

**MOLECULAR BUCKETS: CYCLODEXTRINS FOR ORAL CANCER THERAPY**

Patricia Calleja, Judit Huarte, Maite Agüeros, Luisa Ruiz-Gatón, Socorro Espuelas,  
Juan M. Irache

Department of Pharmacy and Pharmaceutical Technology, University of Navarra,  
Pamplona, Spain

**Correspondence:**

Prof. Juan M. Irache

Dep. Pharmacy and Pharmaceutical Technology

University of Navarra

C/ Irunlarrea, 1

31080 – Pamplona

Spain

e-mail: [jmirache@unav.es](mailto:jmirache@unav.es)

### List of Abbreviations

6-O-CAPRO- $\beta$ -CD	amphiphilic CD derivative modified on the primary face with 6C aliphatic esters
ABC	ATPase binding cassettes transporters
BCS	Biopharmaceutical Classification System
CD	cyclodextrin
CDs	cyclodextrins
$\alpha$ -CD	$\alpha$ -cyclodextrin
$\beta$ -CD	$\beta$ -cyclodextrin
$\beta$ -CDC6	amphiphilic $\beta$ -cyclodextrin modified on the secondary face with 6C aliphatic esters,
$\gamma$ -CD	$\gamma$ -cyclodextrin
CYP450	cytochrome P450
DM $\beta$ CD	dimethyl- $\beta$ -cyclodextrin
E2	17- $\beta$ -estradiol
EXE	exemestane
HP $\beta$ CD	hydroxypropyl- $\beta$ -cyclodextrin
HP $\gamma$ CD	hydroxypropyl- $\gamma$ -cyclodextrin
iv	intravenous
M $\beta$ CD	randomly methylated- $\beta$ -cyclodextrin
PCL	poly( $\epsilon$ -caprolactone)
PLA	poly(lactic acid)
PLGA	poly(lactic-co-glycolic acid)
Pgp	P-glycoprotein
SBE $\beta$ CD	sulfobutylether- $\beta$ -cyclodextrin
TM $\beta$ CD	trimethyl- $\beta$ -cyclodextrin

## **Abstract**

The oral route is preferred by patients for drug administration due to its convenience resulting in improved compliance. Unfortunately, for a number of drugs (i.e. anticancer drugs), this route of administration remains a challenge. Oral chemotherapy may be an attractive option and especially appropriate for chronic treatment of cancer. However, this route of administration is particularly complicated for the administration of anticancer drugs ascribed to the Class IV of the Biopharmaceutical Classification System. This group of compounds is characterised by a low aqueous solubility and low intestinal permeability. This review focuses on the use of cyclodextrins alone or in combination with bioadhesive nanoparticles for oral delivery of drugs. The state-of-the-art technology and challenges in this area is also discussed.

## **Keywords and Defined Keyterms**

- 1. Nanoparticles:** vehicles of submicronic size for drug delivery purposes
- 2. Cyclodextrins:** solubilising excipients with certain ability to disturb p-glycoprotein and cytochrome P450 activities characterised by a unique shape of a truncated cone.
- 3. Oral:** one of the most accepted routes of drug administration by patients.
- 4. Cancer**
- 5. P-glycoprotein:** multidrug efflux pump that hampers absorption of drugs.
- 6. Cytochrome P450:** enzymatic complex involved in metabolism of xenobiotics.
- 7. Paclitaxel:** anticancer agent with very poor oral bioavailability.

## Introduction

Oncology is one of the few areas of medicine where the large majority of patients are treated intravenously (iv) rather than orally. Although oral chemotherapeutic agents have been available for the last 50 years, and currently 10% of cancer chemotherapy is prescribed to patients by means of an oral formulation, doubts on efficacy and limited interest of pharmaceutical companies have hampered their use. The development and approval for clinical use of new oral anticancer agents will probably change in the near future. By 2013, this percentage is predicted to increase by 25% [1].

In the past, anticancer therapies were mainly focused on parenteral drug delivery because the goal was to deliver the maximum tolerated dose of drug to optimize cell kill in a single episode, followed by a free-drug several week period to allow bone marrow recovery [2].

Convenience and easiness of administration make oral chemotherapy an attractive option [3, 4]. It is also especially appropriate where prolonged drug exposure is desirable [5] and also allows the replacement of drugs that require protracted administration periods. It avoids complications and costs derived from intravenous chemotherapy, while maintaining the patients' quality of life [6]. From the economic standpoint, oral administration is more attractive because it reduces the cost for hospitalization and infusion equipment supplies [7], what makes it a “dominant strategy” in pharmacoeconomic terms [6]. Furthermore, oral chemotherapy is particularly attractive as cancer is becoming a chronic disease for an increasing number of patients [8].

However, the oral administration of cancer drugs also possesses challenges. One of them involves time to train patients in addition to remaining uncertainty about their compliance [1]. Another major challenge is the low and variable bioavailability of many drugs after oral administration, due to factors such as rapid degradation, limited solubility, poor permeability or extensive pre-systemic metabolism [9]. Indeed, efflux by P-glycoprotein (Pgp) and/or intestinal and hepatic metabolism by cytochrome P450 (CYP450) metabolizing enzyme system have frequently been classified as limitant factors of oral bioavailability of common anticancer drugs [10]. Currently, the use of nanocarriers has been proposed to improve the gastrointestinal bioavailability of drugs with poor oral bioavailability. Nanocarriers improve the solubility of poorly soluble drugs and the diffusion of the drug within the mucus, enhancing the availability for the drug to be absorbed through the gastrointestinal epithelium or lymphatic transport. In some cases, nanocarriers have also increased the drug permeability across the intestinal barrier. As a matter of fact, several pharmaceutical excipients have shown activity to inhibit pre-systemic metabolism produced by CYP450 [11] and/or Pgp efflux pumps located in the enterocytes [12, 13].

This review focuses on the use of cyclodextrins alone or in conjunction with nanoparticles for oral delivery of drugs. Classical cyclodextrin-drug complexes can enhance the oral absorption of drugs by virtue of their solubilizing properties [14]. Their association with bioadhesive nanoparticles can further facilitate the

bioavailability of encapsulated drugs by increasing the intestinal permeability of the drug. The state-of-the-art technology and challenges in this area are discussed.

### **Cyclodextrins**

Cyclodextrins (CDs) were first described in 1891 by Villiers when he studied the bacterial digestion of starch [15, 16]. Villiers described this substance as some kind of cellulose, which he called “cellulosine”. Years later, Franz Schardinger isolated *Bacillus macerans* and observed the production of 2 different crystalline structures when the microorganism was grown on a starch-containing medium. Observing similar properties to the degradation products of starch, he named them  $\alpha$ -, and  $\beta$ -dextrin [17]. Later Freudenberg and his co-workers elucidated the cyclic structure of these two dextrans and described the main physicochemical properties and their abilities to form complexes [18]. Thus, these compounds were then named, as they are known nowadays, cyclodextrins:  $\alpha$ -cyclodextrins ( $\alpha$ -CD) and  $\beta$ -cyclodextrins ( $\beta$ -CD). In 1948–1950, the  $\gamma$ -cyclodextrin ( $\gamma$ -CD) was discovered and its structure elucidated. The structure, physicochemical properties, inclusion complex forming abilities and the industrial obtention of cyclodextrins were figured out by the end of 1960s. In the 1970s, improvements were performed in the biotechnological areas increasing the production of cyclodextrins by the enzymatic degradation of starch and the production of different derivatives for different applications.

Cyclodextrins are crystalline cyclic oligosaccharides containing six, seven or eight ( $\alpha$ -1,4) linked  $\alpha$ -D-glucopyranose units with amphiphilic properties and a shape of a truncated cone or “bucket” [19, 20]. Cyclodextrins are named depending on the number of glucopyranose units. Major and industrially produced cyclodextrins are named as follows:  $\alpha$ -cyclodextrin possessing six units,  $\beta$ -cyclodextrin possessing seven units and  $\gamma$ -cyclodextrin possessing eight units. The  $\beta$ -cyclodextrin family is the most commonly used cyclodextrin. Cyclodextrins are characterized by 2 flat faces in their structure: the upper face or rim and the lower face or rim. The upper rim corresponds to the wider part of the truncated cone structure, while the lower rim refers to the narrow part of the molecule. Generally, the upper rim and the lower rim are also referred to as the secondary and the primary faces, respectively. Regarding their structure, the external surface is hydrophilic whereas the internal cavity is lipophilic. This central moiety is formed by the skeletal carbons, hydrogen atoms and glycosidic oxygen atoms of the glucose structure conferring the lipophilic characteristics [21-23]. On the other hand, the external surface is hydrophilic due to the presence of secondary hydroxyl groups at the wide edge of the structure and primary hydroxyl groups at the narrow edge.

These natural cyclodextrins form total or partial inclusion complexes with active molecules. This combination CD-drug alters the water solubility, stability, diminishes side effects and promotes compatibility of drugs with other drugs or excipients, as well as ameliorate patient compliance by taste masking [23-25]. However, natural cyclodextrins show some drawbacks such as poor versatility, limited aqueous solubility ( $\beta$ -cyclodextrin) and toxicological limitations. In fact, two of the natural cyclodextrins are known to be parenterally unsafe due to nephrotoxic effects [26]. The exact mechanism of the nephrotoxicity of  $\alpha$ - and  $\beta$ -cyclodextrins is

unknown, but it is believed to be related to either cyclodextrin uptake by kidney tubular cells resulting in disruption of intracellular function, or the extraction of lipid membrane components by the cyclodextrins [16, 27].

For these reasons, natural cyclodextrins have been chemically modified in order to achieve one or more of the following goals: alter their water solubility, reduce the nephrotoxicity and hemolysis encountered on iv administration, ameliorate the interaction with biological membranes and provide controlled drug release profiles. For these purposes, substitution of the hydrogen bonds of these natural CDs by hydroxyl, methoxy or other alkyl groups improves significantly the aqueous solubility of the compounds. Some of these modified CDs are: hydroxypropyl- $\beta$ -cyclodextrin (HP $\beta$ CD), sulfobutylether- $\beta$ -cyclodextrin (SBE $\beta$ CD) and the randomly methylated derivatives (M $\beta$ CD) such as dimethyl- $\beta$ -cyclodextrin (DM $\beta$ CD). Table 1 summarises some of the most useful derivatives based on  $\beta$ -cyclodextrin.

### **Table 1**

Today, cyclodextrins are considered as useful excipients widely spread in pharmaceutical applications. Among other reasons, cyclodextrins may be used as complexing agents since they can alter the water solubility and therefore, stability of poorly water-soluble drugs. Thus, by the oral route, the effect of cyclodextrins may improve the oral bioavailability of lipophilic compounds. Cyclodextrins interact with specific components of the membranes but are rarely absorbed from the gastrointestinal tract. Furthermore, natural CDs ( $\alpha$ -,  $\beta$ - and  $\gamma$ -cyclodextrins) cannot be hydrolyzed by human salivary and pancreatic amylases [28]. Nonetheless, they can be fermented by intestinal microflora. In addition, cyclodextrins may reduce the irritation (a big number of drugs are irritant for the mucus layer of the gastrointestinal tract), they may control the release of the drug from the inclusion complex, prevent or minimize interactions and mask unpleasant tastes [29]. Finally it is also important that, in general, cyclodextrins are not toxic, because of the lack of absorption from the gastrointestinal tract when administered orally [28].

Parallel to this, cyclodextrins have also been under investigation for their capabilities to disturb the activity of the Pgp and CYP450 as well as for their incorporation into or formation of nanoparticulate drug delivery systems. Nanoparticles are of pharmaceutical interest because of their active and passive targeting properties and their ability to deliver poorly available drugs.

### **Cyclodextrins as solubilising agents**

The most extended mechanism by which CDs increase the apparent solubility of poorly water-soluble drugs is the inclusion complex formation. These complexes imply dynamic equilibrium between the molecules involved, the guest and host molecules and the complex [16, 30]. The increased apparent solubility can enable solution-based dosage forms such as oral liquids. Moreover, according to the Whitney equation, increasing the apparent solubility of a drug can increase drug dissolution rate and as a consequence, a rise in the oral bioavailability of the drug

for compounds with limited oral bioavailability caused mainly by its low solubility or dissolution rate [31, 32].

A useful approach in assessing where CDs can be applied in this context is the Biopharmaceutical Classification System (BCS). In consonance with the BCS, drugs can be split into 4 categories based on their aqueous solubility and permeability properties [33, 34]. Class I includes those compounds with both soluble and permeable properties and with an oral bioavailability which may only be limited by the rate at which they reach appropriate sites of absorption in the gastrointestinal tract. Class II drugs (poor solubility, high permeability) are compounds with a limited oral absorption due to drug solubility and dissolution rate. Class III compounds (high solubility, poor permeability) show oral bioavailability limited by the barrier properties of the gastrointestinal tract. Finally, Class IV compounds (low solubility and permeability) combine the limitations of both Class II and III materials. Thus, the use of cyclodextrins may be of main interest to solve the problems associated with Class II and IV compounds. Concerning drugs included in Class IV, it has recently been described that cyclodextrins can act as enhancers of the oral permeability of drugs (see the following section). In any case, the alteration of the properties of drugs included in these classes implies changes such that they become Class I-like in behavior [35, 36].

There are different ways by which the cyclodextrin interacts with the drug. The central CD cavity provides a lipophilic microenvironment into which suitably sized drug molecules may enter and be included. Then, no formal bonds are formed, stabilizing the system CD-drug by means of dispersion forces. However, the interaction implies a dynamic equilibrium between both molecules [37]. The result of these interactions is the increase of the apparent solubility of the drug. These interactions are relatively weak so as to permit the equilibrium of free drug molecules and cyclodextrins [16, 30]. The ability of the host molecule, cyclodextrin, to form complexes with the guest molecule depends on two factors: (i) the size of the guest molecule and (ii) the thermodynamic interactions between all the components (cyclodextrin, guest molecule, solvents). In all cases, the guest molecules should be of the appropriate size to fit in the cavity and the interactions should be favourable energetically.

The most common stoichiometry of drug/cyclodextrin complexes is 1:1, i.e. one drug molecule forms a complex with one cyclodextrin molecule [35]. In fact, studies carried out by several research groups have demonstrated that cyclodextrins form both inclusion and non-inclusion complexes, which can coexist in aqueous solutions. Furthermore, they tend to form aggregates, capable of solubilizing hydrophobic molecules through micellar-type mechanism [35, 36, 38].

Worldwide, more than 30 different drugs are currently marketed as solid or solution-based CD complex formulations (Table 2) [35, 39]. In these pharmaceutical products, CDs are mainly used as complexing agents to increase the aqueous solubility of poorly water-soluble drugs and, thus, their bioavailability and stability [40-42].

## **Table 2**

Concerning anticancer drugs, some of them are ascribed to Classes II and IV of the BCS and show limited possibilities to be administered by oral route [43]. In this context, different anticancer drugs have been studied including paclitaxel [44], danazol [45], noscapine [46] or exemestane [47, 48].

One of the first studies was conducted by Kikuchi and collaborators in 1987. In this study, carmofur (a derivative of 5-fluorouracil) was complexed with  $\beta$ -cyclodextrin, DM $\beta$ CD or trimethyl- $\beta$ -cyclodextrin (TM $\beta$ CD). When orally administered to laboratory animals, the resulting AUCs for the drug-cyclodextrin complexes were up to 7-times that found for the control formulation of carmofur [49]. Later, Cserhàti and Holló studied the interaction between 23 anticancer drugs and HP $\beta$ CD and concluded that the formation of an inclusion complex may influence differently the biological effect of individual anticancer drugs and, thus, result in modified effectivity [44].

More recently, Piette and co-workers evaluated the oral bioavailability of Ro 28-2653 after dissolution in water by means of complexation with HP $\beta$ CD. The Ro 28-2653/HP $\beta$ CD oral solution was compared to a typical suspension of this drug in an aqueous solution of wetting and viscosifying agents. Both formulations were administered orally to sheep at a dose of 15 mg/kg. The absolute bioavailability was significantly higher with the solution (80%) than with the suspension (8%) [50]. Similarly, Yavuz and collaborators prepared inclusion complexes between exemestane (EXE) and M $\beta$ CD, HP $\beta$ CD or HP $\gamma$ CD [47]. The complexes between EXE and M $\beta$ CD displayed a high ability to increase the permeability of the anticancer drug to cross biological membranes. This fact appeared to be due to the capability of this cyclodextrin to interact with the lipids and, then, perturb the membrane integrity [51].

### **Cyclodextrins as P-glycoprotein and cytochrome P450 selective inhibitors**

P-glycoprotein is a transmembrane protein responsible for the transport of a wide range of chemicals and hydrophobic molecules, such as chemotherapeutics, steroidal hormones or immunosuppressive agents. It belongs to the family of the ATP-binding cassettes (ABC) transporters and needs energy of the hydrolysis of ATP to function. Pgp is highly expressed, especially in the small intestinal epithelial cells where it works as an efflux pump, preventing the absorption of different drugs and molecules and avoiding the entrance of these molecules to the blood stream [52]. Pgp may be involved in the relocation of cholesterol from cytosol to the plasmatic membrane and in the stabilization of the cholesterol-rich domains [53]. On the other hand, cytochrome P450 is a metabolic enzyme in charge of the oxidation of different compounds as well as the conversion of highly lipophilic drugs in more water soluble forms in order to facilitate their excretion from the body. CYP450 is a big family of enzymes present all through the gastrointestinal tract and therefore, along with Pgp, both are responsible for the low oral bioavailability of many anticancer drugs.

Cyclodextrins have been reported to act as inhibitors of the Pgp [53] and the CYP450 [54]. Different hydrophilic CD derivatives interact with the cholesterol units



of the membrane resulting in a depletion of these domains and therefore, decrease the ATPase activity and subsequently, the action of the efflux pumps [55]. A schematic representation of this effect is shown in Figure 1.

### **Figure 1**

These properties of CDs have been described previously by different groups, who reported evidence of the appreciable interaction of CDs with cell membranes and their components. Thus, Arima and co-workers reported the effects of the combination of DM $\beta$ CD and tacrolimus on the oral bioavailability of this Class II compound [56]. Their work demonstrated that the enhancing effect of DM $\beta$ CD on the oral bioavailability of tacrolimus was not only due to the solubilizing effect of CD but also, at least in part, to the inhibitory effect of the CD on the Pgp mediated efflux in the gastrointestinal tract. The DM $\beta$ CD showed an interaction with the membrane components, i.e. cholesterol and phospholipids. They concluded that the mechanism by which DM $\beta$ CD inhibits Pgp is different than that of the typical Pgp selective inhibitors (cyclosporin A or verapamil). DM $\beta$ CD is not a substrate of the Pgp and apparently, allows the release of the protein from the membrane of Caco-2 cells. Their findings were in correlation with those of Pathak and coworkers [57], who studied the complexation of saquinavir, an HIV protease inhibitor also ascribed to the Class IV of the BCS, with methyl-beta-cyclodextrin. Their results indicated an improvement of the pharmacokinetic profile of saquinavir and enhance the oral absorption of the drug by the complexing with the CD which showed a similar behavior to that reported for other methylated cyclodextrins. In all cases, the main studied cyclodextrins were the methylated types.

Fenyvesi and co-workers have carried out different experiments with different cyclodextrins, mainly focused on the M $\beta$ CD. They studied the effect of the CDs combined with Taxol® on Caco-2 model. CDs were capable of removing cholesterol from the structure of the membrane and change its physicochemical properties, permeability, and fluidity and in addition, modulate the action of the Pgp efflux pump, resulting in a higher permeability for Taxol® (trademark of paclitaxel). CDs altered the lipid packing of the membrane leading to changes in the disposition of the components of the lipid bilayer, especially cholesterol and phospholipids, affecting to the transport functions [58].

Regarding the effect of CDs on CYP450, Ishikawa and collaborators reported the interactions of HP $\beta$ CD and M $\beta$ CD, on different hepatic isoforms of CYP450. In their studies, the concentration of cyclodextrin present had a different effect on the activity of the isoforms. In some of the studied isoforms, the enzymatic activity was increased or even reduced and in some cases the induction period was altered. While the HP $\beta$ CD did not have the same effect on the isoforms studied (the HP $\beta$ CD influenced on the isoforms CYP2C19 and CYP3A4), the M $\beta$ CD inhibited, in all cases, the metabolism, specifically at high concentrations [54].

### **Cyclodextrin nanoparticles**

Some types of cyclodextrins, apart from their ability to form inclusion complexes, show self-alignment properties and the ability in aqueous media to form nanoparticles spontaneously without the presence of a surfactant [59, 60]. These oligosaccharides are amphiphilic and, initially, they were synthesised (i) to enhance the interaction with biological membranes and (ii) to improve the interaction with hydrophobic drugs by creating a second zone of attraction other than the cyclodextrin cavity [61-63].

Amphiphilic cyclodextrins are generally classified according to their surface charge as follows: non-ionic, cationic and anionic amphiphilic cyclodextrins. The non-ionic amphiphilic cyclodextrins are obtained by grafting aliphatic chains of different length onto the primary and/or secondary face of the CD main glucopyranose unit. Among others, the main types of these oligosaccharides are known as lollipop, cup-and-ball, medusa-like, skirt-shaped, bouquet-shaped and cholesteryl cyclodextrins. More recently, cationic amphiphilic cyclodextrins characterized by the presence of amino groups were synthesised. A series of polyamino- $\beta$ -cyclodextrins have been reported [65] with complete substitution by amine groups at the position 6. Finally, anionic amphiphilic cyclodextrins usually contain a sulfate group that renders anionic properties to their structure. An efficient synthetic route to obtain acyl-sulfated- $\beta$ -cyclodextrins has been introduced in which the upper rim is functionalized with sulfates and the lower rim with fatty acid esters. Other types of anionic amphiphilic cyclodextrins are the fluorine and the fluorophilic cyclodextrins. Table 3 gives some information about all these oligosaccharides (an interesting review about these amphiphilic cyclodextrins was recently written by Bilensoy and Hincal [64]).

### **Table 3**

Cyclodextrin nanoparticles are usually prepared by nanoprecipitation [66, 67], emulsion/solvent evaporation [68] or detergent removal technique [69]. Drug loading into nanoparticles is governed by the loading technique used. Three main strategies are used in order to load the drug into the cyclodextrin nanoparticles: (i) use of pre-formed drug:amphiphilic cyclodextrin complexes; (ii) incubation between amphiphilic cyclodextrins and drug in the same solvent prior to the formation of nanoparticles; and (iii) preparation of nanoparticles directly from pre-formed drug:amphiphilic cyclodextrin complexes and loaded further by the addition of excess drug solution in the organic phase [70, 71].

Nanoparticles prepared from non-ionic amphiphilic cyclodextrins have been loaded with different anticancer agents with bioavailability problems, such as tamoxifen citrate, paclitaxel and camptothecin. Tamoxifen, an antiestrogen drug used for the first-line and adjuvant therapy for metastatic breast cancer, has been incorporated into the  $\beta$ -CDC6 amphiphilic cyclodextrin nanoparticles. The idea was to reduce the severe side effects associated to the non-selective dose-dependent cytotoxicity of tamoxifen during long-term chemotherapy. Tamoxifen citrate-loaded nanoparticles released the drug in a controlled way up to 6 h [63]. Anticancer efficacy of tamoxifen-loaded nanoparticles was demonstrated to be equivalent to a

control solution of the anticancer drug in ethanol against MCF-7 human breast cancer cells. In addition, the transcription efficiency of the tamoxifen-amphiphilic cyclodextrin nanoparticles was evaluated against MELN cells in the presence of 17- $\beta$ -estradiol (E2) for the inhibition of E2-mediated luciferase gene expression and demonstrated concentration-dependent transcription efficiency [72].

More recently, cyclodextrin nanoparticles prepared from amphiphilic  $\beta$ -cyclodextrin modified on the primary face with 6C aliphatic esters (6-O-CAPRO- $\beta$ -CD) were used to load paclitaxel [73]. The resulting nanoparticles were evaluated for their safety and efficacy. Paclitaxel-loaded amphiphilic cyclodextrin nanoparticles were found to be physically stable for a period of 1 month [74]. In addition, nanoparticles significantly reduced the hemolytic properties caused by commercial vehicle (Cremophor EL). Paclitaxel-loaded amphiphilic nanoparticles demonstrated similar anticancer efficacy against MCF-7 cells when compared to paclitaxel solution in the Cremophor vehicle [74].

Another potent anticancer drug, camptothecin, which is reported to be clinically problematic due to its conversion from its active lactone form to its inactive carboxylate form under physiological conditions, was formulated using two different amphiphilic  $\beta$ -cyclodextrins:  $\beta$ -CDC6 and 6-O-CAPRO- $\beta$ -CD. Cyclodextrin nanoparticles have succeeded in maintaining camptothecin in its active lactone form with considerable loading values and release profiles prolonged up to 96 h [75]. This study is significant because amphiphilic cyclodextrin nanoparticles displayed a superior efficiency for drug loading (which was 4 to 6-fold higher) than poly(lactic-co-glycolic acid) [PLGA] or poly( $\epsilon$ -caprolactone) [PCL] nanoparticles' loading values. In addition, these amphiphilic cyclodextrin nanoparticles displayed prolonged release profiles for camptothecin, with  $\beta$ -CDC6 having a release period of up to 6 days and 6-O-CAPRO- $\beta$ -CD releasing the drug within a 14-day period, whereas both PLGA and PCL nanoparticles released the drug completely within 48 h [75]. In vivo, 6-O-CAPRO- $\beta$ -CD nanoparticles displayed a significantly higher survival rate in a rat glioma model than the other types of nanoparticles [76].

Non-ionic amphiphilic cyclodextrins modified with 16C aliphatic chains linked with thiol bonds have also been used to form nanoparticles for docetaxel delivery. When Hep-2 cells were exposed to free docetaxel and docetaxel incorporated in these cyclodextrin nanoparticles, significantly higher cell damage and cell death were observed for nanoparticle-associated docetaxel [77].

Cationic amphiphilic nanoparticles, from heptakis(2-amino-O-oligo(ethylene oxide)-hexylthio- $\beta$ -CD), have been used to encapsulate anionic porphyrins. These nanoparticles preserved the photodynamic properties of the entrapped photoactive agent in studies with tumor HeLa cervical carcinoma cells [78]. On the other hand, nanoparticles from cationic cyclodextrins have shown a great ability to bind nucleotides and enhance delivery by viral vectors. The main advantage of polycationic cyclodextrins and their nanoparticles is their enhanced ability to interact with nucleic acids and act as non viral vectors for gene therapy [65].

## **Combination between cyclodextrins and polymer nanoparticles**

In spite of the different developments in progress with amphiphilic nanoparticles, to date, the majority of these studies have been designed for parenteral administration rather than for oral treatment. Furthermore, information regarding the behavior of these carriers for the oral delivery of anticancer drugs is very scarce. At this point, it is interesting to remember that some of the anticancer drugs with interest for oral delivery are included in the class IV of the BCS and, in the last years, a number of strategies have been proposed to promote the oral bioavailability of these therapeutic agents.

One interesting approach would consist on the combination of a Pgp and/or cytochrome P450 inhibitors with bioadhesive polymer nanoparticles (as drug carriers) containing the drug sensitive to the action of these physiological processes. In the past, Pgp and/or CYP450 inhibitors such as verapamil [79], cyclosporine A [80] or their analogues [81-83] have been proposed. However, most of them have difficulties in formulation of their own and the use of these drugs may be limited in humans, especially for repeated administrations. For these reasons an interesting variation in this approach may be the use of pharmaceutical excipients showing moderate inhibition or disruptive properties of the Pgp and/or the cytochrome P450 (i.e. cyclodextrins).

On the other hand, bioadhesive nanoparticles offer a number of advantages related to their capability to be immobilised at the surface of the gut mucosa. The adhesive phenomenon may slow the particle transit time through the gastrointestinal tract, thereby enhancing the time scale for drug absorption [84]. In addition, this class of colloidal drug carriers can protect the loaded drug from its eventual inactivation or degradation by the pH conditions or enzymes, interact with the mucosa and prolong the contact time with the membrane, where the absorption occurs [84, 85]. The intensity of this interaction phenomenon between these drug carriers and the mucosa is influenced by the stability of the nanoparticles as well as their size and surface characteristics [84, 86, 87]. Among others, a number of polymers and macromolecules have been reported as adequate materials to prepare this type of nanoparticles, including chitosan [88, 89], poly(lactic acid) (PLA) [90], gliadin [91] and poly (methyl vinyl ether-co-maleic anhydride) [92].

Thus, the idea would be to use nanoparticles with improved bioadhesive properties capable of loading the drug and the cyclodextrin. These vehicles would travel through the gastrointestinal tract up to the surface of the mucosa where they would release their content. Then, the inhibitory effect of the cyclodextrins on the activity of the Pgp and the cytochrome P450 would facilitate the oral absorption of the anticancer drug. Figure 2 shows a diagram summarizing this idea. For a maximum of efficiency of the pharmaceutical device, the bioadhesive nanoparticles should develop the adhesive interactions with the surface of the enterocytes rather than the mucus layer covering the gut mucosa. In fact, different reports have suggested that the mucosal administration of particulates concluded with the particles trapped in the mucus layer lining and protecting the mucosa formed by the epithelial cells rather than attached to or internalized by intestinal cells [93-95]. This lack of particle entry into mucosal epithelia has been long attributed to inefficient penetration through the mucus layer. Since nanoparticles are mainly bound to the

mucus layer through interactions with mucin fibers, the transit time of these systems would be determined by the physiological turnover time of the mucus layer. In addition, the release of the cyclodextrin and the drug in a relatively remote area of the enterocyte surface may hamper the drug absorption.

## Figure 2

Recently, this strategy was validated by using poly(anhydride) nanoparticles based on the copolymer of methylvinylether and maleic anhydride (Gantrez AN from Isp. Corp.). These nanoparticles are easily prepared by a desolvation method and the resulting carriers are capable of developing bioadhesive interactions within the gut [96]. More importantly, the surface of these poly(anhydride) nanoparticles can be easily modified by simple incubation with different excipients or ligands including mannosamine [97], thiamine [98] or chitosan [99] in order to modify their fate within the gastrointestinal tract. In this way, the incorporation of cyclodextrins into these poly(anhydride) nanoparticles facilitates their diffusion across the mucus layer and as a consequence, the mean residence time of the nanoparticles adhered to the intestinal gut mucosa is significantly higher than for conventional nanoparticles [100]. The distribution in the gut of these cyclodextrin-poly(anhydride) nanoparticles was confirmed after radiolabeling of these nanoparticles with technetium. It was observed that, after oral administration, nanoparticles remained in the stomach during the first hour. Then, they were slowly discharged in the small intestine and continued to move along the gut during the time of the experiment [101]. From fluorescence microscopy visualization studies, cyclodextrin-poly(anhydride) nanoparticles were found broadly and homogeneously distributed along the ileum mucosa (mucus layer and surface of the enterocytes) whereas conventional nanoparticles were mainly found in the mucus layer of the ileum [100]. In any case, no evidence of translocation or distribution to other organs of the body of animals was observed for these cyclodextrin-poly(anhydride) nanoparticles.

Recently, this strategy of combination between cyclodextrins and bioadhesive nanoparticles has demonstrated effectiveness in improving significantly the oral bioavailability of paclitaxel [102]. This anticancer drug is widely used in clinic for the treatment of several carcinomas including breast [103], advanced ovarian [104], non small cell lung [105] and colon [106]. By the oral route, it shows a very low bioavailability, which is caused by several factors. Firstly, paclitaxel is a highly hydrophobic molecule with a poor aqueous solubility and a very low dissolution rate in biological media [107]. Secondly, paclitaxel is a good substrate for the multidrug efflux pump Pgp [83] and shows a high affinity for the intestinal cytochrome P450 (i.e. CYP3A4) metabolic enzymes [10].

In these carriers, cyclodextrins have been used with a double purpose: as solubilising agents of paclitaxel, which it is an extremely lipophilic compound, and for the capability of these oligosaccharides to disturb and inhibit the activity of the intestinal P-glycoprotein (see Section "Cyclodextrins as P-glycoprotein and cytochrome P450 selective inhibitors").

Paclitaxel was incorporated into nanoparticles as complex with different types of cyclodextrins. This strategy was used by Monza da Silveira and co-workers to increase the loading of poly(alkylcyanoacrylate) nanoparticles with various lipophilic drugs and to modify drug release [108]. In our case, the paclitaxel loading was found to be dependent on the type of cyclodextrin used. Thus, when complexes were formed with either  $\beta$ -CD or HP $\beta$ CD the drug loading was about 4 and 17%, respectively, whereas in the absence of oligosaccharide the paclitaxel loading in poly(anhydride) nanoparticles was only 0.03% [109]. Another possibility to incorporate the drug into nanoparticles may be its incubation with the cyclodextrin and the polymer prior to formation of nanoparticles [110]. Nevertheless, this formation of drug-cyclodextrin complex “in situ” yields, in general, low drug loading values.

Once nanoparticles were orally administered to laboratory animals, the paclitaxel plasma levels were maintained through time from  $T_{max}$  up to 24 hours post-administration, characterized by a plateau close to  $C_{max}$ . These sustained levels of paclitaxel implied a relative oral bioavailability of about 80% [102]. The increase of the relative oral bioavailability would be a result of the combination of the bioadhesive and inhibitory properties of these cyclodextrin-poly(anhydride) nanoparticles. In fact, nanoparticles would efficiently approach the PTX-cyclodextrin complexes to the surface of the enterocytes. Here, the nanocarriers would be immobilised in the absorptive membrane and progressively, release their content. Subsequently, the dissociation of the complexes would occur resulting in the free paclitaxel and the oligosaccharide. Finally, the anticancer agent would be rapidly absorbed while the CDs would disturb the normal activities of the P-gp and CYP450, by interaction with the lipid bilayer at the gut mucosa. Interestingly, the oral administration of the drug-cyclodextrin complexes alone or in physical mixture with empty nanoparticles was unable to promote the permeability of paclitaxel as well as its oral bioavailability (Figure 2) [102, 109].

Also recently, copolymers obtained by the polymerization of cyclodextrin with “pharmaceutical” monomers (i.e. lactic and glycolic acids) have been obtained and proposed for the preparation of biodegradable nanoparticles. Thus, PLGA- $\beta$ CD copolymer was synthesized by reacting L-lactide, glycolide, and  $\beta$ -cyclodextrin in the presence of stannous octoate as a catalyst. Nanoparticles can be obtained by a relatively simple double emulsion method and the resulting carriers displayed high doxorubicin loadings as well as adequate in vitro release profiles for anticancer therapy [111]. In the same way, Wang and collaborators synthesized a novel biodegradable and amphiphilic copolymer composed of hydroxypropyl- $\beta$ -cyclodextrin, polylactide, and 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine. Nanoparticles from this copolymer loaded with doxorubicin demonstrated an antitumor activity against cancer HepG2 and A549 cells comparable to that observed with the free drug [112].

### **Future Perspective**

The oral route is perhaps the preferred route for drug administration thanks to patient convenience and compliance. Still, in a number of cases, factors such as

rapid degradation, low solubility, poor permeability or significant pre-systemic metabolism reduce the oral bioavailability. It is well known that the drug, prior to absorption through the epithelial cells, has to be sufficiently and rapidly dissolved in the aqueous fluids of the gastrointestinal tract. Poor dissolution properties, as observed for lipophilic molecules, may importantly hamper the fraction of drug absorbed. On the other hand, the permeability of a molecule may be negatively affected when the drug is characterised by the presence of hydrophilic or ionisable groups in its chemical structure. Similarly, this permeability is also low when the drug is substrate of the efflux transport systems which are found in the surface of enterocytes. The sensibility to the severe conditions of the gut is another negative factor affecting the bioavailability of a molecule as well as its degradation by luminal enzymes or enzymatic complex located in either the enterocytes (pre-systemic metabolism) or the liver (first-pass metabolism). In all cases, overcoming these hurdles is the major challenge for the development of oral therapies including oral chemotherapy.

A number of antineoplastic drugs are characterized by unfavorable physicochemical properties in tandem with an important sensitivity by the physiological mechanisms of detoxification. These facts limit the possibilities to develop oral formulations and treatments. However, oral chemotherapy is attractive because it improves patients' comfort. In addition, it would also be adequate where prolonged drug exposure is preferable. Currently, many anticancer therapies are cytostatic and thus, are more effective if chronic and continuous tumor exposure is achieved. This mechanism of action virtually requires oral daily and prolonged therapies.

In order to solve these drawbacks a number of strategies have been developed. One of them is based on the use of cyclodextrins. These pharmaceutical excipients offer a number of advantages interesting to solve both the low solubility and low permeability problems characterizing a considerable number of molecules. Thus, cyclodextrins are able to form host-guest complexes with hydrophobic molecules permitting, as a result, increase their aqueous solubility. In addition, the disturbing effect of these oligosaccharides in both the activity of the intestinal P-glycoprotein extrusion pump and the cythochrome P-450 enzymatic complex may dramatically increase the permeability of a pre-systemic metabolized drug. Nevertheless, and in contrast to the solubilizing effect, this enhancement of the intestinal permeability by cyclodextrin "encapsulation" is not found in vivo. This fact may be attributed to the specific conditions that are usually found in the gastrointestinal tract such as presence of high volume of liquids, peristaltism and the presence of the protective mucus layer on the absorptive membrane. In order to solve these inconveniences, one possible solution could be the combination of cyclodextrins with bioadhesive nanoparticles capable of developing adhesive interactions with components of the gut mucosa. The idea is that the bioadhesive nanoparticles would transport the drug-cyclodextrin complexes till the surface of the mucosa where they would be released. Then, the inhibitory effect of the cyclodextrins on the activity of the Pgp and the cytochrome P450 would facilitate the oral absorption of the loaded drug. This strategy has been validated with paclitaxel (and other drugs such as

cyclosporine A and atovaquone). The resulting pharmaceutical device demonstrated the viability of such approach and the capability of these cyclodextrin-polymer nanoparticle vehicles to significantly increase the oral bioavailability of this anticancer drug (about 80% in rat) and, more importantly, to offer sustained and prolonged blood levels of paclitaxel for at least 24 hours.

Another attractive strategy that could be applied is the combination of liposomes and cyclodextrin complexes [131-132]. Although work has been published related to liposomes and oral administration of certain drugs (i.e. anti-inflammatory agents or anti-histamines), little evidence there is for anticancer agents complexed with cyclodextrins and encapsulated in liposomes for their oral delivery. Herein, the development of these systems should be further investigated since they could offer a potential delivery system in the near future.

Although further studies are necessary, the technology and devices capable of offering effective oral delivery of anticancer drugs with both poor characteristics of solubility and permeability is feasible. In the close future, these carriers may facilitate the implementation of chronic cancer treatments. Nevertheless, at this moment, no strategy is able to target a drug specifically to distant cancer cells after oral administration. This goal remains a challenge for the future.

#### **Financial and competing interests disclosure**

This group of research is supported by the University of Navarra, Ministry of Science and Innovation (project SAF2008-02538), Instituto de Salud Carlos III (PFIS grant, ref FI08/00527), Foundations "Universitaria de Navarra", "Asociación de Amigos Universidad de Navarra" and "Caja Navarra" (Project 10828: Nanotechnology and medicines) in Spain. The authors have no other relevant affiliations or financial involvements with any organization or entity with a financial interest in or financial conflict with the subjects matter or materials discussed in the manuscript apart from those disclosed.

#### **Executive summary**

##### ***Applications of cyclodextrins***

Cyclodextrins are pharmaceutical ingredients that may improve the aqueous solubility of lipophilic drugs. As a consequence, the resulting inclusion complex may control the release of the drug and increase the oral bioavailability of the active ingredient.

Cyclodextrins disturb and inhibit the activity of the intestinal P-glycoprotein and the cytochrome P450 and, thus, may modify the permeability of drugs. However, in vivo, this effect is no significant.

##### ***Applications of bioadhesive nanoparticles***

Bioadhesive nanoparticles can protect the loaded drug from its eventual inactivation or degradation in the harsh conditions of the gut. In addition, due to their polymer nature, they can control the release of the loaded drug.



Bioadhesive nanoparticles can interact with the gut mucosa and prolong the contact time with the membrane where the absorption occurs.

***Combination of cyclodextrins and bioadhesive nanoparticles***

The association of cyclodextrins to polymer nanoparticles permits to increase the drug loading of lipophilic compounds.

This combination between cyclodextrins and bioadhesive nanoparticles yields pharmaceutical vehicles capable to increase the intestinal permeability of paclitaxel (a class IV compound with a very low oral bioavailability) and, as a consequence, offer a relative oral bioavailability close to 80%.

## Bibliography

[1] Halfdanarson TR, Jatoi A. Oral cancer chemotherapy: the critical interplay between patient education and patient safety. *Curr. Oncol. Rep.* 12(4), 247-252 (2010).

[2] Weingart SN, Brown E, Bach PB, et al. NCCN Task Force Report: Oral chemotherapy. *J. Natl. Compr. Canc. Netw.* 3, S1-14 (2008).

### ● Interesting report on oral chemotherapy, advances and perspectives.

[3] Payne SA. A study of quality of life in cancer patients receiving palliative chemotherapy. *Soc. Sci. Med.* 35(12), 1505-1509 (1992).

[4] Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. *J. Clin. Oncol.* 15(1), 110-115 (1997).

[5] Pasquier E, Kavallaris M, Andre N. Metronomic chemotherapy: new rationale for new directions. *Nat. Rev. Clin. Oncol.* 7(8), 455-465 (2010).

[6] Irshad S. MN. Considerations when choosing oral chemotherapy: identifying and responding to patient need. *Eur. J. Cancer Care* 19(s1), 5-11 (2010).

[7] Terwogt JM, Schellens JH, Huinink WW, Beijnen JH. Clinical pharmacology of anticancer agents in relation to formulations and administration routes. *Cancer Treat. Rev.* 25(2), 83-101 (1999).

[8] Kuppens IE, Breedveld P, Beijnen JH, Schellens JH. Modulation of oral drug bioavailability: from preclinical mechanism to therapeutic application. *Cancer Invest.* 23(5), 443-464 (2005).

[9] Washington N, Washington C, Wilson C. *Physiological Pharmaceutics: Barriers to Drug Absorption* Taylor and Francis group, London, (2011).

[10] Zhang Y, Benet LZ. The gut as a barrier to drug absorption: combined role of cytochrome P450 3A and P-glycoprotein. *Clin. Pharmacokinet.* 40(3), 159-168 (2001).

[11] Thummel KE. Gut instincts: CYP3A4 and intestinal drug metabolism. *J. Clin. Invest.* 117(11), 3173-3176 (2007).

[12] Cai ZW, Y. Zhu, L. J. Liu, Z. Q. Nanocarriers: a general strategy for enhancement of oral bioavailability of poorly absorbed or pre-systemically metabolized drugs. *Curr. Drug Metab.* 11(2), 197-207 (2010).

### ●● Overview of the use of nanocarriers to increase the oral bioavailability of anticancer drugs with the idea of achieving oral treatment.

[13] Roger E, Lagarce F, Garcion E, Benoit JP. Biopharmaceutical parameters to consider in order to alter the fate of nanocarriers after oral delivery. *Nanomedicine (Lond)* 5(2), 287-306 (2010).

[14] Bansal T, Akhtar N, Jaggi M, Khar RK, Talegaonkar S. Novel formulation approaches for optimising delivery of anticancer drugs based on P-glycoprotein modulation. *Drug Discov. Today* 14(21-22), 1067-1074 (2009).

[15] Villiers A. Sur la fermentation de la fécule par l'action du ferment butyrique. *Compt. Rend. Acad. Sci.* 112(536-538 (1891).

[16] Loftsson T, Duchene D. Cyclodextrins and their pharmaceutical applications. *Int. J. Pharm.* 329(1-2), 1-11 (2007).

### ●● Comprehensive survey of cyclodextrins for pharmaceutical purposes

- [17] Szejtli J. Past, present, and future of cyclodextrin research. *Pure Appl. Chem.* 76(10), 1825-1845 (2004).
- [18] Uekama K, Otagiri M. Cyclodextrins in drug carrier systems. *Crit. Rev. Ther. Drug Carrier Syst.* 3(1), 1-40 (1987).
- [19] Albers E, Muller BW. Cyclodextrin derivatives in pharmaceuticals. *Crit. Rev. Ther. Drug Carrier Syst.* 12(4), 311-337 (1995).
- [20] Uekama K. Design and evaluation of cyclodextrin-based drug formulation. *Chem. Pharm. Bull. (Tokyo)* 52(8), 900-915 (2004).
- [21] Szejtli J. Cyclodextrin Technology. Kluwer Academic Publisher, Dordrecht, (1988).
- [22] Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization. *J. Pharm. Sci.* 85(10), 1017-1025 (1996).
- **Review of the properties of cyclodextrins as solubilising agents**
- [23] Rajewski RA, Stella VJ. Pharmaceutical applications of cyclodextrins. 2. In vivo drug delivery. *J. Pharm. Sci.* 85(11), 1142-1169 (1996).
- [24] Duchene D, Wouessidjewe D. Industrial uses of cyclodextrins and their derivatives. *J. Coord. Chem.* 27(1-3), 223-236 (1992).
- [25] Thompson DO. Cyclodextrins--enabling excipients: their present and future use in pharmaceuticals. *Crit. Rev. Ther. Drug Carrier Syst.* 14(1), 1-104 (1997).
- [26] Frank DW, Gray JE, Weaver RN. Cyclodextrin nephrosis in the rat. *Am. J. Pathol.* 83(2), 367-382 (1976).
- [27] Debouzy JC, Fauvelle F, Crouzy S, et al. Mechanism of alpha-cyclodextrin induced hemolysis. 2. A study of the factors controlling the association with serine-, ethanolamine-, and choline-phospholipids. *J. Pharm. Sci.* 87(1), 59-66 (1998).
- [28] Irie T, Uekama K. Pharmaceutical applications of cyclodextrins. III. Toxicological issues and safety evaluation. *J. Pharm. Sci.* 86(2), 147-162 (1997).
- [29] Singh M, Sharma R, Banerjee UC. Biotechnological applications of cyclodextrins. *Biotechnol. Adv.* 20(5-6), 341-359 (2002).
- [30] Carrier RL, Miller LA, Ahmed I. The utility of cyclodextrins for enhancing oral bioavailability. *J. Control. Release* 123(2), 78-99 (2007).
- [31] Hirayama F, Uekama K. Cyclodextrin-based controlled drug release system. *Adv. Drug Deliv. Rev.* 36(1), 125-141 (1999).
- [32] Challa R, Ahuja A, Ali J, Khar RK. Cyclodextrins in drug delivery: an updated review. *AAPS PharmSciTech.* 6(2), E329-357 (2005).
- [33] Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutical drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm. Res.* 12(3), 413-420 (1995).
- [34] Yu LX, Amidon GL, Polli JE, et al. Biopharmaceutics classification system: the scientific basis for biowaiver extensions. *Pharm. Res.* 19(7), 921-925 (2002).
- [35] Loftsson T, Masson M, Brewster ME. Self-association of cyclodextrins and cyclodextrin complexes. *J. Pharm. Sci.* 93(5), 1091-1099 (2004).
- [36] Loftsson T, Magnúsdóttir A, Masson M, Sigurjonsdóttir JF. Self-association and cyclodextrin solubilization of drugs. *J. Pharm. Sci.* 91(11), 2307-2316 (2002).

- [37] Pitha J, Hoshino T, Torreslabandeira J, Irie T. Preparation of drug - hydroxypropylcyclodextrin complexes by a method using ethanol or aqueous ammonium hydroxide as co-solubilizers. *Int. J. Pharm.* 80(2-3), 253-258 (1992).
- [38] Loftsson T, Magnusdottir A, Masson M. Self association and cyclodextrin solubilization of NSAIDs. *J. Incl. Phenom. Macro.* 44(1-4), 213-218 (2002).
- [39] Davis ME, Brewster ME. Cyclodextrin-based pharmaceuticals: past, present and future. *Nat. Rev. Drug Discov.* 3(12), 1023-1035 (2004).
- [40] Avdeef A, Bendels S, Tsinman O, Tsinman K, Kansy M. Solubility-excipient classification gradient maps. *Pharm. Res.* 24(3), 530-545 (2007).
- [41] Park JS, Kim CK. Solubility Enhancers for Oral Drug Delivery: Can Chemical Structure Manipulation Be Avoided? *Am. J. Drug Deliv.* 2(2), 113-130 (2004).
- [42] Loftsson T, Jarho P, Masson M, Jarvinen T. Cyclodextrins in drug delivery. *Expert Opin. Drug Deliv.* 2(2), 335-351 (2005).
- [43] Park K. Efficient oral delivery of paclitaxel using cyclodextrin complexes. *J. Control. Release* 145(1), 1 (2010).
- [44] Cserhati T, Forgacs E, Hollo J. Interaction of taxol and other anticancer drugs with alpha-cyclodextrin. *J. Pharm. Biomed. Anal.* 13(4-5), 533-541 (1995).
- [45] Badawy SIF, Ghorab MM, Adeyeye CM. Bioavailability of danazol-hydroxypropyl-beta-cyclodextrin complex by different routes of administration. *Int. J. Pharm.* 145(1-2), 137-143 (1996).
- [46] Madan J, Dhiman N, Parmar VK, et al. Inclusion complexes of noscapine in beta-cyclodextrin offer better solubility and improved pharmacokinetics. *Cancer Chemoth. Pharmacol.* 65(3), 537-548 (2010).
- [47] Yavuz B, Bilensoy E, Vural I, Sumnu M. Alternative oral exemestane formulation: improved dissolution and permeation. *Int. J. Pharm.* 398(1-2), 137-145 (2010).
- [48] Yavuz B, Sarisozen C, Vural I, Bilensoy E, Sumnu M. An alternative cyclodextrin based formulation for oral anticancer drug exemestane: In vitro and cell culture studies. *J. Control. Release* 148(1), e83-84 (2010).
- [49] Kikuchi M, Hirayama F, Uekama K. Improvement of chemical instability of carmofol in beta-cyclodextrin solid complex by utilizing some organic acids. *Chem. Pharm. Bull. (Tokyo)* 35(1), 315-319 (1987).
- [50] Piette M, Evrard B, Frankenne F, et al. Pharmacokinetic study of a new synthetic MMP inhibitor (Ro 28-2653) after IV and oral administration of cyclodextrin solutions. *Eur. J. Pharm. Sci.* 28(3), 189-195 (2006).
- [51] Nakanishi K, Nadai T, Masada M, Miyajima K. Effect of cyclodextrins on biological membrane. II. Mechanism of enhancement on the intestinal absorption of non-absorbable drug by cyclodextrins. *Chem. Pharm. Bull. (Tokyo)* 40(5), 1252-1256 (1992).
- [52] Gottesman MM, Pastan I. Biochemistry of multidrug resistance mediated by the multidrug transporter. *Annu. Rev. Biochem.* 62, 385-427 (1993).
- [53] Fenyvesi F, Fenyvesi E, Szenté L, et al. P-glycoprotein inhibition by membrane cholesterol modulation. *Eur. J. Pharm. Sci.* 34(4-5), 236-242 (2008).
- **Comprehensive work on the P-glycoprotein and its modulation**

[54] Ishikawa M, Yoshii H, Furuta T. Interaction of modified cyclodextrins with cytochrome P-450. *Biosci. Biotechnol. Biochem.* 69(1), 246-248 (2005).

[55] Garrigues A, Escargueil AE, Orlowski S. The multidrug transporter, P-glycoprotein, actively mediates cholesterol redistribution in the cell membrane. *Proc. Natl. Acad. Sci. U.S.A.* 99(16), 10347-10352 (2002).

• **Overview of the role of Pgp on the membrane integrity and modulation of its structure**

[56] Arima H, Yunomae K, Hirayama F, Uekama K. Contribution of P-glycoprotein to the enhancing effects of dimethyl-beta-cyclodextrin on oral bioavailability of tacrolimus. *J. Pharmacol. Exp. Ther.* 297(2), 547-555 (2001).

[57] Pathak SM, Musmade P, Dingle S, et al. Enhanced oral absorption of saquinavir with Methyl-Beta-Cyclodextrin-Preparation and in vitro and in vivo evaluation. *Eur. J. Pharm. Sci.* 41(3-4), 440-451 (2010).

[58] Fenyvesi F, Kiss T, Fenyvesi E, et al. Randomly methylated beta-cyclodextrin derivatives enhance taxol permeability through human intestinal epithelial Caco-2 cell monolayer. *J. Pharm. Sci.*, doi: 10.1002/jps.22666 (2011).

[59] Munoz M, Deschenaux R, Coleman AW. Observation of microscopic patterning at the air water interface by mixtures of amphiphilic cyclodextrins: a compression isotherm and Brewster angle microscopy study. *J. Phys. Org. Chem.* 12(5), 364-369 (1999).

[60] Bilensoy E, Dogan L, Sen M, Hincal A. Complexation behavior of antiestrogen drug tamoxifen citrate with natural and modified beta-cyclodextrins. *J. Incl. Phenom. Macro.* 57(1-4), 651-655 (2007).

[61] Duchene D, Ponchel G, Wouessidjewe D. Cyclodextrins in targeting. Application to nanoparticles. *Adv. Drug Deliv. Rev.* 36(1), 29-40 (1999).

[62] Duchene D, Wouessidjewe D, Ponchel G. Cyclodextrins and carrier systems. *J. Control. Release* 62(1-2), 263-268 (1999).

• **Review of cyclodextrins as carrier systems**

[63] Memisoglu-Bilensoy E, Vural L, Bochot A, et al. Tarnoxifen citrate loaded amphiphilic beta-cyclodextrin nanoparticles: In vitro characterization and cytotoxicity. *J. Control. Release* 104(3), 489-496 (2005).

[64] Bilensoy E, Hincal AA. Recent advances and future directions in amphiphilic cyclodextrin nanoparticles. *Expert Opin. Drug Deliv.* 6(11), 1161-1173 (2009).

• **Excellent review of cyclodextrins as materials for the preparation of nanoparticles**

[65] Cryan SA, Holohan A, Donohue R, Darcy R, O'Driscoll CM. Cell transfection with polycationic cyclodextrin vectors. *Eur. J. Pharm. Sci.* 21(5), 625-633 (2004).

[66] Lemos-Senna E., Wouessidjewe D., Lesieur S., Puisieux F., Courraze G., Duchene D. Evaluation of the Hydrophobic Drug Loading Characteristics in Nanoprecipitated Amphiphilic Cyclodextrin Nanospheres. *Pharm. Dev. Technol.* 3(1), 85-94 (1998).

[67] Wouessidjewe D, Skiba M, LeroyLechat F, et al. A new concept in drug delivery based on <<skirt-shaped cyclodextrin aggregates>> - Present state and future prospects. *Stp Pharma. Sciences* 6(1), 21-28 (1996).

- [68] Lemos-Senna E, Wouessidjewe D, Lesieur S, Duchene D. Preparation of amphiphilic cyclodextrin nanospheres using the emulsification solvent evaporation method. Influence of the surfactant on preparation and hydrophobic drug loading. *Int. J. Pharm.* 170(1), 119-128 (1998).
- [69] Lemos-Senna E, Wouessidjewe D, Duchene D, Lesieur S. Amphiphilic cyclodextrin nanospheres: particle solubilization and reconstitution by the action of a non-ionic detergent. *Colloid. Surface. B* 10(5), 291-301 (1998).
- [70] Memisoglu E, Bochot A, Ozalp M, et al. Direct formation of nanospheres from amphiphilic beta-cyclodextrin inclusion complexes. *Pharm. Res.* 20(1), 117-125 (2003).
- [71] Memisoglu E, Bochot A, Sen M, Duchene D, Hincal AA. Non-surfactant nanospheres of progesterone inclusion complexes with amphiphilic beta-cyclodextrins. *Int. J. Pharm.* 251(1-2), 143-153 (2003).
- [72] Vural I, Memisoglu-Bilensoy E, Renoir JM, et al. Transcription efficiency of tamoxifen citrate-loaded beta-cyclodextrin nanoparticles. *J. Drug Deliv. Sci. Tech.* 15(5), 339-342 (2005).
- [73] Bilensoy E, Gurkaynak O, Ertan M, Sen M, Hincal AA. Development of nonsurfactant cyclodextrin nanoparticles loaded with anticancer drug paclitaxel. *J. Pharm. Sci.* 97(4), 1519-1529 (2008).
- [74] Bilensoy E, Gurkaynak O, Dogan AL, Hincal AA. Safety and efficacy of amphiphilic beta-cyclodextrin nanoparticles for paclitaxel delivery. *Int. J. Pharm.* 347(1-2), 163-170 (2008).
- [75] Cirpanli Y, Bilensoy E, Dogan AL, Calis S. Comparative evaluation of polymeric and amphiphilic cyclodextrin nanoparticles for effective camptothecin delivery. *Eur. J. Pharm. Biopharm.* 73(1), 82-89 (2009).
- [76] Cirpanli Y, Allard E, Passirani C, et al. Antitumoral activity of camptothecin-loaded nanoparticles in 9L rat glioma model. *Int. J. Pharm.* 403(1-2), 201-206 (2011).
- [77] Quaglia F, Ostacolo L, Mazzaglia A, et al. The intracellular effects of non-ionic amphiphilic cyclodextrin nanoparticles in the delivery of anticancer drugs. *Biomaterials* 30(3), 374-382 (2009).
- [78] Sortino S, Mazzaglia A, Scolaro LM, et al. Nanoparticles of cationic amphiphilic cyclodextrins entangling anionic porphyrins as carrier-sensitizer system in photodynamic cancer therapy. *Biomaterials* 27(23), 4256-4265 (2006).
- [79] Tsuruo T, Iida H, Tsukagoshi S, Sakurai Y. Overcoming of vincristine resistance in p388 leukemia *in vivo* and *in vitro* through enhanced cyto-toxicity of vincristine and vinblastine by verapamil. *Cancer Res.* 41(5), 1967-1972 (1981).
- [80] van Asperen J, van Tellingen O, van der Valk MA, Rozenhart M, Beijnen JH. Enhanced oral absorption and decreased elimination of paclitaxel in mice cotreated with cyclosporin A. *Clin. Cancer Res.* 4(10), 2293-2297 (1998).
- [81] Bardelmeijer HA, Beijnen JH, Brouwer KR, et al. Increased oral bioavailability of paclitaxel by GF120918 in mice through selective modulation of P-glycoprotein. *Clin. Cancer Res.* 6(11), 4416-4421 (2000).

[82] Dong YC, Feng SS. Poly(D,L-lactide-co-glycolide)/montmorillonite nanoparticles for oral delivery of anticancer drugs. *Biomaterials* 26(30), 6068-6076 (2005).

[83] Woo JS, Lee CH, Shim CK, Hwang SJ. Enhanced oral bioavailability of paclitaxel by coadministration of the P-glycoprotein inhibitor KR30031. *Pharm. Res.* 20(1), 24-30 (2003).

[84] Ponchel G, Irache JM. Specific and non-specific bioadhesive particulate systems for oral delivery to the gastrointestinal tract. *Adv. Drug Deliver. Rev.* 34(2-3), 191-219 (1998).

• **Comprehensive survey about the bioadhesive properties of nanoparticles**

[85] Woodley J. Bioadhesion - New possibilities for drug administration? *Clin. Pharmacokinet.* 40(2), 77-84 (2001).

[86] Bernkop-Schnürch A. Mucoadhesive systems in oral drug delivery. *Drug Discov. Today: Technol.* 2(1), 83-87 (2005).

• **Critical current review of muco-/bioadhesive dosage forms**

[87] Florence AT, Hillery AM, Hussain N, Jani PU. Factors affecting the oral uptake and translocation of polystyrene nanoparticles - histological and analytical evidence. *J. Drug Target.* 3(1), 65-70 (1995).

[88] Bertholon I, Ponchel G, Labarre D, Couvreur P, Vauthier C. Bioadhesive properties of poly(alkylcyanoacrylate) nanoparticles coated with polysaccharide. *J. Nanosci. Nanotechnol.* 6(9-10), 3102-3109 (2006).

[89] Chen J, Yang WL, Li G, et al. Transfection of mEpo gene to intestinal epithelium in vivo mediated by oral delivery of chitosan-DNA nanoparticles. *World J. Gastroenterol.* 10(1), 112-116 (2004).

[90] Feng SS, Mei L, Anitha P, Gan CW, Zhou WY. Poly(lactide)-vitamin E derivative/montmorillonite nanoparticle formulations for the oral delivery of Docetaxel. *Biomaterials* 30(19), 3297-3306 (2009).

[91] Arangoa MA, Campanero MA, Renedo MJ, Ponchel G, Irache JM. Gliadin nanoparticles as carriers for the oral administration of lipophilic drugs. Relationships between bioadhesion and pharmacokinetics. *Pharm. Res.* 18(11), 1521-1527 (2001).

[92] Arbos P, Campanero MA, Arangoa MA, Irache JM. Nanoparticles with specific bioadhesive properties to circumvent the pre-systemic degradation of fluorinated pyrimidines. *J. Control. Release* 96(1), 55-65 (2004).

[93] Arbos P, Campanero MA, Arangoa MA, Renedo MJ, Irache JM. Influence of the surface characteristics of PVM/MA nanoparticles on their bioadhesive properties. *J. Control. Release* 89(1), 19-30 (2003).

[94] Lamprecht A, Schafer U, Lehr CM. Size-dependent bioadhesion of micro- and nanoparticulate carriers to the inflamed colonic mucosa. *Pharm. Res.* 18(6), 788-793 (2001).

[95] Montisci MJ, Dembri A, Giovannuci G, et al. Gastrointestinal transit and mucoadhesion of colloidal suspensions of *Lycopersicon esculentum* L. and *Lotus tetragonolobus* lectin-PLA microsphere conjugates in rats. *Pharm. Res.* 18(6), 829-837 (2001).

- [96] Arbos P, Arangoa MA, Campanero MA, Irache JM. Quantification of the bioadhesive properties of protein-coated PVM/MA nanoparticles. *Int. J. Pharm.* 242(1-2), 129-136 (2002).
- [97] Salman HH, Gamazo C, Campanero MA, Irache JM. Bioadhesive mannosylated nanoparticles for oral drug delivery. *J. Nanosci. Nanotechnol.* 6(9-10), 3203-3209 (2006).
- [98] Salman HH, Gamazo C, Agueros M, Irache JM. Bioadhesive capacity and immunoadjuvant properties of thiamine-coated nanoparticles. *Vaccine* 25(48), 8123-8132 (2007).
- [99] Llabot JM, Salman H, Millotti G, et al. Bioadhesive properties of poly(anhydride) nanoparticles coated with different molecular weights chitosan. *J. Microencapsul.* 28(5), 455-463 (2011).
- [100] Agueros M, Areses P, Campanero MA, et al. Bioadhesive properties and biodistribution of cyclodextrin-poly(anhydride) nanoparticles. *Eur. J. Pharm. Sci.* 37(3-4), 231-240 (2009).
- [101] Areses P, Agüeros MT, Quincoces G, et al. Molecular Imaging Techniques to Study the Biodistribution of Orally Administered <sup>99m</sup>Tc-Labelled Naive and Ligand-Tagged Nanoparticles. *Mol. Imaging Biol.* DOI: 10.1007/s11307-010-0456-0 (2010).
- [102] Agueros M, Zabaleta V, Espuelas S, Campanero MA, Irache JM. Increased oral bioavailability of paclitaxel by its encapsulation through complex formation with cyclodextrins in poly(anhydride) nanoparticles. *J. Control. Release* 145(1), 2-8 (2010).
- **Provides demonstration of the synergistic effect of the combination of cyclodextrins and bioadhesive nanoparticles on the oral bioavailability**
- [103] Sparano JA, Wang ML, Martino S, et al. Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer (vol 358, pg 1663, 2008). *New Engl. J. Med.* 360(16), 1685-1685 (2009).
- [104] Montana M, Ducros C, Verhaeghe P, et al. Albumin-Bound Paclitaxel: The Benefit of This New Formulation in the Treatment of Various Cancers. *J. Chemotherapy* 23(2), 59-66 (2011).
- [105] Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *New Engl. J. Med.* 355(24), 2542-2550 (2006).
- [106] Zhan M, Tao WY, Pan SH, Sun XY, Jiang HC. Low-dose metronomic chemotherapy of paclitaxel synergizes with cetuximab to suppress human colon cancer xenografts. *Anti-Cancer Drug.* 20(5), 355-363 (2009).
- [107] Dhanikula AB, Panchagnula R. Localized paclitaxel delivery. *Int. J. Pharm.* 183(2), 85-100 (1999).
- [108] da Silveira AM, Ponchel G, Puisieux F, Duchene D. Combined poly(isobutylcyanoacrylate) and cyclodextrins nanoparticles for enhancing the encapsulation of lipophilic drugs. *Pharm. Res.* 15(7), 1051-1055 (1998).
- [109] Agueros M, Ruiz-Gaton L, Vauthier C, et al. Combined hydroxypropyl-beta-cyclodextrin and poly(anhydride) nanoparticles improve the oral permeability of paclitaxel. *Eur. J Pharm. Sci.* 38(4), 405-413 (2009).



- [110] Calvo J, Lavandera J, Agüeros M, Irache J. Cyclodextrin/poly(anhydride) nanoparticles as drug carriers for the oral delivery of atovaquone. *Biomed. Microdevices* 1-11 (2011).
- [111] Moogquee M, Omid Y, Davaran S. Synthesis and In Vitro Release of Adriamycin from Star-Shaped Poly(Lactide-co-Glycolide) Nano- and Microparticles. *J. Pharm. Sci.* 99(8), 3389-3397 (2010).
- [112] Wang TW, Zhang CL, Liang XJ, Liang W, Wu Y. Hydroxypropyl-beta-Cyclodextrin Copolymers and Their Nanoparticles as Doxorubicin Delivery System. *J. Pharm. Sci.* 100(3), 1067-1079 (2011).
- [113] Arima H, Yunomae K, Morikawa T, Hirayama F, Uekama K. Contribution of cholesterol and phospholipids to inhibitory effect of dimethyl-beta-cyclodextrin on efflux function of P-glycoprotein and multidrug resistance-associated protein 2 in vinblastine-resistant Caco-2 cell monolayers. *Pharm. Res.* 21(4), 625-634 (2004).
- [114] Uekama K. [Pharmaceutical application of cyclodextrins as multi-functional drug carriers]. *Yakugaku Zasshi* 124(12), 909-935 (2004).
- [115] Bellanger N, Perly B. NMR investigations of the conformation of new cyclodextrin-based amphiphilic transporters for hydrophobic drugs - molecular lollipops. *J. Mol. Struct.* 273, 215-226 (1992).
- [116] Dodziuk H, Chmurski K, Jurczak J, et al. A dynamic NMR study of self-inclusion of a pendant group in amphiphilic 6-thiophenyl-6-deoxycyclodextrins. *J. Mol. Struct.* 519, 33-36 (2000).
- [117] Kawabata Y, Matsumoto M, Tanaka M, et al. Formation and deposition of monolayers of amphiphilic beta-cyclodextrin derivatives. *Chem. Lett.* 11, 1933-1934 (1986).
- [118] Liu FY, Kildsig DO, Mitra AK. Complexation of 6-acyl-o-beta-cyclodextrin derivatives with steroids - effects of chain-length and substitution degree. *Drug Dev. Ind. Pharm.* 18(15), 1599-1612 (1992).
- [119] Zhang P, Ling CC, Coleman AW, Parrotlopez H, Galons H. Formation of amphiphilic cyclodextrins via hydrophobic esterification at the secondary hydroxyl face. *Tetrahedron Lett.* 32(24), 2769-2770 (1991).
- [120] Zhang P, Parrotlopez H, Tchoreloff P, et al. Self-organizing systems based on amphiphilic cyclodextrin diesters. *J. Phys. Org. Chem.* 5(8), 518-528 (1992).
- [121] Lesieur S, Charon D, Lesieur P, et al. Phase behavior of fully hydrated DMPC-amphiphilic cyclodextrin systems. *Chem. Phys. Lipids* 106(2), 127-144 (2000).
- [122] Canceill J, Jullien L, Lacombe L, Lehn JM. Channel-type molecular-structures .2. synthesis of bouquet-shaped molecules based on a beta-cyclodextrin core. *Helv. Chim. Acta* 75(3), 791-812 (1992).
- [123] Wenz G. Synthesis and characterization of some lipophilic per(2,6-di-o-alkyl)cyclomalto-oligosaccharides. *Carbohydr. Res.* 214(2), 257-265 (1991).
- [124] Auzely-Velty R, Djedaini-Pilard F, Desert S, Perly B, Zemb T. Micellization of hydrophobically modified cyclodextrins. 1. Micellar structure. *Langmuir* 16(8), 3727-3734 (2000).

- [125] Mazzaglia A, Angelini N, Darcy R, et al. Novel heterotopic colloids of anionic porphyrins entangled in cationic amphiphilic cyclodextrins: Spectroscopic investigation and intracellular delivery. *Chem. Eur. J.* 9(23), 5762-5769 (2003).
- [126] Matsumoto M, Matsuzawa Y, Noguchi S, Sakai H, Abe M. Structure of hybrid Langmuir-Blodgett films of amphiphilic cyclodextrin and water-soluble azobenzene. *Mol. Cryst. Liq. Cryst.* 425(475-482 (2004).
- [127] Dubes A, Bouchu D, Lamartine R, Parrot-Lopez H. An efficient regio-specific synthetic route to multiply substituted acyl-sulphated beta-cyclodextrins. *Tetrahedron Lett.* 42(52), 9147-9151 (2001).
- [128] Granger CE, Felix CP, Parrot-Lopez HP, Langlois BR. Fluorine containing beta-cyclodextrin: a new class of amphiphilic carriers. *Tetrahedron Lett.* 41(48), 9257-9260 (2000).
- [129] Peroche S, Degobert G, Putaux JL, et al. Synthesis and characterisation of novel nanospheres made from amphiphilic perfluoroalkylthio-beta-cyclodextrins. *Eur. J. Pharm. Biopharm.* 60(1), 123-131 (2005).
- [130] Skiba M, Skiba-Lahiani M, Arnaud P. Design of nanocapsules based on novel fluorophilic cyclodextrin derivatives and their potential role in oxygen delivery. *J. Incl. Phenom. Macro.* 44(1-4), 151-154 (2002).
- [131] McCormack B, Gregoriadis G. Entrapment of cyclodextrin-drug complexes into liposomes: potential advantages in drug delivery. *J. Drug Target.* 2(5), 449-454 (1994).
- [132] Wang X, Deng L, Cai L, et al. Preparation, characterization, pharmacokinetics, and bioactivity of honokiol-in-hydroxypropyl- $\beta$ -cyclodextrin in liposome. *J. Pharm. Sci.* 100(8), 3357-3364 (2011).

Table 1. Some of the most common derivatives based on  $\beta$ CD.

		<b>Derivate</b>	<b>Characteristics</b>	<b>Ref.</b>
Hydrophilic derivates	Methylated	2,6-di-O-methyl- $\beta$ CD per-O-methyl- $\beta$ CD	Soluble in cold water and organic solvents. Pgp inhibitory activity. Hemolytic.	[28, 53, 56, 113]
	Hydroxyalkylated	2-hydroxypropyl- $\beta$ CD 3-hydroxypropyl- $\beta$ CD 2,3-hydroxypropyl- $\beta$ CD	Amorphous mixture of different degrees of substitution. Highly water- soluble, low toxicity.	[28, 114]
	Branched	Glycosyl- $\beta$ CD Maltosyl- $\beta$ CD Glucuronyl-glucosyl- $\beta$ CD	Highly water-soluble, low toxicity.	[20, 28, 114]
Hydrophobic derivates	Alkylated	2,6-di-O-ethyl- $\beta$ CD per-O-ethyl- $\beta$ CD	Poorly water-soluble, soluble in organic solvents, Pgp inhibitory activity.	[113, 114]
Ionizable derivates	Anionic	O-carboxymethyl-O- ethyl- $\beta$ CD Sulfobutylether- $\beta$ CD	Soluble at pH>4.	[20]

Table 2. Some of the currently commercialized pharmaceutical products containing cyclodextrins.

<b>Cyclodextrin</b>	<b>Drug</b>	<b>Commercial Name</b>	<b>Country</b>
$\alpha$ -cyclodextrin	Alprostadi	Caverject Dual	Europe
	OP-1206	Opalmon	Japan
	PGE1	Prostavastin	Japan, Europe
$\beta$ -cyclodextrin	Benexate HCl	Lonmiel, Ulgut	Japan
	Cephalosporin	Meiact	Japan
	Cetirizine	Cetrizin	Europe
	Chlordiazepoxide	Transillium	Argentina
	Dexamethasone	Glymesason	Japan
	Nicotine	Nicorette, Nicogum	Europe
	Omeprazol	Omebeta	Europe
	Piroxicam	Brexin	Europe
	Tiaprofenic acid	Surgamyl	Europe
Methylated- $\beta$ -cyclodextrin	Chloramphenicol	Clorocil	Europe
	Estradiol	Aerodiol	Europe
2-Hydroxypropyl- $\beta$ -cyclodextrin	Cisapride	Propulsid	Europe
	Hydrocortisone	Dexocort	Europe
	Indomethacin	Indocid	Europe
	Itraconazole	Sporanox	Europe, USA
	Mitomycin	Mitozytrex	Europe, USA
2-Hydroxypropyl- $\gamma$ -cyclodextrin	Diclofenac sodium	Voltaren	Europe
	Tc-99m Teboroxime	CardioTec	USA

Table 3. Some properties of the most used amphiphilic cyclodextrins.

Type	Characteristics	Ref.	
Non-ionic amphiphilic cyclodextrins	Lollipop cyclodextrins	Obtained by the grafting of one aliphatic chain to 6-amino- $\beta$ -cyclodextrin.	[115]
	Cup-and-ball cyclodextrins	Synthesized by the introduction of a voluminous group, linked to the end of the aliphatic chain	[116]
	Medusa-like cyclodextrins	Obtained by grafting aliphatic chains (length C10-C16) to all the primary hydroxyls of the CD molecule	[117, 118]
	Skirt-shaped cyclodextrins	They consist of $\alpha$ , $\beta$ and $\gamma$ -cyclodextrins per-modified with aliphatic esters (C2 to C14) on the secondary face.	[119-121]
	Bouquet-shaped cyclodextrins	Obtained from the grafting of 14 polymethylene chains to 3-monomethyl- $\beta$ -cyclodextrin (7 chains on each side of the cyclodextrin ring molecule). Per(2,6-di-O-alkyl)cyclodextrins with alkyl chain propyl, pentyl, 3-methylbutyl or dodecyl are also bouquet-shaped.	[122, 123]
	Cholesteryl cyclodextrins	Cyclodextrin is the hydrophilic head group and cholesterol is the hydrophobic part.	[124]
Cationic amphiphilic cyclodextrins	[2-amino-O-oligo-(ethyleneoxide)-6-hexylthio]- $\beta$ -cyclodextrin has an amino group. The oligoethylene glycol group would facilitate intracellular drug delivery.	[65, 125, 126]	
	Other cationic amphiphilic cyclodextrins: polyamino- $\beta$ -cyclodextrins completely substituted by amine groups at the position 6 and alkylamino - $\alpha$ and $\beta$ -cyclodextrin.		
Anionic amphiphilic cyclodextrins	Acyl-sulfated- $\beta$ -cyclodextrins in which the upper rim is functionalized with sulfates and the lower with fatty acid esters. Fluorine-containing anionic $\beta$ -cyclodextrins functionalized at the position 6 by trifluoromethylthio groups. Fluorophilic cyclodextrins are obtained combining cyclodextrins and a linear perfluorocarbon.	[127-130]	



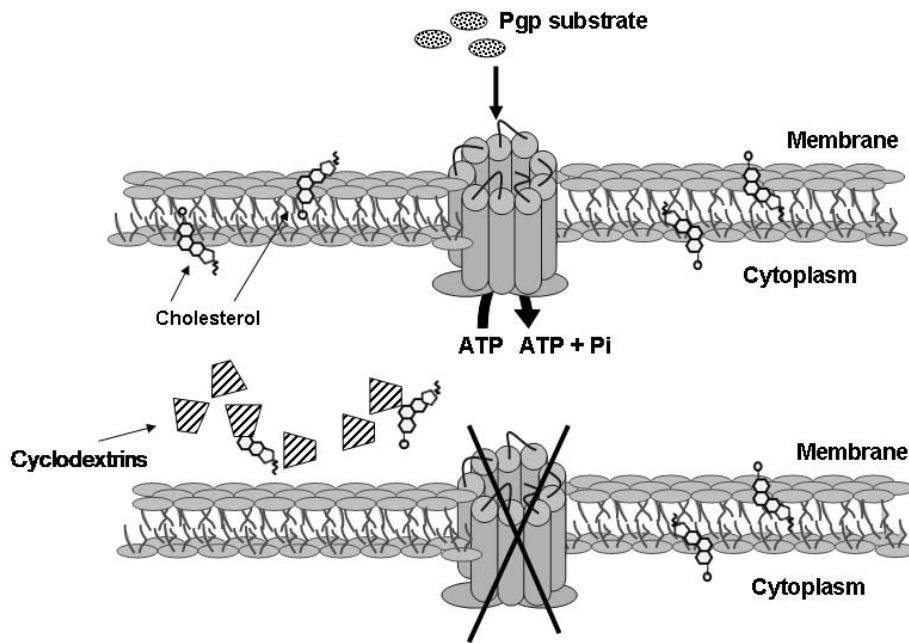


Figure 1. Diagram representing the mechanism of inhibition of P-glycoprotein by cyclodextrins.

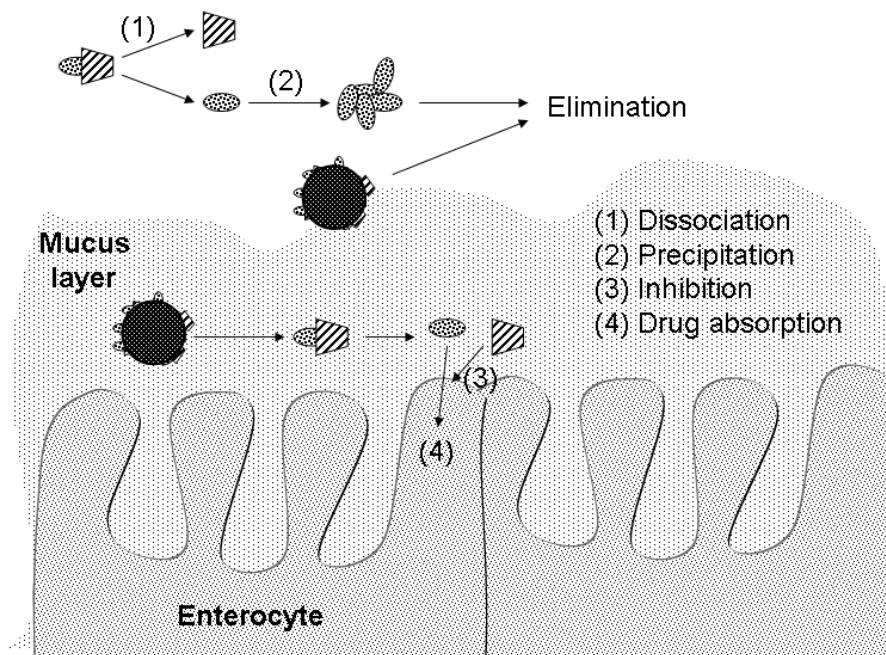


Figure 2. Representation of the hypothetical mechanism by which the combination between cyclodextrins and bioadhesive nanoparticles would promote the oral absorption and bioavailability of paclitaxel and other Class IV compounds.