Sustained release dosage form

introduction

- Sustained release describes the release of drug substance from a dosage form or delivery system over an extended period of time.
- Also referred to as prolonged release , slow release, sustained action, prolonged action.

Merits of SRDF

- Reduction in blood level fluctuations of drug, thus better management of the disease.
- Reduction in dosing frequency
- Enhanced patient convenience and compliance
- Reduction in adverse effect especially in sensitive patient
- Improved efficiency of treatment
- Reduce nursing and hospitalizing time
- Maximum bioavailability with minimum dose.
- Minimize drug accumulation with chronic disease

- Make use of special effect ,e.g. treatment of arthritis
- Drug susceptible to enzymatic inactivation or by bacterial decomposition can be protected by encapsulation in polymer system suitable for SR
- Improved treatment of chronic disease in which the symptoms may return if the plasma conc of the drug falls bellow the minimum effective conc e.g asthma and depression
- Maintenance of the therapeutics action of the drug during the overnight .

Limits of SRDF

- Administration of sustained release medication does not permit prompt termination of therapy .immediate change in the drug if needed during therapy when significant adverse effects are noted cannot be accommodated.
- The physician has less flexibility in adjusting dosage regimen , as it is fixed by dosage form design.
- Sustained release dosage form are designed for normal population . On basis of average biologic half-life ,consequently ,disease states that alter drug deposition , significant patient variation are not accommodated.
- More costly process and equipment are involved in manufacturing many SRDF
- Unpredictable and poor in vitro and in vivo relationship.

- Effective drug release time period is influenced and limited by GI residence time.
- Need additional patient education (such as not to chew or crush the dosage form before swallowing).
- Drug having very short half life or very long half life are poor candidates for SRDF.
- Delayed onset of action , hence sometimes not useful in acute conditions

Characteristics of drugs unsuitable for peroral sustained release forms

drugs	characteristics
Riboflavin, ferrous salts	Not effectively absorbed in the lower intestine
Pencillin G ,furosemide	Absorbed and excreted rapidly , short biological half- lives(<1hr)
Diazepam, phenytoin	Long biological half-lives (>12hr)
sulfonamides	Large dose required (>1g)
Phenobarbital, digitoxin	Cumulative action and undesirable side effect, drug with low therapeutic index
Anticoagulant and cardiac glycoside	Precise dosage titrated to individual is required
griseofulvin	Very insoluble drugs whose availability is controlled by dissolution

The concept of SRDF

- The drug delivery systems that are designed to achieve a prolonged therapeutic effect by continously releasing medication over an extended period of time after adminstration of single dose , in the case of injectable dosage form this period may vary from days to months , in the case of orally adminstered forms , this period measured in hours and critically depends on the residence time of the dosage form in the GIT, the term controlled release has become associated with those systems from which therapeutic agents may be automatically delivered at predefined rates over long period of time.
- The pharmaceutical industries provide a variety of dosage form and dosage level of particular drug , thus enabling the physician to control the onset and duration of drug therapy by altering the dose and mode of adminstration.

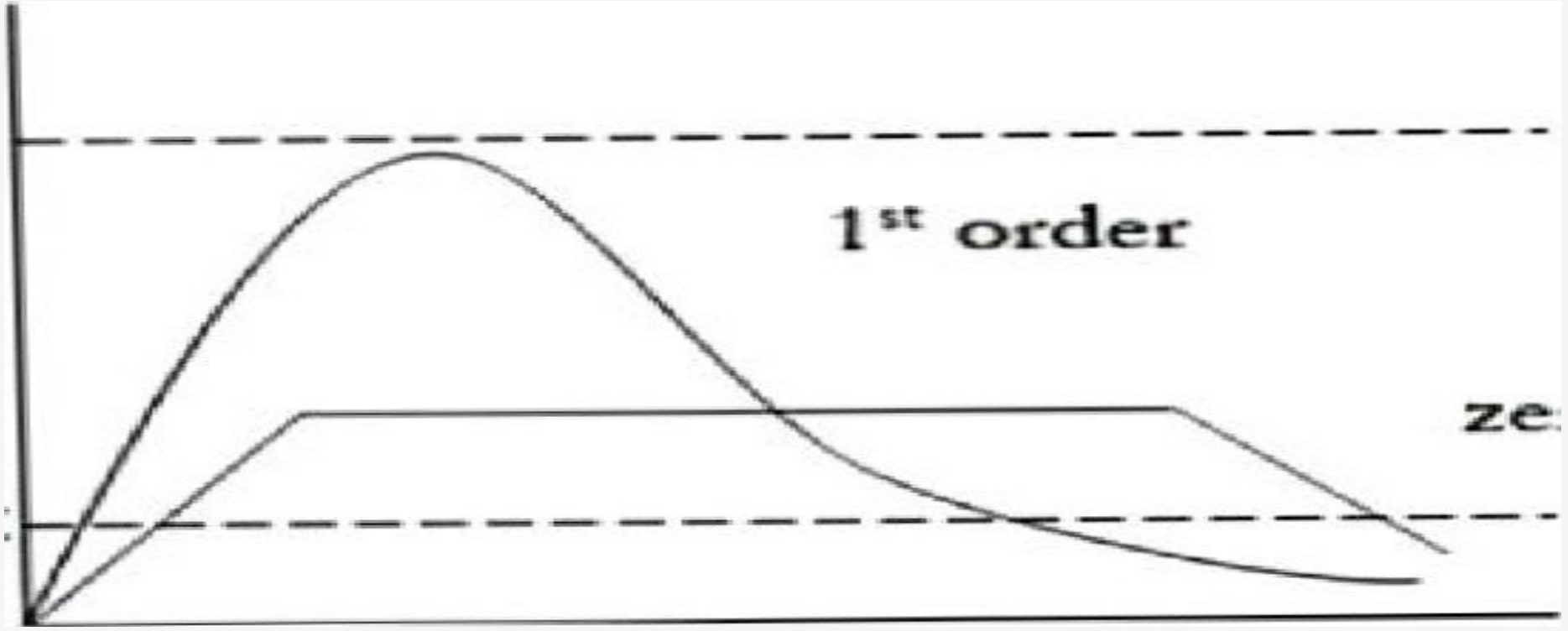
Materials used in coating of sustained release dosage forms

- Mixture of wax: bees wax, carnuba wax,with glyceryl monostearate, stearic acid , glyceryl mono palmitate and cetyl alcohol. These provide coating that are dissolved slowly or broken down in GIT.
- Shellac and zein polymers that remain intact until the PH of the GI contents become less acidic
- Ethyl cellulose which provides a membrane around the dosage form and remain intact throughout the GIT , however , it does permit water to permeate the film , dissolve the drug and diffuse out again
- Acrylic resins, cellulose acetate, silicone elastomers

kinetics

- The drug kinetics can be characterized by three parameters :
- the elimination rate constant (k_e)or the biological half-life($t_{1/2}$=o.693/k_e).
- The absorption rate constant (ka)
- The appearant distribution volume(vd), a large volume of distribution (e.g 100l) means that drug is extensively distributed into extravascular space, a small volume of of distribution e.g(10ml) means that drug is largely confined to the plasma.

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



The design of SR

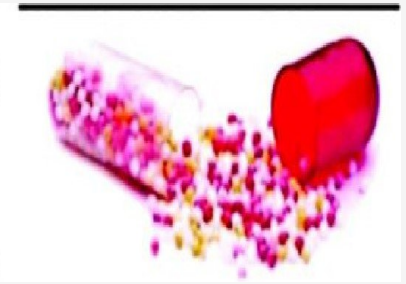
- Two general approaches have been used for the formulation of S.R.' I-Modification of the physical and/or chemical properties of the drug.
- In this method, the drug itself is modified in a manner that retards its release while the dosage form is not. Examples on such approach are complexes and prodrugs.
- DRUG COMPLEXES: The principal advantage of preparing drug complex is that such materials can be formulated into diverse dosage forms (such as tablets, capsules, suspensions, injections). Materials such as tannic acid can be used for drug complexation. In the body, tannate complexes are hydrolyzed gradually by gastric and intestinal-enzymes. Tannic acid is suitable for alkaline drug only .

- Ion exchange resin is another example, 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.

- In general, the S.R. dosage forms contain loading dose (to provide the required onset of action) and maintenance dose (to continue 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 hours. In contrast, the first 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

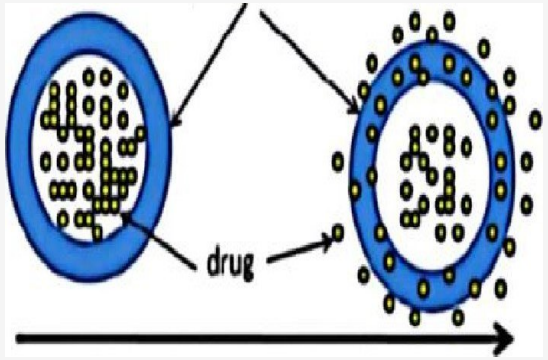
ll- Modification of the properties of the dosage form.

- In this method, only the dosage form has been modified in order to modify the release rate.
- Examples are:
- Encapsulated slow release granules: The encapsulated slow release granules (or pellets) are based on dosage form modification. Routinely, they are formulated as follows: Nono 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.
- 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.

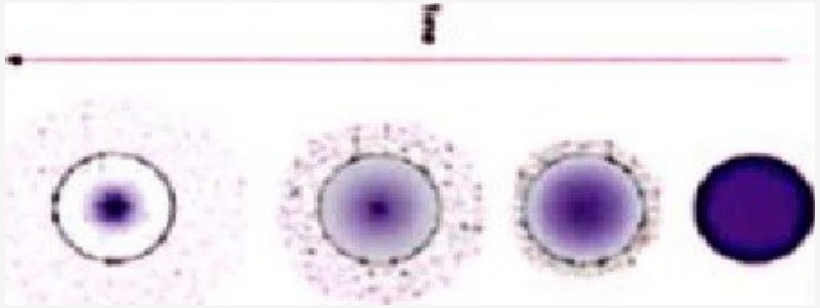


- In the case of relatively high dose drugs, nono pellets are not used. Instead, the drug itself is formulated as pellets then coated by polymer by suitable machine such as pan coater.
- Drug release from these pellets results from diffusion of drug out the barrier (coat) and\or erosion of the coat.
- Tableted 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.

- Reservoir system (tablets or capsules): Consist of a Polymer membrane core of drug and excipients surrounded by a layer of non biodegradable polymer, through which the drug slowly diffuses. properties of the polymer govern the release rate of the formula into the bloodstream. In order to
- Maintain the uniformity of the 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 "drug dumping").



- Matrix tablets: The matrix tablets formulation is one of the simplest methods of 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.



- 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.
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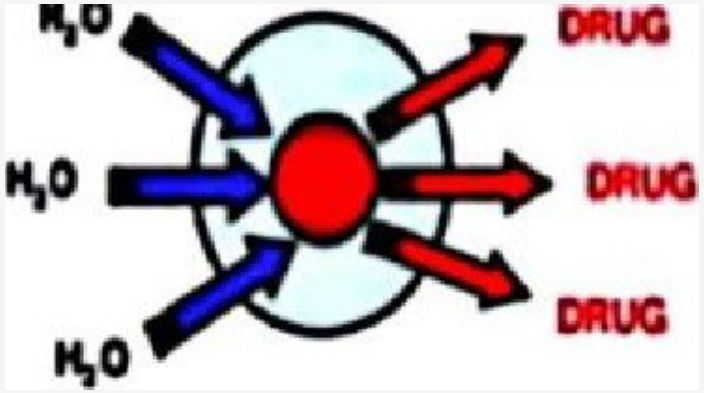

Bioerodible: Biodegradable polymers can be defined as polymers that are degradable vivo enzymatically to produce nontoxic by-products. These polymers can be metabolized and excreted via normal physiological pathways (by liver or kidney). 'Ihey are classified into three groups: natural, semisynthetic and synthetic, based on their sources.

- Examples of commonly used natural polymers are gelatin, alginate, dextran and chitosan, whereas examples of synthetic polymers are poly lactic acid and many of other polymers. Modifications can be made to naturally occurnng 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. Synthetic polymers are preferable to the natural biodegradable polymers because their physicochemical properties are more predictable and reproducible.

- Osmotic pump systems
- Osmotic pump systems are example of membrane-controlled release drug delivery system and work in the following way. A drug is included in a tablet core which is water soluble. The tablet core is coated with a semipermeable membrane which will allow water to pass through into the core, which then dissolves. As the core dissolves, a hydrostatic pressure builds up and forces (pumps) drug solution through a hole drilled in the The rate at which water is able to pass in through the membrane, and how quickly the drug solution (or suspension) can pass out of the hole, govern the rate of release, The rate at which the drug solution/suspension is forced out can be modified by changes in the viscosity of the solution formed inside the
- system.