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Article

Cyclodextrins and ternary complexes: technology to improve solubility of poorly soluble drugs

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Cyclodextrins (CDs) are cyclic oligosaccharides composed of D-glucopyranoside units linked by glycosidic bonds. Their main property is the ability to modify the physicochemical and biological characteristics of low-soluble drugs through the formation of drug:CD inclusion complexes. Inclusion complexation requires that host molecules fit completely or partially within the CD cavity. This adjustment is directly related to the physicochemical properties of the guest and host molecules, easy accommodation of guest molecules within the CD cavity, stoichiometry, therapeutic dose, and toxicity. However, dosage forms may achieve a high volume, depending on the amount of CD required. Thus, it is necessary to increase solubilization efficiency in order to use smaller amounts of CD. This can be achieved by adding small amounts of water-soluble polymers to the system. This review addresses aspects related to drug complexation with CDs using water-soluble polymers to optimize the amount of CD used in the formulation in order to increase drug solubility and reduce dosage form volume.

Uniterms: Cyclodextrins. Ternary complexes. Drugs/complexation. Water-soluble polymers/use. Drugs/solubility. Inclusion complexe.

Ciclodextrinas (CDs) são oligossacarídeos cíclicos, compostos por unidades D-glicopiranosídicas ligadas entre si por meio de ligações glicosídicas e sua principal propriedade está na capacidade de alterar as características físico-químicas e biológicas de fármacos com baixa solubilidade por meio da formação de complexos de inclusão fármaco:CD. Para a formação dos complexos de inclusão a molécula hospedeira necessita ajustar-se total ou parcialmente no interior da cavidade da CD, onde este ajuste está diretamente ligado a propriedades físico-químicas da molécula hóspede e hospedeira, facilidade de alojamento da molécula hóspede no interior da cavidade da CD, estequiometria, dose terapêutica e toxicidade. No entanto, as formas farmacêuticas podem atingir um elevado volume, em função da quantidade de CD requerida, sendo necessário aumentar sua eficiência de solubilização para que seja possível utilizar menores quantidades das mesmas. Isso pode ser obtido com a inclusão de pequenas quantidades de polímeros hidrossolúveis ao sistema. Nessa revisão, são abordados aspectos relacionados à complexação de fármacos com ciclodextrinas empregando-se polímeros hidrossolúveis para otimização da quantidade de CD utilizada na formulação, com a finalidade de aumentar a solubilidade do fármaco e reduzir o volume das preparações.

Unitermos: SCiclodextrinas. Complexos ternários. Fármacos/complexação. Polímeros hidrossolúveis/uso. Fármacos/solubilidade. Complexos de inclusão.

INTRODUCTION

Among several factors, solubility in water is of paramount importance in the development of a sufficiently safe and effective dosage formulation, because preparation, absorption and even the biological activity of a drug are all dependent on its solubility. However, the amount of lipophilic molecules used in treatment is relatively high and tends to increase, considering that many different drugs have low solubility (Lipinski, 2000; Grant, Zhang, 2011).

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Thus, use of cyclodextrins (CDs) is one of several technologies available to improve the solubility of poorly water-soluble drugs. The most remarkable property of CDs is their ability to modify the physicochemical characteristics of molecules that are accommodated within their internal cavity to form the so-called inclusion complexes (Loftsson, Brewster, 1997; Tsai *et al*., 2010).

Typical characteristics of formulations containing inclusion complexes include a faster dissolution rate and shorter drug release time, as well as more efficient absorption. This translates into greater oral bioavailability of the drugs involved and an increase in biological activity, which may result in a reduction in drug dosage (Valle, 2004; Garnero *et al*., 2010).

However, the use of CDs is limited in some cases, because guest molecules need to fit completely or partially within the CD cavity. This adjustment is directly related to the physicochemical properties of the guest and host molecules, easy accommodation of guest molecules within the CD cavity, stoichiometry, therapeutic dose, and CD toxicity (Loftsson, Brewster, 1997).

An increase in formulation volume represents a critical stage in the applicability of CD inclusion complexes. We can consider that 1 g of a solid complex corresponds to 100-250 mg of a drug (when the molecular weights of the drug and the CD are 200-400 g/mol and 1200-1500 g/mol, respectively). Therefore, the use of CDs in oral solid dosage forms is limited to drug doses less than 200 mg that have good complexation properties (Loftsson, Brewster, 1996).

A strategy often used to improve complexation between drugs and CDs is the addition of small amounts of water-soluble polymers to the system, which causes an increase in solubilization efficiency, while requiring smaller amounts of CD (Loftsson, Fridriksdóttir, 1998; Mura *et al.*, 2001). These results can be attributed to the synergistic effect of polymer and CD solubilization on the formation of drug:CD:water-soluble polymer ternary complexes (Carrier *et al*., 2007).

Water-soluble polymers are able to interact with drugs, CD molecules, and even with drug:CD complexes (Loftsson *et al*., 1996). The mechanism involved in increasing CD complexation efficiency in the presence of water-soluble polymers is not yet fully understood; however, it is believed that water-soluble polymers can reduce CD mobility and increase the complex solubility (Veiga *et al.*, 2006)**.** The addition of water-soluble polymers has been shown to increase drug bioavailability and cause an up to 80% reduction in the amount of CD required (Loftsson, Fridriksdóttir, 1998; Mura *et al.*, 2001).

The purpose of this study is to outline the relevance of using CDs to improve the solubility of poorly water-soluble drugs, with special emphasis on their structural characteristics, physicochemical properties, productive processes, toxicity, derivatives, and use in the pharmaceutical industry. Despite the recognized benefits of ternary (drug:CD:water-soluble polymer) complexes, there have been no reviews on the subject in the scientific literature. This review addresses aspects related to drug complexation with CDs using water-soluble polymers to increase drug solubility and reduce dosage form volume.

CYCLODEXTRINS (CDs)

CDs are cyclic oligosaccharides composed of D-glucopyranoside units (glucose) linked by α-1.4 glycosidic bonds. They are obtained from biotechnological processes involving the enzymatic degradation of corn starch and offer greater yield with 6, 7 and 8 units of glucose, known as α-CD, β-CD and γ-CD, respectively (Szejtli, 1998; Heise *et al*., 2010) (Figure 1).

CDs with less than 6 units of glucose do not exist for stoichiometric reasons and those with more than 8 units offer low yields and weak complexing properties, thus making them unsuitable for the pharmaceutical industry (Loftsson, Brewster, 1997; Jug *et al*., 2011).

According to Szejtli (2004), the history of CDs can be divided into three distinct periods (Figure 2), as follows: (a) discovery, from 1891 to 1930; (b) development, from 1930 to 1970, and (c) industrial use, from 1970 onwards.

In the beginning of the industrial production of CDs

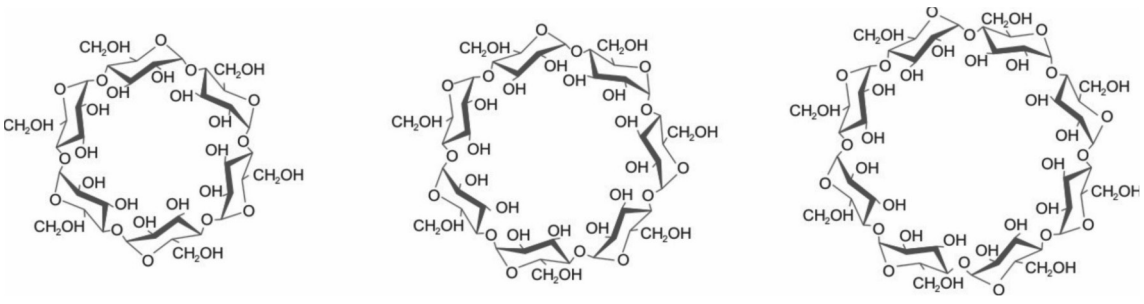

FIGURE 1 - Chemical structure of α-, β- and γ-cyclodextrins, respectively. Adapted from Veiga *et al*., 2006.

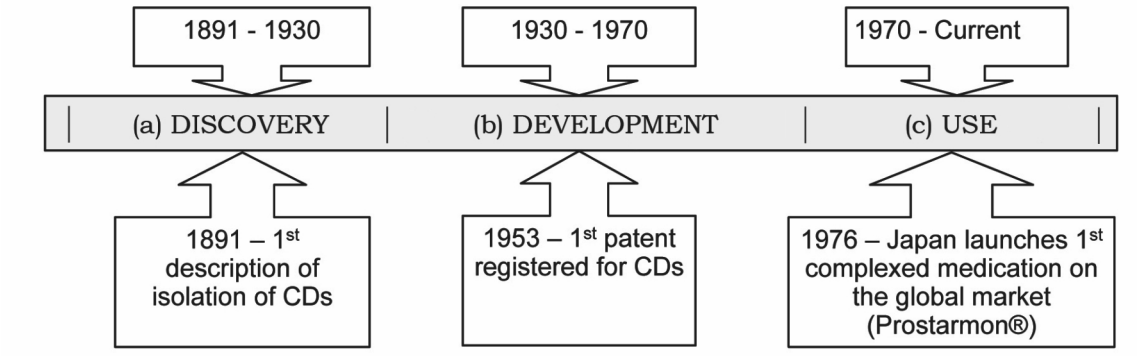

FIGURE 2 - Timeline of relevant events in the history of cyclodextrins (CDs).

(treating the starch with *Bacillus macerans)*, the final product was a mixture of α-CD (60%), β-CD (20%) and γ-CD (20%), as well as small amounts of CDs with more than 8 units of glucose. However, purity was a major hurdle, becoming a critical issue that had to be overcome before the use of CDs could be made possible (Loftsson, Duchêne, 2007).

An alternative to address the issue of impurity was the use of biotechnological processes, which, along with other innovations, led to an increased purity of the resulting CD, thus making their use as pharmaceutical excipients feasible (Loftsson *et al*., 2005b).

Cyclodextrin structure

Due to the lack of *free rotation* about the *glycosidic bonds* and chain conformation of glucose units, CDs display a torus-like or hollow *truncated cone shape*. In this peculiar structure (Figure 3), the secondary hydroxyl groups can be found at the broadest end, bonded to the C2 and C3 atoms of the glucose units, while the primary hydroxyl groups are located at the narrower opposite end, bonded to the C6 atoms of the glucose units (Bekers *et al*., 1991; Loftsson *et al*., 2004; Veiga *et al*., 2006).

The molecular arrangement of CDs is a result of the free rotation of primary hydroxyl groups, which reduces the diameter of the cavity at its narrowest end, i.e., the end with the smallest molecular diameter. CH groups bonded to the H1, H2 and H4 hydrogen atoms can be found on the outside of the molecule, while the hydroxyls find their way outside the truncated cone, thus becoming the external layer of hydrophilic CDs (Brewster, Loftsson, 2007).

In the internal layer, CH groups are bonded to the H3 and H5 hydrogen atoms by glycosidic oxygen bridges. Intramolecular hydrogen bonds between the C2-OH groups of a glucose unit and the C3-OH groups of an adjacent glucose unit stabilize the CD structure, making it rigid (Loftsson, Brewster, 1997; Brewster, Loftsson, 2007).

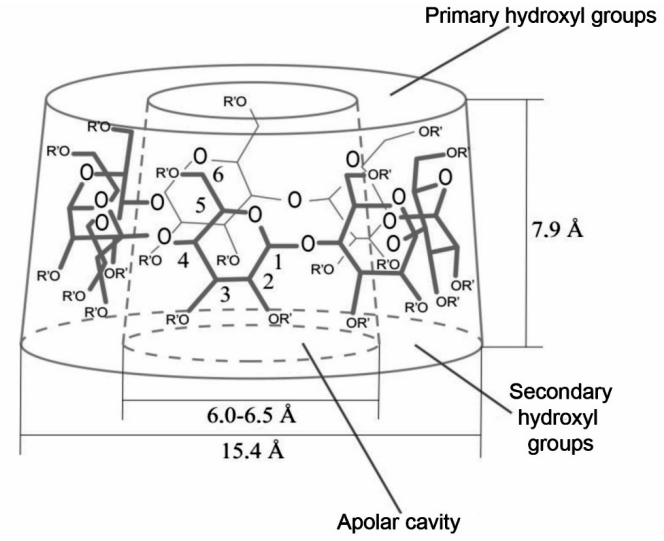

FIGURE 3 - β-cyclodextrin (β-CD) structure, with representations of its size and position of hydroxyl groups.

Properties

The most important property of CDs is their ability to modify the physicochemical and biological characteristics of drugs. Their cavity can establish interactions through intermolecular forces with molecules, ions or radicals, acting as a host substance. The resulting molecular complex is called an inclusion compound or a supramolecular compound (Loftsson, Brewster, 1997; Li *et al*., 2010).

Table I details several characteristics of natural CDs. Table II lists the solubility of natural CDs in water and other organic solvents.

Of all natural CDs, β-CD has the lowest solubility, due to the high number of intramolecular hydrogen bonds among secondary hydroxyl groups within the molecule. These interactions make the structure rigid and prevent hydration by water molecules (Szejtli, 1994; Loftsson *et al*., 2005b).

TABLE I - Properties of natural cyclodextrins (CDs) (Adapted from: Szejtli, 1994; Veiga *et al*., 2006; Brewster, Loftsson, 2007; Wintgens and Amiel, 2010)

Property	α-CD	β-CD	γ-CD
Glucose units	6	7	8
Molecular weight (g/mol)	972	1135	1297
External diameter (Å)	14.6	15.4	17.5
Internal diameter (Å)	4.7-5.3	6.0-6.5	7.5-8.3
Height (Å)	7.9	7.9	7.9
Cavity volume (Å)	174	262	427
Shape of crystals	Hexagonal lattice	Monocyclic parallelograms	Quadratic prism
pKa by potentiometry (25°C)	12.333	12.202	12.081
Diffusion constant at 40°C (m/s)	3.443	3.232	3.000
Hydrolysis by α-amylase	Negligible	Slow	Fast

TABLE II - Solubility (g/100 mL) of natural cyclodextrins (CDs) (Adapted from: Szejtli, 1994; Loftsson *et al*., 2005b)

Solvent	α-CD	β-CD	γ-CD
Water (25°C)	14.5	1.85	23.2
Ethyl ether	Insoluble	Insoluble	Insoluble
Chloroform	Insoluble	Insoluble	Insoluble
Isopropanol	Insoluble	Insoluble	> 0.1
Acetone	Insoluble	Insoluble	> 0.1
Ethanol	Insoluble	Insoluble	> 0.1
Methanol	Insoluble	Insoluble	> 0.1
Glycerin	Insoluble	4.3	___
Propylene glycol	1	2	___
Dimethyl sulfoxide	2	35	___
Pyridine	7	37	___
Ethylene glycol	9	21	___
Dimethylformamide	54	32	___

In α-CD, only 4 of 6 possible hydrogen bonds can be established, because one of the glucose units is in a distorted position. The *γ-CD is a noncoplanar, more flexible structure, thus being the most* soluble of the three CDs (Loftsson *et al*., 2005b).

CDs are stable in alkaline medium, hydrolyze in strongly acidic medium and are resistant to enzymatic degradation by β-amylase, although CDs, particularly γ-CD, are susceptible to attack by α-amylase. CDs can form stable hydrates and their stability is identical to that of starch; thus, they can be stored for years without suffering any degradation (Szejtli, 1994).

Toxicity

The safety profile of natural CDs and their derivatives has been widely studied, and they have generally proven to be atoxic, because they only manage to cross biological membranes with some degree of difficulty. Thus, oral administration of CDs should not be regarded as a problem (Valle, 2004).

Conversely, parenteral administration of γ-CD, 2-hydroxypropyl-β-CD (2-HP-β-CD), sulfobutylether-β-CD (SBE-β-CD), sulfate-β-CD and maltose-β-CD is safe to some degree. Studies have proven that several alkylating derivatives of α- and β-CDs are not recommended for use via this route of administration, because they show nephrotoxicity and hemolytic activity (Loftsson, Duchêne, 2007).

CYCLODEXTRINS AND THEIR DERIVATIVES

It is possible to introduce chemical modifications into the primary and secondary hydroxyl groups of natural CDs through the bonds of several functional groups, thus

improving solubility, toxicity and increasing the inclusion capacity of original CDs and their derivatives (Uekama, Irie, 2004).

CD derivatives can be obtained by substitution with methyl, ethyl, carboxymethyl, hydroxyethyl, hydroxypropyl, sulfobutyl, or saccharide groups or even by polymerization of CDs. Many derivatives of natural CDs have been synthesized and characterized, but only a few are being used in studies involving new pharmaceutical excipients, including derivatives with methyl, hydroxypropyl and sulfobutyl ether substitutes (Mosher, Thompson, 2002; Uekama, Irie, 2004; Veiga *et al.*, 2006).

HYDROPHILIC DERIVATIVES

Methylated derivatives

These derivatives can be obtained by selective methylation of all secondary hydroxyl groups in C2 and all primary hydroxyls in C6, methylation of all hydroxyl groups, including those in C3, or even randomly, in the C2, C3 or C6 positions (Imai *et al*., 1984; Veiga *et al*., 2006).

The methylated derivatives show alterations in their physical and chemical properties, as well as structural alterations when compared to natural CDs (Table III). Solubility in water and organic solvents is significantly greater; however, water solubility decreases as the temperature increases (a reaction similar to that of nonionic surfactants). These derivatives exhibit reasonable stability in alkaline medium and are hydrolyzed by strong acids, giving rise to linear oligosaccharides (Uekama, Irie, 2004; Veiga *et al*., 2006).

Dimethyl-β-CD is the least vulnerable to acid hydrolysis. At the opposite extreme, trimethyl-γ-CD is the most susceptible, due to severe distortion in the configuration of the CD ring (Uekama, Irie, 2004).

Hydroxyalkyl derivatives

Hydroxyalkyl derivatives are one of the derivative groups most commonly used in drug complexation, being represented primarily by 2-hydroxyethyl-β-CD (2-HE-β-CD), 2-HP-β-CD, 3-hydroxypropyl-β-CD (3-HP-β-CD), and 2.3-dihydroxypropyl-β-CD (2.3-DHP-β-CD). Obtaining hydroxylated CDs from α-CD and γ-CD shows no significant benefits compared to β-CD derivatives (Uekama, Otagari, 1998).

Obtaining hydroxyalkyl derivatives is a non-selective process that occurs by the condensation of hydroxyalkylating agents (hydroxypropyl and hydroxyethyl) in alkaline medium. The product of the condensation reaction is invariably a mixture of the respective derivatives, with various degrees of substitution. These mixtures not only prevent recrystallization, but also result in the conversion of the drug from a crystalline state into an amorphous state (Uekama, Otagari, 1998; Uekama *et al*., 2006).

The degree of substitution (S) expresses the number of hydroxyl groups replaced in a unit of glucose, which may range from 1 to 3, and the average degree of substitution (DS) expresses the average number of hydroxyls replaced per unit of glucose, which is between 0 and 3. The average molar substitution (MS) expresses the number of hydroxypropyl groups per unit of glucose (Veiga *et al*., 2006).

Hydroxyalkyl derivatives have high water solubility and low hygroscopicity compared to the original CD; thus, in the presence of high humidity (> 90%), they dissolve in water adsorption. They have a surface tension identical

TABLE III - Physicochemical properties of cyclodextrins (CDs) and their methylated derivatives. Source: Duchêne and Wouessidjewe, 1990a and 1990b

CD	Glucose unit	Molecular weight	Internal cavity diameter (Å)	Melting point (°C)	Aqueous solubility 25 °C (g/100 mL)	Water content	Surface tension (mN/m)
α –CD	6	973	5	275	15	10	71
Dimethyl-α-CD	6	1141	5	260-264	----	----	65
Trimethyl-α-CD	6	1225	3-6	205	20	10	54
β-CD	7	1153	6	280	1.85	10	71
Dimethyl-β-CD	7	1331	6	295-300	57	1	62
Trimethyl-β-CD	7	1430	4-7	157	31	10	56
γ-CD	8	1297	8	275	23	10	71
Dimethyl-γ-CD	8	1521	8	255-260	----	----	60
Trimethyl-γ-CD	8	1634	5-9	135	48	----	56

to that of natural CDs, but this characteristic is altered in derivatives with high degrees of substitution (Uekama, Otagari, 1998; Uekama *et al*., 2006).

Ramified derivatives

This class of CDs is obtained by chemical or enzymatic synthesis, where the substitution of primary or secondary hydroxyl groups for mono- or disaccharides through α-(1.6) bonds results in the formation of ramified CDs with high water solubility and chemical purity (Veiga *et al*., 2006).

Although ramified CDs have physical and chemical properties similar to those of natural CDs, such as surface tension and complexation capacity (Table IV), their solubility in water, as well as in aqueous solutions of ethanol, methanol, acetone, formaldehyde and ethylene glycol, is superior (Duchêne Wouessidjewe, 1990b).

HYDROPHOBIC DERIVATIVES

CDs and their derivatives are mainly used in the pharmaceutical industry to improve the solubility and dissolution speed of poorly soluble drugs by means of inclusion complexation. However, some CD derivatives act in an opposite manner, with the main function of controlling the dissolution speed of water-soluble drugs. These derivatives are represented by ethylated and acylated CDs (Uekama *et al*., 2006).

Ethylated derivatives

The aqueous solubility of CDs is reduced when their hydroxyl groups are replaced with alkyl groups larger than methyl, through an ether or ester bond. Solubility decreases proportionally to the rate of substitution, which increases in less polar solvents, thus presenting fewer hygroscopic characteristics and lower surface tension (Uekama *et al*., 2006; Mosher, Thompson, 2002).

Acylated derivatives

These are obtained by substitution of all β-CD hydroxyl groups for different alkyl chains, resulting in reduced aqueous solubility, melting point and rate of alkaline hydrolysis as the respective alkyl chain increases. In concentrated solutions of β-CD derivatives in organic solvents (ethanol, acetone or chloroform), the viscosity increases due to a gelation process occurring after the solvent has evaporated (Mosher, Thompson, 2002).

Differently from the ethylated β-CD derivatives, acylates are easily eliminated from the organism after alkaline hydrolysis, yielding the original CD (β-CD). This is an important factor in the event of enteral administration, because this CD is not toxic when administered by this route (Mosher, Thompson, 2002).

Ionizable derivatives

The substitution of CD hydroxyl groups for ionizable groups imparts hydrophilic characteristics to the new structure, as well as pH-dependent complexation capacity. In other words, solubility is low in acidic medium, becoming greater in neutral or alkaline media. This pH-dependent characteristic is a result of the ionization of the carboxylic groups that show a pKa value around 3.5 (Ma *et al*., 2000).

Among all ionizable CDs, one in particular stands out: SBE-β-CD. This is a polyanionic CD formed when the 2, 3 and 6 hydroxyl groups of β-CD glucose units are substituted for sulfobutyl ether groups, which are totally ionized over a broad pH range. They provide a negatively

TABLE IV - Physicochemical properties of cyclodextrins (CDs) and their ramified derivatives (Duchêne, Wouessidjewe, 1990a and 1990b)

Molecule	Glucose units	Molecular weight	Aqueous solubility 25 °C (g/100 mL)	Surface tension (mN/m)
α-CD	6	973	18.0	71
Glycosyl-α-CD	7	1135	89.0	----
β-CD	6	1135	18.5	71
Glycosyl-β-CD	8	1297	97.0	71
Diglycosyl-β-CD	9	1459	140	----
Maltosyl-β-CD	9	1459	50	70
Dimaltosyl-β-CD	11	1789	50	71
γ-CD	8	1297	23	71

charged polar head, attached to a hydrophobic tail, which is connected to the internal cavity (Stella *et al*., 2002).

SBE-β-CD has a peculiar structure, where substitute groups that exercise mutual electrostatic repulsion are in a favorable position for entry into the CD cavity. As a result, there is an increase in its hydrophobic properties and complexation capacity, which is the reason for its wide-ranging pharmaceutical application. Another relevant attribute is the fact that the charge of the CD molecule is located at a site as far as possible from the hydrophobic cavity, thus intensifying its solubilizing capacity (Zia *et al*., 2001).

TABLE V - Details of some characteristics of cyclodextrin (CD) derivatives

Derivative	Method	Characteristics	Advantages	Disadvantages
Hydrophilic derivatives				
Methylates	Methylation	Water solubility decreases as temperature increases	Solubility in water greater than natural CD; very soluble in organic solvents	Hydrolyzed in the presence of strong acids
Hydroxyalkyl	Condensation of hydroxyalkylating agents in alkaline medium	Surface tension identical to that of natural CD. Lower surface tension observed only in derivatives with high rate of substitution	Highly soluble in water; low hygroscopicity	In the presence of humidity > 90%, they dissolve in water adsorption
Ramified	Chemical or enzymatic synthesis	Substitution of primary and secondary hydroxyls for mono- and disaccharides through α-(1.6) bonds. They present three types of hydrolyzable glycosidic bonds: α-(1.6) between the CD ring and the ramification unit, α-(1.4) of the glucose units of lateral chain, and α-(1.4) bonds of the chain ring	High solubility in water and aqueous solutions of methanol, ethanol, acetone, formaldehyde and ethylene glycol	Chemical degradation increases as pH decreases
Hydrophobic derivatives				
Ethylates	Partial ethylation of hydroxyl groups	Solubility decreases proportionally to the rate of substitution and increases in less polar solvents	Prolonged drug release time	Reduction in aqueous solubility of CDs
Acylates	Substitution of hydroxyl groups for different alkyl chains	Aqueous solubility, melting point and rate of alkaline hydrolysis decreases as alkyl chain increases	Easily eliminated from the organism after alkaline hydrolysis	High viscosity in solvents such as ethanol, acetone, and chloroform. Gelation occurs after the solvent evaporates
Ionizable	Substitution of hydroxyl groups for ionizable groups	Hydrophily and capacity for pH-dependent complexation	High solubility in neutral or alkaline pH	Low solubility in acidic pH

FORMATION OF INCLUSION COMPLEXES

The truncated cone structure of CDs, which are open at both ends, enables the inclusion of a wide variety of organic molecules (apolar drugs) in their central cavities. Host-guest complexes, or drug-CD complexes also known as inclusion complexes or compounds, result from the association between host molecules (CDs) and encapsulated molecules (drugs) (Szejtli, 1998; Tsai *et al*., 2010).

The formation of a complex (Figure 4) in an aqueous solution takes place when water molecules are removed from the apolar cavity of CDs (which are in an energetically unfavorable environment due to the nature of the polar-polar interaction) and substituted for a guest molecule or lipophilic group with polarity, size and shape compatible with that of the CD structure (Szejtli, 1998; Rafati *et al*., 2009).

This process is energetically favorable and contributes to an increase in complex stability, because it causes changes in enthalpy and a reduction in the total energy of the system (Saenger, 1980; Veiga *et al*., 2006).

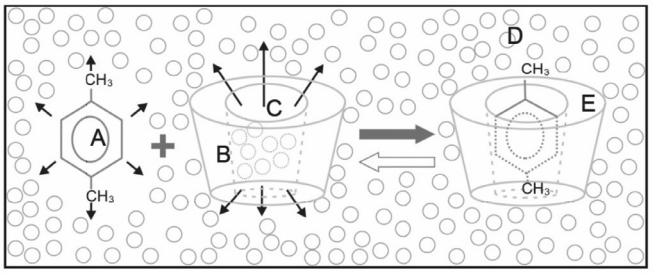

FIGURE 4 - Graphical representation of the formation of inclusion complexes. A: drug molecule; B: cyclodextrin (CD) molecule; C: CD cavity; D: water molecules; E: drug-CD complex. Adapted from: Szejtli, 1998; Veiga *et al*., 2006.

Furthermore, other forces are involved in the formation and stabilization of inclusion complexes, such as van der Waals interactions (dipole-dipole interaction and London dispersion forces), 3-center, 2-electron bonds (between guest molecule and CD hydroxyl groups), hydrophobic interactions, release of deformation energy from the macromolecular ring of CDs, and steric effects (Saenger, 1980; Bekers *et al*., 1991; Szejtli, 1998; Bibby *et al*., 2000; Flasinski *et al*., 2010).

The complexes formed are usually more water soluble than the active ingredients they contain as well as more stable in solution form. They also dissociate easily in order to release the drug molecule (Lofttson *et al*., 2005 a, b; Wintgens, Amiel, 2010).

Obtaining complexes with CDs may occur in the liquid, semi-solid or solid phases. In the liquid phase, the following methods have been suggested: coprecipitation, coevaporation, neutralization, freeze-drying, and drying by pulverization. In the solid phase, the most common methods are grinding or supercritical fluid technology, while malaxation is employed in the semi-solid phase (Valle, 2004).

Drug-CD complexes have an extremely rapid and dynamic formation and dissociation kinetics in solution form, continually forming and dissociating by covalent bonds. Complex dissociation is expressed quantitatively by the dissociation constant (Kc), where [drug-CD], [drug] and [CD] are the concentrations of the complexed drug, the free drug and the free CD, respectively. This dissociation constant ranges from 0 to 10^5, where 0 indicates that the drug is incapable of forming a complex with CD and 10^5 indicates the upper limit of drug-CD complexes (Tompson, 1997; Stella, Rajewski, 1997; Veiga *et al*., 2006; Loftsson *et al*., 2007; Rafati *et al*., 2009).

$$Kc = \frac{[\text{drug-CD}]}{[\text{drug}]\,[\text{CD}]} \qquad (1)$$

The dissociation kinetics will be inversely proportional to the strength of the bond between the CD and the drug, i.e., the slower the dissociation kinetics, the stronger the drug-CD bond (Kc). Even in this situation, the dissociation velocity of the complexes is considered to be practically instantaneous (Loftsson *et al*., 2007).

There are several techniques for characterizing inclusion complexes, with X-ray diffraction, Fourier transform infrared (FTIR) spectroscopy, thermal analysis, Raman spectroscopy, solubility and scanning electron microscopy (SEM) being the most significant ones (Veiga *et al*., 2006; Heise *et al*., 2010; Tsai *et al*., 2010; Jug *et al*., 2011).

Molecular modeling studies have gained strong emphasis in the investigation of complexation with CDs. This allows the construction of three-dimensional models of drug-CD complexes, visualization of structural integrity, and intra- and intermolecular interactions (Seridi, Boufelfel, 2011; Leila *et al*., 2011; Eid *et al*., 2011; Ge *et al*., 2011; Mishur *et al*., 2011).

CYCLODEXTRINS IN THE PHARMACEUTICAL INDUSTRY

CDs and their derivatives are present in several areas, most notably in the pharmaceutical industry, where they are extensively used because of their complexing

properties that are capable of modifying the physicochemical characteristics of poorly water-soluble drugs, thus changing the dissolution profile of their solid dosage forms (Loftsson, Duchêne, 2007).

The first pharmaceutical product using CDs in its formulation was E2/β-CD prostaglandin, in the form of a sublingual tablet, which was launched in Japan in 1976. The use of CDs for the purpose of modifying drug properties is a reality in the pharmaceutical industry, and currently, it is possible to name about 40 products formulated with CDs on the global market, especially in Europe, Japan, and USA. Table VI details several CD-containing pharmaceutical products (Loftsson *et al*., 2005 b; Loftsson, Duchêne, 2007).

TABLE VI - Pharmaceutical products containing cyclodextrins (CDs) (Loftsson *et al*., 2004; Szejtli 2004; Loftsson *et al*., 2005 a, b; Loftsson, Duchêne, 2007)

DRUG / CD	TRADE NAME	DOSAGE FORM	COUNTRY
α-CD			
Alprostadil (PGE1)	Provastatin®, Rigidur®	Solution, intravenous solution	Japan, Europe, USA
OP – 1206	Opalmon®	Tablet	Japan
Cefotiam hexetil hydrochloride	Pansporin T®	Tablet	Japan
β-CD			
Benexate hydrochloride	Ulgut®, Lonmiel®	Capsule	Japan
Cephalosporin (ME 1207)	Meiact®	Tablet	Japan
Chlordiazepoxide	Transillium®	Tablet	Argentina
Dexamethasone	Glymesason®	Cream	Japan
Diphenhydramine hydrochloride, Chlorotheophylline	Stada-Travel®	Sublingual tablet	Europe
Iodine	Mena-Gargle®	Solution	Japan
Nicotine	Nicorette®, Nicogum®	Sublingual tablet, chewing gum	Europe
Nimesulide	Nimedex®	Tablet	Europe
Nitroglycerin	Nitropen®	Sublingual tablet	Japan
Omeprazole	Omebeta®	Tablet	Europe
PGE2	Prostarmon E®	Sublingual tablet	Japan
Piroxicam	Brexin®, Flofene®, Cicladol®	Tablet, suppository, solution	Europe and Brazil
Tiaprofenic acid	Surgamyl®	Tablet	Europe
2-hydroxypropyl-β-CD			
Cisapride	Prepulsid®	Suppository	Europe
Itraconazole	Sporanox®	Oral solution and intramuscular injection	Europe, USA
Mitomycin	Mitozytrex®	Intravenous infusion	Europe, USA
Methyl-β-CD			
Chloramphenicol	Clorocil®	Ophthalmic solution	Europe
17β-estradiol	Aerodiol®	Nasal spray	Europe
Sulfobutylether-β-CD			
Voriconazole	Vfend®	Intravenous solution	Europe, USA
Ziprasidone mesylate	Geodon®, Zeldox®	Intravenous solution	Europe, USA
2-hydroxypropyl-γ-CD			
Diclofenac sodium	Voltaren®	Ophthalmic solution	Europe
Tc-99m teoboroxime	Cardiotec®	Intravenous solution	USA

FORMATION OF TERNARY COMPLEXES

When a water-soluble polymer, a CD and a drug are mixed together in a solution to obtain the so-called ternary complexes, it is possible to increase drug solubilization, when compared to the polymer and CD separately, which is a result of the synergistic effect between these components (Loftsson *et al*., 1994). An example is the synergistic effect resulting from the addition of hydroxypropyl methylcellulose (HPMC) to the complex formed by SBE-β-CD and carbamazepine, with a consequent increase in drug solubility in the resulting ternary complex (Smith *et al*., 2005).

Formulations containing drug:CD complexes with the addition of a water-soluble polymer have proven to be capable of increasing the bioavailability of formulations while reducing the amount of CD by up to 80% (Loftsson, Fridriksdóttir, 1998; Mura *et al.*, 2001). In the presence of water, the polymer aids in the wettability of particles, resulting in accelerated dissolution and increased amount of drug delivered *in vitro* (Lahiani-skiba *et al.*, 2006).

The interaction of water-soluble polymers with drug molecules may occur by means of ion-ion, ion-dipole and dipole-dipole electrostatic bonds, van der Waals force, or 3-center, 2-electron bonds (Ribeiro *et al*., 2003). Similarly, the interaction between polymers and CDs and drug:CD complexes begins to occur on the external surface of the CD molecule. CDs, polymers and drug:CD complexes form aggregates capable of solubilizing drugs and other hydrophobic molecules (Loftsson *et al.,* 2007), as shown in Figure 5.

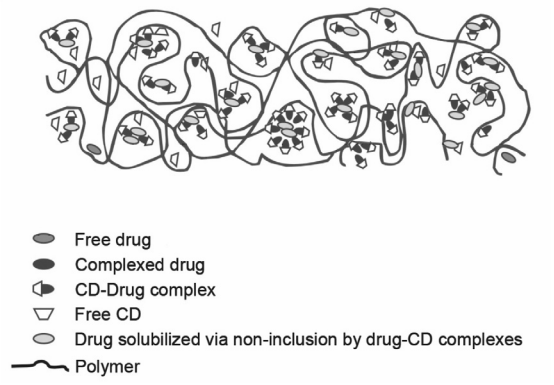

FIGURE 5 - Representation of ternary complex formation between drugs, cyclodextrins (CDs) and water-soluble polymers. Source: Veiga *et al*., 2006.

Several types of interactions between polymers and drugs may be established as a result of the structural difference and polarity of CD molecules, which may give rise to various complexation efficiencies. Povidone (PVP) and HPMC polymers were evaluated in the complexation of vinpocetine with β-CD and SBE-β-CD. The best complexation efficiency results were obtained for PVP with β-CD and for HPMC with SBE-β-CD (Ribeiro *et al*., 2003).

The resulting chemical structure of the drug is still unknown, as is the nature of the interaction between CDs and the water-soluble polymer, but it is recognized that, in aqueous solutions, polymers stabilize micelles and other types of aggregates, reduce CD mobility and increase the solubility of complexes by changing the hydration properties of CD molecules (Loftsson *et al.*, 2005b).

This process can be accelerated by heating the ternary system. Thus, it is possible to activate the bonds between system components during the preparation of complexes by heating them in an autoclave (120 to 140 ºC) for 20 to 40 minutes, in an ultrasound bath (over 30 ºC) for 1 hour, or even with microwaves at 40 ºC for 5 minutes (Loftsson *et al.*, 2005b).

Thermodynamic parameters (entropy and enthalpy) prove that different forces and/or mechanisms are at play in the formation of the complex, depending on the presence or absence of a polymer. Addition of polymers changes the entropy (ΔS^o) of the system, which becomes more negative, indicating the formation of a more organized structure with greater enthalpy (Loftsson *et al*., 1994).

Studies have proven that HPMC and PVP increase the complexation of hydrocortisone, dexamethasone and naproxen with β-CD (Ammar *et al*., 2006). Valero and colleagues (2003) observed that, at low PVP concentrations, the complexation process occurs entropically, and in larger proportions, it occurs enthalpically.

COMPLEXATION EFFICIENCY AND THE STABILITY CONSTANT

The stability constant (K_C), calculated from the phase solubility diagram (drug concentration x CD concentration), can be considered an apparent stability constant for several complexes, describing the combined effect of various structures on the solubility of a drug. Accordingly, a definition for complexation efficiency (CE) as a more precise method for evaluating the solubilizing effect of CDs has been proposed (Loftsson *et al*., 2007).

The stability constant of a complex is determined from the slope of the phase diagram and the intrinsic solubility of a drug (S_0) (Equation 1). Theoretically, the intersection (S_{int}) of the phase solubility diagram should be identical to S_0. However, drugs with an aqueous solubility of less than 0.1 mM show an intersection in the phase solubility diagram that is generally much greater than S_0,

thus resulting in imprecise K_C values. Therefore, CE is calculated from the slope of phase solubility diagrams and is independent of S_0 and S_{int}, in accordance with Equation 2 (Loftsson *et al*., 2007). In Equation 3, $K_{1:1}$ represents the stability constant 1:1 ratio between drug and CD, and D represents drug concentration.

$$K_C = \frac{\text{Slope}}{S_0 \text{ X } (1 - \text{slope})} \quad (2)$$

$$CE = S_0 \,.\, K_{1:1} = \frac{[D/CD]}{[CD]} = \frac{\text{Slope}}{(1 - \text{slope})} \quad (3)$$

Some researchers consider that complexes with K_C values ranging between 200 and 5000 M^{-1} are applicable to dosage formulations, while K_C values between 7 and 100 M^{-1} were deemed sufficient by others, because they were able to improve the physical and chemical properties of drugs compared to non-complexed forms (Veiga *et al*., 2006).

K_C values are widely used to determine the stoichiometry of complexes, as well as to compare the affinity of drugs for CDs, thus determining whether the addition of water-soluble polymers to the system actually results in greater interaction between the components (Loftsson *et al*., 2007).

POLYMERS USED TO OBTAIN TERNARY COMPLEXES

Obtaining complexes with CDs, drugs and water-soluble polymers has gained greater acceptance due to the relatively low cost of polymers (Lahiani-Skiba *et al.*, 2006). The most important requirements in choosing polymers to form inclusion complexes with drugs and CDs are water solubility and absence of biological activity. The most commonly used polymers for this purpose may be classified as natural, semi-synthetic and synthetic (Veiga *et al.,* 2006), as detailed in Table VII.

There is no pre-established range of ideal polymer concentration for obtaining ternary complexes. However, it is known that, at high concentrations, the viscosity of the medium increases, thus impairing complexation. The amount of polymer must be such that the solubilizing effect is maximized, but not sufficient to cause a significant increase in viscosity (Ribeiro *et al*., 2003).

In studies by Loftsson and colleagues (1994) with hydrocortisone, 17β-estradiol and triamcinolone in an HP-β-CD 10% (p/v) aqueous solution, the ideal concentration of polymers ranged from 0.05 to 0.25% (p/v) and greater concentrations led to a reduction in drug solubility. Table VIII details the complexation solubility and efficiency of some drugs in their free form and in ternary complexes.

TABLE VII - Polymers most commonly used to obtain ternary complexes

Nature of polymers	Polymer
Natural	Pectin
	Mucin
	Agar
	Alginic acid
	Carrageenin
	Casein
	Schizophyllan
	Gelatin
Semi-synthetic	Methyl cellulose (MC)
	Hydroxyethyl cellulose (HEC)
	Hydroxypropyl cellulose (HPC)
	Hydroxyethyl methyl cellulose (HEMC)
	Carboxymethyl cellulose (CMC)
Synthetic	Povidone (PVP)
	Polyethylene glycol (PEG)
	Copovidone
	Polyvinyl alcohol (PVA)

PHARMACEUTICAL APPLICATIONS OF TERNARY INCLUSION COMPLEXES

Most drugs with low aqueous solubility have organic solvents, emulsifiers and extreme pH conditions in their formulations, which can cause irritation and other adverse reactions (Del Valle, 2004). The drug:CD:polymer complexes can be administered in any dosage form for the treatment of a variety of ailments, depending on the biological activity of the complexed drug. Research on ternary complexes has gained prominence in recent decades, and it is therefore possible to find a considerable number of studies in which drug:CD:water-soluble polymers obtained for several drugs are described (Table IX).

CONCLUSION

Improving the solubility of poorly soluble drugs is one of the main applications of CDs and their derivatives, which have the ability to encapsulate organic molecules in their cavities, thus forming inclusion complexes, which

TABLE VIII - Solubility values for some drugs in their free form (S_0) and in ternary complexes ($S_{TERNARY}$), and their respective complexation efficiency (CE) values (Adapted from Brewster and Loftsson, 2007)

Drug	Cyclodextrin (CD)	Polymer	Polymer concentration	S_0 (mg/mL)	$S_{TERNARY}$ (mg/mL)	CE
Acetazolamide	HP-β-CD	Absent	-	0.64	3.60	0.197
	HP-β-CD	HPMC	0.10%	0.90	4.40	0.356
	HP-β-CD	CMC	0.25%	0.59	3.60	0.209
	HP-β-CD	PVP	0.25%	0.94	3.70	0.273
Carbamazepine	HP-β-CD	Absent	-	0.26	0.65	0.548
	HP-β-CD	HPMC	0.10%	0.33	8.00	0.829
	HP-β-CD	CMC	0.25%	0.18	8.40	0.709
	HP-β-CD	PVP	0.25%	0.28	8.50	0.701
Finasteride	RM-β-CD	Absent	-	0.06	12.30	0.708
	RM-β-CD	HPMC	0.10%	0.06	11.60	0.789
	RM-β-CD	CMC	0.25%	0.06	11.50	0.805
	RM-β-CD	PVP	0.25%	0.06	11.60	0.844
Oxazepam	HP-β-CD	Absent	-	0.05	2.10	0.109
	HP-β-CD	HPMC	0.10%	0.27	2.10	0.076
	HP-β-CD	CMC	0.25%	0.05	1.50	0.127
	HP-β-CD	PVP	0.25%	0.10	1.40	0.115

CMC = carboxymethyl cellulose; HP-β-CD = hydroxypropyl-β-CD; HPMC = hydroxypropyl methylcellulose; PVP = povidone; RM-β-CD = randomly methylated-β-CD.

TABLE IX - Ternary complexes between drugs, cyclodextrins (CDs) and water-soluble polymers, as described in the scientific literature

Drug	CD	Water-soluble polymer	Reference
17β-estradiol	HP-β-CD	CMC	Loftsson *et al*., 1994
	HP-β-CD	PVP	Loftsson, Brewster, 1996
Acetazolamide	β-CD	HPMC, CMC, PVP	Loftsson, Fridrilksdóttir, 1998
	HP-β-CD	CMC, PVP	Loftsson *et al*., 1994
	HP-β-CD	HPMC, CMC, PVP	Loftsson *et al*., 2005b
Triamcinolone acetonide	HP-β-CD	CMC	Loftsson *et al*., 1994
Alprazolam	β-CD	HPMC, CMC, PVP	Loftsson , Fridrilksdóttir, 1998
	HP-β-CD	CMC	Loftsson *et al*., 1994
Carbamazepine	SBE-β-CD	HPMC, PVP	Smith *et al*., 2005
	HP-β-CD	CMC, PVP	Loftsson *et al*., 1994
	β-CD	HPMC, CMC, PVP	Loftsson, Fridrilksdóttir, 1998
	HP-β-CD	HPMC, CMC, PVP	Brewster, Loftsson, 2007
Celecoxib	HP-β-CD	HPMC, PEG, PVP	Chowdary, Srinivas, 2006
Clotrimazol	HP-β-CD	CMC, PVP	Loftsson *et al*., 1994
Dexamethasone	HP-β-CD	HPMC	Loftsson *et al*., 1994
	β-CD	HPMC, CMC, PVP	Loftsson, Fridrilksdóttir, 1998
Diazepam	HP-β-CD	CMC	Loftsson *et al*., 1994
Econazole	HP-β-CD	CMC, PVP	Loftsson *et al*., 1994
Ethoxzolamide	HP-β-CD	CMC, PVP	Loftsson *et al*., 1994
	β-CD	HPMC, CMC, PVP	Loftsson, Fridrilksdóttir, 1998

TABLE IX - Ternary complexes between drugs, cyclodextrins (CDs) and water-soluble polymers, as described in the scientific literature (cont.)

Drug	CD	Water-soluble polymer	Reference
Finasteride	RM-β-CD	HPMC, CMC, PVP	Brewster, Loftsson, 2007
	HP-β-CD	PVP	Asbahr *et al.*, 2009
Gemfibrozil	β-CD	PVP	Sami, Philip, Pathak, 2010
Gefitinib	HP-β-CD	PVP, HPMC	Phillip Lee *et al*., 2009
Glibenclamide	β-CD, HP-β-CD, SBE-β-CD	HPMC	Savolainen *et al*., 1998
Glimepiride	β-CD, HP-β-CD, SBE-β-CD	HPMC, PEG, PVP	Ammar *et al.*, 2006
Griseofulvin	α-CD, β-CD and γ-CD	PEG	Wulff, Aldén, 1999
	β-CD	CMC	Dhanaraju *et al*., 1998
Hydrocortisone	HP-β-CD	CMC	Loftsson *et al*., 1994
	HP-β-CD	HPMC, PVP	Loftsson, Sigurdardottir, 1994
	HP-β-CD	HPMC, CMC, PVP	Loftsson *et al*., 2005b
	RM-β-CD	HPMC, CMC, PVP	Loftsson *et al*., 2005b
Indomethacin	α-CD, β-CD and γ-CD	PEG	Wulff, Aldén, 1999
Irbesartan	β-CD	PEG, PVP	Hirlekar, Sonawane, Kadam, 2009
Lamivudine	β-CD	PVA	Selvam, Geetha, 2008
Lamotrigine	β-CD	PEG, PVP	Shinde *et al.*, 2008
Lovastatin	β-CD, RM-β-CD	PVP	Süle, Csempesz, 2008
Meloxicam	HP-β-CD	PVP	El-Maradny *et al.*, 2008
Methazolamide	β-CD	HPMC, CMC, PVP	Loftsson, Fridrilksdóttir, 1998
	HP-β-CD	HPMC, CMC, PVP	Loftsson *et al*., 2005b
Miconazol	HP-β-CD	CMC	Loftsson *et al*., 1994
Midazolam	SBE-β-CD	HPMC	Loftsson *et al*., 2001
Naproxen	β-CD, HP-β-CD	PVP	Mura *et al*., 2001
Nicardipine	β-CD	PEG	Quaglia *et al*., 2001
Oxazepam	HP-β-CD	CMC, PVP	Loftsson *et al*., 1994
	HP-β-CD	HPMC, CMC, PVP	Brewster, Loftsson, 2007
Prednisolone	HP-β-CD	CMC	Loftsson *et al*., 1994
	β-CD	HPC	Uekama *et al*., 1983
Progesterone	HP-β-CD	PEG	Nandi *et al*., 2003
	β-CD	PEG	Lahiani-Skiba *et al*., 2006
	HP-β-CD	CMC, PVP	Loftsson *et al*., 1994
Simvastatin	β-CD, RM-β-CD	PVP	Süle, Csempesz, 2008
Sulfamethoxazole	HP-β-CD	CMC, PVP	Loftsson *et al*., 1994
	β-CD	HPMC, CMC, PVP	Loftsson, Fridrilksdóttir, 1998
	HP-β-CD	HPMC, CMC, PVP	Loftsson *et al*., 2005b
Temazepam	HP-β-CD	CMC	Loftsson *et al*., 1994
Terfenadine	β-CD	CMC	Choi *et al*., 2001
Triclosan	β-CD	CMC	Loftsson, 1999
Trimethoprim	HP-β-CD	PVP	Loftsson *et al*., 1994
Tropicamide	HP-β-CD	HPMC, CMC, PVP	Cappello *et al*., 2001
Vinpocetine	β-CD, SBE-β-CD	HPMC, PVP	Ribeiro *et al*., 2003

CMC = carboxymethyl cellulose; HP-β-CD = hydroxypropyl-β-CD; HPMC = hydroxypropyl methylcellulose; PEG = polyethylene glycol; PVP = povidone; RM-β-CD = randomly methylated-β-CD; SBE-β-CD = sulfobutylether-β-CD.

in turn modify the physicochemical characteristics of such drugs. The drug:CD:water-soluble polymer complex represents an attractive alternative, especially in cases where a high amount of CD is required for complexation, which significantly increases the volume of dosage forms. Thus, it is possible to obtain solid-form medications with an optimized dissolution profile, which may result in improved bioavailability.

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