Topic: Selection of drug candidates for CDDS

Definition: Controlled drug delivery System:

Controlled drug delivery is one, which delivers the drug at a predetermined rate, for locally or systemically, for a specified period of time. It maintains constant level of drug in blood and tissue for extended period of time.

Important criteria:

Parameters	Poor candidate	Good candidate
Aqueous solubility	Weak water soluble drugs BCS class- III, IV drugs	Highly water soluble drugs
Partition Coefficient	Having high or low P value	To dissolve in both phases
Ionization	Highly ionized drugs	Non- ionized form of drugs, At least 0.1 to 1% is non ionised form
Molecular weight	Greater than 400 D	Lesser than 400 D

Parameters	Poor candidate	Good candidate
Biological half life (t1/2)	Less than 2 hr More than 8hr	2 to 6 hrs
Does size	High dose	Low dose
Stability	Degraded in the stomach and small intestine	Stable in acid/ base, enzymatic degradation
Absorption mechanism	If absorbed by active diffusion	By passive diffusion

Parameters	Poor candidate	Good candidate
Therapeutic Index	Narrow	Broader
Protein binding	High plasma	Low plasma
Absorption rate	Lower	3-4 hr
Absolute Bioavailability	Less than 75%	Should be 75% or more
General absorbability	Release influenced by pH and enzymes	From all GI segments

1. **Solubility:** The concentration at which the solution phase is in equilibrium with a given solid phase at a stated temperature & pressure.

- Mostly drugs are weakly acidic or basic in nature that affect the water solubility of API.
- Weak water soluble drugs are not good candidates for controlled release formulations.
- High aqueous solubility drug show burst release followed by a rapid increment in plasma drug concentration and are good candidate for CDDS.
- The pH dependent solubility also creates a problem in formulating CDDS.
- as per the permeability & solubility profile, BCS classification is given
- BCS class-III & IV drugs are not a suitable candidate for this type of formulations

2. Partition coefficient

The partition coefficient is defined as" the concentration ratio of unionized drug distributed between two phases at equilibrium."

- P-value denotes the fraction of the drug into oil & aqueous phase that is a significant factor that affects the passive diffusion of the drug across the biological membrane.
- The drugs are having **high or low P value not suitable for CDDS** it should be appropriate to dissolve in both phases

3. Ionization:

Determine the ionization of drug physiological pH in GIT.

- The high ionized drugs are poor candidates for CDDS.
- The absorption of the unionized drug occurs rapidly as compared to ionized drugs from the biological membranes.
- The pKa range for an acidic drug that ionization depends on the pH is 3.0 to 7.5 and for a basic drug it lay between 7 and 11.

4. Molecular weight or Molecular size and Diffusivity:

- The ability of drug to pass through membranes is called diffusivity, is a function of its molecular size (or molecular weight).
- The molecular size & molecular weight are two important factors that affect the molecular diffusibility across a biological membrane.
- The molecular size less than 400D is easily diffuse but greater than 400D create a problem in drug diffusion.
- drugs in many CDDS must diffuse through a rate controlling membrane or matrix.
- Mass spectroscopy are generally used as the most common methods to determine the molecular size of the drug. Fourier Transform IR- spectroscopy (FTIR) is also used to determine the molecular structure.

5. Biological half- life:

Duration of action dependent on the biological half- life.

- Drug having **short half-life** required frequent dosing and are **most suitable** candidate for controlled release system.
- Ideally, the drugs having t1/2 2-3 hrs are a suitable candidate for CDDS.
- Drugs have t1/2 more than 7-8 hrs not used for controlled release system
- Very short (1 hrs) or very long half-life drugs are not suitable for CDDS

6. Dose size:

The CDDS formulated to eliminate the repetitive dosing, so **it must contain the large dose** than conventional dosage form.

- The dose used in conventional dosage form give an indication of the dose to be used in CDDS
- If the dose of a drug in conventional dosage form is high, then it is less suitable candidate for
- CDDS.
- This is because the size of a unit dose controlled release oral formulation would become too big to administer without difficulty

7. Stability:

- Drugs that are stable in acid/base, enzymatic degradation, and other gastric fluids are
- good candidates for CDDS.
- If drug degraded in the stomach and small intestine, it not suitable for controlled
- release formulations because it will decrease in bioavailability of concern drug.

8. Absorption:

- Uniformity in rate and extent of absorption is an important factor in formulating the CDDS.
- The absorption rate should rapid then release rate to prevent the dose dumping.
- If the transit time of dosage forms in the GI tract is about 8-12 hrs, the half-life for absorption should be approximately 3-4 hrs.
- Otherwise, the **dosage form will pass out of absorptive regions** before drug release is complete. Therefore, the compounds with lower absorption rate constants are poor candidates.
- The various factors like aqueous solubility, log P, acid hydrolysis, which affect the absorption of drugs.

9. Therapeutic Index:

Margin of safety can be described by therapeutics index, the ratio of median toxic

dose and median effective dose**.**

- Therapeutic index = TD50/ED50.
- Drugs with low therapeutics index are unsuitable for drug incorporation in controlled release formulation**.**
- The side effects can be minimized by controlling the concentration within therapeutic range.

10. Protein binding:

The drug-protein complex act as a reservoir in plasma for the drug.

- Drug showing **high plasma protein binding** are **not a good candidate** for CDDS because Protein binding increases the biological half-life.
- So there is no need to sustain the drug release.

Characteristics of drug unsuitable for CDDS

- Short elimination half-life
- Long elimination half-life
- Narrow therapeutic index
- Poor absorption
- Active absorption
- Low or slow absorption
- Extensive first pass effect