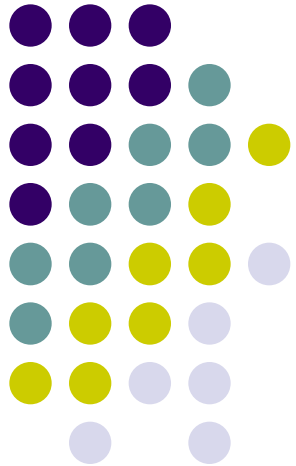
MODIFIED-RELEASE DOSAGE FORMS AND DRUG DELEVERY SYSTEMS

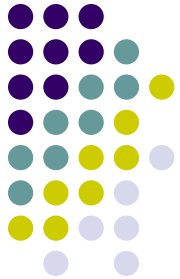


Main ref. (Ansel's)

Outlines

- The rationale for modified-release pharmaceuticals
- Terminology
- Extended-release oral dosage forms
- Types
- USP requirements and FDA Guidance
- Packaging and storing

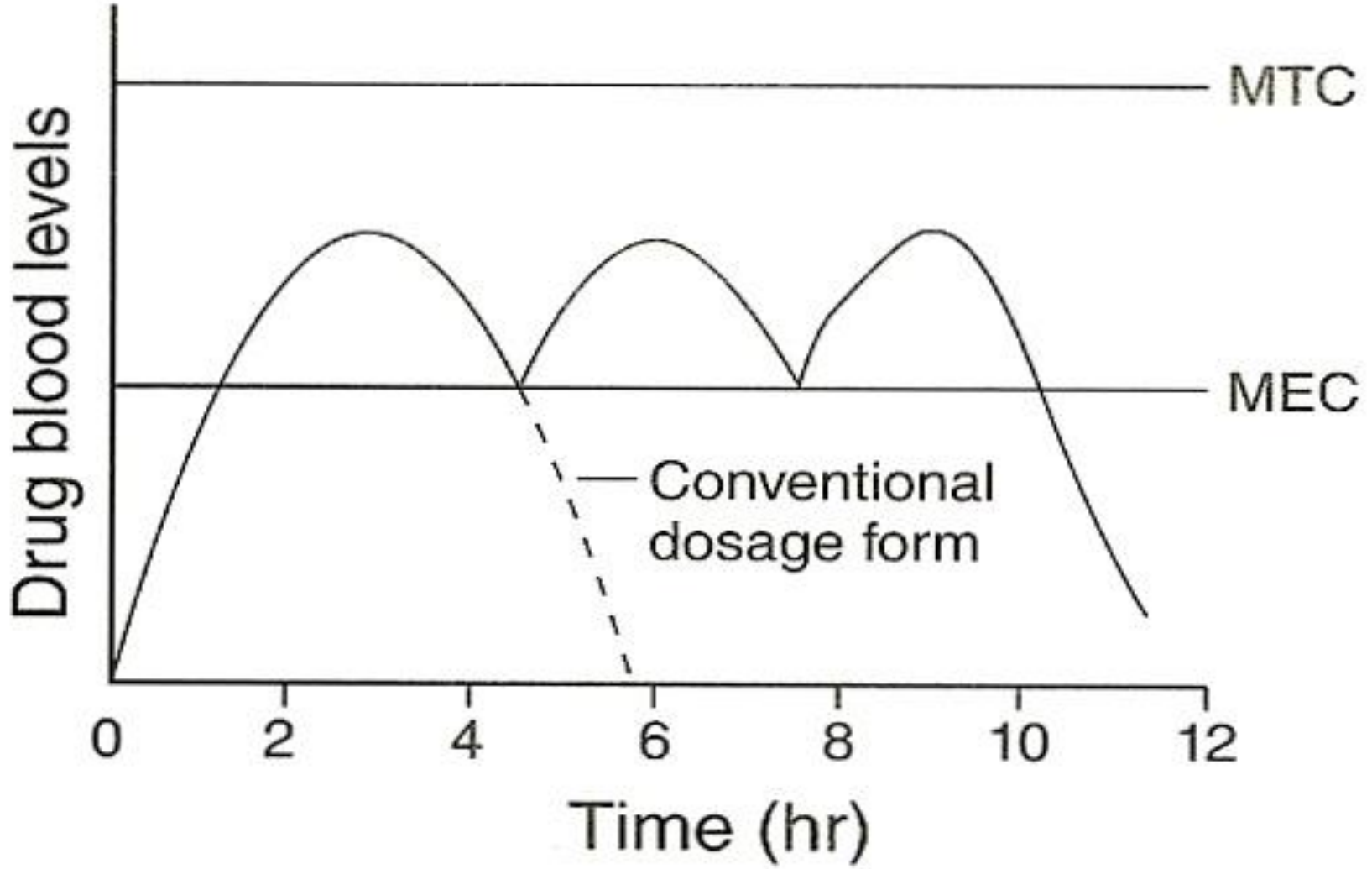
The rationale for modified-release pharmaceuticals



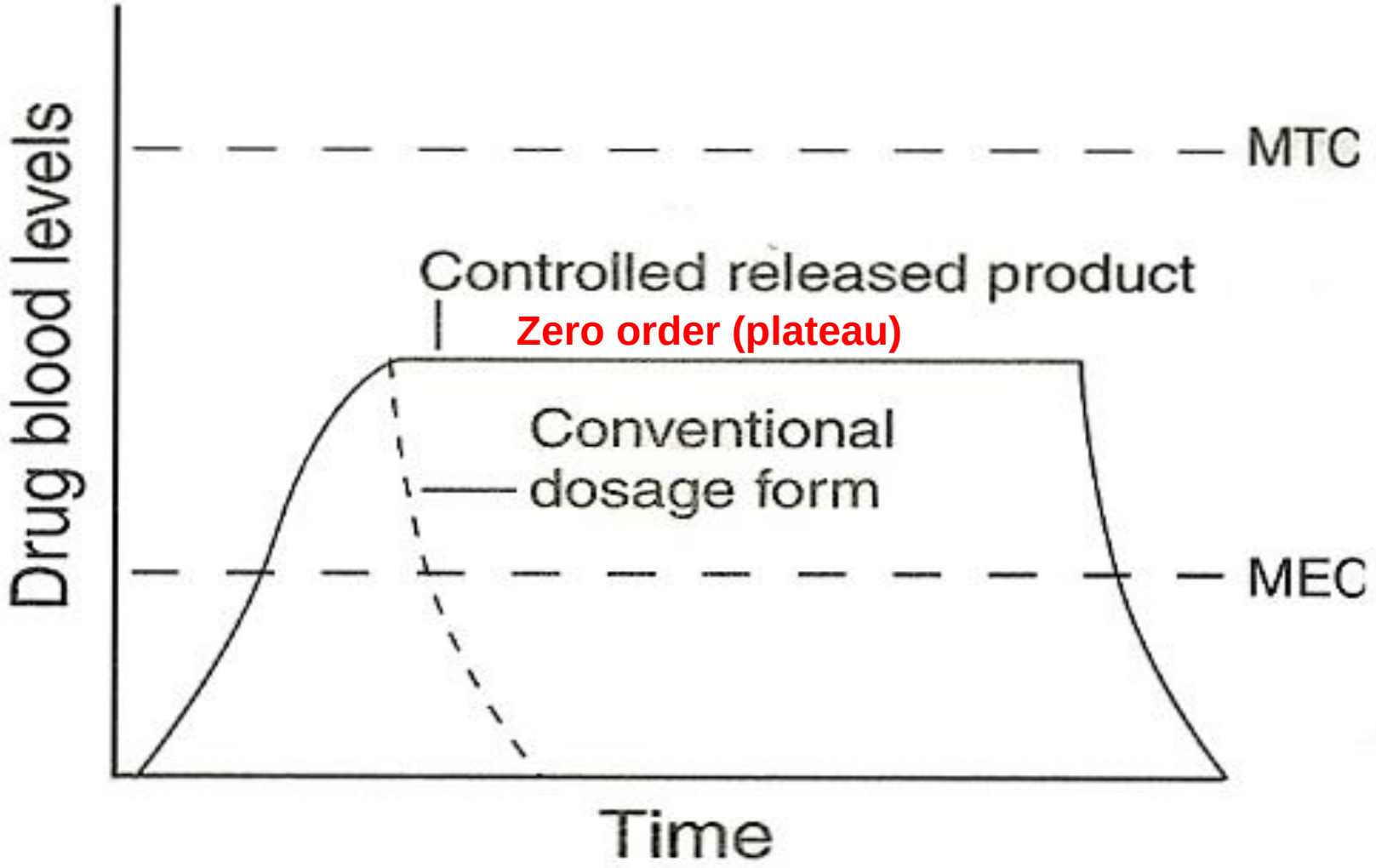
- Modified release may be enhanced ?? or extended release.
- Extended-release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect.

- Typically, extended-release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period.

What is the meaning of (Dose dumping)?



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

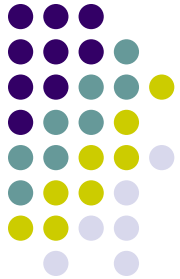


Hypothetical drug blood level-time curves for a conventional solid dosage form and a controlled release product.

Advantages of Extended-Release Dosage Forms Over Conventional Forms

Advantage	*Explanation*
Reduction in drug blood level fluctuations	By controlling the rate of drug release, "peaks and valleys" of drug-blood levels are eliminated.
Frequency reduction in dosing	Extended-release products deliver frequently more than a single dose of medication and thus they may be taken less often than conventional forms.
Enhanced patient convenience and compliance	With less frequency of dose administration, a patient is less apt to neglect taking a dose. There is also greater patient and/or caregiver convenience with daytime and nighttime medication administration.
Reduction in adverse side effects	Because there are fewer drug blood level peaks outside of the drug's therapeutic range and into the toxic range, adverse side effects occur less frequently.
Reduction in overall health care costs	Although the initial cost of extended-release dosage forms may be greater than that for conventional dosage forms, the overall cost of treatment may be less due to enhanced therapeutic benefit, fewer side-effects, and reduced time required of health care personnel to dispense and administer drugs and monitor patients.

Terminology



- Modified-release use to describe dosage forms having drug release features based on time, course, and /or location which are designed to accomplish therapeutic or convenience objectives not offered by conventional or immediate-release forms.
- May be solid (tab., cap., microspheres or liposomes) or liquid (oily suspension, oily solution or oily susp.)

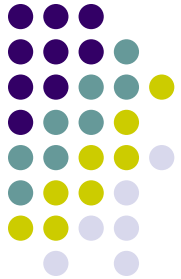
- Extended-release products are designed to release their medication in a controlled manner, at a predetermined rate, duration and location to achieve and maintain optimum therapeutic blood levels of drug.
- Or extended-release dosage forms are defined as one that allows a reduction in dosing frequency to that presented by a conventional dosage form.

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

- **Repeat-action forms usually contain two single doses of medication, one for immediate release and the second for delayed release.**

- **Targeted release describes drug release directed toward isolating or concentrating a drug in a body region, or site for absorption or for drug action.**

Extended-release oral dosage forms



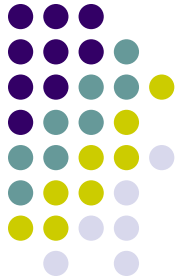
- Drug-candidates for extended-release products:

  The drugs best suited for incorporation into an extended-release product have the following characteristics:

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

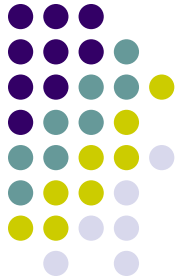
- They are uniformly absorbed from the gastrointestinal tract.
- They are administered in relatively small doses.
- They possess a good margin of safety.
- They are used in the treatment of chronic rather than acute conditions.

❑ Extended-release technology for oral dosage forms



The rate of drug release from solid dosage forms may be modified by the technologies described below:

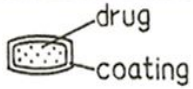
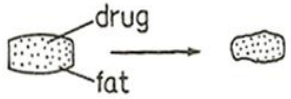
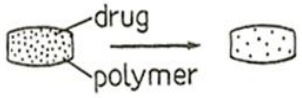
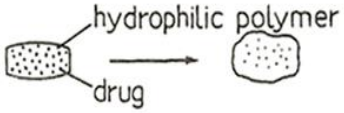
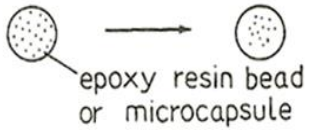
- Modifying drug dissolution by controlling access of biologic fluids to the drug through the use of barrier coatings.



- Controlling drug diffusion rates from dosage forms.

- Chemically reacting or interacting between the drug substance or its pharmaceutical barrier and site-specific biologic fluids.

table 8.10 **Depot forms employing polymeric films and matrices†**

	Type	Materials*	Diagrammatic representation	Mechanisms
1	Barrier coating	Beeswax, glyceryl monostearate, ethylcellulose, nylon (Ultramid IC), acrylic resins (Eudragit retard)		Diffusion
2	Fat embedment	Glycerol palmitostearate (Precirol), beeswax, glycowax, castorwax, aluminium monostearate, carnauba wax, glyceryl monostearate, stearyl alcohol		Erosion, hydrolysis of fat, dissolution
3	Plastic matrix	Polyethylene Poly(vinyl acetate) Polymethacrylate Poly(vinyl chloride) Ethylcellulose		Leaching, diffusion
4	Repeat action	Cellulose acetylphthalate		Dissolution of enteric coat
5	Ion exchange	Amberlite Dowex		Dissociation of drug–resin complex
6	Hydrophilic matrix	Carboxymethylcellulose Sodium carboxymethylcellulose Hydroxypropylmethylcellulose		Gelation, diffusion
7	Epoxy resin beads	Epoxy resins		Dissolution of resin or swelling, diffusion
8	Microcapsules	Polyamides, gelatin		
9	Soft gelatin depot capsules	Shellac–PEG Poly(vinyl acetate)–PEG		Diffusion

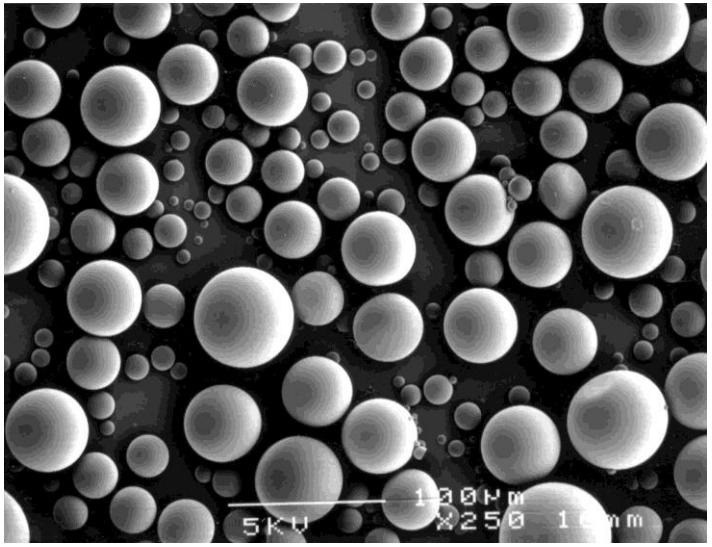
*Materials are not all polymeric. The waxes are included for completeness; these depend on conferring a hydrophobic layer on the drug, tablet, or granule to prevent access of solvent

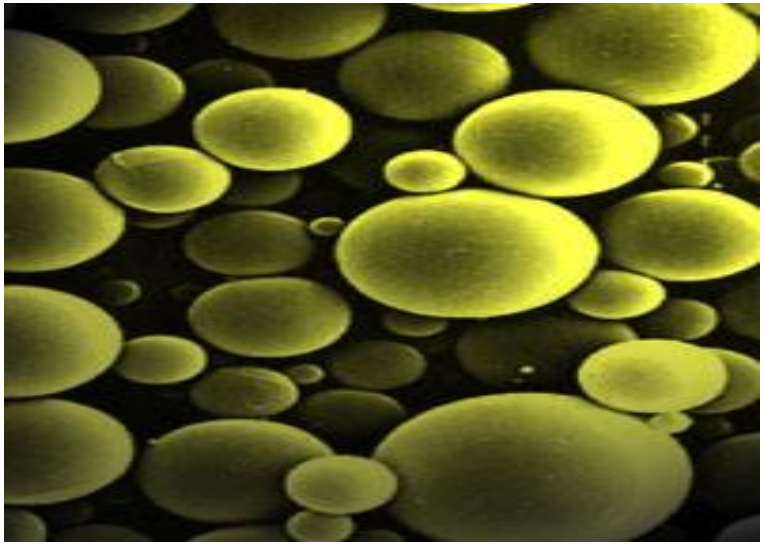
†After Ritschel, reference 21

We have different types of modified released DF

1) Coated beads, granules, microspheres or microcapsules

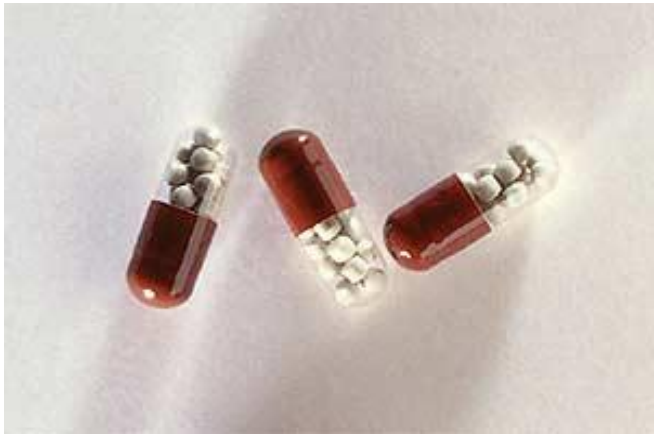
- In these systems, the drug is distributed onto beads, pellets, granules, or other particulate systems.





2) Multitablet system

- Small spheroid compressed tablets 3 to 4 mm in diameter may be prepared to have varying drug release characteristics.
- They may be placed in gelatin capsule shells to provide the desired pattern of drug release.
- Each capsule may contain

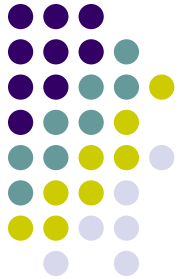


8 to 10 minitablets,

some uncoated for

immediate release and others coated for extended drug release.

3) Embedding drug in slowly eroding or hydrophilic matrix system



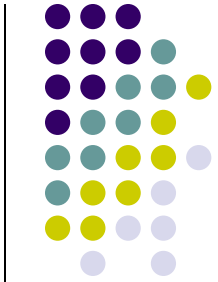
By this process, the drug substance is combined and made into granules with an excipient material that slowly erodes in body fluids, progressively releasing the drug for absorption.

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

4) Embedding drug in inert plastic matrix

- By this method, the drug is granulated with an inert plastic material such as polyethylene, polyvinyl acetate, or polymethacrylate, and the granules are 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



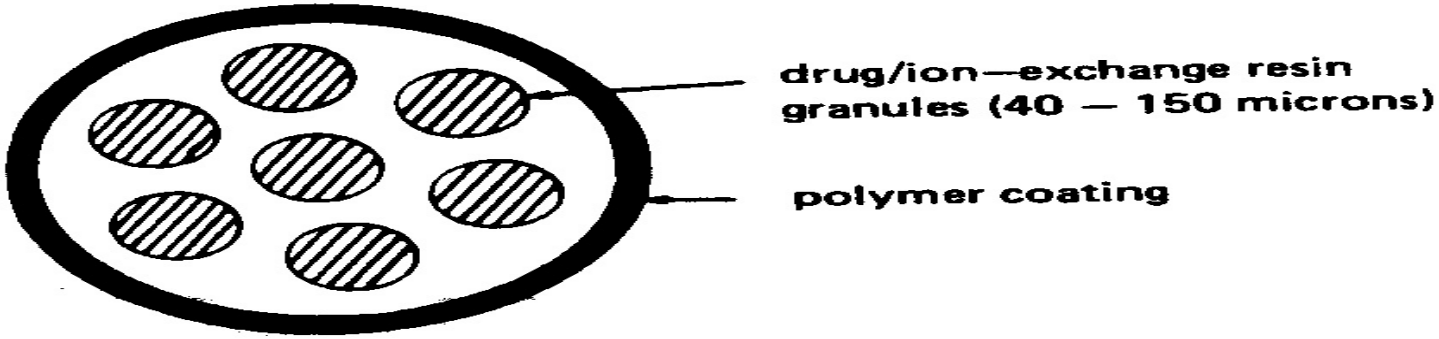
- Certain drug substances when chemically combined with certain other chemical agents form chemical complexes that may be only slowly soluble in body fluids, depending upon the pH of the environment.

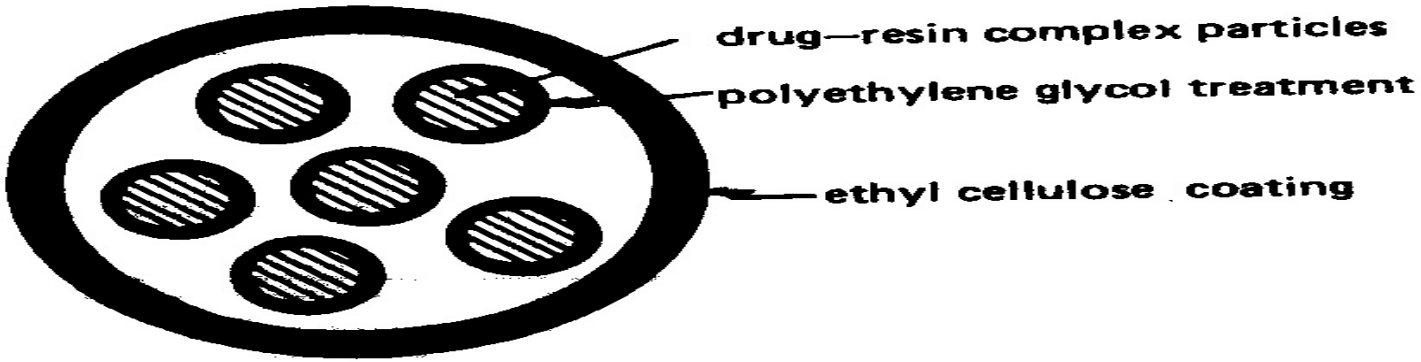
- This slow dissolution rate provides the extended release of the drug.

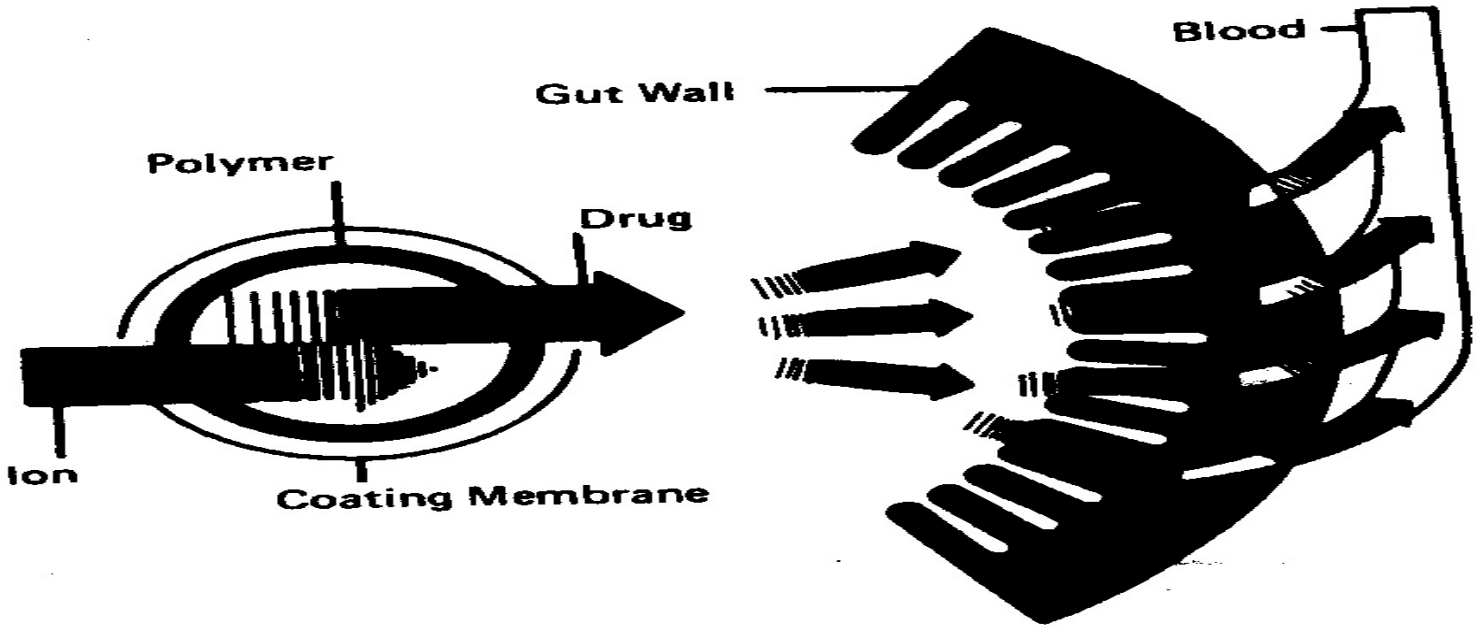
- Salts of tannic acid, tannates, provide this quality in a variety of proprietary produced by the trade name Rynatan.

6) Ion-exchange resins

- A solution of a cationic drug may be passed through a column containing an ion-exchange resin, forming a complex by the replacement of hydrogen atoms.
- The resin-drug complex is then washed and may be tableted, encapsulated, or suspended in an aqueous vehicle.
- The release of the drug is dependent upon pH and the electrolyte concentration in the gastrointestinal tract.


drug/ion—exchange resin granules (40 — 150 microns)
polymer coating


drug—resin complex particles
polyethylene glycol treatment
ethyl cellulose coating


Blood
Gut Wall
Polymer
Drug
Ion
Coating Membrane

7) Osmotic pump

- The pioneer oral osmotic pump drug delivery system is the Oros system.
- The system is composed of a core tablet surrounded by a semipermeable membrane coating have a 0.4 mm diameter hole produced by laser beam.

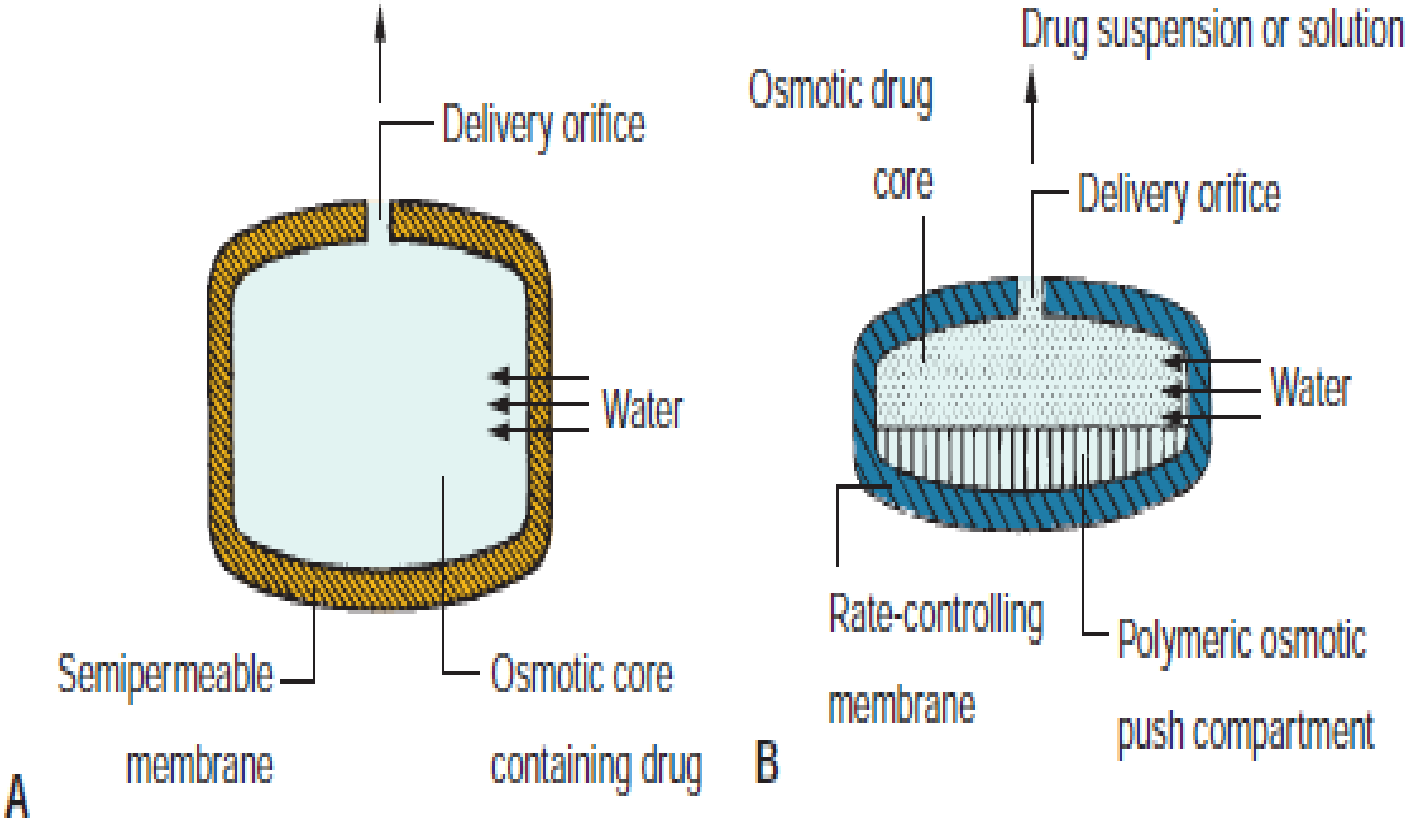


FIGURE 9.5 A: Elementary OROS (oral release osmotic system) osmotic pump drug delivery system. B: Push–pull osmotic system.

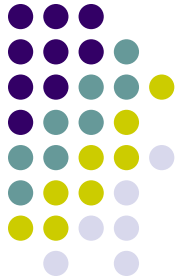
- **The system is designed such that only a few drops of water are drawn into the tablet each hour.**
- **The rate of inflow of water and the function of the tablet depends upon the existence of an osmotic gradient between the contents of the bi-layer core and the fluid in the GI tract.**
- **Drug delivery is essentially constant as long as the osmotic gradient remains constant.**

The drug release rate may be altered by

- Changing **the surface area**,
- The **thickness** or **composition** of the membrane,
- Changing the **diameter of the drug release orifice.**

The drug-release rate is not affected by gastrointestinal acidity, alkalinity, fed conditions, or GI motility.

8) 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 GI transit for drugs which are better absorbed from the intestines.

- **Capsules and tablets specially coated to remain intact in the stomach and to yield their ingredients in the intestines are termed enteric coated.**

The enteric coating may be

- **pH dependent, breaking down in the less acidic environment of the intestine,**
- **time dependent, eroding by moisture over time during gastrointestinal transit,**

- **enzyme dependent, deteriorating as a result of the hydrolysis-catalyzing action of intestinal enzymes.**

  Among the many agents used for enteric coating of tablets and capsules are fats, fatty acids, waxes, shellac, and cellulose acetate phthalate.

USP requirements and FDA guidance for modified-release dosage forms

1) Drug release

The USP test for drug release in the extended-release and delayed-release tablets is based on drug dissolution from the dosage unit against elapsed test time.

Time (hr)	Amount dissolved
1.0	between 15% and 40%
2.0	between 25% and 60%
4.0	between 35% and 75%
8.0	not less than 70%

2) Uniformity of dosage units

Uniformity of dosage units may be demonstrated by either of two methods, weight variation or content uniformity.

3) In vitro/in vivo correlations (IVIVCs)

IVIVCs is critical to the development of oral extended-release products. Assessing IVIVCs is important throughout the periods of product development, clinical evaluation, submission of an application for FDA-approval for marketing, and during postapproval for any formulation or manufacturing changes which are proposed.

Three categories of IVIVCs are included in the document

- Level A

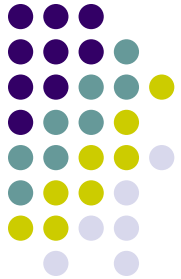
  A predictive mathematical model for the relationship between the entire in vitro dissolution/release time course, e.g., the time course of plasma drug concentration or amount of drug absorbed.

- Level B

  A predictive mathematical model of the relationship between summary parameters (e.g. Cmax or AUC) that characterize the in vitro and in vivo, time courses.

- Level C

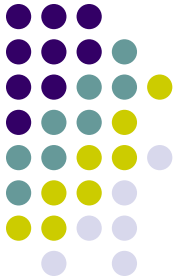
  A predictive mathematical model of the relationship between the amount dissolved in vitro at a particular time (or $T_{50}\%$) and a summary parameter that characterizes the in vivo time course.



4) Labeling

The USP indicates labeling requirements for modified-release dosage form articles in addition to general labeling requirements.

Packaging and storing modified-release tablets and capsules



Modified-release tablets and capsules are generally packaged and stored in the same manner as conventional products.

H.w

- **Give the meaning of:**

1) **Cmax.**
2) **Tmax.**
3) **AUC**
4) **Onset of action**
5) **Duration of action**