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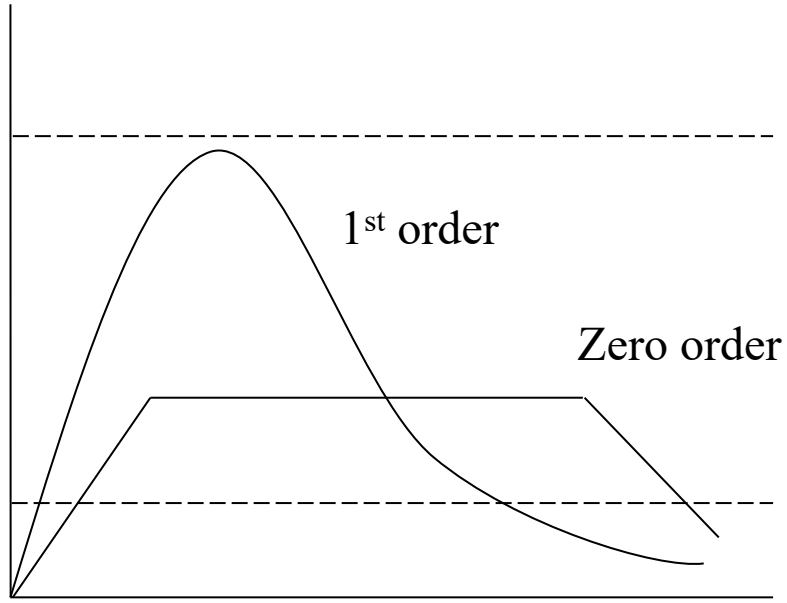
Sustained Release Dosage Forms

Sustained Release Dosage Forms

- The sustained release (S.R.), is a term used to identify drug delivery systems that are designed to **achieve a prolonged therapeutic effect** by the continuous release of the medication over an extended period of time after administration of a single dose.
- In the case of injectable dosage forms (depot), this period may vary from days to months while in oral dosage forms, it lasts for hours depending on the residence time in the GIT.
- Many terms are used to describe extended-release (**ER**) dosage form: controlled release (**CR**), sustained or slow release (**SR**), long-acting (**LA**), controlled delivery (**CD**), programmed or prolonged delivery (**PD**), slow-acting (**SA**), timed delivery (**TD**), timed release (**TR**).

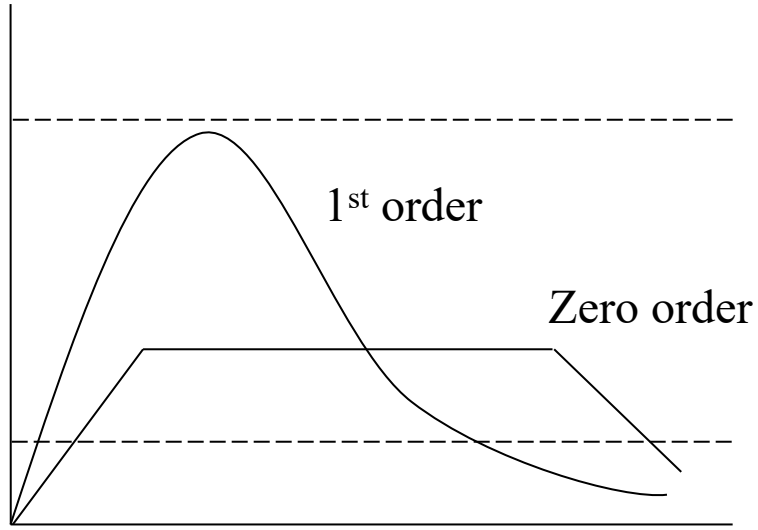
Kinetic Consideration of SR Formulations

- Kinetically, the drug release from S.R. dosage forms is usually a **zero-order** release profile.
  - In contrast, conventional dosage forms show 1st order kinetics, as shown in the following curve:
- In general, the S.R. dosage forms contain a **loading dose** (to provide the required onset of action) and a **maintenance dose** (to keep out the therapeutic action).
- Regarding the **zero-order** formulas, the release process is **independent** of the magnitude of the maintenance dose and does not change during the maintenance period.



Kinetic Consideration of SR Formulations

- The zero-order kinetic, dosage form releases a constant **amount** of drug per unit of time.
  - For ex., if we have S.R. formula containing 100 mg of a drug and the release of this formula is a zero-order at a rate of 10 mg\hr, then the formula will last exactly for 10 hr.
- In contrast, the 1st order formulas release a constant **percentage** per unit of time (**not** amount).
  - For ex., if we have 100 mg in a 1st order formula that releases the drug at a rate of 10% per hour; it will release 10 mg in the first hour, then release 9 mg in the second hour, and so on until the completion of the drug.



Advantages

1. More **patient compliance** since the frequency of drug administration is reduced.
2. **Less fluctuation** in the drug plasma concentration if compared with conventional multiple-dosing dosage forms.
3. Reduction of **the side effects** associated with the sudden release of conventional dosage forms.
4. **Less amount** of drug can be used so maximizing availability with a minimum dose.
5. **Better control** of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high-availability drug can be reduced by formulation in an extended action form.
6. Improved treatment of some **chronic diseases** in which the symptoms may return if the plasma concentration of the drug falls below the minimum effective concentration, e.g. asthma and depression.

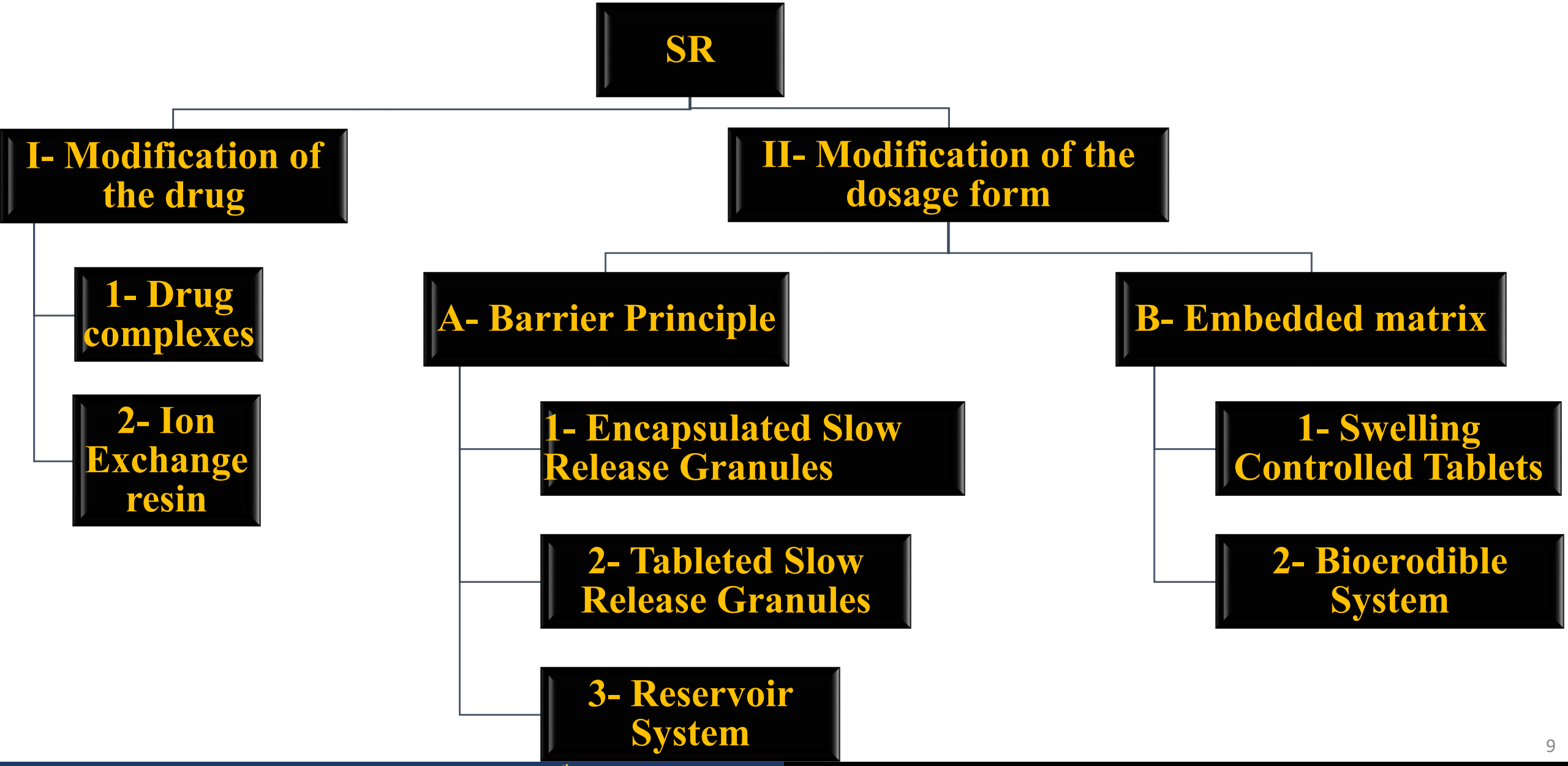
Disadvantages

1. Administration of S.R. dosage forms does not allow the **prompt termination** of the therapy as in the case when the patient develops severe side effects.
2. The physician has less **flexibility** in adjusting dosage regimens.
3. The S.R. is designed for the **normal population**.
   - Patient variations and disease states that alter drug kinetics (e.g. renal failure) are not accommodated by S.R.
4. Breakage of sustained release dosage form may cause **dose dumping**.
5. **Economic** factors since it is relatively costly to produce SR formulation compared to the conventional dosage form.

Drugs NOT Suitable for S.R.

1. Drugs with a **short half-life** ($T_{1/2}$ < 1 hr), e.g. furosemide.
2. Drugs with **long half-lives** ($T_{1/2}$ > 12 hr), e.g. diazepam (since they already have some SR properties).
3. If **large doses** are required (drug dose > 1 g) ex sulfonamide such as trimethoprim.
4. Drugs with **narrow therapeutic index**, e.g. digoxin, warfarin.
5. Drugs that have specific requirements for absorption such as those with **window absorption** phenomena ex B2 (riboflavin) and ferrous sulfate are not effectively absorbed in the lower GIT.
6. **Water-insoluble** drugs whose bioavailability is controlled by dissolution (dissolution is the rate-limiting step). The amount of drug available for absorption is limited by the poor solubility of the compound (ex Griseofulvin).

The Design of S.R.



The Design of S.R.

- Two general approaches have been used for the formulation of S.R:

I- Modification of the physical and/or chemical properties of the drug.

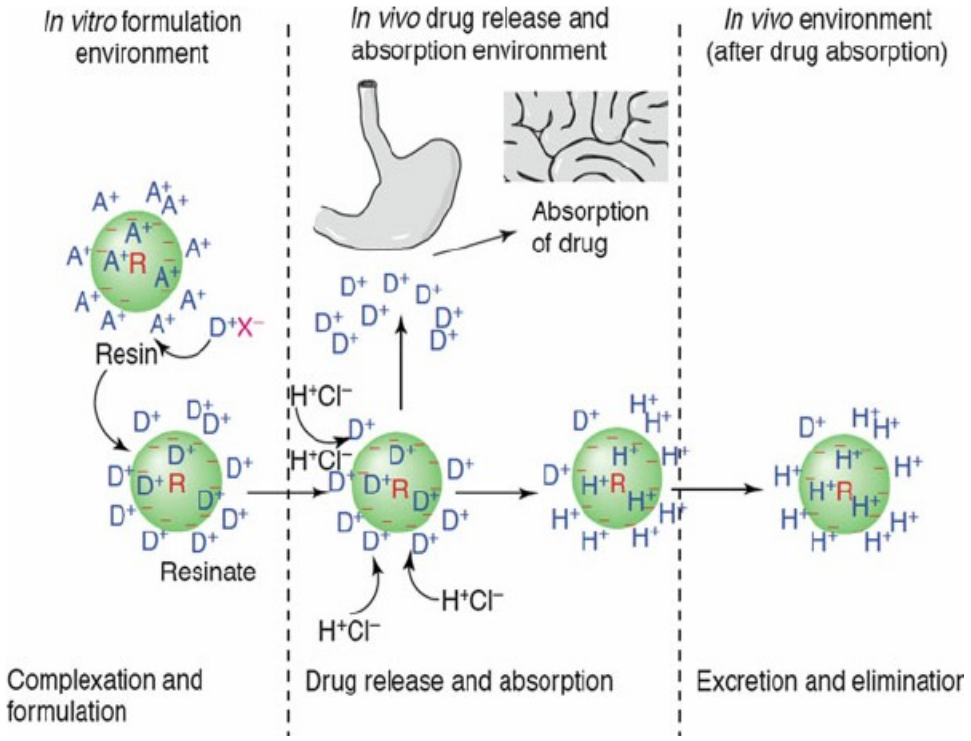
- In this method, the drug itself is modified in a manner that retards its release while the dosage form is not. Examples of such approaches are complexes and prodrugs.
- The **principal advantage** of preparing drug modification is that such materials can be formulated into diverse dosage forms (such as tab., cap., susp., inj.)

1- Drug complexes:

- Materials such as **tannic acid** can be used for drug complexation. In the body, tannate complexes are **hydrolyzed gradually** by gastric and intestinal enzymes. It is worth mentioning that tannic acid is **suitable for alkaline drugs only**.

The Design of S.R.

- **2- Ion exchange resin:**
- It is another approach for modifying drug molecules.
- It can be used for **both acidic and basic** drugs and it is **more widely** used than tannic acid.
- Drug-resin complexes are **water-insoluble** in which drug release results from the exchange of drugs in the complex with ions normally present in the GIT such as H^+, CI^-, and OH^-.
- **However**, the amount of drug that can be incorporated in the resin is limited to a maximum of **300 mg** since larger doses require too much resin.



The Design of S.R.

II- Modification of the properties of the dosage form.

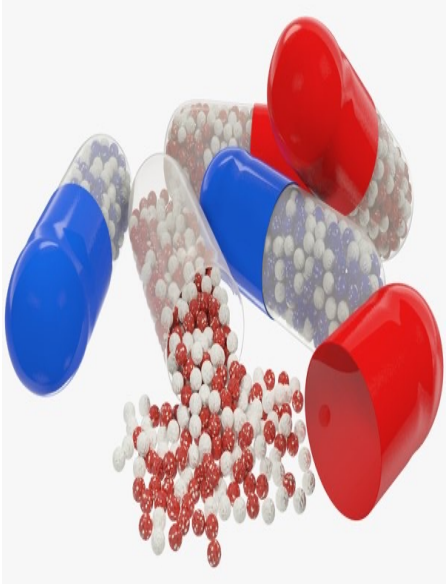
- In this method, only the dosage form has been modified in order to modify the release rate. Approaches include the **barrier** principle or embedded **matrix**.

- **A- Barrier Principle**: can be classed into **three** product types:

1. **Encapsulated Slow Release Granules**: Routinely, they are formulated as follows:
   - **Nonpareil pellets** (which are small spheres composed of sugar and starch) are initially coated with an adhesive material followed by the incorporation of drug powder on the surface of the pellets. Then the pellets are dried and this procedure is repeated until the desired amount of drug is applied.
   - The resultant pellets are then coated with certain polymers (such as cellulose polymers). This coat acts as a barrier that controls the release of drugs **depending on its thickness.**

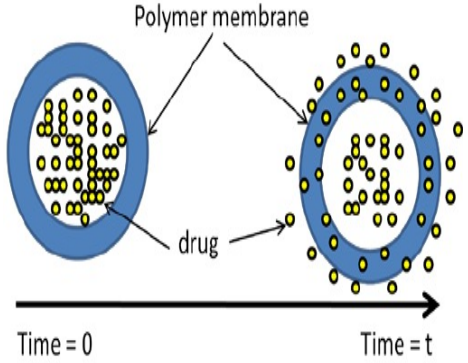
The Design of S.R.

- An example of this type of formula is what is called in commercial terms as **spansules**. ➔
- They are capsules containing hundreds of colored pellets divided into 3-4 groups which differ in the **thickness** of the coat.
- A typical system (capsule) consists of **uncoated** pellets to provide the loading dose and pellets **designed** to release the drug at 2-3 hr, 4-6 hr, and 6-9 hr.
  - The key factor that controls the drug release from these pellets is the **thickness of the coat**.
- In the case of relatively **high-dose drugs**, nonpareil pellets are not used. Instead, the drug itself is formulated as pellets and then coated by polymer by a suitable machine such as a pan coater.
- **Drug release** from these pellets results from the 1) **diffusion** of drug out of the barrier (coat) and 2) **erosion** of the coat.



The Design of S.R.

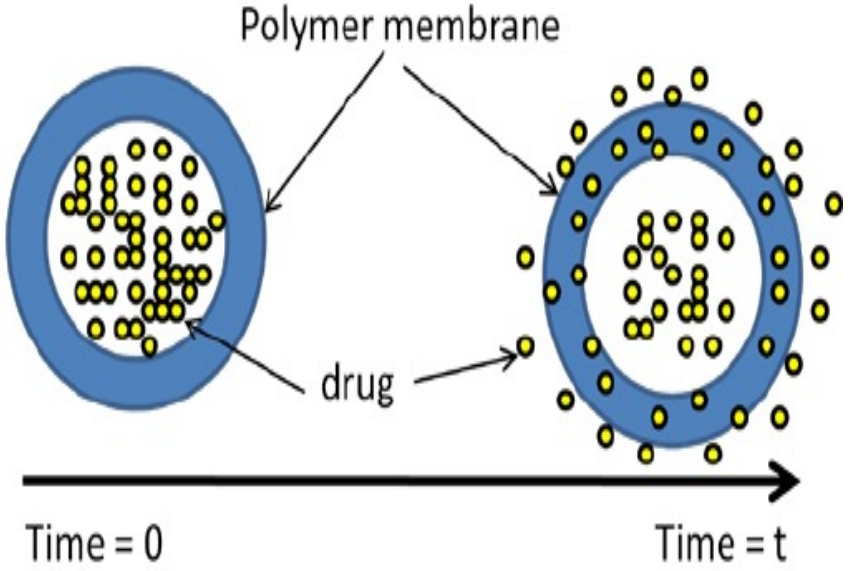
2. **Tableted slow-release granules**: Instead of formulating the pellets as capsules, they can be compassed into tablets that **disintegrate** in the stomach to **liberate the controlled-release pellets**.
   - Although both (1 and 2 techniques) contain controlled-release pellets, tablets retain the general advantages stated previously for the tablet dosage form.
3. **Reservoir system ((slow release (core) tablet):**
   - consist of a **drug core and excipients** surrounded by a layer of **nonbiodegradable polymer**, through which the drug slowly **diffuses**.
   - The properties of the polymer govern the release rate of the formula into the bloodstream.
   - To maintain uniformity of drug delivery, the thickness of the polymer must be consistent.



The Design of S.R.

- **Disadvantages of the reservoir system**:

1. One of the **problems** with the reservoir system is that such a system must be removed from the body after the drug is depleted because the polymer remains intact.
2. Another potential **problem** is that if the reservoir membrane accidentally ruptures, a large amount of drug is suddenly released into GIT (known as "**dose dumping**").



Drug Facts

Active ingredients (in each extended-release tablet) — **Purpose**

Dextromethorphan Hydrobromide USP 60 mg ..... Cough suppressant

Guaifenesin USP 1200 mg ..... Expectorant

Uses

- helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and make coughs more productive
- temporarily relieves:
  - cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants
  - the intensity of coughing
  - the impulse to cough to help you get to sleep

Warnings

Do not use

- for children under 12 years of age
- if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have ■ persistent or chronic cough such as occurs with smoking, asthma, chronic bronchitis, or emphysema ■ cough accompanied by too much phlegm (mucus)

When using this product ■ do not use more than directed

Stop use and ask a doctor if ■ cough lasts more than 7 days, comes back, or occurs with fever, rash, or persistent headache. These could be signs of a serious illness.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center (1-800-222-1222) right away.

Directions

■ do not crush, chew, or break tablet ■ take with a full glass of water ■ this product can be administered without regard for timing of meals ■ adults and children 12 years and older: 1 tablet every 12 hours; not more than 2 tablets in 24 hours ■ children under 12 years of age: do not use

Other information

■ store at 20° to 25°C (68° to 77°F)

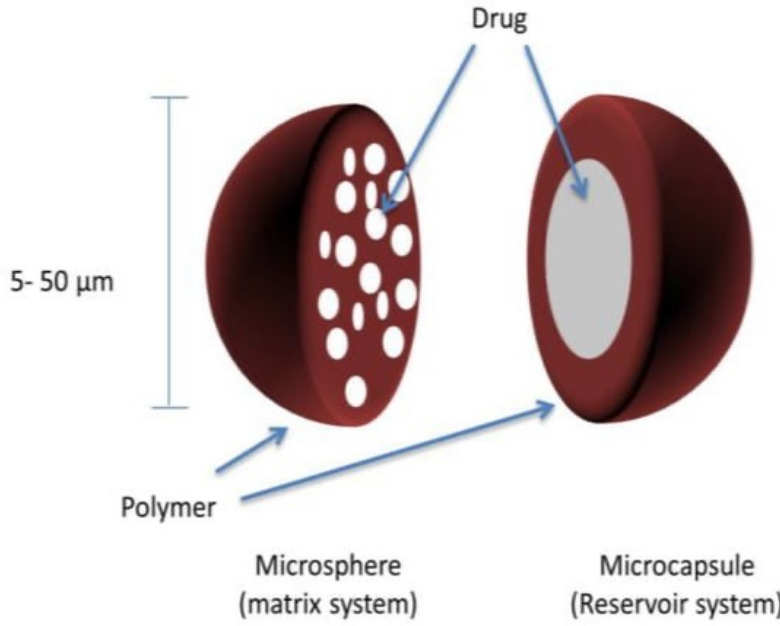
Inactive ingredients

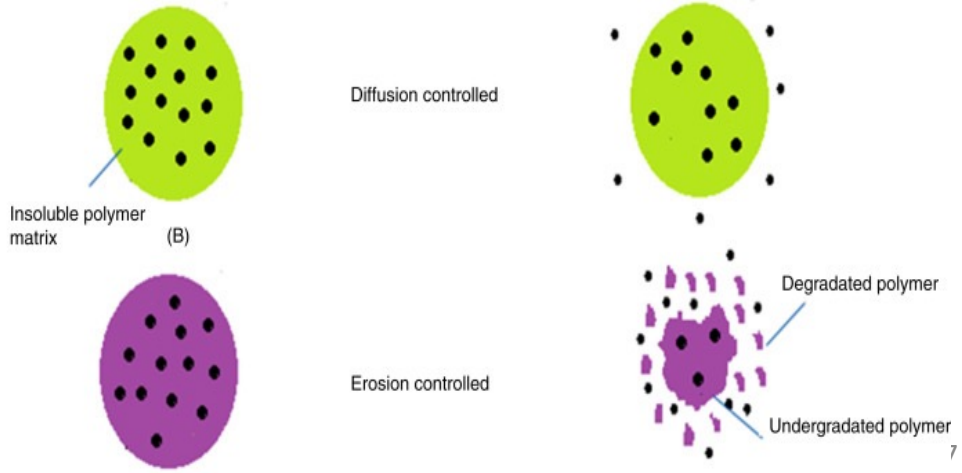
colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch (maize)

Questions or comments? Call toll-free, **1-855-874-0970** (English/Spanish) weekdays
You may also report side effects to this phone number.

B- Embedded Matrix Modifications

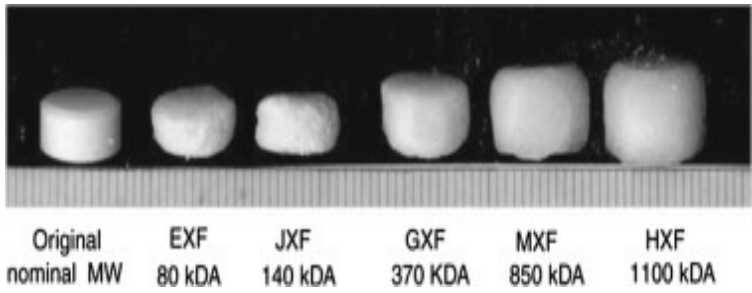
- The matrix tablet formulation is one of the simplest methods of dosage form modification.
- It involves the compression of a mixture of drug, **retardant polymer,** and other excipients to form a tablet in which the drug is embedded in the retardant.
- The drug is released from the matrix at a uniform rate as it dislodges from the polymer network. The release of the drug is achieved either by **1) diffusion or 2) erosion**.
- The loading dose is included as a **bi-layer**.
- Unlike the reservoir, there is **no danger of drug dumping**.



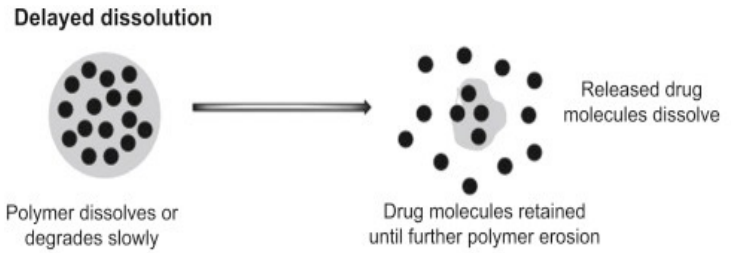


Embedded Matrix Modifications

1. **Swelling-controlled tablets**:
   - The system consists of **hydrophilic polymer** cross-linked to form a three-dimensional network.
   - The polymer holds a large quantity of water **without dissolving**.
   - As the polymer swells, a characteristic of such a system is its **permeability for the drug at a controlled rate**.



2. **Bioerodible (Biodegradable) system**:
   - The controlled release of the drug involves polymers that **gradually decompose**.
   - The drug is dispersed uniformly throughout the polymer and is slowly released from the tablet as the polymer disintegrates (slowly).



Embedded Matrix Modifications

- Two major **advantages** of bioerodible systems are:
  1. The polymer **does not have to be removed** intact from the body after the drug is depleted.
  2. The drug does not have to be water-soluble.

- In fact, **because of** these factors, the future use of bioerodible polymers is likely to increase more than any other type of polymers.
- Biodegradable polymers can be defined as polymers that are degradable in vivo **enzymatically** to produce nontoxic by-products.
- These polymers can be metabolized and excreted via normal physiological pathways (by liver or kidney).
- They are classified into **three** groups: ➔

Embedded Matrix Modifications

1. **Natural**:
   - Examples of commonly used natural polymers are gelatin, alginate, dextran, and chitosan.
2. **Synthetic**:
   - Synthetic polymers are polylactic acid and many other polymers such as PLGA. Synthetic polymers are **preferable** to natural biodegradable polymers **because** their physicochemical properties are more predictable and reproducible.
3. **Semisynthetic:**
   - Modifications can be made to naturally occurring polymers, such as chitosan and alginate to produce semisynthetic biodegradable polymers. These modifications can result in **altered physicochemical properties**, such as mechanical strength and degradation rates.

Embedded Matrix Modifications

- The **factors** that affect the **degradation rate** of the polymer involve:
  1. Chemical properties such as the structure of monomers, can affect the liability of the cleavable bonds.
  2. Physical properties, such as **hydrophilicity**, **crystallinity,** and **molecular weight** of the polymers.
- **Biodegradation** of these polymers usually involves four steps: 1) hydration, 2) mechanical strength loss, 3) integrity loss, and 4) mass loss.
  - The **hydration** step is critical and is determined by the hydrophilicity/ hydrophobicity of the polymer.
- **Natural biodegradable** polymers are hydrophilic and undergo degradation by hydrolysis, whereas most of the synthetic biodegradable polymers are hydrophobic.
  - Polymers that are **hydrophobic** can undergo **surface degradation** (i.e., degradation occurs on the outer layer exposed to the aqueous fluid).

Controlled Release

- It's another form of delayed or sustained release formulation. It is a dosage form which designed to release the drug in vivo **according to predictable rates**.
- **Hydrodynamically balanced system (floating tablet)**. These formulations do float either because of their low density compared to the GI fluids or due to the gaseous phase formed inside the system after they come in contact with the gastric fluids. Particles will float on the surface and **delayed gastric emptying** time.
- **Osmotic pressure-activated system**: The tablet contains an **osmotic pressure-generating material** and is covered with a semipermeable membrane (permeable only to water not to the drug). Then laser is used to form a **precision orifice** in the barrier from which the drug can diffuse out of the formulation.