# Modified-Release Dosage Forms & Drug Delivery Systems

Drug delivery systems can be classified into immediate-release and modified –release dosage forms**.**

➢ **Immediate release**

- Many dosage forms are designed to release the drug immediately or at least as quickly as possible after administration. This is useful if a fast onset of action is required for therapeutic reasons. For example, a tablet containing a painkiller should disintegrate quickly in the gastrointestinal tract to allow a fast uptake into the body.
- The onset of action is very fast for intravenous injection and infusions and the pharmacological effect may be seen in a mater of seconds after administration.
- Allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug.

There are some situations in which this rapid onset is not desirable, and a modification of the drug release pattern (or profile) is necessary to slow it down or make the drug's effects last longer (e.g. for 24 h).

These more advanced oral drug delivery formulations are often referred to as oral modified-release drug delivery systems.

•**Modified-release drug delivery** refers to the manipulation or modification of drug release from a dosage form.

• The term modified release dosage form is used to describe products that alter the timing and rate of release of the drug substance.

• **A modified release dosage form** is defined as one for which the drug – release characteristics of time course and / or location are choosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms.

## Advantages of modified release dosage

1- Improved patient compliance:- by reducing the frequency of medications or administration. Once-daily dosing is considered to be more convenient for patients and reduces the risk of missed doses throughout the day.

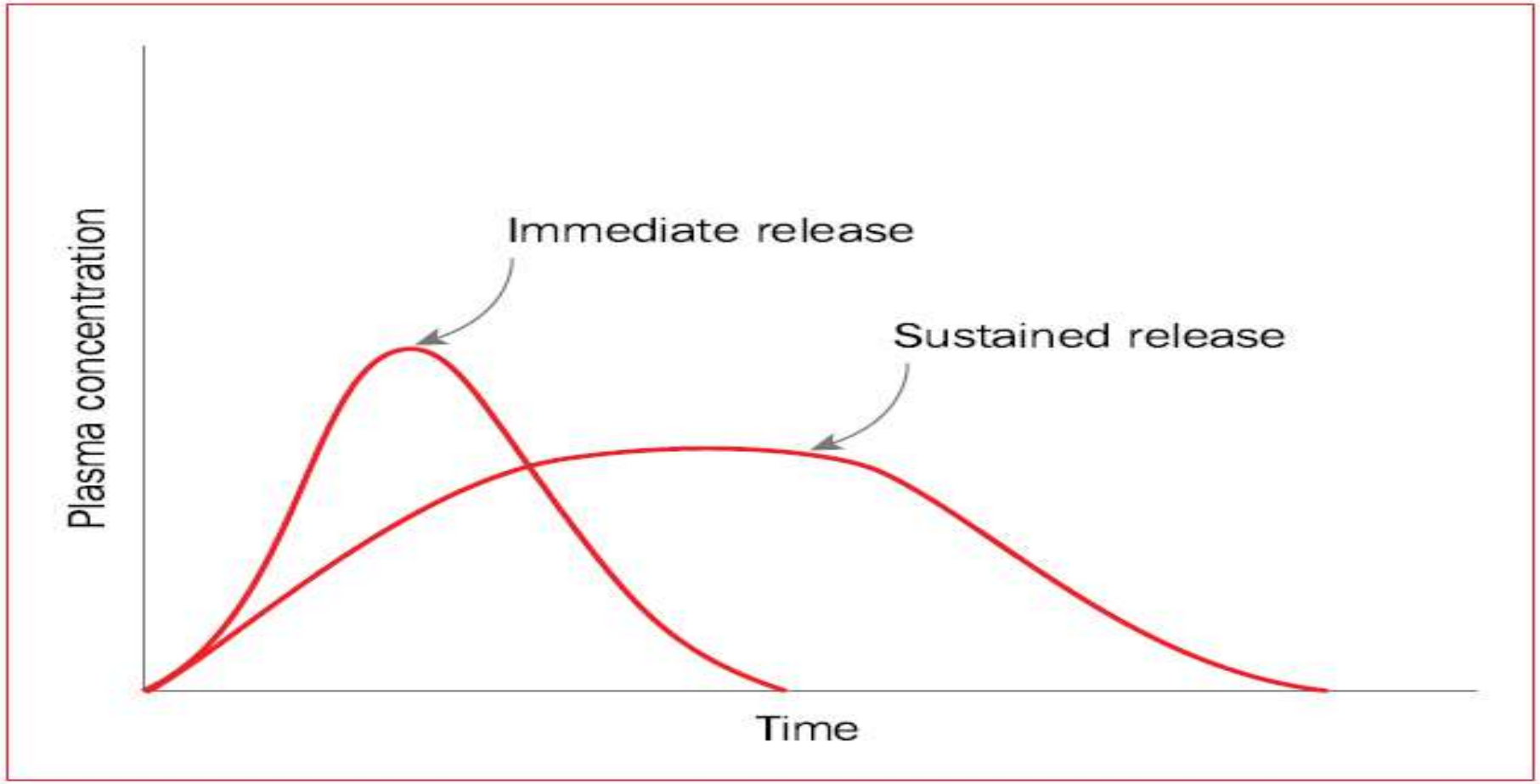
2- Cost effective.

3- Increase effectiveness of drug by localization at the site of action

4- Reducing the dose required.

5- Maintaining drug levels overnight: It is often not acceptable that patients be required to take medications during the night, with consequent loss of sleep.

6- Avoidance irregular drug plasma concentration and thus avoiding undermedication and overmedication which can be caused by convenient dosing.




Plasma concentration versus time profile of a sustained-release oral dosage form compared to an immediate-release dosage form

- ✓ **Keeping the drug in the therapeutic range:** Modified release is often used to improve therapeutic outcomes for a patient relative to an immediate release medication.

For example, a drug which is rapidly absorbed and eliminated can have a steep plasma profile in an immediate-release formulation. An extended-release formulation can keep the drug at therapeutic levels for longer. For example, when an opioids pain killer is administered to a patient with terminal cancer, any time that the drug concentration is below therapeutic concentrations the patient experiences pain.

**7- Reducing side effects.** Immediate-release formulations can often have a high maximum concentration in the blood ($C_{max}$). If $C_{max}$ is above the maximum safe concentration of the drug, adverse events may be more likely.

Using modified-release formulations to reduce $C_{max}$ can reduce the incidence and severity of the side effects of some drugs.

Additionally, some drugs, such as potassium chloride, can be irritating to the gastrointestinal tract if delivered in an immediate-release bolus. A slow, sustained release is required to minimize the build-up of irritant concentrations.

**Disadvantages of controlled drug delivery systems:**

1. Chances of dose dumping.
2. Dose withdrawal is not possible.
3. Higher cost of formulation: For pharmaceutical companies the development costs for a modified release formulation are much higher than those for a conventional immediate-release dosage form

# TYPES OF MODIFIED RELEASE DOSAGE FORM

**1- Extended Release**: extended-release dosage defined as form as one that allows a reduction in dosing frequency from that necessitated by a conventional dosage form, such as a solution or an immediate-release dosage form. Extended release systems allow for the drug to be released over prolonged time periods. By extending the release profile of drug, the frequency of dosing can be reduced.

**2- Delayed Release**: dosage form is designed to release the drug at a time other than promptly after administration. The delay may be time based or based on the influence of environmental conditions, like gastrointestinal pH.

**Delayed-release dosage forms**: These release the drug at a time later than immediately after administration (i.e. there is a lag time between a patient taking a medicine, and the drug being detected in the blood).

**3- TARGETED RELEASE:**

Drug release that is directed towards isolating or concentrating a drug in a body region, tissue, or site for absorption or drug action

**4- REPEAT ACTION:**

These are dosage forms usually containing two single doses of medication, one for immediate and the second for delayed release e.g. bi-layered tablets

- Modified-release formulation can be designed as a single entity (usually a tablet). A **single-unit dosage** form is advantageous from a manufacturing standpoint, as it can often be manufactured using conventional techniques, such as compaction and film coating.
- There may be some biopharmaceutical disadvantages to tablet formulations however. For example, as they do not disintegrate in the stomach, the dosage form could become trapped in the stomach for a long time (with food). For drugs targeted to the small or large intestine, this could prevent them reaching their site of action.
- **Multiple-unit systems** (e.g. pellets or granules filled into a hard capsule shell) may have more reproducible gastric emptying, have a reduced risk of dose dumping, and it spreads over a large area and avoid the exposure of high conc. of drug to the mucosa . However, these can be more difficult to manufacture and to scale up.

- Modified-release formulation can be designed as **matrix formulation or coated formulation.** The release of an active pharmaceutical ingredient can be modified by two main methods.

- Firstly, the release-modifying ingredients can be incorporated throughout the matrix of the dosage form, wherein the whole dosage form encompasses the modified-release element.
- The second option is the application of a modified-release coating to a dosage form, wherein the drug is usually contained in the core and is released through, or via the dissolution of the modified-release coat.

# Extended-Release Oral Dosage Forms

## Drug Candidates for Extended- Release Products:

1-They exhibit neither very slow nor very fast rates of absorption and excretion

2- They are uniformly absorbed from the gastrointestinal tract.

3- They are administered in relatively small doses.

4- They possess a good margin of safety.

5- They are used in the treatment of chronic rather than acute conditions.

# Extended-Release Technology for Oral Dosage Forms

For orally administered dosage forms, extended drug action is achieved by affecting the rate at which the drug is released from the dosage form and/or by slowing the transit time of the dosage form through the gastrointestinal tract.

**The rate of drug release from solid dosage forms may be modified by**:

(a)Modifying drug dissolution by controlling access of biologic fluids to the drug through the use of barrier coatings.

(b) Controlling drug diffusion rates from dosage forms.

(c) chemical reaction or interaction between the drug substance or its pharmaceutical barrier and site-specific biologic fluids.

# TYPES OF EXTENDED RELEASE PRODUCTS

## 1- Coated Beads, Granules, and Microspheres:

In these systems, the drug is distributed onto beads, pellets, granules, or other particulate systems.

•In the dosage form, some of granules may remain uncoated to provide immediate drug release. Other granules (about two-thirds to three-fourths) receive varying coats of a lipid material like beeswax, carnauba wax, glyceryl monostearate, or cetyl alcohol or a cellulosic material like ethylcellulose.

•Then, granules of different coating thicknesses are blended to achieve a mix having the desired drug-release characteristics. The coating material may be colored to distinguish granules or beads of different coating thicknesses (by depth of color) and to provide distinctiveness to the product.

•When properly blended, the granules may be placed in capsules or formed into tablets.

## 2- Multitablet System:

- Small spheroid compressed tablets 3 to 4 mm in diameter may be prepared to have varying drug-release characteristics.
- They then may be placed in gelatin capsule shells to provide the desired pattern of drug release.
- Each capsule may contain 8 to 10 minitablets, some uncoated for immediate release and others coated for extended drug release.

# MINI TABLETS

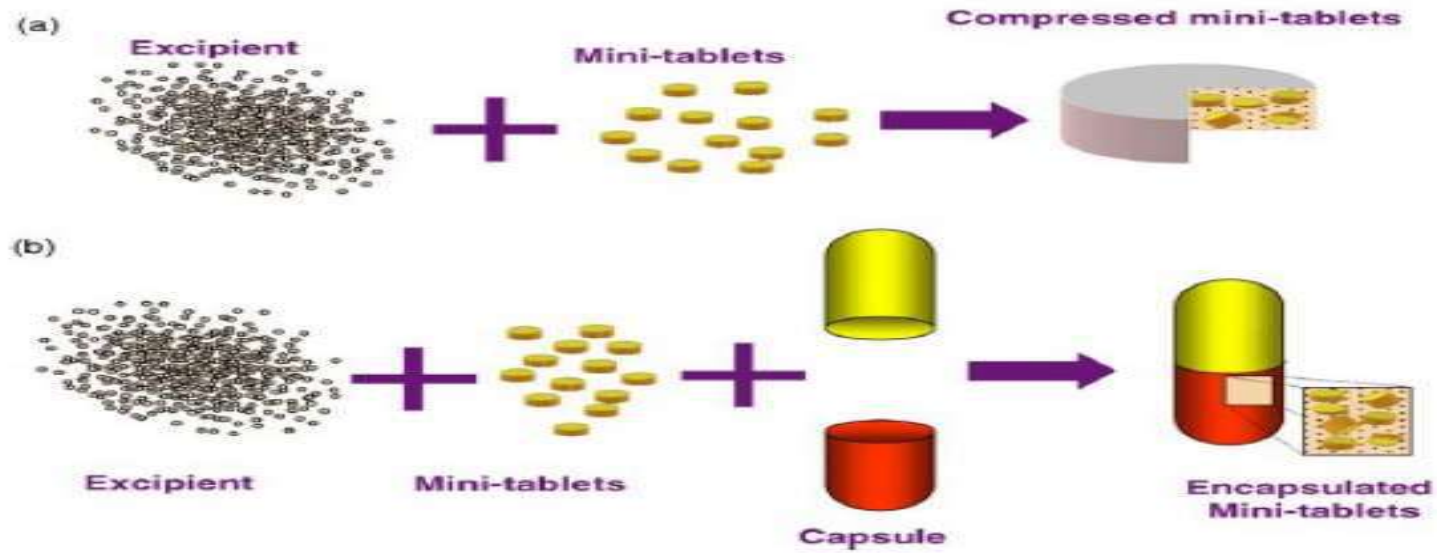



Fig. Mini-tablets delivered as a tablet (a) or a capsule (b).

## 3- Embedding Drug in Slowly Eroding or Hydrophilic Matrix System:

•The drug substance is combined and made into granules with an excipient material that slowly erodes in body fluids, progressively releasing the drug for absorption.

•When these granules are mixed with granules of drug prepared without the excipient, the uncombined granules provide the immediate effect, and the drug–excipient granules provide extended action.

•The granule mix may be formulated as tablets or capsules for oral delivery.

Hydrophilic cellulose polymers are commonly used as the excipient base in tablet matrix systems. The effectiveness of these hydrophilic matrix systems is based on the successive processes of hydration of the cellulosic polymer, gel formation on the polymer's surface, tablet erosion, and the subsequent and continuous release of drug.

• Hydroxypropyl methylcellulose (HPMC is commonly used to provide the hydrophilic matrix.

## 4- Embedding Drug in Inert Plastic Matrix:

•The drug is granulated with an inert plastic material such as polyethylene, polyvinyl acetate, or polymethacrylate, and the granulation is compressed into tablets.

•The drug is slowly released from the inert plastic matrix by diffusion.

•The inert tablet matrix, expended of drug, is excreted with the feces.

## 5- Complex Formation:

Some drug substances, when chemically combined with certain other chemical agents, form complexes that may be only slowly soluble in body fluids, depending on the pH of the environment.

This slow dissolution rate provides the ER of the drug.

## 6- Ion-exchange resins

• It is based on the drug resin complex formation when an ionic solution is kept in contact with ionic resins. Drug molecules attached to the resins are released by appropriate charged ions in the gastrointestinal tract, followed by diffusion of free drug molecules out of the resins.

$$Resin^{-}\,Drug^{+} + X^{+} \rightarrow Resin^{-}....X^{+} + Drug^{+}$$

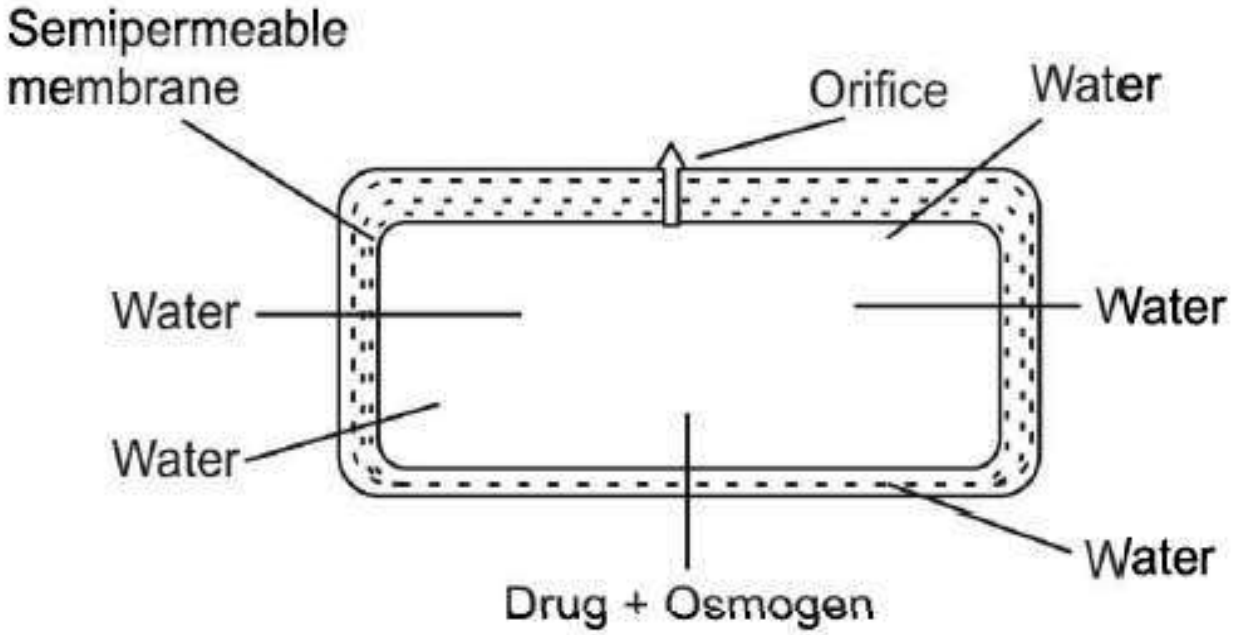
$$Resin^{+}\,Drug^{-} + X^{-} \rightarrow Resin+...X^{-} + Drug^{-}$$

where, X and Y are ions in the gastrointestinal tract.

## 8- Osmotically Controlled Delivery Systems

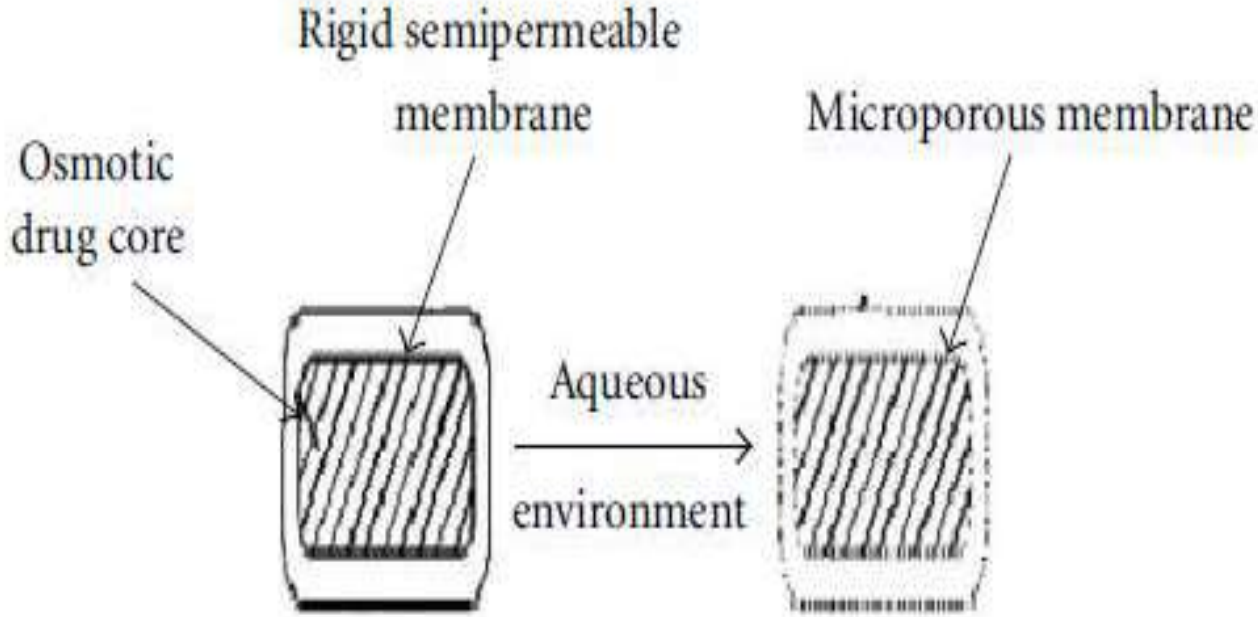
- The process of diffusion of a solvent through a semipermeable membrane from a less concentrated solution into a more-concentrated solution is called osmosis.
- Basically, when two different concentrations are separated by a semipermeable membrane, osmotic pressure builds up on the higher-concentration side.
- Several attempts have been made to use osmotic pressure as a driving force to deliver drugs.
- Osmotic pump tablets were developed by compressing drug and osmogen (NaCl) into a hard tablet, followed by coating the tablet with a semipermeable membrane (e.g. cellulose acetate) and then drilling an orifice in the coating by a laser.

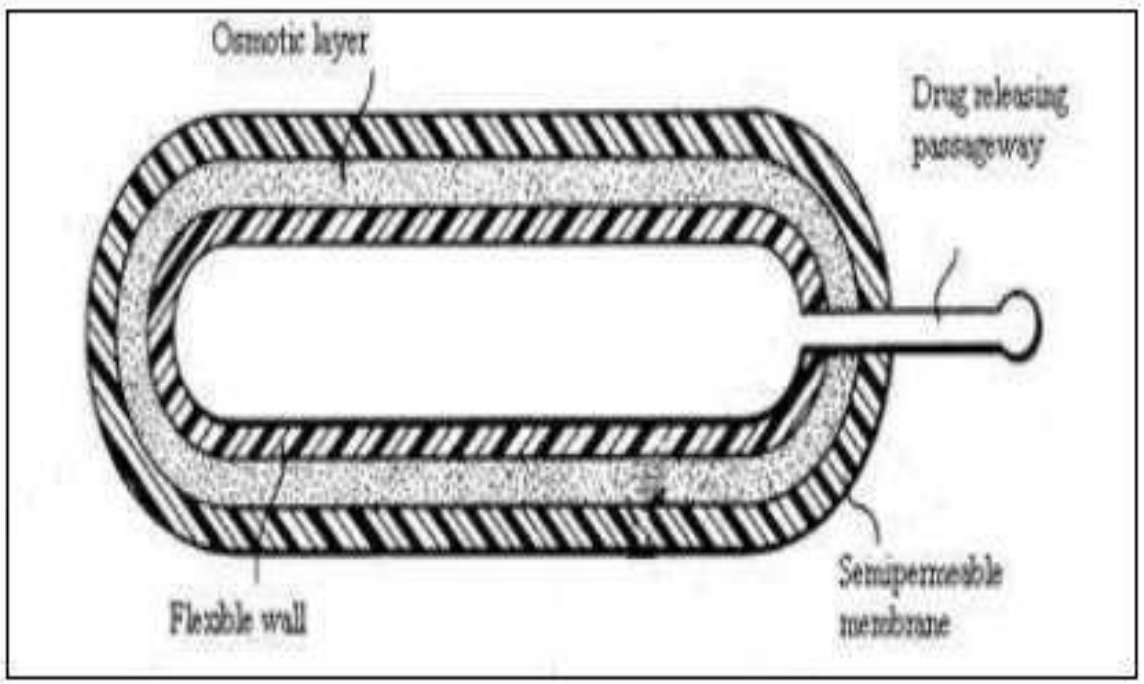
Upon contact with water, the semipermeable membrane of an osmotic pump tablet absorbs water, and water diffuses through the membrane and dissolves water soluble substances, resulting in a concentrated solution and high osmotic pressure inside the membrane. This leads to drawing more water across the membrane




**An elementary osmotic pump**

**Controlled porosity osmotic pump**




**Osmotic pump "Implant"**

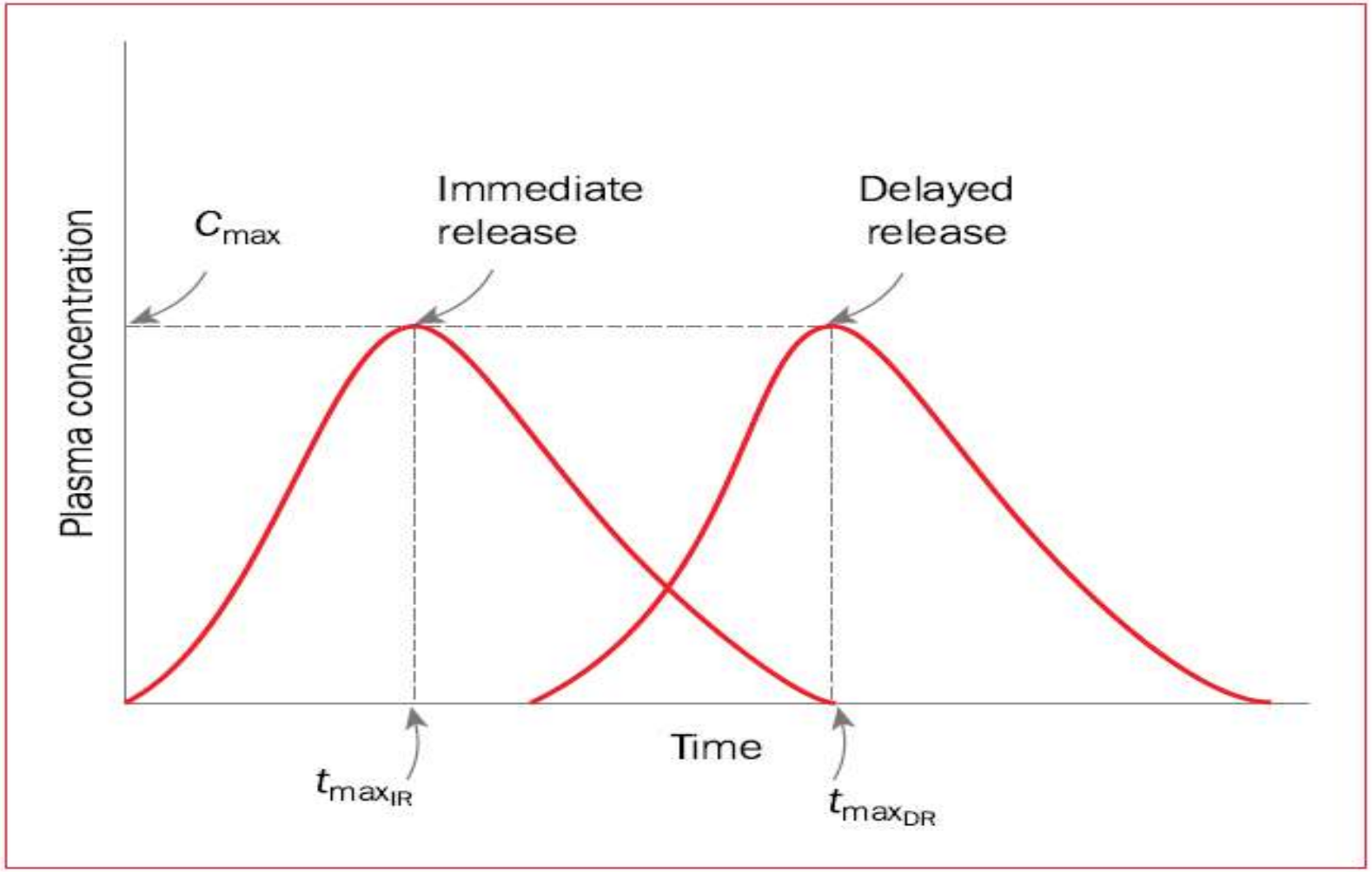
## 9- Repeat-action tablets:

- Repeat action tablets are prepared so that an initial dose of drug is released immediately followed later by a second dose.
- The tablets may be prepared with the immediate-release dose in the tablet's outer shell or coating with the second dose in the tablet's inner core, separated by a slowly permeable barrier coating.
- Repeat action dosage forms are best suited for the treatment of chronic conditions requiring repeated dosing.
- The drugs utilized should have low dosage and fairly rapid rates of absorption and excretion.

# Delayed-release oral dosage forms

The release of a drug from an oral dosage form may be intentionally delayed until it reaches the intestines for several reasons:

- To protect a drug destroyed by gastric fluids.
- To reduce gastric distress caused by drugs particularly irritating to the stomach.
- To facilitate gastrointestinal transit for drugs that are better absorbed from the intestines.




Plasma concentration versus time profile of delayed-release oral dosage form compared to an immediate-release dosage form.

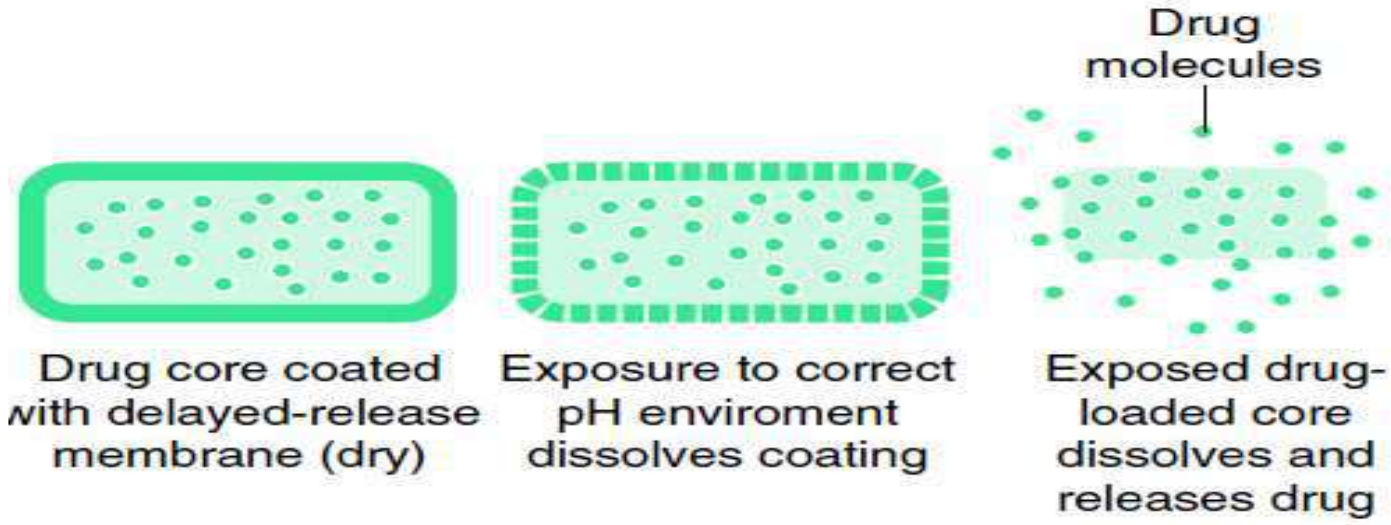
- Delayed release aims to target specific regions of the gastrointestinal tract, e.g. the small intestine or colon.

## 1- Gastro-resistant coatings

The concept here is similar to that of membrane controlled extended release, except that the membrane is designed to disintegrate or dissolve at a predetermined point.

The most common trigger for delayed-release coatings is pH. Gastro-resistant coatings are polymer coatings which are insoluble at low pH but are soluble at higher pH (e.g. somewhere between pH 5 and pH 7 depending on the polymer).

The drug release rate is controlled by its exposure to the correct pH.

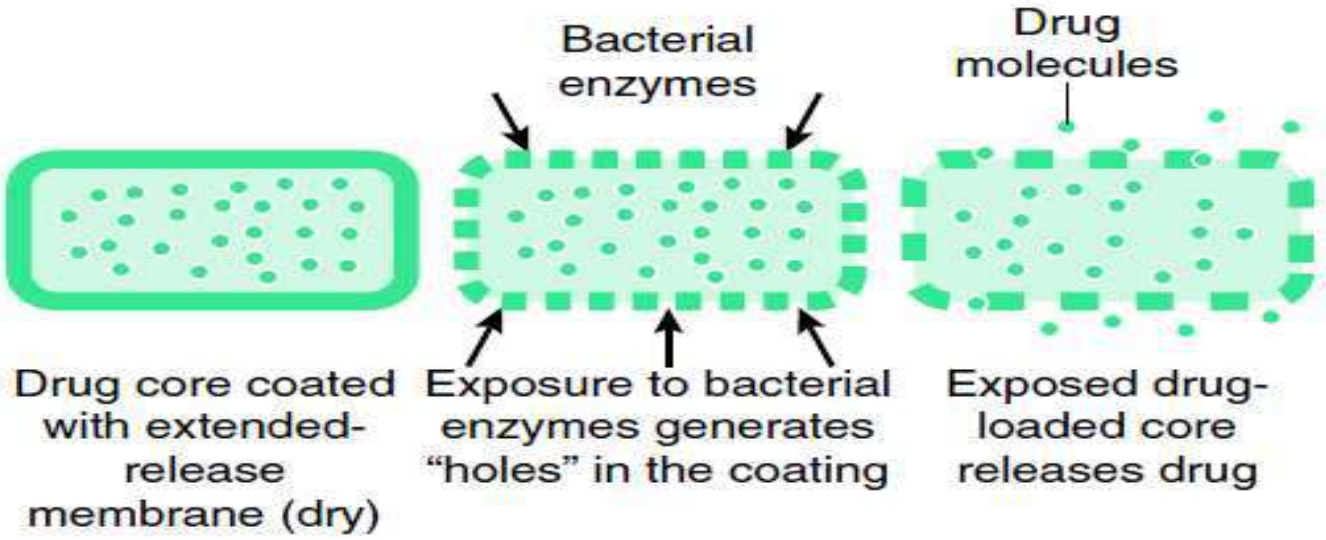



Drug release mechanism for a dosage form with a gastro-resistant coating.

## 2- Colonic drug delivery

- Colonic drug delivery can be achieved by the utilization of pH-responsive polymers (e.g. Eudragit S, which dissolves at around pH 7) to target the colon. Targeting the colon is difficult as a tablet or pellet may be in the region of highest pH for only a short time, and the target pH (often pH 7) may not be reached. This can lead to dosage form failure (i.e. it does not disintegrate and is passed intact in the stools, consequently not releasing the drug).
- An alternative approach is the use of the gut bacteria as a trigger for drug release. A coating is prepared from a material which is insoluble in the gastrointestinal fluids (e.g. ethylcellulose), but it will also contain a component that can be digested only by colonic bacteria (not by pancreatic enzymes).

- An example of a material that can be used is the polysaccharide known as ‘resistant starch’. This type of starch can only be broken down by bacterial enzymes in the colon. When the dosage form reaches the colon, the starch component of the coat is digested and dissolves, leaving pores through which drug can be released.




Release mechanisms for bacterially triggered colonic targeting

- One of the examples is colonic delivery of mesalazine for the treatment of inflammatory bowel disease.
- However, there may be some patient populations in which gastrointestinal microorganism levels are affected by disease, and the effect on such modified-release drug delivery  systems is not fully known