REVIEW ARTICLE

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Pharmaceutical Potential of Cyclodextrins

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The use of cyclodextrins (CD) in pharmaceutical formulation is a topic of interest to the pharmaceutical scientists from industry, research and development, academia, drug control administration and profession. This review presents an overview of the ideal requirements for the complexation, advantages, inclusion complexes and their preparation, pharmacotechnical characteristics, metabolism, toxicity, different derivatives, recent developments and future prospects of cyclodextrins.

During last few decades a number of methods to improve the dissolution rate of poorly soluble drugs from solid dosage forms have been described. In the first half of this century the cyclodextrin chemistry was laid down which gained potential drive in the field of modified delivery of drugs. Cyclodextrins are widely used in the pharmaceutical field owing to their high aqueous solubility and the ability to stabilize insoluble drug molecules. The formulation of monomolecular inclusion complexes led to the development of promising dosage forms. Molecular encapsulation involves spatial entrapment of single guest molecule in the cavity of one host molecule without the formation of any covalent bonds[1,2]. Cyclodextrins are toroidal oligosaccharides known to form inclusion complexes in aqueous solutions with various types of organic substances. The complexation largely depends on the dimension and the steric arrangements of the functional group of the cyclodextrin molecule, which would result in a relatively hydrophilic outside and hydrophobic inside within the cavity. The apolar cavity is the part of the molecule that would bind guest molecule by hydrophobic forces.

IDEAL REQUIREMENTS FOR COMPLEXATION

The ideal requirements for complexation are as follows :

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- As larger molecules do not fit in to the cyclodextrin cavity, the molecular weight of active drug should be in range of 100-400.
- Water solubility of drug to be complexed should not be less than 10 mg/ml.
- Melting temperature of the drug should be below 250°.
- Molecule must have less than five condensed rings.
- Stability constant of the molecule should not be extremely high.
- In case of injection, volume should be less than 5 ml.

ADVANTAGES OF CYCLODEXTRIN COMPLEXES[3,4]

- It improves bioavailability from solid and semisolid formulations.
- Stability and shelf life can be increased.
- Side effects can be reduced significantly.
- Aqueous injectable solution from poorly soluble drugs can be prepared.
- Complexation may convert oils and liquid drugs into microcrystalline or amorphous powders.
- Gastrointestinal and ocular irritation may be reduced, minimized or eliminated.

- Complexation prevent drug-drug or drug-additive interaction.
- It can be used to mask unpleasant odor and taste.

CYCLODEXTRINS

Amylose and amylopectin are formed when several thousand glucopyranose structures are linked. The partial degradation of these molecules causes formation of dextrins. There are specific enzymes which not only degrade the macromolecule to smaller units, but simultaneously have the two ends of newly formed dextrin molecules combined to form cyclic structures[5,6]. The cyclic structures are called cyclodextrins. Due to steric reasons three types of cyclodextrins are formed i.e. alpha cyclodextrins (having six glucopyranose units), beta cyclodextrins (having seven glucopyranose units) and gamma cyclodextrins (having eight glucopyranose units)[7]. These glucose molecules are linked together by alpha [1,4] bonds forming torous shaped molecule, where primary -OH groups are situated on largest side. Its interior portion is hydrophobic and exterior is hydrophilic. This enables the cyclodextrin molecule entrap guest molecule, which apparently have to satisfy a single requirement, a steric hindrance compatible with the size of cyclodextrin cavity. Interior area of alpha cyclodextrin, beta cyclodextrin and gamma cyclodextrin are 5°A, 6°A & 8°A respectively.

MODIFIED CYCLODEXTRINS

Beta cyclodextrin is the most widely used one due to its availability, price and better complexing efficiency. Its low aqueous solubility is a serious barrier in its wider application which, fortunately, can be enhanced significantly by chemical and enzymatic modification. In cyclodextrins every glucopyranose unit has three free hydroxyl groups which can be modified by substituting the hydrogen atoms by variety of groups such as alkyl, hydroxyalkyl, carboxyalkyl, amino, and thio. Derivation improves solubility of cyclodextrin derivatives, fittings and association between cyclodextrin and the guest molecules[1].

CYCLODEXTRIN INCLUSION COMPLEXES

When the cavity of cyclodextrin molecule is filled with another molecule of another substance, it is called an inclusion complex. In an aqueous solution the slightly apolar cyclodextrin cavity is occupied by water molecules which are energetically unfavored and therefore can be substituted by appropriate guest molecule, which are less polar than water. The main driving force for complex formation, atleast in the case of beta cyclodextrin and its derivatives, appear to be the release of enthalpy-rich water molecules from the cavity which lowers the energy of system[8,9]. Inclusion complexes so formed can be isolated as stable crystalline substances. The inclusion results in hydrophilization of the host molecule with a concomitant improvement of its apparent solubility and dissolution rate[10]. Furthermore there is generally an improvement in stability in air and light[11].

PREPARATION OF INCLUSION COMPLEXES

Various methods have been reported for the preparation of drug and cyclodextrin complexes. Solutions of complexes are usually prepared by the addition of an excess amount of the drug to an aqueous cyclodextrin solution. The suspension formed is equilibrated and then filtered to form a clear solution of the cyclodextrin complex. The rate determining step in complex formation is often the phase-to-phase transition of the drug molecule. Therefore, it is possible to shorten this process by formation of supersaturated solution through sonication followed by precipitation. The foremost requirement for the preparation of complexes is that the guest molecule must fit at least partly in the cyclodextrin cavity. The best method reported is co-precipitation[12]. In this method, the cyclodextrin and active ingredient are dissolved in water and/or organoaqueous solvent. The inclusion compound is obtained by simultaneous precipitation or cooling. Alternately, there is heating method which involves heating of drug and cyclodextrin hydrate in a sealed container. In this case water content of a-cyclodextrin and vapor pressure of the drug play very important role in the formation of inclusion complex[13,14].

Kneading method is also very interesting which involves adding active ingredient to a slurry of cyclodextrin to obtain a paste[15]. In some cases cyclodextrin and the drug in stoichiometric ratios are dissolved separately in water and ammonium hydroxide or any water miscible organic solvent and both solutions are mixed together to form a clear solution. The solvent from the solution is then rapidly removed by freeze drying or spray drying[16]. In neutralization method, the drug is dissolved either in an acidic or basic medium and the solubility is then lowered through appropriate pH adjustment (acidic solution for basic drug and, basic solution for acidic drugs).

PHARMACOTECHNICAL CHARACTERISTICS OF INCLUSION COMPLEXES

Cyclodextrins and their derivatives have been used in pharmaceutical formulations to enhance solubility, dissolution rate, membrane permeability and bioavailability. These pharmacotechnical characteristics are further described below.

Enhancement of Stability in the Solid State

Cyclodextrin complexation is of immense application in improving chemical, physical and heat stability. Chemical stability can be improved by deccelerating rate of hydrolysis, oxidation, decarboxylation, isomerization etc. through cyclodextrin complexation. Physical stability includes other changes, not of chemical nature, like sedimentation and caking of suspension, recrystallisation to less soluble but thermodynamically more stable polymorphic crystal forms. The deliquescence of hygroscopic substances is also reduced. Heat stability can be increased both by reducing the volatility of liquids and also by reducing tendency of some solid products to sublimate. Oxidation resistance can also be increased as reported[17].

Resistance to Hydrolysis

It varies considerably depending on the type of guest molecule and pH e.g. when hydrocortisone is included in betacyclodextrin, resistance to hydrolysis is accelerated in alkaline medium, while it is unchanged in neutral medium[18].

Enhancement of Aqueous Solubility

The aqueous solubility can also be improved by complexation with beta cyclodextrin and the crystalline nature of powder made by different procedures. Improvement in solubility of steroids[19], benzodiazepines[20], bezothiazides[21], barbiturates[22], naproxen[23], flurbiprofen[24], and retionic acid[25] has been reported.

Improvement in Bioavailability

When poor bioavailability is due to low solubility but not due to rate of absorption, cyclodextrin is of extreme value. Precondition for the absorption of an orally administered drug is its release from the formulation in dissolved form. When drug is complexed with cyclodextrin, dissolution and consequently absorption is enhanced. Improvement in bioavailability of digoxin when complexed with cyclodextrin has been reported[26].

METABOLISM AND TOXICITY

Various cyclodextrin derivatives can be formed by specific modification by substituting one or more H-atom of the primary and/or secondary hydroxyls to form ester or ether or glycosyl-cyclodextrins. The hydrolysis based metabolism of betacyclodextrin occurs only in colon and in small intestine. Metabolism is slower initially as these are totally resistant to beta amylases which degrade only the free end groups but can be attacked by alpha amylases active inside the molecule. Gamma cyclodextrin has fastest[27] metabolism rate. Oral administration does not result in acute toxicity. Long term administration led to significant change in biological values but if given intramuscularly then it causes ulceration of legs and if given intravenously it causes nephrotoxicity and hemolytic effects. Alpha-and beta-cyclodextrins are poorly absorbed by the small intestine[28]. Intraperitoneal administration causes increase in blood urea nitrogen[29].

CYCLODEXTRIN DERIVATIVES

Various cyclodextrin derivatives can be formed as described in the previous section, by substituting one or more primary and/or secondary hydroxyls (deoxyhalogeno-amino etc.), eliminating the hydrogen atom of the C_5 CH_2 OH and (C_5-COOH), group splitting one or more C_2-C_3 bonds by periodate oxidation (dialdehyde cyclodextrin) or after reduction of macrocrown-ethers. Derivatization of cyclodextrins modifies their solubility and simultaneously reduces toxicity. Various derivatives of cyclodextrin, as outlined below, have been reported (30).

Methylated cyclodextrin

This results from methylation of all C-2 secondary hydroxyls and all C-6 primary hydroxyls and trimethyl cyclodextrins result from methylation of all the hydroxyls (C-2, C-3 and C-6). Their water solubility is much higher as compared to parent cyclodextrins. Their solubility decreases with increasing temperature. On methylation, solubility of beta cyclodextrin increases, but beyond two thirds of methylation, it decreases again. When administered by oral route they act as xenobiotics. They exhibit higher hemolytic effect than beta-cyclodextrins[29].

Hydroxypropylated Cyclodextrins

These derivatives are highly water soluble, due both to chemical nature and amorphous property. Their dissolution is endothermic so there is no decrease in solubility

Table I - Improvement in Solubility of Various Drugs through cyclodextrin Complexation

Drug	Cyclodextrin used	solubility	bioavailibility	stability	Ref.
Barbiturate	beta	+			37
Cephaline	Meth. beta			+	38
Cinnarizine	beta		+		39
Clotazole	Meth. beta		+		40
Chlorambucil	HP. beta	+		+	41
Diazepam	beta	+			42
Dicoumarol	beta	+	+		43
Digoxin	gamma		+		27
Emetine	Meth beta			+	38
Fendiline	beta		+		44
Flufenamic acid	beta		+		45
Flurbiprofen	beta		+		46
Hydrocortisone	HP. beta		+		47
Ibuprofen	beta		+		48
Melphalan	HP beta	+		+	41
Naproxen	beta	+	+		49
Nemsulide	beta	+	+		52
Nifedipine	HP beta	+	+		50
Retionic Acid	beta	+			51

Abbreviations : Meth-Methyl cyclodextrin, HP-Hydroxypropyl cyclodextrin

with increase in temperature. Unlike methyl cyclodextrins, they are not hydrolyzed by gastrointestinal amylases. Main interest is in parentral administration as they have lower hemolytic effect than original cyclodextrins. Dihydroxypropyl beta-cyclodextrins are less hemolytic than hydroxypropyl form. Hemolytic effect decreases with increase in degree of substitution[31].

Hydroxyethylated Cyclodextrins

Hydroxyethylation of cyclodextrins results in a mixture of hydroxyethyl cyclodextrins with varying degress of substitution, having low hemolytic effect than hydroxypropyl form of derivative.

Branched Cyclodextrins

Various branched cyclodextrins have been described as alpha-and beta-cyclodextrins and diglucosyl, dimaltosyl and dipyronosyl beta-cyclodextrins. All are more water soluble than gamma cyclodextrins, most soluble being diglucosyl beta-cyclodextrins and less hemolytic than parent cyclodextrins and least hemolytic among branched beta cyclodextrins[32,33].

Other Cyclodextrins

Ethylated cyclodextrins

Ethylation reduces water solubility in proportion to degree of substitution. It can be used to sustain the release of an active ingredient[34].

Carboxymethylated Cyclodextrins

These have pH dependent solubility. Solubility is almost constant below pH 2.5, increases sharply above pH 4.0 and at pH 7.6 it is freely soluble. It is proposed for preferential drug release in intestinal fluids with slight release in gastric fluid[35]. It has two cyclodextrin units,

cyclodextrin polymers with low molecular weight [3000-6000] are readily soluble in water, while those with molecular weight ranging to 10000 can only swell to form gels[36].

SOME UNUSUAL DERIVATIVES

Some derivatives can also be prepared by connecting crown ethers through a long spacer arm to beta-cyclodextrin which results in an amphibian complexing agent : a receptor with two recognition sites. In this, cyclodextrin cavity includes apolar part of a guest, while sodium cation is complexed by the crown ether part. Cyclodextrin complexes of drugs alongwith their objectives as reported in the literature are given in table 1.

FUTURE PROSPECTS AND RECENT DEVELOPMENTS

The future prospects of cyclodextrins are quite substantial, as they posses remarkable property of complexing problematic drugs (poorly soluble and bioavailable, unstable, irritating, difficult to formulate substances). The cyclodextrin complexation generally results in improved wettability, dissolution and solubility, improved stability and milder undesirable properties, such as bitter taste, and bad smells. This can be used practically in any dosage form such as oral, rectal, pulmonal, ocular. Complexation with cyclodextrins, enhanced transdermal permeation[53] and nasal absorption[54] can be achieved successfully. Using appropriate, highly soluble cyclodextrin complex, parentral formulations of poorly soluble drugs can also be prepared.

Lonkos and Gregoriadis[54] recently reported reduction in drug leakage from liposomes by incorporating drug cyclodextrin complex in liposomes. Bibby *et al.*[56] synthesized microspheres containing polyacrylic acid cross-linked with beta-cyclodextrin. Rekkas *et al.*[57] reported increase in oral and intramuscular absorption of ibuprofen after administration of freeze-dried ibuprofen complexed with 2-hydroxypropyl cyclodextrin. Croyle *et al.*[58] reported enhancement in gene delivery to the intestine with betacyclodextrin. Worth *et al.*[59] successfully delivered pulmonally steroid complexed with cyclodextrin.

In conclusion, owing to an unique architecture, cyclodextrins have now became an integral part of the scientist option in drug development and is being served as modalities as diverse as enzyme mimics, chiral separation phases and complexing agents in the food, cosmetics and pharmaceutical industries. Since the potential of cyclodextrins is only now being realized, it is expected that many new derivatives, methods of drug complexation and uses may be unfolded in the future, with the objective of optimizing drug delivery for the benefit of suffering mankind.

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