

Cyclodextrin Complexes: Utility in Improving Drug Bioavailability and Other Applications

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Editorial

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Editorial

Drugs and Bioavailability

The oral route is the most common and preferred method of drug administration because of its convenience and ease of delivery as well as cost-effectiveness and better patient compliance. However, for many active pharmaceutical ingredients (APIs), this route of administration is associated with some drawbacks such as poor aqueous solubility and low permeability of the compound resulting in limited drug absorption and consequent poor bioavailability. For any drug to be absorbed, it must be available in an aqueous solution at the site of absorption. It is known that for drugs with solubilities < 0.1 mg/ml, their absorption are likely to be dissolution limited. Conversely, if a drug is extremely water soluble, its ability to traverse lipophilic biomembranes (permeability) will be poor and this also limits the bioavailability. The critical impacts of aqueous solubility and intestinal permeability of drugs on their bioavailability have been utilized in classifying APIs into four classes, as reflected in the Biopharmaceutics Classification Systems (BCS). These two factors along with dissolution process, govern the rate and extent to which a drug appears in the systemic circulation, and this depicts bioavailability. For the BCS class II drugs (low aqueous solubility/high permeability) the rate-limiting step in drug absorption is the dissolution process. While for the BCS Class IV drugs (low aqueous solubility/low permeability), both dissolution process and intestinal permeability determine the drug absorption. Thus, increasing the aqueous solubility can translate to increase in the dissolution rate with a resultant improvement in the oral bioavailability of BCS Classes II and IV drugs. The

BCS classes 1 and III drugs are not subject to bioavailability problems since they both have high aqueous solubility but with high and low permeability, respectively.

The oral bioavailability of poorly water soluble drugs has been enhanced by a variety of processes and techniques and these include the use of micronization, salt formation, and modification of crystal structure, solid dispersions, inclusion complexes, micro emulsions, self-emulsifying drug delivery systems, and novel techniques such as nano-based formulations [1]. There is copious literature on different carrier materials that can be used to enhance the bioavailability of drugs, and the use of cyclodextrins to produce complexes have been found highly valuable.

Inclusion Complexes

These are chemical entities consisting of two or more molecules in which one of the molecules called the 'host' has a cavity into which is accommodated the second molecule called the "guest" molecule. Cyclodextrins (CD) are well established hosts for the formation of inclusion complexes relevant for pharmaceutical formulations. Although CDs were discovered about 100 years ago, their utility in enhancing the bioavailability of drugs is still being investigated especially for the development of newer formulations. In addition to forming inclusion complexes CDs are also able to form non-inclusion complexes and self-assembled aggregates that can enhance drug solubility. These have provided opportunities for novel drug delivery systems.

Chemistry of Cyclodextrins

Cyclodextrins (CDs) are cyclic oligosaccharides which are of glucopyranose units with the groups arranged such that there is a central cavity that is relatively hydrophobic while the outer surface is hydrophilic. With this structure, hydrophobic drug moieties are taken up into the central cavity to form hydrophilic inclusion complexes without the involvement of any covalent bonds. This complexation results in alteration of the solubility characteristics of the drug but the intrinsic properties to permeate biological membranes remain unaltered. The CD complexes dissociate in aqueous media to gradually release drug molecules which remain in equilibrium with the molecules entrapped within the cavity. The most abundant naturally occurring CDs are the alpha, beta and gamma CD which consist of 6, 7 or 8 glucopyranose units, respectively. Although numerous derivatives of CDs have been synthesized only a few of them have been used in pharmaceutical preparations due to limitations of their toxicity profiles. The commonly commercially used CD derivatives include hydroxypropyl- β -CD, methyl- β -CD and sulfobutylether- β -CD [2].

Applications of Cyclodextrin Complexes

Studies from my research group and from several other authors have clearly demonstrated that inclusion complexation with CD remarkably increases the aqueous solubility, dissolution rate profile and bioavailability of poorly water soluble drugs [1-3]. The therapeutic relevance of CD complexes in enhancing drug oral bioavailability is evident in the availability of numerous marketed products of CD formulations. A few examples include β -cyclodextrin inclusion complexes of piroxicam, aceclofenac, itraconazole, indomethacin, diclofenac, nimesulide and others [1,2]. In addition to enhancing oral bioavailability, CDs have several other applications such as being used to reduce or prevent gastrointestinal irritation; masking unpleasant odour or tastes; and application in improving the chemical, physical and thermal stability of drugs. Since CDs can form inclusion and non-inclusion complexes, it has found application in drug delivery systems other than the oral route. For example, products incorporating CDs have been developed as delivery systems for ophthalmic, nasal, rectal, and dermal administrations. Rapidly dissolving complexes with CDs have also been formulated for buccal and sublingual administration. In all these delivery systems, CDs act by enhancing the aqueous solubility and systemic availability, or increasing the stability or decreasing the drug irritation.

Improved Cyclodextrin Complexes

Interest in research on cyclodextrin complexation has been sustained by the possibilities of further modifying the formulation to enhance the solubilizing ability of cyclodextrins or to develop newer drug delivery systems. For example, incorporation of water-soluble polymers into the drug-CD complex to form ternary systems have been shown to remarkably enhance the dissolution rate and therapeutic efficacy of the drug compared to the drug-CD complex alone. These polymers synergistically interact with CD with resultant enhancement of aqueous solubility. Water soluble polymers commonly used are either natural, synthetic or semi-synthetic and these include gelatin, pectin, methyl cellulose (MC), carboxymethyl cellulose (CMC), hydroxypropyl cellulose (HPC), polyethylene glycol (PEG), and polyvinyl alcohol (PVA) [4]. In recent decades research on ternary complexes has attracted increased attention resulting in substantial number of studies that investigated several drugs formulated with water soluble polymer and CD.

Newer research area on CDs has also involved their evaluation as carriers in controlled release drug delivery systems. This is being achieved with the use of hydrophobic CDs such as alkylated and acylated derivatives rather than the hydrophilic derivatives that have been used to enhance the drug release rate. Thus, using different hydrophobic CDs, a variety of drugs have been formulated as controlled and targeted delivery systems.

Furthermore, innovative applications of modified CDs are being investigated with amphiphilic cyclodextrins obtained by chemical or enzymatic modifications of the parent molecule using a variety of anchor molecules. These amphiphilic compounds can self-assemble in an aqueous medium to form different types of aggregates or supramolecular nano-assemblies. Inclusion complexation in these nanoparticulate structures provide potential carriers as novel targeted drug delivery systems [5].

Conclusion and Future Potentials of Cyclodextrins

The traditional use of CDs for enhancing bioavailability of poorly water-soluble drugs has been extended. The CD ternary systems containing water-soluble polymer offer improved alternative, especially in situations where a high amount of CD is required to achieve reasonable aqueous drug solubility. CD derivatives that self-assemble are being extensively studied for their utilization in novel formulations such as nanoparticulate structures for targeted drug delivery. It is

anticipated that the scope of applications of cyclodextrins will still increase with the synthesis of different CD derivatives. Evaluation of the utility of CDs to enhance the characteristics of other nanoparticulate drug carriers also has good prospects [6].

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