Cyclodextrin – a super molecule, beyond drug vector: When the administration matters

Cyclodextrins are able to form water-soluble inclusion complexes with many lipophilic poorly-soluble compounds

Dr Tamas Sohajda, CEO, CYCLOLAB, Budapest, Hungary

Dr Naseem Khan, Head INDIA, Drug Delivery and Excipients, Sredstva Regionale Chemie, Mumbai, India

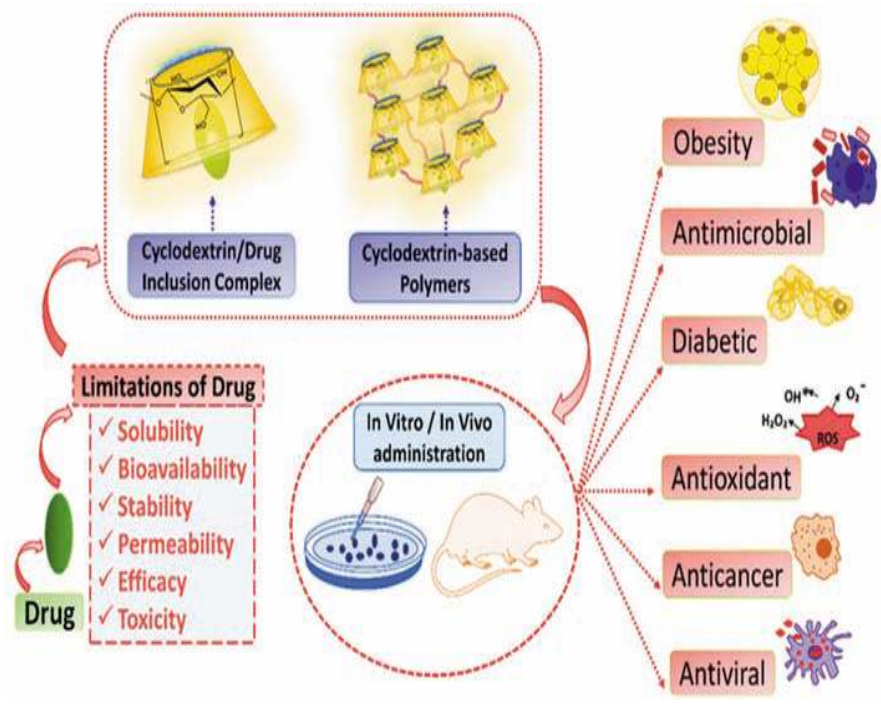
Cyclodextrin (CD) are classically known to be an excellent drug carrier, although applications as active drug have been studied (orphan drug, antiviral, etc). However, there is no clear explanation about the increase of activity of drugs when they are administered by cyclodextrin. The team of Dr Francesco Trotta (Turin, Italy) tried to obtain the possible explanation of this issue in his recent review "Cyclodextrin Monomers and Polymers for Drug Activity Enhancement" on polymers. Based on numerous studies reviewed, the drug appeared more active in a complex form because of increasing the stability and the establishment of a pure drug reservoir preventing its degradation by different physicochemical agents (pH, temperature, ROS). The increase of bioavailability seems to be justified by the increase of apparent solubility of the molecule. On the other hand, the intrinsic activity of CDs against some agents could generate an apparent increase of drug activity.

Remarkably, this review indicates that not only the concentration, but also different bioactivities can be improved if the inclusion complex is formed opening up a new realm of other advanced applications expected to arise soon.

Aqueous solubility is one of the key determinants in development of new chemical entities as successful drugs. However, new drug development technologies, such as combinatorial chemistry and high throughput screening, are based on the basic principles of medicinal chemistry, teaching that the most reliable method to increase in-vitro potency is to add lipophilic moiety at appropriate position of the lead structure. This has led to an increase in the number of lipophilic and poorly-soluble molecules being investigated for their therapeutic activity (Lipinski, 2000). Various formulation techniques are applied to compensate for their insolubility and consequent slow dissolution rate. These include formulation of the amorphous solid form, nanoparticles, microemulsions, solid dispersions, melt extrusion, salt formation and formation of water-soluble complexes.

By such techniques, pharmaceutical formulators try to increase the apparent solubility of lipophilic compounds without decreasing their optimised potency. Cyclodextrins are cyclic oligosaccharides, with hydrophilic outer surface and a somewhat lipophilic central cavity. They are able to form water soluble inclusion complexes with many lipophilic poorly-soluble compounds (Loftsson and Brewster, 1996; Rajewski and Stella, 1996; Loftsson et al., 2004a). However, cyclodextrins (the hosts) are also known to form non-inclusion complexes (Loftsson et al., 2002, 2004b). Most lipophilic compounds (the guests) form apparent 1:1 guest/host complex although apparent higher order complexes are not uncommon. Cyclodextrins and cyclodextrin complexes have been studied intensively for the past couple of decades and these studies have generated a wealth of information on the structural requirements for complex formation and the forces involved (Bodor and Buchwald, 2002; Katritzky et al., 2004).

However, most of these studies have been performed in dilute aqueous solutions under close to ideal conditions, or conditions that can almost never be found in pharmaceutical formulations. Lipophilic drug molecules, as well as drug/cyclodextrin complexes, are known to form aggregates in aqueous solutions, and common pharmaceutical excipients, such as water-soluble polymers and surface-active preservatives, are known to solubilise drugs in aqueous solutions (Loftsson and Masson, 2004; Loftsson et al., 2004b). Still, current stoichiometric models treat aqueous formulations as ideal solutions in which dissolved drug and cyclodextrin molecules, and individual complexes, are independent of each other as well as of other excipients. In the present paper, we will investigate some of the discrepancies caused by this over simplification and how they affect the determination of stability constants of drug/cyclodextrin complexes. We will also suggest an alternative constant, the complexation efficiency, for evaluation of drug/cyclodextrin complexes under different conditions.



Bibliography

1- Matencio, A., Hoti, G., Monfared, Y. K., Rezayat, A., Pedrazzo, A.R., Caldera, F., & Trotta, F. (2021). Cyclodextrin Monomers and Polymers for Drug Activity Enhancement. Polymers, 13(11), 1684.

2- Anderson, P.O., Knoben, J.E., Troutman, W.G. (Eds.), 1999. Handbook of Clinical Drug Data, ninth ed. Appelton & Lange, Stamford.

3- Bergstrom, C.A.S., Luthman, K., Artursson, P., 2004. Accuracy of ¨calculated pH-dependent aqueous drug solubility. Eur. J. Pharm. Sci.22, 387–398.

4-Bodor, N., Buchwald, P., 2002. Theoretical insights into the formation, structure, and energetics of some cyclodextrin complexes. J. Incl. Phenom. Macroc. Chem. 44, 9–14.

*5- Thorsteinn Loftsson *, Dagny Hreinsdottir, Mar Masson, Evaluation of cyclodextrin solubilization of drugs, Faculty of Pharmacy, University of Iceland, Hofsvallagata 53, IS 107 Reykjavik, Iceland, International Journal of Pharmaceutics, 11 August 2005.*