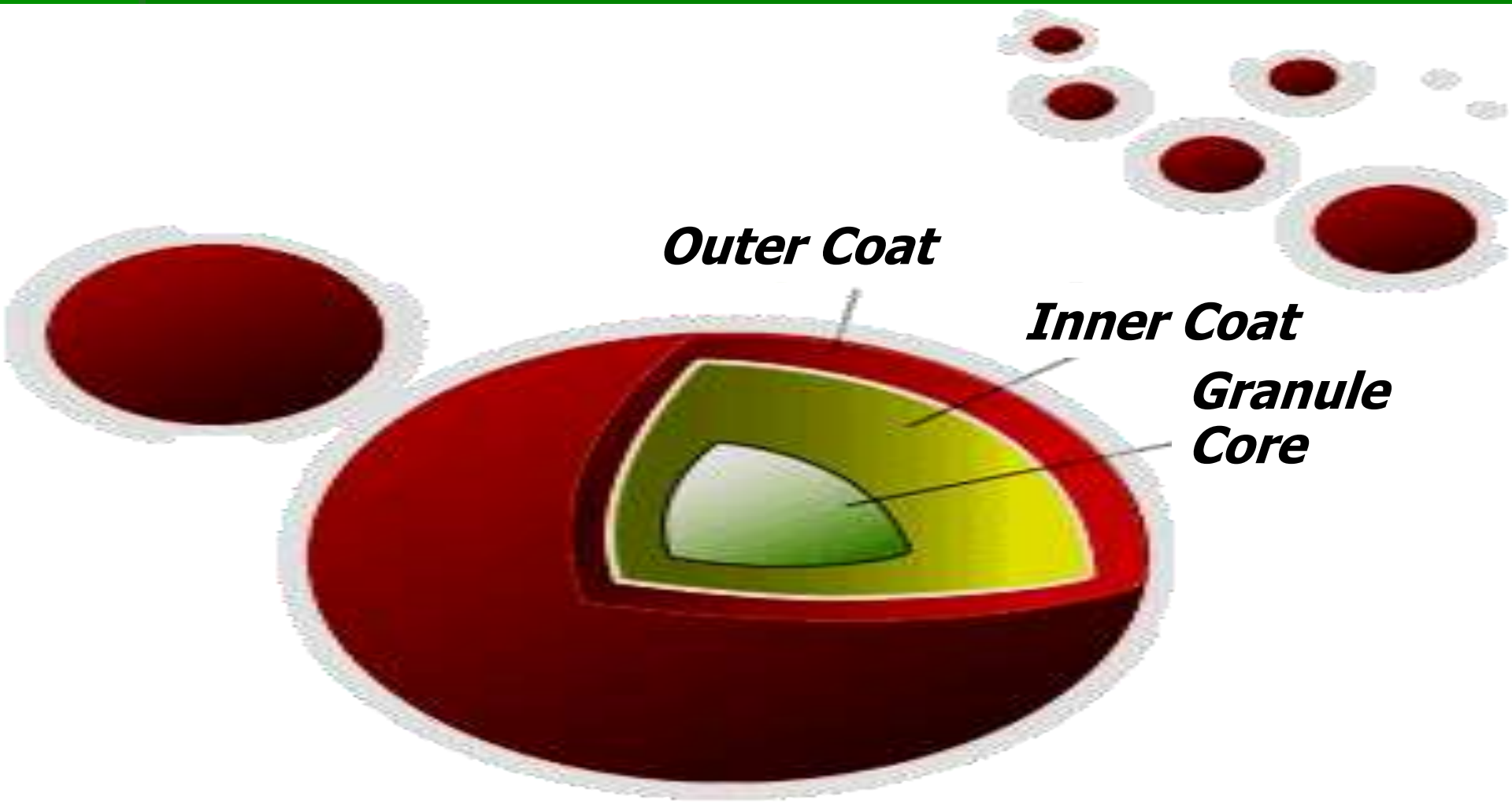
Include:

- **Active drug**
- **Release-controlling agents (s):**
  - **Membrane formers**
  - **Matrix formers**

SUSTAINED RELEASED Membrane Systems

Coated granules

- Coated granules produce a blood level profile similar to that obtained with multiple dosing.

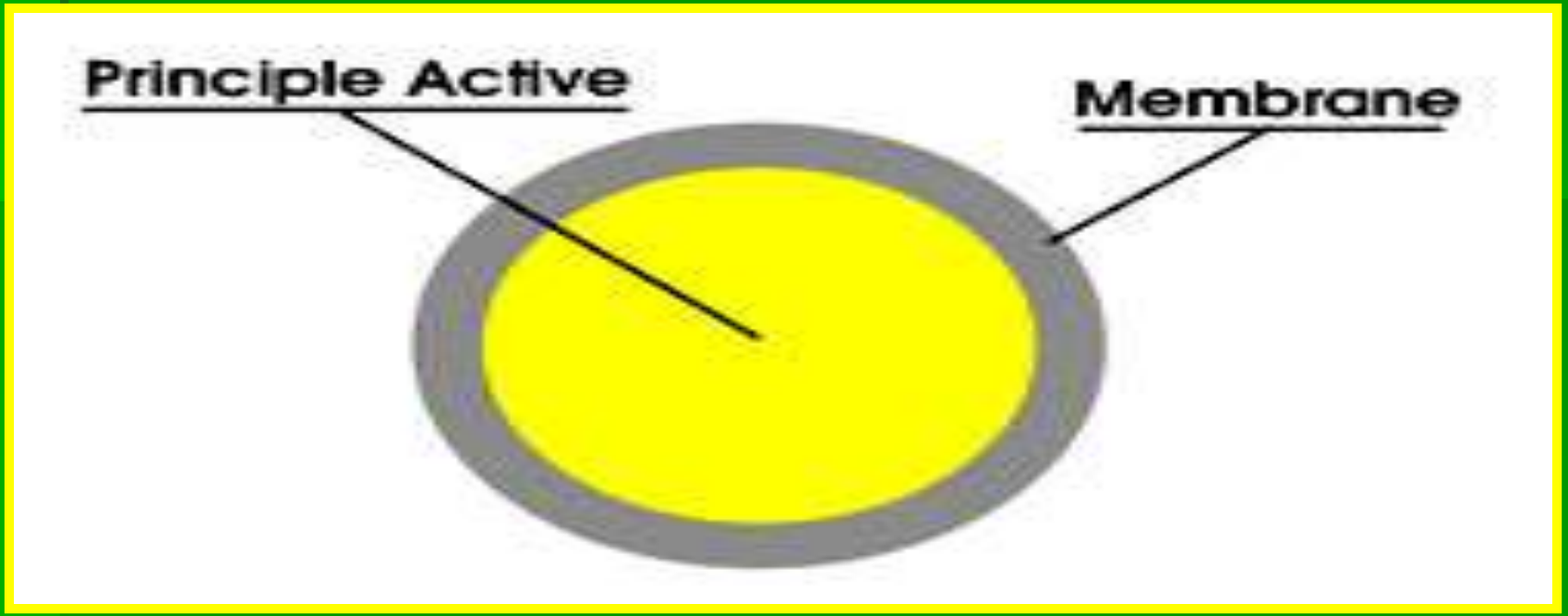


- Some of the granules are left uncoated to Provide immediate release of the drug.

- Coats of a lipid material (e.g., **beeswax**) or a cellulosic material (e.g., **ethylcellulose**) are applied to the remaining granules.
- Some granules receive few coats, and some receive many.
- The various coating thicknesses produce a sustained-release effect.

Microencapsulation

- Microencapsulation is a process by which solids, liquids, or gases are encased in microscopic capsules.
- Thin coatings of a "wall" material are formed around the substance to be encapsulated.
- An example is Bayer timed-release aspirin.



Film-forming substances used as coating material include Natural and synthetic polymers

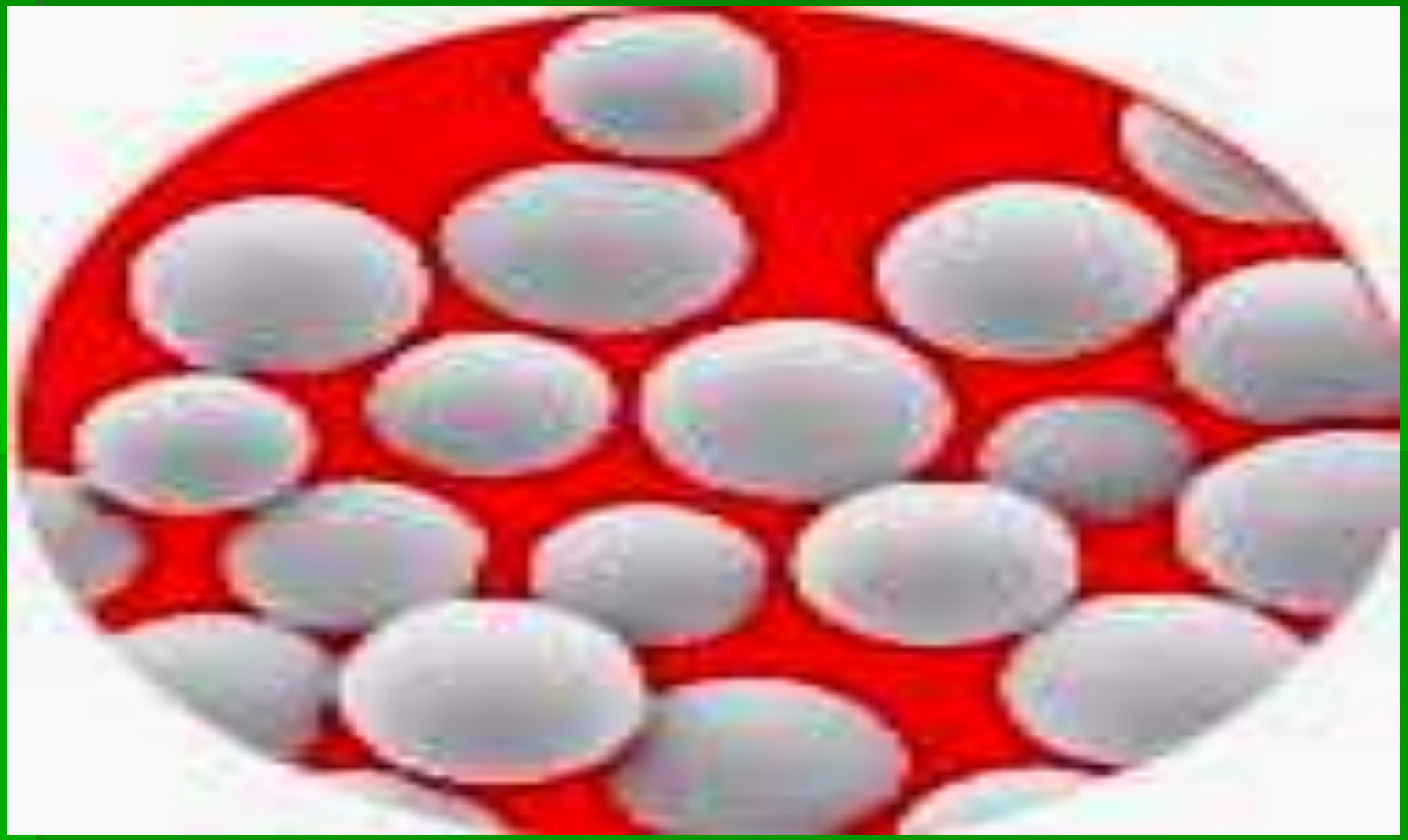
Hydrophilic Polymers

- Alginates
- Carbopol
- Gelatin
- Hydroxypropylcellulose
- Methyl and ethyl cellulose
- Starches
- Cellulose acetate phthalate,.

Hydrophobic Polymers

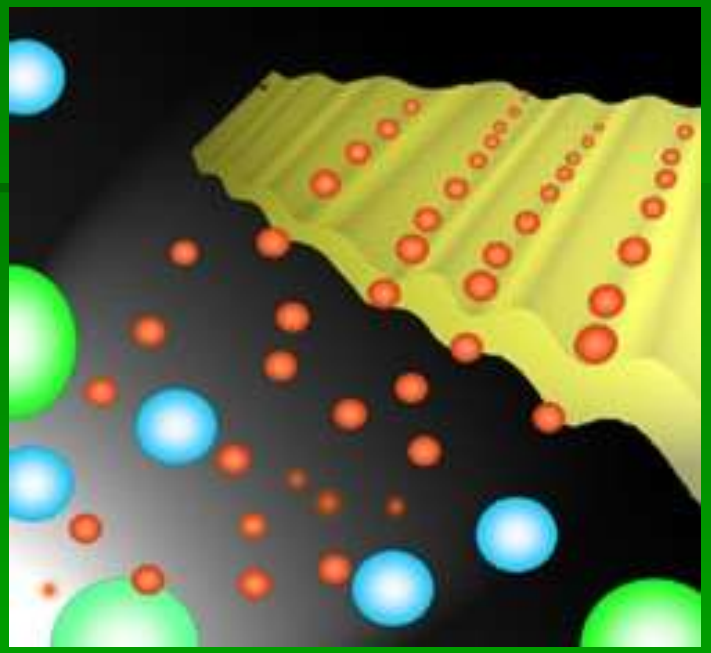
- Carnauba wax
- Cetyl alcohol
- Hydrogenated vegetable oils
- Microcrystalline waxes
- Mono-and triglycerides
- PEG monostearate

- The thickness of the wall can vary from 1-200 μm, depending on the amount of coating material used (3%-30% of total weight).



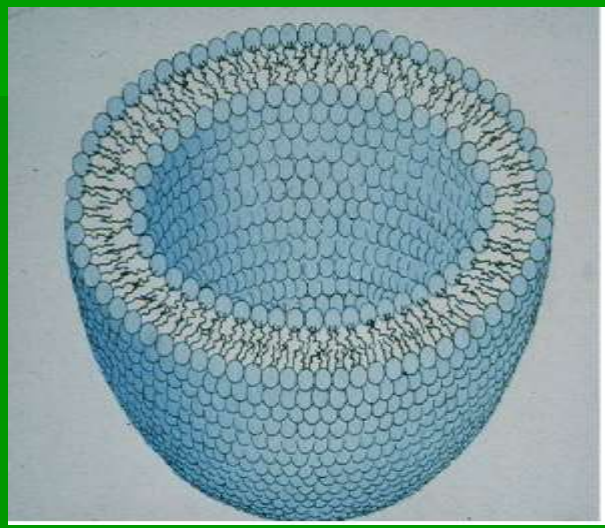
Nanoparticles

Nanoparticles are drug delivery systems with many applications, including anti-tumour therapy, gene therapy.



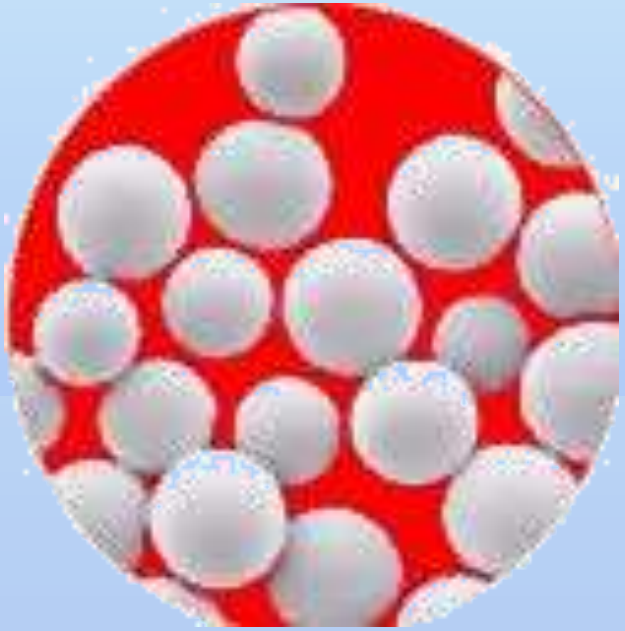
The main goals are to improve drug stability in the biological environment, to mediate the bio-distribution of active compounds, improve drug loading, targeting, transport, release, and interaction with biological barriers.

- Nanoparticles of size **10-200 nm** are in the solid state and are either amorphous or crystalline.
- They are able to adsorb and/or encapsulate a drug, thus protecting it against **chemical and enzymatic degradation**.
- Nanocapsules are **vesicular systems** in which the drug is confined to a cavity surrounded by a unique polymer membrane.
- **Liposomes** are a form of nanoparticles that consist of phospholipid bilayers.



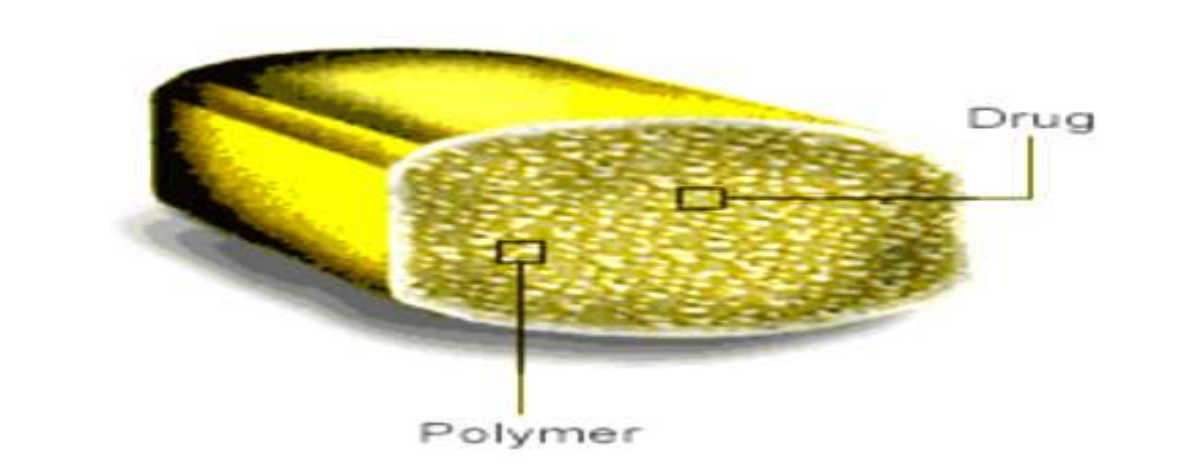
SUSTAINED RELEASED

Matrix Systems



Matrix Systems

- It involves the direct compression of blends of drug and retardant matrix material in a into tablets .
- Drug bioavailability is dependent on drug : polymer ratio
- The primary dose, or the portion of the drug to be released immediately, is placed on the tablet as a layer, or coat. The rest of the dose is released slowly from the matrix.



Matrix materials used are:

- **Insoluble plastics** (e.g., polyethylene, polyvinyl acetate, polymethacrylate);
- **Hydrophilic polymers** (e.g., methylcellulose, hydroxypropyl methylcellulose);
- **Fatty compounds**

(e.g., various waxes, glyceryl tristearate).

Diffusion

In diffusion controlled delivery systems, rate control is obtained by the penetration of fluids into the system.

Two general types of these systems include:

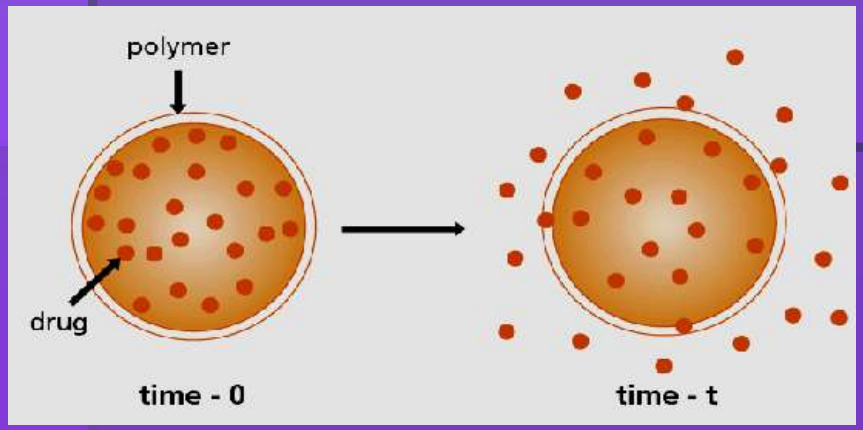
Swelling controlled release systems

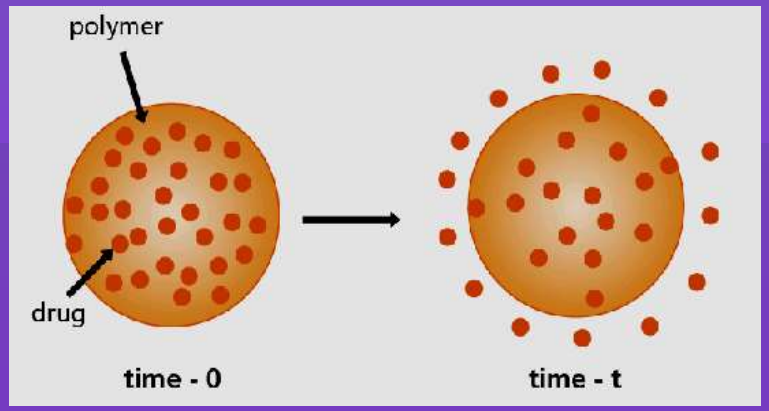
Osmotically controlled delivery systems .

Swelling Controlled Systems:

Swelling controlled release systems when placed in the body absorb body fluids and swell.

Swelling increases the aqueous solvent content within the formulation and the polymer mesh size, enabling the soluble drug to diffuse through the swollen network into the external environment.





Swelling Reservoir and Matrix Systems

- Most of the materials used in swelling controlled release systems that will swell without dissolving, when exposed to water or other biological fluids as hydrogels.

- Thus the release of active agent from the system is a function of rate of uptake of water

- As the release continues, its rate normally decreases with this type of system, since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release

Erosion

In this process, the release of drug is maintained by gradual erosion of the surface and continuous exposure of fresh surface from which drug is dissolved.