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Review Article

CYCLODEXTRINS AND THEIR APPLICATION IN ENHANCING THE SOLUBILITY, DISSOLUTION RATE AND BIOAVAILABILITY

SURYA PRAKASARAO KOVVASU[1,2], PRIYANKA KUNAMANENI[2], RAVI SANKAR KUNDERU[3]

[1]A. U. College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, Andhra Pradesh, India- 530003. [2]College of Pharmacy, Western University of Health Sciences, Pomona, California, USA- 91766. [3]Department of Pharmaceutics, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, Andhra Pradesh, India- 520008

Email: skovvasu@westernu.edu

ABSTRACT

Objective: The main objective is to describe the applications of cyclodextrins in enhancing the solubility, dissolution rate, and bioavailability. **Methods and Sources:** Low aqueous solubility is the major problem come across with formulation development of drug product. The drug with poor water solubility cause slow dissolution rates generally shows erratic and incomplete absorption leading to low bioavailability when administered orally. In the present paper, the applications of the cyclodextrin are discussed. In the pharmaceutical industry, cyclodextrins have mainly been used as complexing agents to increase the aqueous solubility of poorly soluble drugs and to increase their bioavailability and stability in a few cases. **Conclusion:** Bioavailability of poorly water-soluble drugs can be enhanced by using cyclodextrins.

Keywords: Biopharmaceutical classification system, solubility, absorption, bioavailability.

INTRODUCTION

Most of the new potential therapeutic drugs exhibit low and variable oral bioavailability due to their poor aqueous solubility or permeation at physiological pH. These drugs are classified into four categories under BCS classification. The biopharmaceutical classification system (BCS) is a scientific framework for categorizing a drug substance based on its aqueous solubility and intestinal permeability. Briefly, the BCS places a given active pharmaceutical ingredient (API) in one of four categories depending on its solubility and permeability as they refer to oral dosing. A drug substance is considered to be highly soluble when the highest clinical dose strength is soluble in 250 ml or less of aqueous media over a pH range of 1-7.5 at 37 °C of temperature. A drug substance is considered to be highly permeable when the extent of the absorption (parent drug and its metabolites) in humans is determined to be ≥90% of an administered dose based on a mass balance determination or in comparison to an intravenous (IV) reference dose. Permeability can be determined in a number of ways but is most often done using Caco-2 cell lines an assay that offers itself to high throughput automation [1]. In this system, a monolayer of cells is grown, and drug permeation from the drug donor (apical side) to the acceptor (basolateral side) compartments is assessed, usually by using a direct UV or HPLC or LC-MS assay.

The classification of drugs into four classes according to the biopharmaceutical classification system (BCS) can help in knowing many *in vivo* parameters which can be of great help in the formulation of the dosage form.

Class I- high permeability, high solubility: Where the metabolism of these drugs is not rated limited. If dissolution is very rapid, then gastric emptying rate becomes the rate-determining step, e.g., either by dissolution or permeability. Intake of meals along with these drugs also does not have any significant effects in their dissolution and permeability e.g. verapamil, diltiazem, metoprolol, and propranolol. *In vitro- in vivo* correlation (IVIVC) is usually expected for the class I drugs. These drugs are the least problematic when one aims to prepare their dosage form. The major challenge in the development of drug delivery system for the class I drugs is to achieve a target release profile associated with a particular pharmacokinetic and/or pharmacodynamic profile. Formulation approaches include both controls of release rate and certain physicochemical properties of drugs like the pH-solubility profile of the drug.

Class II- high permeability, low solubility: Where *in vivo* drug dissolution is the rate limiting step for absorption except at a very high dose number. The absorption of class II drugs is usually slower than class I and occurs over a longer period of time. High- fat diet generally increases their absorption into the bloodstream due to inhibition of efflux transporters in the intestine and a solubilizing effect of the drug into intestinal lumen [2]. With these drugs efforts to increase the dissolution rate would enhance their bioavailability. Therefore these drug candidates are preferred for dissolution enhancement in industries. The systems that are developed for class II drugs are based on micronization, lyophilization, the addition of surfactants, formulation of emulsions and microemulsions systems, use of complexing agents like cyclodextrins, etc., e.g., phenytoin, danazol, ketoconazole, mefenamic acid, and nifedipine.

Class III- low permeability, high solubility: These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. High- fat meals would decrease the absorption [2] of these drugs due to the inhibition of uptake transporter peptides and proteins constitute the part of class III and the technologies handling the local and systemic delivery of proteins and peptides are on the rise now a day, e.g., cimetidine, acyclovir, neomycin, and captopril.

Class IV- low permeability, low solubility: Extreme examples of class I compound are the exception rather than the rule and are rarely developed and reach the market. Nevertheless, the number of class IV drugs do exist. The route of choice for administering such drugs is parenteral with the formulation containing solubility enhancers, e.g., taxol. It has been found out that highly permeable class I and class II compounds have easy and a greater access to the metabolizing enzymes within hepatocytes. It has noted that more permeable lypophilic compounds are good substrates for cytochrome P450 enzymes [3]. Therefore according to BCS classification, it becomes obvious that class I and class II compounds are eliminated via metabolism while class III and class IV

compounds are eliminated unchanged into urine and bile. Upon reviewing the elimination characteristics of some of the drugs it was observed that most of the drugs follow this correlation except a few like mebendazole which is predominantly eliminated in the unchanged form in the urine and bile.

The great use of the BCS is emphasized as a simple tool in initial drug development to determine the rate-limiting step in the oral absorption process, which has enabled the information involved in the overall drug development process.

Solubility

Solubility is the property of a solid, liquid, or a gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the maximum quantity of solute in a certain amount of solvent at a specified temperature and pressure. USP and BP solubility criteria are given in Table 1.

Table 1: USP and BP solubility criteria

Descriptive term	Part of the solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

Techniques to enhance solubility and dissolution rate [4]

There are different techniques available for enhancing the solubility and dissolution rate. Which includes particle size reduction, solid dispersion, nanosuspension, supercritical fluid (SCF) process, cryogenic techniques, inclusion complex formation-based techniques, co-solvency, hydrotrophy, microemulsion, nanocrystal, micellar solubilisation, self-emulsifying drug delivery systems etc., In this paper cyclodextrins and their application in enhancing the solubility, dissolution rate and bioavailability are discussed.

Cyclodextrins

Cyclodextrins are natural cyclic oligosaccharides that were discovered 100 years ago [5], but only recently did highly purified cyclodextrins become available as pharmaceutical excipients. In the pharmaceutical industry, cyclodextrins have mainly been used as complexing agents to increase the aqueous solubility of poorly soluble drugs and to increase their bioavailability and stability. In addition, cyclodextrins can, for example, be used to reduce gastrointestinal drug irritation, convert liquid drugs into microcrystalline or amorphous powder, and prevent drug-drug and drug-excipient interactions. A number of books and review articles have been published on the pharmaceutical applications of cyclodextrins [6-15].

Cyclodextrins (CDs) have long been known to increase the apparent solubility of many lipophilic drugs through non-covalent inclusion complexation [16]. 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 [8, 17].

Cyclodextrins are cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. They consist of (α-1,4)-linked α-D-glucopyranose units with a lipophilic central cavity. Due to the chair formation of the glucopyranose units, cyclodextrin molecules are shaped like cones with secondary hydroxyl groups extending from the wider edge and the primary groups from the narrow edge. This gives cyclodextrin molecules a hydrophilic outer surface, whereas the lipophilicity of their central cavity is comparable to an aqueous ethanolic solution [18]. The most common natural cyclodextrins consist of six (α-cyclodextrin), seven (β-cyclodextrin) and eight (γ-cyclodextrin) glucopyranose units. Although the natural cyclodextrins and their complexes are hydrophilic, their aqueous solubility is rather limited, especially that of β-cyclodextrin. This is thought to be due to relatively strong binding of the cyclodextrin molecules in the crystal state (i.e., relatively high crystal lattice energy) [17]. Random substitution of the hydroxy groups, even by hydrophobic moieties such as methoxy functions, will result in dramatic improvements in their solubility (Table 2). The main reason for the solubility enhancement is that the random substitution transforms the crystalline cyclodextrins into amorphous mixtures of isomeric derivatives. Cyclodextrin derivatives of pharmaceutical interest include the hydroxypropyl derivatives of β- and γ-cyclodextrin, the randomly methylated β-cyclodextrin, sulfobutylether β-cyclodextrin, and the so-called branched cyclodextrins such as glucosyl-β-cyclodextrin.

Table 2: Cyclodextrins that can be found in marketed pharmaceutical products

Cyclodextrin	Substitution*	MW (Da)	Solubility in water (mg/ml)±	Applications
α-cyclodextrin	-	972	145	Oral, parenteral, topical
β-cyclodextrin	-	1135	18.5	Oral, topical
2-hydroxypropyl-β-cyclodextrin	0.65	1400	> 600	Oral, parenteral, topical
Randomly methylated β-cyclodextrin	1..8	1312	> 500	Oral§, topical
β-cyclodextrin sulfobutyl ether sodium salt	0.9	2163	> 500	Oral, parenteral, topical
γ-cyclodextrin	-	1297	232	Oral, parenteral§, topical
2-hydroxypropyl-γ-cyclodextrin	0.6	1576	> 500	Oral, parenteral, topical

***Average number of substituents per glucopyranose repeat unit; ± Solubility in pure water at ~ 25°C; § In very limited amounts; MW: Molecular weight**

While it is thought that, due to steric factors, cyclodextrins having fewer than six glucopyranose units cannot exist, cyclodextrins containing nine, ten, eleven, twelve and thirteen glucopyranose units, which are designated δ-, ε-, ζ-, η, and φ- cyclodextrin, respectively, have been reported [19]. Of these large-ring cyclodextrins only δ-cyclodextrin has been well characterized [20]. Chemical and physical properties of the four most common cyclodextrins are given in Table 3. The melting points of α-, β- and γ-cyclodextrins are between 240 and 265 ˚C, consistent with their stable crystal lattice structure [21].

Table 3: 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

Production of cyclodextrins

CDs are produced from starch by the action of an enzyme, cyclodextrin glycosyltransferase (CGTase). Starch containing both amylopectin and amylose can be used as raw materials for cyclodextrin production but a higher percentage of amylopectin (70-75%) found in potato starch is preferred as it gives higher yield [22-24]. CGTases have attracted major interest from industry due to their unique capacity of forming large quantities of cyclic α-(1,4)-linked oligosaccharides (cyclodextrins) from starch. CGTase(s) are predominantly extracellular enzymes which are produced by various bacteria like *Bacillus macerans, Bacillus circulance, Bacillus megaterium, Klebsiella pneumonia, Bacillus stearothermophillus, Bacillus amyloliquefaceins* etc.

The structure of β-cyclodextrin and some of its derivatives are shown in Fig. 1 [25]. The 'torus' shaped macro-ring is built of α-1,4-D-glucose units. As a consequence of confirmation 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 a torus). The lining of the internal cavity is formed by OH-atoms and glucosidic oxygen-bridge atoms. Therefore, the inner surface is hydrophobic, but the outer surface is hydrophilic. Different types of β-cyclodextrins and their functional groups are given in Table 4.

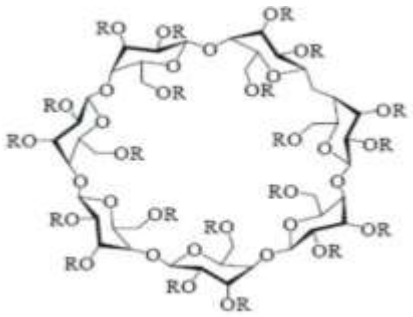

Fig. 1: The structure of β-cyclodextrin and some of its derivatives

Table 4: Different types of β- cyclodextrins and their functional groups

Cyclodextrin	R= H or
β-cyclodextrin	-H
2-hydroxypropyl-β-cyclodextrin	$-CH_2CHOHCH_3$
Sulfobutylether-β-cyclodextrin	$-(CH_2)_4SO_3$-Na+
Randomly methylated- β-cyclodextrin	$-CH_3$
Branched β-cyclodextrin	Glucosyl or maltosyl group

Absorption and toxicity

On oral administration, only insignificant amounts of intact CDs are absorbed from the gastrointestinal tract because of their bulky and hydrophilic nature. Any absorption is by passive diffusion. The parent α-CD and β-CD are practically resistant to stomach acid and salivary and pancreatic enzyme digestion, whereas γ-CD is digested partly by amylases in the gastrointestinal tract (GIT). The oral administration of CDs does not result in acute toxicity. Long-term administration leads to no significant change in organs or biological values. Natural CDs are highly toxic when given parenterally. α- and β- cyclodextrins induce hemolysis and nephrotoxicity upon i.v. injection γ CD is relatively less toxic parenteral.

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 [26].

Inclusion complexation occurs when an aqueous solution of CD is shaken with drug molecules or its solution. In aqueous solution, the hydrophobic cavities of CD are occupied by water molecules, which can be replaced by appropriate drug molecules that are less polar than water. The solubility of the complex is usually lesser than the solubility of CD and hence the complex may be precipitated from its saturated solution, as microcrystalline powder and this powder is subsequently separated by filtration [27]. 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 [28]. 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 equilibrium with the molecules bound within the cyclodextrin cavity Measurements of stability or equilibrium constants (K_c) or the dissociation constants (K_d) of the drug-cyclodextrin complexes are important properties of a compound upon inclusion.

Methods of preparation of CD complexes

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

Physical blending/ grinding method

Inclusion complexes can be prepared by simply grinding/ triturating the drug with cyclodextrin in a mortar, on small scale. Whereas on large scale, the preparation of complexes is based on the extensive blending of the drug with cyclodextrin in a rapid mass granulator usually for 30 minutes [29].

Kneading method

Paste of cyclodextrin is prepared with the small amount of water to which the drug is added without a solvent or in a small amount of ethanol. After grinding paste, solvent gets evaporated and powder like complex is formed. The laboratory scale kneading can be achieved by using a mortar and pestle [30-33]**.** On large scale, the kneading can be done by utilizing the extruders and other machines.

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 [34] had studied the solid-state characterization and dissolution characteristics of gliclazide-Beta- cyclodextrin inclusion complexes.

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 [29].

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 dropwise with stirring until pH reaches 7.5, whereupon complexes precipitate. The residue is filtered and washed until free from chlorine, It is dried at 250 ˚C for 24 h. and stored in desiccators Doijad [35] had studied the enhancement of solubility of piroxicam by complexation with beta-cyclodextrin.

Spray drying

In this method, a 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 [36] had developed complexation of budesonide in cyclodextrins and particle aerodynamic characterization of the complex solid form for dry powder Inhalation.

Lyophilization/ Freeze drying technique

To get a porous, amorphous powder with a high degree of interaction between drug and cyclodextrin, lyophilization/freeze-

drying technique is considered as a suitable. 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.

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 [37].

Microwave irradiation method

This technique involves the microwave irradiation reaction between the drug and complexing agent using a microwave oven. The drug and CD in the 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 a short time of about one to two minutes at 60 °C in the microwave oven. After the reaction completes, an adequate amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed free drug and CD. The precipitate obtained is separated using Whatman filter paper, and dried in a vacuum oven at 40 °C for 48 hours [38].

Supercritical antisolvent technique

In the supercritical fluid antisolvent technique, carbon dioxide is used as anti-solvent for the solute but as a solvent with respect to the organic solvent. The use of supercritical carbon dioxide is advantageous as its low critical temperature and pressure make it attractive for processing heat-labile pharmaceuticals. It is also non-toxic, non-flammable, and inexpensive and is much easier to remove from the polymeric materials when the process is complete, even though a small amount of carbon dioxide remains trapped inside the polymer, it poses no danger to the consumer. Supercritical particle generation processes are a new and efficient route for improving the bioavailability of pharmaceutically active compounds [39]. 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 [40-41]. This method constitutes one of the most innovators methods to prepare the inclusion complex of drug with CD in the 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 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 fluid flow [42-43].

Methods for detection of inclusion complex formation and determination of complex stability constant

One of the most interesting properties of CDs is their ability to form inclusion complexes with a wide variety of guest molecules. Molecular encapsulation may occur both in solution and solid state. In solution, there is equilibrium between complexed and non-complexed guest molecules. In the solid state, guest molecules can be enclosed within the cavity or may be aggregated to the outside of CD molecule [44]. Upon inclusion within the CD cavity a guest molecule experiences changes in its physicochemical properties. These changes provide methods to detect whether guest molecules are really included in the CD cavity.

Detection of inclusion complexation in the solution state

Phase solubility technique [45-48] is one of the widely used methods to detect the inclusion complexation in the solution state. The general experimental operation in studying molecular interactions by means of phase solubility method entails the addition of an equal weight (in considerable 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, the total molar concentration of S found in the solution phase against the molar concentration of L.

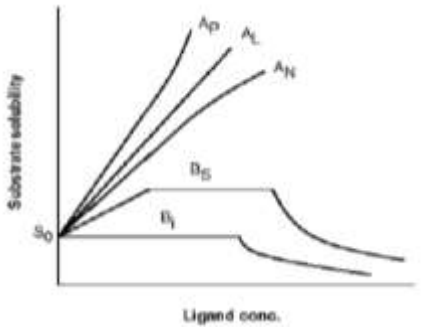

Fig. 2: Phase solubility diagram

The phase diagrams are observed to fall into two main classes, type A and type B with some variation within 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 the 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 stoichiometry gives the a_l type diagram, whereas 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 HP-type diagram is indicative of the formation of insoluble complexes in water. The stability constant (Ks) and stoichiometry 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 X-ray powder diffraction (XRPD), X-ray powder diffraction (XRPD) [49], Differential scanning calorimetry **(**DSC) [50], Thermogravimetric analysis (TGA), UV-Vis spectroscopy [51], Differential solubility, Fourier Transform Infrared Spectroscopy (FTIR) [37], Thin layer chromatography, Paper chromatography and Scanning electron microscopy have been cited in the literature and are discussed below

X-ray powder diffraction analysis (XRPD)

Osadebe *et al.*, [49] prepared the inclusion complexes of piroxicam and beta-cyclodextrin by different methods such as physical mixture, kneading, coprecipitation, evaporation and heating under reflux. XRPD analysis of different 1:1 complexes showed that there was increase in the halo of the diffractograms seen between the arbitrary units of 0 and 0.25 (y-axis) formed on mixing of two compounds and the reduction of intensity of the prominent

piroxicam peak at 2θ= 8.7^0 and resulted in increase in the volume of the beta-cyclodextrin due to inclusion of piroxicam.

Differential scanning calorimetry (DSC) and Thermogravimetric analysis (TGA)

Thermal analyses (DSC and TGA) are useful for determining whether the product of the complexation protocol is true complex or not [50]. In DSC, The samples (10 mg) are placed in aluminum pans and the experiments run in a calorimeter at a 10 °C/min heating rate over a wide range (0- 450 °C). An empty pan served as reference and indium are used to calibrate the temperature. Thermograms are determined for the samples: CD, guest or drug, the physical mixture of the guest/CD and solid complex guest-CD. DSC analysis gives supporting evidence for the complexation of guest or drug with CD.

Ultraviolet-visible (UV-Vis) spectroscopy

Spectrophotometric methods are useful to determine the value of stability constant if the complexation events induce changes in the compound spectra as a function of the guest-host interaction. These changes in the compound spectra generally reflect an alteration in the microenvironment of the drug. The changes observed in UV and related processes are similar to those associated with the dissolution of the drug in a solvent of decreased polarity [51].

Differential solubility

Van Hees *et al.* determined the concentration of free and bound piroxicam from piroxicam-β-cyclodextrin complex using differential solubility method and compared these results with the results of conventional DSC. Bratu *et al.*, [52] prepared the inclusion complexes of β-cyclodextrin with fenbufen and ibuprofen by the two different methods such as co-precipitation and the freeze-drying methods and they used FTIR spectroscopy to characterize the inclusion complexes. They found the fundamental changes which appear in the FTIR spectra of inclusion complexes of fenbufen and ibuprofen are mainly in the C=O stretching region. These changes suggest drug-CD complex formation.

Applications

Cyclodextrins applications in the pharmaceutical industry

The uses and benefits of cyclodextrin complexation are bioavailability enhancement [53], active stabilization, odors or taste masking [54], irritation reduction [55] and material handling benefits [45, 56]. CD derivatives (hydroxypropyl-β-cyclodextrin and sulfobutylether-β-cyclodextrin) have been widely investigated for parenteral dosage forms. There are 30- 40 different drugs are now marketed as cyclodextrin complexes and few of them are listed in Table 5.

Table 5: Cyclodextrin containing pharmaceutical products

Drug/Cyclodextrin	Category	BCS Class	Trade Name/ Dosage form	Company/ Country
PGE2/βCD	-	-	Prostarmon E/ Sublingual tablet	Ono, Japan
PGE1/αCD	-	-	Prostavastin i.v./ Solutions and infusions	Ono, Japan Schwarz, Germany, USA
OP-1206/αCD	-	-	Opalmon/ Tablet	Ono Japan
Piroxicam/βCD	NSAID	II	Brexin, Flogene Cecladon/ Tablet and suppository liquid	Chiesi, Italy several European countries Aché, Brasil
Benexate HCl/βCD	Anti-ulcer	II	Ulgut Lonmiel/ Capsule	Teikoku, Japan Shionogi, Japan
Iodine/βCD	Antiseptic		Mena-Gargle/ Solution	Kyushin, Japan
Dexamethasone/βCD	Corticosteroid	I/III	Glymesason/ Ointment	Fujinaga, Japan
Nitroglycerin/βCD	Antianginal	II	Nitropen/ Sublingual tablet	Nihon Kayaku, Japan
Cefotiam-hexetil/αCD	Antibiotic	IV	Pansporin T/ Tablet	Takeda, Japan
Cephalosporin (ME 1207)/βCD	Antibiotic	-	Meiact/ Tablet	Meiji Seika, Japan
Tiaprofenic acid/βCD	NSAID	II	Surgamyl/ Tablet	Roussel-Maestrelli, Italy
Diphenhydramine, Chlortheophyllin/ βCD	Antihistaminic	I	Stada-Travel/ Chewing tablet	Stada, Germany
Chlordiazepoxide/ βCD	Anxiolytic	II	Transillium/ Tablet	Gador, Argentina
Hydrocortisone/ HPβCD	Glucocorticoids	II	Dexocort/ Solution	Actavis, Iceland
Itraconazole/HPβCD	Antifungal	II	Sporanox / Oral and i.v. Solutions	Janssen, Belgium, USA
Cisapride /HPβCD	Gastroprokineti-c agent	II	Propulsid/ Suppository	Janssen, Belgium
Nimesulide/βCD	NSAID	II	Nimedex/ Tablets	Novartis and others, Europe
Alprostadil/αCD	Endocrine-metabolic agent	-	Rigidur/ i.v. Solution	Ferring, Denmark
Nicotine/βCD	-	I	Nicorette/ Sublingual tablets	Pharmacia, Sweden
Chloramphenicol/ MβCD	Antibiotic	III	Clorocil/ Eye drop solution	Oftalder, Portugal
Diclofenac-Na/HPγCD	NSAID	II	Voltaren/ Eye drop solution	Novartis, France
17β-Estradiol/RMβCD	Estrogen steroid hormone	I	Aerodiol/ Nasal Spray	Servier, France
Indomethacin/HPβCD	NSAID	II	Indocid/ Eye drop solution	Chauvin, France
Omeprazole/βCD	Proton Pump Inhibitor	II	Omebeta/ Tablet	Betafarm, Germany
Voriconazole/SBEβCD	Antifungal	II	Vfend/ i.v. Solution	Pfizer, USA
Ziprasidone mesylate/ SBEβCD	Antipsychotic	II	Geodon, Zeldox/ i.m. Solution	Pfizer, USA & Europe
Mitomycin/HPβCD	Antineoplastic	-	MitoExtra Mitozytrex/ i.v. Infusion	Novartis, Switzerland
Tc-99 Teoboroxime/HPγCD	Radiopharmaceuticals	-	Cardiotec/ i.v. Solution	Bracco, USA
Meloxicam	NSAID	II	Mobitil/ Tablet and suppository	Medical Union Pharmaceuticals, Egypt
Aripiprazole/SBEβCD	Antipsychotic	IV	Abilify/ i.m. Solution	Bristol-Myers Squibb, USA Otsuka Pharm. Co., Japan

Applications of CDs can be summarized as follows

1. Enhancement of solubility of materials with low solubility in water;
2. Controlled release of drugs and flavors;
3. Catalytic action in a chemical reaction;
4. Protection of materials against oxidation and UV-degradation during storage or processing;
5. Conversion of liquid materials to dry form;
6. Stabilization of flavors and spices;
7. Masking of bitterness and the unpleasant odor of foods and drugs.

Research work on CD complexation

Several studies reported the cyclodextrin complexation of a variety of drugs for various purposes. A summary of recent research work on cyclodextrin complexation for enhancing the dissolution rate and bioavailability is given in Table 6.

Table 6: Summary of recent research work on cyclodextrin complexation

S.No.	Drug	Category of Drug	BCS Class	Cyclodextrin (CD)	Purpose/ Result	Ref. No
1.	Loteprednol etabonate	Anti-inflammatory Corticosteroid	II	γ -, HPβCD, Maltosyl-β- and Dimethyl-βCD	Higher solubility and stability was observed in Dimethyl β CD than HPβCD	[57]
2.	Tolbutamide	Anti-diabetic	II	βCD	Improved dissolution by the presence of CD and surfactant	[58]
3.	Omeprazole	Proton Pump Inhibitor	II	γCD	Improved dissolution rate prepared by co precipitation method	[59]
4.	Ofloxacin	Antibiotic	I	βCD	Enhanced solubility, but not photo stabilization	[60]
5.	Piroxicam	NSAID	II	HPβCD	Increased permeation and release of drug from the gel	[61]
6.	Sulfamethiazole	Sulfonamide antibiotic	II	βCD, HPβCD	Improved dissolution rate	[62]
7.	Ciprofloxacin	Antibiotic	IV	βCD	Conformation of existence of inclusion complexation	[63]
8.	Bromazepam	Antianxiety	-	βCD, HPβCD	Enhanced solubility	[64]
9.	Furosemide	Loop Diuretic	IV	HPβCD	Characterization of inclusion complexes by DSC and XRD	[65]
10.	Nifedipine	Antihypertensive	II	βCD, HPβCD and DMβCD	Enhanced solubility and photostability and characterization of inclusion complexes by DSC, XRD, and IR	[66]
11.	Nicardipine HCl	Antihypertensive	II	Triacetyl βCD	*In vitro* release was markedly retarded	[67]
12.	Natamycin	Antimycotic	II	βCD, γCD, HPβCD	Enhanced dissolution rate	[68]
13.	Nimodipine	Antihypertensive	II	βCD, HPβCD and HEβCD, MβCD	MβCD was found as efficient solubilizer	[69]
14.	β–lapachone	Antineoplastic	II	α-, β-, γ- and HPβCD	Improved solubility and bioavailability, complex formation proved by ^{1}H-NMR and fluorescence spectroscopy	[70]
15.	Artemisinin	Antimalarial	II	α-, β- and γ- CD	Enhanced solubility and dissolution rate	[71]
16.	Acitretin	Oral retinoid	IV	HPβCD and RMβCD	Enhanced solubility and photostability. characterization of inclusion complexes by IR, DSC, XRD	[72]
17.	Carbamazepine	Anticonvulsant	II	βCD	Improvement in release rate	[73]
18.	Dehydroepiandrosterone	Neurosteroid	II	αCD	Improved dissolution rate, solubility and bioavailability	[74]
19.	Lorazepam	Antianxiety	II	HPβCD/ HPγCD/ SBE-βCD/ MEβCD	Improved dissolution rates and bioavailability	[75]
20.	Fenoxaprop-p-ethyl	Herbicide	-	βCD/ HPβCD/ RMβCD	Enhanced dissolution rates and bioavailability	[76]
21.	Diazepam	Antianxiety	II	HPβCD/ HPγCD/ SBE-βCD/ MEβCD	Dissolution rate was markedly increased	[77]
22.	Lorazepam	Antianxiety	II	HPβCD	Improved aqueous solubility and dissolution rate	[78]
23.	Lamotrigine	Anticonvulsant	II	βCD	Improved solubility and bioavailability	[79]
24.	Doxepin	Antidepressant	I	βCD	Enhanced dissolution rate	[80]
25.	Lovastatin and Simvastatin	HMG-CoA reductase inhibitors	II	RMβCD	Improved solubility	[81]
26.	Irbesartan	Antihypertensive	II	βCD PEG 4000 PVP K90	Improved aqueous solubility, dissolution rate	[82]
27.	Carvidilol	Antihypertensive	II	βCD Citric acid	Improved aqueous solubility, dissolution rate	[83]
28.	Aceclofenac	NSAID	II	βCD HPβCD	Enhancement in solubility and dissolution rate	[84]

29.	Hydrocortisone/ Amphotericin B/ Diclofenac sodium/ Indomethacin	Glucocorticoids/ Antifungal/ NSAID/ NSAID	II/IV/II/II	γCD 2-HPγCD	Enhanced permeation	[85]
30.	Noscapine	Antitussive	II	βCD	Improved aqueous solubility and pharmacokinetics	[86]
31.	Bupivacaine HCl	Local anaesthetics	-	βCD βCD - epichlorohydrin	Improved buccal delivery and	[87]
32.	Felodipine	Antihypertensive	II	Cyclodextrins	FTIR, DSC, and XRPD showed the confirmation of complexation of cyclodextrin with felodipine	[88]
33.	Naproxen	NSAID	II	Amorphous β-cyclodextrin-epichlorohydrin	Both cyclodextrin polymers were more effective in improving the naproxen dissolution properties	[89]
34.	Warfarin	Anticoagulant	II	βCD	Improvement in the in vitro bioavailability of the drug in acidic media	[90]
35.	Valsartan	Antihypertensive	II	βCD, HP βCD, PVP K30	Solubility and dissolution rate was increased	[91]
36.	Nimesulide	NSAID		βCD, HP βCD, Poloxamer 407 PVP K30	Enhancement in solubility and dissolution rate	[92]
37.	Etoricoxib	NSAID	II	βCD, HP βCD, Poloxamer 407 PVP K30	Solubility and dissolution rate was enhanced	[93]
38.	Aripiprazole	Antipsychotic	IV	HP βCD	Increased solubility	[94]
39.	Raloxifene	Selective estrogen receptor modulator	II	HPβCD	Increased solubility	[95]
40.	Efavirenz	Antiretroviral	II	βCD, Soluplus, PVP K30	Enhancement in solubility	[96]
41.	Limaprost	Peripheral vasodilator	I	β cyclodextrin	Addition of *β*-CD as an excipient to tablets of lyophilized composites remarkably improved the stability of limaprost	[97]
42.	Pioglitazone	Antihyperglycemic	II	β cyclodextrin	Enhanced solubility, dissolution rate, and bioavailability	[98, 99]
43.	Domperidone	Antiemetic	II	Hydroxypropyl-β-cyclodextrin	Enhanced solubility and dissolution rate	[100]
44.	Atorvastatin	HMG CoA reductase inhibitors	II	B-cyclodextrin	Fast absorption and increased oral bioavailability of atorvastatin	[101]
45.	Ritonavir	Antiretroviral	II	βCD, Soluplus, PVP K30	Enhancement in solubility and dissolution rate	[102]
46.	β- Carotene	Provitamin A	II	β-CD	Increase in solubility	[103]
47.	Norfloxacin	Antibiotic	II	βCD, HP βCD	Inclusion complexes of HPβCD gave higher solubility than β-CD	[104]
48.	Ziprasidone	Antipsychotic	II	Kollidon, Soluplus, Pluronic, and HPβCD	Increased solubility	[105]

CONCLUSION

The versatility of cyclodextrins and modified cyclodextrins is demonstrated in their range of applications in cosmetics, food and drug products. In the pharmaceutical industry, cyclodextrins have mainly been used as complexing agents to increase the aqueous solubility of poorly soluble drugs, and to increase their bioavailability and stability but sometimes as stabilizers or to reduce local drug irritation. Several studies reported the cyclodextrin complexation of a variety of drugs for various purposes. Cyclodextrins in drug formulation development is gaining the interest because of multiple advantages; the same is reflected in high approval rates and availability of these products in different regulatory markets.

DECLARATIONS

Conflict of interest: The Author(s) declare(s) that they have no conflicts of interest to disclose.

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