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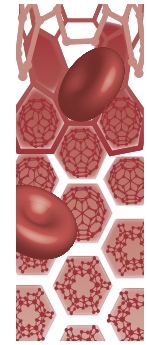

Cyclodextrin complexes for treatment improvement in infectious diseases

Infectious diseases are a heterogeneous group of maladies that represent a serious burden to healthcare systems worldwide. Most of the available antimicrobial drugs display poor biopharmaceutical properties that compromise their effectiveness. Cyclodextrins (CDs) are cyclic oligosaccharides of glucopyranose formed by a variable number of repeating units that combine a hydrophilic surface with a hydrophobic cavity. The production of drug/CD complexes has become one of the most extensively investigated technology approaches to improve the stability, solubility, dissolution rate and bioavailability of drugs. The present work overviews the applications of CDs for the formulation of anti-infective agents along with the most relevant administration routes. Finally, an update on the complexes with CDs available on the market to treat infectious diseases is presented.

Keywords: cyclodextrins • drug/cyclodextrin complex • infectious diseases • low physical stability • poor aqueous solubility

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Viruses, bacteria, fungi and parasites cause a broad spectrum of infectious diseases of variable morbidity. Some infections may be asymptomatic or, conversely, present mild-to-severe symptoms that can be life-threatening, becoming a serious burden to healthcare systems worldwide [1,112,113]. For example, malaria, the most prominent parasitic infection, causes around 1 million deaths every year [114]. The same is valid for tuberculosis, a curable bacterial disease that still represents the leading cause of preventable death [115]. Viruses also have a great impact on health, with chronic HIV annually claiming the lives of approximately 1.5 million people [116]. In addition, each year 500 million people become infected with one of the following bacterial or protozoal sexually transmitted infections (STIs): chlamydia, gonorrhea, syphilis and trichomoniasis [117]. Moreover, fungal infections are very frequent appearing in many cases with bothersome symptoms. For example, *Candida albicans* is one of the most common causes of vaginitis and affects 75% of women in reproductive age [2].

There are many drugs on the market to treat these infections. However, most of them display poor biopharmaceutical properties that directly compromise their bioavailability in the action site. In addition, the most incidental infections especially hit developing nations. Thus, the development of new and more effective antimicrobial agents and pharmaceutical products aimed to treat resistant strains has been relegated over the years owing to market constraints. In this complex scenario, the development of innovative drug delivery systems for the administration of anti-infective agents might represent a breakthrough in the field.

Native or nonsubstituted cyclodextrins (CDs) are cyclic oligosaccharides composed usually of six (α-CD), seven (β-CD) or eight (γ-CD) glucopyranose units linked by α-1,4-glucosidic bonds [3,4]. These compounds adopt the conformation of a truncated cone where the hydroxyl groups and the carbon backbones are arranged in such a way that they display an outer hydrophilic surface that favors its dissolution in water and an inner

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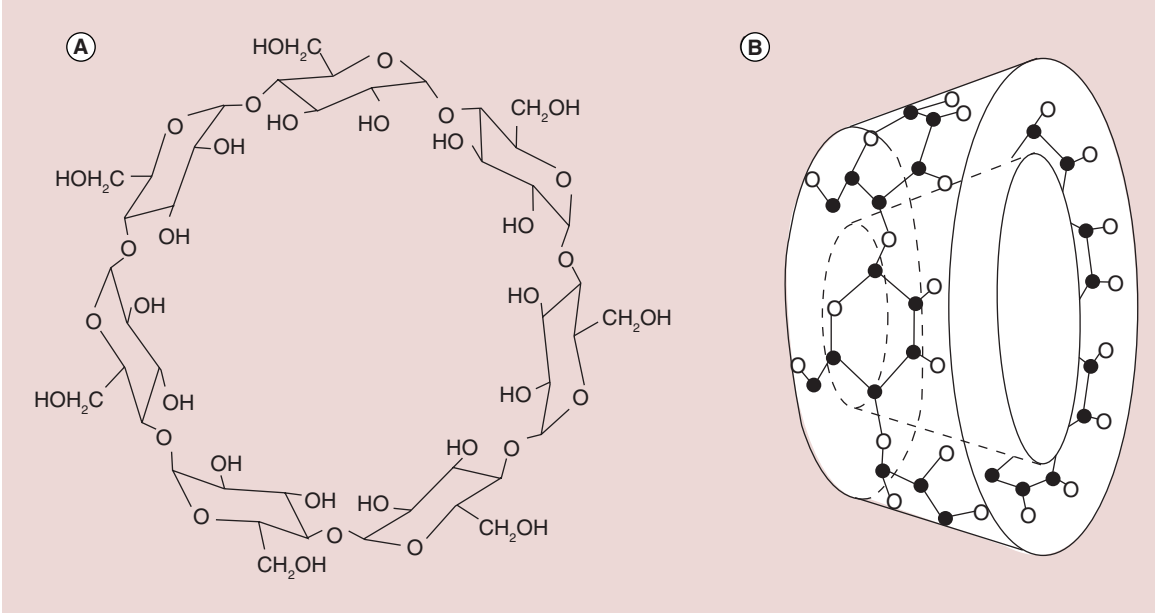

Figure 1. β-cyclodextrin. (A) Chemical structure and **(B)** truncated cone shape of β-cyclodextrin. Reproduced with permission from [4].

hydrophobic cavity able to partly or completely host hydrophobic drugs through noncovalent interactions (Figure 1) [4]. Drug/CD compounds are known as inclusion complexes.

The number of glucopyranose units in the CD determines the size of the cavity and the size of the molecule that can be incorporated into it [3–5] (Table 1). Thus, α-CD, the smallest one typically forms complexes with low molecular weight drugs or those with aliphatic side chains. Conversely, β-CD complexes drugs containing aromatic and heterocyclic moieties and γ-CD may incorporate larger drugs like macrocycles and steroids [3].

Regardless of the type of CD, they present a hydrodynamic diameter of 1–2 nm [6]. However, they undergo aggregation above a critical aggregation concentration and form aggregates of several hundreds of nanometers (Table 2) [6]. Drug/CD inclusion complexes can also self-aggregate, hindering the ability of the drug to cross biological barriers [7]. Either way, the absorption and/or permeation of CDs and their complexes through epithelia is negligible owing to their bulky and hydrophilic nature [8,9]. Thus, CDs act as reservoirs that release the drug in the absorption site at a rate determined by a dissociation constant that is unique for each drug/CD couple [3,5,9] and that can be determined from the phase-solubility diagrams as described by Higuchi and Connors [10]. At the same time, it is worth mentioning that sustained drug delivery is limited to administration routes where the complex undergoes a relatively low dilution and the dissociation extent is minimal. For example, efficient corneal absorption can be achieved by prolonging the residence time of the complex in the ocular mucosa [5,9].

In this scenario, CDs have been used to increase the solubility and dissolution rate and to improve the physicochemical stability of diverse drugs in aqueous media, to reduce local irritation and to mask unpleasant taste [11]. CDs can also solubilize lipophilic drug molecules by other mechanisms that do not involve the cavity such as drug/CD aggregates [12] and noninclusion molecular associations [13]. These mechanisms have been also described for hydrophilic drugs [13]. Among the natural CDs, β-CD is the most afford-

Table 1. Physicochemical properties of natural cyclodextrins.

CD type	Glucose units	Molecular weight	Cavity diameter (nm)	Cavity volume (ml/mol)	Aqueous solubility at 25°C (% w/v)
α-CD	6	973	0.47–0.53	174	14.5
β-CD	7	1135	0.60–0.66	262	1.85
γ-CD	8	1297	0.75–0.83	472	23.2

α-CD: α-cyclodextrin; β-CD: β-cyclodextrin; γ-CD: γ-cyclodextrin.
Adapted with permission from [4].

Table 2. Critical aggregate concentration (*CAC*) and hydrodynamic diameter (D_h) of native and modified drug-free cyclodextrin aggregates in water measured by dynamic light scattering, at 25°C.

CD type	CAC		Mean size of CD-aggregates and monomeric forms of CAC			
			Peak 1		Peak 2	
	mM	% (w/v)	D_h(nm) (±SD)	% (±SD)	D_h (nm) (±SD)	% (±SD)
α-CD	6.43	0.63	188.6 (11.7)	100.0 (0.0)	-	-
β-CD	1.87	0.21	172.0 (43.9)	100.0 (0.0)	-	-
γ-CD	12.00	1.55	230.7 (20.3)	100.0 (0.0)	-	-
HPβ-CD	21.43	3.00	180.9 (4.5)	88.8 (1.6)	1.4 (0.3)†	11.2 (1.6)
Mβ-CD	85.00	11.00	282.6 (27.0)	84.8 (1.1)	1.6 (0.0)†	15.2 (1.1)
HPγ-CD	57.20	9.00	158.1 (16.7)	87.6 (1.9)	1.7 (0.1)†	12.4 (1.9)

α-CD: α-cyclodextrin; β-CD: β-cyclodextrin; γ-CD: γ-cyclodextrin; HPβ-CD: 2-hydroxypropyl β-cyclodextrin; HPγ-CD: 2-hydroxypropyl γ-cyclodextrin; Mβ-CD: Methyl β-cyclodextrin.
†Monomeric forms of chemically-modified CDs.
Adapted with permission from [6].

able, cost-effective and versatile owing to a cavity size that is appropriate for the broadest range of drugs [3,9]. However, its use has been constrained due to a crystalline structure that precludes its dissolution in water at concentrations greater than 1.8%. Thus, over the last decades, several amorphous semisynthetic CD derivatives have been synthesized by the chemical modification of hydroxyl groups in the molecule (Table 3). These derivatives disrupt the crystalline structure of β-CD and enable the preparation of more concentrated solutions and the attainment of more efficient drug solubilization [14,15]. In addition, the toxicity of the CD is reduced with respect to the natural counterpart [16].

The most representative chemically modified CDs available on the market include 2-hydroxypropyl β-cyclodextrin (HPβ-CD), methylated β-cyclodextrins and sulfobutylether β-cyclodextrin (SBEβ-CD). Furthermore, CDs can be covalently attached or physically assembled to polymer chains to form polymeric CD derivatives. These type of smart systems show exceptional features for drug delivery owing to the capitalization of the advantages of each component [17,18]. It is worth mentioning that CDs exhibit excellent biocompatibility, in fact natural CDs have been categorized as 'Generally Recognized as Safe' (GRAS) by US FDA and approved by most of the regulatory agencies. Moreover, depending on the type of CD, they can be administered either by oral, parenteral and topical route becoming very versatile platforms that can be used as a first approach to improve the biopharmaceutical performance of drugs.

The present article overviews the applications of CDs for the formulation of anti-infective agents along with the routes of administration that were more intensively explored. Finally, an update on the complexes with CDs available on the market to treat infectious diseases is presented.

Application of cyclodextrins in infectious diseases

The main application of CDs lies in their capability to form inclusion complexes with a broad range of hydrophobic drugs. This section addresses the most relevant applications of CDs to optimize the performance of approved anti-infective agents and new chemical entities with potential antibacterial, antiviral, antifungal and antiprotozoal activity (Table 4).

Table 3. Comparative solubility profile of derivatives cyclodextrin with respect to its natural counterpart.

CD type	Glucose units	Molecular weight	Aqueous solubility at 25°C (mg/ml)
β-CD	6	1135	18.5
HPβ-CD	6	1400	>600
RMβ-CD	6	1312	>500
SBEβ-CD	6	2163	>500

β-CD: β-cyclodextrin; HPβ-CD: 2-hydroxypropyl β-cyclodextrin; RMβ-CD: Randomly methylated β-cyclodextrin; SBEβ-CD: Sulfobutylether β-cyclodextrin
Adapted with permission from [14].

Table 4. Summary of studies where cyclodextrins successfully enhanced the performance of anti-infective agents.

	CD	Improvement	Drug	Administration route/s	Pathogen†	Animal	Ref.
Bacterial	β-CD	Solubility	Ofloxacin	Oral	ND	ND	[106]
	RMβ-, HPβ-CD	Solubility	Rifampicin	Inhalatory	*A. baumannii*	ND	[29]
	β-CD	Dissolution rate	Rifabutin	Oral	*E. coli*, *S. aureus*, *E. faecalis*, *P. vulgaris*, *P. aeruginosa*	ND	[31]
	HPβ-CD	Solubility and dissolution rate	Cefpodoxime proxetil	Oral	*E. coli*, *S. aureus*, *P. aeruginosa*, *E. faecalis*	ND	[26]
	HPβ-CD	Solubility and dissolution rate	Cefdinir	Oral	ND	ND	[27]
	HPβ-CD	Solubility, dissolution rate and stability	Rifampicin	Oral	*E. coli*, *S. aureus*	ND	[44]
	HPβ-CD	Solubility and stability	Ciprofloxacin	Ocular	ND	ND	[33]
	γ-CD	Stability	Dicloxacillin	ND	ND	ND	[34]
	β-CD	Stability	Erythromycin	Parenteral	*S. aureus*	ND	[30]
	β-, γ-CD	Stability	Amoxicillin	Oral	ND	ND	[35]
	β-CD	Stability	Doxycycline	ND	*E. coli*	ND	[38]
	HPβ-CD	Stability	Doxycycline	Ocular	ND	ND	[24]
	HPβ-CD	Stability	Doxycycline	Ocular	*E. coli*, *P. aeruginosa*, *S. aureus*	ND	[39]
	HPβ-CD	Stability	Ciprofloxacin	Ocular	*P. aeruginosa*, *S. aureus*	ND	[32]
	β-CD	Controlled release	TSC	Ocular	*P. aeruginosa*, *S. aureus*	ND	[48]
Viral	β-CD	Solubility	Acyclovir	Ocular	ND	ND	[62]
	HPβ-CD	Solubility	Saquinavir	Oral	ND	ND	[56]
	HPβ-CD	Solubility	Saquinavir	Vaginal	HIV-infected MT-4 cells	ND	[61]
	β-, HPβ-, Mβ-CD	Solubility	UC781	Vaginal	ND	ND	[60]
	β-CD	Solubility	Acyclovir	ND	Two clinical isolates of HSV-1	ND	[63]
	HPβ-, HPγ-, Mβ-CD	Solubility and stability	TSC	ND	ND	ND	[6]
	HPβ-CD	Solubility and stability	TSC	ND	Hepatitis C virus	ND	[107]
	HPβ-CD	Solubility and stability	Ganciclovir	Ocular	ND	Rabbit (*ex vivo* assay)	[51]
	HBenβ-CD	Solubility and bioavailability	Saquinavir	Oral	ND	Rat	[55]
	Mβ-CD	Solubility and bioavailability	Saquinavir	Oral	ND	Rat	[57]

α-CD: α-cyclodextrin; β-CD: β-cyclodextrin; γ-CD: γ-cyclodextrin; AD169: A reference ganciclovir susceptible HCMV strain; HBenβ-CD: hydroxybutenyl β-cyclodextrin; HCMV: Human cytomegalovirus; HIV-infected MT-4 cells: HIV-infected CD4+ T-cell line MT-4; HPβ-CD: 2-hydroxypropyl β-cyclodextrin; HPγ-CD: 2-hydroxypropyl γ-cyclodextrin; HSV-1: Herpes simplex virus type I; Mβ-CD: Methyl β-cyclodextrin; ND: Not determined; RMβ-CD: Randomly methylated β-cyclodextrin; RC11: A ganciclovir-resistant HCMV strain; SBEβ-CD: Sulfobutylether β-cyclodextrin; TSC: 1-indanone thiosemicarbazone candidate drugs; UC781: An HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) under evaluation.
†*In vitro* assays.

Table 4. Summary of studies where cyclodextrins successfully enhanced the performance of anti-infective agents (cont.).

	CD	Improvement	Drug	Administration route/s	Pathogen†	Animal	Ref.
Viral (cont.)	β-CD	Solubility and bioavailability	Acyclovir	Oral	ND	Rat	[108]
	β-CD	Efficacy	Ganciclovir	ND	Two HCMV strains (AD169, RCL1)	ND	[49]
	β-CD	Efficacy	Ganciclovir	Oral	Two HCMV strains (AD169, RCL1) and four clinical isolates	ND	[50]
	α-, β-CD	Efficacy	Ribavirin	ND	Two clade A laboratory strains of MEV (Edmonston and CAM/RB)	ND	[13]
	α-CD	Efficacy	Ribavirin	Parenteral	CAM/RB strain	Mouse	[52]
	HPβ-, RMβ-CD	Dissolution rate	Efavirenz	Oral	ND	ND	[59]
Fungal	β-, HPβ-, γ-CD	Solubility	Natamycin	ND	*S. cerevisiae*, *C. albicans*	ND	[70]
	γ-CD	Solubility	Amphotericin B	Parenteral	*S. cerevisiae*	ND	[69]
	γ-CD	Solubility and stability	Natamycin	Vaginal	*Candida* spp.	ND	[65]
	γ-CD	Solubility and efficacy	Amphotericin B	Topical	*Candida* spp., *Trichosporon* spp., *Saccharomyces* spp.	ND	[68]
	γ-CD	Stability and efficacy	Amphotericin B	Ocular	*Candida* spp., *Saccharomyces* spp., *Trichosporon* spp.	ND	[67]
	HPβ-CD	Solubility	Terbinafine	Topical	ND	ND	[85]
	SBEβ-CD, HPβ-CD	Solubility	Econazole	Buccal	ND	ND	[80]
	HPβ-, HBenβ-CD	Solubility	Itraconazole	Oral	ND	ND	[76]
	HPβ-CD	Solubility	Itraconazole	Inhalatory	ND	ND	[81]
	β-CD	Solubility	Itraconazole	ND	ND	ND	[74]
	HBenβ-CD	Solubility and bioavailability	Itraconazole	Oral and parenteral	ND	Rat	[55]
	HPβ-CD	Solubility and bioavailability	Itraconazole	Inhalatory	ND	Mouse	[109]
	HBenβ-, Mβ-CD	Dissolution rate	Voriconazole	Oral	ND	ND	[73]
	β-CD	Dissolution rate and bioavailability	Itraconazole	Oral	ND	Rat	[75]
	SBEβ-CD	Efficacy	Itraconazole	Vaginal	*C. albicans*	ND	[72]
	β-CD	Bioavailability	Clotrimazole	Oral	ND	Rat	[110]
Protozoal	HPβ-, RMβ-CD	Solubility	Melarsoprol	Oral and parenteral	ND	ND	[88]

α-CD: α-cyclodextrin; β-CD: β-cyclodextrin; γ-CD: γ-cyclodextrin; AD169: A reference ganciclovir susceptible HCMV strain; HBenβ-CD: hydroxybutenyl β-cyclodextrin; HCMV: Human cytomegalovirus; HIV-infected MT-4 cells: HIV-infected CD4+ T-cell line MT-4; HPβ-CD: 2-hydroxypropyl β-cyclodextrin; HPγ-CD: 2-hydroxypropyl γ-cyclodextrin; HSV-1: Herpes simplex virus type I; Mβ-CD: Methyl β-cyclodextrin; ND: Not determined; RMβ-CD: Randomly methylated β-cyclodextrin; RC11: A ganciclovir-resistant HCMV strain; SBEβ-CD: Sulfobutylether β-cyclodextrin; TSC: 1-indanone thiosemicarbazone candidate drugs; UC781: An HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) under evaluation.
†*In vitro* assays.

Table 4. Summary of studies where cyclodextrins successfully enhanced the performance of anti-infective agents (cont.).

	CD	Improvement	Drug	Administration route/s	Pathogen†	Animal	Ref.
Protozoal (cont.)	β-CD	Solubility	Metronidazole	Oral	ND	ND	[90]
	β-, HPβ-, Mβ-CD	Solubility, dissolution rate, bioavailability	Benznidazole	Oral	ND	Rat	[91]
	HPβ-CD	Solubility and bioavailability	Albendazole	Oral	ND	Sheep	[87]
	β-, γ-CD	Bioavailability	Artemisinin	Oral	ND	Human	[92]
	γ-CD	Solubility and efficacy	Amphotericin B	Topical	*Leishmania* spp.	Hamster	[68]
	HPβ-, RMβ-CD	Efficacy	Melarsoprol	Oral	*T. brucei brucei*	Mouse	[89]
	β-CD	Bitter taste masking	Artemether	Oral	ND	Human	[96]

α-CD: α-cyclodextrin; β-CD: β-cyclodextrin; γ-CD: γ-cyclodextrin; AD169: A reference ganciclovir susceptible HCMV strain; HBenβ-CD: hydroxybutenyl β-cyclodextrin; HCMV: Human cytomegalovirus; HIV-infected MT-4 cells: HIV-infected CD4+ T-cell line MT-4; HPβ-CD: 2-hydroxypropyl β-cyclodextrin; HPγ-CD: 2-hydroxypropyl γ-cyclodextrin; HSV-1: Herpes simplex virus type I; Mβ-CD: Methyl β-cyclodextrin; ND: Not determined; RMβ-CD: Randomly methylated β-cyclodextrin; RC11: A ganciclovir-resistant HCMV strain; SBEβ-CD: Sulfobutylether β-cyclodextrin; TSC: 1-indanone thiosemicarbazone candidate drugs; UC781: An HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) under evaluation.
†*In vitro* assays.

Bacterial infections

Nowadays, antibiotics are among the most frequently prescribed medications worldwide [19]. However, the improper prescription and/or dispensation and the misuse of antibiotics by consumers led to the development of resistance [20]. This phenomenon is recurrent in developing nations with laxer regulations and controls. Antibacterial treatments generally involve the frequent administration of the medication up to several daily doses in a period that can range from one week to several months or even years (e.g., multidrug-resistant tuberculosis) and that are associated with light-to-severe adverse effects. Altogether, therapy conditions usually result in patient incompliance and treatment cessation, a phenomenon that might aggravate the resistance problem [21]. Besides, although most of the approved antibiotics are highly effective, inherent problems concerning their solubility and stability have extremely limited their oral bioavailability. Hence, a higher dose is commonly administered to achieve therapeutic levels in plasma, an approach that exacerbates the adverse effects at the absorption site (e.g., GI tract) and increase the cost of the treatment. Another noteworthy drawback is their low physicochemical stability under storage conditions or in the biological environment. In view of this, several technological strategies have been investigated to improve the performance of antibiotics [118]. The development of CD inclusion complexes emerged as an innovative tool in this field.

Groups of antibiotics such as fluoroquinolones and tetracyclines suffer from photodegradation resulting in the reduction of the antibacterial activity [22,23]. Moreover, tetracyclines are unstable in aqueous solution [24] and macrolides (e.g., erythromycin) are often inactivated in basic (pH higher than 10) as well as acidic

Table 5. Antimicrobial activity and photostability profile of free DOX and DOX/β-CD.

Sample	*In vitro* antimicrobial susceptibility		Photostability studies†	
	MIC‡	MBC	Remained DOX after 3 h§	Remained DOX after 6 h
DOX	1.22	625	84	68
DOX/β-CD	<0.009	78.12	99.1	96.8

†Photostability studies were performed by exposing an aqueous solution of DOX or DOX/β-CD to UV light, at 30°C, for 6 h.
‡Data obtained from [40].
§Data obtained from [38].
β-CD: β-cyclodextrin; DOX: Doxycycline; MBC: Minimal bacterial concentration reflecting the bactericide effect of DOX; MIC: Minimal inhibitory concentration reflecting the bacteriostatic activity of DOX.
Adapted with permission from [40].

media (pH lower than 4) [25]. Likewise, all these drugs display poor aqueous solubility.

Results obtained by different research groups have confirmed the potential of CD complexes to improve both the aqueous solubility and the chemical stability of different antibiotics (Table 4) [26–31]. In fact, ciprofloxacin hydrochloride (CPH), a second-generation light-sensitive fluoroquinolone, was successfully complexed with HPβ-CD, increasing its stability under daylight at 25°C for over 30 days as opposed to the free CPH solution that degraded after 10 days [32,33]. Similarly, the solubility and stability of penicillins such as amoxicillin and dicloxacillin in acid solution were improved by complexation with β- and γ-CD, respectively [34,35]. At the same time, it is worth stressing that the complexation, solubilization and stabilization efficiency depended on the CD type and the drug [35]. Thus, a thorough assessment of the optimal CD for each given molecule is needed. In this sense, computational methods such as molecular dynamics are an interesting tool to predict the formation of drug/CD complexes [36,37].

In recent studies, the complexation of doxycycline (DOX), a tetracycline that is highly photosensitive and unstable in aqueous solution, with β- or HPβ-CD resulted in a significant reduction of the degradation rate [24,38,39]. In addition, a greater antibacterial activity against pathogens that cause common ocular infec-

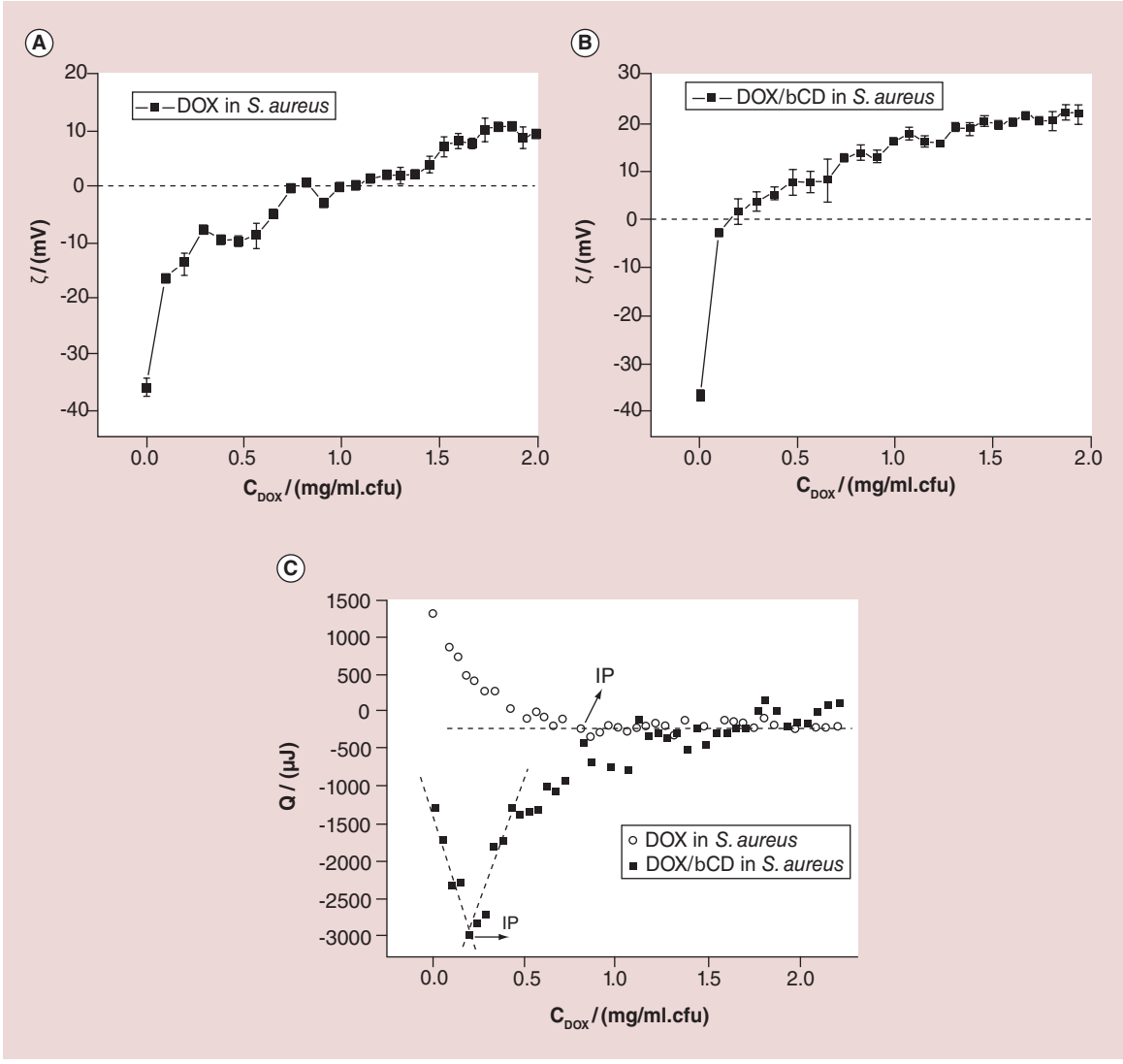

Figure 2. Zeta potential of *Staphylococcus aureus* as a function of (A) DOX and (B) DOX/β-CD concentrations.
(C) isothermal titration calorimetry of DOX (◦) and DOX/β-CD (▪). ZP studies were performed using both samples with 10 mg/ml DOX into 1-ml aqueous suspensions of *S. aureus* (10^8 CFU/ml). ITC analysis was conducted using both samples with 50 mg/ml DOX added into 1-ml suspensions of *S. aureus* (6×10^8 CFU/ml) after subtracting blank values.
Reproduced with permission from [40].

tions (e.g., *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*) was observed when compared with the unprocessed drug *in vitro* (Table 5) [38,40].

These results were related to the greater amount of intact drug available to exert the antibacterial action. In addition, CDs can adhere to the pathogen surface through the formation of hydrogen bonds by means of the hydroxyl groups present in its structure, providing a local and sustained delivery of drug that further strengthens the antibacterial activity. This hypothesis was supported by zeta potential (ZP) and isothermal titration calorimetry studies [40]. For example, *S. aureus* exhibits a negative surface charge while DOX is a cationic molecule [40]. Thus, a gradual change in the ZP of *S. aureus* first to less negative and then to positive values was observed as the concentration of free DOX increased (Figure 2A) [40]; when the drug neutralized the bacterial surface, the isoelectric point (IP) was reached. A similar ZP profile was obtained with a DOX/β-CD inclusion complex (Figure 2B), although the IP was achieved at lower drug/CD concentrations with respect to those of the free DOX [40]; for example, 0.16 mg DOX per ml of colony-forming units (CFU) for DOX/β-CD versus 0.74 mg DOX/ml CFU for DOX. Complementary calorimetry analyses evidenced a maximum exothermic reaction at 0.2 mg DOX/ml CFU (Figure 2C) [40]. This release of energy at a concentration that is close to the one where the IP was detected strongly suggested that CDs spontaneously form hydrogen bonds with several components of the cellular membrane [40]. This point highlights the possibility of using the drug at significantly lower concentrations, reduce the exposure to antibiotics and thus, delay the onset of antibiotic resistance or prevent its emergence. In addition, adverse effects would decrease, so that the adherence to the administration regimens may increase and consequently prevent the development of resistance. Finally, a reduction of the therapeutic dose might have a great impact in the cost of the medication and in patient affordability, especially in constrained-setting countries and for state-of-the-art drugs such as third generation cephalosporins and new antituberculosis drugs [119]. Moreover, several research groups demonstrated the ability to reduce resistance to β-lactams by CD complexation [41,42].

Tuberculosis is the second leading cause of death from infectious diseases worldwide, after HIV (204). Rifampicin (RIF) is one of the first-line drugs used for the treatment of tuberculosis. However, this drug exhibits poor aqueous solubility and low stability in acidic medium leading to low oral bioavailability, especially when co-administered with isoniazid in nonsegregated formulations. For this reason, large doses and a long-cycle therapy are required, jeopardizing patient compliance. Several groups reported on the increased aqueous solubility of RIF upon complexation with different CDs [29,43,44]. For example, Tewes *et al.* produced RIF/CDs inclusion complexes with HPβ- and RMβ-CD (randomly methylated β-cyclodextrin) achieving an increase of 22- and 7.6-times, respectively, in the apparent solubility of the drug [29]. Aerosolization of these RIF/CD complexes with nebulizers resulted in micro-sized droplets compatible with pulmonary deposition. Thus, the drug could be delivered directly in the lungs, not only minimizing systemic adverse effects but also avoiding the gastric medium that degrades RIF after oral administration [29].

Besides binary drug/CD complexes, CDs have been incorporated into delivery systems that are more sophisticated. For example, medicated soft contact lenses (SCLs) loaded with a drug cargo have the ability to combine the correction of vision defects and the treatment of ocular affections [45,46]. The advantage of SCLs with respect to conventional ophthalmic formulations is that the former may maintain the drug in the eye for prolonged time, increasing the probability of drug absorption [47]. However, the constituent monomers of SCLs are typically hydrophilic, preventing the load of hydrophobic drugs. Glisoni *et al.* developed SCLs conjugated with either β-CD or HPβ-CD for the loading and sustained release of 1-indanone thiosemicarbazones (TSCs), a group of novel extremely

Table 6. Evaluation of the IC_{50} of free ganciclovir and complexed with β-CD.

HCMV strain	IC_{50} of free GCV (μM)	IC_{50} of [GCV:β-CD] (μM)	Improvement in IC_{50}
AD169	2.70 ± 0.55	0.20 ± 0.05	13.5
RCL-1	14.50 ± 2.50	1.60 ± 0.12	9.1
1558	3.25 ± 2.50	0.20 ± 0.06	16.2
539	6.45 ± 0.82	2.50 ± 0.51	2.6
731	6.70 ± 0.55	5.80 ± 0.51	1.1
2288	18.25 ± 2.25	0.75 ± 0.80	24.3

1558, 539, 731, 2288: four clinical isolates of HCMV from four unrelated patients; β-CD: β-cyclodextrin; AD169: Susceptible HCMV strain; GCV: Ganciclovir; IC_{50}: Drug concentration leading to a 50% decrease in viral production; RCL-1: Resistant HCMV strain.
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Table 7. Solubility enhancement of saquinavir after its complexation with cyclodextrins.

Drug	CD type	Solubility in water at 25°C		Solubility enhancement	Ref.
		SQV	SQV/CD		
SQV-free base	HBenβ-CD†	207 μg/ml	5.5-fold	27-fold	[55]
SQV-free base	HPβ-CD†	35.8 μg/ml	15.8 mg/ml	400-fold	[56]
SQV mesylate	HBenβ-CD†	2.1 mg/ml	11.5 mg/ml	5.5 mg/ml	[55]

†CD concentration was 10% w/w.
HBenβ-CD: Hydroxybutenyl β-cyclodextrin; HPβ-CD: Hydroxypropil β-cyclodextrin; SQV: Saquinavir.

poorly water-soluble compounds that have shown antiviral, antibacterial, antifungal, antiprotozoal and antileukemic activity [48]. Results showed that these modified SCLs provided a controlled drug release for at least 2 weeks *in vitro*, concentrations being within an optimal therapeutic window for the treatment of ocular infections [48].

Viral infections

In an attempt to control viral infections employing cost-effective nanotechnology approaches, researchers have focused on approved platforms extensively used in pharmaceutical product development such as CDs. Several antiviral drugs display dose-limiting toxicities. Among them ganciclovir, a slightly water-soluble drug, that is extensively used in the treatment of human cytomegalovirus (HCMV) has been complexed with β-CD [49], showing higher *in vitro* effectiveness against different HCMV strains by virtue of an increased solubility and stability and hence an enhanced cellular uptake (Table 6) [50]. This would enable to decrease the dose and thus, to reduce drug toxicity. In addition, a prodrug of ganciclovir (dibutyrate ester prodrug) was complexed with HPβ-CD showing a substantial improvement of ganciclovir corneal permeation [51] that would enable to reduce the dose and again, diminishing drug toxicity. This study was conducted *in vitro* using isolated rabbit cornea [51].

The potential of CDs has been also supported by the fact that the ability to form complexes has been found in highly water-soluble drugs [13]. For example, the therapeutic use of ribavirin, a broad-spectrum antiviral used in the treatment of viral hepatitis, is limited by its toxicity. Grancher *et al.* reported on the *in vitro* efficacy of ribavirin/CD complexes to reduce the toxic effect of the drug against two clade A laboratory strains of measles virus (Edmonston and CAM/RB) grown in Vero cells [13]. However, since the drug is water soluble it could not be incorporated into the hydrophobic cavity to form a true host-guest inclusion system, but rather a noninclusion complex. Remarkably, the three native CDs exhibited a different performance. For example, α- and β-CD led to a five- and two-fold decrease in the 50% inhibitory concentration (IC_{50}), respectively. While complexation with γ-CD had no effect [13]. Based on these results, ribavirin was complexed with α-CD and administered *in vivo* by intraperitoneal injection to a measles virus encephalitis model exhibiting a higher antiviral activity [52] when compared with free drug. Indeed, the amount of drug in the brain after the administration of ribavirin/α-CD was 1.5–2-times higher than the obtained with free ribavirin [53].

Irrespective of the broad range of existing viruses, HIV currently represents the major public health challenge [120]. Drugs used to treat HIV are called antiretrovirals and the chronic administration of a minimum

Table 8. Evaluation of the solubility and antifungal activity achieved after complexation of different antifungal with cyclodextrins.

Drug	Intrinsic solubility in water, 25°C	Drug/CD	Solubility enhancement	Antifungal activity compared with free drug	Ref.
NTM	30–50 mg/l	NTM/β-CD	16-fold	Enhanced against *C. albicans* and *S. cerevisiae*	[70]
		NTM/γ-CD	73-fold	Enhanced against *C. albicans*	[70]
		NTM/HPβ-CD	152-fold	Enhanced against *C. albicans* and *S. cerevisiae*	[70]
AFB	<1 mg/l	AFB/γ-CD	200-fold	Equal against *S. cerevisiae*	[69]
ITC	0,5–30 μg/ml	ITC/HPβ-CD	3.8-fold	ND	[77]
		ITC/HBenβ-CD	17-fold	ND	[77]

β-CD: β-cyclodextrin; γ-CD: γ-cyclodextrin; AFB: Amphotericin B; HBenβ-CD: Hydroxybutenyl β-cyclodextrin; HPβ-CD: Hidroxypropil β-cyclodextrin; ITC: Itraconazole; NTM: Natamycin.

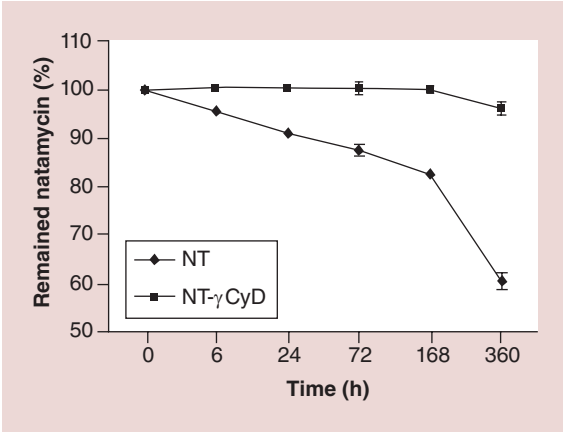

Figure 3. Stability of natamycin and natamycin/γ-CD inclusion complex in distilled water at 37°C.
Reproduced with permission from [65].

of three antiretrovirals of at least two different families with high frequency is indispensable to maintain undetectable viral levels in plasma [54]. Protease inhibitors (PIs) are a group of first-line antiretrovirals included in the combined therapy that display a series of biopharmaceutical disadvantages. In general, they display poor aqueous solubility that redounds in poor dissolution and absorption and they are substrates of the efflux pump P-gp in the intestinal epithelium and the cytochrome CYP3A metabolic pathway in the liver. Altogether, these phenomena result in low oral bioavailability. For example, the oral bioavailability of saquinavir (SQV), the first PI to reach the market in 1995, is 0.7–8.0%. Complexation of SQV with HPβ-, hydroxybutenyl β-cyclodextrin (HBenβ-CD) and methyl β-cyclodextrin (Mβ-CD) significantly increased the aqueous solubility of the drug (Table 7) [55–57].

The significant increase of the aqueous solubility has a positive impact on the oral bioavailability. For

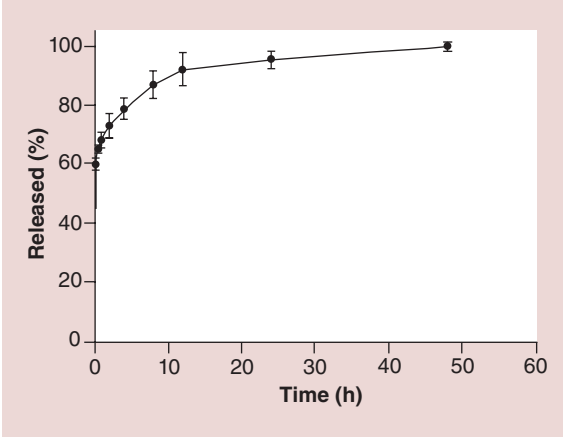

Figure 4. Itraconazole release profile from chitosan:tripolyphosphate nanoparticles where the drug was primarily complexed with HPβ-CD.
Reproduced with permission from [81].

example, Pathak *et al.* compared the performance of SQV/Mβ-CD with that of the free drug in Wistar rats [57]. The area-under-the-curve in plasma increased from 439.7 to 2312.0 ng/ml/h, while the maximum plasma concentration increased from 117 to 1347 ng/ml [57]. However, not only a poor solubility but also a dissolution rate lower than 0.1 mg/cm^2/min [58] can limit the gastrointestinal absorption of a drug. Efavirenz (EFV), an antiretroviral belonging to the non-nucleoside reverse transcriptase inhibitors family, presents an aqueous solubility of 4–9 μg/ml and an intrinsic dissolution rate of 0.037 mg/cm^2/min. Based on this, Sathigari *et al.* complexed EFV with HPβ- and RMβ-CD obtaining in both cases a substantial increase of the drug dissolution rate [59]. In HIV, vaginal administration is an appealing approach to prevent sexual transmission of the infection. CDs offer excellent opportunities to improve the performance of prophylactic antiretrovirals. Yang *et al.* reported on the complexation of the poor aqueous soluble anti-HIV non-nucleoside reverse transcriptase inhibitor UC781 with β-, Mβ- and HPβ-CD providing, in all the cases, a dramatic increase in UC781 aqueous solubility that is critical for the development of a vaginal dosage form [60]. However, it is mandatory to take into account that upon vaginal application, the dosage form will undergo dilution in vaginal fluids and after coitus with semen. These physicochemical changes (e.g., pH, ionic strength) can alter the solubility of the drug resulting in its precipitation. Indeed, SQV has two pKa values of 2 and 7, after its dilution in vaginal fluid simulant the pH was 4.5 allowing SQV to be fully ionized and soluble. However, after dilution in seminal fluids simulant, the pH increased to 7.5 and a significant fraction of drug precipitated in nonionized form, a phenomenon that hampered absorption. Brouwers *et al.* have demonstrated that HPβ-CD avoided the precipitation of SQV in seminal fluid simulant restoring its antiviral activity [61].

It is important to highlight that the strength of drug/CD interaction relies on an association constant that could be capitalized to develop CD-based controlled release systems [9]. However, any drug/CD inclusion complex could be included in a more sophisticated system for the controlled release of drugs. Deshpande *et al.* incorporated the inclusion complex of the poorly water soluble acyclovir (ACV) with β-CD into a polymeric matrix of hydroxypropyl methylcellulose sandwiched between two rate-controlling membranes of cellulose acetate phthalate [62]. In this design, the aqueous solubility and the dissolution rate of the drug were increased by complexation, while a controlled release of up to 20 h was achieved using the biodegradable polymeric membranes. These results demonstrate

Table 9. Effect of HPβ-CD on the hydration enhancement factor, HEF_{24}.

Concentration of HPβ-CD (% w/v)	Hydration enhancement factor HEF_{24}† (mean ± SD)
0	1.00 ± 0.02
1	1.04 ± 0.28
2	1.04 ± 0.03
5‡	1.15 ± 0.13
10‡	1.23 ± 0.17

†Hydration enhancement factor measured after 24 h of exposure.
‡Significant increase of nail hydration with respect to the control (0% w/v of hydration).
HPβ-CD: Hydroxypropyl β-cyclodextrin.
Reproduced from [85].

the great versatility to adjust the role of CDs to different systems. As mentioned before, polymeric CDs are an interesting option to enhance the performance of CD complexes. In this context, Bencini *et al.* produced a synthetic, biocompatible, biodegradable, nontoxic and water-soluble derivative based on β-CD and poly(amidoamine) that was used to complex ACV [63]. This ACV/complex was evaluated *in vitro* against two clinical isolates of herpes simplex virus revealing a higher antiviral activity than the free drug [63]. These findings are an additional example of the versatility that can be achieved with CDs in drug delivery.

Fungal infections

Avoiding the proliferation of fungal diseases is another great challenge, especially in immunocompromised HIV-infected patients [64]. Thus, there is an urgent need to develop more powerful antifungal agents and to optimize the performance of the already approved ones. Based on the chemical structure, antifungals are classified into three major groups, namely polyenes, azoles and allylamines.

Nystatin, amphotericin B and natamycin are the main representatives of the polyenes group, characterized by possessing a ring containing a lactone moiety and a series of conjugated double bonds. This typical structure confers them low chemical stability. Furthermore, all these drugs display poor aqueous solubility and low bioavailability by the oral and topical routes. In addition, to be acceptable candidates for parenteral administration, the solubility must be ensured. Several polyene/CD complexes have been developed, achieving a statistically significant increase of the aqueous solubility and the antifungal activity (Table 8) [64–70].

Besides, CDs protect the drug against adverse environmental conditions, preventing degradation and prolonging its shelf life. For example, Cevher *et al.* produced natamycin/γ-CD inclusion complexes to protect it from hydrolysis [65]. The chemical stability of the drug under hydrolytic conditions was assessed *in vitro* at 37°C for 15 days, 98% of the complexed drug remaining intact in solution versus 60.5% of the free counterpart (Figure 3) [65].

The azole group is widely used for the treatment of both topical and systemic fungal infections. Structurally, these compounds may contain an imidazole (e.g., econazole, clotrimazole, ketoconazole) or a triazole ring (e.g., voriconazole, itraconazole, fluconazole). Members of the triazole family display a lower toxicity profile than the imidazole group, and are some of the most widely used antifungal agents today [71]. However, they display an extremely low aqueous solubility that can be improved through complexation with CDs (Table 8) [72–77]. Depending on the CD and the technique selected to prepare the complex, it was possible to attain different solubilizing extents. For example, several research groups have complexed itraconazole with CDs enabling a greater solubilization that enhances the absorption of the drug after its oral administration in human volunteers [78]. This type of system could even cure thrush in pediatric and adult HIV patients that are a population more difficult to treat owing to the presence of an immunocompromised immune system [78].

A complementary strategy to further increase the complexation efficiency was to include the inclusion complex in a ternary system [79] where pharmaceutical excipients such as citric acid or hydrophilic polymers (e.g., Soluplus®) are added as a third compound to the complexation medium [76,80]. Similarly, some researchers emphasized the advantage of including CD inclusion complexes within polymeric nanoparticles [81], resembling the so-called Nanoparticle-in-Microparticle Delivery Systems [82]. In this context, Jafarinejaf *et al.* produced itraconazole/HPβ-CD inclusion complexes loaded within chitosan nanoparticles that were re-encapsulated in mannitol/lactose microparticles [81]. This groundbreaking system allowed, on one hand, enhancing the aqueous solubility by virtue of the CD complex formation and, on the other, achieving pulmonary deposition of the drug through the microparticulate carrier that undergoes instantaneous

Table 10. Effect of HPβ-CD on *in vitro* drug permeation (expressed by flux) of terbinafine hydrochloride from nail lacquer drug delivery formulations across nail clippings in 48 h.†

Concentration of HPβ-CD (% w/v)	Flux (μg/ml/cm²) (mean ± SD)
0	0.868 ± 0.06
6	3.908 ± 0.05
7	4.140 ± 0.11
8	4.076 ± 0.15
9	4.214 ± 0.05
10	4.586 ± 0.08

HPβ-CD: Hydroxypropyl β-cyclodextrin.
Reproduced from [85].

dissolution in the lung mucus [83]. After that, itraconazole/HPβ-CD loaded chitosan nanoparticles released the drug up to 48 h (Figure 4) [81].

Finally, terbinafine is one of the major representatives of the allylamines group. Along with itraconazole, it is the drug of choice to treat onychomycosis, a common nail fungal disease [84]. Since the infection is embedded within the nail, drugs scarcely reach the site of action. For that reason, the infection is usually chronic, difficult to eradicate and with a tendency to relapse [84]. Although a topical administration can replace the oral route that is associated with hepatotoxicity, the poor permeability through the nail limits its application. In this context, HPβ-CD resulted effective as a drug permeation enhancer [85]. Moreover, as reflected in Table 9, HPβ-CD could significantly increase the hydration of nail by using a concentration in the 5–10% w/v range and thus, increase the flux across the nail plate.

In vitro transungual permeation results showed that by virtue of the permeation enhancement of HPβ-CD, terbinafine hydrochloride could significantly permeate the nail and the minimal inhibitory concentration (1 μg/ml) be overcome (Table 10) [85].

Protozoal infections

The spectrum of protozoal infections ranges from asymptomatic to severe manifestations that can be life-threatening in some cases such as malaria, visceral leishmaniasis or Chagas disease (American trypanosomiasis) [86,121,122].

Most antiprotozoals currently used display poor aqueous solubility that directly affects not only their bioavailability but also the ability to formulate them. In this context, drug complexation with CDs has become a straightforward approach to improve their biopharmaceutical performance (Table 11) [87–91].

Based on this, several researchers looked at the impact of this solubility enhancement in animal models such as mouse [89], rat [91] and even sheep [87].

For example, Leonardi *et al.* complexed benznidazole (BZL, intrinsic solubility in water of 0.4 mg/ml) with β-, HP-β and Mβ-CD obtaining a significantly higher dissolution rate with any of the CDs tested with respect to free BZL (Figure 5) [91].

This increase in the dissolution rate improved the AUC_{0-5} for BZL/β-CD, BZL/HPβ-CD and BZL/Mβ-CD by 1.4-, 2.3- and 2.6-fold, respectively, when compared with the free BZL (Table 12) [91]. The maximum plasma concentration of BZL increased in an equivalent manner (Table 12) [91].

In another *in vivo* study, Rodgers *et al.* administered daily melarsoprol inclusion complexes with HPβ- and RMβ-CD to *Trypanosoma brucei* infected mice for a period of 7 days by oral route on day 21 post-infection during the CNS stage of the Human African Trypanosomiasis (sleeping sickness). Results showed that the parasite load in the brain was rapidly reduced, achiev-

Table 11. Solubility enhancement of different antiprotozoals after complexation with cyclodextrins.

Drug	Intrinsic solubility in water, 25°C (μg/ml)	Drug/CD	Fold solubility enhancement	Ref.
ABZ	0.2	ABZ/HPβ-CD	2860	[87]
ABZ	8.9†	ABZ/HPβ-CD	191	[87]
MLS	6.0	MLS/HPβ-CD	7200	[88]
MLS	6.0	MLS/RAMβ-CD	7200	[88]
MTN	143.5	MTN/β-CD	9.7	[90]

ABZ: Albendazole; MLS: Melarsoprol; MTN: Benzoyl metronidazole.
Solubility of ABZ in citric acid (50 mM).

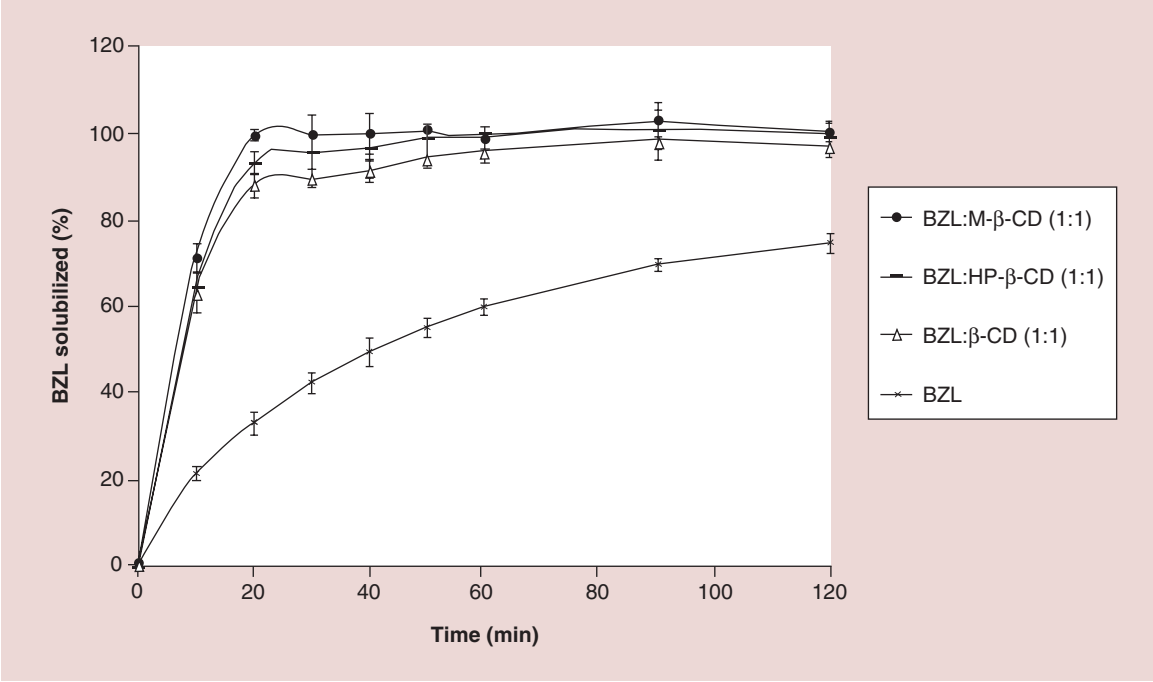

Figure 5. Dissolution profiles of BZL alone, BZL/β-CD, BZL/HPβ-CD and BZL/Mβ-CD (ratio 1:1) in HCl 0.1N.
Reproduced with permission from [91].

ing the cure of mice that were treated with a dose from 0.05 mmol/kg (Figure 6A) [89].

These findings revealed the superiority of the complex with respect to the free drug (melarsoprol) and both water soluble commercialized antitrypanosomal drugs, namely melarsamine hydrochloride (MelCy, Cymelarsan®) and melarsonyl potassium (MelW, trimelarsen®). In fact, no cures were achieved in mice treated with MelCy or MelW with an equivalent dosing regimen to that of the inclusion complexes and only 33% of mice given melarsoprol 0.05 mmol/kg were cured (Figure 6B) [89]. This strongly suggested that melarsoprol/HPβ-CD and melarsoprol RMβ-CD could be used to treat patients in this phase of the disease. Interestingly, Wong *et al.* evaluated the pharmacokinetic profile of the antimalarial artemisinin after complexation with β- and γ-CD in healthy human volunteers using the commercially available formulation Artemisinin 250® as control. Results confirmed the statistically significant increase in oral bioavailability that was reflected by the total plasma area-under-the-curve ($AUC_{0-\infty}$), the maximum plasma concentration (C_{max}) and the time to reach the C_{max} (t_{max}) (Table 13) [92].

Another disadvantage displayed by many antiprotozoals is the bitter taste that has a crucial role in the treatment of pediatric patients and that jeopardizes compliance and therapy efficacy [93]. Several research groups have proved that drug/CD complexes mask bitterness [94–97]. Noticeably, Shah and Mashru have developed a dry powder consisting of the antimalarial artemether complexed with different CDs that could be extemporaneously reconstituted into a palatable suspension [96]. This formulation showed complete bitter taste masking through a gustatory sensation test carried out in 20 adult volunteers [96]. Thus, a formidable opportunity to improve pediatric and geriatric patient compliance becomes apparent.

Table 12. Major pharmacokinetic parameters after the oral administration of BZL, BZL/β-CD, BZL/HPβ-CD and BZL/Mβ-CD at 1:1 drug:carrier molar ratio (n = 3).

	C_{max} (ng/ml)	AUC_{0-5} (ng/h/ml)	T_{max} (h)
BZL	665.2 ± 23.5	455.7 ± 18.2	2 ± 0.0
BZL/β-CD	918.6 ± 41.6	665.5 ± 17.9	2 ± 0.0
BZL/HPβ-CD	1480.0 ± 62.1	1051.1 ± 20.1	2 ± 0.0
BZL/Mβ-CD	1536.0 ± 51.4	1184.8 ± 17.5	2 ± 0.0

Adapted with permission from [91].

Table 13. Pharmacokinetic parameters obtained with artemisinin inclusion complexes with β- and γ-CD and Artemisinin 250® used as control.

Pharmacokinetic parameter	Artemisinin 250®	β-CD complex	γ-CD complex
$AUC_{0-\infty}$ ± SD (ng/h/ml)	782.3 ± 392.0	1329.4 ± 562.4	1131.3 ± 456.6
C_{max} ± SD (ng/ml)	271.7 ± 174.6	651.5 ± 604.9	458.1 ± 182.2
t_{max} ± SD (h)	2.0 ± 0.6	1.6 ± 0.8	1.4 ± 0.6

β-CD: β-cyclodextrin; γ-CD: γ-cyclodextrin.
Adapted with permission from [92].

Routes of administration

The safety profile, efficacy in terms of complexation, cost and acceptance by the regulatory agencies are some important factors of consideration demanding evaluation in the context of the envisioned administration route. In this section, we will concisely outline the possible applications and types of CDs that are more suitable based on the route of administration.

Oral route

Many toxicity studies have proved that CDs can be administered by the oral route because they are practically non-toxic due to a negligible absorption in the gastrointestinal tract [8]. However, at high doses, some side effects related to the poorly digestible nature of these carbohydrates (e.g., flatulence and diarrhea) may occur [3]. The only CD that does not follow this security profile is RMβ-CD because it is slightly more lipophilic than the other CDs and forms less hydrogen bonds. Hence, its oral bioavailability is somewhat higher than the other derivatives, becoming potentially toxic. For that reason, oral administration of RMβ-CD is limited and only small amounts can be included in oral products [14]. In this context, Boulmedarat *et al.* indicated that 10% RMβ-CD induced toxic and inflammatory effects on human oral epithelium model cell depending on the exposure time, while lower concentrations (2–5%) did not provoke tissue damage [98].

Drug inclusion complexes with any of the aforementioned CDs could be administered to enhance drug oral bioavailability based on increased drug solubility [90]. Moreover, as described above, it is possible to mask the taste of drugs [96] and to decrease local drug irritation [9]. For example, a formulation with reduced drug gastrointestinal irritation containing an itraconazole/HPβ-CD complex is commercialized in the US

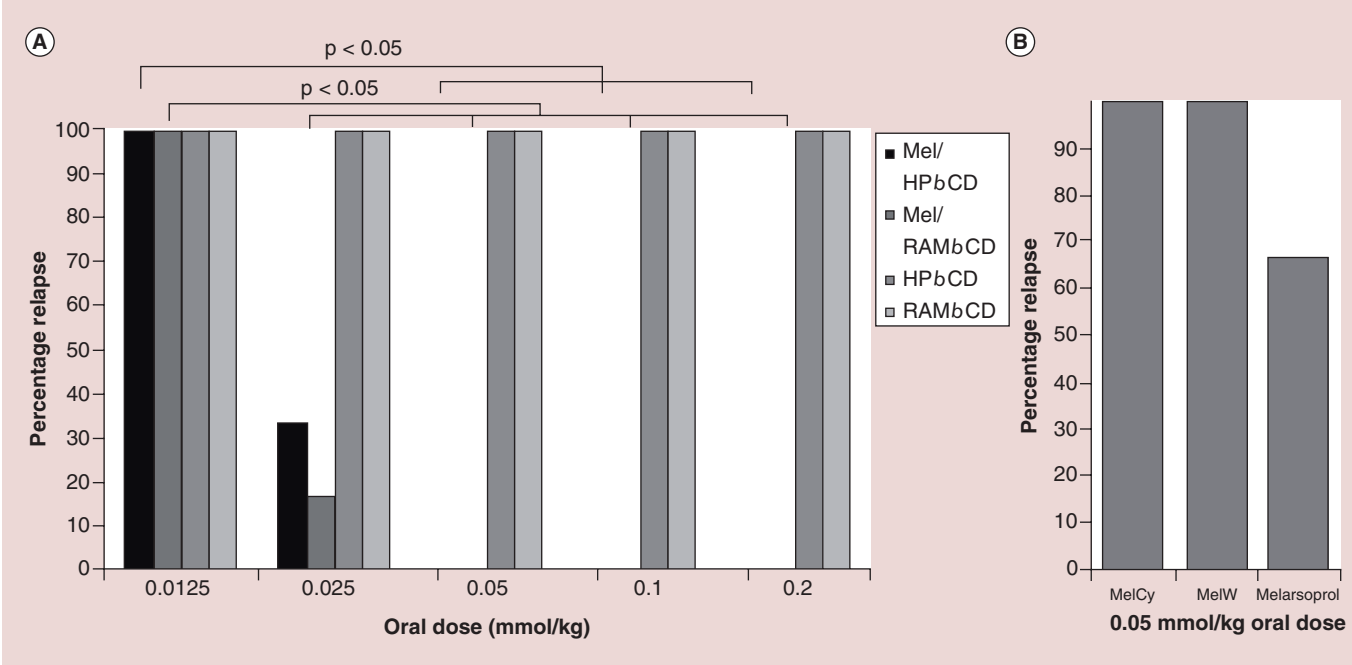

Figure 6. Relapse rates of mice after the administration of (A) different doses of CDs and melarsoprol/CDs and (B) a fixed dose of melarsoprol, Cymelarsan® (MelCy) and Trimelarsen® (MelW) used as control.
Reproduced with permission from [89].

Table 14. Anti-infective medicines containing CDs on the market.

Trade name	CD type	Infection type	Drug	Administration route	Pharmaceutical form	Company	Country
Meiact®	β-CD	Antibacterial	Cephalosporin	Oral	Tablet	Meiji Seika	Japan
Pansporin T®	α-CD	Antibacterial	Cefotiam hexetil hydrochloride	Oral	Tablet	Takeda	Japan
Vibativ®	HPβ-CD	Antibacterial	Telavancin	Parenteral	Solution	Astellas Pharma/ Therevance,	Europe
Mitozytrex®	HPβ-CD	Antibacterial	Mitomycin	Parenteral	Dry powder for reconstitution	Novartis	Europe
Clorocil®	RMβ-CD	Antibacterial	Cloramphenicol	Topical (ocular)	Solution	Oftalder	Europe
Vorzu®	HPβ-CD	Fungal	Voriconazole	Oral	Tablet	Rhambaxy	India
Sporanox®	HPβ-CD	Fungal	Itraconazole	Oral and Parenteral	Solution	Janssen	Belgium/USA
Vfend®	SBEβ-CD	Fungal	Voriconazole	Parenteral	Solution	Pfizer	USA
Metrogel®/ Flagyl®/ Vandazol®/ Nidagel®	β-CD	Antiprotozoal	Metronidazole	Topical	Vagina gel	Curatek/ Fougera/ Tolmar	USA/Canada
Entronor-TZ®/ Noroxin®	β-CD	Antibacterial/ antiprotozoal	Norfloxacin and tinidazole	Oral	Tablet	Genpharma	India
Mena-Gargle®	β-CD	Disinfectant	Iodine	Topical (buccal)	Solution	Kyushin	Japan
Vitaseptol®	β-CD	Antiseptic	Thiomersal	Topical (ocular)	Solution	Europhta/ Novartis Pharma SA	Monaco/ Switzerland

α-CD: α-cyclodextrin; β-CD: β-cyclodextrin; HPβ-CD: 2-hydroxypropyl β-cyclodextrin; RMβ-CD: Randomly methylated β-cyclodextrin; SBEβ-CD: Sulfobutylether β-cyclodextrin.
Data taken from [14,111,123].

and Europe with the name of Sporanox® (Table 14). It is worth highlighting that HPβ-CD is one of the most widely used CDs despite the greater cost when compared with β-CD [16] due to a greater water solubility and safety profile (Table 3).

Parenteral route

Applications of CDs by parenteral route include drug solubilization, stabilization of sensitive drugs in aqueous solution and reduction of drug irritation at the injection site [9]. Obviously, the number of CDs (and the dose) approved for parenteral use is more restricted than for the oral one. Several of them, such as γ-CD, HPβ-CD, SBEβ-CD, sulfated-β-cyclodextrin (Sβ-CD) and maltosyl β-cyclodextrin (Mβ-CD) seem to be safe for this route. Conversely, α-CD, β-CD and the methylated β-CD are not suitable for parenteral administration due to solubility and toxicity issues [3]; for example, β-CD displays a low aqueous solubility and side effects like nephrotoxicity that are related to the ability to extract cholesterol from cellular lipid rafts [8,99]. Among the different CDs, HPβ-CD and SBEβ-CDs are the most widely used for parenteral route owing to their high aqueous solubility and low toxicity. Not surprisingly, there is a parenteral version of injectable itraconazole in HPβ-CD complex, Sporanox® Injection, available in the market (Table 14).

Topical route

Topical administration is employed to treat local infections in skin and other mucosal tissues (e.g., ocular, nasal, vaginal, rectal) and minimize or prevent systemic exposure. In general, natural and hydrophilic CD derivatives are nontoxic to the skin, the eye, the vaginal and respiratory mucosa because their permeation through the epithelium is negligible [3]. However, some of them such as α-CD could cause some ocular irritation [3]. Special attention should be paid to methylated CDs. Several reports indicate that this CD can irritate the eye, the nasal mucosa and the stratum corneum. However, by controlling both the concentration and the application frequency, they could be eventually used [100,101]. A clear example is the commercial product named Clorocil® containing RMβ-CD and

the antibacterial drug chloramphenicol (Table 14). Along with methylated CDs, α-CD has demonstrated to cause some ocular irritation [3]. This phenomenon stems from the detrimental interaction with components of the corneal membrane such as phospholipids and proteins. The recommended CDs for ocular route are γ-CD, HPβ-CD and SBEβ-CD [9]. Usually, the topical route is pursued to increase drug solubility and thus, reduce the therapeutic concentration. This is especially apparent in ophthalmic delivery because usually only less than 5% of the instilled dose can penetrate the cornea and the intraocular tissues. Furthermore, several researchers have reported that CDs can enhance drug permeability through biological membranes like the cornea or the skin, an effect that potentiates the already increased bioavailability due to the increased solubility. In addition, complexation with CDs could protect sensitive drugs from degradation in epithelium. Similarly, the inclusion of irritating drugs into CDs has been shown to protect cornea, mucosa or skin from irritation [9].

Dosage forms of CDs for infectious diseases

Dosage forms currently commercialized to treat infectious diseases are extremely diverse and include solid, semisolid and liquid forms. At the same time, it is important to emphasize that usually large amounts of CD are required to solubilize the drug [102]. Hence, the total mass containing not only drug/CDs but also excipients needed to form a suitable dosage form should be considered to develop an acceptable amount of formulation. Probably, drug inclusion complexes prepared as a suspension or a powder for extemporaneous reconstitution would enable a greater dose than a tablet or a capsule [15].

Cevher *et al.* obtained bioadhesive tablets intended for vaginal route containing either natamycin or itraconazole in the form of inclusion complexes with γ- and SBEβ-CDs, respectively [65,72]. Depending on the flow, the apparent density, the compressibility and the compactability of the material to be compressed, the tablet may be produced by direct compression or subjected to a granulation process. Obviously, the former is the simplest but not always possible production process, mainly due to flowability constraints. However, if the amount of drug in the inclusion complex was low, the mixture would flow appropriately enabling direct compression [103]. In the present, there are physically modified CDs with improved flowability and compressibility properties designed to be used by direct compression, though with an economic value associated. For example, Gundogdu *et al.* have complexed the antibiotic cefpodoxime with HPβ-CD to improve its aqueous solubility and dissolution rate and developed a tablet by direct compression [26]. For this, a binder diluent special for direct compression was added to the complex. Another alternative when direct compression is not technically possible is to subject the inclusion complexes to a granulation process whereby agglomerates are formed by mechanical force (dry granulation process) or binders (wet granulation process). This step improves the flowability of the powder for a later compression. However, in wet granulation method, factors like solvent, binder and mixer must be assessed because the apparent stability constant of the complexes could change [104].

Besides solid forms, it is possible to formulate a semisolid product like a gel for topical administration. This type of formulation enables the prolongation of the residence time of the drug at the application site. This is especially relevant for ophthalmic formulations because liquid formulations are rapidly removed by lacrimal secretion and nasolacrimal drainage [24], leading to low bioavailability. An interesting strategy is to use temperature (Pluronic®) or pH (Carbopol®) sensitive polymers as part of the formulation. Thus, the polymer solution containing the drug inclusion complexes is applied as a solution and undergoes a sol-gel transition *in situ* upon heating or pH changes under the physiological conditions of the eye [105]. Several researchers have developed these type of systems containing either doxycycline or ciprofloxacin [24,32,33]. Finally, drug inclusion complexes with CDs can be prepared as a liquid form. For this, complexes are re-suspended in a solution containing the suitable excipients and if the formulation is stable over time, it could be administered as such. Conversely, the liquid could be freeze- or spray-dried to produce redispersible powders [96]. The latter strategy is suitable when the stability of the suspension is not high enough. It is worth mentioning that these liquid forms are usually appropriate for children and the addition of sweeteners and flavors could be used to enhance patient compliance. Remarkably, more than ten different antimicrobial drugs are currently marketed in the form of CD complexes, highlighting the usefulness of this proven technology platforms to improve the biopharmaceutical performance of drugs and ensure a timeous bench-to-bedside translation (Table 14).

Conclusion & future perspective

Infectious diseases remain the leading cause of death in the world and their treatment remains extremely challenging as many different types of microorganisms and with variable susceptibility to anti-infective agents provoke them. The infection-causing microorganisms are adapting (and developing resistance) to drugs faster than the research in new drug discovery and pharma-

ceutical product innovation, especially in the case of poverty-related diseases with higher incidence in poor nations. In this context, technology tools that are biocompatible, versatile and approved by regulatory agencies in North America, Europe and Japan remain fundamental players to overcome the most relevant biopharmaceutical drawbacks of drugs. In this milieu, CDs will continue to play a key role not only for the improvement of approved drugs but also for new chemical entities in different stages of development. At the same, following the extensive work done in the development of drug-loaded hydrogels, the use of CDs as building blocks for more sophisticated drug delivery systems remains an undercapitalized field that will ensure a preponderant place for these pharmaceutical excipients also in the future.

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Executive summary

- Bacterial, viral, fungal and protozoal infections represent a leading cause of death and a significant burden to healthcare systems worldwide.
- Poor biopharmaceutical performance reduces the efficacy of anti-infective agents.
- Cyclodextrins have been extensively employed to overcome the most relevant biopharmaceutical drawbacks of anti-infective agents by means of the production of different types of drug/cyclodextrin complexes and aggregates.
- The use of cyclodextrin as building blocks of more sophisticated drug delivery systems ensures the central role of these pharmaceutical excipients in the development of innovative medicines for the treatment of infectious diseases also in the future.

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