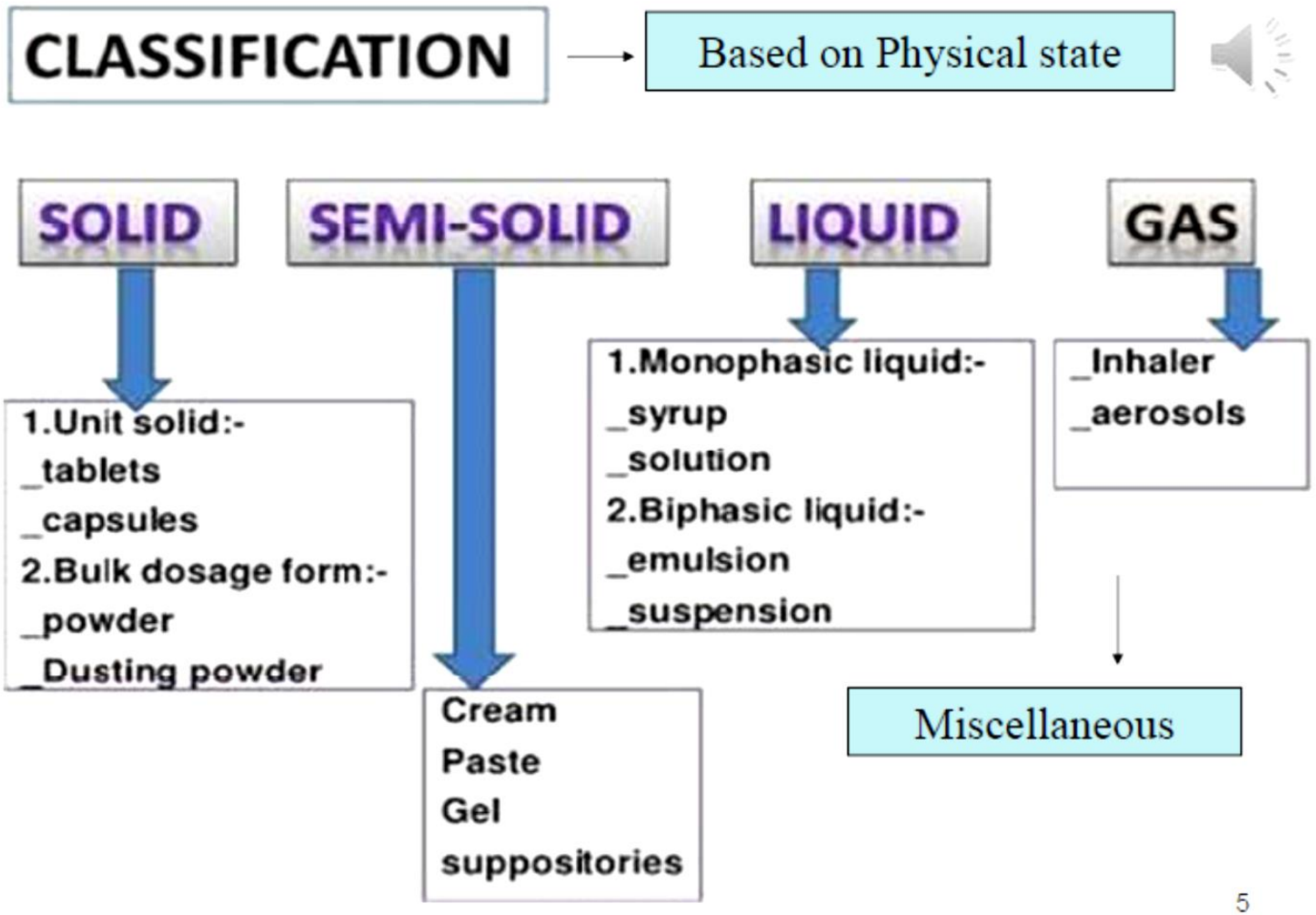
SUMPh Nicolae Testemitanu, Drug technology department

MODIFIED-RELEASE DOSAGE FORMS

Lecture 8

Ciobanu Cristina, Dr., Associat professor

CONVENTIONAL DOSAGE FORMS
1st generation of pharmaceutical forms



DISADVANTAGES OF CONVENTIONAL DOSAGE FORMS

- 1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life forwhich frequent administration is necessary.
- 2. The unavoidable fluctuations of drug concentra-tion may lead to under medication or over medica-tion.
- 3. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
- 4. The fluctuations in drug levels may lead to pre-cipitation of adverse effects especially of a drug with small Therapeutic Index whenever over medication occur

MODIFIED-RELEASE DOSAGE FORMS

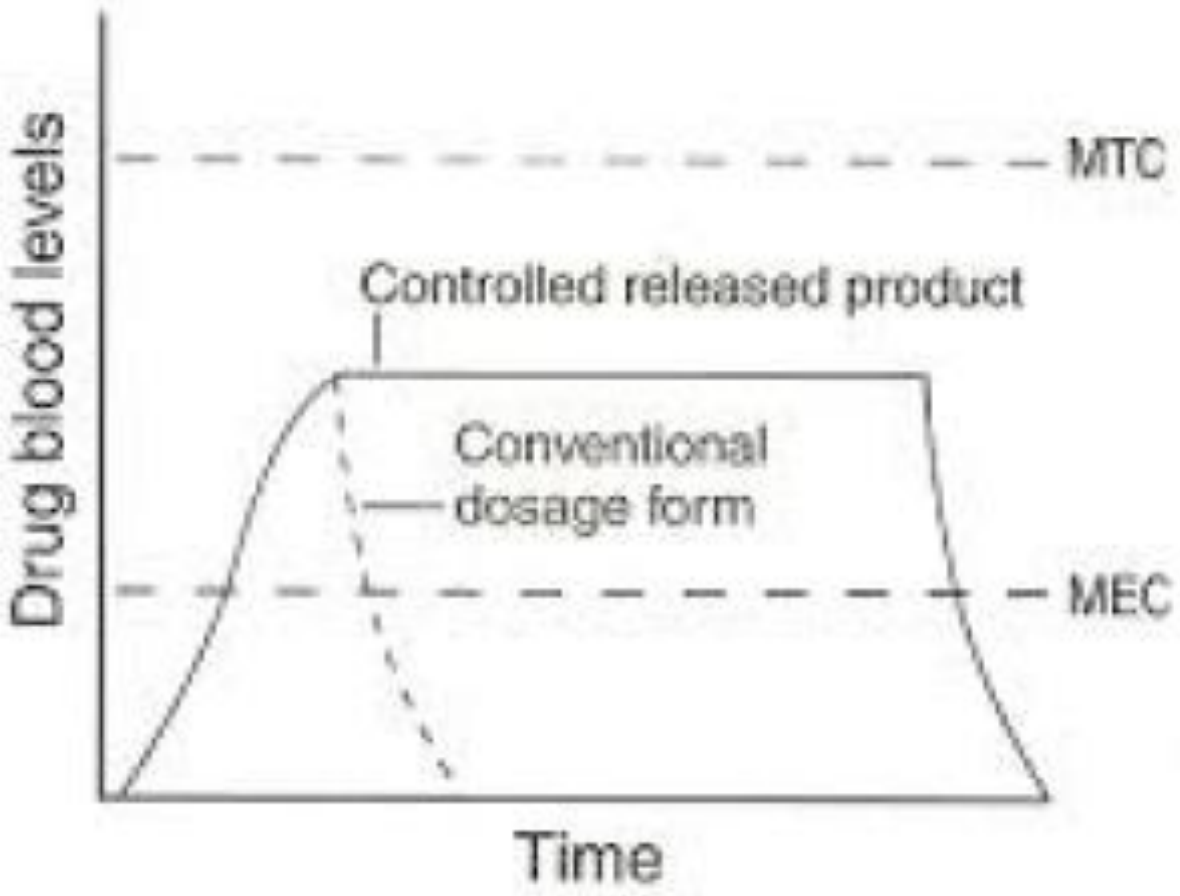
- **IMMEDIATE-RELEASE** - *Orally disintegrating tablets* (ODT). ODT have been developed to disintegrate rapidly in the saliva after oral administration.
- **SUSTAINED-RELEASE** - the drug is released slowly at a rate governed by the delivery system.
- **CONTROLLED-RELEASE** - the drug is released at a constant rate and plasma concentrations after administration do not vary with time.
- **DELAYED-RELEASE** - the drug is released at a time other than immediately after administration i.e. the site of release is controlled.

Any modified release dosage form is characterized by two things:-

A) First order kinetics:- The drug is not coated or not in a matrix system, its just simple dosage that releases drug into the body by first order kinetics. This helps in achieving instant onset of action needed to reach the drug for its minimum effective concentration

B) Zero order release :- The drug is either coated in membrane or placed in a matrix system. The zero order release ensures constant rate of drug release and thus prolonging the duration of action in the body.

- There are two specific paterns available for modified release dosage forms:–
- A) Constant pa埆ern :- Once the drug starts releasing the drug by zero order kinetics, the concentration in the plasma remains constant and remains above minimum effective concentration(MEC) but below maximum toxic concentration(MTC) for plasma drug concentration v/s time profile. This will ensure prolonged duration of drug therapy.
- B) Reducing pa埆ern:- Once the drug release starts by zero order kinetics, over the time, the concentration of drug in plasma starts reducing but it remains above MEC and below MTC.



Hypothetical drug blood level-time curves for a conventional solid dosage form and a controlled release product.

CHARACTERISTICS THAT MAKE DRUGS SUITABLE FOR SUSTAINED RELEASE MATRIX

- **BIOLOGICAL HALF-LIFE**
- The active therapeutic drugs with short half lives are excellent candidates for sustained release formulations since this can reduce dosing frequency. In general, drugs with half lives shorter than 2 hours are poor candidates for sustained release formulations.
- Drugs with long half lives, more tha n 8 hours, are also generally not used in sustained release formulations, since there effect is already sustained
-

HALF-LIFE is the length of **time** required for the concentration of a particular substance (a **drug**) to decrease to **half** of its starting dose in the body due to elimination.

- **ABSORPTION**
- The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. Drugs that demonstrate true lower absorption rate constants will be poor candidates for sustaining the system.
- **DISTRIBUTION**
- Drugs with a high apparent volume of distribution, which influence the rate of elimination of the drug, are poor candidate for oral sustained release formulations e.g. Chloroquine.
- **METABOLISM**
- Metabolism of drugs before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during a specific period, allowing a complete conversion of the drug to its metabolites.

Challenges for formation of modified release systems:-

- **Drug solubility and permeability:-** class IV drugs having low water solubility and low permeability drugs cannot be used as modified release systems. It's always advised to use solubility enhancers and permeability enhancers in given dosage form.
- **Concentration of polymer:-** When polymers are used for forming membrane controlling devices, their concentration will decide the release rate of drug into blood stream. Too much concentration of polymer around the dosage form may not cause release of the drug since drug may become stagnant in polymeric membrane.
- **Integrity of the membrane:-** If the membrane integrity is not proper, there are chances of dose dumping. Integrity of depends upon the type of polymer used for the coating.For optimum integrity and concentration of polymer, it is always to advised to use the Design of Experiment tool to get productive results.

IVIVC correlation:- For any dosage form obtaining Invitro-invivo correlations are major concern. The same case is for modified release systems. One possible solution is to use simulated models for obtaining in predicting the results.

Therapeutic index/Therapeutic window:- Smaller the therapeutic index or therapeutic window, potent is the concentration for API. Any slight deviation from safety margin will lead to toxicity and slight deviation from MEC will lead to undermedication. Hence the drugs having higher therapeutic index are considered for modified release systems. Ideal therapeutic index for API should be greater than 10 to form modified release systems.

Dosage strength:- Larger dosage strength should be avoided since increasing the dosage strength increases the size of the dosage form and thus patient compliance is reduced.

Types of MODIFIED-RELEASE DOSAGE FORMS

- ☐ Dissolution Granules
- ☐ Diffusion Granules
- ☐ Enteric Coated Granules
- ☐ Reservoir
- ☐ Matrix
  - o Inert
  - o Erodible
  - o Swellable
  - o Hydrophilic
- ☐ Osmotic Pump
- ☐ Repeat Action
- ☐ Altered Density
- ☐ Hydrodynamically Balanced
- ☐ SODAS
- ☐ Microparticles
- ☐ Meter Release
- ☐ Ion Exchange Resins

MR format	Objective	Formulation technology
Gastro-retention	• Delay gastric emptying from the stomach to deliver the drug over a prolonged timeframe to the upper GI tract when an absorption window exists.	Swellable, raft, floating, and bioadhesive systems
Gastric bypass	• Prevent release of the drug in the stomach and/or upper gastrointestinal tract • Overcome gastric irritation or instability of the drug	Enteric coated tablets or capsules
Sustained or extended release	• Extend the *in vivo* release profile of the drug or enable 1-2x daily dosing	Matrix tablets, coated tablets, or multiparticulates
Delayed release	• Release the drug at or near the intended site of absorption or action such as upper small intestine or colon • Deliver time, pH, and/or microbially triggered release	Tablets, capsules, or multiparticulates
Biphasic release	• Eliminate the need for repeat dosing • Provide rapid therapeutic effect from an immediate release layer and extended dosing via a sustained release layer	Bilayer tablets or multiparticulates
Pulsatile release	• Drug release as a pulse after a predetermined lag time — designed according to the body's circadian rhythm • Beneficial release mechanisms for time-dependent dosing or for drugs that undergo first-pass metabolism	Bilayer tablets or multiparticulates

A selection of MR formats, their behaviors, and the technologies they represent.

MATRIX TABLET

- Matrix tablets can be defined as the oral solid dosage forms in which **the drug is homogeneously dispersed or dissolved** within the hydrophilic or hydrophobic polymeric matrices.
- The preparation of sustained release matrix tablets involves the direct compression of blend powder mixture of drug, retardant material and other additives to formulate a tablet in which the drug is dispersed in a matrix of the retardant. Alternatively, drug, retardant blend and other additives may be granulated prior to compression.
- These systems release the drug in a continuous manner by dissolution controlled and diffusion controlled mechanisms

Advantages of matrix systems

- Easy to manufacture.
- Versatile, effective, low cost.
- Can be made to release high molecular weight compounds.
- Accidental leakage of the total drug component is less likely to occur.

Hydrophilic matrix tablet

- Hydrophilic matrix may be formulated by a wet granulation of the drug and hydrophilic matrix materials or by direct compression of the blended mixture of active ingredient and certain hydrophilic carriers.
- The hydrophilic matrixes offer several advantages, such as ease of manufacture, cost effectiveness, uniformity of matrix tablets and broad regulatory acceptance.
- When immersed in fluid the drug release is controlled by a gel diffusion barrier that is formed and tablet erosion.

(

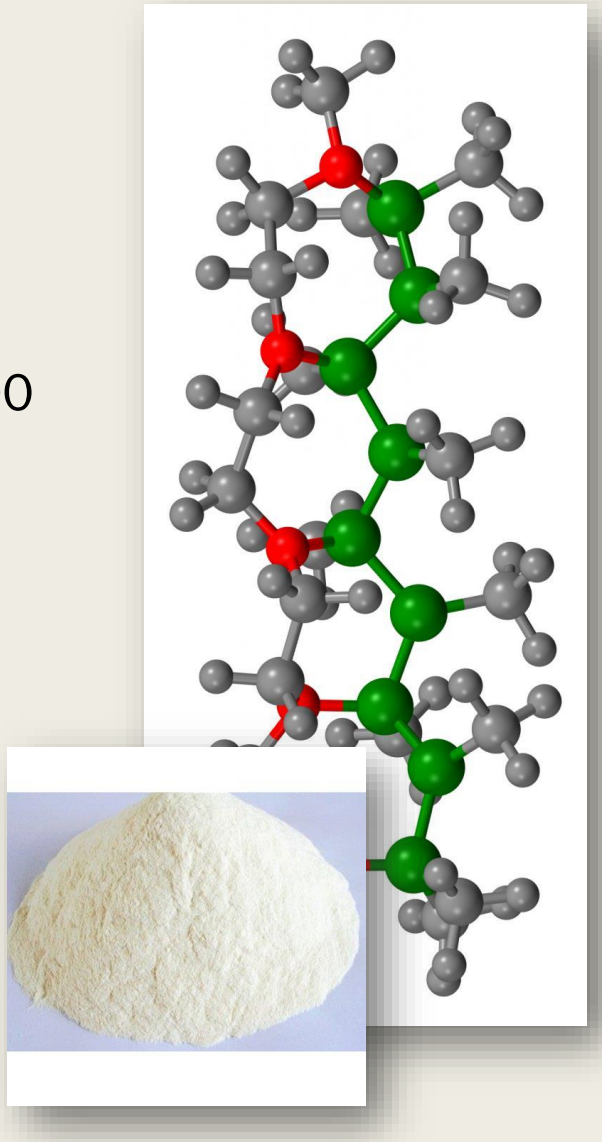
The polymers used in the preparation of hydrophilic matrices.

POLYMER Cellulose derivatives Hydroxypropylmethylcellulose (HPMC)25,100,4000 and 15000 cps, Hydroxyethylcellulose(HEC), Sodium carboxymethyl cellulose and Methylcellulose 400 and 4000 cps.

NATURAL OR SEMISYNTHETIC POLYMERS Agar-agar, Carob Gum, Alginates, Molasses, Polysaccharides of galactose and mannose, Chitosan and Modified starches.

POLYMERS OF ACRYLIC ACID Carbopol 934

OTHER HYDROPHILIC MATERIALS Alginic acid, gelatin and natural gums

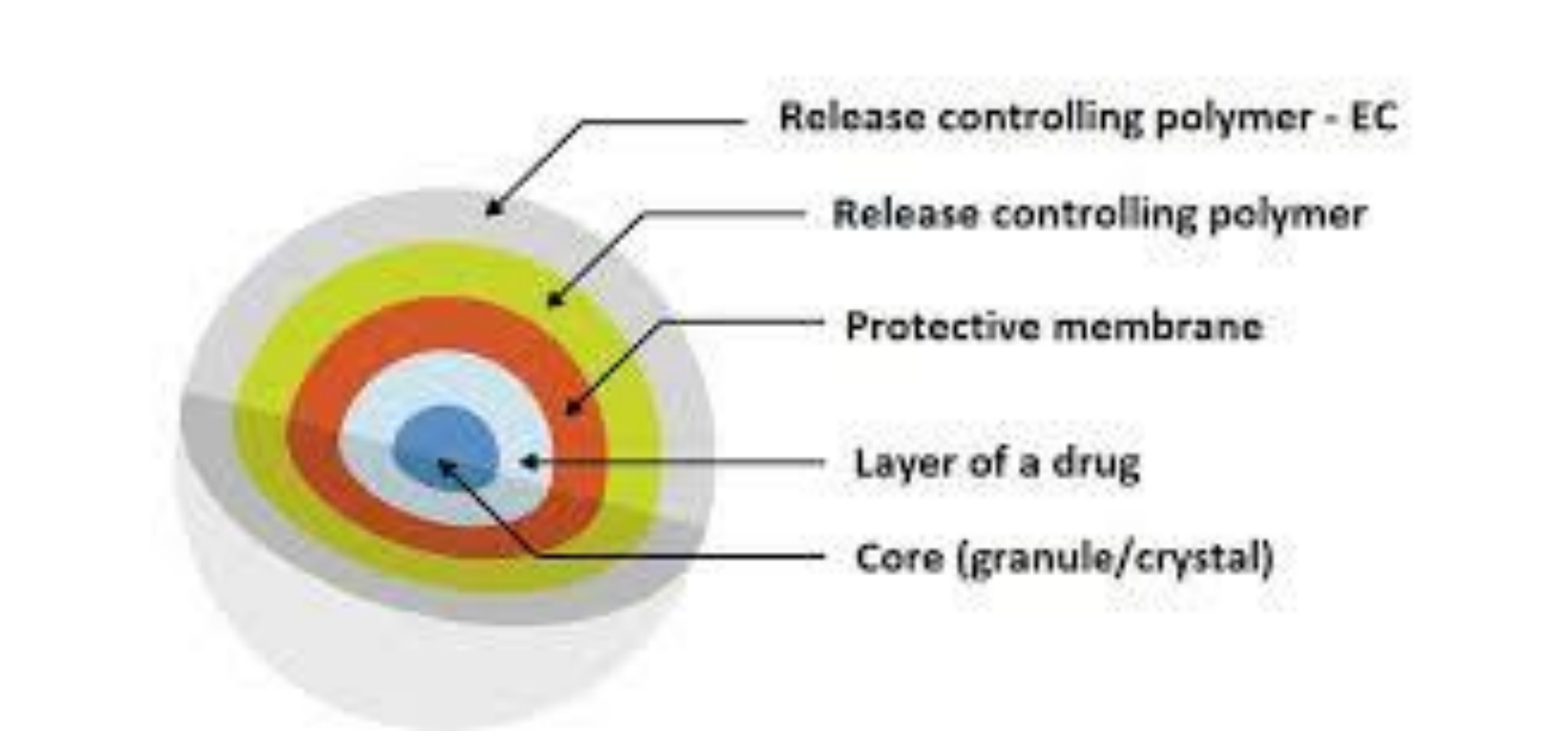


Hydrophobic matrices (Plastic matrix tablet)

- Sustained release tablets based upon an inert compressed hydrophobic matrix have been used widely.
- In plastic matrix, usually, the drug release is delayed because the dissolved drug has to diffuse through capillary network between the compacted polymer particles
- For example: Polyvinyl Chloride, Ethylcellulose, Cellulose acetate and Polystyrene

Polyvinyl Chloride

Ethyl cellulose



Biodegradable matrices

- These consist of the polymers which composed of monomers that linked to one another through functional groups and have unstable linkage in the backbone. It is biologically degraded or eroded by enzymes generated by the living cells or by non-enzymatic process into oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins, polysaccharides and modified natural polymers, synthetic polymers such as polyanhydrides and aliphatic polyesters

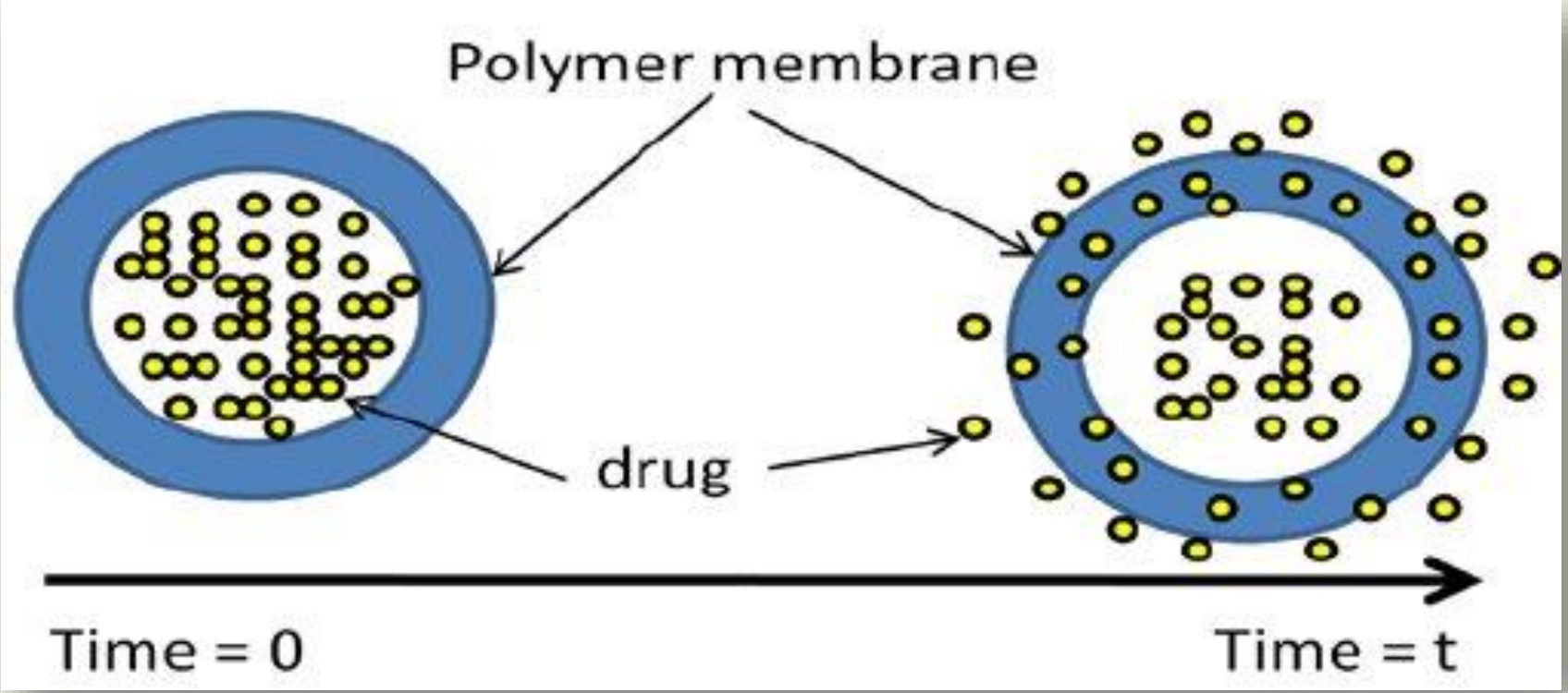
Mineral matrices

- These type of matrices is consist of polymers which are obtained from various species of seaweeds. Example is alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds by the use of dilute alkali.

- ## According to the porosity, matrix systems can be classified as:

- 1. **Macroporous systems**
- In these systems, the drug diffusion occurs through pores of the matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.
- 2. **Microporous system**
- In this system, drug diffusion occurs essentially through pores. In microporous systems, pore size ranges between 50 - 200 A°, which is slightly larger than diffusant molecules size.
- 3. **Non -porous system**
- These systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present

Reservoir matrix systems

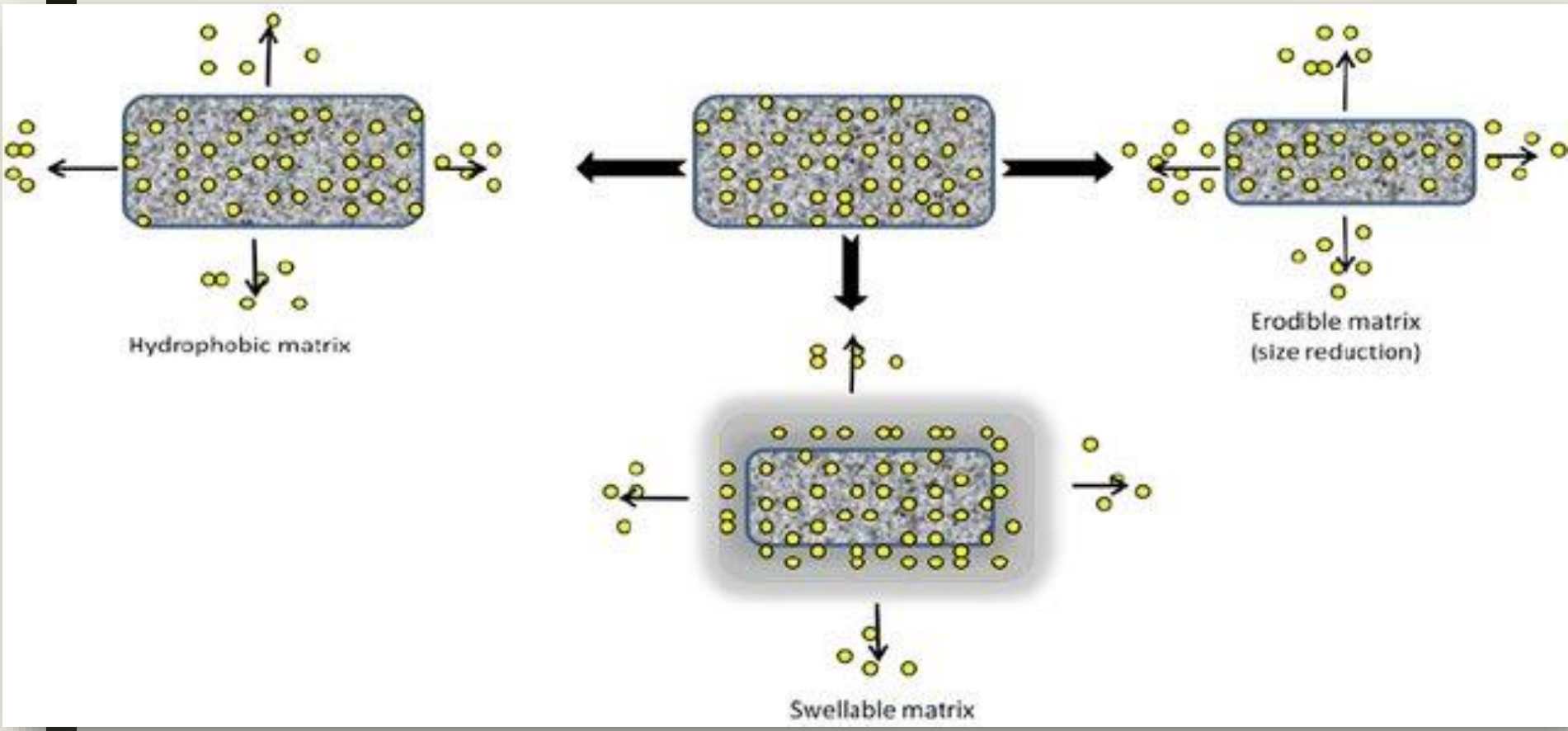


- Images sourse: https://www.researchgate.net/publication/236913076_The_Role_of_Oral_Controlled_Release_Matrix_Tablets_in_Drug_Delivery_Systems/figures?lo=1

Membrane controlled systems

- The system is coated with polymeric membrane. The amount of coating membrane and type of polymer
- used will be the deciding factor for controlling the rate of release for the drugs. One more important factor is the integrity of the polymeric
- membrane. If the membrane integrity is not proper, the drug release can be rapid and may lead to dose dumping .The membrane integrity
- can be studied by using Scanning Electron Microscopy. If the amount of coating is applied in more quantity, the drug will not be able to
- release and may remain stagnant in the membrane and leading to the undermedication. Hence, it is always advised to use optimum
- concentration of polymer coating for particular dosage form. The membrane coated dosage form should not be crushed otherwise it may
- cause sudden release of drug in the blood plasma and leading to dose dumping.

Schematic representation of drug release from different types of matrix tablets.

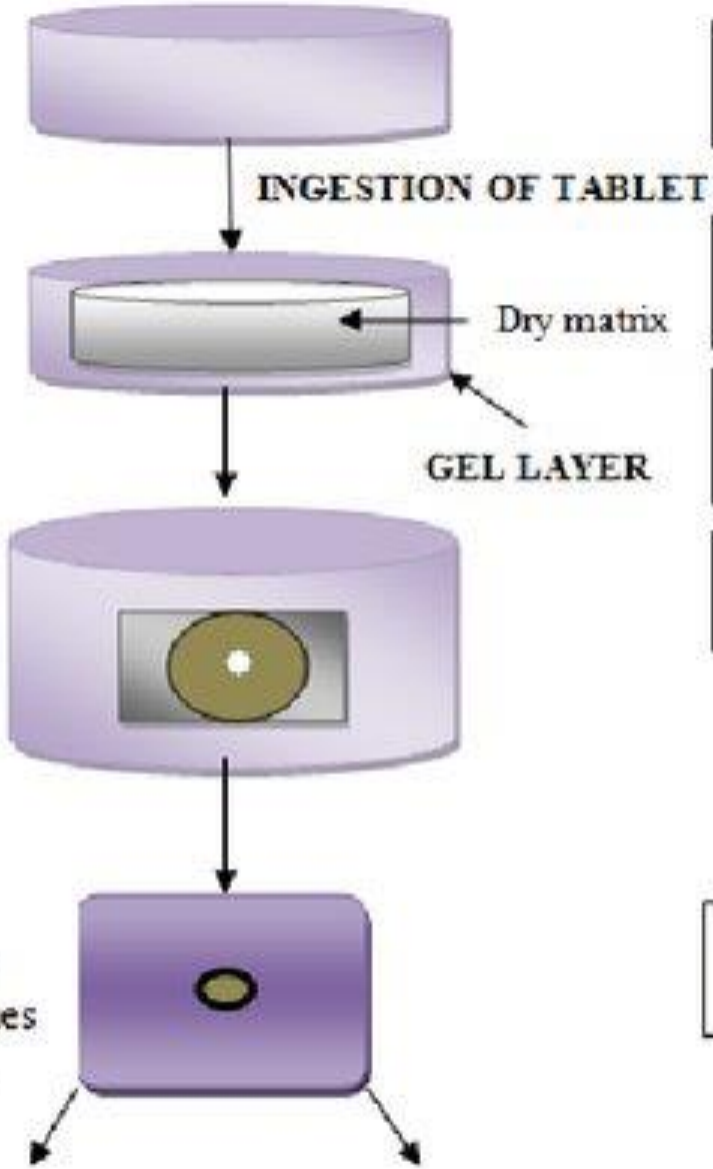


Mechanism of drug release from a hydrophilic matrix tablet (adapted from The Dow Chemical Company 2000).

Initial wetting
The tablet surface wets as it becomes immersed in aqueous media. The polymer then begins to hydrate forming a gel layer. Drug near the surface of the tablet is released.

Expansion of gel layer
As water permeates into the tablet, the polymer swells causing an increase in size. The soluble drug diffuses through the gel layer. The dry core also contributes to the swelling.

Tablet Erosion
Outer polymer layer becomes fully hydrated which eventually dissolves into the gastric fluids. Water continues to permeate towards the tablet core.



STEP 1: POLYMER WETTING

STEP 2: POLYMER HYDRATION

STEP 3: GEL FORMATION

STEP 4: GEL SWELLING

STEP 5: POLYMER DISSOLUTION

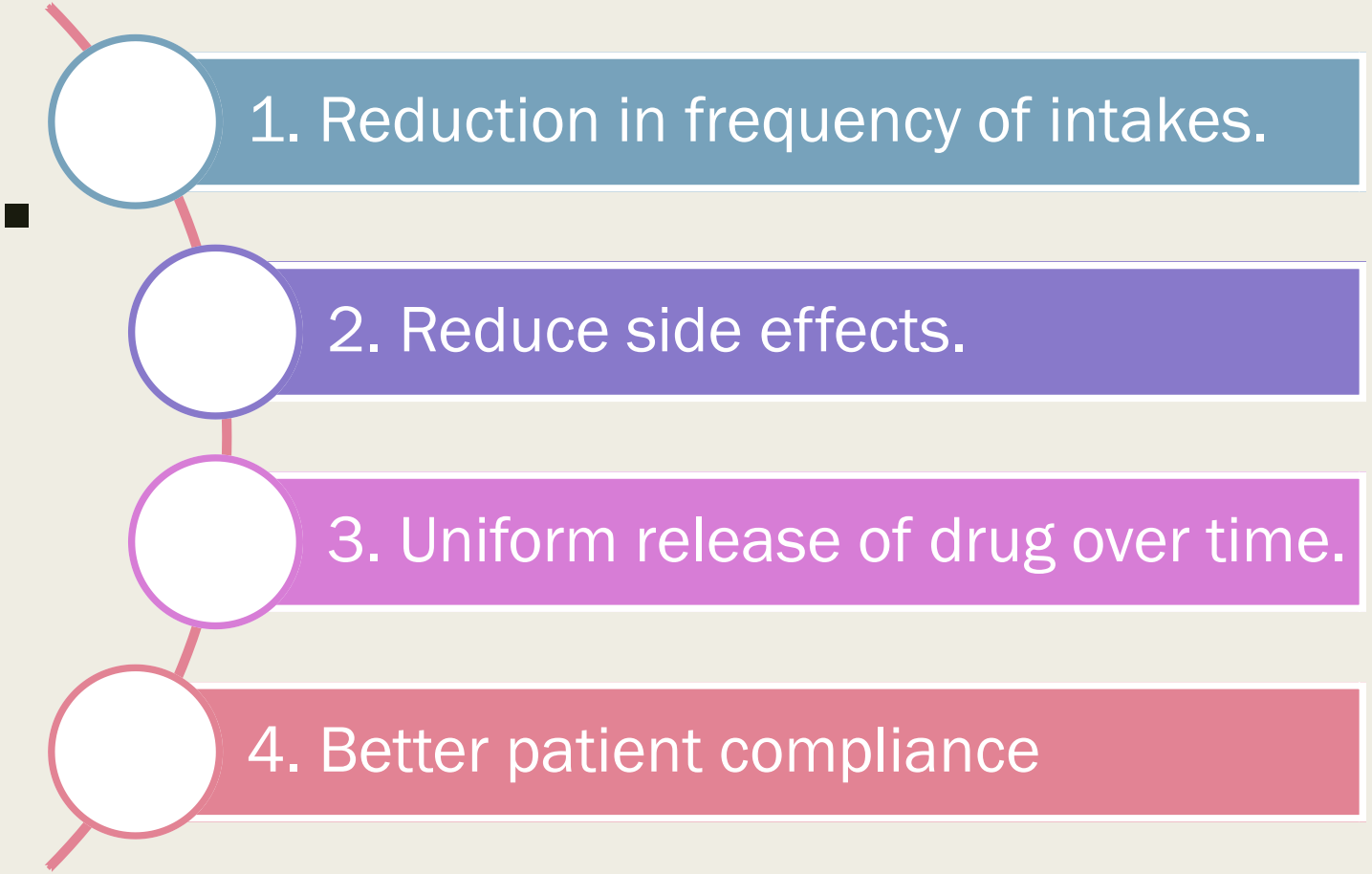
SOLUBLE DRUG
Released primarily by DIFFUSION through the gel layer

INSOLUBLE DRUG
Released primarily by tablet EROSION.

Sustained release, sustained action, prolonged action controlled release, extended release, depot

- release these are the various terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over a long period of time after administration of a single dose of drug.

ADVANTAGES OF SUSTAIN RELEASE DOSAGE FORMS



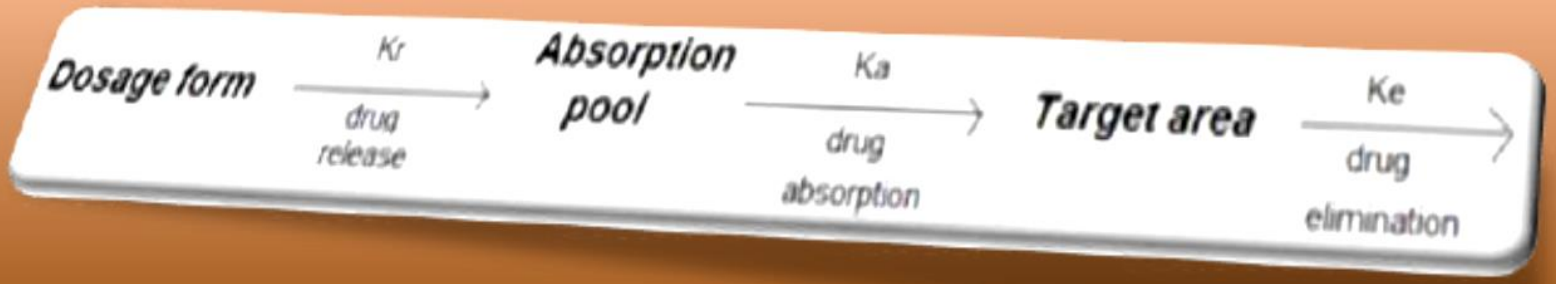
Concept of sustained release formulation

Biopharmaceutical consideration and dose calculation

The Concept of sustained release formulation can be divided in to two considerations i.e. ***release rate & dose consideration***

A) Release rate consideration :-

In conventional dosage form *Kr>Ka* in this the release of drug from dosage form is ***not rate limiting step.***



The above criteria i.e. ***(Kr>Ka)*** is in case of ***immediate release,*** where as in ***non immediate (Kr<Ka)*** i.e. release is rate limiting step.

So that ***effort for developing S.R.F*** must be directed primarily ***altering the release rate.*** the rate should be independent of drug removing in the dosage form over constant time.

The release rate should follow zero order kinetics

$$Kr = rate\ in = rate\ out = KeVd.Cd$$

Where

Ke = overall elimination (first order kinetics).

Vd = total volume of distribution.

Cd = desired drug concentration.

B) Dose consideration :-

To achieve the therapeutic level & sustain for a given period of time for the dosage form generally consist of 2 part

a) Initial (primary) dose ***b) maintenance dose***

there for the total dose 'W' can be.

$$W = Di + Dm$$

In a system, the therapeutic dose ***release follows zero order process*** for specified time period then,

$$W = Di + K^0 r.\ Td$$

Td = time desired for sustained release from one dose.

If ***maintenance dose begins to release*** the drug during dosing t=O then,

$$W = Di + K^0 r\ Td - K^0 r\ Tp$$

Tp = time of peak drug level.

However a ***constant drug*** can be obtained by suitable ***combination of Di & Dm*** that release the drug by first order process, then

$$W = Di + (Ke\ Cd / Kr)\ Vd$$

Technical challenge	Skyepharma's solution	Benefit	Product examples
Zero order release	Geomatrix™	Once- or twice-daily dosing	Paxil CR™ Requip® Once-a-day Coruno® Xatral® / Uroxatral®
Biphasic release	Geomatrix™	Rapid onset followed by sustained duration	Diclofenac-ratiopharm® uno Zyflo CR®
Controlled release of several drugs in a single tablet	Geomatrix™	Several drugs that need to be released at different times or different rates can be combined in a single dose form	Madopar® DR
Ascending profile	Geomatrix™	Absorption of drugs in the lower GI tract	Sular®
Multiple pulses	Geoclock™	Two or more pulses of drug release separated by periods of no release Suitable for drugs having undesirable side effects that can be minimised at certain times of the day	
Timed release	Geoclock™	The drug effect can be achieved at a pre-determined time after administration	LODOTRA® / RAYOS® SKP-1041 SKP-1052
Colonic delivery	Geoclock™	Delivery to the colon where absorption of specific drugs is high or for topical effect in the colon	
Improved bioavailability and food effect	IDD® DissoCubes™	Improvement of bioavailability of BCS II and BCS IV drugs	Triglide®
Buccal delivery	Medicated chewing gum	Buccal absorption for improved systemic delivery or local effect	

zero order release from prolonged or sustained forms

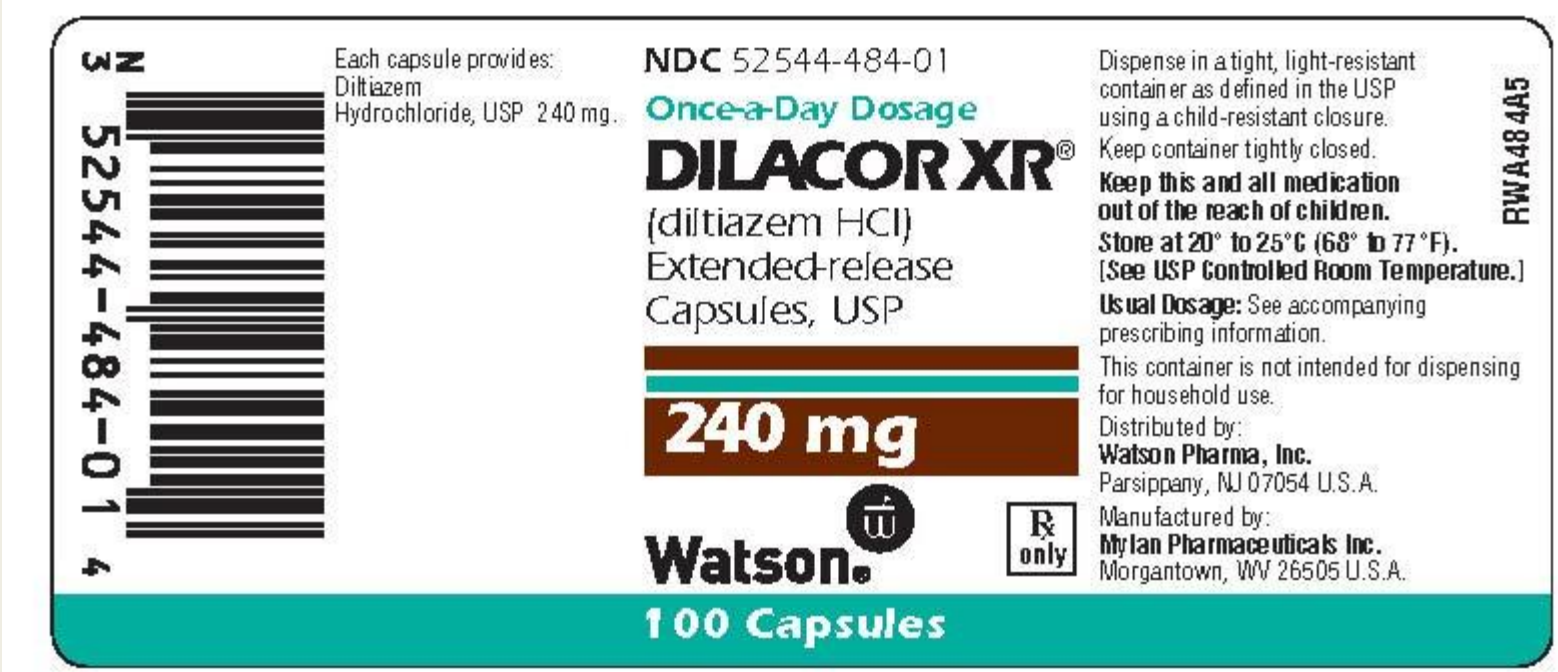
- This type of release provides a constant rate of drug release over a well-defined period of time

PAXIL CR (paroxetine hydrochloride) is an orally administered psychotropic drug with a chemical structure unrelated to other selective serotonin reuptake inhibitors

PAXIL CR should be administered as a single daily dose, usually in the morning

XR®

- Dilacor XR® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist).



binary release from prolonged or sustained release forms

- . The system provides a controlled release of two different medicinal substance in a single formulation

Each capsule contains 100.0 mg Levodopa and 25 mg Benserazide (as benserazide hydrochloride)

- **List of excipients**
- ***Capsule contents:***
- Hypromellose (E464)
- Hydrogenated vegetable oil
- Calcium hydrogen phosphate, anhydrous (E341)
- Mannitol (E421)
- Talc (E553b)
- Povidone (E1201)
- Magnesium stearate (E572)
- ***Capsule shell:***
- Gelatin
- Indigo carmine (E132)
- Titanium dioxide (E171)
- Yellow iron oxide (E172)

fast-slow release from prolonged or sustained pharmaceutical forms

- Initially a rapid, immediate release of medicinal substance is expected, followed by a constant rate over a certain period of time

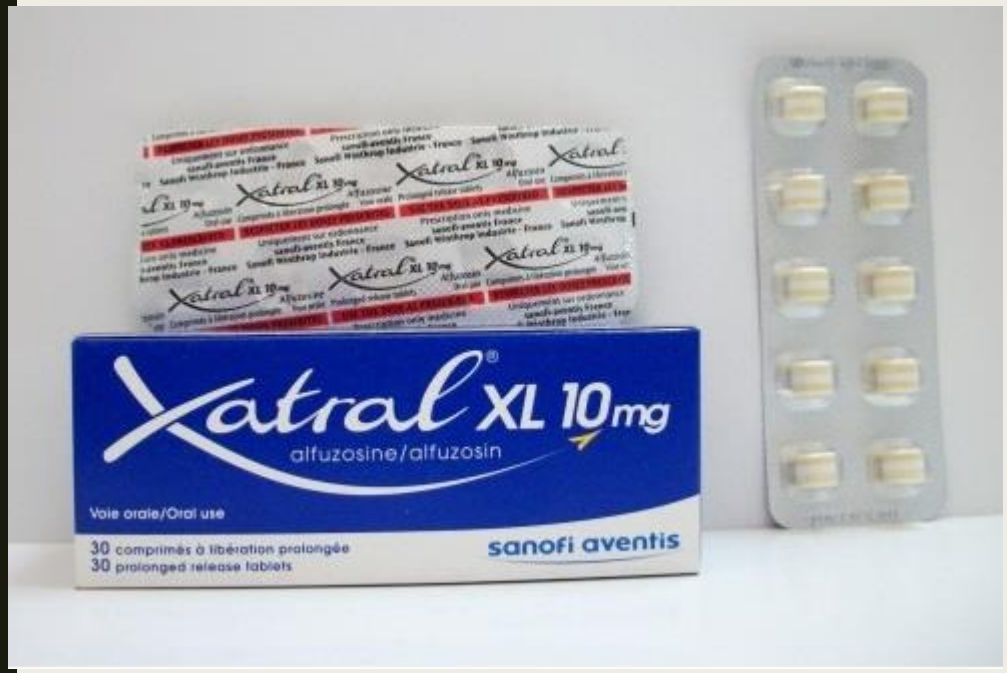
slow - quickly release from prolonged or sustained pharmaceutical forms

- Initially a constant rate of drug is released followed by a rapid, immediate release at a certain time interval

- SULAR ® (nisoldipine)

positioned release from prolonged or sustained pharmaceutical forms

- The system assume localization in a certain portion of the digestive tract (colon) and then the release of medicinal substance



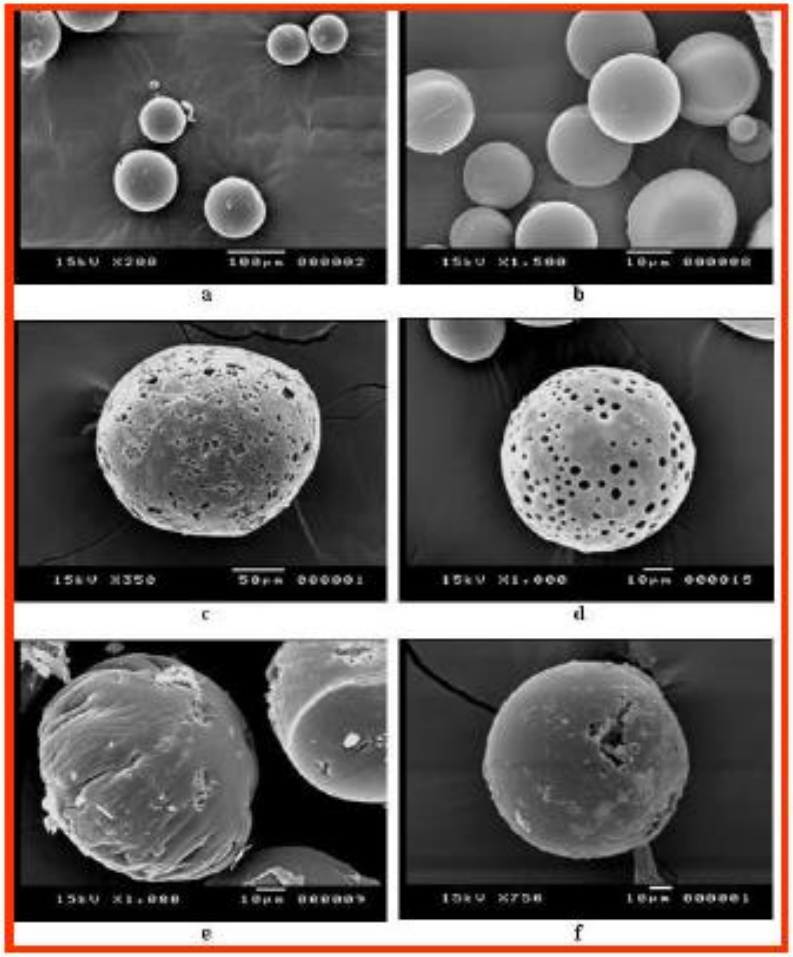
Each tablet contains 10mg alfuzosin hydrochloride.

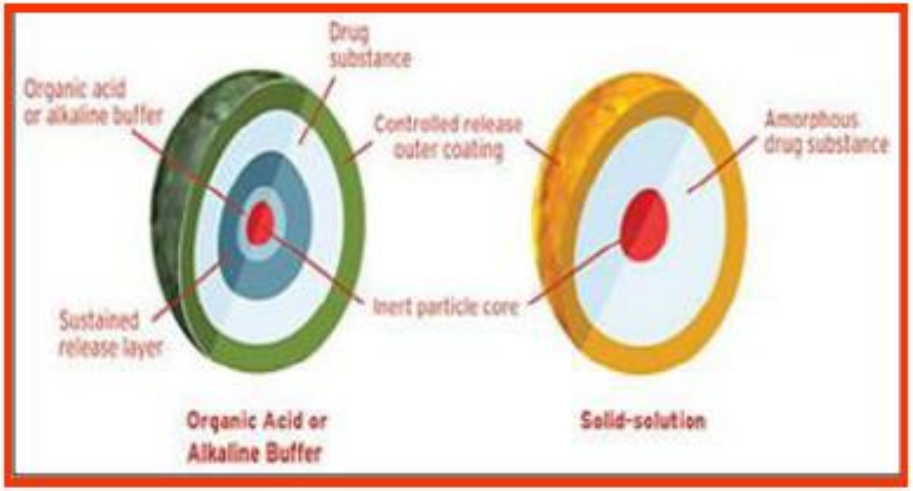
- **Therapeutic indications**
- Treatment of the functional symptoms of benign prostatic hypertrophy (BPH).

accelerated release from prolonged or sustained release forms

- The system provides a constant accelerated delivery of several doses of drug
-

Indometacine





EURAND'S DIFFUCAPS®MULTIPARTICULATE SYSTEM

circadian release from prolonged or sustained release forms

- circadian release from prolonged or sustained release forms

prednison “Lodotra”.

multiple-pulsed release defined from sustained or sustained release forms

- Medicinal substance is initially released immediately, shortly, for rapid action, followed by a slow period, after which a second assignment occurs and so on.

Phendimetrazine

***Delayed Release System*).**

Carbamazepine capsules with extended release

- 3 types of pellets: A - immediate release; B - prolonged release; C - delayed release
-