Modified-release oral drug delivery

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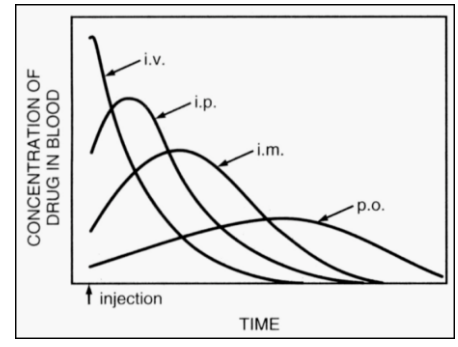
Introduction

- The ideal situation in therapy is the maintenance for the desired time and at the site of action only of a drug concentration that is therapeutically effective, non toxic that perfectly matches the real need *in vivo*.

- Drug level in the blood can be controlled when a solution is administered by IV infusion so that the drug concentration can be measured or simply the effect of drug is monitored (ex. blood pressure, glucose level, pain relief).



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Introduction

- More than 70% of all medicines are delivered by the oral route.
- Oral medicines are easy to administer, improve patient compliance and are cheaper than some of the alternatives (e.g. injections).
- Most medicines administered by the oral route provide what is known as 'immediate-release' drug delivery or 'conventional' drug delivery.

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Maintenance of therapeutic drug concentrations by modified release oral dosage forms

Limitations associated with the use of conventional oral dosage forms:

- When the drug is given orally as conventional immediate release dosage forms (tablets, capsules, suspensions…), it is given on a schedule which in some cases requires more than one dose daily.
- This gives therapeutic blood level peaks and valleys associated with the taking of each dose.
- The concentration of drug in plasma and hence at the site of action fluctuates over successive dosing intervals, even when the steady state condition is achieved.

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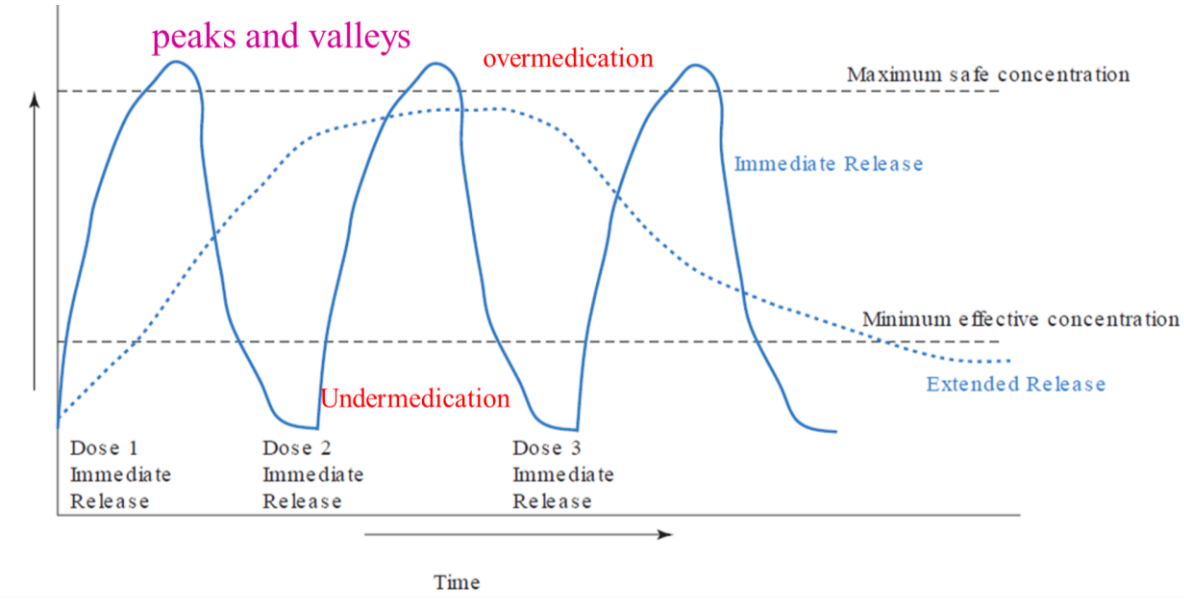

Theoretical plasma (blood) profiles of immediate and extended[5] release.

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Maintenance of therapeutic drug concentrations by modified release oral dosage forms

Limitations associated with the use of conventional oral dosage forms:

- The fluctuations in the steady state can lead to overmedication or undermedication of the patient, if the values of C^{SS}_{max} and C^{SS}_{min} are outside the therapeutic range of drug.
- For drugs with short biological half-lives, frequent doses are required and maintenance of therapeutic plasma concentrations are susceptible to the consequence of forgotten doses, lack of compliance and the over-night no-dose period.

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Modified release dosage forms

The concept of extended release

- A basic objective in dosage form design is to optimize the delivery of medication so as to achieve a measure of control of the therapeutic effect:

1. To avoid fluctuations in the blood concentration and
2. To reduce the number of daily doses.

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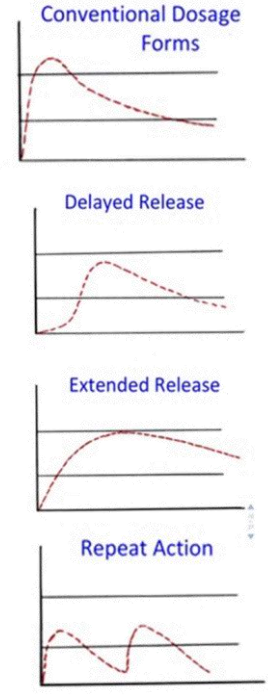
Terminology

Modified release

- Modified release dosage forms are defined by the USP as those whose drug release characteristics of time course/ or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms.

Delayed release

- This describes the release of drug from the dosage form at a time other than promptly after administration.
- The delay may be time-based or based on the environment conditions, as gastrointestinal pH.



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Terminology

Gastro-resistant dosage forms

- these are delayed release dosage forms designed to have a type of mechanism which enables that the drug is released when a certain environmental pH is met (e.g. in the higher pH of the small intestine).
- Such products may also be known as enteric dosage forms.

Repeat action

- Repeat action dosage forms usually contain two or three single doses of medication, one is released soon after administration and the second or third are subsequently released at intermittent intervals.

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Terminology

Extended release dosage forms

- These are dosage forms that release drug slowly and allow a reduction in dosing frequency compared to immediate release dosage forms.
- These are also known as *prolonged-release* or *sustained release* dosage forms and are also referred to as *controlled-release* dosage forms.
- ➢ Extended release systems which are retained in the stomach are known as *gastroretentive systems*.

Chronotherapy

- Timing the drug release to coincide with when it is required

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Repeat action versus sustained action

- Repeat action product does not release the drug in a slow controlled manner.
- A repeat action tablet usually contain two doses of drug, the first being released immediately following oral administration.
- The release of second is delayed, usually by means of enteric coating.

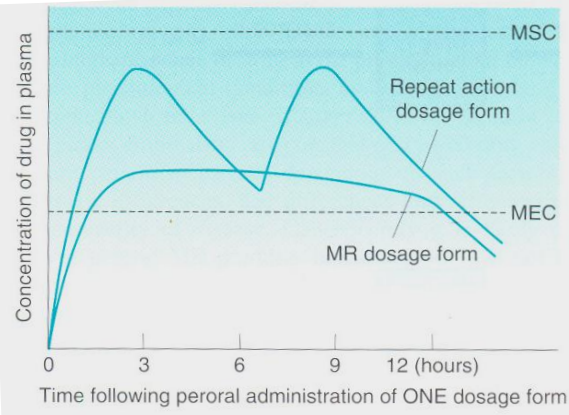

Fig. 32.1 Plasma concentration–time curves obtained following peroral administration of (a) one repeat-action dosage form containing two doses, and (b) one MR dosage form containing the same drug. MSC = maximum safe concentration, MEC = minimum effective concentration (see Chapter 23).

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Prolonged release

- Prolonged-release products are generally designed to provide either:
  a) The prompt achievement of a plasma concentration that remains essentially constant at a value within the therapeutic range of the drug for a satisfactory period of time.
  b) The prompt achievement of a plasma concentration which, although not remaining constant, declines at such a slow rate that the plasma level remains within the therapeutic range for a satisfactory period of time.

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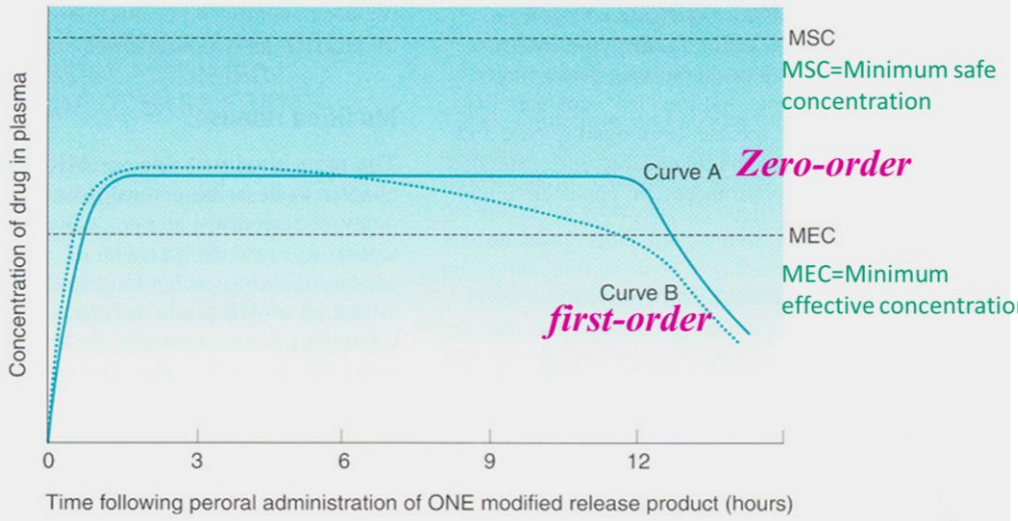

Fig. 32.2 Typical plasma concentration–time profiles for MR peroral products which, following rapid attainment of a therapeutic plasma concentration of drug, provide a period of prolonged therapeutic action by either (a) maintaining a constant therapeutic plasma concentration (curve A) or (b) ensuring that the plasma concentration of drug remains within the therapeutic range for a satisfactorily prolonged period of time (curve B).

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Kinetic pattern for drug release required for the ideal modified controlled-release dosage form

- To achieve a therapeutic effect promptly in the body and then to maintain that concentration for a given period of time requires that the total drug in the dosage form consists of two portions,

1. one that provides the ***initial*** loading/priming dose and
2. one that provides the ***maintenance dose***.

- The priming dose provides a rapid onset of the desired therapeutic effect.
- The rate of release of drug from the maintenance portion of the dosage form should be ideally ***zero-order*** (constant) so that the amount of drug at the absorption site to be constant and independent of the magnitude of the maintenance dose.

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Kinetic pattern for drug release required for the ideal modified controlled-release dosage form

- The zero-order rate of release of drug from the maintenance dose must be rate determining with respect to the absorption rate so that the kinetics of absorption of the maintenance dose will be characterized by the same zero-order release constant.

- The rate of release and hence absorption (input) of the maintenance dose must be equal to the rate of drug output from the body when the concentration of drug in the body is at the required therapeutic value.

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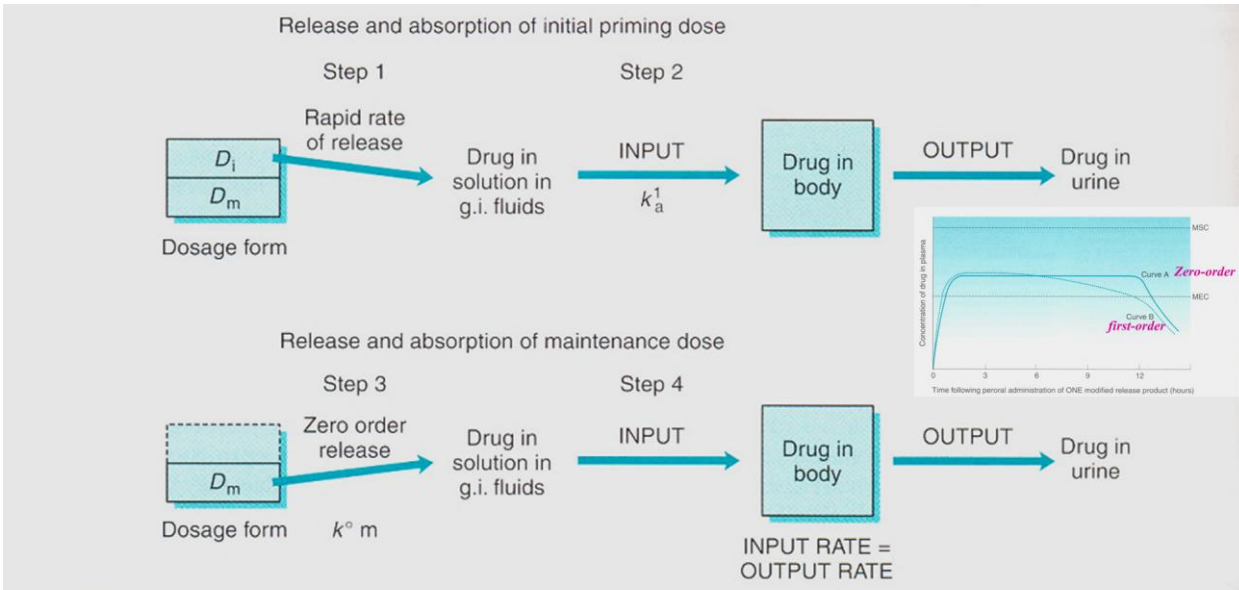

Fig. 32.3 A one-compartment open model of drug disposition in which the source of drug input is an ideal MR peroral drug product. D_i is the initial priming dose of drug in the dosage form; D_m is the maintenance dose of drug in the dosage form; k_a^1 is the first-order apparent absorption rate constant of drug from the priming dose; k_m° is the zero-order release rate constant of drug from the maintenance dose.

Kinetic pattern for drug release required for the ideal modified controlled-release dosage form

- Most currently marketed modified release formulations do not release drug at constant rate (zero order (very ideal)) and consequently do not maintain the relative constant activity. Blood levels decrease with time until the next dose is administered.

- In many instances the rate of release of drug can be approximated to a ***first-order*** process in which the rate of drug release is function only of the amount of drug remaining in the dosage form.

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Advantages of modified-release dosage forms

1. Improving patient compliance, resulting from the reduction in the number and frequency of doses .
2. Improved treatment of many chronic illnesses.
3. Maintenance of the therapeutic action of a drug during overnight no-dose period.
4. Reduction in the drug blood level fluctuations
5. Reduction of local and systemic side effects
6. Reduction of the total amount of drug administered over the period of treatment.

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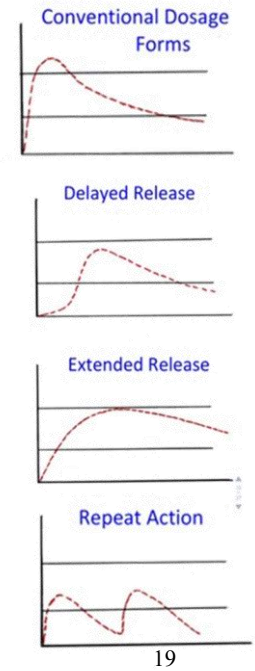
Advantage	Delayed release	Repeat action	Modified (sustained) release
Reduction in the number of doses	×	√	√
Reduction of local side effects	√ √ √	√	√ √
Reduction of systemic side effects (blood level fluctuation)	×	×	√



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Limitations of modified-release dosage forms

1. Administration of modified- release medications does not allow the prompt termination of therapy (as in cases of significant side effects)
2. The physician has less flexibility in adjusting dosage regimens.
3. Modified- release dosage forms are designed for the normal population (on the basis of average drug half-life). Consequently, disease states that alter drug disposition are not accommodated.

The variable physiological factors that often influence the precision of control of release include:

a) Gastrointestinal pH
b) Enzyme activity
c) Gastric and intestinal transit rates
d) Severity of disease

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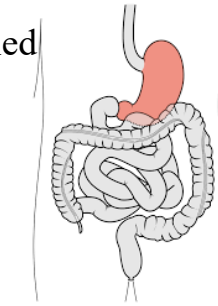
Limitations of modified-release dosage forms

4. Their manufacture may involve more costly processes and equipments.
5. Not all drugs are suitable candidates for formulation as modified release.
6. Danger of dose dumping if an MR product is improperly made.
7. MR products, which tend to remain intact, may become lodged at some site along the gastrointestinal tract causing local irritation to the gastrointestinal mucosa.
8. The maximum period is limited to 12 hrs plus the time that the absorbed drug continues to exert its therapeutic activity.



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Ideal properties of drug candidates

A. They exhibit neither very slow nor very fast rates of absorption and excretion (half-life between 2 and 6 hours).

- Drugs with long half-life (ex. Digoxin, 34 hours) are inherently long acting.
- Drugs with very short half-life need high amount (dose) which may present a potential hazard and a large mass that may be limited orally.

B. They are uniformly absorbed from the GI tract. Drugs absorbed from a small part (ex. Stomach) will not have enough time for sustained releasing.

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Ideal properties of drug candidates

C. They are administered in relatively small doses (not exceeding 125–325 mg).

Drugs administered conventionally in large doses will be difficult to be formed as oral extended release dosage forms because of large amount needed which is limited by the volume.

- Exceptions: Ibuprofen and Metformin HCl

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Ideal properties of drug candidates

D. They posses a good margin of safety.

Drugs with narrow therapeutic indices are poor candidates for extended release formulation because of technological limitations of precise control over release rates.

E. They are used in treatment of chronic rather than acute conditions.

F. Drugs for acute conditions usually require greater physician adjustment of the dose than that provided by extended release.

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Formulation methods of achieving sustained drug release

- All SR formulations use a chemical or physical barriers to provide slow release of maintenance dose.
- Many formulation techniques have been designed to build the barrier into the oral dosage form.
- These include the use of:

i. coatings,
ii. embedding the drug in wax or plastic matrix,
iii. microencapsulation,
iv. chemical binding to ion-exchange resins, and incorporation into an osmotic pump.

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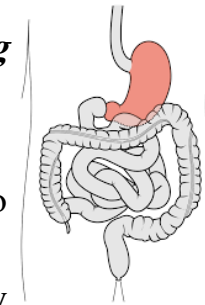
Design of oral modified-release drug delivery

Factors influencing design strategy

The physiology of the gastrointestinal tract and drug absorption



- Solution and pellets (<2 mm) leave the stomach rapidly
- Single dose units (>7 mm) can stay in the stomach for up to 10 hours if the delivery system is taken with a heavy meal
- The transit time through the small intestine is approximately 3 hours*******

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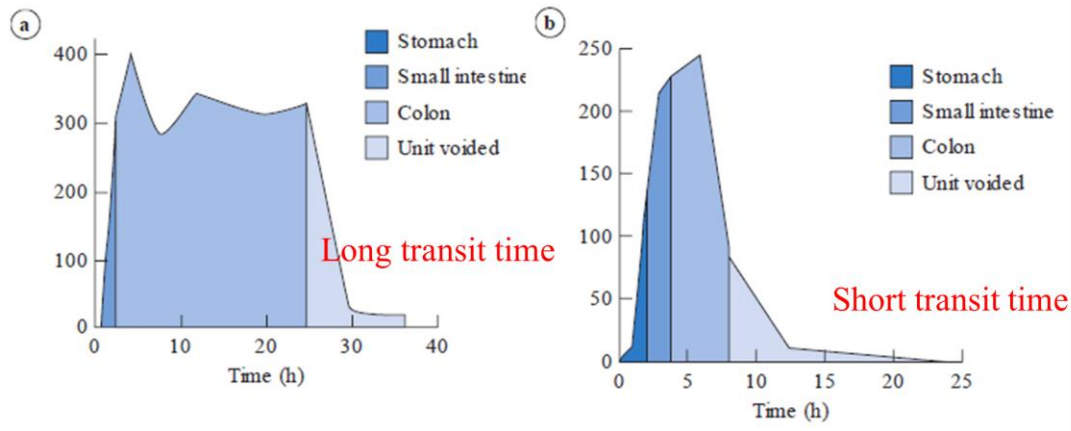
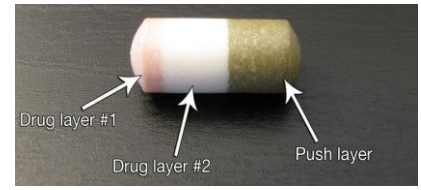


Plasma concentration-time profiles or oxprenolol delivered from an OROS device in an individual, with a long **(a)** and a short **(b)** colon transit time.

Osmotic-controlled release oral delivery system (OROS)



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Design of oral modified-release drug delivery

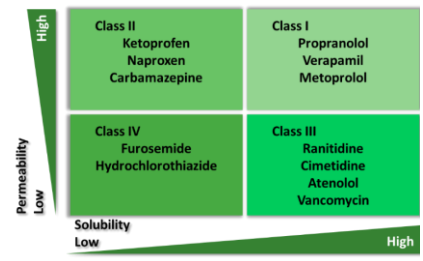
Factors influencing design strategy

Physicochemical properties of drug

- These include: aqueous solubility and stability, pKa, partition coefficient and salt form.
- The **Biopharmaceutical Classification System (BCS)** made by Amidon et al (1995) whereby a drug can be considered to belong to one of four categories:

➢ Class I: High solubility and high permeability (best case)

➢ Class II: Low solubility and high permeability



➢ Class III: High solubility and low permeability

➢ Class IV: Low solubility and low permeability (worst case)

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Choice of the dosage form

Single unit systems

- Tablets
  - Coated tablets
  - Matrix tablets
- Some capsules

Multiple unit systems

- Granules
- Beads
- Microcapsules

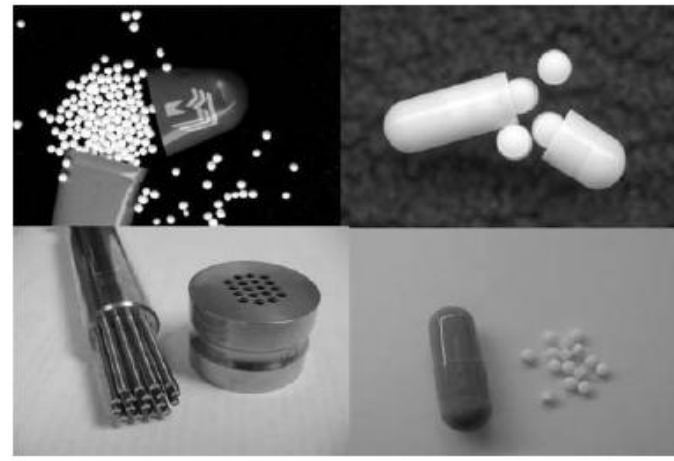

FIGURE 21.2 Examples of beads and mini-tablets prepared with single-head or multi-head tooling

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Drug-release mechanisms

- The two basic mechanisms controlling drug release are dissolution of the active drug component and the diffusion of dissolved species.
- Within the context of these mechanisms there are four processes operating:
  - Hydrating of the device (swelling of the hydrocolloid or dissolution of the channeling agent)
  - Diffusion of water into the device
  - Dissolution of the drug
  - Diffusion of the drug out of the device
- These mechanisms may operate independently, together or consecutively.

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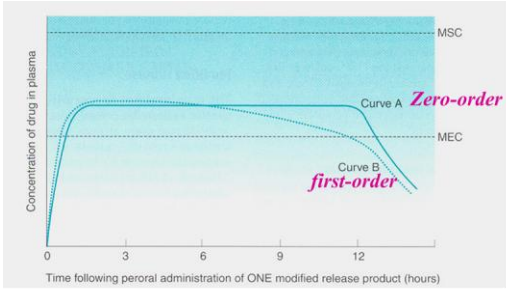
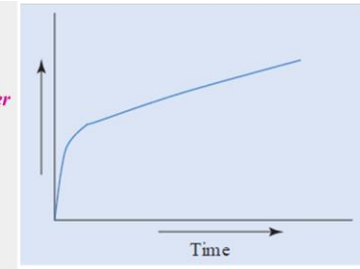
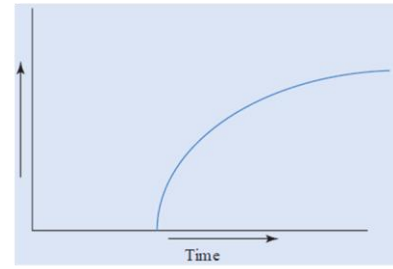
Drug release may be:

1. constant (zero order)
2. declining (Drug release from these systems is commonly a function of the square root of time or follows first order kinetics)
3. Bimodal: First slow release in the stomach and then increased rate in the intestine or vice versa







Bimodal drug release

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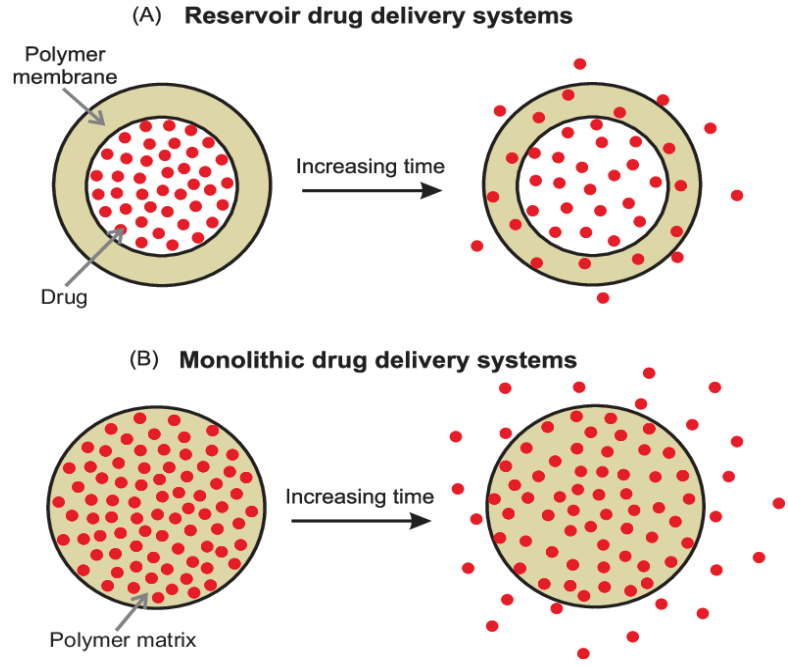
Formulation of modified release dosage forms

Oral modified release tablets can be considered under the following main headings:

A. Matrix (monolithic) systems
B. Membrane-controlled (reservoir) systems
C. Osmotic pump systems
D. Ion exchange resins



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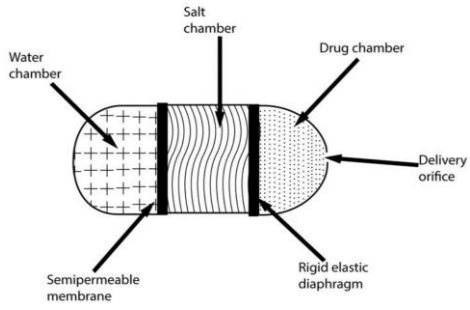
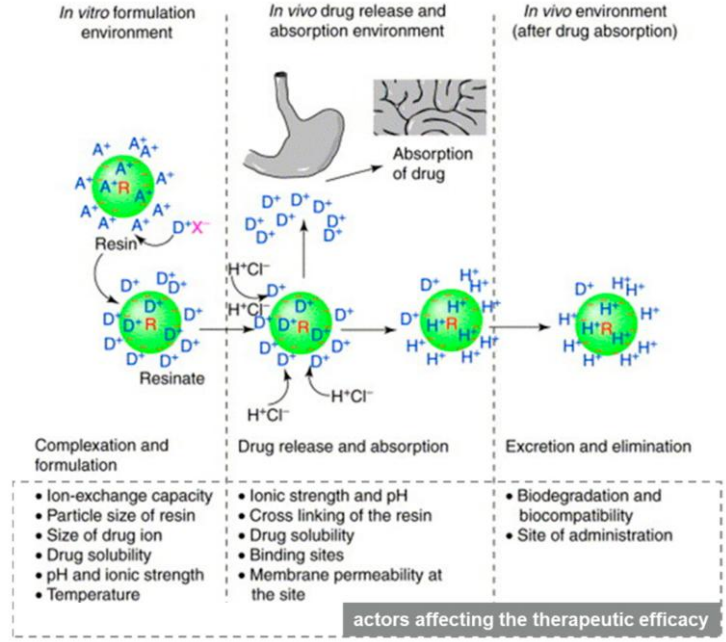


Osmotic pump system



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Ion exchange resins

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Formulation of modified release dosage forms

Components of modified release delivery system:

a. Active drug
b. Release-controlling agent: Matrix former, membrane former
c. Matrix or membrane modifier such as channeling agents
d. Solubilizer, pH modifier or density modifier
e. Lubricant and flow aid
f. Supplementary coating

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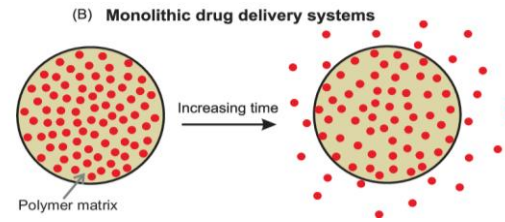
Matrix (monolithic) delivery systems

A matrix can be defined as a coherent uniform distribution of drug and release controlling agent

These systems can be classified to three types:

1) lipid matrices
2) insoluble polymer matrices
3) hydrophilic colloid matrices



- In case of hydrophilic colloid matrices, drug particles are dispersed in a **soluble** matrix, with drug becoming available as the matrix dissolves.
- In cases of lipid matrices and insoluble polymer matrices, drug particles are **dispersed** in an insoluble matrix, with drug becoming available as a solvent enters the matrix and dissolve the particles.

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Lipid excipients	Insoluble polymers	Hydrophilic swellable polymers
•Carnauba wax •Cetyl alcohol •Hydrogenated vegetable oils •Microcrystalline waxes •Mono- and triglycerides •PEG monostearate	•Ethyl cellulose •Methacrylate copolymer •Polyamide •Polyethylene •Polyvinyl acetate	•Alginates •Carbopol (polyacrylic acid) •Gelatin •Hydroxypropylcellulose •Hydroxypropyl methylcellulose •Methylcellulose

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Table 6 Matrix Diffusional Products

Product (tablets)	Active ingredient(s)	Manufacturer
Desoxyn-Gradumet	Methamphetamine hydrochloride	Abbott
Fero-Gradumet	Ferrous sulfate	Abbott
Tral Filmtab	Hexocyclium methylsulfate	Abbott
PBZ-SR	Tripelennamine	Geigy
Procan SR	Procainamide hydrochloride	Parke-Davis
Choledyl SA	Oxtriphylline	Parke-Davis

Table 4 Reservoir Diffusional Products

Product	Active ingredient(s)	Manufacturer
Duotrate	Pentaerythritol tetranitrate	Jones
Nico-400	Nicotinic acid	Jones
Nitro-Bid	Nitroglycerin	Marion
Cerespan	Papaverine hydrochloride	Rhône-Poulenc Rorer
Nitrospan	Nitroglycerin	Rorer
Measurin	Acetylsalicylic acid	Sterling Winthrop

Table 9 Ion-Exchange Products

Product	Active ingredient(s)	Manufacturer
Biphetamine capsules	Amphetamine, dextroamphetamine	Fisons
Tussionex suspension	Hydrocodone, chlorpheniramine	Fisons
Ionamin capsules	Phenteramine	Pennwalt
Delsym solution	Dextromethorphan hydrobromide	McNeil

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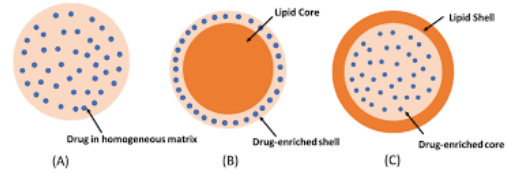
Matrix (monolithic) delivery systems

Lipid matrix systems

- ❑ The active compound is dispersed in a hydrophobic matrix that remains intact during drug release.
- ❑ Release depends on an aqueous medium dissolving the channeling agent forming a porous matrix.
- ❑ Wax matrices are examples.



They are simple, easy to manufacture using standard direct compression, roller compaction or hot melt granulation.

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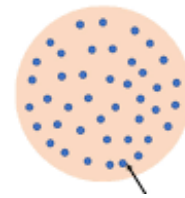
Matrix (monolithic) delivery systems

Lipid matrix systems



A typical formulation consists of:

1. Active drug
2. Wax matrix former
   - This forms generally 20 – 40% of formulation
   - Hydrophobic materials that are solid at room temperature and do not melt at body temperature.
   - Ex. Hydrogentated vegetable oils, microcrystalline wax and carnauba wax.
3. Channeling agent
   - These materials are soluble in the GI tract and leach from the formulation leaving tortuous capillaries through which the dissolved drug may diffuse.
   - Examples: NaCl, sugars and polyols
   - Typical concentration is 20 –30 %

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Matrix (monolithic) delivery systems

Lipid matrix systems

A typical formulation consists of:

4. Solubilizer and pH modifier
   - It is often necessary to enhance the dissolution of the drug by inclusion of a solubilizer (such as PEGs, polyols or surfactants) or if the drug is ionizable by inclusion of a buffer.
5. Antiadherent/Glidant
   - They are used to prevent sticking to the punches due to the melting of wax during compaction.
   - These material also act as glidant.

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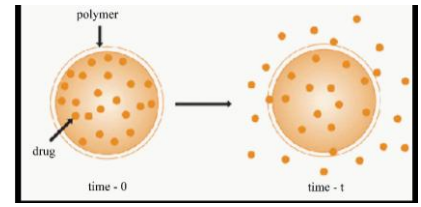
Matrix (monolithic) delivery systems

Insoluble polymer matrix systems

- A drug is embedded in an inert polymer that is insoluble in the GI fluids such as polyethylene, polyvinyl acetate, ethylcellulose or polymethacrylate.
- They can be manufactured by direct compression or by wet granulation
- The matrix remains <u>intact</u> during gastrointestinal transit.
- An immediate release portion of the drug may be compressed onto the surface of tablet.
- The release rate depends on drug molecules in aqueous solution **<u>diffusing</u>** through a network of capillaries formed between compacted polymer particles.



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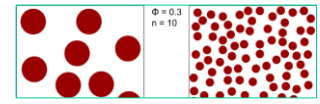
Matrix (monolithic) delivery systems

The release rate of a drug from insoluble polymer and lipid matrix systems can be modified by:

First: changes in the porosity and tortuosity of the matrix. This can be achieved by:

- The addition of pore-forming hydrophilic salts or solutes
- Control of the compression force



Second: The addition of excipients

- Generally, water soluble excipients enhance the wetting of the matrix and increase rate of release, while water insoluble excipients will decrease wettability and decrease rate of release.

Third: The particle size of the insoluble matrix components

- Larger particles lead to an increase in release rate because they produce matrices with a more open structure.

Fourth: The drug loading

- An increase in drug loading tends to enhance drug release

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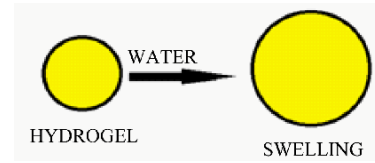
Matrix (monolithic) delivery systems

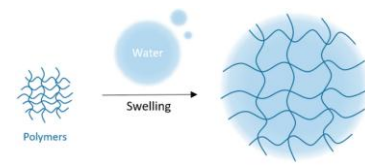
Hydrophilic colloid (swellable-soluble) matrix systems

- They consist of a compressed mixture of

1. drug,
2. water–swellable hydrophilic polymer,
3. release modifiers,
4. and lubricant/glidant.



- On contact with water the hydrophilic colloid components swell to form a hydrated matrix layer.
- Diffusion of drug through the hydrated matrix layer controls its rate of release.
- The outer hydrated layer will erode as it becomes more dilute.



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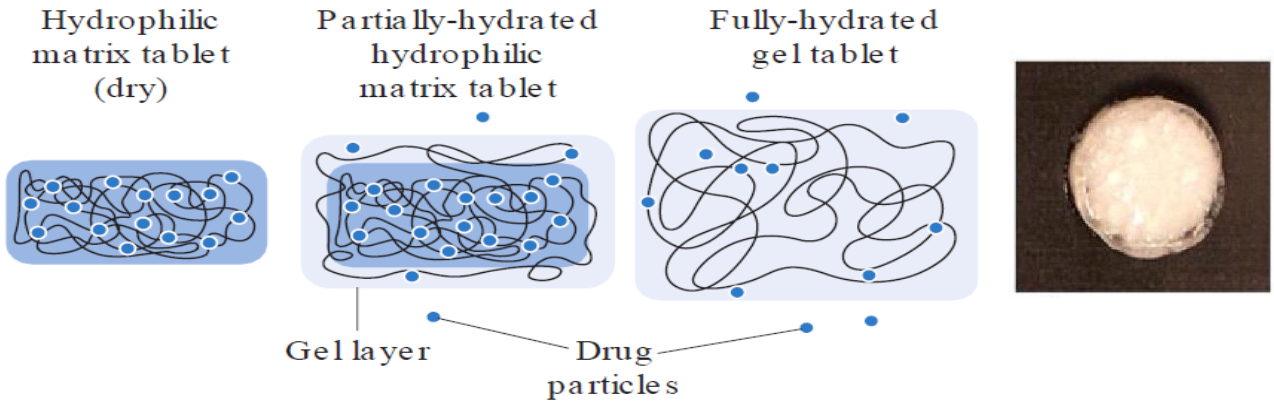
Swelling of hydrophilic colloid matrices



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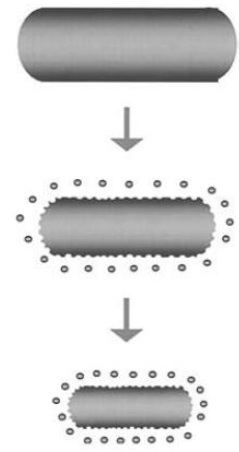
Matrix (monolithic) delivery systems

Drug release from hydrophilic colloid matrix

1) Surface drug dissolves and gives an immediate effect
2) The polymer hydrates and an outer gel layer forms
3) The gel layer becomes a barrier to uptake of further water and to the transfer of drug.
4) Drug release occurs by diffusion through the gel layer, insoluble drug is released by erosion followed by dissolution.
5) following erosion the new surface become hydrated and forms a new gel layer.



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Components of hydrophilic matrix systems

1. **Active drug**
2. **Matrix forming agent**
   - Hydrophilic colloids which, on contact with water for a hydrated gel that remains sufficiently intact during passage through the GIT are suitable as matrix formers.
   - Ex. HPMC (high viscosity grades), Na CMC, alginates, xanthan gum, carbopol
   - They occupy 20 - 80 % of the mass.

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Components of hydrophilic matrix systems

3. **Gel modifiers**
   - These are materials incorporated into the matrix to modify the diffusional characteristics of the gel layers and enhance drug diffusion and to allow more uniform and complete hydration of the gel matrix.
   - Ex. Sugars, polyols and soluble salts.
4. **Solubilizers**
   - These are used to improve dissolution of drug from matrix.
   - Ex. PEGs, polyols, surfactants.
5. **Lubricant, glidant and anti-adherent.**

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Matrix (monolithic) delivery systems

Advantages of hydrophilic matrix systems

1. Comparatively simple concept
2. Erodible
3. Easy to manufacture using commonly available equipments by direct compression, wet granulation or roller compaction.
4. Capable of sustaining high drug loadings
5. Well established technology

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Matrix (monolithic) delivery systems

Disadvantages of hydrophilic matrix systems

1. Release of drug is dependent on two diffusional processes, Penetration of water through the hydrated matrix into the non-hydrated core, and diffusion of the drug through the hydrated matrix.
2. If the outer layer of the hydrated matrix erodes, this can complicate the release profile.
3. Requires batch to batch consistency in the matrix forming materials, other components and process parameters
4. Scale-up of the manufacture can be a problem
5. Need optimal rate-controlling polymers for different actives.

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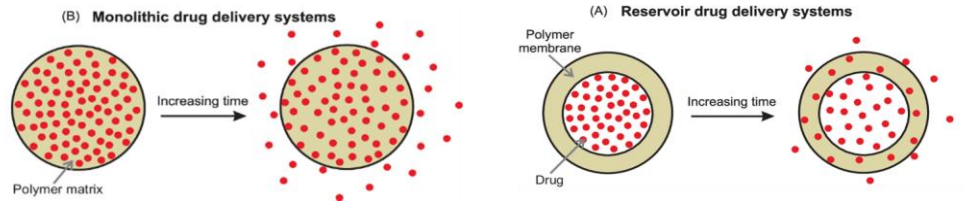
Membrane-controlled drug delivery systems

- The rate controlling of such systems is a membrane through which the drug must diffuse.
- The essential difference between a membrane and a matrix system is that in the membrane-controlled systems the polymer is found as a membrane at the surface of the system only, while in the matrix system the polymer is throughout the whole system.

- In both cases the hydration of the polymer is the step that allows the drug to diffuse.



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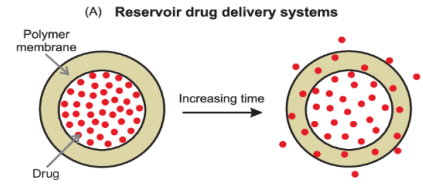
Membrane-controlled drug delivery systems

- Unlike hydrophilic matrix systems the membrane polymer does not swell.
- A drug reservoir, e.g tablet or multiparticulate pellet, is coated with a membrane.
- Aqueous medium diffusing into the system and forming a continuous phase through the membrane initiates drug diffusion and release.
- There are two diffusion processes: "water in" followed by "drug out".



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Components of a membrane controlled system

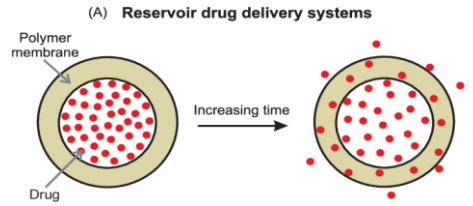
- The delivery systems may be presented either as single or multiple unit systems.

Core

- Active drug
- Filler
- Solubilizer
- Lubricant/glidant

Coating

- Membrane polymer
- Plasticizer
- Membrane modifier
- Color/opacifier



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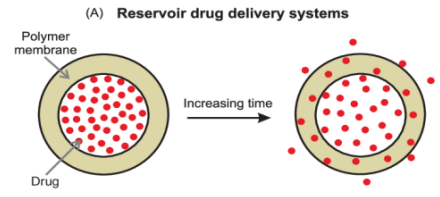
Membrane-controlled drug delivery systems

Single unit systems

- This is essentially a tablet formulation, but with differences from conventional dosage forms in that extended-release tablet core should not disintegrate but dissolve.
- A formulation is required to allow water to penetrate and the drug to dissolve so that diffusion through membrane can occur.



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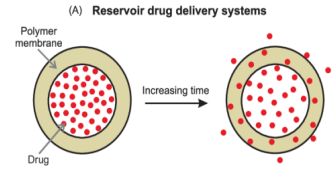
Membrane-controlled drug delivery systems

Single unit systems



Core formulation

- Suitable diluents (fillers) include lactose, microcrystalline cellulose, dextrose, sucrose and polyols (mannitol, sorbitol, xylitol etc)
- Note: Soluble fillers can minimize osmotic effects.
- An inappropriate choice will result in increased internal osmotic pressure followed by rupture of the membrane.
- The choice of solubilizer if required is governed by the solubility characteristics of the drug. (ex. Surfactants, buffer, polyols and PEGs).
- Satisfactory lubricant and glidant are required

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Membrane-controlled drug delivery systems

Multiple unit systems

- This type of dosage form comprises of more than one discrete unit. These are typically coated spheroids (pellets approximately 1 mm) in diameter filled into hard gelatin capsule shell or , less commonly, compressed into a tablet.

- The most common approaches for manufacturing

of drug-containing multiple units:

  - The use of inert sugar spheres (nonpareils) coated first with drug and then with the release controlling membrane.
  - The formulation of small spheroids containing the drug using an extrusion spheronization process.

This approach is better if a high drug loading is required.

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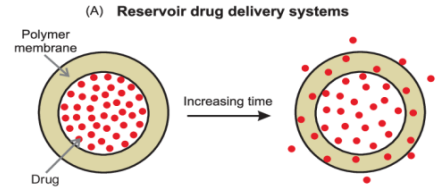
Release controlling membrane

- The membrane must be **intact** during the period of release (i. e. there should be no erosion, swelling or bursting).
- Typical polymers used include ethyl cellulose, acrylic polymers (e. g. Eudragit RL and RS), polyvinylacetate, silicone elastomers.
- The release-controlling polymer is film-coated onto the system.
- Plasticizers and colors can be added
- Release modifiers:
- These include polyethylene glycols, propylene glycol or other polyols and water-soluble polymers.



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Membrane-controlled drug delivery systems

Advantages of multiple unit membrane controlled systems

1. They allow the release to be optimized for individual drugs in a system delivering two or more active drugs.
2. They are less likely to suffer from problems associated with film failure.
3. The GIT transit is more consistent than that of a large single unit systems.
4. Less local irritation.

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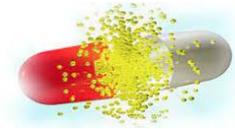
Membrane-controlled drug delivery systems

Disadvantages of membrane controlled systems

1. Dose dumping can occur from single unit systems as a result of film failure.
2. Multiple unit systems can be difficult to retain in the upper GIT.
3. The control of membrane characteristics may be difficult.
4. Filling of the multiunit spheroids (pellets) into capsules can be a problem due to build-up of static charge.



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Osmotic pump systems

- Osmotic pump systems are another form of membrane-controlled release drug delivery system.
- A drug is included in a tablet core which is water soluble, and which will solubilize the drug in the presence of water.
- The tablet core is coated with a semi permeable membrane which will allow water to pass through into the core, which then dissolves.
- As the core dissolves a hydrostatic pressure builds up and pumps drug solution (or suspension) through a hole drilled in the coating (by laser beam).

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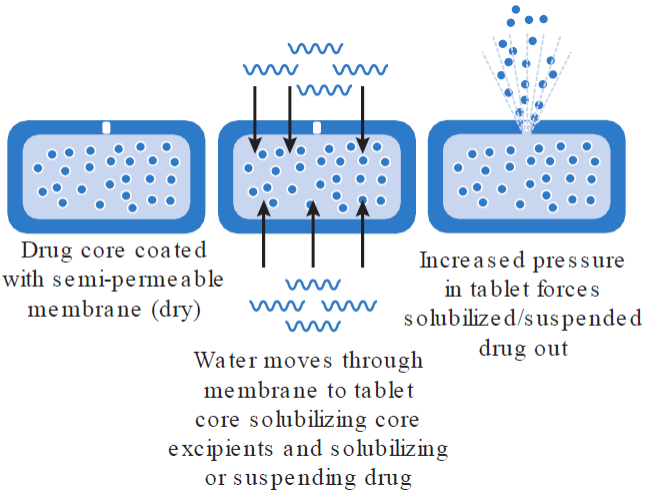
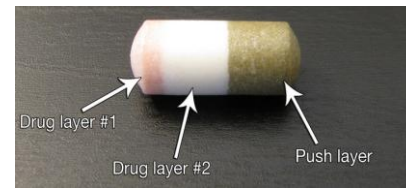


Osmotic pump



Osmosis is the spontaneous net movement or diffusion of solvent molecules through a selectively-permeable membrane from a region of high water potential (region of lower solute concentration) to a region of low water potential (region of higher solute concentration)

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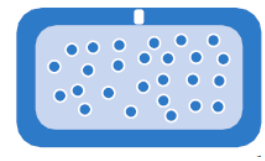
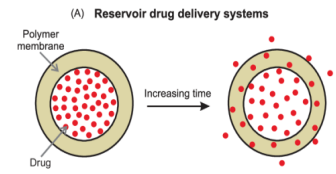
Osmotic pump systems

- The rate of release is governed by the permeability of membrane and the rate that the drug solution is able to pass through the hole.
- The drug release rate may be altered by changing:
  - the surface area
  - the thickness or composition of membrane
  - the diameter of the hole
  - The viscosity inside the core
- The essential difference between osmotic pumps and classic membrane controlled systems is that in the osmotic pump one diffusion process is necessary (water in) while in classic membrane controlled systems two diffusion processes (water in and drug out).





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Osmotic pump systems

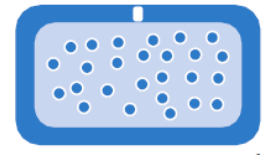
Components of osmotic pump systems

Core

- This consists of active drug, a filler, a viscosity modifier, solubilizer and lubricant/glidant.

Coating

- This consists of a membrane polymer (film former) a plasticizer, a membrane modifier, and color/opacifier.
- The coating should be permeable **only** to water.



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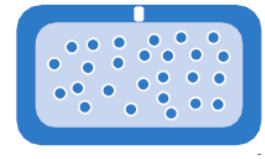
Osmotic pump systems

Advantages of osmotic pump systems

- They are well characterized and understood
- Modification of the rate of diffusion of water is more straightforward than for many drugs
- The release mechanism is not dependent on the drug
- They are suitable to wide range of drugs
- They typically give a zero-order release profile after an initial lag.

Disadvantages of osmotic pump systems

- Size of hole is critical
- Laser drilling is capital intensive



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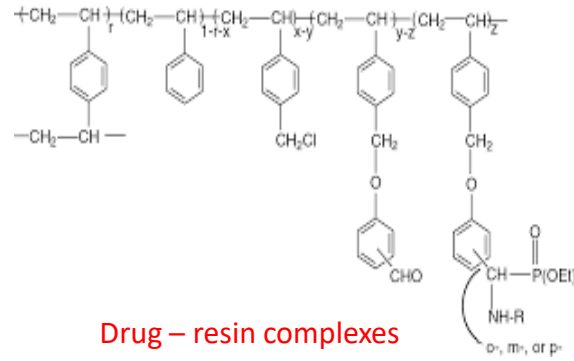
Ion Exchange resins (drug complexes)

- Resins used are special grades of styrene/divinyl benzene copolymers (Water-insoluble) that contain appropriately substituted groups:
  - Carboxylic or sulfonic for **cation** exchangers
  - Quaternary ammonium for **anion** exchangers



Drug – resin complexes

Complex formation:

- Resin-$SO_3^-Na^+$ + Drug HCl ⟶ NaCl + Resin-SO_3. Drug H

Drug release:

- Resin-SO_3^-. Drug H + NaCl ⟶ Drug HCl + Resin-SO_3Na

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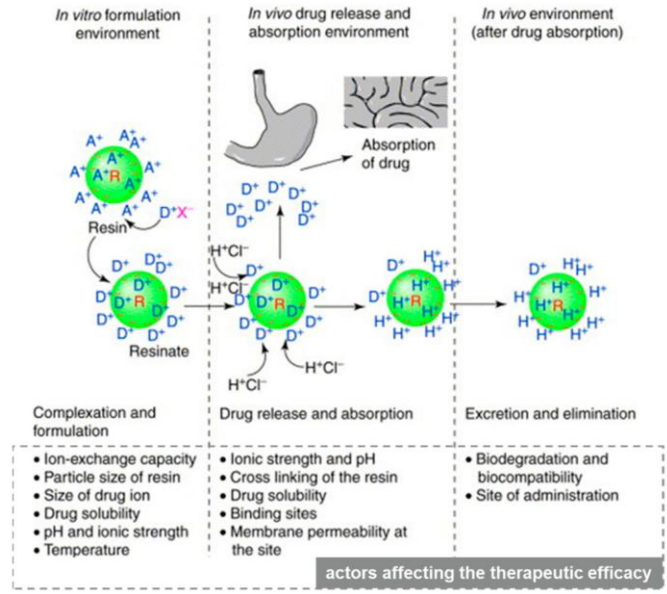
Drug – resin complexes



Complex formation:

- Resin-$SO_3^-Na^+$ + Drug HCl ⟶ NaCl + Resin-SO_3. Drug H

Drug release:

- Resin-SO_3^-. Drug H + NaCl ⟶ Drug HCl + Resin-SO_3Na

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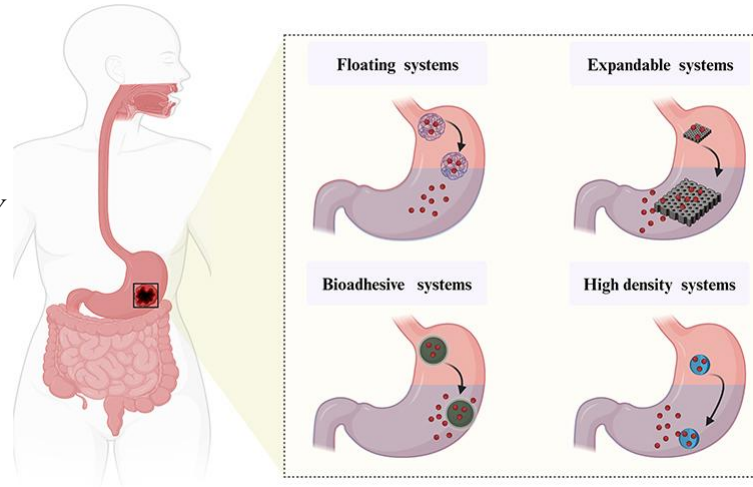
Delivery systems for targeting to specific sites in the GIT

- Targeting drug delivery can be achieved by:

1. ***Gastric Retentive Drug Delivery Systems*** (GRDDS)
2. ***Colonic drug delivery systems***



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Gastric retentive systems

- Aims of using such systems include:
  1. reduced variability of drug release
  2. local drug delivery and action (e.g. against H. Pylori)
  3. enhanced bioavailability for some drugs with restricted absorption window in the GIT.
  4. For drugs that are degraded in the colon.
- Success with gastroretention has been limited, mainly due to the challenge presented by the stomach and gastric emptying which is incredibly difficult to overcome by formulation methods alone.

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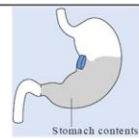
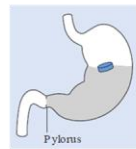
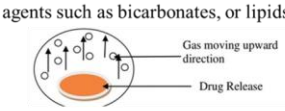
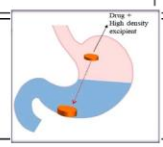
- Main methods to achieve gastric retention are:

Approach to achieve gastro-retention	Concept
Mucoadhesiom 	Mucoadhesive polymers (such as carbopol and chitosan) could theoretically adhere a dosage form to the stomach mucosa to retain it in the stomach.
Floating dosage forms ***Low density*** 	Dosage form should float on the stomach contents, thus avoiding gastric emptying. Can use gas generating agents such as bicarbonates, or lipids (low density). 
Size increasing systems 	A dosage form that swells and increase in size as soon as it reaches the stomach to avoid being able to pass through the pyloric sphincter. Swellable polymers such as hydroxypropyl methyl cellulose, polyethylene oxide, and xanthan gum have all been investigated
High density (sinking) systems 	Pellets that are small enough to be held in the folds of the stomach body close to the pyloric area have been maintained with the use of sedimentation.

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Colonic delivery systems

- Applications for these systems include:
  - local drug delivery
    - for the treatment of inflammatory diseases, infections and diarrhea.
  - systemic drug delivery
    - Ex. Peptides (destroyed by enzymes in stomach and small intestine)
    - **Note: colon pH 7.8-8.5**

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Colonic delivery systems

- Design principle for these delivery systems make use of:
  - The specific pH of the colon: pH sensitive polymers are used in their manufacture, ex.
  - Combination of Eudragit 100-55 (pH 5.5) with Eudragit S (pH 7.0).
  - The principle is that drug is released at specific pH environment.

  - Small intestine transit time.
  - These depend on timed release of the active drug

  - Colonic bacteria: The principle here is to coat the drug delivery system with a polymer that is degraded by the bacteria of the coon. Polymers used include glassy amylose (mixed with ethylcellulose); or pectin as a thick compression coat, cross-linked with calcium

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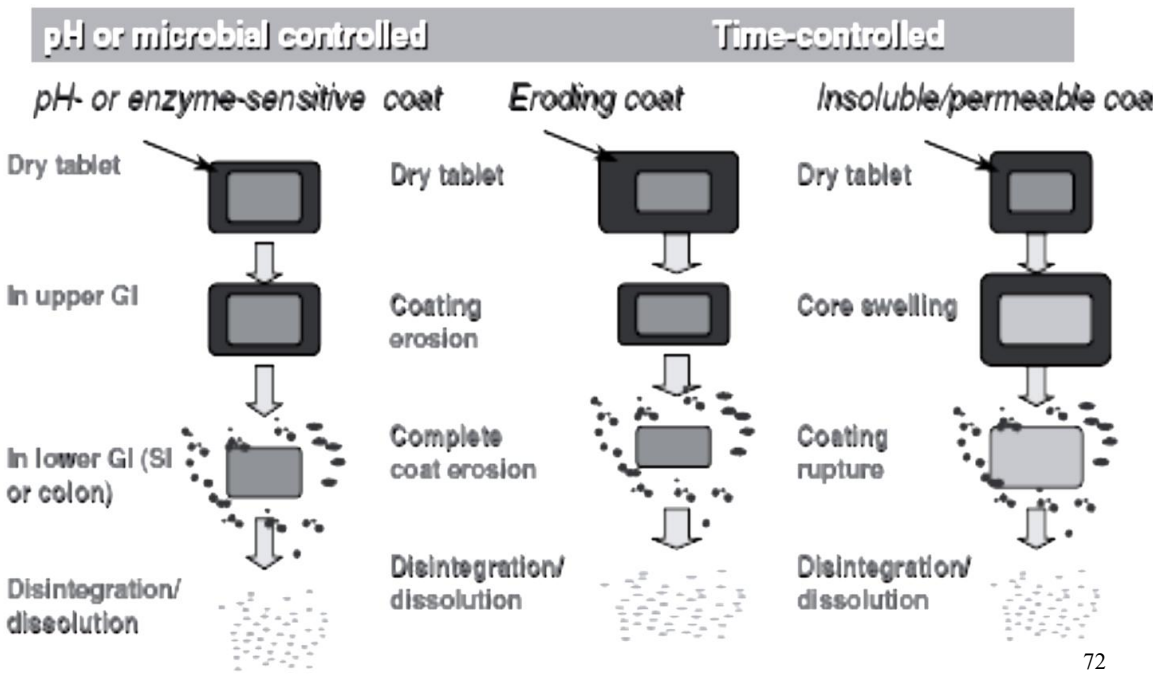

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