

PHYSICAL FORM:**TECHNOLOGY TYPE:****1) What are cyclodextrins?**

Cyclodextrins belong to a family of cyclic oligosaccharides. Pharmaceutically applicable cyclodextrin molecules contain between six to eight units in a ring, creating a cone-like shape.

- α -cyclodextrins have six sugars
- β -cyclodextrins have seven sugars
- γ -cyclodextrins have eight sugars

2) Which administration route is our Cyclodextrin technology suitable for?

Cyclodextrins can be administered orally and parenterally. Due to renal toxicity after systemic administration, the preferred types for (intravenous) parenteral use are hydroxypropyl-beta-cyclodextrin and sulfobutyl-ether-cyclodextrin.

The pharmaceutical form of cyclodextrins may be as liquids or solids. The choice of the pharmaceutical form will depend on the physical and chemical stability of the complex created.

3) Which types of compound are suited to cyclodextrins?

Insoluble compounds which are lipophilic or crystalline may be suited to cyclodextrins. Molecules with aromatic rings which fit preferentially into the cavity interact to form water soluble complexes.

From experience, 1 to 1 molar inclusion complexes are usually very rare. In general, a large molar excess of cyclodextrin is needed to dissolve most poorly soluble compounds.

4) How do cyclodextrins increase bioavailability?

The interior of the cyclodextrin cavity is considerably less hydrophilic than the exterior aqueous environment and can thus host less hydrophilic guest molecules. In contrast, the exterior surface is sufficiently hydrophilic to give cyclodextrins high aqueous solubility. Cyclodextrins may increase the solubility of highly insoluble drugs up to several thousand-fold, compared to the aqueous solubility of

the drug alone. Well formulated systems do not depend on rate-limiting dissolution for absorption after oral administration.

Cyclodextrin structures have a fixed shape, unlike other solubilizers such as micelles, where the host molecules are in dynamic equilibrium.

The degree of physical interaction to form a complex between the molecule and a cyclodextrin can be derived from the dissociation constant. The term 'complex' is frequently used to describe the interaction with molecules.

The complex may reduce drug precipitation from oral and parenteral administration. The speed of drug release from the complex is governed by the specific dissociation constant and is, therefore, compound dependent.

5) Which Phares services use the Cyclodextrin technology?

Solubilization with cyclodextrins is suitable for any development stage if the association is sufficient. It is used in Survey as a pathfinder tool to explore solubilization. If the amount of cyclodextrin required to solubilize the poorly soluble compound is sufficiently low, it can be used in our Speed service. If the poorly soluble drug has a good affinity for cyclodextrin and is sufficiently potent, it can be applied in Icebreaker for the development of a clinical form.

6) Advantages and disadvantages of cyclodextrins

Advantages

- Cyclodextrins can increase the chemical stability of API (compared to other solubilized approaches) by protecting chemically labile regions
- Certain cyclodextrins have a high aqueous solubility (>40%) and low viscosity enabling relatively high compound concentrations to be achieved (where affinity to the poorly soluble drug is satisfactory)

Disadvantages

- If a compound does not dissociate rapidly, the pharmacokinetics of the poorly soluble compound may be altered as release is not immediate
- Although parenteral grades have a good tox profile in man, certain types of cyclodextrin have specific toxicity in pre-clinical models potentially thereby limiting their use in tox studies

7) Scale up of cyclodextrin formulations

Production of aqueous solutions may be straightforward if compounds are readily complexed. However, if the insoluble compound cannot form a complex easily, production may be cumbersome. Solvents and additional excipients may be required to assist with the solubilization of the drug.

8) Phares cyclodextrin expertise

We assess the suitability of insoluble compounds in cyclodextrins and have the experience to compare and select the best solubilization principle impartially. Freedom to operate with specific types of cyclodextrins in certain fields may be limited by third party patents.

9) Cyclodextrin products

Itraconazole oral liquid and Itraconazole concentrate for Intravenous infusion (Sporanox[®], Janssen-Cilag) are examples of cyclodextrin formulations.

KEY SERVICES:

