SUSTAINED RELEASE DRUG DELIVERY SYSTEMS

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✧ **USP classifies the dosage forms in two groups:**

1) **Conventional dosage forms**
2) **Modified release dosage forms**

Modified Release Dosage Forms

1) Delayed Release Dosage Forms

2) Extended Release Dosage Forms

a) Controlled Release Dosage Forms

b) Sustained Release Dosage Forms

Differences Between Sustained and Controlled Release Dosage Forms

Sustained Release Dosage Forms	Controlled Release Dosage Forms
They provide medication over extended period of time.	They provide constant drug levels in blood / tissue.
They generally do not attain zero order release kinetics.	They maintain constant drug levels in the blood by releasing the drug in a zero order pattern.
In general, they do not contain mechanisms to promote localization of the drug at the site of action.	They provide localization of the drug at the site of action.

Factors Affecting the Design of SRDFs

Biological Factors	*Physicochemical Properties*
Absorption	**Dose size**
Distrubition	**Partition coefficient**
Metabolization	**Molecular size**
Biological half life	**Aqueous solubility and pKa**
Adverse effects	**Drug stability**
Terapeutic index	**Binding to proteins**
Role of the disease	

Physicochemical Properties

1) Aqueous Solubility&pKa (Ionization Constant):

Aqueous Solubility:

- **Before absorption, API must be dissolved in the aqueous phase surrounding the site of administration.**

- **Water-soluble APIs, especially if pH independent, serve as a good candidates for SRDFs.**

- **ka < kr ⟹ Conventional tablet**
- **ka >>kr ⟹ Sustained effective tablet**

2) Partition Coefficient:

- **Between the time an API is administrated and is eliminated from the body, it must diffuse through a variety of biological membranes.**

- **Since the membranes are in lipid structure, the oil/water partition coefficient (K) has an important role in evaluating the API penetration.**

$$K=Co/Cs$$

Co=Equilibrium concentration in oily phase

Cs=Equilibrium concentration in aqueous phase

3) Stability of API:

- **APIs undergo slower degradation in the solid form than in the liquid form such as solution or suspension.**
- **APIs that stable in stomach are released in stomach and are unstable when they are released in intestine.**
- **APIs with stability problems in any particular area of GIT are less suitable for the preparation of SRDFs.**
- **APIs may be protected from enzymatic degradation by incorporation into a polymeric matrix.**

4) Protein binding:

- **APIs bind to plasma proteins such as albumin and these properties result in increased blood residence time.**
- **API-protein complex can serve as a reservoir in vascular space.**
- **Main forces for binding to proteins are vander Waal forces, hydrogen bonds and electrostatic forces.**
- **Charged compounds have greater tendency to bind proteins than uncharged ones.**

5) Molecular size& diffusivity:

- **The ability of an API to diffuse through membranes is called diffusivity (D) which is a function of molecular weight.**
- **The value of D is related to the size and shape of the cavities, as well as the APIs.**
- **The APIs with high molecular weight show very slow kinetics.**

6) Dose size:

- **For the APIs that require large conventional doses, the volume of sustained dose may be too large to be practical.**
- **APIs with an oral dose of more than 500 mg are not suitable for SRDFs.**
- **The greater the dose size, the greater the fluctuation in the blood profile.**

Biological Properties

1) Absorption

- **Absorption rate constant (ka) should be high (0.17-0.23/h).**

kr << ka

- **It is desirable that the rate of absorption is constant and uniform. Absorption should not increase as the dose increases.**

- **The API must be absorbed equally in all areas of the GIT.**

2) Distribution

Two important parameters used to describe the distribution properties of APIs in the body; the apparent distribution volume (Vd) and the relative distribution ratio (T/P) between the compartments.

Vd is an approximate proportional constant calculated by the ratio of API concentration in the blood to the amount of active substance in the body.

$$Vd = Dose/C_0$$

C_0= Initial concentration of the API in the blood after IV injection

3) Metabolization

- **Especially in enzyme-rich tissues (such as liver), the APIs are activated/inactivated by metabolizing.**
- **Generally, SRDFs of APIs, metabolization rates of which are not very high can be prepared.**
- **It is difficult to prepare SRDFs of APIs which are highly metabolized, show complex metabolism, increase/decrease the enzyme synthesis and have active metabolites.**

4) Duration of Drug Activity

- ☆ **APIs with a high half-life ($t_{1/2}$<2 hours) and a high dose are not suitable for SRDFs.**
- ☆ **APIs with $t_{1/2}$ = 4-6 hours are suitable for SRDFs.**
- ☆ **The API that has a very long half-life can act as SRDF.**

5) Side Effects

Increased blood concentration increases the potential for side effects.

Terapeutic index (Tİ) = Toxic dose (LD_{50})/Effective dose (ED_{50})

Tİ ⇧ Safety ⇧

Tİ ≥ 10 suitable for SRDF
Tİ< 2 not suitable for SRDF

Methods Used in Preparation of SRDFs

- **Addition of the API to the capsule prepared from the polymeric material in a solid/liquid/suspended state,**
- **Placing the API in a biodegradable solid matrix,**
- **Encapsulating the API into the viscous solution of the polymer,**
- **Adding a second layer onto the tablet prepared from the API mixture (Sandwich tablet),**
- **Preparation of the heterogeneous dispersion of the API in the hydrophilic matrix (hydrogel),**

- **Mechanical/chemical controlled-release pumps,**
- **Chemical bonding of API to polymeric structure,**
- **Adhesion of the polymer containing the API to the mucin-coated surface of GIT and release at the constant rate and remain there for the desired time,**
- **Floating of low density dosage forms prepared as micropellet in GI fluid (floating dosage forms).**

Methods of Microencapsulation:

- Coaservation
- Interfacial Polymerization
- Electrostatic Methods
- Precipitation Method
- Melting by Heat
- Precipitation with Salt Effect
- Solvent Evaporation Method

Classification of Controlled Drug Delivery Systems (DDSs) According to the API Release Mechanism

1) Dissolution Controlled DDSs

- Matrix Type Dissolution Controlled DDSs
- Encapsulation Type Dissolution Controlled DDSs

2) Diffusion-Controlled DDSs

- Matrix Type Diffusion-Controlled DDSs
- Membrane Type (Depot) Diffusion-Controlled DDSs

3) Solvent Activated DDSs

- Swelling Controlled DDSs
- Osmotic Controlled DDSs

4) Magnetically Conrolled DDSs

5) Mechanical Force-Triggered DDSs

Polymers Used in Preparation of SRDFs

Natural Polymers

Xanthan gum, Polyurethanes, Guar gum, Polycarbonates etc.

Semi-synthetic Polymers

Cellulose (HPMC, NaCMC, Ethyl cellulose etc.)

Synthetic Polymers

Polyesters, Polyamides, Polyolefins etc.

	Properties of Polymer	Material
1.	Insoluble, inert	Polyethylene, polyvinyl chloride, methyl acrylates-methacrylate copolymers, ethyl cellulose
2.	Insoluble, degradable	Carnauba wax Stearyl alcohol Stearic acid Polyethylene glycol Polyethylene glycol monostearate Triglycerides
3.	Hydrophilic	Methylcellulose, HEC, HPMC, Na-CMC, Sodium alginate