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A Review on Cyclodextrins

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ABSTRACT

Cyclodextrin have been used in the pharmaceutical industry from a long time. Cyclodextrins are cyclic oligosaccharides. They are revolutionary excipient in the pharmaceutical industry to enhance the physiochemical properties of the lipophilic drugs. They are able to form inclusion with numerous active pharmaceutical ingredients. Cyclodextrin form inclusion complex without altering the biological properties of the drug. As they have low toxicological profile, they are widely used in various formulations like in ophthalmic, nasal, intravenous, etc. Various techniques have been developed for the preparation of inclusion complex with cyclodextrin. Here in this article, the physicochemical properties, method of preparation, pharmacokinetics and toxicological profile of the cyclodextrin have been discussed.

KEYWORDS

Cyclodextrin, inclusion complex, pharmacokinetics, toxicology, metabolism, drug liberation.

1. INTRODUCTION

More than 100 years back, the cyclodextrins were discovered, they are natural oligosaccharides [1], however recently the highly purified cyclodextrins are accessible as pharmaceutical excipients. Cyclodextrins mostly have been used as a complexing agent in the pharmaceutical industry, to enhance the aqueous solubility of the poorly soluble drugs and also for the improvement of stability and bioavailability. Other than that, cyclodextrins can be used in different ways such as, to decrease gastrointestinal drug irritation, to transform the liquid drugs into microcrystalline or amorphous powder, to inhibit drug-drug interaction, and drug-excipient interactions. On the pharmaceutical application of cyclodextrins, variety of books and review published have been published [2-13]. Internationally, approximately there are 30 different pharmaceutical formulations, which incorporate cyclodextrin as excipients.

2. STRUCTURE

Cyclodextrins belong to class of cyclic oligosaccharides which comprise (α-1,4)-connected D-glucopyranose [1]. Chair like configuration of glucopyranose units result in bucket shaped CD molecules, in which secondary hydroxy groups broadening from the extensive end and the primary groups from the narrow end. Hydrophilic external surface and lipophilic centre cavity is due to their unique structure.[3] Most commonly pharmaceutically used naturally occurring cyclodextrins are αCD, βCD and γCD containing 6, 7, and 8 D-glucopyranose units.[10] CDs having larger ring are expensive, less complexation ability as compared to natural CDs, are less applicable in pharmaceutical industry.

Steps involve to prepare most common natural CDs (i.e.α-CD, β-CD and γ-CD) are-

1. bacterial fermentation and CD glycosyltransferase extraction;
2. enzymatic CD formation from starch and precipitation of CD via complexation; and
3. complexing agent elimination and purification of product. CDs which have glucopyranose units above 8 (i.e. the large-ring CDs) are generally manufactured via enzymatic product obtained by chromatographic dissociation of the with absence of precipitation. [7,14]

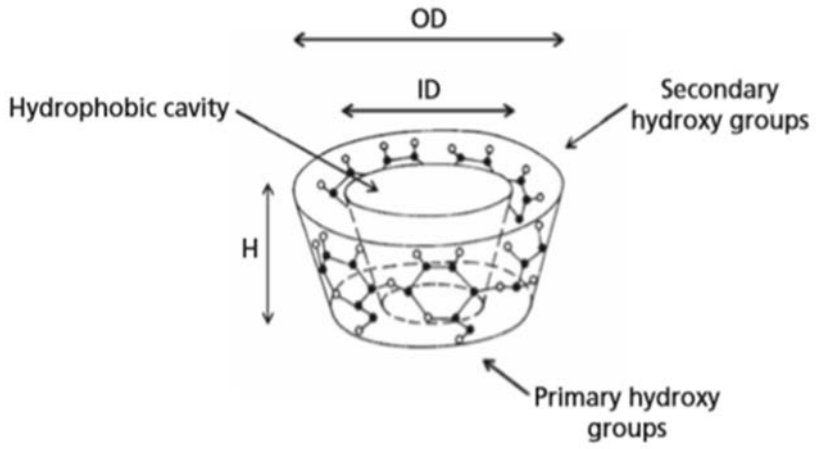

Figure 3.6 Structure of cyclodextrin

The natural cyclodextrins α, β, and γ and their complexes are hydrophilic in nature yet their solubility is somewhat restricted particularly β cyclodextrin, which supposed to be because of powerful binding of the CD molecules in the crystal state (i.e. relatively high crystal lattice

energy). Enhancement in the solubility results from the random substitution of the hydroxy groups, even by hydrophobic moieties like methoxy functions. CD derivatives of pharmaceutical interest include the hydroxypropyl derivatives of β- and γCD (HPβCD and HPγCD), randomly methylated βCD (RMβCD), sulfobutylether βCD sodium salt (SBEβCD) and the so-called branched cyclodextrins, such as maltosyl-βCD (MbCD). [15,16,17]

3. PHYSICAL AND CHEMICAL PROPERTIES OF CYCLODEXTRINS

1. Cavity size

Cavity size is a significant criterion during selection of appropriate cyclodextrin for inclusion complex. If the size of API is too large compared to the cavity size, incorporation of drug will not be appropriate. According to the dimensions, compounds having low molecular weight or having aliphatic side chain complex with α cyclodextrin. Heterocyclic molecules form complex with β cyclodextrin and larger molecules such as macromolecules and steroid with γ cyclodextrin [18]

2. Aqueous solubility

The natural cyclodextrins α β and γ and their complexes are hydrophilic in nature still their solubility is restricted particularly β cyclodextrin which is due to powerful intramolecular hydrogen bonds between secondary hydroxy groups, that weaken their capability to form hydrogen bonds with the adjoining water molecules. To overcome this, various chemically modified derivates have invented which includes hydroxypropylated βCD and γCD (HPβCD and HPγCD), the randomly methylated βCD (RMβCD) and sulfobutyl ether βCD sodium salt (SBEβCD). [8,15,16]

3. Enzyme Stability

Cyclic nature of cyclodextrin provide them resistance toward both enzymatic and non-enzymatic hydrolysis than the linear analogues. They are stable in presence of β-amylase, which hydrolyse starch from the non-reducing end of glucose polymer, but α-amylase gradually hydrolyse them. α CD and β CD are resistant to α-amylase in saliva, but salivary and pancreatic α-amylase rapidly digest γ CD. Natural CDs and their derivates are vulnerable to bacterial digestion in g.i.t. [17]

4. Stability

Cyclodextrin are vulnerable to hydrolytic cleavage at low pH in aqueous solution which cause opening of ring and various linear oligosaccharides and glucose units are formed. they are stable in the presence of bases. [19,20]

4. INCLUSION COMPLEX

Inclusion complex is a complex in which one molecule (host molecule) forms a cavity into which the guest compound accommodates. The guest molecule does not interfere with the host framework structure. Cyclodextrins have the capability to cooperate with several ionic and molecular species [3].

5. Complex formation

In aqueous medium, by entrapping the central cavity or more often lipophilic part of the therapeutic moiety cyclodextrin is able to form inclusion complex with numerous drugs. During the process of inclusion complex no bonds are formed or broken, and the inclusion complex is in dynamic equilibrium with its constituents. Initial equilibrium to form complex is achieved rapidly whereas it takes longer time to reach final equilibrium. After reaching the cyclodextrin cavity, drug molecules go through conformational adjustment to grasp the maximum advantage of weak van der waal's forces. The driving forces behind complex formation includes hydrogen bonding, dipole-dipole, electrostatic interaction, van der waal's hydrophobic interaction, reduction of conformational strain, still the leading driving force is substitution of unfavoured polar- apolar interaction between both the included water molecules and the CD cavity on one hand, and water and the hydrophobic guest on the other one, by more favoured a polar–apolar interactions between the guest and the cavity . (https://www.eurocdsoc.com/index.php).

6. FACTORS INFLUENCING INCLUSION COMPLEX FORMATION

- **Type of cyclodextrin**

Type of CD can have an important impact on the development also on the functioning of CD. Size of cavity should be appropriate to incorporate a drug molecule of precise size. In comparison with neutral CDs, when the drug and cyclodextrin bear different charge complexation can be improved, although decline when they bear same charge [21-27].

- **Temperature**

In general, as the temperature is increased the intensity of apparent stability constant of drug/CD complex is decreased. Reason reported for this was possible decline of drug/CD interaction force, such as Van der waal's, hydrophobic forces with rise of temperature [27,28].

- **Method of preparation**

Physical and chemical properties of drug and CD determine the efficacy of the method used. In majority of cases, most efficient methods for drug complexation were spray drying and freeze drying [29-34].

- **Molar substitution**

In comparison of CD derivates with high molar substitution, same type of derivative with low molar substitution are better complexing agents.

- **pH and ionization**

It was observed that change in Ph and ionization cause change in interaction between drug and CD [35].

7. RUG RELEASE FROM CYCLODEXTRIN COMPLEX

Main mechanisms involved in drug liberation from the CD complex are-

- Simple dissolution of solid/drug complexes
- Dilution of aqueous complexation media

Other processes which provide rapid drug release from complexes are drug-protein binding, direct partitioning from complex to tissue and competitive binding [36-39].

8. METHODS FOR THE PREPARATION ON INCLUSION COMPLEX

There are various techniques employed for the preparation of inclusion complex, every technique has its own advantages and disadvantages. Selection of the method for inclusion complex depends on the physiochemical properties of the drug, available resource, quantity required and cost.

To get the better result method should be optimised. Methods which are widely used are

- physical mixing,
- kneading,
- co-precipitation,
- solvent evaporation,
- freeze drying
- spray drying techniques
- microwave irradiation

1. PHYSICAL MIXTURE

In laboratory, inclusion complex is formed by mixing the drug and CDs by mechanical trituration then this mixture is passed through an appropriate sieve, selection of sieve depends on the particle size desired for the final product.

2.KNEADING

In this method slurry of CDs is prepared using minimum amount of water/ hydroalcoholic solution then drug is added and kneaded properly for required time. After that dried and mixture is passed by an appropriate sieve, in case needed [40].

3.CO-PRECIPATATION

Sufficient amount the drug is solubilised in the alcoholic solution then drop wise drop was added in the CDs solution with constant agitation. Prepared precipitate is isolated via vacuum filtration then allowed to dry at room temperature.

4.SOLVENT EVAPORATION

Separate solution of drug and CDs are prepared using two mutually miscible solvents, then slowly CDs solution is added in drug solution with constant agitation. The mixture is left on stirrer for 24 hours, then the solvent is evaporated using vacuum and final product is recovered.

5.FREEZE DRYING

In freeze drying method, the API and CDs are dissolved in water or water-cosolvent mixture, kept for 48 hours stirring at room temperature. Resultant solution is primarily freeze then lyophilized and the resultant product is recovered.

6.SPRAY DRYING TECHNIQUE

Drug and CDs are dissolved in water then the resultant solution is dehydrated using spray-dryer. this technique requires adequate surrounding to work properly such as temperature and sample feeding speed [54-56]. Only used for thermostable molecules [41].

7.MICROWAVE IRAADIATION

In definite molar ration, homogenous mixture of drug and CDS is prepared in minimum amount of water-organic solvent in appropriate proportion. Then the solution is reacted at 60° C in microwave for 60-90 seconds. The formed product was washed with solvent mixture (water and organic solvent) to remove residue, then filtered using whatman filter paper and dried under vacuum.

METHOD	ADVANTAGES	DISADVANTAGES
PHYSICAL MIXING	simple and most common economical	not as effective as other methods
KNEADING	equipment commonly available simple method	less effective
CO-PRECIPITATION	none compared to others	low yield risk of using organic solvent
SOLVENT EVAPORATION	Simple economic	limited commercial utility
SPRAY DRYING	common technique scalable	not for highly volatile and heat labile molecules low yield
FREEZE DRYING	gold standard method as compared to other	Expensive Long processing time
MICROWAVE IRRADIATION	Minimum solvent required Shorter reaction time High product yield	Not for volatile and thermolabile molecules

Table 3.1 Comparison of different methods of preparing inclusion complexes

9. METABOLISM AND PHARMACOKINETICS

Cyclic structure of CD provides them resistance toward enzymatic and non-enzymatic hydrolysis as compared to linear dextrin. [7] From the non-reducing edge β-amylases hydrolyse starch, but does not hydrolyse CDs, however α-amylases is able to hydrolyse starch from inside the carbohydrate chain, hydrolyse CDs but slowly. Size of the ring and concentration of free CD determine the hydrolytic rate. By concealing all bridge oxygens within the central cavity, CD are able to resist hydrolysis, which the reason behind rapid hydrolysis of free CD than CD tied in an inclusion complex, increase in cavity size increase rate of hydrolysis. [42]

orally delivered, γCD is approximate entirely digested in the gastrointestinal tract, while αCD as well as βCD are principally processed by bacteria present in the colon.

αCD is processed slowly as compared than βCD. CDs are mostly (>90%) excreted unaltered in urine through glomerular filtration in case of intravenous administration. Most probably if their slight residual CD left it is abolished via other routes, for example liver metabolism and biliary excretion by the gastrointestinal tract, that is an alternative for the excretion of the low molecular weight dextrans.

The pharmacokinetics of HPβCD, SBEβCD and sugammadex have been reviewed in humans and it was observed that mostly (i.e., 93–100%) excreted unaltered via glomerular filtrations. CD pharmacokinetic parameters are often evaluated by non-compartmental technique, after administration by parenteral route to humans. Though, the plasma concentration–time profiles of cyclodextrin demonstrate a short distribution phase which is trailed by an elimination phase, and the pharmacokinetics profile of sugammadex has been observed to obey a three-compartment open model after administration by parenteral to humans. There is similarity in the pharmacokinetics between the three natural Cyclodextrins and also with the linear dextrin which having equivalent molecular weight. The elimination phase ranges are about 1.4 to 2 h which is the range of t1/2, and nearly 0.2 L/kg is the VD for all three natural cyclodextrins. The pharmacokinetic studies demonstrated, more than 90% of CD given by parenteral route will be eradicated from the body within the period of about 6 h and over 99.9% will be in approximately 24 h. Therefore, CD accumulation will not be observed in individuals with normal kidney function, even at high doses. However, accumulation of CD

will be observed in patients with severely renally impaired, i.e., individuals with renal clearance (ClCr) below approximately 10 ml/min.

10. REGULATORY STATUS

As progressively more products are improved, the regulatory status is also updating. In the European Pharmacopoeia (Ph.Eur.), US Pharmacopeia/National Formulary (USP/NF) and Japanese Pharmaceutical Codex (JPC) α-CD and β-CD both are documented. Whereas in the JPC, γ-CD is mentioned and shortly will also be added in the Ph.Eur. and USP/NF.

In ph.Eur. monograph for HPβCD is accessible and for USP/NF a draft has been circulated. However other derivates have not been documented yet, still attempt are in progress for their inclusion. FDA's list of inactive pharmaceutical ingredients has citied both HPβCD and SBEβCD.

In the food industry, toxicity studies in animal is the criteria for regulatory status, in which no-observable-effect level (NOEL; the maximum administered dose which does not produce any evident adverse effect) is calculated. To determine acceptable daily intake (ADI) for humans the overall NOEL obtained from the most sensitive species divided by a safety factor.

Approved ADI according to The Joint (FAO/ WHO) Expert Committee on Food Additives (JECFA) for β-CD is 5 mg/kg per day in food products, whereas defined ADI for α-cyclodextrin and γ-cyclodextrin is not recommended as they have favourable toxicological profile.

GRAS 'generally recognized as safe' is the list by FDA of flavour stabilizers in US contain α-CD, β-CD and γ-CD.

11. TOXICOLOGY OF CYCLODEXTRIN

Cyclodextrin molecules are poorly absorbed through biological membranes due to their size (range of molecular weight 1000 to > 2000 Da) and have huge number of hydrogen givers and receiver. Human salivary and pancreatic amylase are not able to hydrolyse natural α- and β-CD, however they can hydrolyse γ-CD. Hydrophilic cyclodextrins are nontoxic at low to moderate oral dosages [10,12]. Natural cyclodextrins and their respective derivatives, can be

utilized in topical and oral preparations, however only α-cyclodextrin and the hydrophilic derivatives of β- and γ-CD can be utilized in the intravenous preparations. In aqueous solutions γ-Cyclodextrin produce perceptible clusters and because of this they are not suitable for the intravenous formulations [17]. Because of potential to cause nephrotoxicity by β-cyclodextrin, it is not utilized in intravenous formulations. Hydrophobic CD derivatives, as the methylated cyclodextrins are able to be absorbed at certain degree from the gastrointestinal tract to the systemic circulation and it has been observed have toxic effect when delivered via parenteral route [12]]. Now, use of methylated β-cyclodextrin in oral delivery system is restrained by its possible toxicity.

12. CONCLUSION

Cyclodextrin are an innovative excipient used to the pharmaceutical industry, which are able to enhance the physiochemical properties of the lipophilic drugs. Cyclodextrin form inclusion complex by entrapping the central cavity or more frequently the lipophilic portion of the drug. The drugs can be released from the inclusion complex by simple dilution. there are various factors which can influence the inclusion complex. The enhancement in the physiochemical properties of the drug also depends on the method which is selection for formation of the inclusion complex. As per the data available on the pharmacokinetics and toxicological profile of the cyclodextrin, they can be used in the different types of the formulation. Cyclodextrin have wide range of application.

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