

Considerations in using Cyclodextrins as solubilizers for early toxicology studies.

Lisa Z. Crandall, MS

Early stage drug development can frequently be hindered by compound solubility and the need to deliver large doses to animals with as little vehicle toxicity as possible. Formulators have a powerful tool in the Cyclodextrin (CD) molecules; however there are several complicating factors that must be considered.

What are Cyclodextrins?

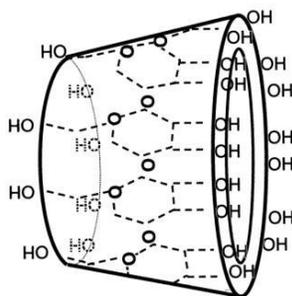


Figure 1: 3D representation of γ CD

Cyclodextrins are cyclic oligosaccharide molecules (of at least 6 subunits) derived from starch, which form structures with lipophilic inner cavities and hydrophilic outer surfaces. In essence, they create a lipophilic “bucket” (Figure 1.) that can interact with a lipophilic compound, creating an inclusion complex. This interaction and the exposure of the hydrophilic outer Cyclodextrin surface allow CD molecules to solubilize some poorly soluble lipophilic compounds. Modified Cyclodextrins are highly water-soluble themselves.

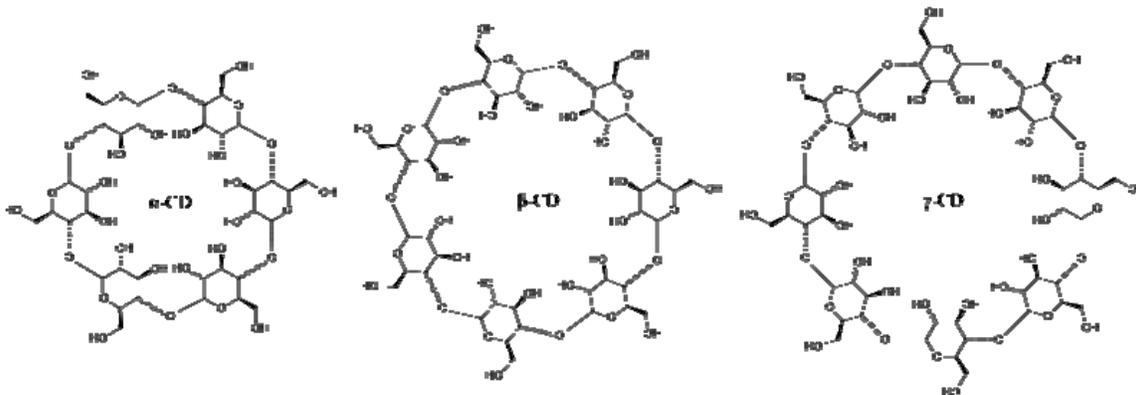


Figure 2: Structures of α , β , γ - Cyclodextrins

There are several Cyclodextrin versions available, but the most commonly used are substituted α , β , or γ -CDs that contain 6, 7, or 8 glucose molecules respectively. The higher the number of glucose molecules, the larger the diameter of the inner “bucket” (Figure 2) (approximately 0.5, 0.6, and 0.8 nm respectively for α , β , and γ CD). Substitutions are typically hydroxypropyl, although many other options are available.

Formulation with Cyclodextrins has also been shown to improve chemical and physical stability of some compounds, possibly due to their behaving as a “molecular shield”. For early toxicology studies, this is an added bonus to using CDs, but usually not a pivotal reason for their use.

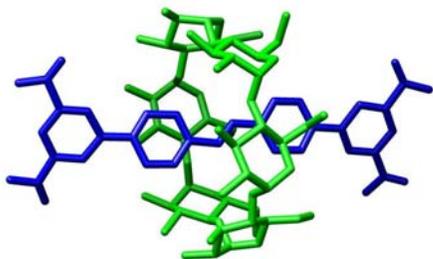


Figure 3: Crystal structure of a molecule (blue) with α -CD (green)

How do compounds interact with Cyclodextrins?

It is not always simple to predict the relationship between compound size and which CD will be the best solubilizer. Some compounds can be solubilized with only a small portion of their structure in the CD “bucket”. Other compounds are solubilized by complexing with two CD molecules. Figure 3 shows another example, where the molecule is threaded through the Cyclodextrin.

How can Cyclodextrins be used in toxicology studies?

Cyclodextrins can be dosed by several routes for early toxicology studies: oral, parenteral, IV, ocular, subcutaneous, and intrathecal. Typical CD loads are 15-40% w/v in water or other aqueous environment. An advantage of having an early formulation in Cyclodextrin is that it is typically trouble free to dilute further in aqueous environment. This can very much simplify formulation preparation for multiple animal studies. In some cases, though, the interaction between CD and drug is not linear and precipitation will occur upon dilution.

It is important to involve your toxicology and formulation personnel in a discussion over acceptable levels of Cyclodextrin. There can be varied toxicologist comfort levels with dosing CDs to mice or rats. CDs are slowly gaining more acceptances in the pharmaceutical industry, with hydroxypropyl- β -cyclodextrin being the most commonly used.



How are Cyclodextrins used in the laboratory?

CDs are highly soluble in water, but can take some time to wet. Current advancements in spray dried Cyclodextrins are decreasing wetting times.

In later drug development, there are multiple methods to prepare Cyclodextrin-API inclusion complexes, including grinding and spray drying. These are time consuming and not practical for quick early phase solubility experiments. Typically, for early stage experiments, CDs are dissolved in water by stirring (typically 25 – 40% w/v), which can take several hours depending on the cyclodextrin. The API is then added and stirred until in solution. Manufacturers may have varied recommendations on the best way to handle their specific Cyclodextrin product. Some suggest that Cyclodextrins should not be sonicated or treated by any other high energy methods. Others encourage sonication. Check with your manufacturer for specific handling instructions.

Later stage considerations

Of course, one must always plan for the success of their compound and think of the future impact of developing a Cyclodextrin based formulation. Some CDs can be rather expensive, especially when used at the 40% (w/v) level. However, if the compound shows efficacy, the cost might be justified.

The native Cyclodextrins (α , β , γ - Cyclodextrins) are labeled as GRAS (Generally Regarded As Safe) in the United States and are found in many pharmaceutical, cosmetic, and food products. Alprostadil (α -CD) is an example of a pharmaceutical product approved in the US containing the native CD. γ -Cyclodextrin is listed in the FDA's compiled list of inactive ingredients. Many more products are approved in Japan and Europe such as Cephalosporin in β -CD (Japan).

There are multiple products on the market using substituted β -Cyclodextrin formulations, such as Vfend (Voriconazole, sulfobutylether β - Cyclodextrin). Hydroxypropyl β -Cyclodextrin and sulfobutylether β - Cyclodextrin are listed in the FDA's compiled list of inactive ingredients. Sugammadex, a modified γ - Cyclodextrin is approved for use in Europe. It is only a matter of time before the formerly rare substituted γ -Cyclodextrins are approved in clinical formulations.

References:

- M.E. Brewster, T. Loftsson, Cyclodextrins as Pharmaceutical Solublizers. *Advanced Drug Delivery Reviews*. 59 (2007) 645-666.
- E. Bilensoy, *Cyclodextrins in Pharmaceuticals, Cosmetics, and Biomedicine*. John Wiley & Sons, (2011).
- Loftsson T., Másson M., Brewster M.E., 2004. Self-association of cyclodextrins and cyclodextrin complexes. *J. Pharm. Sci.*, 93: 1091–1099.