Sustained Release Dosage Forms

Sustained Release Dosage Forms

- The sustained release (S.R.), are 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**).

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 that 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 on 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

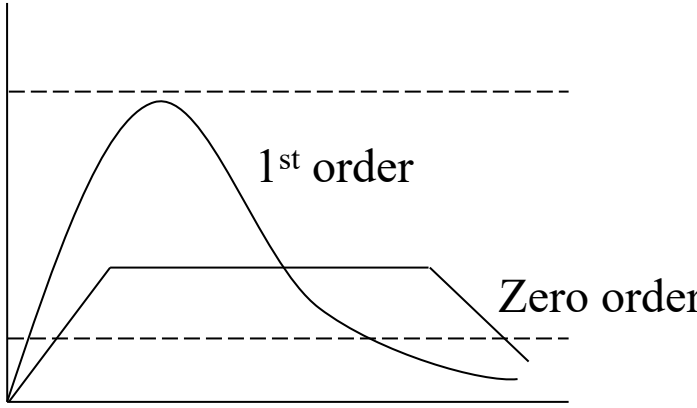
1. Administration of S.R. dosage forms does not allow the prompt termination of the therapy as in case when the patient develops severe side effect.
2. The physician has less flexibility in adjusting dosage regimens.
3. The S.R. are designed for the normal population. Patient's variations and disease 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 its relatively costly to produce SR formulation compared to conventional dosage form.

Drugs NOT suitable for S.R.

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

Kinetic Consideration of SR Formulations

- Kinetically, the drug release from S.R. dosage forms is usually **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 **loading dose** (to provide the required onset of action) and **maintenance dose** (to keep out the therapeutic action).
- Regarding the **zero order** formulas, the release process is **independent** on the magnitude of the maintenance dose and does not change during the maintenance period.
- This type releases a constant **amount** of drug per unit time. For ex., if we have S.R. formula contain 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 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.



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.

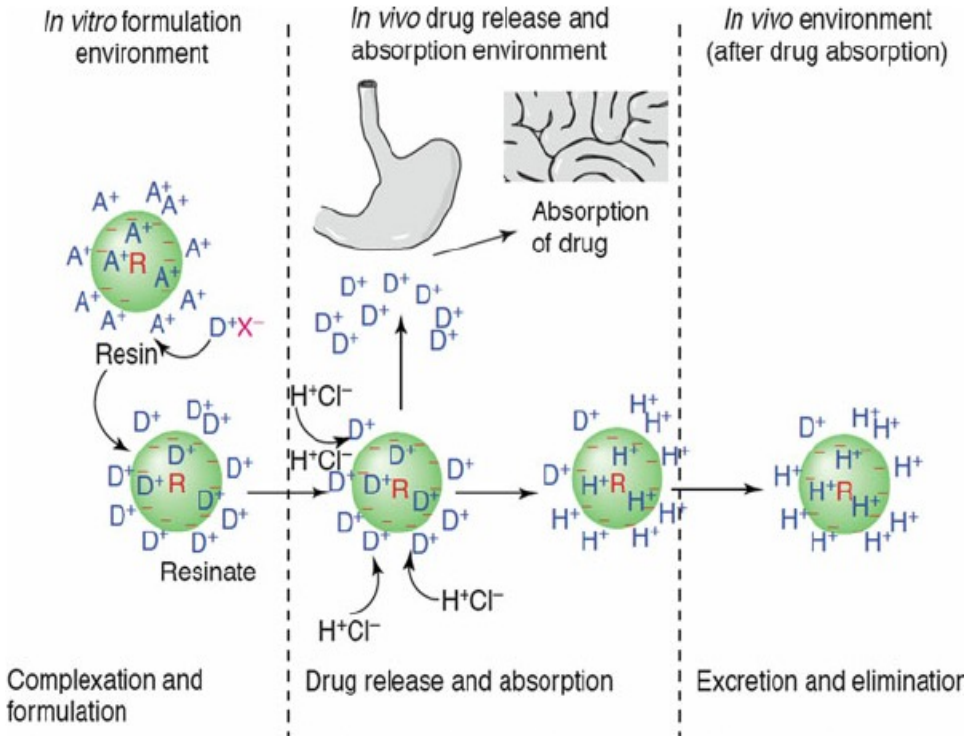
- In this method, the drug itself is modified in a manner that retards its release while the dosage form is not. Examples on such approach are complexes and prodrugs.
- The principal advantage of preparing drug complex is that such materials can be formulated into diverse dosage forms (such as tab.,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

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 to mention that tannic acid is suitable for alkaline drugs only.

The Design of S.R.

- **Ion exchange resin:**
- It is another approach for modifying drug molecule.
- It can be used for both acidic and basis 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 drug 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 limited to a maximum of 300 mg since larger doses require too much resin.



The Design of S.R.

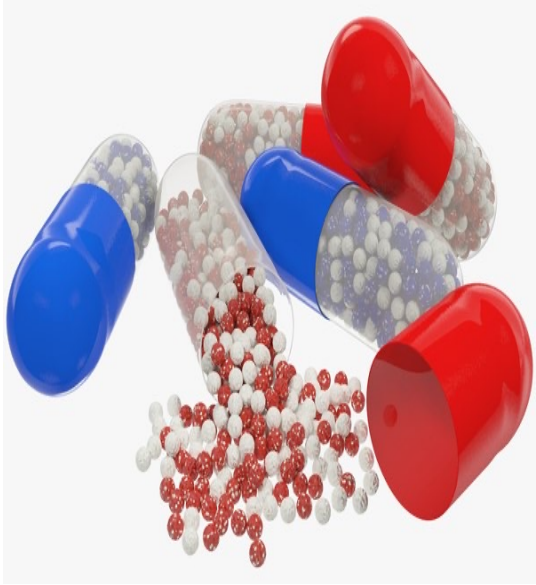
II- Modification of the properties of the dosage form.

- In this method, only the dosage form has been modified in order to modify the release rate. Approached include **barrier** principle or embedded **matrix**.
- Formulations based on these **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 compose of sugar and starch) are initially coated with an adhesive material followed by the incorporation of drug powder on the surface of 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 drug **depending on its thickness.**

The Design of S.R.

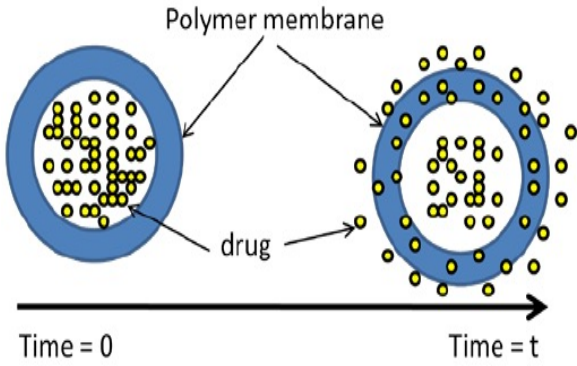
- Example on this type of formulas is what is called commercially as **spansules**. They are capsules containing hundreds of colored pellets divided into 3-4 groups which differ in the thickness of the coat.
- A typical system (capsule) consists of **uncoated** pellets to provide the loading dose and pellets **designed** to release 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 then coated by polymer by suitable machine such as pan coater.
- Drug release from these pellets results from **diffusion** of drug out the barrier (coat) and\or **erosion** of the coat.



The Design of S.R.

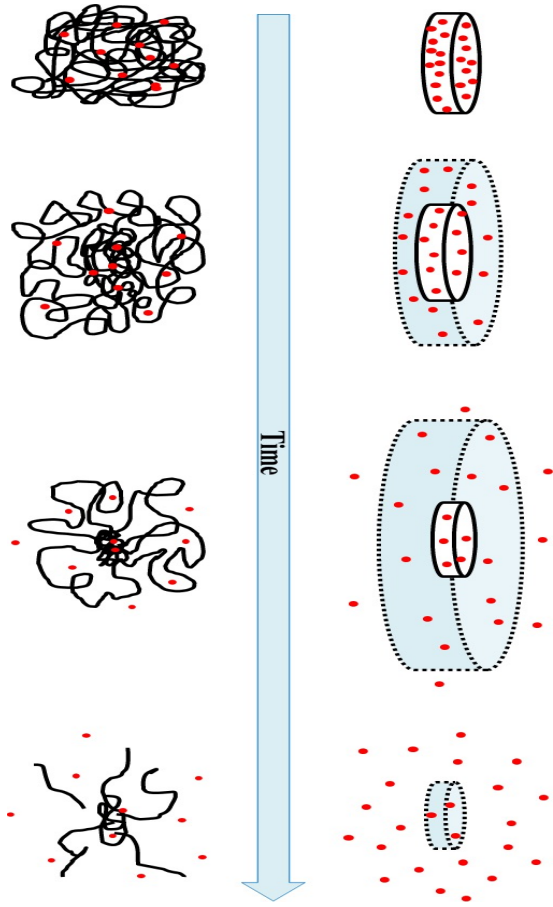
2. **Tabletted slow release granules**: Instead of formulating the pellets as capsules, it can be compassed into tablets that disintegrate in the stomach to **liberate the controlled-release pellets**. Although both of them contain controlled-release pellets, tablets retain the general advantages stated previously for tablet dosage form.
3. **Reservoir system ((slow release (core) tablet):**

- consist of a core of drug and excipients surrounded by a layer of **non biodegradable polymer**, through which the drug slowly diffuses.
- The properties of the polymer govern the release rate of the formula into the bloodstream. In order to maintain uniformity of drug delivery, the thickness of the polymer must be consistent.
- 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.
- 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**").



Embedded Matrix Modifications

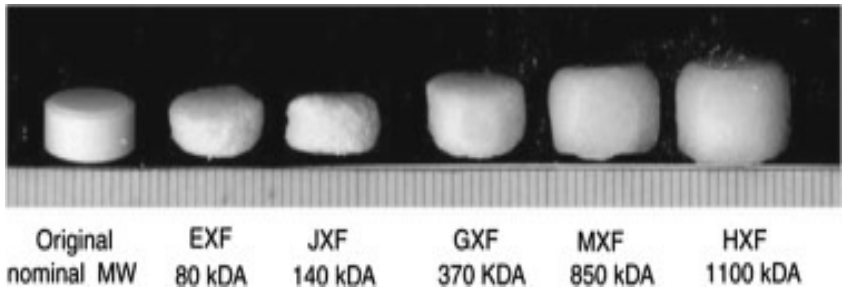
- The matrix tablets formulation is one of the simplest methods of dosage form modification. It involves the compression of a mixture of drug, **retardant polymer** and other excipients to form a tablet in which the drug is embedded in the retardant.
- The drug is released from the matrix at a uniform rate as it dislodges from the polymer network. The release of drug is achieved either by **diffusion or erosion**. The loading dose is included as a bi-layer.
- Unlike the reservoir, there is no danger of drug dumping. examples of matrix tablet.
- Formulations based on these **embedded matrix** can be classed into **two** product types:



Embedded Matrix Modifications

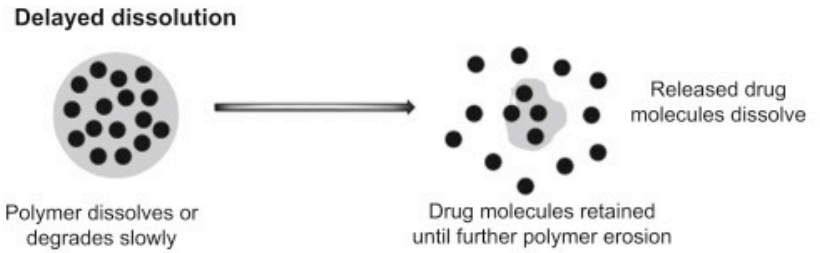
1. Swelling-controlled tablets:

- 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 system is their 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, 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 poly lactic acid and many of other polymers such as PLGA. Synthetic polymers are **preferable** to the 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 chemical properties such as structure of monomers, which can affect the liability of the cleavable bonds, physical properties, such as **hydrophilicity**, **crystallinity** and **molecular weight** of the polymers.
- **Biodegradation** of these polymers usually involves four steps: hydration, mechanical strength loss, integrity loss, and 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 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 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**: tablet contains an osmotic pressure generating material and 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 drug can diffuse out of the formulation.