Review Article

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RECENT RESEARCH ON CYCLODEXTRIN COMPLEXATION IN FORMULATION DEVELOPMENT- A REVIEW

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ABSTRACT

Cyclodextrin complexation is a topic of current interest in pharmaceutical product development. Cyclodextrins and their derivatives play an important role in the formulation development of poorly soluble BCS class II drugs. Several studies reported the application of cyclodextrins for enhancing the solubility, dissolution rate and bioavailability of BCS class II drugs. Literature on cyclodextrins, their properties and applications, pharmacokinetics and toxicity along with recent research on cyclodextrin complexation is reviewed in this article.

Key words: Cyclodextrins,Complexation, Formulation development, Recent research, Review

INTRODUCTION

Cyclodextrins (CDs), homologous cyclic oligosaccharides have long been known to increase the apparent solubility of many lipophilic drugs through non-covalent inclusion complexation[1,2]. Cyclodextrins and their derivatives play an important role in the formulation development due to their effect on solubility, dissolution rate, chemical stability and absorption of a drug[3, 4].

The α-, β- and γ-cyclodextrins are cyclic oligosaccharides consisting of six, seven and eight glucose units respectively. While it is thought that, due to steric factors, cyclodextrins having fewer than six glucopyranose units cannot exist. Chemical and physical properties of the four most common cyclodextrins are given in Table 1. The melting points of α-, β- and γ-cyclodextrins are between 240° and 265°C, consistent with their stable crystal lattice structure[5].

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Table 1: Some Characteristics of α-, β-, γ- and δ-Cyclodextrins

	α	β	γ	δ
No. of glucopyranose units	6	7	8	9
Molecular weight	972	1135	1297	1459
Central cavity diameter (A°)	4.7-5.3	6.0-6.5	7.5-8.3	10.3-11.2
Water solubility at 25°C (g/100 ml)	14.5	1.85	23.2	8.19

They are enzymatic conversion products of starch. The enzyme cyclodextrin-glucosyl transferase produced by B. macerans acts on partially hydrolysed starch (a mixture of linear dextrins) and produces a mixture of cyclic and acyclic dextrins, from which pure cyclodextrins (CDs) are isolated[6].

The structure of the most important CD, β-cyclodextrin is shown in Fig. 1.

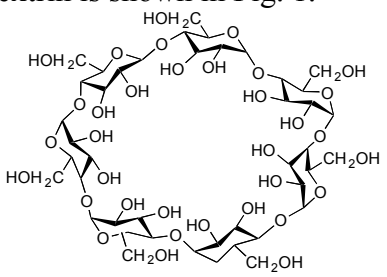

Fig.1: The Structure of β-cyclodextrin

The 'torus' shaped macro-ring is built of α-1,4-D-glucose units. As a consequence of conformation of glucopyranose units, all secondary OH- groups are located on one edge (wider edge) of the 'torus' like CD molecule while all primary OH-groups are on the other side (narrow side of torus). The lining of the internal cavity is formed by OH-atoms and glucosidic oxygen-bridge atoms, therefore, the inner surface is hydrophobic, but outer surface is hydrophilic.

Pharmacokinetics of Cyclodextrins[7]:

- The parent CDs are poorly absorbed from the g.i. tract
- Oral absorption studies have shown ≤ 2%, 0.1-0.3% and ≤ 0.1% absorption respectively with α-, β-, and γ - CDs.
- Intravenously administered CDs disappear rapidly from systemic circulation; excreted mainly through kidney.The $t_{1/2}$ of β-CD 23.9 – 50.2 min in rat.
- The $t_{1/2}$ of HP-β-CD is 24 min in rat, 48 min in dog and 72-108 min in human.
- α- and β-CDs are excreted almost completely in their intact form
- Little or no distribution of most CDs into other tissues or storage compartments is observed.

Safety of Cyclodextrins:

- Parent CDs are reported to be non-toxic and safe even at high oral doses.
- The LD_{50} in rats is reported to be greater than 12.5, 18.8 and 8.0 g /kg body weight for α-, β-, and γ-CD respectively.
- α-andβ-CDs produced no toxic effects when fed to rats for 30-90 days at 1%, of the diet or at 1 and 2 g /kg daily doses.

Regulatory Status of Cyclodextrins:

- Accepted as new pharmaceutical excipients by USFDA
- A monograph on β CD in USP 23/NF 18, 1995 and European Pharmacopoeia 3rd Ed., 1997
- Monographs on cyclodextrins in Hand book of Pharmaceutical Excipients.

Formation of Complexes:

One of the most important characteristics of CDs is their ability to form inclusion complexes. Inclusion complexation involves entrapment of a guest molecule totally or partially in the cavity of host molecule without formation of any covalent bonds. CDs are typical host molecules and can entrap a wide variety of drug molecules resulting in the formation of monomolecular inclusion complexes[8].Usually 1 : 1 complexes are formed, but when a guest molecule is too long to find complete accommodation in one cavity, its other end is also amenable to complex formation leading to 2 : 1 (CD : drug) or sometimes 3 : 1 or 4 : 1 complexes. It may also be possible to form 1: 2 and 1: 3 (CD: drug) complexes. The central cavity of the cyclodextrin molecule is linked with skeletal carbons and ethereal oxygens of the glucose residues. It is therefore lipophilic, the polarity of the cavity has been estimated to be similar to that of aqueous ethanolic solution. It provides a lipophilic microenvironment into which suitably sized drug molecules may enter and be included. No covalent bonds are formed or broken during drug-cyclodextrin complex formation, and in aqueous solutions, the complexes are readily dissociated. Free drug molecules are in equilibriumwith the molecules bound within the cyclodextrin cavity Measurements of stability or equilibrium constants (K_c) of the drug-cyclodextrin complexes are important properties of a compound upon inclusion.

Detection of inclusion complexation in the solution state:

Phase solubility technique[9] is the one of the widely used methods to detect the inclusion complexation in solution state. The general experimental operation in studying molecular interactions by means of phase solubility method entails the addition of an equal weight (inconsiderable excess of its normal solubility) of a slightly soluble compound, S (substrate or guest) into each of several vials containing increasing concentrations of a relatively soluble compound, L (ligand or host or complex agent), which are closed and brought to solubility equilibrium at constant temperature. The solution phases are then analyzed, by any suitable means, for their total concentration of compound S (guest), no matter what its

molecular state may be. A phase diagram is constructed by plotting, on the vertical axis, total molar concentration of S found in the solution phase against the molar concentration of L.

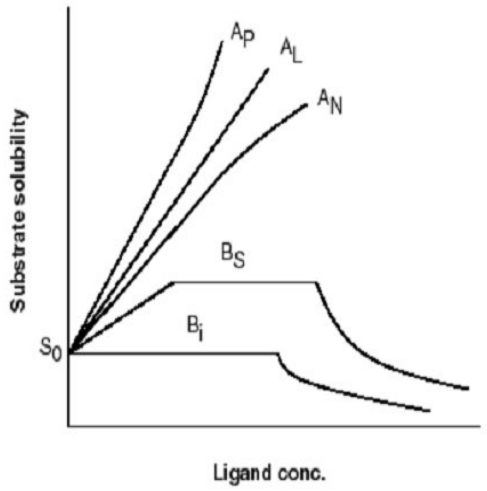

Fig. 2: Phase solubility diagram

The phase diagrams are observed to fall into two main classes, type A and type B with some variation wit in the classes (Fig 2).

The type A can be further classified in subtypes A_L, A_P and A_N, where the guest solubility of first type increases linearly with cyclodextrin concentration while those of the second and third types deviate positively and negatively, respectively from the straight line.

The complex formation with a 1:1 stoechiometry gives the $A_L$type diagram, where as the higher order complex formation in which more than one cyclodextrin molecules are involved in the complexation gives the A_P-type. The interaction mechanism for the A_N-type is complicated, because of a significant contribution of solute-solvent interaction to the complexation.

In the case of the B_s type, the initial ascending portion of the solubility change is followed by a plateau region and then a decrease in the solubility at higher cyclodextrin concentrations accompanying a microcrystalline precipitation of the complex. The Bi-type diagram is indicative of the formation of insoluble complexes in water. The stability constant (K_s) and stoechiometry of complexes are determined by analyzing quantitatively the phase solubility diagram.

Detection of inclusion complexation in the solid state:

Detection of the inclusion complexation in solid state can be done by Powder X-ray diffractometry, Single crystal X-ray structure analysis, Thermo analytical, Thin layer chromatography, Paper chromatography, Infrared spectroscopy, Scanning electron microscopy and Dissolution study methods

Methods of Preparation of CD Complexes:

Many techniques are known to form complexes with cyclodextrins, these are briefly described below.

1. Physical blending / Grinding method: Inclusion complexes can be prepared by simply grinding/ triturating the drug with cyclodextrin in mortar, on small scale. Whereas on large scale, the preparation of complexes is based on extensive blending of the drug with cyclodextrin in a rapid mass granulator usually for 30 minutes[10]

2. Kneading method: Paste of cyclodextrin is prepared with small amount of water to which the drug is added without a solvent or in a small amount of ethanol. After grinding paste, solvent get evaporated and powder like complex is formed. On laboratory scale kneading can be achieved by using a morter and pestle[11-13]**.** On large scale the kneading can be done by utilizing the extruders and other machines. Parikh[14] reported the dissolution enhancement of Nimesulide using complexation method.

3. Co-precipitation: Cyclodextrin is dissolved in water and the guest is added while stirring the cyclodextrin solution. By heating, more cyclodextrin can be dissolved (20%) if the guest can tolerate the higher temperature. The cyclodextrin and guest solution must be cooled under stirring before a precipitate is formed. The precipitate can be collected by decanting, centrifugation or filtration and washed. Moyano[15]had studied the solid-state characterization and dissolution characteristics of Gliclazide-Beta- cyclodextrin inclusion complexes.

4. Solid dispersion / Co- evaporated dispersion: In this method, drug and cyclodextrin are dissolved in ethanol and in water separately. Both the solutions are mixed

and stirred to attain equilibrium. The resulting solution is evaporated to dryness preferably under vacuum.[10]

5. Neutralization method: Drug and cyclodextrin are separately dissolved in 0.1 N sodium hydroxide, mixed and stirred for about half an hour, pH is recorded and 0.1 N HCl is added drop wise with stirring until pH reaches 7.5, where upon complexes precipitates. The residue is filtered and washed until free from chlorine, It is dried at 250^0C for 24 h. and stored in desiccators Doijad[16]had studied the enhancement of solubility of Piroxicam by complexation with beta-cyclodextrin.

6. Spray drying: In this method, first monophasic solution of drug and cyclodextrin is prepared using a suitable solvent. The solution is then stirred to attain equilibrium following which the solvent is removed by spray drying. Vozone[17]had developed complexation of budesonide in cyclodextrins and particle aerodynamic characterization of the complex solid form for dry powder Inhalation.

7. Lyophilization/ Freeze drying technique: To get a porous, amorphous powder with high degree of interaction between drug and cyclodextrin, lyophilization/freeze drying technique is considered as a suitable[18-19]. Here, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug and cyclodextrin at reduced pressure. Thermolabile substances can be successfully made into complex form by this method.

8. Melting: Complexes can be prepared by simply melting the guest, mixed with finely powdered cyclodextrin. In such cases there should be a large excess of guest, and after cooling this excess is removed by careful washing with a weak complex, forming solvent or by vacuum sublimation[20].

9. Micro wave irradiation method: This technique involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. The drug and CD in definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a round bottom flask. The mixture is reacted for short time of about one to twominutes at 60 °C in the microwave oven. After the reaction completes, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed free drug and CD. The precipitateso obtained is separated using whatman filter paper, and dried in vaccum oven at 40 °C for 48 hrs.[21]

10. Supercritical anti-solvent technique: In the super critical fluid anti solvent technique, carbon dioxide is used as anti-solvent for the solute but as a solvent with respect to the organic solvent. The use of super critical carbon dioxide is advantageous as its low critical temperature and pressure makes it attractive for processing heat-labile pharmaceuticals. It is also non-toxic, nonflammable, in expensive and is much easier to remove from the polymeric materials when the process is complete, even through small amount of carbon dioxide remains trapped inside the polymer, it poses no danger to the consumer. Supercritical particle generation processes are new and efficient route for improving bioavailability of pharmaceutically active compounds[22]. In addition, supercritical fluid processes were recently proposed as a new alternative method for the preparation of drug cyclodextrin complexes. Supercritical carbon dioxide is suggested as a new complexation medium due to its properties of improved mass transfer and increased solvating power[23-27]. This method constitutes one of the most innovators methods to prepare the inclusion complex of drug with CD in solid state. This is a non-toxic method as it is not utilizing any organic solvent, fast process, maintenance cost is low with promising results, but it requires a quite high initial cost. In this technique, first, drug and CD are dissolved in a good solvent then the solution is fed into a pressure vessel under supercritical conditions, through a nozzle (i.e. sprayed into supercritical fluid anti-solvent). When the solution is sprayed into supercritical fluid anti-solvent, the anti-solvent rapidly diffuses into that liquid solvent as the carrier liquid solvent counter diffuses into the anti-solvent. Because of the supercritical fluid expanded solvent has lower solvent power than the pure solvent, the mixture becomes supersaturated resulting in the

precipitation of the solute and the solvent is carried away with the supercritical fluidflow[28-29]

Applications of Cyclodextrins:

Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and lipophilic central cavity, which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favorably affected[30-41]

Recent Research Work on CD Complexation:

Several studies reported the cyclodextrin complexation of a variety of drugs for various purposes. A summary of recent research on cyclodextrin complexation for enhancing the solubility, dissolution rate and bioavailability is given in Table 2.

CONCLUSION

Cyclodextrins have become versatile pharmaceutical excipients. Cyclodextrin complexation has been successfully used for enhancing the solubility, dissolution rate and bioavilabilityof several poorly soluble drugs in their formulation development. Cyclodextrins have been receiving increasing application in pharmaceutical product development in recent year due to their approval by various regulatory agencies.

Table 2: Summary of Recent Research on Cyclodextrin Complexation[42-77]

Sl. No	Drug	Cyclodextrin used	Purpose/Result	Ref. No
I Analgesic ,Antipyretic, Anti-inflammatory Drugs				
1	Nimesulide	βCD, HP βCD ME- βCD	Improved solubility and oral bioavailability	42
2	Aceclofenac	βCD HP βCD	Improve solubility and dissolution rate	43
3	Diclofenac sodium	γCD 2-HPγCD	Investigated aggregation of complexes through semi- permeable membranes and transmission electron microscopy	44
4	Indomethacin	Cationic βCD CP βCD	Drug loading capacities of CP βCD were studied and complexes were confirmed by 1H NMR and DSC	45
5	Capsaicin	HPβCD	Improved percutaneous absorption	46
6	Etoricoxib	βCD,HP βCD, Poloxamer 407, PVP K30	Enhancement in solubility and dissolution rate	47
7	Ketrolac	HPβCD	Higher Transdermal Transport	48
8	Paracetamol	α, β and γ cyclodextrin	γ complexes are most stable than β complexes which are more stable thanα complex	49
II Antimicrobial,Antifungal,Antiviral,Antibiotic Drugs				
9	Acyclovir	Fluorinated amphiphilicα cyclodextrins hexakis	To prepare aqueous suspensions of nanoparticles	50
10	Rifampin Novabiocin Vancomycin	βCD	Affinity based antibiotic delivery mechanisms were developed	51
11	Sulfamethoxazole	Hydroxypropyl-β-cyclodextrin	Increased solubility	52
12	Trimethoprim Sulfamethoxazole	cyclodextrins (*α*-, *β*-,and *γ*-CDs)	The solubility enhancement of trimethoprim is much higher than that of sulfamethoxazole in the presence of SDS micelles	53
13	Vancomycin	β-cyclodextrin	modified release with improved bioavailabity	54
14	Quercetin	β-cyclodextrin	Enhamced drug release	55

III Anti hypertensive, Antianginal, Drugs				
15	Irbesartan	βCD, PEG 4000, PVP K90	Improved aqueous solubility, dissolution rate and Characterization of inclusion complexes by XRD, DSC,FTIR and SEM	56
16	Carvidilol	βCD Citric acid	Improved aqueous solubility, dissolution rate and Characterization of inclusion complexes by XRD, DSC,FTIR and SEM	57
17	Felodipine	Cyclodextrins	FTIR, DSC and XRPD showed the confirmation of complexation of cyclodextrin with felodipine	58
18	Statins (Lovastatin,Simvastatin)	RMβCD	Improved solubility	59
19	Valsartan	βCD,HP βCD, PVP K30	Enhancement in solubility and dissolution rate	60
IV Sedatives, Antidepressant, Anti anxiety, Anticonvulsant Drugs				
20	Lorazepam	HPβCD	Improved aqueoussolubility and dissolution rate	61
21	Lamotrigine	βCD	Improved solubility and bioavailability	62
22	Doxepin	βCD	Characterization of inclusion complexes byNMRspectroscopy	63
23	Promethazine	monochlorotriazinyl-β-cyclodextrin	alkaline medium is more favourable for producing the complex	64
24	Olanzapine	methyl- β –CD	Higher dissolution efficiency and stability	65
V Anti cancer Drugs				
25	Tacrolimus	Dimethyl- β-cyclodextrin	improved delivery efficiency	66
26	Diferuloylmethane	hydroxypropyl-β-cyclodextrin	improved the physical properties and antitumor activity	67
27	Betulin	γ-Cyclodextrin	Improved solubility both invitro and in vivo	68
VI Miscellaneous				
28	Omeprazole (Anti Ulcer)	βCD, MEβCD, L- arginine	Improved buccal permeation	69
29	Noscapine (Anti Tussive)	βCD	Improved aqueous solubility and pharmacokinetics	70
30	Bupivacaine HCl (Local Anaesthetic)	α –CD β-CD epichlorohydrin	Improved buccal delivery and Characterization of inclusion complexes by XRPD, DSC,FTIR and Environmental scanning electron microscopy	71
31	Warfarin (Anti Coagulant)	βCD	Improvement in the in vitro bioavailability of the drug in acidic media	72
32	Naringin (Antiatherogenic)	β-cyclodextrin	Improved aqueous solubility	73
33	Albendazole (Anthelminthic)	2-hydroxypropyl-β-cyclodextrin	Improved solubility, pharmacokinetic profile and antitumor efficacy	74
34	Meclizine (Anti Histamine)	2-Hydroxypropyl-β-cyclodextrins and β-cyclodextrins	Better release than marketed tablets	75
35	Thalidomide (Imunimodulator)	Hydroxypropyl-β-cyclodextrin	Improved gastrointestinal absorption	76
36	RosuvastatinCa (antihyperlipedimic)	β-cd	Phase solubility profile indicated that the solubility of rosuvastatinCa was significantly increased in the presence of β-CD	77

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