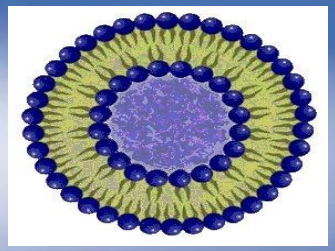
Sustained release dosage forms (SRDF'S)



drug release

time

- *Mohamed Akl*

Assistant Prof. of Pharmaceutics

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The Sustained Release

- **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.

Basic goal of the therapy

to achieve **a steady state blood level** that therapeutically **effective and non-toxic for an extended period of time.**

Also referred to as sustained action, prolonged action, controlled release, extended action, timed release, depot, and repository (storage area) dosage forms

The Sustained Release Concept

- 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.

Objectives of drug delivery

- **Temporal drug delivery:** تسليم الأدوية المؤقتة

  controlling the rate or specific time of drug delivery to the target tissue.

- **Spatial drug delivery:** توصيل الدواء المكاني

  targeting a drug to a specific organ or tissue.

Advantages of extended-release pharmaceuticals

1. Reduction in dosing frequency → ↑ convenience & patient compliance .إلتزام المريض بالعلاج
2. Avoid adverse side effects of drugs have a narrow therapeutic index (small difference between toxic level and therapeutic level), because of fewer blood level peaks above MTC.

– Requires multiple injections → Poor patient compliance → Increased incidence of infection and hemorrhages

4. **Avoid danger of systemic toxicity with more potent drugs.**
5. Improves bioavailability of certain drugs with short half lives in vivo. Some peptides have half-lives of a few min or even secs.
6. Reduction in overall health care costs

→Although ↑ initial cost of extended-release dosage forms, overall cost of treatment may be less **(WHY???)**

because of enhanced therapeutic benefit, ↓ side effects, ↓time for health care personnel to monitor patients (Reduces nursing and hospitalizing time)

Advantages of extended-release pharmaceuticals

7. Targeted delivery is possible.
8. Reduced fluctuations التقلبات in circulating drug levels. i.e., the variable drug-blood level of multiple dosing of conventional dosage forms is reduced because a more even drug-blood level is maintained. → As a result, increasing the treatment's efficacy will result in →

- Cure or control condition more promptly بسرعة أكبر
- Improve bioavailability

9. 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

Disadvantages of extended-release pharmaceuticals

1. The physician has less flexibility in adjusting the drug dose and/or dosage regimen.

– This is fixed by the dosage form design.

2. Risk of sudden and total drug release (**dose dumping**), due to a sustained release medication technology does not permit the prompt termination of therapy.
3. High cost of the formulation technology. → Economic factors must also be assessed, since more costly processes and equipment are involved in manufacturing many sustained release forms.
4. Difficulty to adopt all extended-release formulations into the large-scale production due to formulation complexity.

N.B:

- Dose dumping is a phenomenon of drug metabolism in which environmental factors can cause the premature and exaggerated release of a drug. This can greatly increase the concentration of a drug in the body and thereby produce adverse effects or even drug-induced toxicity.

Disadvantages of extended-release pharmaceuticals

5. Not all drugs are suitable candidates for formulation as prolonged action medication.
6. Delayed onset of action, hence sometimes not useful in acute conditions
7. Patient education is required for successful therapy (such as not to chew or crush the dosage form before swallowing)
8. Sustained release forms are designed for the normal population, i.e., based on average drug biologic half-lives. Consequently, disease states that alter drug disposition as significant patient variation, are not accommodated.

Characteristics of Drugs unsuitable for oral Sustained Release Forms

Characteristics		Drugs
Not effectively absorbed in the lower intestine		Riboflavin, ferrous salts
Absorbed and excreted rapidly; short biologic half lives (<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 مطلوب جرعه دقيقة معايرة للفرد		Anticoagulants, cardiac glycosides
No clear advantage for sustained release formulation		Griseofulvin

Concept

- The goal of SRDF's is to obtain Zero order release from the dosage form.
- Zero order release is a release which is independent of the amount of drug present in the dosage form.
- Usually SRDF's do not follow zero order release but they try to mimic zero order release by releasing the drug in a slow first order fashion.
- Pharmacological action is seen as long as the drug is in therapeutic range, problems occur when drug concentration is above/below therapeutic range.
- With many drugs, the basic goal of therapy is to achieve a steady-state blood or tissue level that is therapeutically effective and nontoxic for an extended period of time.

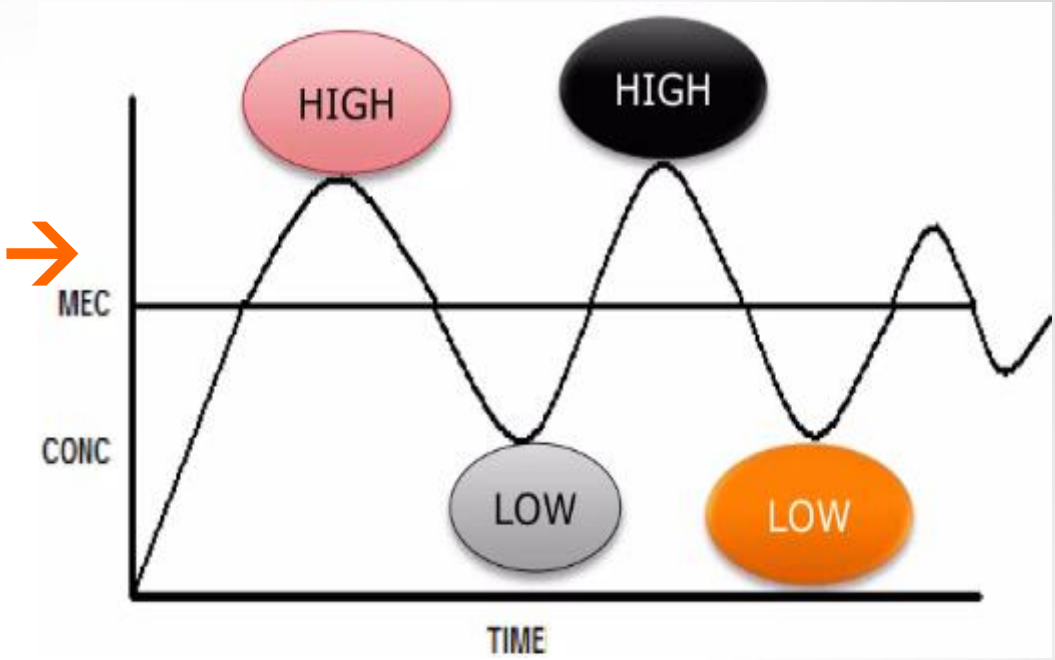
NB:

Dosage regimen: the frequency of administration of drug in a particular dose is called as dosage regimen

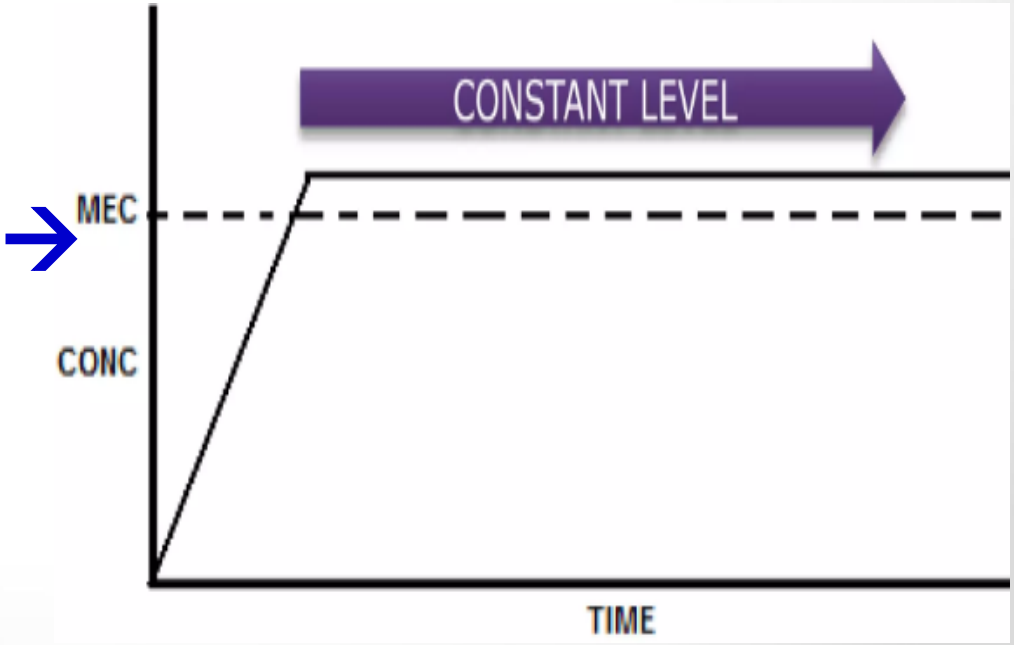
Design (Theory)

- 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, however control of drug action through formulation also implies controlling bioavailability to reduce drug absorption rates.
- To establish a procedure for designing SRDF, it is useful to examine the properties of drug blood level time profile characteristic of multiple dosing therapy of immediate release forms (conventional drug therapy).

In the conventional therapy aliquot quantities of drugs are introduced into the system at specified intervals of time with the result that there is considerable fluctuation in drug concentration level as indicated in the figure.



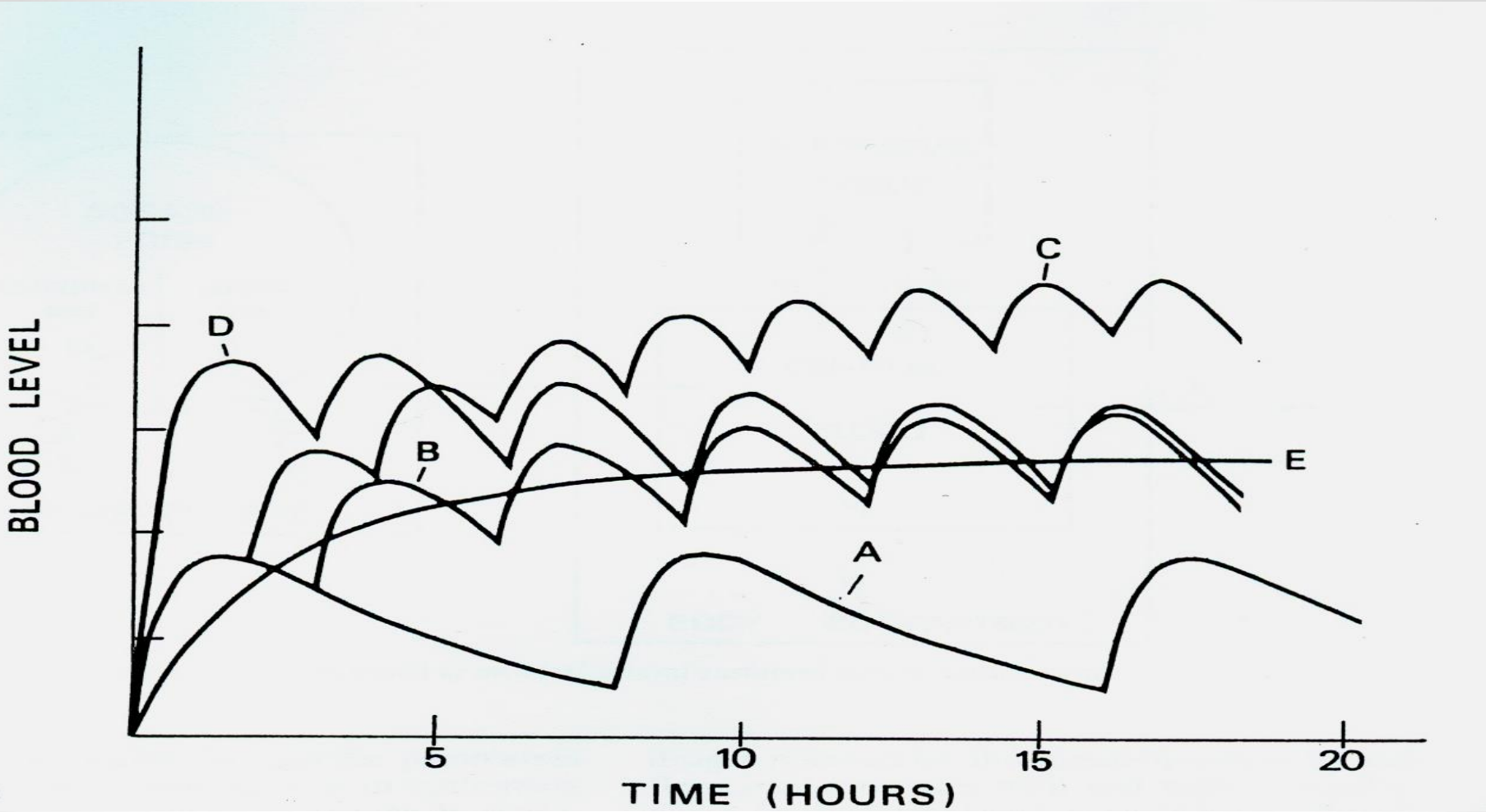
However, an ideal dosage regimen would be one, in which the concentration of the drug, nearly coinciding يتزامن with minimum effective concentration (M.E.C.), is maintained at a constant level throughout the treatment period.



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

Special notes:

- **Loading dose** is the dose required to attain a target (desired) concentration within therapeutic window immediately.
- **Maintenance dose** is the dose that maintains a target concentration within therapeutic window on repeated administration.
- **Therapeutic window (range):** Difference between MTC and MEC (Any concentration falling within this range produces a pharmacological effect).



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).

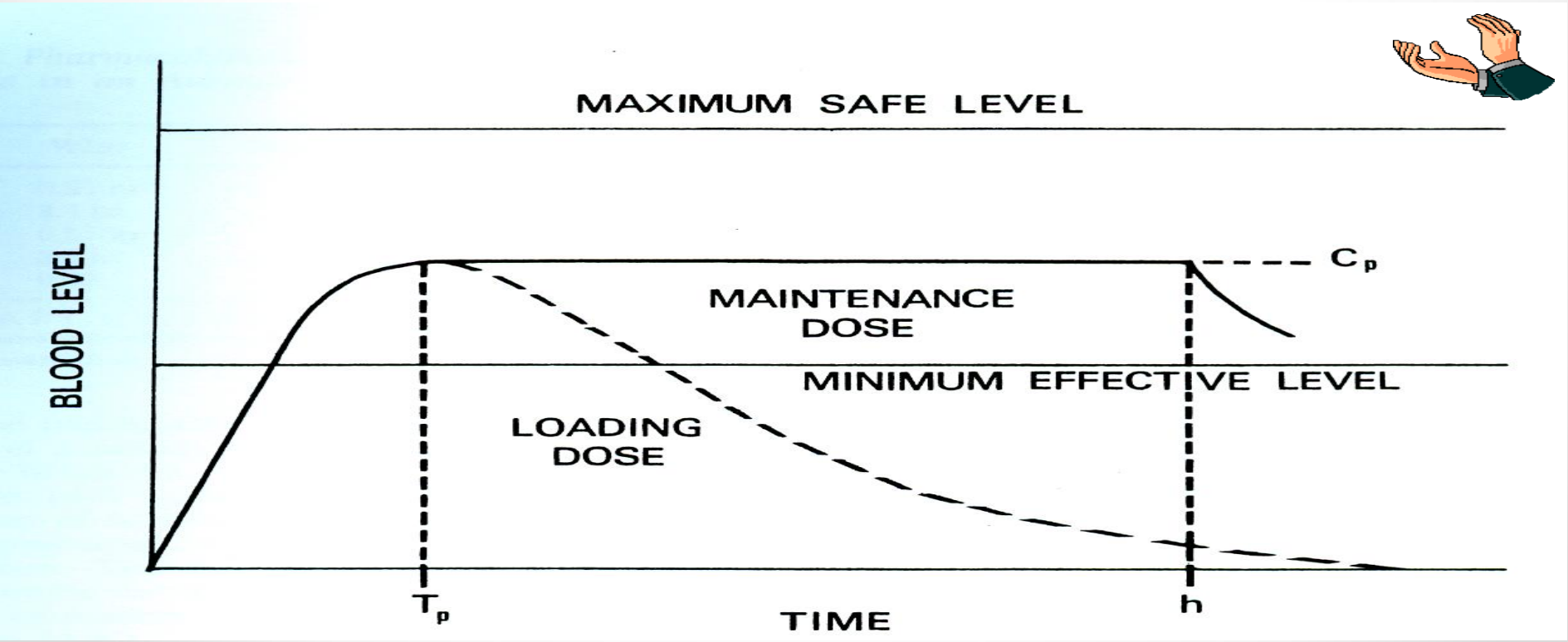
- Selection of the proper dose and dosage interval is a prerequisite to obtaining a blood-drug level pattern that will remain in the therapeutic range.
- Drug must be provided by the dosage form at a rate that keep drug concentration constant at the absorption site (To obtain a constant drug level, the 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.



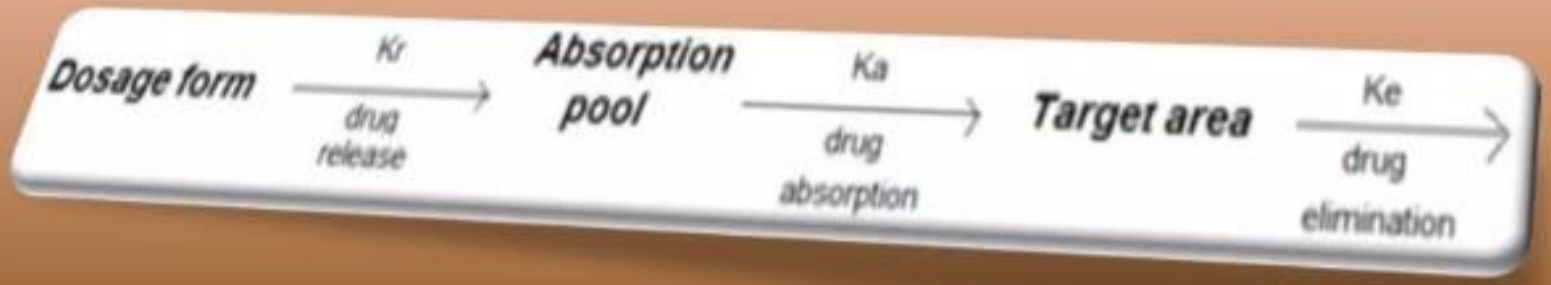
Concept of sustained release formulation

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

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

Terms used to describe Drug Release

1. Delayed release (DR):

- A dosage form designed to release the drug at a time other than immediately (at later time) after administration.

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, that allows the drug to be released over prolonged period → the frequency of dosing can be reduced..

Terms used to describe Drug Release

4. **Modified Release (MR):**

- Dosage forms can be designed to modify the release of the drug over a given time (for a prolonged period) or after the dosage form reaches the required location (to a specific target in the body).

5. **Controlled Release (CR):**

- Drug delivery systems which maintain constant level of drug in the target tissue or plasma for an extended period of time, independently of the biological environment of the application site.

6. **Sustained Release (SR):**

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

Differentiating drug delivery systems according to their mechanism of drug release

I- Immediate release

Drug is released immediately after administration

II- Modified release

Drug release only occurs some time after the administration or for a prolonged period of time or to a specific target in the body.

Modified release systems can be classified as:

a) Delayed release

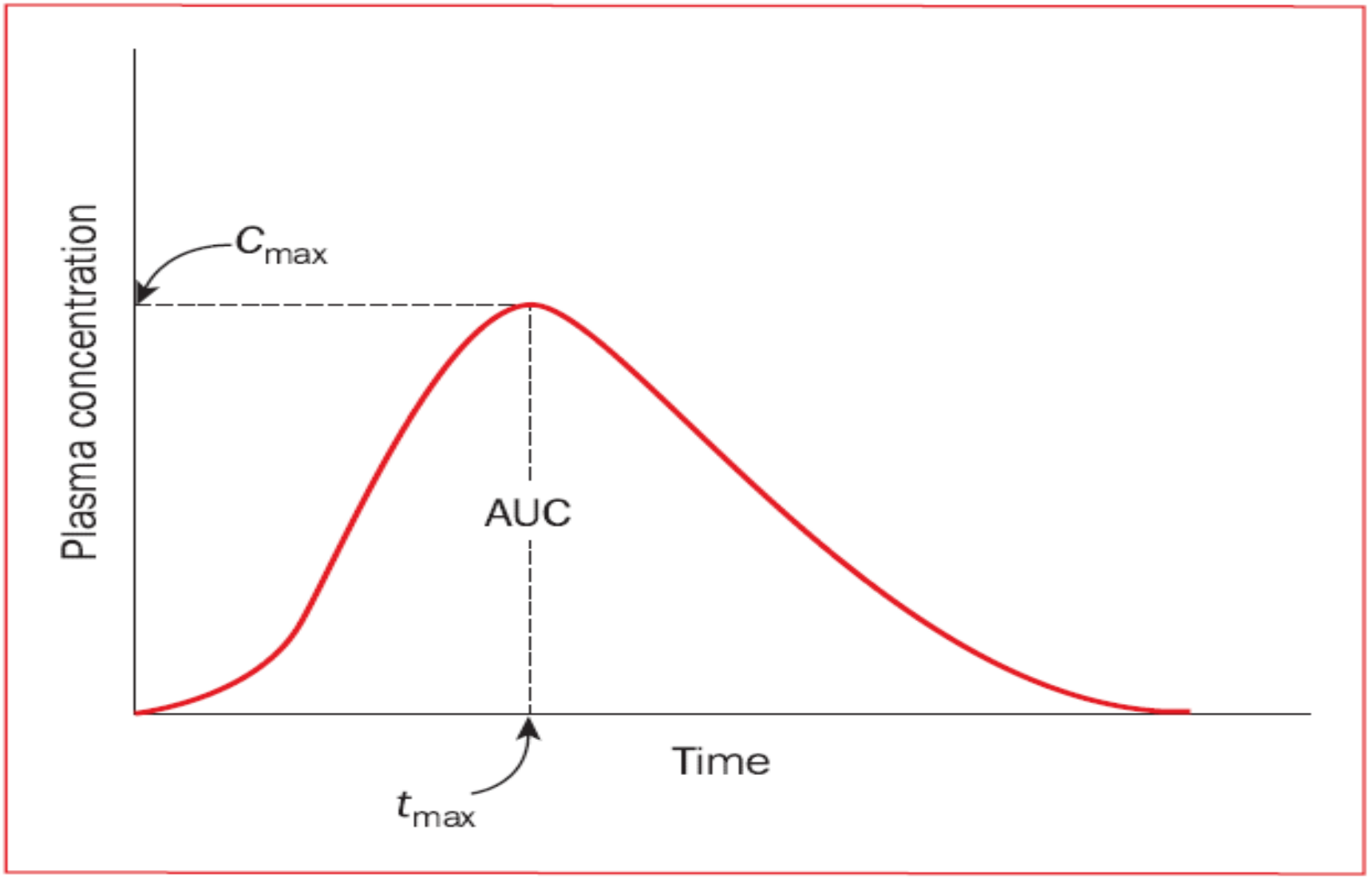
b) Extended release

c) Targeted release

I- Immediate Release

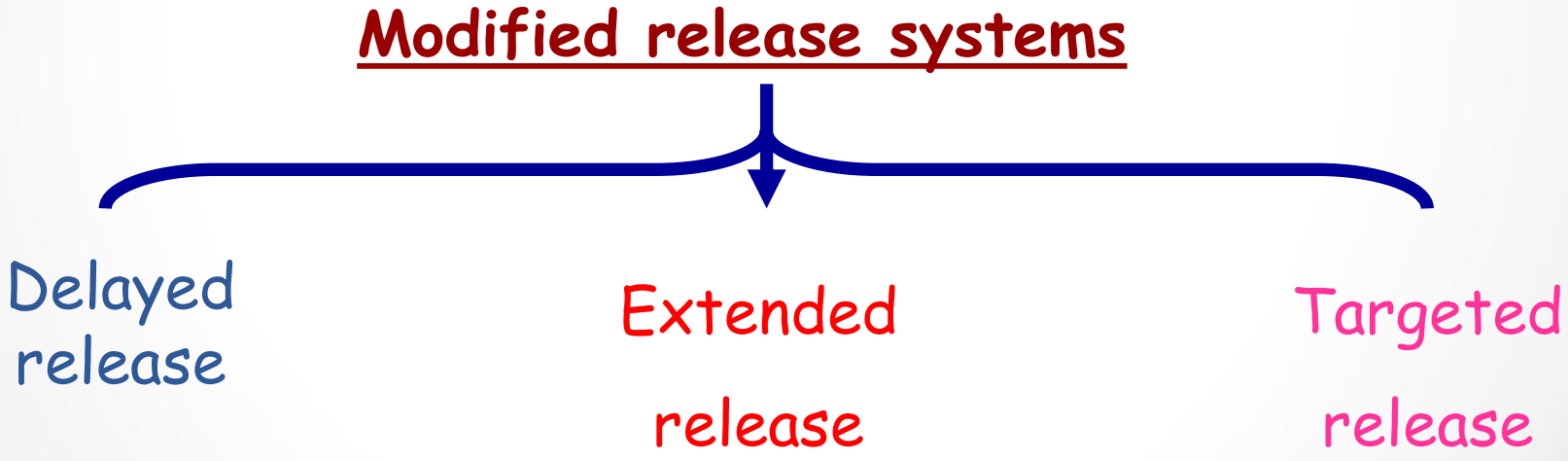
- The drug is released immediately or at least as quickly as possible after administration.
- This is useful if a fast onset of action is required for therapeutic reasons (such as tablets containing a painkiller).
- Immediate release dosage forms → release the drug at **a first-order kinetics** profile
  - i.e, the drug is released initially very quickly → the highest plasma level (C_{max}) in a short time (t_{max}).
  - **Then,** the drug is distributed throughout the body and elimination of the drug occurs following 1st-order kinetics.

I- IMMEDIATE RELEASE



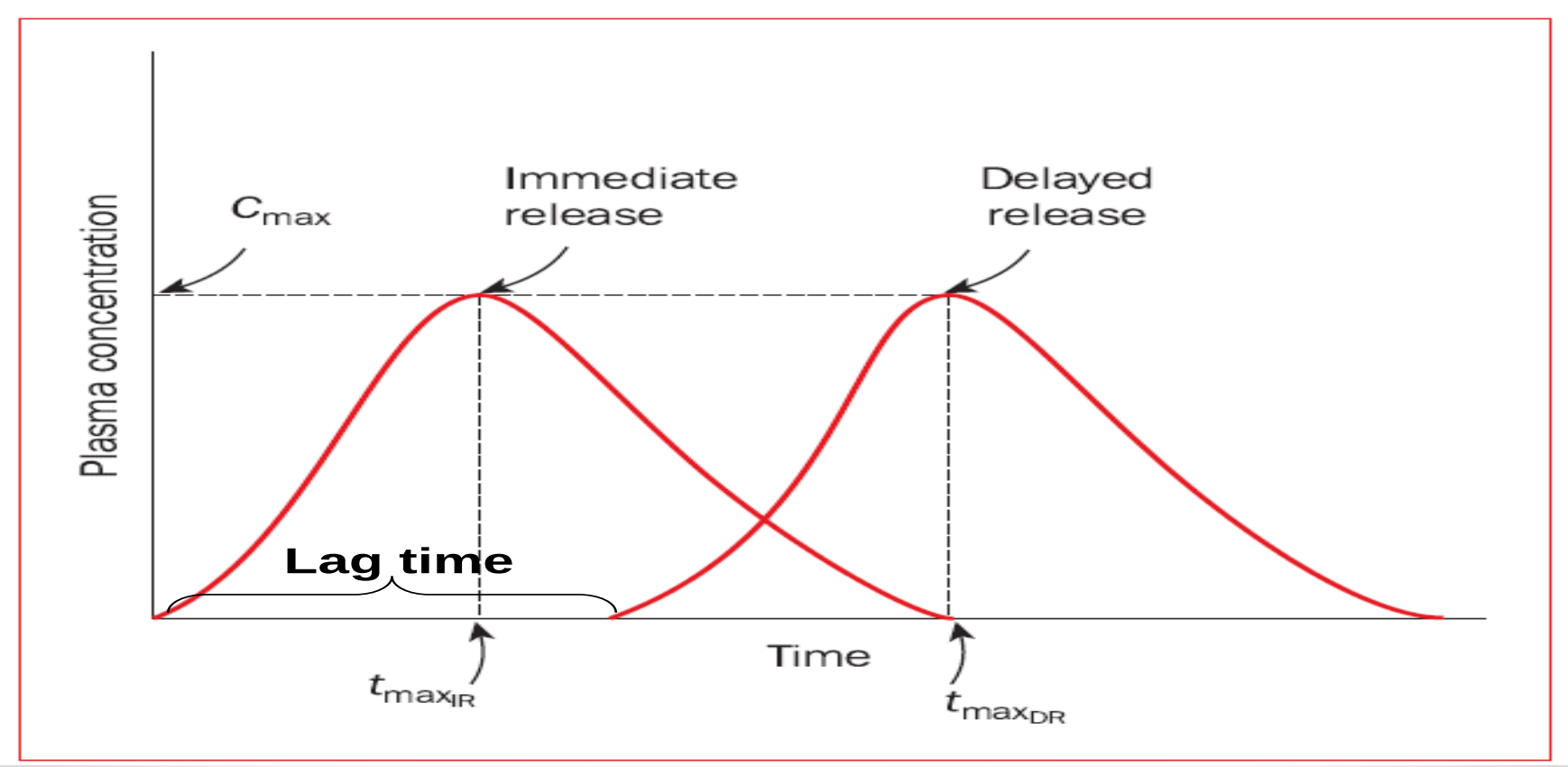
II- Modified release

- Drug release only occurs some time after the administration or for a prolonged period of time or to a specific target in the body.



A) Delayed release dosage forms

- A dosage form designed to release the drug **at a time other than immediately** (at later time) after administration.
- e.g, enteric-coated tablets, pulsatile-release capsules.



A) Delayed release dosage forms

- The delay may be **time** based or based on the influence of **environmental conditions**, like G.I.T. pH.
- The delay of drug release → by coating the dosage form with specific polymers

(N.B) Polymer films are also used in the formulation of immediate-release dosage forms. *The reasons for this include:*

a- Facilitating swallowing of the dosage form

b- Masking taste and odor

c- Facilitating identification of the dosage form

d- Enhancing the appearance of the dosage form

e- Protecting the dosage form against environmental conditions (e.g. light and moisture).

f- Protecting the dosage forms from breaking or abrasion during packaging or handling.

- however, such coats are dissolved quickly in the stomach and do not interfere with the release of the drug.

I- Small intestine-specific delivery (enteric-coated)

- Enteric-coated dosage forms → prevent drug release until the small intestine is reached.

The reasons for enteric coating are:

a. To protect the drug from degradation by the acidity of stomach e.g. Azole-type proton pump inhibitors (omeprazole and pentoprazole) and antibiotics (erythromycin and penicillins)

b. To prevent gastric mucosa irritation by irritant drugs such as aspirin and some NSAID such as naproxen.

c. For drugs locally acting in the small intestine and a high drug conc. in this part of G.I.T is desired such as anthelmintics.

d. For drugs that are absorbed only in the small intestine.

I- Small intestine-specific delivery (enteric-coated)

Mechanism of enteric coatings

- The pH in the stomach → 1.5 - 2 in the fasted state

  → 4-5 in the fed state.

- In the small intestine → the pH between 6 (in the duodenum) and 6.5 - 7 (in the jejunum and ileum).

- If a polymer is insoluble polymer at pH 5 but soluble above pH 5 → pH-triggered release (i.e. pH-controlled release) in the small intestine.

I- Small intestine-specific delivery (enteric-coated)

Polymers used for enteric coating include:

- cellulose derivatives such as cellulose acetate phthalate (CAP) and hydroxypropyl methylcellulose acetate phthalate (HPMCAP)
- Polyvinyl derivatives such as poly (vinyl acetate phthalate) (PVAP)
- Poly(methacrylate) derivatives such as Eudragit L which dissolves at pH 5.5-6 and Eudragit S which dissolves at pH 6.5
- Shellac or fatty or waxy materials such as beeswax and carnuba wax.

II- Colon-specific drug delivery

Advantages

1. For drugs (e.g. peptides and proteins) → pH conditions in the colon are more favorable than in the stomach.

- The colonic environment lacks endogenous digestive enzymes and little mixing takes place, which makes it possible to create local environment with optimal absorption conditions.

2. For the treatment of local (e.g. colorectal cancer) and systemic diseases.

- The residence time in the colon can be 12 hours or longer, giving massive opportunity for molecules to be absorbed.

II- Colon-specific drug delivery

Disadvantages

1. Absorption from the colon will lead to drug transport to the liver via the portal vein → degradation via hepatic first-pass effect.
2. The conc. of micro-organisms in the colon is very high → induce pre-systemic drug metabolism by these micro-organisms.

➢Colon-specific delivery can be achieved by 3 different strategies:

a. Enzyme-triggered release by using either pro-drugs or polymers
b. Time-controlled release by using suitable polymers
c. pH controlled release by using suitable polymers

II- Colon-specific drug delivery

a- Enzyme-triggered release

- Enzyme-triggered drug release exploits micro-organisms present in the colon to release drug by:

1- converting pro-drugs to the parent drug

2- digesting polymer coatings on solid dosage forms

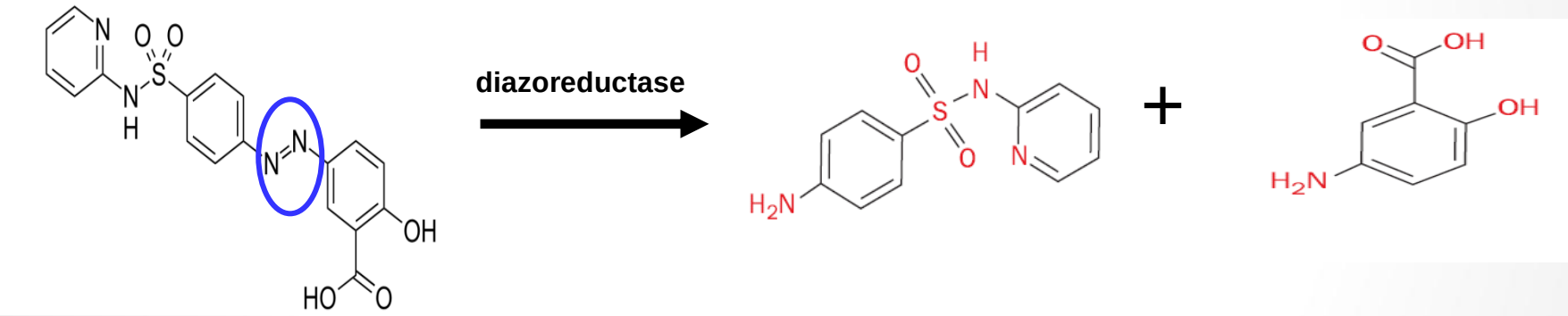
(**N.B**) Care must be taken when antibiotics are administered → antibiotics may affect colon micoflora → adversely affect the release of the drug.

II- Colon-specific drug delivery

a- Enzyme-triggered release

1. Pro-drug for enzyme-triggered release

EX: The pro-drug of sulfasalazine (used in the ttt. of Crohn's disease and inflammation of the colon).



Sulfasalazine **Sulfapyridine** **5-aminosalicylic acid**

- The azo group (-N=N-) in sulfasalazine is cleaved in the colon by **bacterial diazoreductases** into sulfapyridine and the active drug 5-aminosalicylic acid.

II- Colon-specific drug delivery

a- Enzyme-triggered release

2. Polymers for enzyme-triggered release

- Natural and semi-synthetic polysaccharides (e.g. chitosan, pectin, inulin, cyclodextrins and xylan)
- These polymers are not digested in the upper parts of G.I.T but degraded by microflora in the colon.

II- Colon-specific drug delivery

b- pH controlled release

- Polymer coatings that dissolve at pH 7 → used to trigger release in the colon.

e.g. Poly(methacrylate) derivatives such as ***Eudragit FS 30D***.

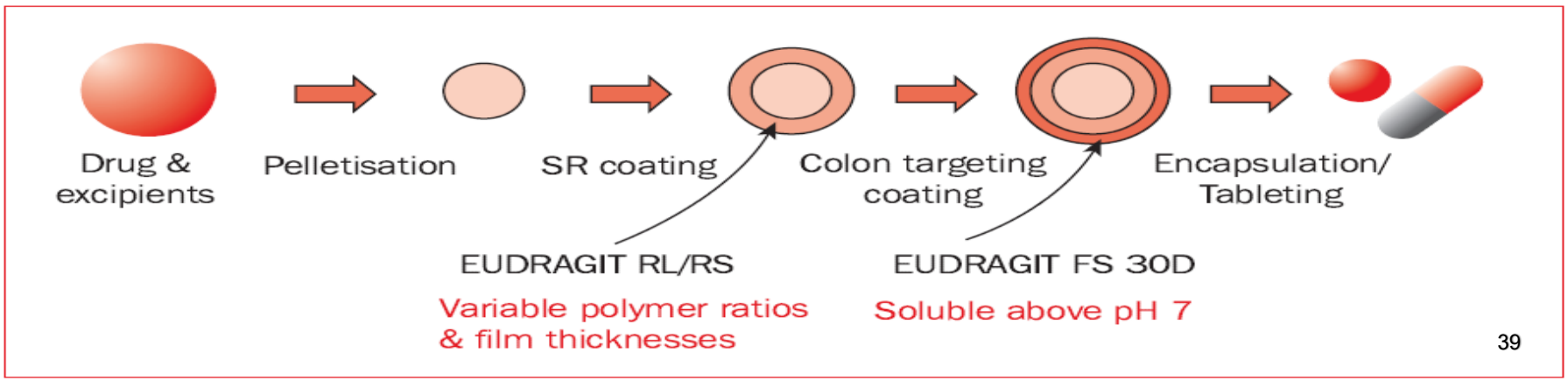
- Unlike **Eudragit L and S** used for **enteric coating**, the ratio of the free carboxyl gps : ester groups in Eudragit FS 30D → 1:10 → the polymer dissolves at a pH of 7.

II- Colon-specific drug delivery

c- Time-controlled release

- By double coating of a dosage form with an outer enteric coat & inner coat of a slow-release polymer → promote release in the colon.
- The outer polymer prevents drug release in the stomach and the inner coat will retard release of the drug → drug is released in the colon.
- In this case drug release is **not affected by pH**, but depends on the **nature and thickness of the inner coat.**

e.g. Eudracol system



B) Extended-Release dosage forms

- A dosage form that allows the drug to be released over prolonged period → the frequency of dosing can be reduced.

❑ **Extended release can be achieved by using**

1. Sustained release dosage forms
2. Controlled release dosage forms.

1. Sustained-release (SR) dosage forms

- are drug delivery system that achieve slow release of drug over an extended period of time after administration of single dose.

➢ Sustained-release can be achieved by use of polymers through

a) Coat granules or tablets → reservoir systems

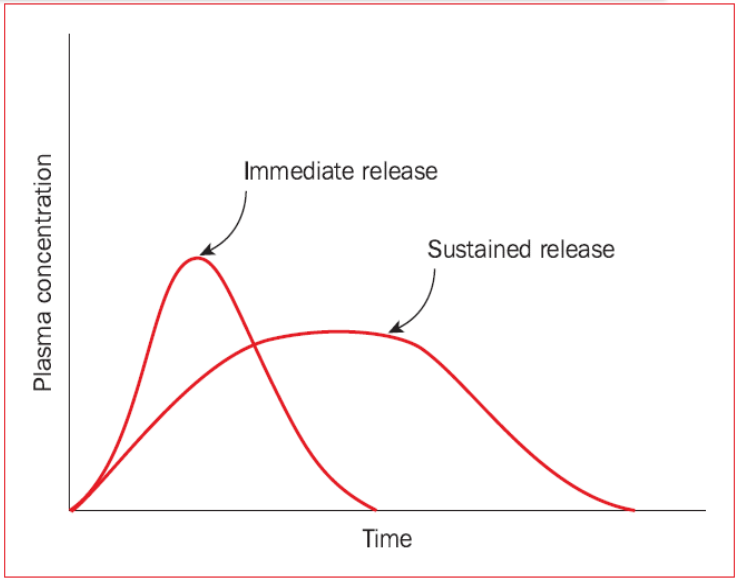
b) Form a matrix in which the drug is dissolved or dispersed → matrix systems.

B) Extended-Release dosage forms

1. Sustained Release dosage forms

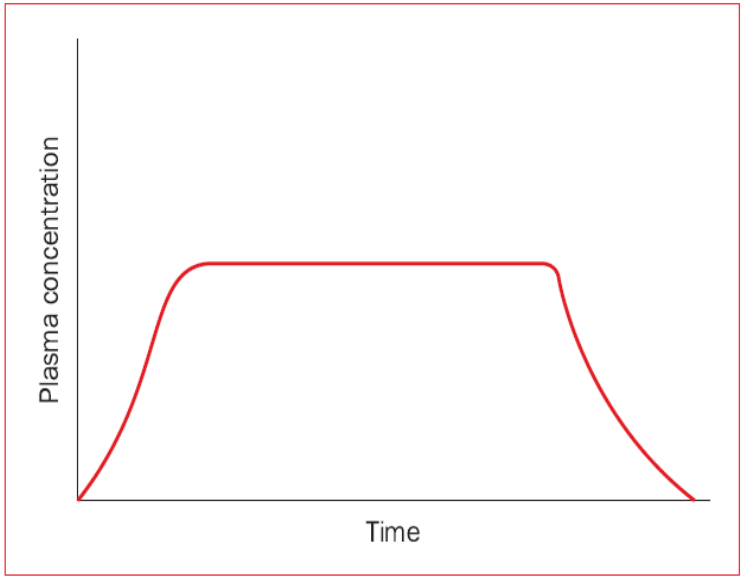
N.B:

– There are sustained release systems that cannot be considered controlled delivery systems.



2. Controlled Release dosage forms

- Drug delivery systems in which maintain constant level of drug in the target tissue or plasma for an extended period of time.



Rationale for extended-release pharmaceuticals

1. Drugs with short $t_{1/2}$ → require multiple daily dosing to achieve the desired therapeutic results.

   - Multiple daily dosing → inconvenient & result in missed doses and noncompliance with the regimen.
   - Multiple daily dosing → therapeutic blood level peaks and valleys.

   a. If doses are administered too frequently → reach MTC of drug → toxic side effects.

   b. If doses are missed → sub-therapeutic drug blood levels → no benefit to the patient.

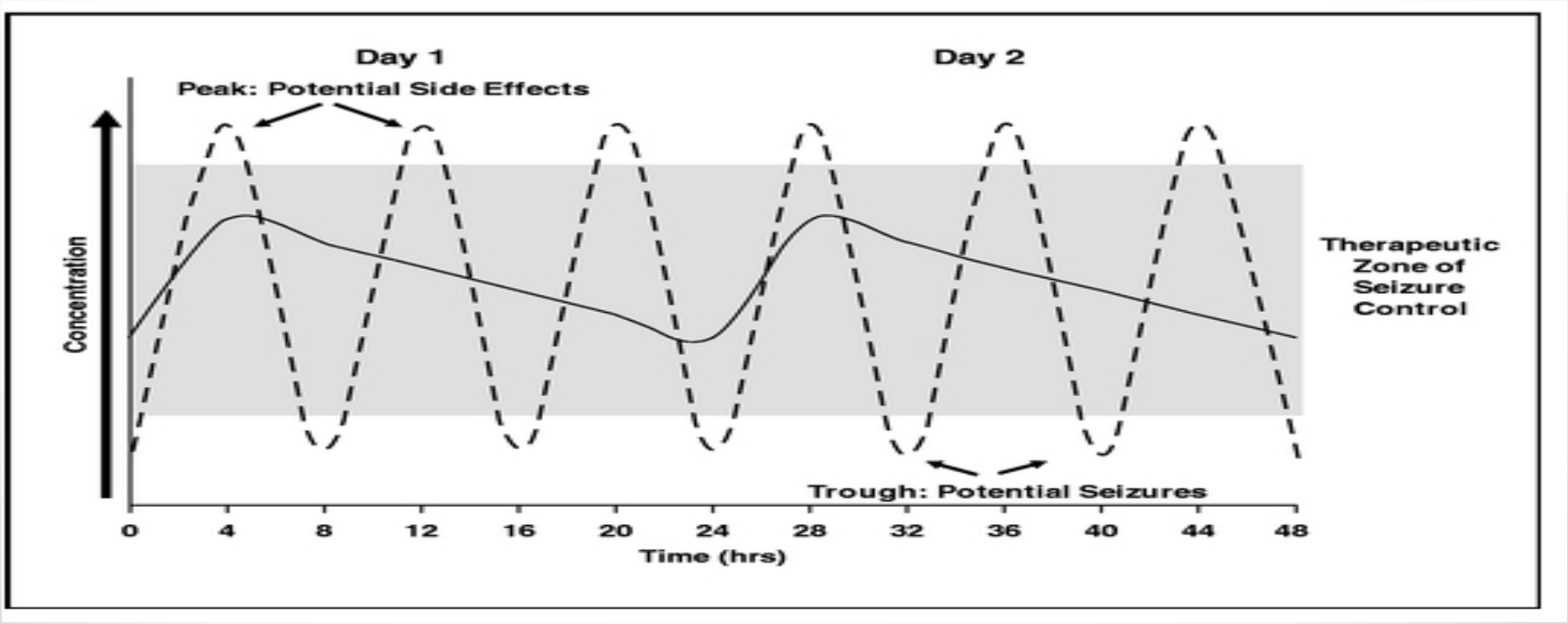
By contrast,

1. Extended-release formulations → taken only once or twice/d.

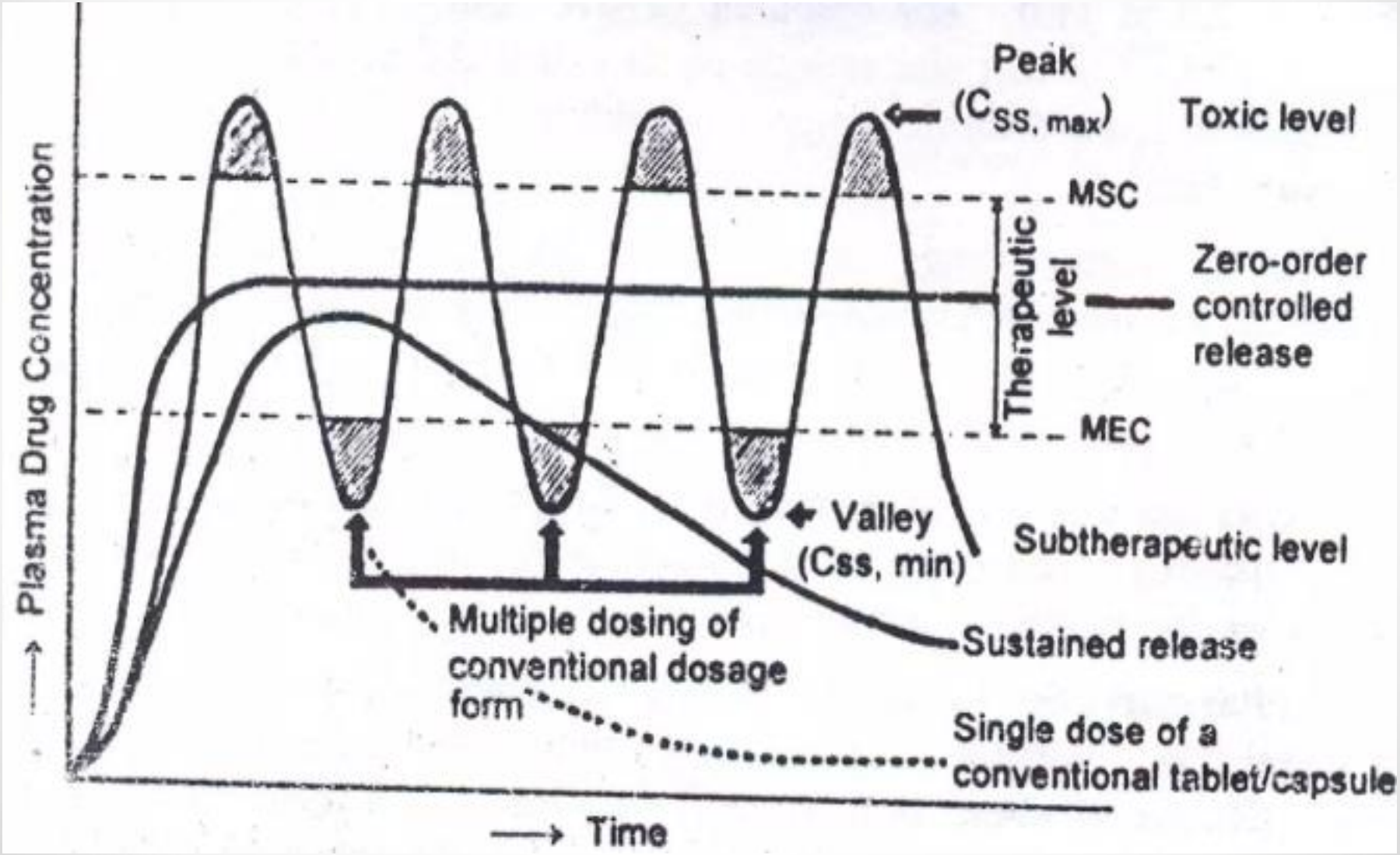
Rationale for extended-release pharmaceuticals

By contrast,

2. Extended-release formulations → ↑ the time drug plasma concentration is within the therapeutic range → ↓ fluctuations (peaks and troughs قمم وقيعان) in the drug plasma concentration → ↓ side effects and ↑ patient compliance. ,



Comparison of drug release profile



C) Targeted-release dosage forms

- Whilst controlling the rate of release of a drug from its delivery system can control plasma drug concentration levels, once released there is a little control over the distribution of the drug in the body.

❑ **Targeted release** describes selective drug release at a specific body region, tissue, or site for drug action.

Advantages:

1. Enhancing the activity of the drug and reduce its toxicity → improve its therapeutic profile.
2. Protecting the drug from inactivation before it reaches its target.

C) Targeted-release dosage forms

Requirements of effective drug targeting system

1. There must be no non-specific interactions with biological components, tissue or organs other than the target site.
2. The targeting system should be nontoxic.
3. The drug targeting system should not be cleared too quickly → allow the drug to interact with its physiological target.
4. It should retain the drug during transit to the target site i.e., no premature release.
5. The system should allow drug release at the target site.

C) Targeted-release dosage forms

Candidates for drug targeting

1. Drugs with high total clearance are most appropriate for targeting since drug not retained at the target site will be cleared rapidly.
2. Highly toxic drugs such as chemotherapeutic agents →improve their therapeutic efficacy while significantly reducing the side effects

Targeted delivery systems consists mainly of

a. Drug
b. Carrier
c. Targeting moiety

Types of drug targeting

I- Passive targeting

- Exploits the natural physiological conditions of the target organ to allow the preferential accumulation of drug carrier at the target site.

Ex_1: Local physiological conditions:

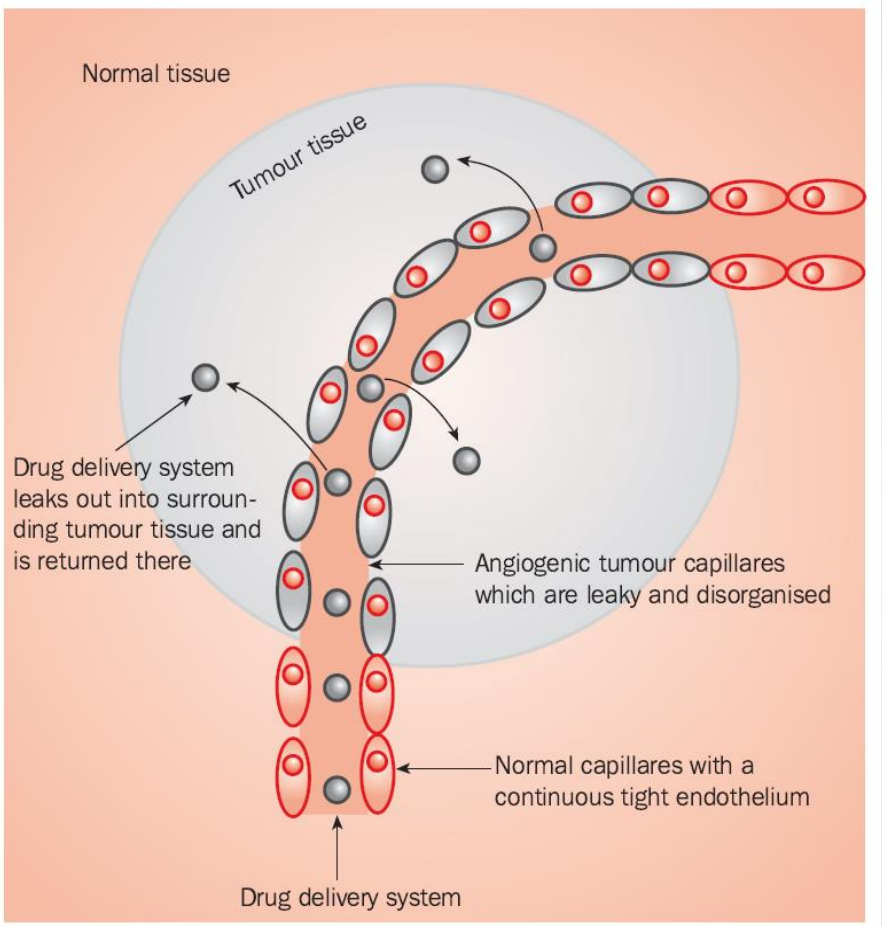
- The local pH or presence of specific enzymes within a target organ can be used to facilitate the release of the active drug from its carrier system. e.g. elevated enzyme levels at a target site can be used to release the active drug selectively from its pro-drug or carrier system.

Types of drug targeting

I- Passive targeting

Ex$_2$: **Enhanced permeability and retention (EPR) effect**:

- The integrity of the endothelial barrier **at sites of inflammation or tumors** is disrupted by the presence of endothelial gaps as large as **200-300 nm.**



- This leaky nature of blood vasculature can be exploited via EPR effect to target drug carriers passively to a sites of inflammation or tumors

Types of drug targeting

II- Active targeting

- Active targeting is based on **ligand-receptor binding** and takes advantage of **elevated levels of such receptors at a target site**.

Ex_1: Targeting via folate receptors

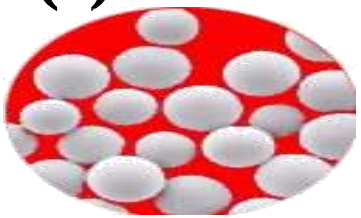
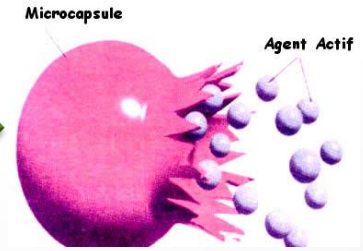
– Folate receptors are normally found at low levels in most tissues, but these receptors are **over-expressed** in tumor tissues. →Therefore, folate-targeted drug delivery systems are widely used for active targeting of tumor tissues over-expressing folate receptors.

SUSTAINED RELEASED

Formulation

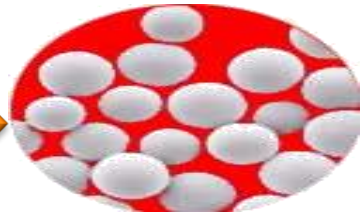
Components of a sustained- release delivery systems

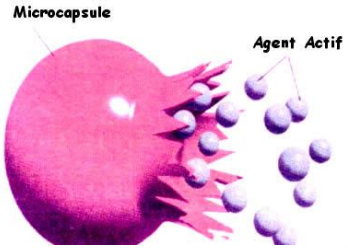
Include:

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

Mechanism aspects of Oral drug delivery formulation

- Dissolution
  - Matrix
  - Encapsulation
- Diffusion
  - Matrix
  - Reservoir
- dissolution & diffusion





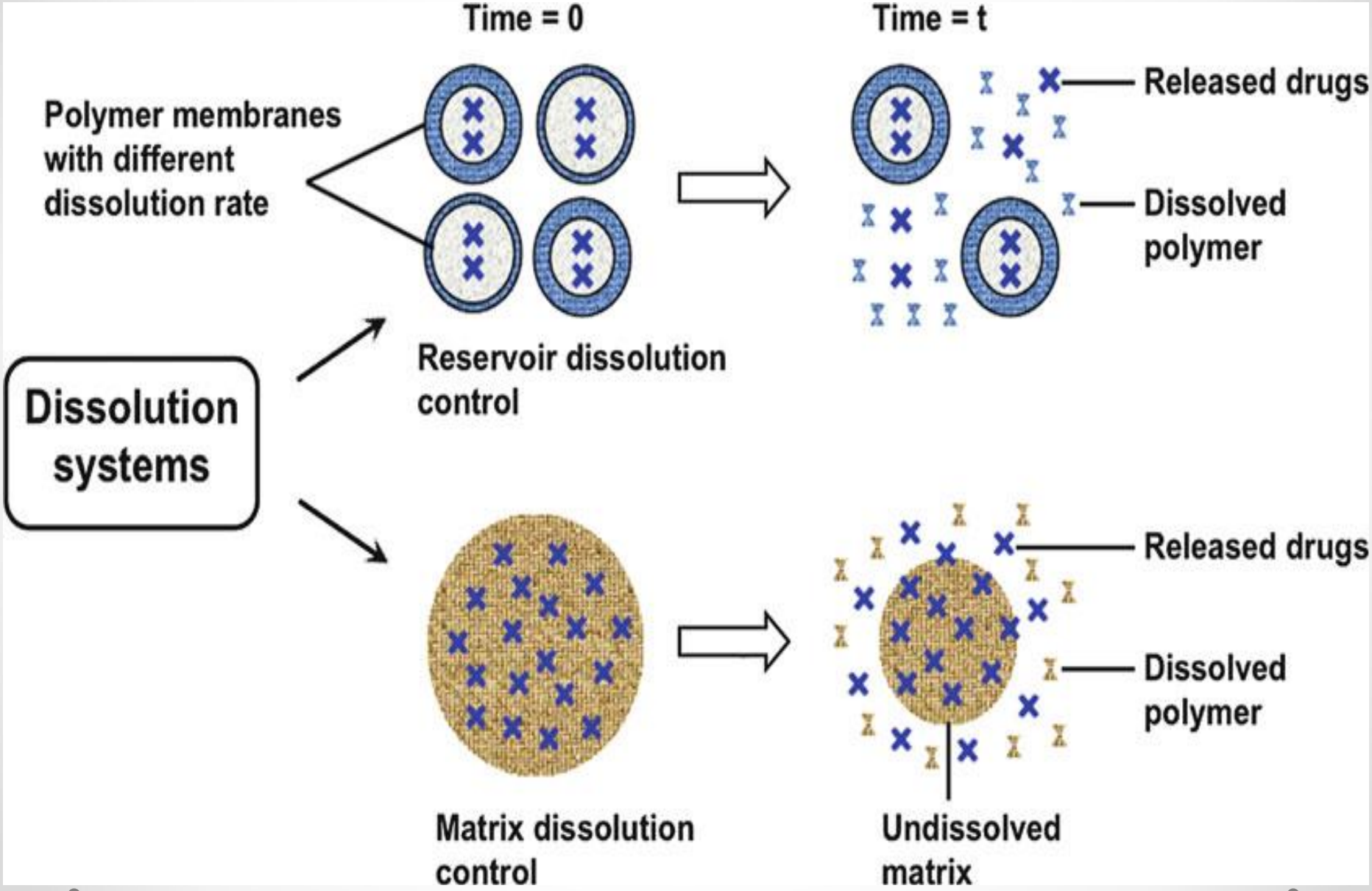
- Osmotic pressure
  - Elementary osmotic pump
  - Push-pull
  - OROS-CT

I- Dissolution-based sustained-release dosage forms

- These system are most commonly employed in the production of enteric dosage forms.
- The rate of drug release can be decreased by lowering the drug dissolution rate.
- This can be achieved by increasing the drug particle size via:

a. Incorporating the drug into a slowly dissolving matrix (matrix dissolution dosage forms)

b. Coating the drug with a slowly dissolving polymeric membranes (encapsulated dissolution dosage forms)


Time = 0
Time = t
Polymer membranes with different dissolution rate
Released drugs
Dissolved polymer
Dissolution systems
Reservoir dissolution control
Released drugs
Dissolved polymer
Matrix dissolution control
Undissolved matrix

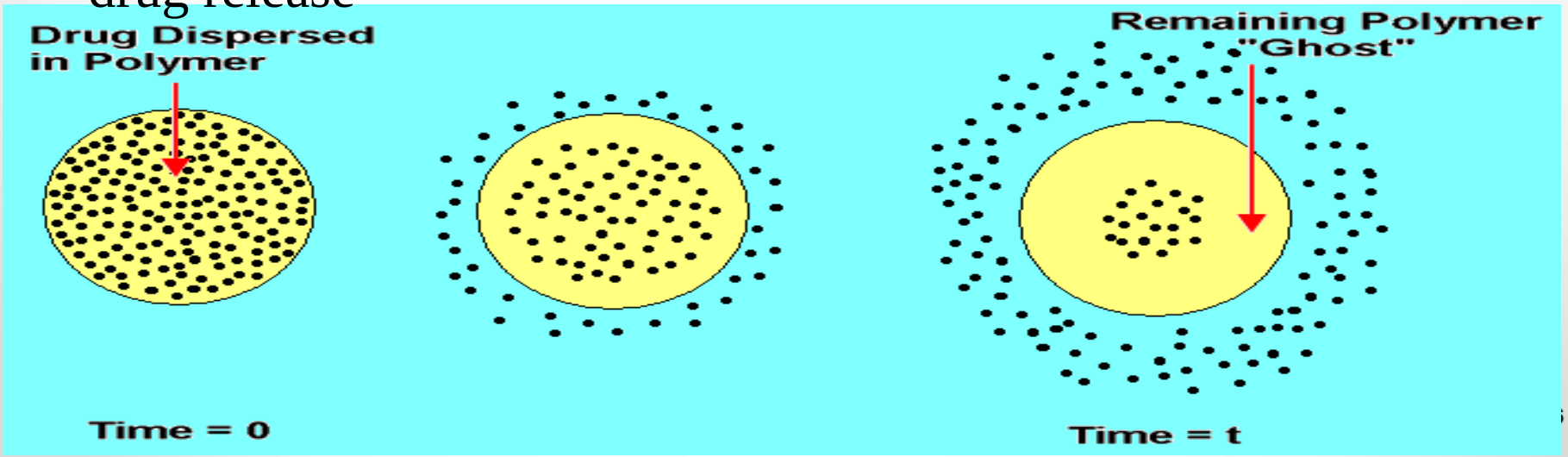
I- Dissolution-based sustained-release dosage forms

a. Matrix devices (matrix dissolution control)

- Matrix devices: Drug particles or granules are uniformly dispersed into polymeric or a non degradable matrix.
- The release of the dissolved drug result when the matrices dissolve.
- It is also called as monoliths متراصة since the drug is homogenously dispersed throughout a rate-controlling medium.

Dissolution is controlled by:

1. The solubility of the polymeric carriers is a key factor in controlling drug release



I- Dissolution-based sustained-release dosage forms

a. Matrix devices (matrix dissolution control)

- In this model (polymeric matrix) drug in outside layer exposed to the bathing solution is dissolved first and diffused out of the matrix followed by subsequent layers.
- The release rate of drug from such a device is not zero order, since it decreases with time (rate not constant) because the active agent has a progressively longer distance to travel and therefore requires a longer time to release however, this may be clinically equivalent to constant drugs (zero order drugs).

❑ **Rate Limiting step**

- Drug coated with a polymer;

– Dissolution of the polymer (Controlled by the nature of the polymer)

- Drugs dispersed in a polymer;

– The release of the drug from the solid surface of the polymeric matrix to the bulk solution side

I- Dissolution-based sustained-release dosage forms

b. Reservoir device (Coating dissolution-controlled system)

- Systems involve coating or encapsulated of individual particles of drug (core) with a slow dissolving material (polymeric membranes) of specified thicknesses and/or dissolution characteristics.
  - Some granules are ***not coated*** that provide immediate release of the drug→ immediate action.
  - whilst the others are coated with polymer such as ***EC*** → Sustained action

  →Some granules receive few coats, and some receive many.

  →The various coating thicknesses produce a sustained-release effect.

- These granules are then compressed into a tablet or filled into a hard gelatin capsule.
- Upon ingestion, the drug is released over a prolonged period of time depending on the rate of the dissolution of the polymeric coat; the thicker the initial coat, the later the drug will be released

I- Dissolution-based sustained-release dosage forms

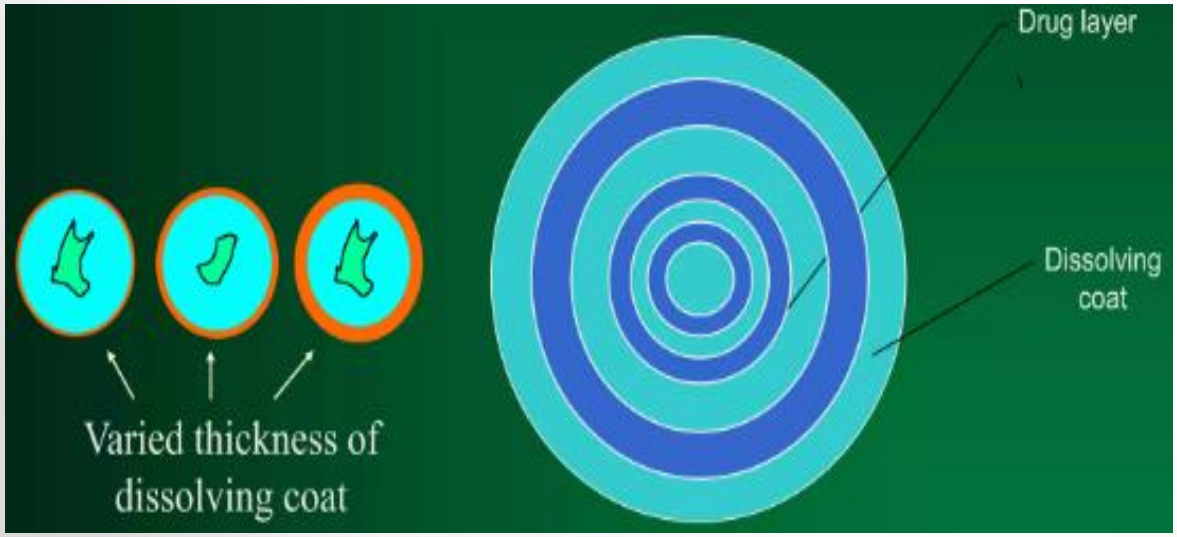
b. Reservoir device (Coating dissolution-controlled system**)**

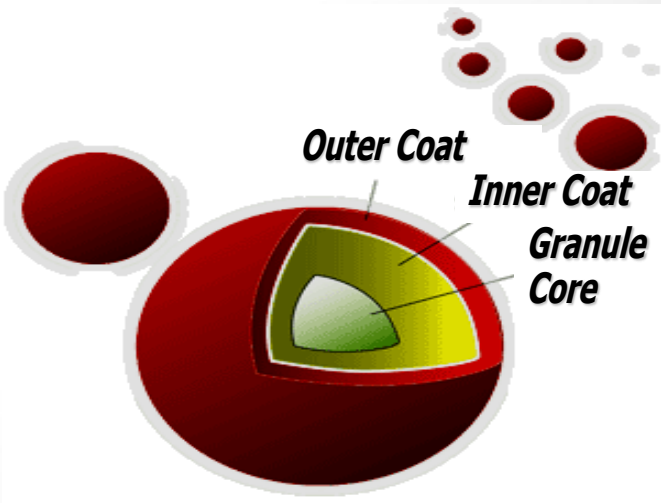
- It masks colour, odour, taste, and minimizing GI irritation.
- Examples: Ornade spansules, Chlor trimeton Repetabs

Two types of dissolution controlled; pulsed delivery systems are present:

i. Single bead type device with alternating drug and rate controlling layers

ii. Beads containing drug with differing thickness of dissolving coats





I- Dissolution-based sustained-release dosage forms

b. Reservoir device (Coating dissolution-controlled system)

❑ The nature of the polymeric membrane and its thickness determines the rate and site of release of drug from the system.

- **Thickness:** delay of release
- **Multi-layers**: delay of release, targeting site of release, sustained release.
- **Type of polymer**: targeting site of release as when using pH sensitive polymers e.g. methyl vinyl ether maleic anhydride copolymer.

– pH sensitive polymers have a characteristic pH above which they are completely soluble and below which they are completely insoluble.

II- Diffusion-based sustained-release dosage forms

- In these systems, the polymer itself should **not dissolve**, but **should allow** the drug to diffuse through the polymer membrane/matrix to outside.
- In diffusion-controlled delivery systems, rate control is obtained by the penetration of fluids into the system.
  - Major process for absorption,
  - No energy required.
  - Drug molecules diffuse from a region of higher concentration to lower concentration until equilibrium is attained

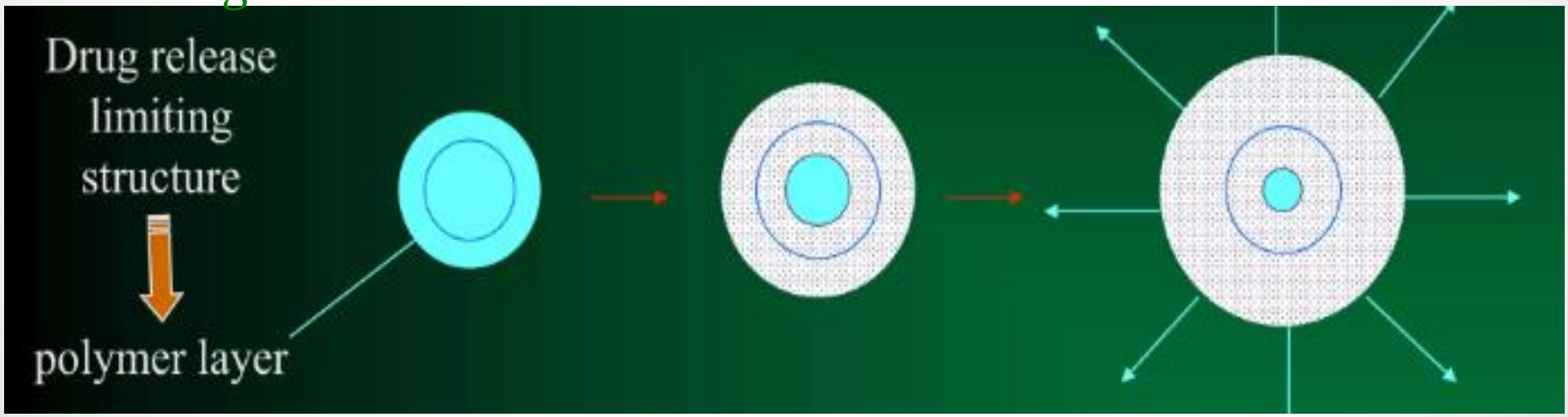
Diffusion-based sustained-release dosage forms can be divided into

A. Polymer membrane (reservoir) system

B. Polymer matrix systems

A) Polymer membrane (Reservoir) system

- These system are hollow أجوف containing an inner core of drug (reservoir), which is surrounded by an inert water insoluble polymeric membrane (film) & release by diffusion through the rate limiting membrane

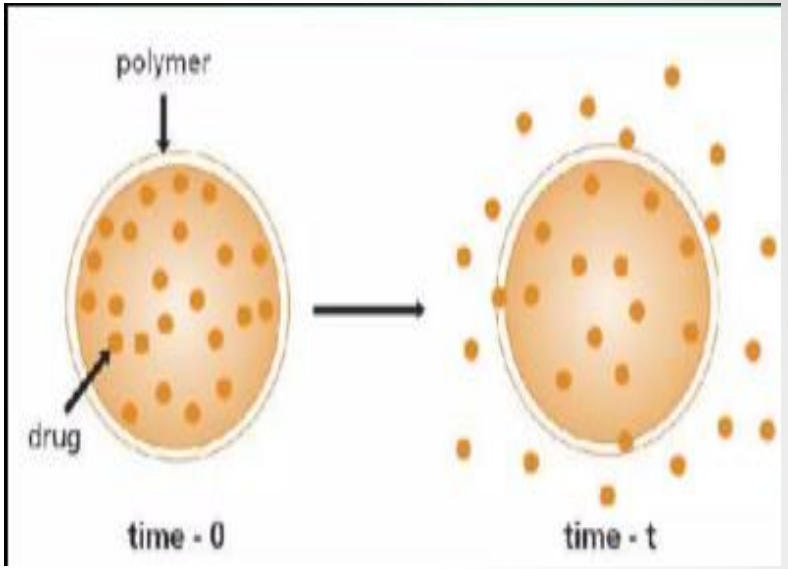


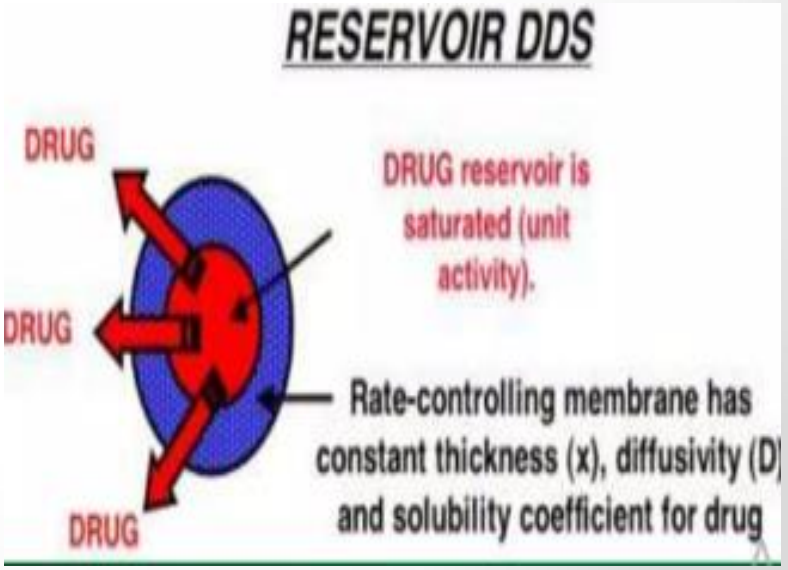
- Also called as Laminated مغلفة matrix device.
- Polymer can be applied by coating or microencapsulation.

A) Polymer membrane (Reservoir) system

Characters

1. The release of the drug occurs by diffusion of drug molecules through the film.
2. The release profile usually follows **zero-order kinetics.**
3. Factors controlling drug release through the film include
   a. Nature of the drug & the polymer film
   b. The permeability of the drug across the polymer film.
   c. Polymeric content and the polymer film thickness.
4. To ensure a sustained release, membrane integrity سلامة must be maintained.





A) Polymer membrane (Reservoir) system

Advantages

1. Reservoir systems lead to a near-zero-order release of drugs → allow the release of the drug for a sustained period of time

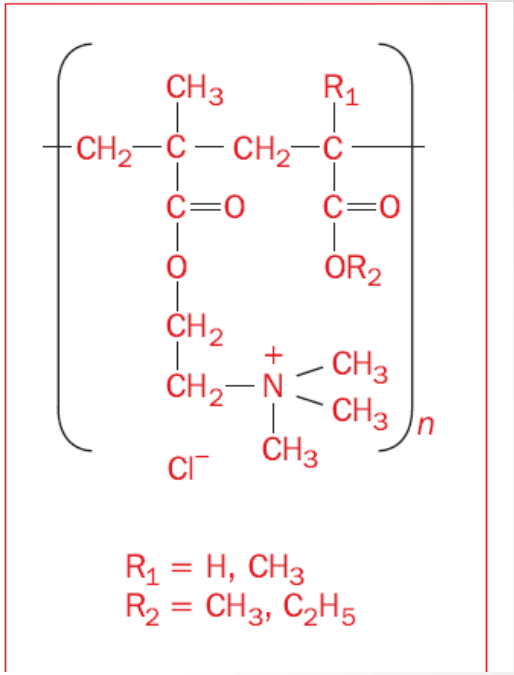
Disadvantages

1. If the polymeric membrane is not dissolved/degraded after passage through G.I.T. → the dosage form will appear in the stool of the patient → who might assume that the drug has not been absorbed.
2. If such systems are used for administration routes other than oral route → they must be removed from the body after the drug is released.
3. If the polymeric coat is faulty → dose dumping may occur.

A) Polymer membrane (Reservoir) system

Commonly used Polymers

Ethylcellulose (EC) and Eudragit RS or RL

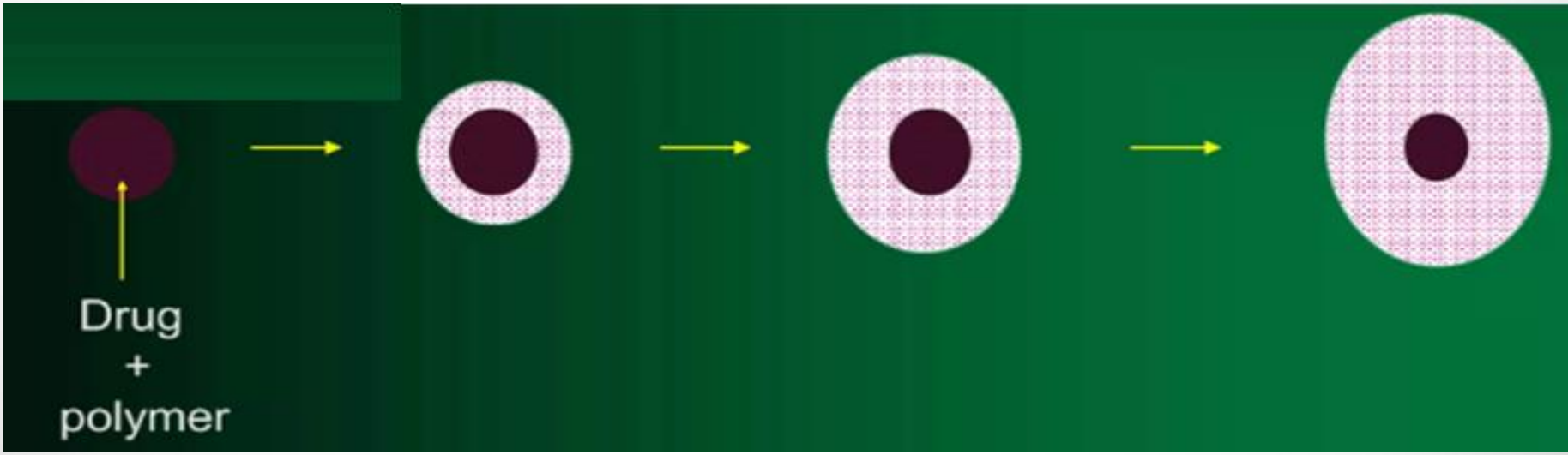


- The presence of the **quaternary ammonium group** gives the polymer the necessary polarity to allow water and drug diffusion after administration.

- **Eudragit RS** sustains drug release for longer time than Eudragit RL, → because Eudragit RL contains double the amount of quaternary ammonium groups as Eudragit RS.

B) Polymer matrix systems

- The drug is uniformly dispersed in insoluble matrix of rigid non-swellable hydrophobic materials or swellable hydrophilic substances, which acts as the release matrix.



B) Polymer matrix systems

Characters

1. Drug release from matrix systems is controlled by its diffusion throughout the matrix into the surrounding environment.
2. Polymer matrix systems can either be:
   a. Homogenous: the drug is partly dissolved and evenly distributed in the polymer matrix
   b. Porous: the matrix contains an additional soluble polymer which after administration dissolves quickly → leaving pores in the release matrix
3. Drug release from matrix systems does **not follow zero-order** kinetics instead the system shows a linear release of the drug as a function of the square root of time **(Higauchi order)**

B) Polymer matrix systems

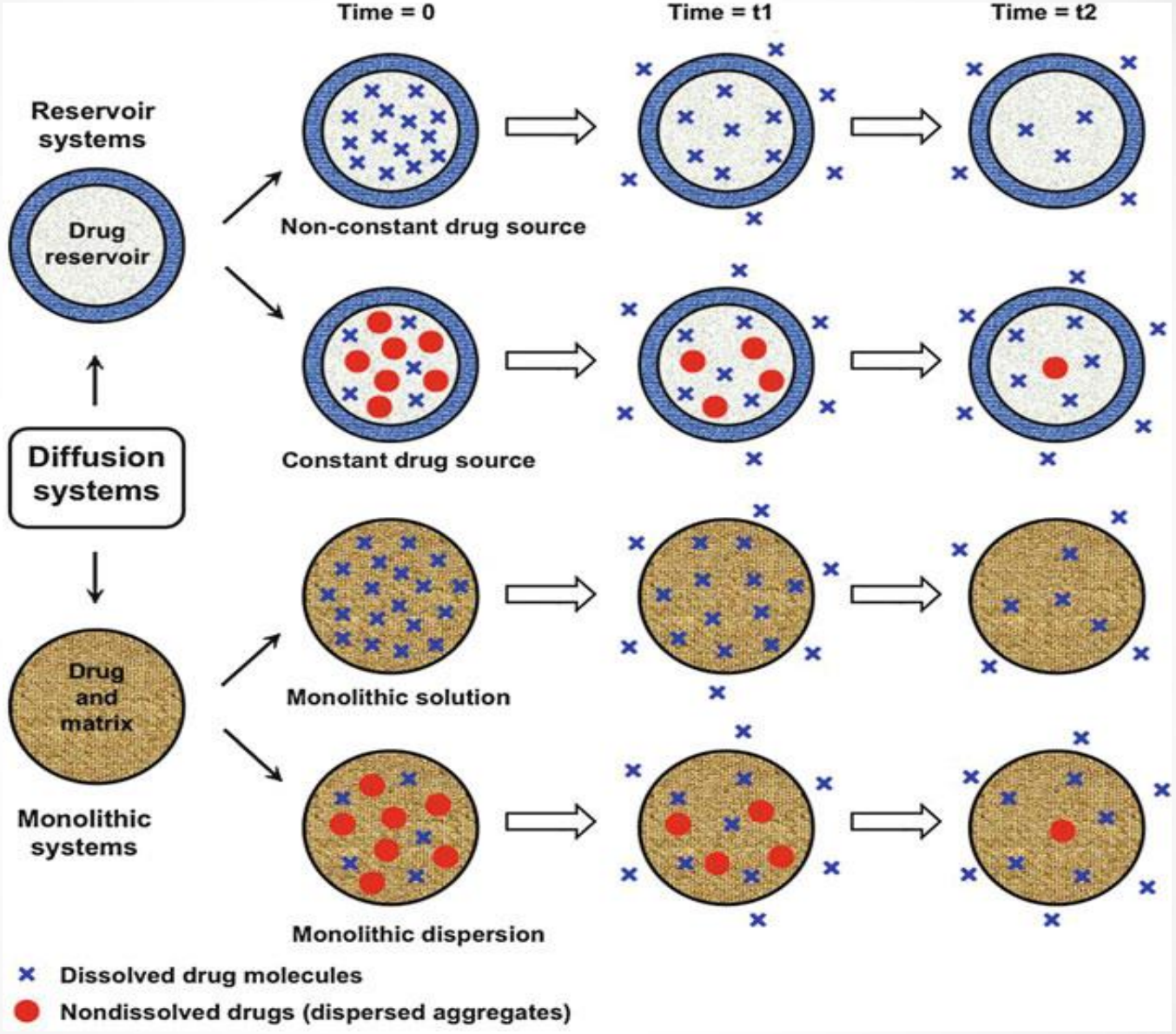
Advantage

1- They are less expensive than reservoir systems.

2- There is no risk of dose dumping.

Polymers used

- Hydrophobic matrix formers such as poly (ethylene), poly (propylene) and ethylcellulose (EC).
- Hydrophilic matrix formers such as MC, HPMC, Eudragit NE 40D


Time = 0
Time = t1
Time = t2
Reservoir systems
Drug reservoir
Non-constant drug source
Constant drug source
Diffusion systems
Drug and matrix
Monolithic solution
Monolithic systems
Monolithic dispersion
Dissolved drug molecules
Nondissolved drugs (dispersed aggregates)

Matrix system

- Achievement of zero order- is difficult
- No danger of dose dumping
- Not all drugs can be blended with a given polymeric matrix.
- Can deliver high mol. w.t compounds.
- do not need to be surgically removed.

Reservoir system

- Achievement of zero order is easy
- Rupture can result in dangerous of dose dumping
- Drug inactivation by contact with the polymeric matrix can be avoided
- Difficult to deliver high mol. w.t compounds

- Materials used as retardants in matrix tablet formulations :

MATRIX CHARACTERISTICS	MATERIAL
Hydrophobic carriers	
(a) Insoluble, inert matrix	Polyethylene Polyvinyl acetate Polyvinyl chloride Ethyl cellulose
(b) Insoluble, erodable	Carnauba wax Polyethylene glycol Fatty alcohol Fatty acids
Hydrophilic carriers	Methyl cellulose Hydroxy Ethyl cellulose HPMC CMC, Na CMC Sodium alginate

III- Bio-erodible sustained-release dosage forms

Dissolution & Diffusion Controlled Release DDs

- They are matrix systems in which the drug are trapped in partly soluble polymeric membranes or matrices which erode over a period of time such as waxes, glycerides, stearic acid, ….etc
- In this type, dissolution of the polymer matrices and diffusion of the drug molecule are both involved simultaneously.
- **The** polymeric membranes is partly soluble in nature, upon contact with physiological fluid will dissolve to create pores, → flow into the core of the system → dissolve the encapsulated drugs → intiate the release by diffusion,
- The **erosion and/or degradation** of the polymer is the **rate-limiting step** for drug release.

Principle

- Portion of drug intended to have sustained action is combined with lipid or cellulosic material and then granulated.
- Untreated drug granulated
- Both mixed

III- Bio-erodible sustained-release dosage forms

Dissolution & Diffusion Controlled Release DDs

Advantage:

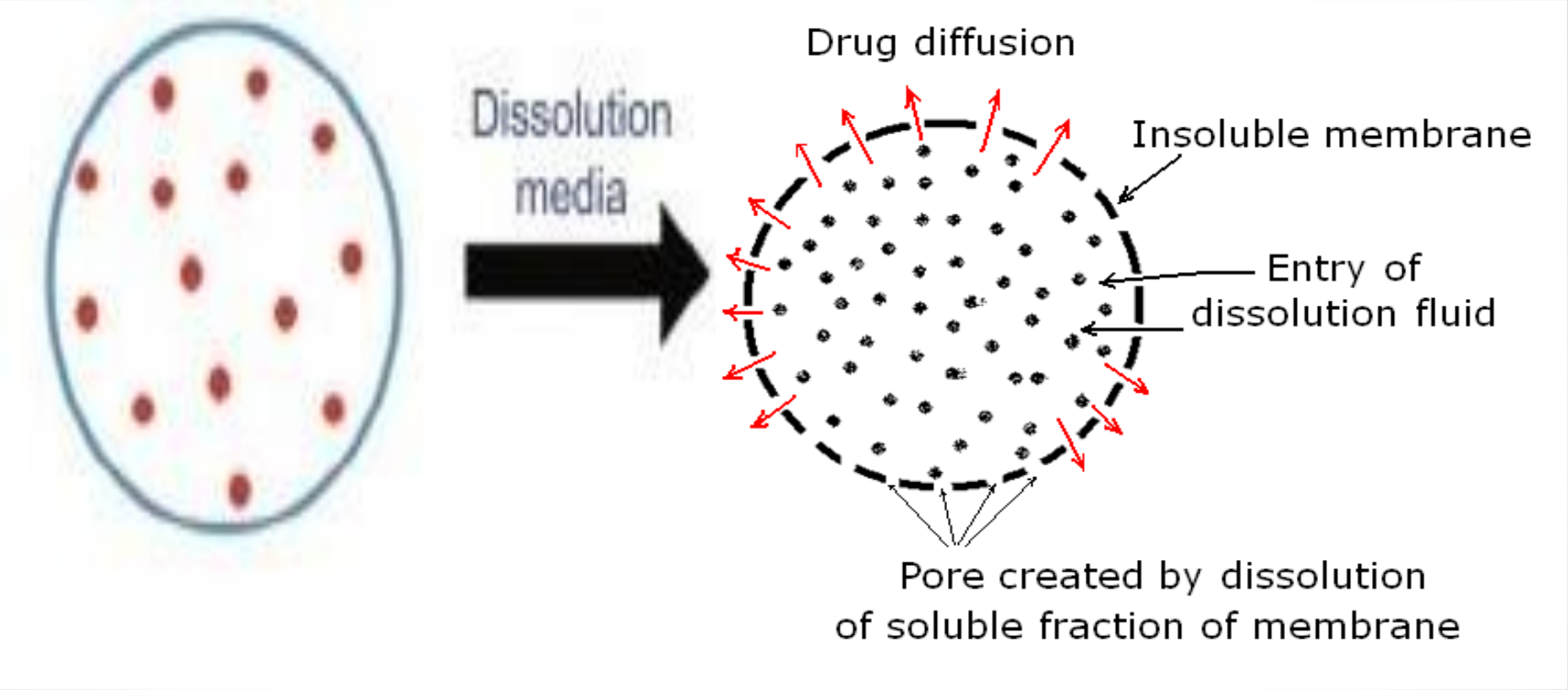
- *No "ghost matrix" will be formed* as in the case of matrix systems with insoluble and non-degrading polymers.

Disadvantage:

- It is difficult to control/predict the release kinetics of these systems.
- Potential toxicity of degraded polymer

III- Bio-erodible sustained-release dosage forms

Dissolution & Diffusion Controlled Release DDs



- Erosion of a polymer matrix is defined as the loss of polymer mass from the matrix.

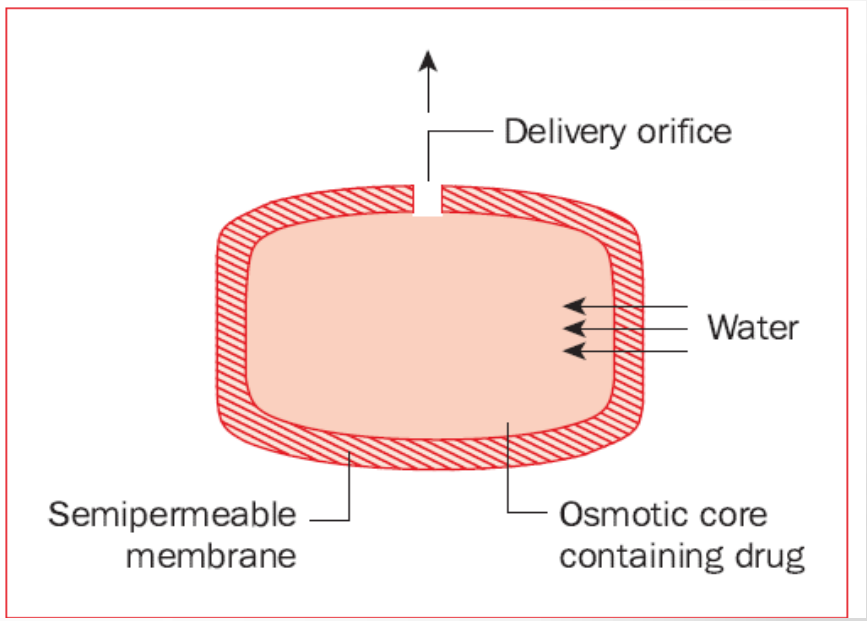
Polymers used: poly (lactides) or copolymers of lactic and glycolic acid.

IV- Osmotic pressure-activated controlled DDS

- The system operates on the principle of **osmotic pressure**.
- Drug release from these systems is independent of pH and other physiological parameter to a large extent and it is possible to modulate the release characteristic by optimizing the properties of drug and system.

The basic components of an osmotic pump are:

1. Drug
2. Osmotic agent
3. Semi-permeable membrane



IV- Osmotic pressure-activated controlled DDS

❑ Drug:

- Biological half-life [2-6 h]
- Highly potent drug
- Required for prolonged treatment (e.g. nifedipine, glipizide, virapamil).

❑ Osmotic agent = Osmogent

It may be inorganic or organic in nature.

- Inorganic water soluble osmogents: Mg. sulphate, NaCl.
- Organic polymer osmogents: Sodium CMC, HPMC.

❑ Semi-permeable membrane

The membrane must be:

- Stable at both the outer and the inner environment of the device.
- Sufficiently rigid to retain its dimensional integrity during the operational lifetime of the device.
- Relatively impermeable to the contents of dispenser so that osmogent is not lost by diffusion across the membrane.
- Biocompatible.

IV- Osmotic pressure-activated controlled DDS

Advantages of osmotically controlled DDS

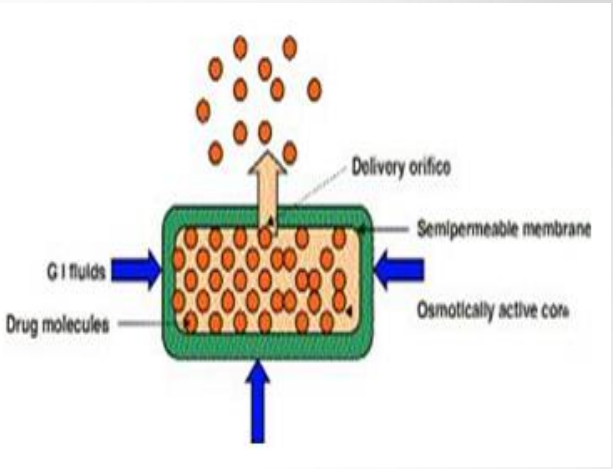
1. They typically give a zero-order release profile after an initial lag.
2. Drug release is independent of gastric pH.
3. A high degree of in-vitro and in vivo correlation (IVIVC).
4. The rationale for this approach is that the presence of water in G.I.T is relatively constant, at least in terms of the amount required for activation and controlling osmotically based technologies.

Disadvantage of osmotically controlled DDS:

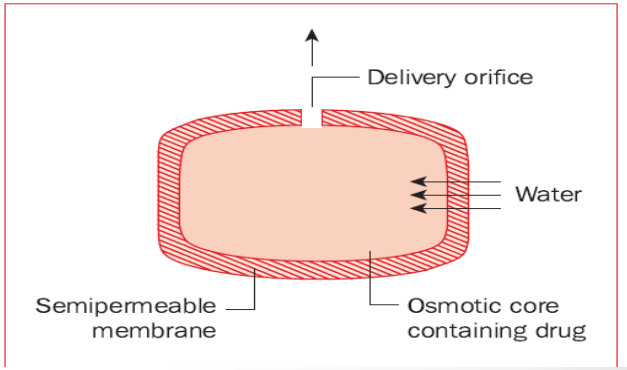
1. High Cost.
2. If the coating process is not well controlled there is a risk of film defects, which results in dose dumping
3. Size of the hole is critical

A- Elementary osmotic pump

- The system consists of a tablet core (drug + osmotic active agent) coated with a semi-permeable membrane in which a delivery orifice is drilled by a laser beam.



- When such a system is ingested → water from the G.I.T. diffuses in → the drug dissolves and is pushed out through the exit hole via the created osmotic pressure within the system.



Drug release rate may be altered by

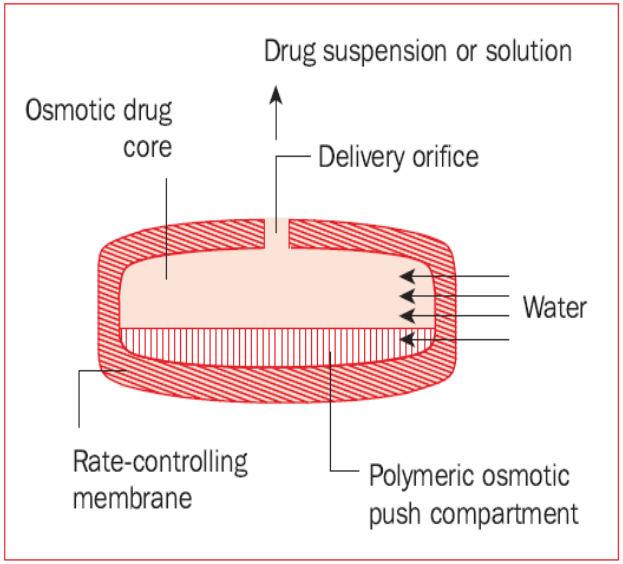
a) Changing surface area
b) Thickness or composition of the membrane
c) Diameter of the release orifice.
d) Solubility
e) Osmotic pressure

- The drug release rate is not affected by GIT acidity, alkalinity, fed conditions, or gastrointestinal motility.
- The system is *not suitable* for delivery of *poorly soluble drugs.*

IV- Osmotic pressure-activated controlled DDS

B- Push-pull systems

- They comprise one push layer (which is drug-free but contains osmotic active agents and water-swellable polymers) and one or more drug layers.

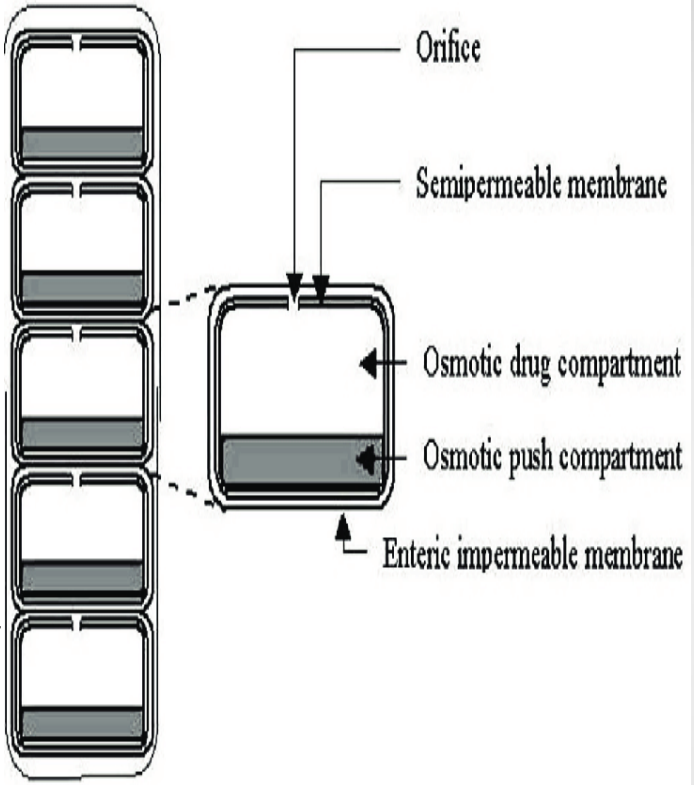


- These multi-layered tablets are coated with a semi-permeable membrane into which a small orifice for drug release is drilled.
- Upon ingestion → water from G.I.T. is drawn in → push layer swell → formation of a liquid suspension in the drug layers → The expanding push layer pushes the drug suspension out of the exit hole drilled into the drug layer

IV- Osmotic pressure-activated controlled DDS

C. OROS-CT system

- It is used as a once or twice daily formulation *for targeted delivery of drugs to the colon.*
- The OROS-CT contains an enteric coat and a semi-permeable membrane and can be formed of a single or of as many as *five to six push pull osmotic units filled in a hard gelatin capsule.*



- After coming in contact with the gastric fluids, gelatin capsule dissolves and the enteric coating prevents entry of fluids from stomach to the system,→ as the system enters into the intestine the enteric coating dissolves and water is imbibed into the core thereby → causing the push compartment to swell.

IV- Osmotic pressure-activated controlled DDS

OROS-CT system

- At the same time flowable gel is formed in the drug compartment, which is pushed out of the orifice at a precisely controlled rate.

❑ Application for OROS-CT system: Verapamil HCl (Covera HS) used for the treatment of angina pectoris.

Marketed product

Tablets		
Composition	**Product name**	**Manufacturer**
Carbamazepine	Zen retard	Intas
Diclofenac sodium	Dic-SR	Deep pharma limited
Diclofenac sodium	Nac-SR	Systopic
Diclofenac sodium	Voveran-SR	Ciba- Geigy
Nifedipine	Depine retard	Cadila health care
Theophylline	Theo PA	Welcome
Capsules		
Diazepam	Elcoin	Ranbaxy
Diclofenac sodium	Diclotal CR	Blue cross
Indomethacin	Indoflam TR	Recon
Nitroglycerine	Angispan	Lyka
Transdermal		
Nitroglycerine	Nitroderm TTS	Ciba-Geigy
Nicotine	Nicotine patch	Ciba-Geigy