Sustained Release Dosage Forms

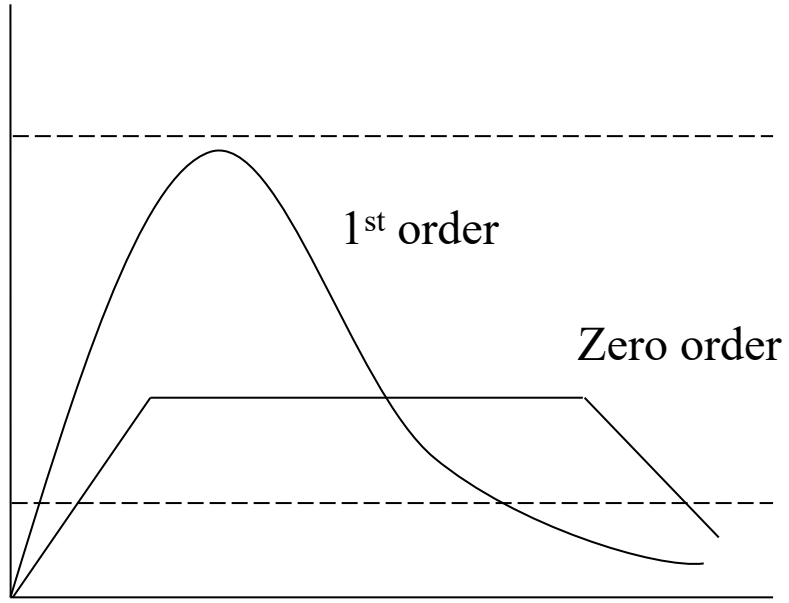
Mohammed Albarki, PhD

Sustained Release Dosage Forms

- **Sustained release (S.R.)** is a drug delivery system designed to achieve a prolonged therapeutic effect by releasing the medication over an extended time.
- In the case of **injectable** dosage forms (depot), this period may vary from **days to months**;
- In oral dosage forms, it lasts for hours depending on the residence time in the GIT.
- Many terms are used to describe modified-release dosage forms: extended-release (**ER**), 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

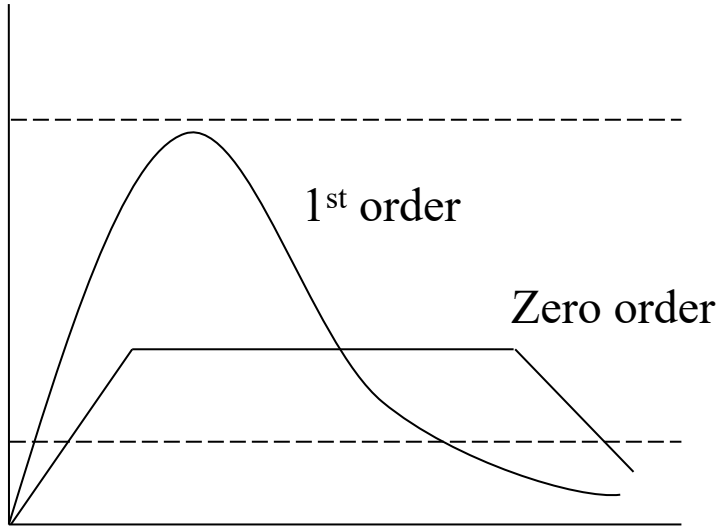
- Kinetically, the drug release from S.R. dosage forms is usually a **zero-order** release profile.
  - In contrast, conventional dosage forms show 1st order kinetics, as shown in the following curve:



- 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 example, if we have an 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. 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.

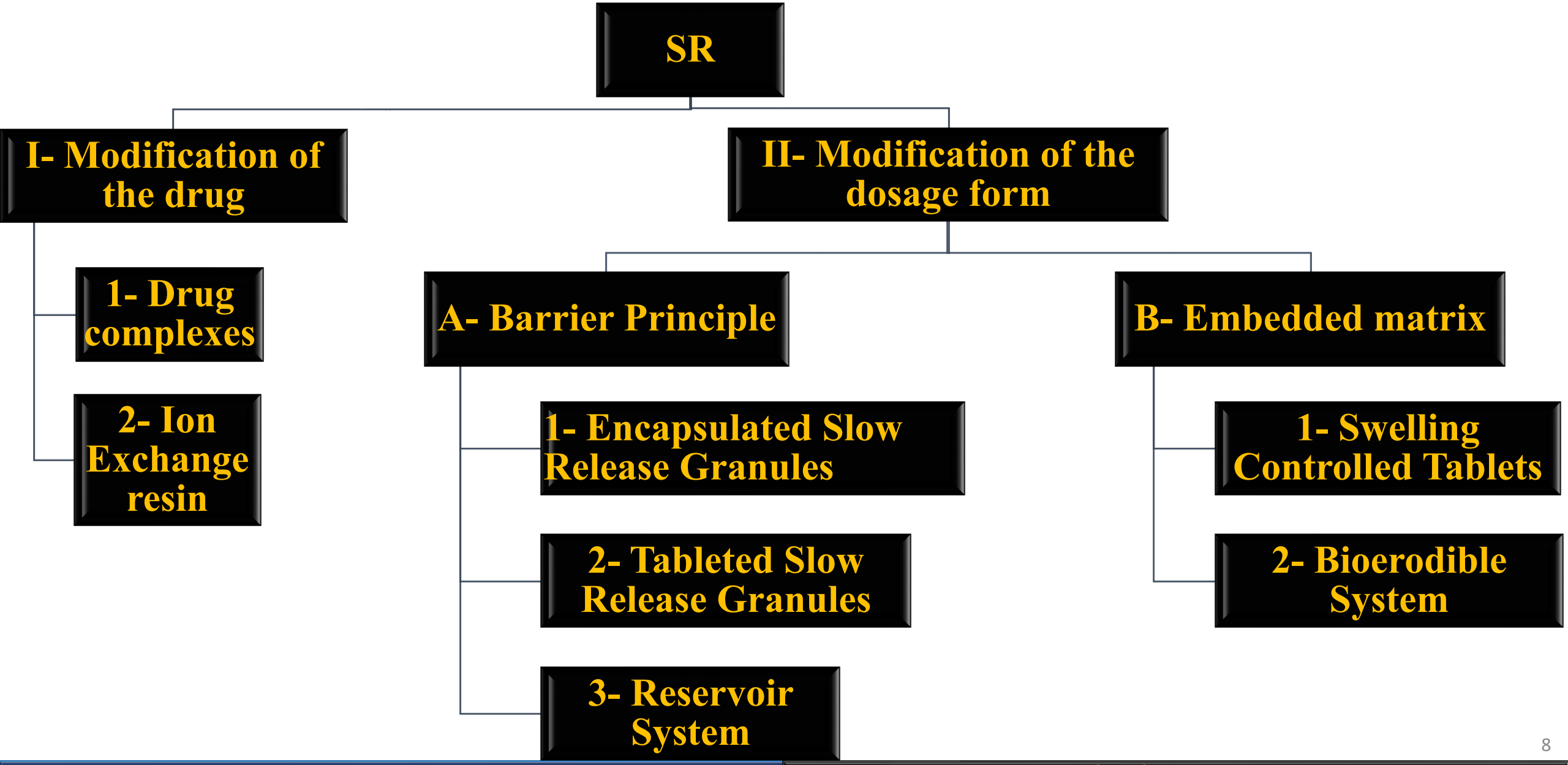
Disadvantages

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.

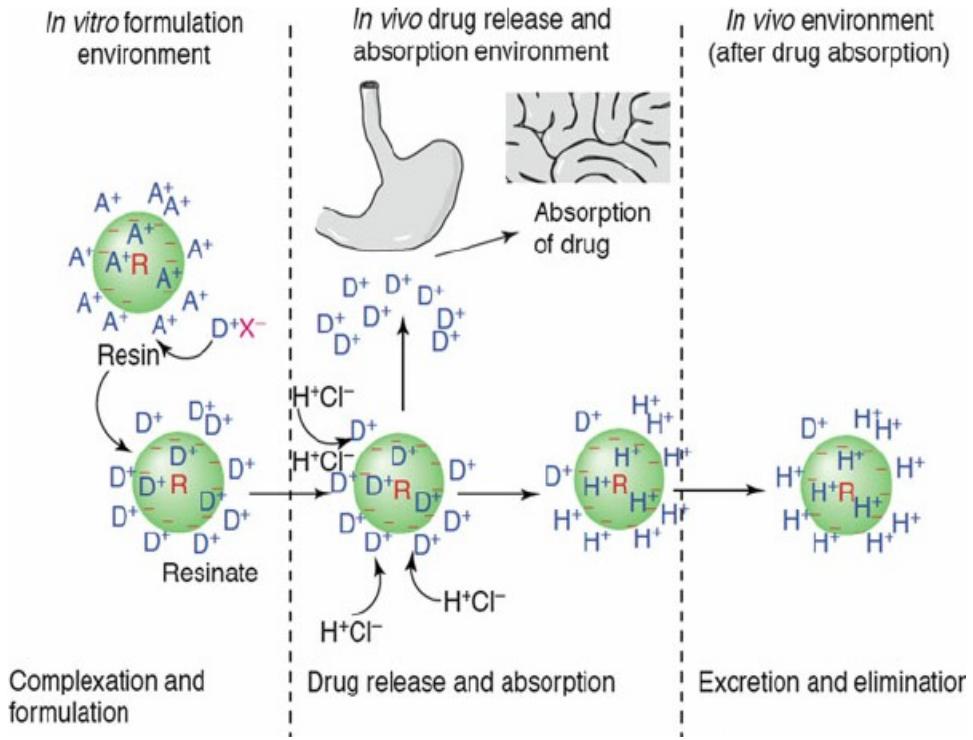
- In this method, the drug itself is modified in a manner that retards its release while the dosage form is not. Examples of such approaches are complexes and prodrugs.
- The **principal advantage** of preparing drug modification is that such materials can be formulated into diverse dosage forms (such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

The Design of S.R.

- **2- Ion exchange resin:**
- 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.

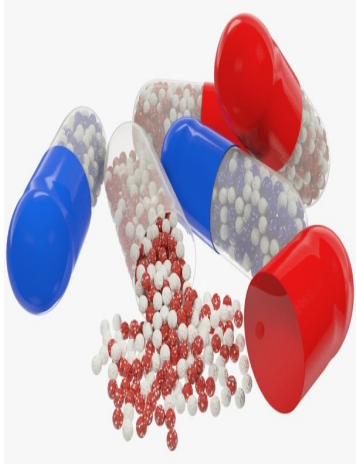
- In this method, only the dosage form has been modified. Approaches include the A) **barrier** principle or B) embedded **matrix**.

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

1. **Encapsulated Slow Release Granules**: 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.**

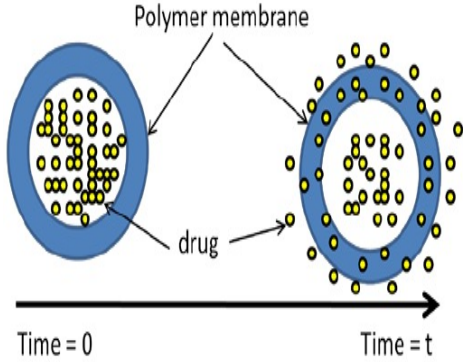
The Design of S.R.

- An example of this type of formula is what is called in commercial terms **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**.
- **NOTE:** 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 1) **diffusion** of the drug out of the barrier (coat) and 2) **erosion** of the coat.



The Design of S.R.

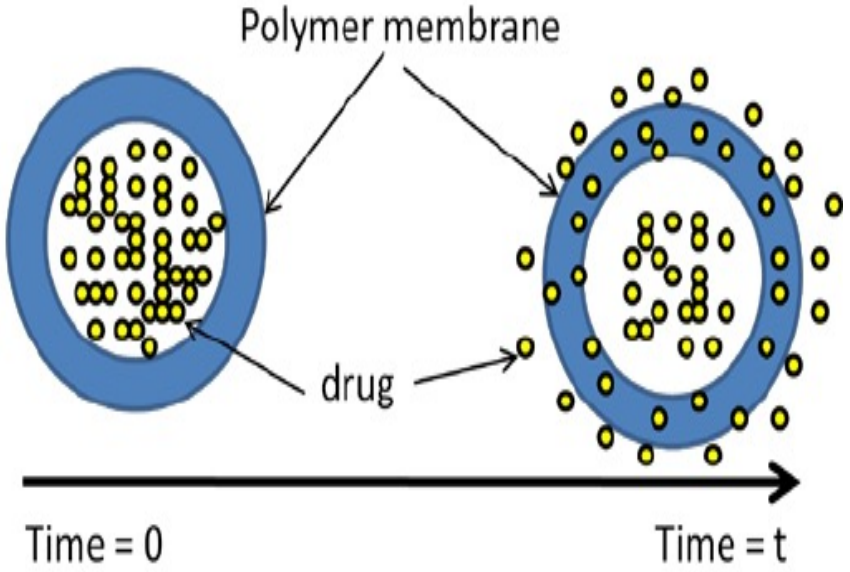
2. **Tableted slow-release granules**: Instead of formulating the pellets as capsules, they can be compassed into tablets that **disintegrate** in the stomach to **liberate the controlled-release pellets**.
   - Although both (1 and 2 techniques) contain controlled-release pellets, tablets retain the 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

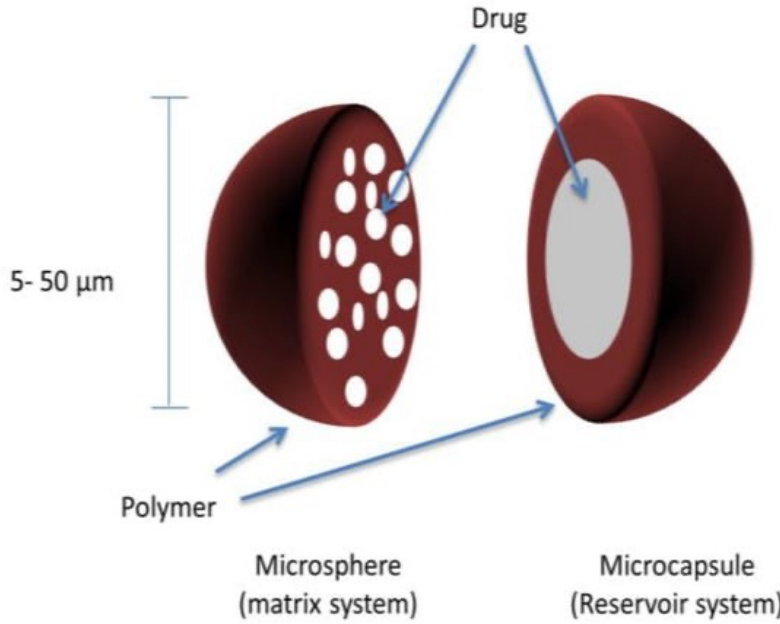
Other information
■ store at 20° to 25°C (68° to 77°F)

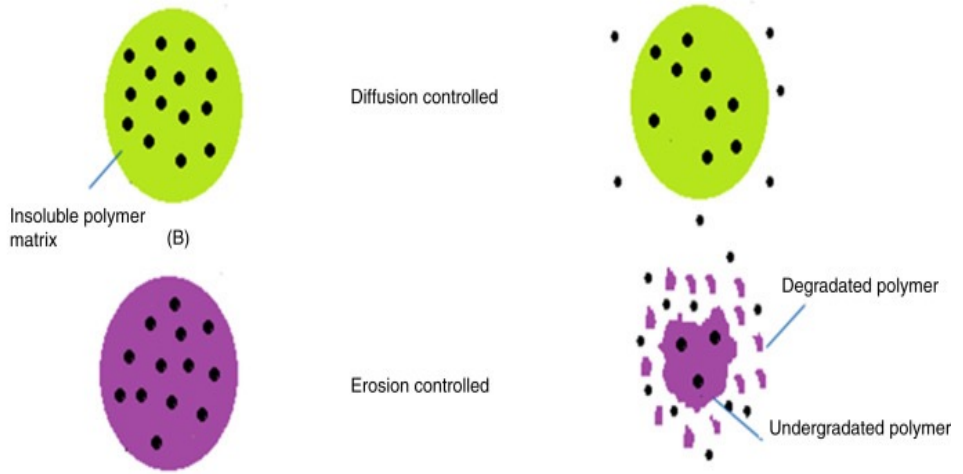
Inactive ingredients
colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch (maize)

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

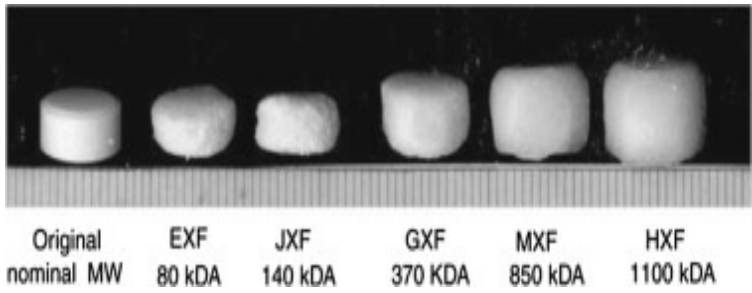
- The matrix tablet formulation is one of the **simplest** methods of dosage form modification.
- It involves the compression of a mixture of drug, **retardant polymer**, and other excipients to form a tablet in which the drug is embedded in the retardant.
- The drug is released from the matrix at a uniform rate. 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**.



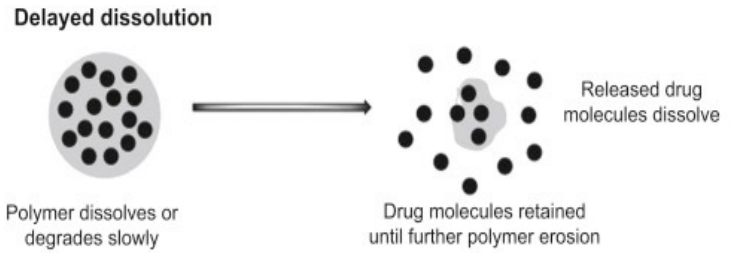


Embedded Matrix Modifications

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.
- 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.
  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,
- 4) mass loss.
  - The **hydration** step is critical and is determined by the hydrophilicity/ hydrophobicity of the polymer.

Controlled Release

- It is a dosage form 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.