Advanced Technologies for Oral Controlled Release: Cyclodextrins for oral controlled release

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ABSTRACT

Cyclodextrins (CDs) are used in oral pharmaceutical formulations, by means of inclusion complexes formation, with the following advantages for the drugs: (1) solubility, dissolution rate, stability and bioavailability enhancement; (2) to modify the drug release site and/or time profile; and (3) to reduce or prevent gastrointestinal side effects and unpleasant smell or taste, to prevent drug-drug or drug-additive interactions, or even to convert oil and liquid drugs into microcrystalline or amorphous powders. A more recent trend focuses on the use of CDs as nanocarriers, a strategy that aims to design versatile delivery systems that can encapsulate drugs with better physicochemical properties for oral delivery. Thus, the aim of this work was to review the applications of the CDs and their hydrophilic derivatives on the solubility enhancement of poorly water soluble drugs in order to increase their dissolution rate and get immediate release, as well as their ability to control (to prolong or to delay) the release of drugs from solid dosage forms, either as complexes with the hydrophilic (e.g. as osmotic pumps) and/ or hydrophobic CDs. New controlled delivery systems based on nanotechonology carriers (nanoparticles and conjugates) have also been reviewed.

KEYWORDS: controlled release, cyclodextrin, inclusion complex, solid dosage forms, solubility.

Introduction

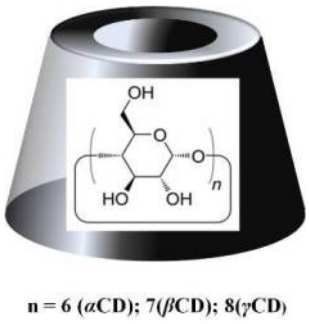
Drugs need to be released from their carriers (formulations and/or delivery systems) in order to produce their therapeutic effects (1), and difficulties on the design of the formulation may arise depending on drugs' solubility. Currently, many platforms are available for a prolonged or delayed releasing of highly water soluble drugs (2). However, if drugs are poorly water soluble, their formulation is more challenging (solubilization and/or particle engineering) especially when a controlled release drug profile is desired. For these drugs the absorption and bioavailability could be influenced by their intrinsic solubility and dissolution rate in the gastrointestinal (GI) tract. There are many strategies to enhance the solubility of poorly water soluble drugs in order to formulate them as oral dosage forms. These strategies include salt formation, microenvironmental pH control, solubilization with surfactants (3), complexation with cyclodextrins (CDs) (4), solid dispersions (5), lipid based formulations (6) and nanoparticle (NP) formulations (7). Besides the solubility, the pharmacokinetic and pharmacodynamic properties of pharmacologically active moieties can be changed by using novel drug delivery systems or by modifying the molecular structure and/or physiological parameters depending on the route of administration. The interaction between CD, drug and dosage form influences the kinetics of key processes of oral drug delivery, including dissolution and absorption (8,9). Thus, the choice of the best drug delivery system will aim to enhance drug bioavailabilty and reduce their toxicity. In the complexation processes the different interactions between chemistry species (molecules, ions, radicals) that do not involve covalent bonds are mostly of the host-guest type. CDs seem to be the most important ones in this domain. Also, the incorporation of CDs into a drug dosage form may affect the activity of basic pharmaceutical ingredients and may modify the properties of the whole drug formulation. Nearly 40 marketed commercial drug products currently benefited from such CD technology (10). The complexation can influence the drug release, but the process does not affect the drug intrinsic ability to permeate lipophilic biomembranes. However, CDs have been used as permeation enhancers in topical formulations (11) and to increase the permeability of water-insoluble drugs by making the drug available at the biological membrane surface (skin, mucosa or the eye cornea). For water-soluble drugs CDs increase drug permeability by direct action on membrane and enhance drug absorption and/or bioavailability (12-19). The drug release can be modified by using CDs and their derivatives. Among the different CDs, for example the hydrophobic CD derivatives such as ethylated and peracylated ones have been employed as slow-release carriers for water-soluble drugs (20). In addition, the use of CDs in biological system often requires amphiphilic properties; thus, several modifications have been performed on CDs with the aim to provide versatile carriers and delivery systems for hydrophilic and hydrophobic drugs (21,22). Many studies have been developed where CDs are used as modified release carriers (eg., colon-specific delivery systems) (23-26). In the last two decades, synthetic macromolecules with functional groups of pharmacological potential have received considerable attention. CDs are potent candidates for such role through the formation of drug conjugates improving certain drug properties such as solubility and/or bioavailability (27). However, physic and pharmaceutical properties of CD conjugates in which a drug is covalently bonded to the CD may be significantly different from those of the inclusion complexes (28). The use of the CD conjugate-based repeated- and prolonged-release systems is described in various studies (13,29,30).

Cyclodextrins

Parent / Natural

Naturally occurring CDs are obtained through the enzymatic reaction on the starch. CDs are cyclic oligosaccharides built up from glucopyranose units linked by α-1,4 bonds, thus forming a torus-like macro-rings. They are characterized as crystalline, homogeneous and non hygroscopic substances. The natural CDs are: αCD (Schardinger's α-dextrin, cyclomaltohexaose, cyclohexaglucan, cyclohexaamylose, αCD, ACD, C6A) comprising six glucopyranose units; βCD (Schardinger's β-dextrin, cyclomaltoheptaose, cycloheptaglucan, cycloheptaamylose, βCD, BCD, C7A) comprising seven of such units, and γCD (Schardinger's γ-dextrin, cyclomaltooctaose, cyclooctaglucan, cyclooctaamylose, γCD, GCD, C8A) that comprises eight of such units (Fig. 1) (4,31,32). The most important characteristics of the natural CDs are summarized in Table 1 (4,31).

The CDs may modify important properties of the drugs through their inclusion complex formation ability. For a long time only the parent (or major) CDs (α, β, and γCD) were known and well characterized. Subsequently other CDs have been discovered. CDs containing less than seven units cannot be formed due to steric hindrance while the homologues with nine or more glucose units are very difficult to purify (33,34).



n = 6 (αCD); 7(βCD); 8(γCD)

Fig. 1. Schematic cyclodextrins structure

Table I. Characteristics of α, β, and γCD

	α	*β*	*γ*
Nº of glucose units	6	7	8
Mol weight	972	1135	1297
Solubility in water (g/100ml), room T	14.5	1.85	23.2
$[R]_D$25 ºC	150.0 ± 0.5	162.5 ± 0.5	177.4 ± 0.5
Cavity diameter (Å)	4.7-5.3	6.0-6.5	7.5-8.3
Height of torus (Å)	7.9 ± 0.1	7.9 ± 0.1	7.9 ± 0.1
Diameter of outer periphery (Å)	14.6 ± 0.4	15.4 ± 0.4	17.5 ± 0.4
Approx. cavity volume ($Å^3$)	174	262	427
Approx. cavity volume in 1 mol CD (ml)	104	157	256
Approx. cavity volume in 1 g CD (ml)	0.10	0.14	0.20
Crystaline forms (from water)	Hexagonal plates	Monoclinic parallelograms	Quadratic prisms
Crystal water, wt%	10.2	13.2-14.5	8.13-17.7
Diffusion constant at 40 ºC	3.443	3.224	3.000
Hydrolysis by A. *oryzae* α-amylase	Negligible	Slow	Rapid
V_{max} value, min^{-1}	5.8	166	2300
Relative permittivity at pH 5.3, 25 ºC (on incorporating the toluidinyl group of 6-p-toluidynilnaphthalene 2-sulphonate)	47.5	52.0	70.0
(on incorporating the naphthalene group)	a	29.5	39.5
pK (by potentiometry) at 25 ºC	12.332	12.202	12.081
Partial molar volumes in solution (ml/mol)	611.4	703.8	801.2
Adiabatic compressibility in aqueous solutions ml (mol^{-1} bar^{-1}) x 10^4	7.2	0.4	-5.0

[a] Naphthalene group is too bulky for the *α*CD cavity

Derivatives

In recent years, many CD derivatives have been synthesized. These derivatives usually are produced by aminations, esterifications, or etherifications of their primary and secondary hydroxyl groups. These CD derivatives and also CD polymers have been prepared to obtain better properties (i.e. better solubility, stability, and inclusion abilities) than those of the parent CDs (35,36). Depending on the substituent, the CD derivatives may change their hydrophobic cavity volume and also solubility, stability against light or oxygen, and help to control the chemical activity of guest molecules in comparison to their parent CDs. In the Table II, various CD derivatives are presented (30,37-39). Other type of CD derivatives - the amphiphilic ones - can be obtained by the introduction of long alkyl or fluoroalkyl chains at primary and/or secondary sides of the CDs. These CDs have shown the ability to form monolayers at the air-water interface and supramolecular structures, such as micelles or bilayer vesicles in water and NPs. In many cases, the CD cavities retain their full capacity to include external guests, showing promise for a possible application in drug delivery (21,40).

Table II. Cyclodextrins Derivatives and Their Release Behavior

Hydrophilic derivatives		
Methylated *β*-Cyclodextrin		
methyl-*β*-cyclodextrin	Me*β*CD	
randomly methylated-*β*-cyclodextrin	RM*β*CD (RAMEB)	
dimethyl-*β*-cyclodextrin	DM*β*CD (DIMEB)	
randomly dimethylated-*β*-cyclodextrin	RDM*β*CD	
trimethyl-*β*-cyclodextrin	TM*β*CD	Immediate release
acetylated dimethyl-*β*-cyclodextrin	DMA*β*CD	
Hydroxyalkylated *β*-Cyclodextrin		Enhanced dissolution and absorption
2-hydroxyethyl-*β*-cyclodextrin	2-HE*β*CD	of poorly water-soluble drugs
2-hydroxypropyl-*β*-cyclodextrin	2-HP*β*CD	
3-hydroxypropyl-*β*-cyclodextrin	3-HP*β*CD	
hydroxybutenyl-*β*-cyclodextrin	HBen*β*CD	
2,3-dihydroxypropyl-*β*-cyclodextrin	2,3-DHP*β*CD	
Branched *β*-Cyclodextrin		
glucosyl-*β*-cyclodextrin	G_1*β*CD	
maltosyl-*β*-cyclodextrin	G_2*β*CD	
glucuronyl-glucosyl-*β*-cyclodextrin	GUG*β*CD	
Hydrophobic derivatives		
Alkylated *β*-Cyclodextrin		
2,6-di-O-ethyl-*β*-cyclodextrin	DE*β*CD	
2,3,6-tri-O-ethyl-*β*-cyclodextrin	TE*β*CD	
Acylated *β*-Cyclodextrin		Prolonged release
2,3,6-tri-O-acyl$_{(C2\text{-}C18)}$-*β*-cyclodextrin	TA*β*CD	
2,3,6-tri-O-butanoyl-*β*-cyclodextrin	TB*β*CD	Sustained release of water-soluble
2,3,6-tri-O-valeryl-*β*-cyclodextrin	TV*β*CD	drugs
2,3,6-tri-O-octyl-*β*-cyclodextrin	TO*β*CD	
Ionizable derivatives		
Anionic *β*-Cyclodextrin		
O-carboxymethyl-O-ethyl-*β*-cyclodextrin	CME*β*CD	Delayed release (pH-dependent release)
β-cyclodextrin sulfate	*β*CD sulfate	
sulfobutyl ether group-*β*-cyclodextrin (d.s.4)	SBE_4*β*CD	Immediate release
sulfobutyl ether group-*β*-cyclodextrin (d.s.7)	SBE_7*β*CD	
Cationic *β*-Cyclodextrin		Prolonged release
tri-methyl-ammonium-*β*-cyclodextrin	TMA*β*CD	
Drug-CD conjugate		Delayed release (site-specific release)

d.s. = degree of substitution

Complexation

In an aqueous solution, the slightly apolar CD cavity is occupied by water molecules of high enthalpy (polar-apolar interaction). These water molecules can be readily substituted by appropriate "guest molecules" which are less polar than them (Fig. 2). The complexation process is most frequently a 1:1 host:guest ratio, however 2:1, 1:2, 2:2, or even more complicated associations, and higher order equilibrium exists, almost always simultaneously (4).

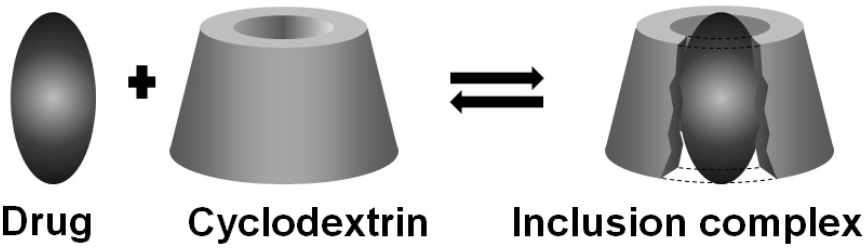


Fig. 2. The interaction of a drug with a cyclodextrin to form an inclusion complex

Applications

The most interesting property of CDs is their ability to form inclusion complexes with a large variety of apolar and hydrophobic molecules. In some cases, only a portion of the molecule is included (4). CDs have been used in pharmaceutical formulations in order to enhance the solubility, dissolution rate, stability, bioavailability, and oral absorption or to modulate biological activity of drugs (41-43). In addition, CDs have been also used to reduce or prevent GI and ocular irritation, to reduce or eliminate unpleasant smells or tastes, to prevent drug-drug or drug-additive interactions, or to convert oil and liquid drugs into microcrystalline or amorphous powders (8,44). Moreover, these substances are also used to modify the drug release from different systems: The hydrophilic CD derivatives such as 2-HPβCD and SBEβCD are used for improving solubility and dissolution rate of poorly water-soluble drugs (45), while hydrophobic CD derivatives such as ethylated and acylated CD are used as slow-release carriers for water-soluble drugs (46). Furthermore, advanced controlled-release profiles can be achieved by a combination of CD derivatives and pharmaceutical additives (47). It is noteworthy that the CDs toxic effects can be minimized by appropriate choice of the CD or its derivative to the administration route (4,31)**.**

Release behavior

For better understanding, the drugs release behavior is convenient considering the Biopharmaceutics Classification System (BCS) that is divided into four classes regarding the expectations on the *in vitro-in vivo* correlations: class 1 - high solubility-high permeability, class 2 - low solubility-high permeability, class 3 - high solubility-low permeability, class 4 - low solubility-low permeability (48,49).

The relative contribution of the different mechanisms involved in the drug release leads to a change in their dissolution profiles. The influence of CDs derivatives on the drug release place and/or time profile is presented in Table II (24). Some selected studies where the CDs have been used to modify the release of drugs will be presented below.

Immediate release

All drugs that have poorly water solubility (classes 2 and 4) may improve this property through complexation with hydrophilic CDs or their derivatives and consequently their dissolution rate enhancement. Several examples are shown in the Table III. Thus, the inclusion complexes can be used for immediate release applications allowing the drug to dissolve in the GI contents, without delaying or prolonging the dissolution or absorption of drugs (24,50).

Table III. Examples of the Increase the Solubility by the use of Cyclodextrins and Their Derivatives

Ciclodextrin	Drug	Therapeutic group	Other enhanced effect	Observation (Ref)
HPβCD	Alkannin/shikonin enantiomer	Antioxidant	*in vitro* permeability, photostability	(113)
βCDs and derivatives	Naringenin	Antioxidant		Combined with pH variation (114)
γCD > αCD and βCD	Coenzyme Q_{10} (CoQ_{10})	Antioxidant		Higher C_{max} and AUC in adult male and female (115)
βCD < HPβCD	Resveratrol	Antioxidant		Antioxidant activity in free form has little difference with Res in complexed form (116)
HPβCD, βCD	dl-alpha-tocopheryl acetate	antioxidant	Water penetration, wettability HPβCD	βCD does not solubilize the drug; drug-HPβCD at 1 : 2 molar ratio (117)
HEβCDs, HPβCDs	Naproxen	NSAID		βCD derivative in the 1:1 molar ratio; similar solubilising effect (118)
βCD, MeβCD	Ketoprofen Ibuprofen Naproxen	NSAIDs		MeβCD is the most effective amorphizing agent for ibuprofen and ketoprofen; ibuprofen shows comparable dissolution rates from IB-βCD and IB-MeβCD (119)
MeβCD	Ibuprofen	NSAID	Improved wettability	Complex increased dissolution rate was attributed to its amorphous nature (120)
αCD, βCD, γCD	Meloxicam	NSAID		Drug hydrophilicity may be due either to the formation of inclusion complexes or to a highly homogeneous assembly between the CD and the drug in the solid state (121)
SBEβCD, TMAβCD, βCD, MeβCD	Naproxen	NSAID		All SBEβCD products exhibited significantly better dissolution properties than the TMAβCD corresponding ones (38)
βCD	*RS*(±) Ibuprofen	NSAID	Bioavailability increase and minimizing the drug dose	Dissolution rate coefficient and the dissolved amount of the complex after 75 min was higher than that of unprocessed drug and of its untreated physical mixture (122)
$SBE_7\beta$CD, βCD	Ketoprofen	NSAID		$SBE_7\beta$CD is more effective solubilising agent for drug than βCD (123)
βCD MeβCD	Ketoprofen	NSAID		Synergistic effect by combined use of phospholipids and CDs (124)
βCD γCD	Ppiroxicam	NSAID		Complex was found to be significantly higher than that of the physical mixture (125)
βCD	Ibuprofen Indomethacin	NSAIDs		Water amount is not important to obtain complexes if the drug intrinsic solubility is not modified by complex formation (126)
βCD	Meloxicam	NSAID		NaOH was employed to increase βCD solubility to achieve uniform coating (127)
βCD	Ketoconazol	Antifungal		No differences between binary and multicomponent complexes from the same molar ratio (1:2) at pH 5; at pH 6, inclusion complex formed in presence of HCl lead to higher drug solubility (128)
βCD and its amorphous, MeβCD	Econazole	Antifungal		MeβCD complexes exhibited better performance than those with βCD (129)
HPβCD	Itraconazole	Antifungal		(130)

Continuation Table III

Ciclodextrin	Drug	Therapeutic group	Other enhanced effect	Observation (Ref)
*β*CD	Oxazepam	Benzodiazepine		(131)
*β*CD, HP*β*CD	Bromazepam	Benzodiazepine		(132)
SBE*β*CDs	Danazol	Steroid		SBE*β*CDs (with different d.s.) (133)
HP*β*CD (SBE)$_{7m}$*β*CD	Phenytoin	Antiepileptic		(134)
HP*β*CD, Me*β*CD, HP*γ*CD	Phenytoin	Antiepileptic		(135)
HP*β*CD	Bropirimine	Antiepileptic	Bioavailability improved	(136)
*β*CD	Atenolol	Antiepileptic		(137)
HP*β*CD	Oxcarbazepine	Antiepileptic		Blend of HP*β*CD with NaCMC (138)
DM*β*CD	Paclitaxel	Anticancer		The mostly effective was 2.3mM in a 0.1M 2,6-DM*β*CD aqueous solution (139)
*β*CD, *γ*CD	Artemisinin	Anti-parasites		Drug higher rate and extent of absorption compared to reference preparation using 12 healthy human volunteers (140)
*α*CD, *β*CD *γ*CD, HP*β*CD, SBE*β*CD, DM*β*CD, PM*β*CD, G1*β*CD, G2*β*CD	Artemisinin	Anti-parasites		*α*<*γ*≤*β*CD G2*β*CD≈G1*β*CD≈PM*β*CD[b]≈*β*CD<HP*β*CD< SBE7*β*CD<DM*β*CD most effective CD was DM*β*CD (141)
*β*CD	Carvedilol	Beta blocker		(142)
*β*CD	Warfarin	Anticoagulant		Preparation method and pH influence the *β*CD ability to include the drug (143)
*β*CD, HP*β*CD	Theophylline	Respiratory diseases		HP*β*CD doesn't influence drug solubility probably due to the bulky OH groups (144)
HBen*β*CD	Saquinavir	Antiretroviral in HIV therapy	Enhance the bioavailability	(39)
*β*CD, HP*β*CD, DM*β*CD	Tadalafil	Erectile dysfunction		Drug dissolution was markedly enhanced (>75% in the first 5 min) (145)
*α*CD, *β*CD, *γ*CD, HP*β*CD, DM*β*CD, TM*β*CD	Azadirachtin	Anti-malarial, Anti-tuberculosis, Anti-worms, Antifungal	High bioactivity low toxicity	Herbal medicine/healthcare products (146)
*β*CD, HP*β*CD	Rhein	Antiviral, anticancer		(147)
HP*β*CD	Celecoxib	Anticoagulan		Evaluation of the effect of hydrophilic polymers on the complexation and solubilizing efficiencies of HP*β*CD (148)
HP*β*CD SBE*β*CD	XK469[a] PPA	Anticancer		Synergistic effect of pH adjustment with cosolvency, micellization, or complexation (149)
HP*β*CD	Sulfisoxazole	Antibacterial		Solubilization can be improved by addition of the triethanolamine to the complexation medium or by ionization of the drug through pH adjustments (150)
HP*β*CD	Tanshinone IIA	Antibacterial, antitumor, anti-inflammatory In vitro permeability		(18)

2-Phenoxy-propanoic acid

[a] 2-[4-[(7-Cloro-2-quinoxalinyl)oxy]phenoxy]propanoic acid

[b] 2,3,6-Partially methylated-*β*CD

Modified release

This term is defined in the Eur. Pharm. (51) as a modification of the rate or place at which the active substance is released. Modified release products cover a wide range of release models, the principal types of which would include “delayed-release” and “prolonged-release” products.

Prolonged release

Most of the slow-release preparations have been aimed at achieving zero-order or pH-independent release of drugs to provide a constant blood level for a long period of time; this kind of formulation has many advantages, such as reducing the frequency of dosing, prolonging the drug’s efficacy and avoiding the toxicity associated with the administration of a simple plain tablet; for this purpose, hydrophobic CDs, such as alkylated and acylated derivatives, are useful as slow-release carriers for water-soluble drugs (classes 1 and 3) (22,24,50,52).

Conventional. It was shown that the freeze-drying method is simple and suitable for obtaining an inclusion complex of salbutamol with *β*CD and ethylated-*β*CD (Et-*β*CD). The different sustained-release behaviors obtained suggest that both the solubility and the dissociation of the complexes are responsible for the dissolution rates of the drug. The results indicate that Et-*β*CD may be considered as a good carrier for the sustained release of salbutamol (53).

The pharmaceutical application of triacetyl-*β*CD (TA*β*CD) as a slow release carrier for flufenamic acid (FA) was evaluated. An initial high-plasma peak concentration does not occur after the administration of FATA*β*CD complexes when compared with other excipients. The FATA*β*CD complex used appears to be appropriate for practical clinical applications that would result in reduced side effects of the drug and prolonged action (20).

The combination of hydrophilic CDs such as HP*β*CD and hydrophobic CDs such as perbutanoyl-*β*CD (TB*β*CD) has been analyzed as controlled-release systems for extremely hydrophilic drugs (captopril, Cap). The binary system of CapHP*β*CD or CapTB*β*CD and the ternary system of CapTB*β*CD/HP*β*CD were prepared. The release rate of drug from the binary HP*β*CD system was rather fast, whereas that from the binary TB*β*CD system was comparatively slower. The retarding effect was dependent on the amount of hydrophobic CD and was attributable to a gel formation of HP*β*CD in the TB*β*CD hydrophobic matrix. During this period, a viscous gel layer of the hydrophilic CD gradually forms on the surfaces or inside the tablets, and at a later stage of the release, the drug or the complex may be released through diffusion of the gel layer. This release rate can be controlled by adjusting the relative molar ratio of both components (54).

The controlled-release of metoprolol (Met), a water-soluble *β*1-selective adrenoreceptor antagonist, by means of a combination of HP*β*CD and a hydrophobic polymer, ethylcellulose (EC) was reported. The release rate of Met is HP*β*CD amount dependent, when formulated as complexes in the EC tables, i.e., the release rate decreased when appropriate amounts of HP*β*CD were added to hydrophobic EC matrix. This rate decrease may be attributable to a gel formation at high concentrations of HP*β*CD. HP*β*CD is widely used as a solubilizer and a fast-dissolving carrier for poorly water soluble drugs. However, the present study showed that it may work as a retarding carrier for the release control of water-soluble drugs such as Met (55).

Fernandes *et al.* studied the nicardipine release rate using hydrophilic (HP*β*CD) and hydrophobic (TA*β*CD) complexes. They observed that required sustained period could be controlled by adjusting the mixing ratio of its complexes, pointing out the importance of the carrier choice. This study showed that both CDs inclusion complexes achieved prolonged action, improved bioavailability, and reduced side effects after oral administration in rabbits (25).

The piroxicam (PX) following complexation with HP*β*CD was used to develop a controlled-release formulation for buccal administration. Matrix tablets containing the PXHP*β*CD complex and swellable hydrophilic polymers, such as hydroxypropylmethyl cellulose (HPMC) and Carbopol (C940), were prepared. Their release profiles were evaluated and showed the faster PX release (*in vitro*) when compared to those containing a physical mixture or "free" drug. The PX behavior from the polymer matrices in a constant mode over the passage of time was characterized by prolonged effect. The differences observed in release rates of PX from the all tablets could be attributed to the presence of the polymers and inclusion complexes (56).

The CD was also studied in relation to its relative contribution in the different mechanisms involved in the drug release from tablets produced with a wide range of HPMC proportions. The results showed that the *β*CD and HP*β*CD strongly determine the dissolution rate of drugs due to inclusion complexes formation. For some HPMC and drug ratios was observed that low CD concentrations promote drug diffusion due to the decrease on drug interactions with the polymer, while the opposite effect was observed for high CD concentrations (free CDs increase the tortuosity of the diffusional path). CD solubilising capacity plays an important effect on hydrophobic sulphamethizol release profile, where the release rate was greater for HPMC matrix tablets containing CDs. In contrast, the delay in the hydrophilic diclofenac (Dic) release profile may be attributed to the hindering effect of free CDs on drug diffusivity. The simplex centroid design used to prepare the tablets allowed to obtain the second-order canonical equations, which are particularly useful to predict the release behavior of tablets containing mixtures of HPMC, CD, and lactose (57).

Dic, as poorly soluble-free acid (DicH) or freely water-soluble sodium salt (DicNa), was analyzed following addition of the hydrophilic CD (HP*β*CD) in erodible hydrophilic poly(ethyleneoxide) matrices. This study, intended for oral drug delivery, has demonstrated that this incorporation affects drug release behavior and transport properties through artificial and biological membranes. Their modulator effect is observed not only on drug dissolution rate but also on environment where drug release occurs (aqueous medium, membrane interface) (58).

The behavior of the vinpocetine (VP), a poorly soluble base-type drug, following multicomponent complexation (MCC) with *β*CD, SBE*β*CD, tartaric acid (TA), PVP, and HPMC, on the design of controlled-release hydrophilic HPMC tablets was evaluated. The *in vitro* release profiles were carried out by a pH gradient method. The addition of *β*CD and SBE*β*CD, either in MCC or as physical mixture forms, improved the VP release profiles as a consequence of VP complexation, and the tablet formulations with VPSBE*β*CD-TA and VP*β*CD-TA MCC showed some variation on the rate and extent of VP dissolved as a result of different solubility performances of both CDs (59).

Hydrogels of different CDs cross linked with ethylene glycol diglycidyl ether (EGDE) were prepared. Estradiol presented a higher affinity for *β*CD, M*β*CD, and SB*β*CD than for HP*β*CD. The affinity for this last CD was greatly enhanced when HPMC (0.25%) was added to the medium and the system was autoclaved. The application of a one-step cross-linking with EGDE, under mild conditions, enabled the

formation of MβCD and HPβCD hydrogels. By contrast, the low solubility of βCD and the high anionic character of SBβCD hindered obtaining hydrogels. The estradiol loading was driven by the interaction of the drug with the CD network. The high loading ability of the hydrogels may enable the incorporation of a therapeutic dose of estradiol in a small piece of hydrogel, being the release sustained for several days owing to the affinity of the CD for the drug (60).

In other study with hydrogels consisting of polyvinylpyrrolidone/polyethylene glycol dimethacrylate (PVP/PEG-DMA), the CDs were grafted to the polymer matrix in 4-5 % (w/w) in an attempt to retard the release of water-soluble drugs. Vinyl derivatives of α, β and γCD were produced, added to the prepolymer blend, and cured by UV light. During this curing process, the CD derivatives were covalently incorporated into the hydrogel matrix, which was loaded with ibuprofen by swelling. The release of the model drug from CD modified hydrogels shows that especially covalently bonded βCD can change both the release rate and the release profile of ibuprofen (61).

The interactions between meglumine antimoniate (MA) and βCD induced by heating and freeze-drying were investigated, and their impact on antimony (Sb) absorption, administered by oral route, was evaluated. As a consequence of the slow drug release property of MAβCD nanoassemblies (sustained-release system of MA), following dilution in water, one can expect a change of the drug absorption site in the GI tract, when compared to MA alone or to the heated MAβCD physical mixture (62).

The combination of the metformin hydrochloride (MH) with a hydrophobic CD (TAβCD) and its dispersions in a suitable polymeric matrix (i.e., HPMC, xanthan gum, chitosan, EC, EudragitL100-55, Precirol), varying the relative amounts of MHTAβCD, was effective in adequately modulating the drug release rates. The matrix-tablet formulation containing the 1:1 (w/w) blend of MHTAβCD as co-ground and spray-dried systems fully achieved the prefixed goal. The results showed about 30% released drug after 2 h at gastric pH and overcoming 90% released drug within the subsequent 3 h in jejunal fluid (9).

Floating. The enhancement of the furosemide (FR) bioavailability by prolonging its duration in the stomach via the floating dosage forms with controlled release was evaluated. In this study, the floating dosage forms (bilayer floating tablets) with controlled release were prepared using solid dispersions of FR with βCD in a 1:1 proportion, and both *in vivo* and *in vitro* results were studied. The results show that the bioavailability of FR was excessively increased compared to conventional forms and that absorption of FR taken place vastly in stomach and upper part of small intestine (63).

The floating tablets of curcuminβCD (CURβCD) complex were formulated to provide sustained release of drug with an aim to provide an effective therapy with enhanced solubility and bioavailability, targeted action, and better absorption to treat stomach cancer. The formulation CURβCD complex exhibited maximum sustained release of curcumin with excellent floating and swelling properties. Also, *in vivo* antitumor studies confirmed that the overall rate of tumor incidence and number of tumors/mouse is less in animal group treated with CURβCD complex compared to animals treated with CUR and CURβCD (control II) (64).

The gastroretentive floating effervescent and non-effervescent tablets of silymarin (flavonolignans) were analyzed with purpose to increase the efficacy and stability of the drug in the stomach. The short half-life of the silymarin, poor bioavailability, and faster solubility in acidic medium make it a suitable candidate for gastroretentive drug delivery system. It was concluded that HPMC in combination with

crospovidone and microcrystalline cellulose can be promising polymers for effervescent gastroretentive drug delivery system. Swelling studies indicate significant water uptake and contributed to drug release and could be significant in gastric retention. On the other case, non-effervescent floating formulations based on polypropylene foam powder studied for their ability to control drug release over prolonged period of time. The drug release pattern can effectively be adjusted by varying formulation parameters such as concentration of swelling agent and *β*CD, type of matrix forming polymers, and blend of matrix forming polymers. The developed floating tablets of silymarin may be used for prolonged drug release, thereby improving the bioavailability and patient compliance (65).

Mucoadhesive. The interactions between a cationic polymer hexadimethrine bromide (HDMBr) and an anionic CD, SBE*β*CD, were investigated, as well as the potential of such a system for mucoadhesive, sustained drug delivery. The results show that interactions between the anionic SBE*β*CD and the cationic HDMBr can be used to obtain mucoadhesive sustained drug delivery system under certain conditions. Triclosan/SBE*β*CD/ HDMBr complex is better retained on a cation-exchange media than the triclosan/HP*β*CD/HDMBr complex. The positive charge of HDMBr did not have the expected effect on the buccal mucosa. Thus, was concluded that although a positive charge is likely to promote mucoadhesion, other polymers attributes, such as molecular weight and viscosity, may have equally beneficial effects (66).

In the continuing challenge to improve the properties of delivery systems, the possibility to modify chitosan by introducing *β*CD was analyzed, and then the mucoadhesive properties of this synthesized CD polymer were investigated. The use of *β*CD in combination with chitosan resulted in a polymer which showed substantial mucoadhesive properties, although lower compared to that of chitosan alone. The molecular size of CD-chitosan might lead to a decrease of the interpenetration into the mucus layer with a subsequent decrease in mucoadhesivity. In fact, it is known that, besides molecular weight, mobility and flexibility of polymeric chains play an important role in mucoadhesion. A monosubstituted *β*CD derivative could be efficiently grafted on chitosan, yielding a CD polymer with promising inclusion and mucoadhesive properties (67).

In another study, a novel thiolated carboxymethyl chitosan-g-*β*-cyclodextrin (CMC-g-*β*CD) was synthesized and characterized as mucoadhesive drug carrier. For the drug delivery study, tablets were prepared and the transfection of the hydrophobic model drug, ketoprofen (KP), was investigated as well as the swelling and mucoadhesive properties of the compacts. The swelling may have contributed to the mucoadhesiveness of the thiolated polymers. The KP release results indicate that this system seems to be a very promising vehicle for the administration of controlled release of hydrophobic drugs. The ability of *β*CD present in the thiolated polymers to form host–guest inclusion complexes with the drug molecules and disulfide cross-linking between the polymer chains could be the main reasons for the slow and steady drug release from thiolated CMC-g-*β*CD tablets. Perhaps the release of drug may be controlled by swelling followed by a diffusion-controlled mechanism (68).

Other formulations, aimed for buccal delivery, involving binary products containing bupivacaine hydrochloride (BVP HCl), an amide-type local anesthetic, with parent *β*CD and its soluble epichlorohydrin-*β*CD polymer (EPI-*β*CD) were prepared and evaluated as a novel mucoadhesive system. It was possible to properly tailor the drug release rate according to the desired effect, i.e., a rapid onset of anesthetic action for simple dental procedures or a prolonged effect in post surgical procedures or in the treatment of oral

mucositis. The inclusion complex with *β*CD reduced the drug dissolution rate, while the complexation of BVP HCl with EPI-*β*CD increased the drug dissolution rate (69).

The effect of flufenamic acid (FLU) complexation with HP*β*CD on its dissolution properties and release rate from buccal film formulations was investigated, with the objective of improving the therapeutic efficacy. Chitosan, a natural cationic polysaccharide consisting in a copolymer of N-acetyl-D-glucosamine and D-glucosamine, was selected as the mucoadhesive polymer for the development of the buccal film formulation. Moreover, it was demonstrated that CD complexation could be a suitable strategy to optimise the drug release feature from the system. In fact, introduction of drug as complex with HP*β*CD enabled a clear improvement of drug release with respect to the film containing the plain drug, allowing achievement of complete release within 4-5 h, which is considered the usual maximum duration for buccal drug delivery. The main advantage expected from this formulation in comparison with traditional oral therapy is the reduction of drug dose because its direct localization in the inflammation site, with the consequent minimization of potential systemic side effects. Future *in vivo* studies on human voluntaries are planned to evaluate the actual therapeutic effectiveness of the developed film formulation of FLU, and the effect of different drug loads will be studied (70).

Osmotic pump - Stella *et al*. (71-76) developed various studies involving osmotic pump tablets (OPT) and SBE*β*CD which are described below.
The effect of SBE*β*CD on the release of poorly water-soluble drugs (testosterone) from therapeutic systems (controlled porosity osmotic pump tablets) showed that CD derivative was capable of increasing the solubility and enhancing the release of the steroid. Moreover, it was proposed that current tablets containing SBE*β*CD (due to its seven negative charges and seven sodium ions per molecule, in average) may also exhibit osmotically controlled release-properties for drugs (71).

The factors responsible for controlling drug release of the chlorpromazine through the porous membrane were evaluated from release studies. The results suggest that the membrane factors responsible for drug release from OPTs containing cores utilizing $SBE_{7m}\beta CD$, as both a solubilizing and osmotic agent, are the amount of micronized lactose and triethyl citrate (TEC), the size of micronized lactose, and the type of plasticizer in the membrane. Moreover, it was also confirmed that the pores in the OPT membranes are formed by leaching micronized lactose into the dissolution medium and by a decreasing plasticizer effect observed with decreasing amounts of TEC. In addition, the change in membrane pores which resulted from all these factors was well indicated by the total membrane surface area per unit weight after the release studies and by the mechanical permeability of the membranes (72).

The osmolality of HP and SBECD solutions over the large concentration range relevant to tablet formulations was measured, and a model capable of describing the osmolality generated in CD solutions as a function of concentration was developed. This study was conducted in water with eight CDs: HP*β*CD, HP*γ*CD, $SBE_{4m}\beta CD$, $SBE_{7m}\beta CD$, $SBE_{9m}\beta CD$, $SBE_{4m}\gamma CD$, $SBE_{9m}\gamma CD$, and $SBE_{12m}\gamma CD$. Both HPCDs had a total degree of substitution (TDS) of four, and the TDS in the SBECD nomenclature was indicated by the number in subscript, followed by the letter “m” indicating that these materials were composed of mixtures of (SBE)CDs of various degrees of substitution. As expected, it showed that osmolality was directly dependent on the number of particles in solution. This term may be related to the effect of the solute addition on water structure and could be considered as an indicator of the amplitude of deviation from ideality. The unified empirical model applied in this study of the osmotic

properties of CDs for use in osmotic pump tablets; it is reasonably for predicted the osmolality of the HP and SBECD solutions solely based on solution concentration and TDS (73).

The role of the $SBE_{7m}\beta CD$-to-drug ratio in the OPT core with seven model drugs, including both highly and poorly water-soluble drugs, was studied. $SBE_{7m}\beta CD$ serves as both a solubility modulator and as an osmotic pumping agent for OPTs, from which the release rate of both water-soluble and poorly water-soluble drugs can be controlled. An appropriate composition ratio was determined for $SBE_{7m}\beta CD$ to drug (those requiring solubility enhancement) for complete release of drugs over 12 h from the OPTs. For soluble drugs, $SBE_{7m}\beta CD$ acts primarily as an osmotic and an OPT control agent. Significantly, $SBE_{7m}\beta CD$ not only enhances the delivery of poorly soluble drugs from OPTs but acts as a controlling excipient for soluble drugs such that the release rate, corrected for tablet surface area, of both poorly soluble and soluble drugs are similar (74).

A controlled porosity-osmotic pump pellets (CP-OPP) using $SBE_{7m}\beta CD$ as a solubilizing and osmotic agent and prednisolone (PDL) as drug was prepared in order to deliver a sparingly water-soluble drug, in a controlled-release fashion. The evaluation of this system includes the factors influencing drug release and the probable mechanisms of drug release. The incorporation of $SBE_{7m}\beta CD$ significantly improves the solubility and thus the release of PDL through preformed as well as *in situ* complex formation. The pellet performance can be fabricated to achieve a desired release rate by modifying the molar ratio of $SBE_{7m}\beta CD$ to PDL, thickness of the microporous coating, and coating composition (e.g., polymer or pore former). In addition, a significant change in the drug release rate with a change in the osmotic pressure difference across the membrane indicates that osmotic pumping may be part of the mechanism of drug release from pellet formulations (75).

The release mechanisms from the CP–OPPs containing precomplexed PDL were investigated. The PDL or CD release rate follows zero-order kinetics for up to 30–40% of drug release during the first 1–2 h and nonzero-order kinetics thereafter. The initial zero-order drug release is attributed to the constant driving forces mainly caused by the approximately constant concentration of CD with time. In contrast, the nonzero order drug release is associated with the combination of more significant diffusion with time as well as the change in concentration of CD resulting in changes in viscosity, diffusivity, and osmotic pressure in the pellet with time (76).

Others. The incorporation of the physical mixtures of $SBE_{7m}\beta CD$ and a sparingly water-soluble drug into hydrophilic matrices to provide controlled and complete *in vitro* release, as well as the mechanisms by which $SBE_{7m}\beta CD$ increases the drug release from HPMC matrix tablets, was investigated. The *in situ* inclusion complex formation is the main mechanism by which $SBE_{7m}\beta CD$ improves the drug release rate. Higher medium penetration rate into the $SBE_{7m}\beta CD$-containing matrices may also contribute to the improved release rate and is dependent on the ratio of solubility to drug load, on the molar ratio of $SBE_{7m}\beta CD$ to drug and not the absolute amount of $SBE_{7m}\beta CD$ (77).

In another work, the $HP\beta CD$ was used to evaluate its potential to control zolpidem (ZP) release (prolonged-release system) from zolpidem-loaded poly(dl-lactide) or poly(dl-lactide-co-glycolide) microparticles. The release profiles of ZP from these systems showed an initial burst effect, and a subsequent slow ZP release was analyzed (78).

The potential of $SBE_7\beta CD$ together with HPMC or PVP to solubilize and deliver the carbamazepine (CAR) (poorly soluble model drug) from sustained release (SR) beads was analyzed. $SBE_7\beta CD$ increases the aqueous solubility of CAR as well as HPMC, but not PVP. HPMC acts both alone and synergistically with $SBE_7\beta CD$. Within a SR bead, $SBE_7\beta CD$ increases the CAR release rate, potentially by enhancing solubility and hence diffusion, while also increasing the osmotic drives through the aqueous ethylcelulose dispersions (Surelease® aqueous pores). The addition of HPMC does not improve the rate of CAR release, but does reduce the ratio of $SBE_7\beta CD$ needed to deliver CAR and therefore has potential advantages over the binary system. Both binary and ternary approaches are considered as suitable techniques to potentially improve the delivery and *in vivo* bioavailability of poorly soluble drugs, which have previously exhibited slow or incomplete release from SR beads (79).

The γCD derivatives (variation on the alkyl chain length of γCD alkylcarbonates) complexation properties were analyzed, and it was shown that these CDs can improve both the solubility and the release rate of poorly water-soluble drugs. Also it was observed that the combination of various ratios of different alkylcarbonate complexes in a pharmaceutical formulation could enable drug release to be modulated (80).

An innovative particulate system, called "beads" composed of αCD and vegetable oil, safe substances for oral administration, was proposed. The drug used was isotretinoin, a lipophilic molecule, sensitive to heat, oxygen and light, which was encapsulated in those beads. The results showed that αCD/oil beads were able to efficiently encapsulate and facilitate oral delivery of the drug (81).

The possibility of controlling the release rate of simvastatin (SVA) from SVA/βCD coatings with different pH values was investigated. Results showed that the lower the pH value of the solution, the lower were the release kinetics of SVA, indicating that the release character of SVA could be controlled by adjusting the pH value (82).

In another study, it was assessed whether oral administration of the ethinyl estradiol (EE)βCD clathrate/ drospirenone (drsp) formulation affects the bioavailability and pharmacokinetics of EE and drsp. The results showed the relative bioavailability of EE and drsp after the administration of EEβCD clathrate/drsp was comparable with that achieved with EE/drsp or a reference suspension. Therefore, complete *in vivo* release of EE and drsp was achieved in healthy postmenopausal women following oral administration of EEβCD clathrate/ drsp tablets. A βCD clathrate formulation of EE, when combined with drsp, did not influence the relative bioavailability of EE or drsp, or alter the pharmacokinetic profile of these hormones (83).

The potential of βCD to control drug release from poly[methylenebis(acrylamide)aminoethylpiperazine] (HPMA) was investigated and the *in vitro* release behavior of anticancer chlorambucil (CLB) from these hyperbranched drug carriers was studied. The βCD introduction into HPMA showed that the initial burst release was slowed down. Furthermore, the release rate of CLB from HPMA-βCDs increased with decreasing βCD content, and the corresponding cumulative amounts of CLB released were between 42.3% and 66.0% for 10h. This result indicates that the CLB release from the HPMA-βCDs is a function of βCD content and the presence of βCD in HPMA retarded the CLB release rate. Thus, the controlled release experiments showed that the presence of βCD can appropriately slow CLB release from HPMA-βCDs and adjust the ratio of CLB released in relation to the total drug load (84).

Highly structured and porous poly(methyl methacrylate) PMMA membranes functionalized with HPβCDs, impregnated with ibuprofen using scCO2 in batch mode, were tested as controlled drug delivery devices by *in vitro* tests into buffer solution at

pH 7.4, and the drug release data was modeled using a mathematical theory based on Fick's second law of diffusion. The introduction of CDs physically entrapped in the PMMA matrix leads to an increase of drug release to the buffer solution at pH 7.4 when compared to the neat PMMA membrane. The supercritical fluid-assisted membrane formation is a greener alternative to produce porous polymeric matrixes containing CDs, with improved characteristics such as enhanced drug loading, controlled drug release ability, which might have promising biomedical applications (85).

Delayed release

An enteric preparation can be classified as time-controlled release, since the drug is preferentially released in the intestinal tract; hydrophobic excipients having a weak acidic group are preferable because they are less soluble in water at low pH, but soluble in neutral and alkaline regions due to the ionization of the acidic group; under the control of this pH dependence, the delayed-release dosage form, which passes from the stomach into the higher pH environment of the upper small intestine, would experience increased drug release; for this purpose, CMEβCD has been developed to exhibit pH-dependent solubility for use in selective dissolution of the drug-CD complex (24,50). The release property of the CD conjugates can be classified as a delayed release (30).

Colon specific. The oral administration of PDL - a typical glucocorticoid with significant systemic side effects (higher PDL plasma concentrations) - was compared with its CD conjugate. The results showed that PDLsuc-αCD conjugate (PDL prodrug) is useful as a delayed-release system. Thus, their application is advantageous for colon-specific delivery due to the decrease of the systemic side effect, while maintaining the therapeutic effect (86).

Other authors also have designed CD conjugates for delayed-release systems; the KP, a NSAID, was covalently bound to one of the αCD's primary hydroxyl groups. The release behavior of the resulting conjugate was investigated, *in vitro* and using rats. The repeated- and prolonged-release systems based in the CD conjugate also were prepared. The repeated-release system of KP was prepared by combining the CD conjugate with a fast-release fraction such as the KPHPβCD complex. The prolonged-release system of KP was prepared by combining the CD conjugate with a slow-release fraction such as the KP-EC solid dispersion. These CD conjugate-based approaches may be useful for controlled release (30).

Formation of prodrugs has improved the delivery properties of the parent drug molecule (87-89).

Activated by the microbial enzymes in the large intestine, 5-aminosalicylic acid (5-ASA) is released from CD-5-ASA at a controlled rate. These results showed the oral administration of 5-ASA gives much higher plasma and urine concentrations of 5-ASA than CD-5-ASA, and the conjugate can lower the plasma concentration of 5-ASA. The lower concentration is attributable to the passage of the conjugate through the stomach and small intestine without significant degradation or absorption, followed by the degradation of the conjugate site-specifically in the cecum and colon (87).

The release behavior of the 5-fluorouracil-1-acetic acid (5-FUA) - βCD conjugate, through ester or amide linkage was investigated in enzymatic solutions and rat cecal contents. The results have shown that the 5-FUA-βCD ester conjugate may survive passing through stomach and small intestine, and the release of 5-FUA occurs

preferentially in cecal and large intestinal tracts of rats after the fermentation of *β*CD to small oligosaccharides (88).

Others. The *in vivo* release behavior of antiinflammatory drug (4-biphenylylacetic acid - BPAA) from its CD ester and amide-type prodrugs in rat intestines, together with the anti-inflammatory effect after oral administration of the prodrugs was evaluated. The results suggest that CD/drug prodrugs can survive passage through stomach and small intestine, and drug release is triggered by enzymatic degradation of the CD ring in the colon. The ester prodrugs, particularly the *α* and *y*CD forms, are subject to ring opening followed by hydrolysis to the maltose and triose conjugates. The ester bond of the small saccharide conjugates is subsequently hydrolyzed to form BPAA which is absorbed from the rat cecum and colon. On the other hand, the amide prodrugs are hydrolyzed to small saccharide conjugates, but the amide bond resists the hydrolysis and thus resides as the maltose conjugate in these tracts. This type of drug release is essentially classified as delayed release with a fairly long lag time (89).

Physic and pharmaceutical properties of CD conjugates in which a drug is covalently bonded to the CD may be significantly different from those of the inclusion complexes. The preparation of conjugated ibuprofen (IB)- and indomethacin (IN)-*β*CD as prodrugs and the preparation of linked poly(ethylene glycol)-*β*CD in conjugation with IB or IN were reported. The hydrolysis of CD linked to poly(ethylene glycol) (M_w = 600) containing IB and IN was studied in aqueous buffer solutions at physiological conditions. In comparison, the hydrolysis of IB in this prodrug/drug compound at the first five hours is higher than IN (28).

The binding of the bisphosphonate-derivatized *β*CD conjugate to hydroxyapatite (HA), its complexation with dexamethasone (Dex), and the *in vitro* drug release profile of the complex immobilized on HA surfaces were investigated. The *β*CD-based delivery system alendronate-*β*-cyclodextrin conjugate (ALN-*β*CD) shows very strong binding to HA, and it formed a molecular inclusion complex with Dex (1:1). In an *in vitro* release study, the ALN-*β*-CD/Dex complex bound to HA could gradually release Dex upon repeated extraction with phosphate buffer saline. Potentially, this delivery system may be formulated into a topical formulation with different therapeutic agents and applied in clinical treatment of a variety of diseases in the oral cavity (90).

The capacity of CDs polymers to modulate (to enhance or to retard) the release of a model drug (diflunisal, DF) from HPMC matrices was studied: the incorporation of DF*β*CD inclusion complex enhanced the release of the drug when compared with its physical mixture. In this study, it was also possible to modify the drug release from HPMC matrices by incorporating *β*CDPs with different solubilities; soluble polymers promoted drug release while insoluble ones delayed it. This fact can be explained mainly by inclusion of the drug within the CD cavities which is present in the polymeric structure (91).

Nanotechonology

More recently CDs have also been used in nanotechonology as drug delivery and carrier systems (10,46,92) Various studies have been developed in this area involving CDs in nanometric particles in order to design versatile delivery systems that can encapsulate drugs with different physicochemical properties (i.e. hydrophilic and hydrophobic). The most popular formation of the nanoparticles (NPs) containing CDs consists of the incorporation of previously formed drug-CD inclusion complexes into

polymer NPs. Thus, the presence of CDs generally results in an increase in lipophilic or hydrophilic drug loading. Other nanocarriers may result from the design of amphiphilic CDs that self-assemble in the form of stable NPs (21,93) and also from the design of CD conjugates that can transport the drug encapsulated or connected to the block (10,30,46). The CDs may be excellent building blocks for the synthesis of safe and water-soluble polymers for drug delivery. However, due to the multi-functionality of CD molecules, most CD-containing polymers that have been extensively studied are heavily cross-linked. The structures of these polymers are complex and make their characterization difficult (94).

Nanoparticles

Solid lipid nanoparticles (SLN) containing hydrocortisone and progesterone alone or hydrocortisone and progesterone/*β*CD or HP*β*CD complexes were prepared, and the release of both drugs was lower when they were incorporated as inclusion complexes than as free molecules after oral administration (95). Another study for the same route of administration tested two useful techniques for NPs preparation using CDs in the design of colloidal carriers. The first possibility consisted on increasing the loading capacity of poly(isobutyl cyanoacrylate) nanospheres prepared by anionic polymerization, employing HP*β*CD, and the second possibility consisted on the spontaneous formation of either nanocapsules or nanospheres by nanoprecipitation of amphiphilic CD diesters. The new amphiphilic derivatives do not need any polymerization process to form NPs, nanocapsules, or nanospheres presenting a high loading capacity of the lipophilic or even hydrophilic drugs (96). In order to improve the aqueous solubility and bioavailability of ONO-8713, the method of co-grinding using CDs and CD derivatives in an attempt to prepare crystalline NPs was applied. The results show that this method could be applied effectively as a NPs preparation method for poorly water soluble drugs, being the amount of water used, the CD content in the mixture, and the interaction between drug and CDs significant factors for the NP formation process (97). Some of the most successful cationic polymers bear CD rings linked together by cationic spacer chains. The novel per(6-guanidino-6-deoxy)CDs display very strong binding toward phosphorylated and very weak binding toward non-phosphorylated guest molecules. Furthermore, they interact with DNA and actually compact it into NPs, a basic requirement for its entry inside cells. It was clearly shown that guanidinylated CDs bind tightly to phosphorylated substrates. Therefore, investigation of the binding behavior toward DNA was considered, as shown recently, that amino CDs can be used in DNA transfection studies (98). Other authors studied the interaction of the isophorone diisocyante with HP*β*CD showing that the enhanced molar ratio of isophorone diisocyanate to HP*β*CD could increase the reaction ratio between the hydroxyl groups of HP*β*CD and isocyanate groups of isophorone diisocyanate. An increase on the cross-linked polymeric network formation and its cross-link degree was also demonstrated. This fact might reduce the spaces in cross-linked polymeric matrices for the diffusion of drug (nimodipine, NI) and consequently to increase the entrapment efficiencies of nanocapsules decreasing the NI release rate. HP*β*CD-based nanocapsules showed a slower NI release rate when compared to chitosan based nanocapsules due probably to the fact that the drug can be included into the HP*β*CD cavity increasing the molecular interactions between them (99). CDs have also been used in NPs to overpass problems resulting from proteins oral administration. The very low bioavailability of these substances results mainly from their susceptibility to proteolysis and inability to cross biologic membranes. This problem can be solved through CD complexation thus

improving the protein therapy by stabilizing them against aggregation, thermal denaturation and degradation. Proteins hydrophilic characteristics and size may be a problem in the inclusion process. However, inclusion of the hydrophobic side chains into the *β*CD cavity leads to the formation of non-covalent inclusion complexes, and CDs' ability to sequester hydrophobic moieties helps in improving the stability of proteins. It was also observed that the NPs displayed good insulin encapsulation efficiency and pH-dependent release profile at acidic/alkaline conditions without changing their biological activity (100). Zhang *et al.* reported that alginate/chitosan NP system exhibited an effective protection and controlled the release of insulin complexes with cationic *β*CD polymers (CP-*β*CDs). An oral insulin formulation of CP-*β*CDs-insulin-loaded alginate/chitosan NPs has shown a significantly higher (40%) cumulative insulin release in simulated intestinal fluid than that without CP-*β*CDs (18%). This fact can be explained because the insulin was mainly retained in the core of the NPs and well protected against degradation in simulated gastric fluid (101). The preparation, characterization, and evaluation of the NPs formed by the copolymer of methyl vinyl ether and maleic anhydride (Gantrez® AN) and CDs, including *β*CD, HP*β*CD and 6-monodeoxy-6-monoamino-*β*-cyclodextrin (NH*β*CD), were also described. The incorporation of CDs in Gantrez® AN NPs increased the bioadhesive capacity of poly(anhydride) NPs. This fact may be related with the high content of hydroxyl groups in the resulting NPs which can increase the possibilities of these carriers to interact with mucosa components by means of hydrogen bonds. In addition, the high bioadhesive capacity for 2-hydroxypropl-*β*-cyclodextrin-poly(anhydride) NPs (HP*β*CD-NP) and NH*β*CD-poly(anhydride) NPs (NH*β*CD-NP) could be related with their rough morphology and, thus, a higher specific surface than for smooth NPs. Finally, from *in vivo* imaging studies, it was observed that the HP*β*CD-NP remained in the gut not showing any evidence of translocation of distribution to other animals organs (male wistar rats) (102). The paclitaxel (PTX) from PTX*β*CD NP and PTXHP*β*CD NP (poly(anhydride) NPs) shows high relative oral bioavailability (>80%) while for PTXNH*β*CD NPs the oral bioavailability was found to be 18%. This important difference observed when aminated CD was used can be explained by two reasons: (1) the presence of amino groups would decrease or suppress the inhibitory effect over the P-glycoprotein that has been observed for CDs and (2) the rapid release of an important fraction of PTX (about 70% in less than 30 min) from NPs of PTXNH*β*CD when dispersed in a stomach simulated fluid. The results corroborate the synergistic effect obtained by the combination of bioadhesive NPs and CDs on the oral bioavailability of PTX. In addition, when the PTX was encapsulated in poly(anhydride) NPs as complex with either HP*β*CD or *β*CD, the relative oral bioavailability of this anticancer drug was calculated to be higher than 80% (103). The addition of relatively small amounts of the water-soluble HP*y*CD to aqueous *y*CD formulations increases the complexation efficiency (CE) of *y*CD and reduces the turbidity of *y*CD solutions. It was hypothesized that the observed effect was somehow related to formation of *y*CD and HP*y*CD NPs. Thus, the purpose of this work was to investigate further the solubilizing effects of *y*CD, HP*y*CD, and *y*CD/HP*y*CD mixtures and their formation of nanosize aggregates. The results show that the mixtures of *y*CD and HP*y*CD have synergistic solubilizing effects on hydrocortisone and Dic. Both indomethacin and amphotericin B have very low affinity for *y*CD and HP*y*CD as observed by their very low CE value, indicating that only about 2-7% of the CD molecules in the solution are forming complexes with these drug molecules. The parent *α*CD, *β*CD and *y*CD; their derivatives, such as HP*β*CD and HP*y*CD; and complexes self-assemble to form nanoscale aggregates in aqueous solutions. At CD concentration of about 1% (w/v) or lower, the relative mass

contribution of these aggregates is less than 0.01%, but it gradually increases with increasing CD concentration up to about 5-10% (w/v) when all increase in dissolved drug/CD complexes is in the form of CD aggregates. (104).

Conjugates

A new class of CDs conjugated to polymers through covalent bounds has been synthesized as nontoxic vectors for the delivery of macromolecules. Some examples are described below.

*β*CD-based linear polymers extremely soluble in aqueous solution and show low toxicity to cultured cells were synthesized and used for the conjugation of camptothecin (CPT). Conjugation increased the CPT solubility by more than 3 orders of magnitude. These polymer-CPT conjugates have been tested in a xenograft mouse model. Initial tumor reduction studies reveal that these conjugates have enhanced efficacy over CPT alone and one of the commercial analogues of CPT (irinotecan). By comparison, the CD-containing polymer conjugates of CPT gave median tumor sizes that ranged from 10 to 12% of the median size of the tumors in the control group (94). CD derivatives conjugated with saccharide(s) were synthesized in order to be drug carrier molecules capable of specific cell recognition and might be useful as targeting drug delivery systems. It was possible to synthesize mono-glucose-branched CDs, which had an appropriate spacer between the *β*CD and a glucose moiety. These mono-glucose-branched CDs indicated significantly high association constants for doxorubicin (DXR) in the range of 10^5-10^6 M^{-1}. The introduction of an appropriate spacer can also enhance the CD´s inclusion ability for drugs having an aromatic ring like DXR (105). Innovative system resulting from the association between a CD polymer (poly*β*CD) and amphiphilic cationic connectors was developed. The results showed that CDs polymers (poly*β*CD) complexed with adamantly cationic derivatives (Ada) constitute novel and efficient nonviral vectors for gene delivery (106). Porphyrin-*β*CD conjugate was used for PTX delivery and porphyrin-*γ*CD conjugate for DXR transport. This study presented a novel versatile supramolecular "Lego system" suitable for the combined cancer therapy, which is based on the effective drug binding as inclusion complexes with porphyrin-CD carriers and on known tumor targeting by porphyrin macrocycles (10). Davis's group has successfully conjugated low molecular weight polyethylenimine (PEI; M_w 600) with *β*CD. The resultant PEI600-CD polymeric conjugates (PC) with the molar ratio of 1:1 are capable of mediating efficient gene transfection in cultured neurons and in the central nervous system. Incorporating anticancer drugs onto PEI600-CD conjugates may endow them with new and interesting properties for great applications in combination therapy. A new locally injectable bifunctional delivery system (FU-PEI600-CD, FPC) of an anticancer drug and a gene was developed by combining PEI600-CD (PC) and 5-Fluoro-2′-deoxyuridine (FdUrd). The effects of the developed FPC on cancer cells were systematically investigated through a series of experiments including cancer cell viability, invasion, migration, cell cycle, apoptosis, and uptake of FPC. In addition, *in vitro* and *in vivo* gene transfection was also conducted. In comparison with an equivalent dose of FdUrd, the antitumor therapeutic effects were largely enhanced by FPC, which still exhibited good gene expression efficiency. Thus, the prepared bifunctional FPC composed of *β*CD, low molecular weight PEI, and FdUrd showed improved bioavailability, significantly stronger ability to induce apoptosis, and more efficient cellular uptake than equivalent dose of free FdUrd. Such bifunctional FPC with good ability to deliver drugs and transfer genes may have great potential applications for combination therapy of glioma cancer (107).

Other delivery systems

The efficacy of carboplatin (Carb) or 5-fluorouracil (5-FU) on MCF-7 and MDA-MB 231 breast cancer cell lines, either alone or in combination was improved after MeβCD pretreatment. The results obtained suggest that MeβCD pretreatment enhances the susceptibility of breast cancer cells towards low doses of Carb or 5-FU by increasing the intracellular accumulation of these drugs. These data provide a biological basis for the potential therapeutic application of MeβCD in cancer chemotherapy in combination with other conventional cytotoxic drugs (108). The design and *in vitro* and *in vivo* evaluations of polypseudorotaxanes of pegylated insulin with CDs as a sustained-release system was reported. The pegylated insulin forms polypseudorotaxanes with α and γCD in a similar manner as poly(ethylene glycol). The polypseudorotaxanes prepared are less soluble in water, and the release rate of the pegylated drug can be controlled by changing the threading and dethreading rates of the polypseudorotaxanes by adjustment of administration conditions such as amount of injection and concentration of CDs in the medium (109). Later a new slow-release system of pegylated lysozyme/CD polypseudorotaxanes was developed. This technology suggests that it may be applicable as a new method of pegylated proteins, peptides, and low-molecular weight drugs slow-release systems. For that, PEG (M_w 2,200) chains were introduced into lysozyme molecules and formed polypseudorotaxanes with α and γCD, by inserting one PEG chain in the αCD cavity and two PEG chains in the γCD cavity. The results demonstrated that the pegylated lysozyme/CD polypseudorotaxanes were less soluble in water, and the release rate of the pegylated protein decreased in the order of the pegylated lysozyme>the γCD polypseudorotaxane>the αCD polypseudorotaxane (110). The formation of the complex constituted by genistein (Gen) with the modified amphiphilic CD SC6OH at 1:1 molar ratio in water medium demonstrated that Gen molecules are shown to be not included inside the SC6OH cavity but to interact with the side chains of SC6OH nanoaggregates. The lack of inclusion of the guest molecules inside the host macrocycle was confirmed, in solid phase, by monitoring the significant differences in the spectral features of the FTIR–ATR spectrum of complex. The evidences found in this study shed light on the complexation of drugs in host nanocarriers at solid phase and open the way to detect the supramolecular interactions in complexed species host/drug and host/drug/receptor in targeted drug delivery (111). Quaternization of βCD grafted with chitosan (CD-g-CS) using glycidylt rimethyl ammonium chloride leads to water-soluble CD-g-CS derivative (QCD-g-CS). All QCD-g-CSs showed self-aggregates behavior in water while quaternized native chitosan did not. The surfactant-like or micelle-like structures of QCD-g-CS are firstly presented with the βCD moiety inner core and the quaternary ammonium moiety outer shell. Atomic force microscopy (AFM) and transmission electron microscopy images revealed that self-aggregates of the QCD-g-CS were spherical shape. It was found that the particle sizes increased with an increasing in degrees of substitution (DS) (βCD moiety) into the CS backbone, leading to large aggregation in water. The stronger mucoadhesive strength, the higher degree of quaternization (DQ), zeta-potential, slope value and the lower critical concentration value were observed. In this study, DQ played an important role on mucoadhesive property while the cytotoxicity did not correlate with DQ (112).

Conclusion

This review highlights the beneficial applications of the CDs and their derivatives on the solubility / dissolution rate and bioavailability enhancement of poorly water-soluble drugs. Their ability for immediate and modified (to prolong or to delay) release of drugs from solid dosage forms, either as complexes or as nanotechnology carriers, is also demonstrated. CDs may also enhance drug absorption across biological barriers. The increased number of CD derivatives / carriers that have been synthesized up to now demonstrates the CDs versatility on the oral dosage forms formulations. The research accomplished that has contributed for the great success of those formulations, may be the base of new achievements on oral controlled release. Although a high number of studies using CDs and their derivatives have been reported, there is plenty of room for new discoveries and applications on controlled release of oral pharmaceutical dosage forms especially at the nanotechnology level and on the delivery of peptides and proteins. CDs may be a useful strategy in life cycle management of medicines.

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