REVIEW ARTICLE

Am J Drug Deliv 2004; 2 (4): 1
1175-9038/04/0004-0001/$31.00/0

Role of Cyclodextrins in Improving Oral Drug Delivery

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Abstract

The use of high-throughput screening and similar techniques in drug discovery has put a number of evolutionary pressures on drug candidates such that over time there is a tendency for them to increase in molecular weight, increase in log $K_{(octanol/water)}$ and decrease in water solubility. These trends provide an ever-increasing series of challenges for the drug formulator to generate effective, orally bioavailable dosage forms. An important tool in this regard is the use of cyclodextrins, especially chemically modified cyclodextrins. These starch derivatives interact via dynamic complex formation and other mechanisms in a way that camouflages undesirable physicochemical properties, including low aqueous solubility, poor dissolution rate and limited drug stability. Through these effects, cyclodextrins and their derivatives have become popular modalities for increasing oral bioavailability and absorption rate. These actions have positioned cyclodextrins as important enabling and functional excipients. This review aims to assess the use of cyclodextrins in oral and other administration routes in the context of the Biopharmaceutical Classification Systems (BCS), a US FDA-based characterization approach that bins drugs based on solubility and permeability features. Specifically, a framework based on Fickian theory as well as the Noyes-Whiney relationship is constructed to assess where cyclodextrins are likely to be useful and where their use is probably not justified. This working model is examined in the context of a number of published examples in which cyclodextrins have been applied to class I, II, III, and IV drugs and drug candidates.

Oral drug administration is the preferred route of drug delivery and solid oral dosage forms are the most common drug formulations. Conventional tablets are relatively easy to produce, inexpensive, and patient friendly. Systemic drug absorption from, for example, immediate-release tablets, consists of a series of rate processes:

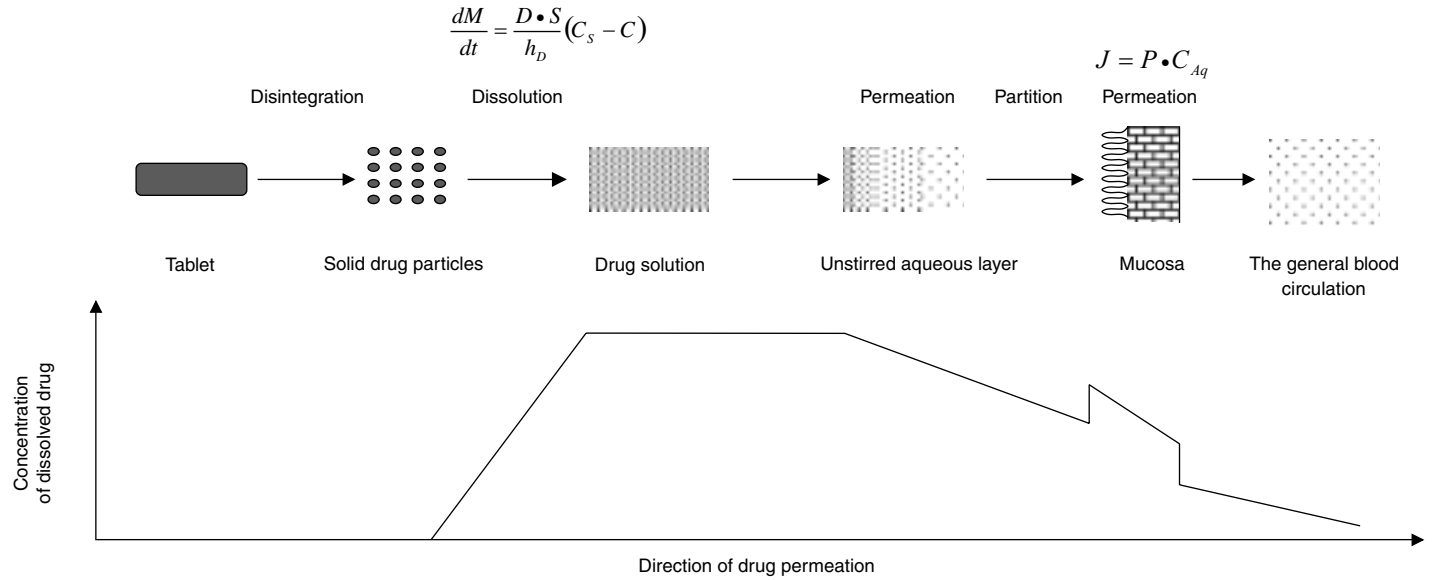


Fig. 1. The rate processes of drug bioavailability in the gastrointestinal tract and hypothetical concentration of dissolved drug. Here it is assumed that the drug has higher affinity for mucosa than the aqueous exterior. The concentration gradient is the driving force of passive drug permeation from the gastrointestinal tract into the blood circulation. The equations are explained in the text.

1. tablet disintegration and release of solid drug particles;
2. dissolution of the drug particles in the aqueous gastrointestinal fluid;
3. permeation of the drug molecules from the intestinal fluid through unstirred aqueous layer immediately adjacent to the mucosal surface;
4. partition of drug molecules from the aqueous exterior into the mucosa; and finally
5. drug permeation through the mucosa and absorption into the blood circulation (figure 1).

By definition, the slowest process within the absorption scheme will be the rate-limiting step. For example, if aqueous solubility of a drug is below 0.1–0.05 mg/mL then dissolution of the drug particles will be slow and the absorption will, in many cases, be dissolution rate-limited.[1,2] The rate-limiting step for absorption of very hydrophilic drugs is frequently partition from the aqueous exterior into the lipophilic mucosa. Drug efflux transporters can also limit drug permeation through the mucosa which then becomes the rate-limiting step in the drug absorption process from the gastrointestinal tract. Various formulation techniques have been developed in an effort to overcome these and other obstacles in oral drug delivery. Here the role of cyclodextrins in oral drug delivery is reviewed. For a general appraisal of cyclodextrins and their pharmaceutical applications the reader is referred to several excellent reviews which have been published in recent years.[3-12]

1. Theoretical Background

Disintegration of well-designed solid dosage forms is seldom the rate-determining step in drug absorption from the gastrointestinal tract, whereas dissolution of the solid drug particles frequently is, especially for drugs of low aqueous solubility. The mass rate of dissolution (dM/dt) can be described by the Noyes-Whitney equation (equation 1):

$$\frac{dM}{dt} = \frac{D \bullet S}{h_D}(C_S - C) \quad \text{(Eq. 1)}$$

where M is the mass of drug dissolved in time t, D is the diffusion coefficient of the drug through the aqueous diffusion layer (i.e. the stagnant layer at the particle surface), S is the total surface area of the solid drug particles, h_D is the thickness of the diffusion layer at the particle surface, C_S is the saturation solubility of the drug in the aqueous fluid, and C is the drug concentration in the bulk solution at time t. The dissolution rate is proportional to both S and C_S, and C_S is influenced by the composition of the aqueous dissolution medium, including its pH. Thus, the drug solubility and dissolution rate are not constant throughout the gastrointestinal tract.

After dissolution the individual drug molecules have to permeate from the bulk fluid through the unstirred aqueous layer immediately adjacent to the mucosal surface. The thickness of this diffusion layer has been estimated to be between 30 and 100μm.[13] The barrier effect of this aqueous layer is considered to be negligible for slowly absorbed drugs but can be significant, and even rate-limiting, for intestinal absorption of rapidly absorbed drugs.[13]

According to Fick's first law the drug concentration gradient (or more correctly the chemical potential gradient) across the aqueous diffusion layer is the driving force for drug permeation to the mucosal surface.

The gastrointestinal mucosa can be regarded as a lipophilic membrane with an aqueous exterior where drugs permeate the membrane via passive diffusion. The vast majority (≈90%) of drugs are absorbed from the gastrointestinal tract via passive diffusion through the transcellular route. The fundamental equation describing passive drug transport through mucosa is based on a form of Fick's first law (equation 2):

$$J = P \bullet C_{Aq} \quad \text{(Eq. 2)}$$

where J is the drug flux through mucosa (mass/area/time), P is the permeability coefficient of the drug through the lipophilic mucosa and C_{Aq} is the drug concentration in the aqueous exterior immediately adjacent to the mucosal surface. The permeability coefficient is defined as equation 3:

$$P = \frac{D \bullet K}{h} \quad \text{(Eq. 3)}$$

where D is the diffusion coefficient of the drug within the membrane, K is the partition coefficient of the drug from the aqueous exterior into mucosa and h is the effective thickness of the mucosal membrane. Finally the diffusion coefficient can be estimated by the Stokes-Einstein equation (equation 4):

$$D = \frac{R \bullet T}{6\pi \bullet \eta \bullet r \bullet N} \quad \text{(Eq. 4)}$$

where R is the molar gas constant, T is the absolute temperature, η is the apparent viscosity of the mucosal membrane, r is the radius of a spherical drug molecule permeating the mucosa, and N is Avogadro's number.

The equations show that for a drug molecule to be successfully delivered through mucosa, the drug must possess sufficient aqueous solubility (C_S) to allow efficient drug dissolution and delivery of dissolved drug molecules to the mucosal surface (resulting in high C_{Aq} value), but at the same time the drug must possess sufficient lipophilicity to be able to partition from the aqueous exterior into the lipophilic mucosal membrane (resulting in high K value). In addition, according to equation 4, small drug molecules (with a small radius, r) permeate across the mucosa more easily than large molecules. Active transportation through mucosa, efflux, and metabolism, as well as paracellular transportation of small hydrophilic molecules, all generate deviations to these general equations, but overall the equations are applicable for the vast majority of drugs. Consequently, these equations provide the basis for various computational approaches that are designed to predict drug bioavailability.[2,14,15]

In addition, even empiric observations are based on these equations. For example, Lipinski's 'rule of five' paradigm predicts that poor absorption or permeation is more likely when a drug molecule contains more than 5 H-bond donors (as expressed by the sum of OHs and NHs), more than ten H-bond acceptors (as expressed by the sum of Ns and Os), has a molecular weight (MW) greater than 500Da (Daltons) or has a calculated logarithmic value of the octanol-water partition coefficient (log $K_{(octanol/water)}$ value) greater than 5.[2] The H-bond donors and acceptors can be related to the extent of drug hydration, the molecular weight is related to the radius of the drug molecule (r in equation 4), and the log $K_{(octanol/water)}$ value can be related to the aqueous solubility of the drug (resulting in higher C_{Aq} in equation 2) and its ability to partition from the aqueous exterior into the lipophilic mucosa.

2. Biopharmaceutics Classification System

The US FDA has introduced a binning system for oral drug products known as the Biopharmaceutical Classification System (BCS). In this system, drugs are classified into four groups based on their ability to permeate biologic membranes and their aqueous solubility: i.e. parameters that can be found in the previously mentioned equations (table I).[1,14,16-18] A given drug substance is

Table I. The biopharmaceutics classification system and the effect of drug/cyclodextrin complexation on the oral bioavailability of drugs

Parameters	Class I	Class II	Class III	Class IV
Aqueous solubility[a]	High	Poor	High	Poor
Permeability[b]	High	High	Poor	Poor
In vitro–in vivo correlation	Can be good	Good	Poor	Poor
Absorption rate control	Gastric emptying	Dissolution	Permeability	Dissolution and permeability
Effect of cyclodextrins on drug bioavailability	Can decrease	Can enhance	Can decrease	Can enhance

a Solubility of the drug dose in aqueous solution (high: D : S ≤250mL; poor: D : S >250mL).

b Permeability of a drug through a lipophilic biomembrane.

considered 'highly soluble' when the highest dose strength is soluble in ≤250mL water, i.e. the US FDA defined standard glass of water, over a pH range from 1.0 to 7.5, and 'highly permeable' when the extent of oral absorption in humans is determined to be ≥90% of an administered dose (in solution), based on mass-balance or related to an intravenous reference dose. For an immediate-release tablet, ≥85% of the labeled amount of drug substance must dissolve within 30 minutes.[1,16,19] However, it has been argued that these definitions of 'highly permeable' and 'highly soluble' are too conservative,[20] in particular, the solubility restrictions of permeable acidic drugs, like some nonsteroidal anti-inflammatory drugs (NSAIDs), which fail the minimum solubility requirements at pH below their pKa values but fulfill the requirements at pH > 5 (i.e. at pH in duodenum).[21]

Class I materials consist of water-soluble drugs (i.e. they have a relatively high C_S value resulting in a high C_{Aq} value) that are well absorbed from the gastrointestinal tract (i.e. they have a relatively large P value) and, in general, possess the preferred physicochemical properties for optimum drug availability. For immediate- release dosage forms, the absorption rate will be controlled by the rate at which the drug solution is delivered to the absorption site, i.e. the gastric emptying rate. To secure a constant high bioavailability, the dissolution rate must be relatively rapid, or over 85% dissolution in 15 minutes.[16] Drugs in class I are frequently lipophilic with a MW less than about 500Da and aqueous solubility about or greater than 1 mg/mL. Examples of drugs in class I are acetaminophen (paracetamol), piroxicam, propranolol, and theophylline.

Class II compounds comprise relatively lipophilic and water-insoluble drugs (i.e. C_S ≤0.1 mg/mL) that, when dissolved, are well absorbed from the gastrointestinal tract (i.e. large P). Drug dissolution is usually the rate-limiting step in drug absorption. Commonly, drugs in this class have variable absorption because of the numerous formulation effects and *in vivo* variables (such as food intake) that can affect the dissolution profile.[16] Diverse formulation techniques can be applied to compensate for the insolubility of the drugs and the consequent slow dissolution rate. These include formulation of the amorphous solid form, nanoparticles, addition of surfactants, salt formation, and complexation.[1,18] By such techniques, the formulator tries to 'move' the drugs from class II to class I without changing the intrinsic ability of the drug molecules to permeate biomembranes. Examples of drugs in class II include carbamazepine, cinnarizine, and glibenclamide.

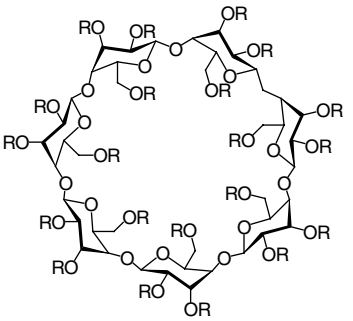
Class III drugs are water-soluble pharmaceuticals (i.e. large C_S) that do not readily permeate biomembranes (i.e. low P). For these drugs, the rate-limiting factor in drug absorption is their membrane permeability. The inclusion of absorption-enhancing excipients in formulations can enhance their bioavailability. Examples of drugs in class III are acyclovir, atenolol, and ranitidine.

Class IV materials consist of water-insoluble drugs which when solubilized do not readily penetrate biomembranes (i.e. low C_S and low P). These drugs can be very difficult to formulate for effective oral delivery. Examples of drugs in class IV are cyclosporine A (cyclosporin A) and furosemide (frusemide).

3. Cyclodextrins

Cyclodextrins are a group of structurally related natural products formed during bacterial digestion of cellulose.[22] These cyclic oligosaccharides consist of (α-1,4)-linked α-D-glucopyranose units and contain a somewhat lipophilic central cavity and a hydrophilic outer surface. Because of the chair conformation of the glucopyranose units, the cyclodextrins are shaped like a truncated cone rather than perfect cylinders. The hydroxyl functions are orientated to the cone exterior with the primary hydroxyl groups of the sugar residues at the narrow edge of the cone and the secondary hydroxyl groups at the wider edge. The central cavity is lined by the skeletal carbon and ethereal oxygen atoms of the glucose residues, which gives it a lipophilic character.[5,7,10,22,23] The polarity of the cavity has been estimated to be similar to that of an aqueous ethanolic solution.[6] The natural α-, β- and γ-cyclodextrin consist of six, seven, and eight glucopyranose units, respectively. The natural cyclodextrins, in particular β-cyclodextrin, are of limited aqueous solubility meaning that complexes resulting from interaction of lipophiles with these cyclodextrins can be of limited solubility resulting in precipitation of solid cyclodextrin complexes from water and other aqueous systems. In fact, the aqueous solubility of the natural cyclodextrins is much lower than that of comparable acyclic saccharides. This is thought to be due to relatively strong intermolecular hydrogen bonding in the crystal state. Substitution of any of the hydrogen bond-forming hydroxyl groups, even by lipophilic methoxy functions, results in dramatic improvement in their aqueous solubility.[5] Cyclodextrin derivatives of pharmaceutical interest include the hydroxypropyl derivatives of β- and γ-cyclodextrin, the randomly methylated β-cyclodextrin, sulfobutylether β-cyclodextrin, and the so-called branched cyclodextrins, such as glucosyl-β-cyclodextrin (figure 2 and table II).[5,7-9,23,24]

The natural α- and β-cyclodextrins, unlike γ-cyclodextrin, cannot be hydrolyzed by human salivary and pancreatic amylases.[9,25] However, both α- and β-cyclodextrin can be fermented by the intestinal microflora. Cyclodextrins are both large (MW ranging from almost 1000 to over 2000Da) and hydrophilic, with a significant number of H-donors and acceptors and, are thus not absorbed from the gastrointestinal tract in their intact form. Hydrophilic



Cyclodextrin	R = H or
β-Cyclodextrin	–H
2-Hydroxypropyl-β-cyclodextrin	$-CH_2CHOHCH_3$
Sulfobutylether β-cyclodextrin sodium salt	$-(CH_2)_4SO_3^-\ Na^+$
Randomly methylated β-cyclodextrin	$-CH_3$
Branched β-cyclodextrin	Glucosyl or maltosyl group

Fig. 2. The chemical structure of β-cyclodextrin and some of its derivatives.

cyclodextrins are considered nontoxic at low to moderate oral dosages.[9,24] Lipophilic cyclodextrin derivatives, such as the methylated cyclodextrins, are to some extent absorbed from the gastrointestinal tract into the systemic circulation and have been shown to be toxic after parenteral administration.[9] Presently, oral administration of methylated β-cyclodextrin is limited by its potential toxicity.

About 30 different pharmaceutical products containing cyclodextrins are now on the market worldwide. Some of these products are listed in table III. In the pharmaceutical industry cyclodextrins have mainly been used as complexing agents to increase the aqueous solubility of poorly water-soluble drugs and to increase their bioavailability and stability. In addition, cyclodextrins can be used to reduce or prevent gastrointestinal and ocular irritation, reduce or eliminate unpleasant smells or tastes, prevent drug-drug or drug-additive interactions, or to convert oils and liquid drugs into microcrystalline or amorphous powders.[7,26]

The regulatory status of cyclodextrins is evolving. α-Cyclodextrin and β-cyclodextrin are listed in a number of pharmacopeia sources including the US Pharmacopeia, European Pharmacopoeia, and Japanese Pharmacopoeia. γ-Cyclodextrin will soon be included in the US Pharmacopeia and subsequently in the European Pharmacopoeia as well. A monograph for 2-hydroxypropyl-β-cyclodextrin (hydroxypropyl betadex) has recently been published in both the European Pharmacopoeia (Ph. Eur. 5th Ed.) and in the US Pharmacopoeia (USP28/NF23). Other derivatives are not yet compendial but efforts are underway for their inclusion. β-Cyclodextrin and γ-cyclodextrin are also listed in the generally-regarded-as-safe list of the US FDA for use as a food additive. Cyclodextrins are relatively new from a regulatory point of view and policies on their use are still not standardized. Consensus seems to be building among regulators that cyclodextrins are excipients and not part of the drug substance, although various opinions have been given and interpretation related to this point can be division- and product-specific.

3.1 Cyclodextrin Complexes

Cyclodextrins are able to form dynamic molecular inclusion complexes with many drugs by incorporating the drug molecule, or more commonly a lipophilic moiety of the molecule, into the central cavity. No covalent bonds are formed or broken during the drug/cyclodextrin complex formation. The driving forces leading to the inclusion complex formation include release of enthalpy-rich water molecules from the cavity, electrostatic interaction, van der Waals interaction, hydrophobic interaction, hydrogen bonding,

Table II. Natural cyclodextrins and some of their derivatives that can be found in marketed pharmaceutical products

Cyclodextrin	Substitution[a]	MW[b]	Solubility in water (mg/mL)[c]	Indicative bulk price[d] ($US/kg)
α-Cyclodextrin		972	145	45
β-Cyclodextrin		1135	18.5	5
2-Hydroxypropyl-β-cyclodextrin	0.65	1400	>600	300
Randomly methylated β-cyclodextrin	1.8	1312	>500	350
β-Cyclodextrin sulfobutyl ether sodium salt	0.9	2163	>500	
γ-Cyclodextrin		1297	232	80
2-Hydroxypropyl-γ-cyclodextrin	0.6	1576	>500	400

a Average number of substituents per glucopyranose repeat unit.

b Molecular weight (MW) in Daltons (Da).

c Solubility in pure water at approximately 25°C.

d Approximate bulk price given as the price of 1kg in US dollars.

release of conformational strain, and charge-transfer interaction.[7,27,28] All these forces are relatively weak, allowing free drug molecules in solution to be in rapid equilibrium with drug molecules bound within the cyclodextrin cavity.[10] Most drug molecules (D) form 1 : 1 complexes with cyclodextrin molecules (CD) and the value of the stability constant ($K_{1:1}$) is most often between 50 and 2000 mol^{-1} with a mean value of 129, 490 and 355 mol^{-1} for α-, β-, and γ-cyclodextrin, respectively (equation 5):[10,29-31]

$$D + CD \underset{}{\overset{K_{1:1}}{\rightleftharpoons}} D/CD\ Complex$$

or

$$K_{1:1} = \frac{[D/CD]}{[D] \bullet [CD]} \qquad \text{(Eq. 5)}$$

This is a somewhat oversimplified description of a much more complex mechanism,[32,33] but is sufficient to explain the role of cyclodextrins in oral drug delivery. In a given aqueous complexation medium, saturated with the drug, the concentration of free drug ([D]) is constant and equal to the apparent intrinsic solubility of the drug in the aqueous medium (i.e. drug solubility in absence of cyclodextrin). Cyclodextrin encapsulation of a drug will change the drug's physicochemical properties, such as its aqueous solubility and chemical stability. The cyclodextrin molecule forms a hydrophilic shield around applicable lipophilic moiety of the drug molecule. This will, in general, increase the apparent aqueous solubility of the drug. The cyclodextrin can also protect chemically labile drug molecules from potentially corrosive environments and, in this way, reduce or even prevent drug hydrolysis, oxidation, racemization and enzymatic decomposition.[7,34]

In the solid-state, cyclodextrins, especially hydrophilic chemically modified cyclodextrins, convert the drug of interest, which is usually crystalline, into a dispersion of the amorphous drug in the cyclodextrin carrier. This is akin to solid dispersions or solutions generated by pharmaceutical polymers or monomers using solvent or melt methods.[35,36] Importantly, the dispersions are unique as a result of molecular encapsulation related to the presence of the cyclodextrins. In such a system, the rate of dissolution can be predicted by two models: complex solubility or carrier-control.[37] In their assessment of β-cyclodextrin interaction of bendrofluazide, chlorothiazide, and hydrochlorothiazide, Corrigan and Stanley found that dissolution kinetics were intermediate between the two limiting conditions.[38]

Including cyclodextrins in solid dosage forms will increase the formulation bulk and, thus, cyclodextrins can only be included in solid dosage forms of relatively potent drugs. Various methods have been applied to enhance the complexation efficacy.[39] These include addition of polymers to the complexation media,[40] drug ionization and salt formation,[41,42] addition of hydroxy carboxylic acids to the complexation media,[43] addition of volatile acids or bases to the complexation media,[44] addition of organic salts,[45] and addition of cosolvents.[46] However, even under the best conditions, cyclodextrin complexation will result in an over 4-fold increase in the formulation bulk.[39] The feasibility of using cyclodextrins as solubilizer in dosage forms can frequently be calculated from a few simple experiments.[31]

3.2 Cyclodextrins and Drug Permeability Through Biologic Membranes

Negligible amounts of hydrophilic cyclodextrins and drug/cyclodextrin complexes are able to permeate lipophilic membranes such as the intestinal mucosa.[9,47-49] Only the free form of the drug, which is in equilibrium with the drug/cyclodextrin complex, is capable of penetrating lipophilic membranes.[23] Cyclodextrins are able to extract lipophilic components of biomembranes such as stratum corneum,[50,51] but both pre- and post-application of hydrophilic cyclodextrins does not affect, for example the skin barrier.[52,53] Cyclodextrins do not, in general, enhance permeability of hydrophilic water-soluble drugs through lipophilic biologic membranes[47,48] and numerous studies have shown that excess cyclodextrin can reduce drug permeability through biologic membranes.[47] The composition of the drug formulation, and the physicochemical and physiologic composition of the membrane barrier, will determine whether cyclodextrins will enhance or hamper drug delivery through a biologic membrane. Cyclodextrins will enhance drug delivery through aqueous diffusion-controlled barriers but can hamper drug delivery through lipophilic membrane-controlled barriers.[48] Frequently, biologic barriers to drug permeation are related to a lipophilic membrane with an unstirred aqueous layer, i.e. an aqueous diffusion layer at the surface (figure 1). Cyclodextrins can often enhance drug delivery via these barriers if drug permeation through the aqueous diffusion layer is the rate-limiting step, but usually not if the rate-limiting step is drug permeation of the lipophilic barrier.

Cyclodextrins can, at least in theory, enhance drug bioavailability by stabilizing drug molecules at the biomembrane surface. For example, cyclodextrins have been shown to prevent insulin aggregation and to enhance insulin stability at the nasal mucosa. It has been suggested that cyclodextrin-enhanced insulin bioavailability after nasal administration is partly due to this stabilizing effect.[54] In general, drug stabilization associated with cyclodextrin complexation plays only a very minor role when it comes to drug delivery through biologic membranes since it is their solubilizing effect that is usually related to improved drug delivery.

Table III. Examples of marketed products containing cyclodextrin

Drug	Administration route	Trade name	Market
α-Cyclodextrin			
Alprostadil (PGE_1)	IV	Prostavastin	Europe, Japan, USA
Cefotiam hexetil HCl	Oral	Pansporin T	Japan
β-Cyclodextrin			
Benexate HCl	Oral	Ulgut, Lonmiel	Japan
Dexamethasone	Dermal	Glymesason	Japan
Iodine	Topical	Mena-Gargle	Japan
Nicotine	Sublingual	Nicorette	Europe
Nimesulide	Oral	Nimedex, Mesulid	Europe
Nitroglycerin (glyceryl trinitrate)	Sublingual	Nitropen	Japan
Omeprazol	Oral	Omeeta	Europe
PGE_2	Sublingual	Prostarmon E	Japan
Piroxicam	Oral	Brexin	Europe
Tiaprofenic acid	Oral	Surgamyl	Europe
2-Hydroxypropyl-β-cyclodextrin			
Cisapride	Rectal	Propulsid	Europe
Hydrocortisone	Buccal	Dexocort	Europe
Indomethacin	Eye drops	Indocid	Europe
Itraconazole	Oral, IV	Sporanox	Europe, USA
Mitomycin	IV	Mitozytrex	USA
Randomly methylated β-cyclodextrin			
17β-Estradiol	Nasal spray	Aerodiol	Europe
Chloramphenicol	Eye drops	Clorocil	Europe
Sulfobutylether β-cyclodextrin			
Voriconazole	IV	Vfend	Europe, USA
Ziprasidone maleate	IM	Geodon, Zeldox	Europe, USA
2-Hydroxypropyl-γ-cyclodextrin			
Diclofenac sodium	Eye drops	Voltaren	Europe

HCl = hydrochloride; **IM** = intramuscular; **IV** = intravenous; **PGE_2** = prostaglandin E_2.

4. Cyclodextrins in Immediate-Release Oral Dosage Forms

The BCS states that for a class I material, the maximum dose to solubility (D : S) ratio has to be below about 250mL in the pH range of 1–7.5 for immediate-release oral dosage forms or, in other words, that the aqueous solubility of the drug/cyclodextrin complex in the gastrointestinal tract has to be sufficient to prevent dissolution rate-limited absorption of the drug. Drugs with aqueous solubility >0.1–0.05 mg/mL will seldom exhibit dissolution rate-limiting absorption after oral administration in a conventional immediate-release tablet.[1] Also, the upper limit in size of conventional oral tables is about 800mg. As a result of excipient requirements, only about 700mg of complex (or about 70–150mg of drug) can be included in conventional immediate-release tablets and, thus, cyclodextrins can only be applied to drugs that possess high (dose 0.1 mg/kg) to average (dose 1 mg/kg) potency. These are the two basic requirements for cyclodextrin-based oral dosage forms.

The effects of cyclodextrins on oral, sublingual and buccal bioavailability of about 50 different drugs have been investigated in both animals and humans (table IV). In these studies the effect of cyclodextrins varies from no effect, to reduced bioavailability, to significant bioavailability enhancement. In most of these studies the bioavailability was determined for a cyclodextrin formulation and for a simple solid or suspension formulation, which did not contain any enabling excipients. In some cases only a small increase in bioavailability or no effect was observed with the

Table IV. Cyclodextrins in oral, sublingual, and buccal formulations; clinical, intestinal perfusion, and/or bioavailability studies

Drug	Cyclodextrin	Formulation	Species	F_{rel}[a]	References
Acyclovir	βCD	Oral suspension	Rat	1.1	56
Albendazole	HPβCD	Oral solution	Sheep, mouse	≤2.5	57-59
Amobarbital (amylobarbitone)	HPβCD	Oral solution	Mouse	(≈4)	60
Artemisinin	βCD, γCD	Capsule cont. powder	Human	≤1.7	61
Benzaldehyde semicarbazone	βCD	Oral suspension	Rat	(≤4)	62
4-Biphenylacetic acid	βCD, DMβCD, TMβCD, HPβCD	Oral suspension or solution	Rat	≤2.9	63,64
para-Boronophenylalanine	GluαCD, MalαCD, DmalαCD	Complex powder	Rat	≤1.5	65
Carbamazepine	DMβCD	Oral powder and solution, tablet	Rabbit, dog, rat	≤5.6	66-70
β-Carboline norharman	Not specified	Sublingual tablet	Human	Not determined	71
Chloramphenicol palmitate	HPβCD	Oral powder	Dog	≤3.8	72
Cinnarizine	βCD, SBEβCD, HPβCD	Tablet, oral solution and capsule cont. powder	Dog	≤48	73-75
Clomipramine	HPβCD	Sublingual	Rat	1.6[b]	76
Cyclosporin A	DMβCD	Oral suspension	Rat	4.7	77,78
Danazol	SBEβCD, HPβCD	Buccal tablet and capsule cont. powder	Dog, rat	≤34	79-82
Dehydroepiandrosterone	αCD	Tablet	Human	2.0	83
Digoxin	γCD	Tablet	Dog	5.4	84
Diphenhydramine HCl	DMβCD, HPβCD	Solution	Rat	≤0.9	85
Dipyridamole	βCD	Capsule cont. powder	Dog, Human	≤1.6	86,87
Entacapone	HPβCD	Oral solution	Rat	1.9	88
17β-Estradiol	HPβCD	Sublingual tablets	Human	5.8[b]	89-91
Fenbufen	αCD , γCD	Aqueous suspension	Rabbit	≤5.5	92
Fluoxetine HCl	γCD	Solid dosage	Human	2.5	93
Flutamide	HPβCD	Oral solution	Rat	≈2	94
Glibenclamide	βCD, SBEβCD	Capsule cont. powder	Dog, rat	≤6.2	95,96
Gliclazide	βCD	Aqueous suspension	Rat	6	97
Gliquidone	HPβCD	Oral powder	Rat	2.0	98
Indomethacin	EαCD, βCD, HEβCD, HPβCD	Capsule cont. powder	Human, rabbit	≤1.3	99,100
Itraconazole	HPβCD	Oral solution	Human		101,102
Ketoprofen	βCD, HPβCD	Aqueous suspension	Rat	≤2.9	103
Miconazole	HPβCD	Aqueous suspension	Rat	2.3	104
Naproxen	βCD	Capsule cont. powder	Human	(≈1)	105
Nicardipine	HPβCD	Capsule cont. powder	Rabbit	3.2	106
Nifedipine	βCD, HPβCD	Capsule cont. powder	Rabbit, dog	≤2.9	107-110
Nitrendipine		Oral suspension	Rat	1.9	111

Continued next page

Table IV. Contd

Drug	Cyclodextrin	Formulation	Species	F_{rel}[a]	References
Phenytoin	EβCD, GluβCD, MalβCD, SBEβCD, HPβCD	Suspension, capsule cont. powder	Rat, Dog	≤5	112-114
Piroxicam	βCD	Tablet, capsule and oral suspension	Human, rat, rabbit	≤1.4	115-119
Renin inhibitors	βCD	Oral suspension	Rat	Not determined	120
all-trans-Retinoic acid	HPβCD	Oral suspension/solution	Rat	2.9	121
Rofecoxib	βCD	Tablet	Human	1.3	122
Rutin	HPβCD, βCD	Tablet	Dog	≤2.9	123
Silybinin	βCD	Suspension	Rat	(≈6)	124
Spironolactone	βCD, γCD, DMβCD, SBEβCD, HPβCD	Oral solution and powder	Rat, dog	≤3.6	125-127
Tacrolimus	DMβCD, SBEβCD, HPβCD	Oral suspension	Rat	≤4.5	128
Testosterone	HPβCD	Sublingual tablet	Human	(2.4)	129,130
Tiaprofenic acid	DEβCD	Solid powder	Rats	≈0.5	131
Tolbutamide	βCD, HPβCD	Suspension, oral powder	Rabbit, dog	≤1.5	132,133
α-Tocopheryl nicotinate	DMβCD	Capsule cont. powder	Dog	≈70	134
Ursodeoxycholic acid	HPβCD	Oral solution, tablet	Rat, human	≤2.1	135,136
Zidovudine	HPβCD, DMβCD	Oral solution	Rat	Not determined	137

a F_{rel} = relative bioavailability, i.e. the area under the curve (AUC) of the plasma concentration versus time profile when the cyclodextrin-containing formulation was given divided by the AUC for the formulation containing no cyclodextrin. The values in brackets are estimates based on the pharmacologic effect, maximum concentratin values in plasma, or bile and urine excretion data.

b Sublingual versus oral delivery.

αCD = α-cyclodextrin; **βCD** = β-cyclodextrin; **γCD** = γ-cyclodextrin; **DEβCD** = heptakis(2,6-di-*O*-ethyl)-β-cyclodextrin; **DMalαCD** = dimaltosyl-α-cyclodextrin; **DMβCD** = dimethyl-β-cyclodextrin; **EαCD** = α-cyclodextrin epichlorohydrin polymer; **EβCD** = β-cyclodextrin epichlorohydrin polymer; **GluαCD** = glucosyl-α-cyclodextrin; **GluβCD** = glucosyl-β-cyclodextrin; **HEβCD** = hydroxyethyl-β-cyclodextrin; **HPβCD** = 2-hydroxypropyl-β-cyclodextrin; **MalαCD** = maltosyl-α-cyclodextrin; **MalβCD** = maltosyl-β-cyclodextrin; **SBEβCD** = sulfobutylether-β-cyclodextrin sodium salt; **TMβCD** = trimethyl-β-cyclodextrin.

cyclodextrin formulation. This could be explained in two ways; either that cyclodextrin was not a suitable enabling excipient or that the bioavailability was good (i.e. >50%) with the simple formulation. The absolute bioavailability was determined in only a few of these studies. Thus, the data available from these studies are not sufficient to construct a quantitative bioavailability-property relationship. For example, the octanol-water partition coefficient (log $K_{(octanol/water)}$) of half (21) of the drugs can be obtained from the literature,[55] but there was not any significant correlation between the partition coefficients and the effects of cyclodextrins on maximum relative bioavailability (F_{rel}). However, the general effect can, in most cases, be explained from the physicochemical properties of the drugs, their aqueous solubility, D:S ratio and ability to permeate biologic membranes, or equations 1 to 4 and the BCS classifications.

4.1 Class I Drugs

Class I drugs are water-soluble and generally have good bioavailability after oral administration (high C_S and high P). Since the drug/cyclodextrin complex does not permeate the mucosal membrane, addition of cyclodextrin can reduce absorption of class I drugs. However, cyclodextrins can have some beneficial effects on drugs in class I that have relatively low aqueous solubility. For example, piroxicam is practically insoluble in water but is a potent drug with low enough D:S ratio to be classified as a class I drug.[21] Consequently, cyclodextrin complexation does not have any significant effect on the absolute bioavailability of the drug but results in more rapid drug absorption, more rapid onset of analgesia, and improved gastrointestinal tolerability.[115,116]

In general, NSAIDs have oral bioavailability of about or greater than 90% in humans (that is a large P value in equation 2). In spite of good bioavailability, many acidic NSAIDs (pKa about 4.5), such as indomethacin, ketoprofen, naproxen, and tiaprofenic acid

are classified as class II drugs based on their solubility at pH 1.0, but they would be classified as class I drugs based on their solubility at pH >5 (i.e. pH in duodenum).[21] Oral administration of these drugs as water-soluble cyclodextrin complexes does not result in any significant improvement of their bioavailability (table IV), although formation of water-soluble complexes of the drugs might result in more rapid drug absorption, less variable bioavailability, and reduced gastrointestinal irritation. Oral bioavailability of the NSAID ketoprofen (pKa 4.5; log $K_{(octanol/water)}$ 0; D : S about 4000mL; oral bioavailability in humans ≤100%), fenbufen (pKa 4.5; log $K_{(octanol/water)}$ 3.2) and 4-biphenylacetic acid, which is an active metabolite of fenbufen, have been enhanced by cyclodextrin complexation when tested in animals.[55,63,64,92,103,138]

Rofecoxib is a non-ionizable NSAID with a reported mean oral bioavailability of 93% but with a highly variable absorption rate (t_{max} between 2 and 9 hours).[139] Since the oral bioavailability of the drug is over 90%, cyclodextrin complexation does not result in any dramatic improvement of the absolute bioavailability. However, cyclodextrin formulations could provide enhanced and less variable drug absorption.

4.2 Class II Drugs

Class II consists of water-insoluble drugs that easily permeate lipophilic biologic membranes once they are in solution, displaying dissolution-limited drug absorption after oral administration (low C_{Aq} and high P).

Carbamazepine (log $K_{(octanol/water)}$ 2.5; D : S about 1000mL) is a class II drug that has several polymorphs and pseudopolymorphs (dehydrate) with a highly variable bioavailability (from 33% to almost 100%).[140,141] Formulation of carbamazepine with cyclodextrins can significantly improve the oral bioavailability of the drug.[66-70]

Digoxin can be considered a class I drug (MW 781Da; maximum dose 500 µg/day; solubility about 70 µg/mL; D : S about 7mL; log $K_{(octanol/water)}$ 1.26). However, it dissolves very slowly (small C_S value in equation 1) in the gastrointestinal tract resulting in dissolution rate-limiting absorption unless the particle size of the drug powder is small enough to enhance the surface area (large S value in equation 1).[17] Consequently, digoxin is referred to as a class II drug. Formulation of digoxin as a cyclodextrin complex can enhance the bioavailability of the drug.[84]

Glibenclamide is a typical class II drug with aqueous solubility of 6 µg/mL at pH 7.4, log $K_{(octanol/water)}$ of 4.8 and dose of 5–15 mg/day or D : S ratio of about 2500mL.[55,95] Because of its very low aqueous solubility, the oral absorption of the drug is dissolution-rate limited with 14.7% absolute bioavailability in dogs. Formulation of the drug as a cyclodextrin inclusion complex enhanced the bioavailability to 90.5% (virtually moving the drug from class II into class I).[95] Gliclazide and gliquidone are closely related, both chemically and pharmacologically, to glibenclamide and the bioavailability of both drugs is enhanced through cyclodextrin complexation.[97,98]

Miconazole is a lipophilic drug with MW of 416Da, D : S ratio of about 5000mL and absolute bioavailability of 18.4% in rats.[104] Thus, the drug is a class II drug. Cyclodextrin complexation significantly enhanced the oral bioavailability of miconazole.[104]

Nifedipine has D : S ratio of about 6000mL and oral bioavailability of about 50%, partly because of its low aqueous solubility but partly as a result of first-pass metabolism.[107,142] Water-soluble cyclodextrin complexes enhance the oral bioavailability of nifedipine.[107-110]

Nitrendipine has an aqueous solubility of about 2 µg/mL, log $K_{(octanol/water)}$ of 2.2 and dose of 20mg or D : S ratio of about 10 000mL, and manifests variable oral bioavailability of 10–20%.[55,111,143] The low bioavailability is most probably due to the very low aqueous solubility of the drug, resulting in dissolution-rate limiting absorption. Formulation of the drug as a cyclodextrin inclusion complex significantly enhances the oral bioavailability.[111]

Phenytoin has an aqueous solubility of 24 µg/mL, log $K_{(octanol/water)}$ of 2.5 and D : S ratio of about 2000mL, and although oral bioavailability of phenytoin (or its sodium salt) is frequently about 90%, it is variable – which is most probably due to its poor aqueous solubility.[55,112] Cyclodextrin complexation of phenytoin enhances its oral bioavailability.[112-114]

Spironolactone has an aqueous solubility of 28 µg/mL, log $K_{(octanol/water)}$ of 2.8, D : S ratio of about 10 000mL and oral bioavailability of about 25%.[55,125,138] Formulation of spironolactone as a cyclodextrin inclusion complex resulted in about a 2.4-fold enhancement in oral bioavailability.[125-127]

Tolbutamide has very limited aqueous solubility, with a D : S ratio greater than 10 000mL but oral bioavailability of about 93%.[138,144] Cyclodextrin complexation increases the absorption rate and bioavailability of tolbutamide after oral administration.[132]

α-Tocopheryl nicotinate is a very lipophilic water-insoluble compound (C_S <1 pg/mL)[134] with a limited oral bioavailability associated with an absorption-limited dissolution rate. Formulating the vitamin as a water-soluble cyclodextrin complex resulted in as much as 70-fold enhancement in oral bioavailability.[134]

Finally, itraconazole is a lipophilic antifungal agent (log $K_{(octanol/water)}$ >5) that is practically insoluble in water (C_S ≈1 ng/mL at neutral pH) with a MW of 705.6Da and daily dose of 100–400mg.[55] When the drug is administered as such to man (i.e. in a simple gelatin capsule), bioavailability is negligible.[145] On

the other hand, administration of a 2-hydroxypropyl-β-cyclodextrin-based solution of itraconazole (which increases the solubility of the drug to 10 mg/mL) results in a fraction absorbed of approximately 85%, while the oral bioavailability is approximately 55%, the difference being associated with first-pass metabolism, mainly hydroxylation.[145-147] This class II (apparent class IV) compound with a D : S of >10 000 000 is converted to (an almost) class I drugs with a D : S of 10.

4.3 Class III Drugs

Class III drugs comprise those with a D : S ratio <250mL but have some difficulties permeating lipophilic biologic membranes (high C_{Aq} and low P). Thus, poor bioavailability of drugs in this class is due to inability of the drugs to permeate biologic membranes. Therefore, cyclodextrins do not enhance their bioavailability after oral administration.

Diphenhydramine hydrochloride is a very water-soluble drug, with a D : S ratio of about 50mL and oral bioavailability of about 75%.[55,138] As a result of its high solubility and somewhat limited oral bioavailability (i.e. less than 90%), diphenhydramine hydrochloride can be classified as a class III drug and since the low bioavailability is not due to low aqueous solubility, or slow drug dissolution, formulating the drug as a cyclodextrin complex does not improve the drug bioavailability.

Acyclovir is a class III drug with the rate-limiting factor in acyclovir absorption from the gastrointestinal tract being the membrane permeability of the drug (figure 1). Again, since cyclodextrins can only enhance drug delivery through the aqueous diffusion barrier, including cyclodextrin in the oral formulation has an insignificant effect on the oral bioavailability of the drug.

4.4 Class IV Drugs

Class IV consists of water-insoluble drugs that do not readily permeate lipophilic biomembranes (low C_{Aq} and low P). Cyclosporine A is a large (MW 1202Da) water-insoluble peptide (C_S 16 pg/mL) with a dose of about 500mg.[148] Cyclosporine A exhibits a poor oral bioavailability (about 23%) with a large intra- and inter-subject variation, mainly because of its low aqueous solubility but also as a result of first-pass metabolism and poor membrane permeability.[77,138] Thus, cyclosporine A is classified as class IV drug. However, oral administration of cyclosporine A to rats as an inclusion complex of the lipophilic dimethyl-β-cyclodextrin has been shown to result in a 5-fold enhancement of the oral bioavailability, although the maximum absolute bioavailability was only 25%.[77]

One note which should be added is that often very poorly water-soluble class II compounds can masquerade as class IV materials since if the material cannot dissolve, or if it precipitates at the barrier interface, it will not be permeable through biologic membranes. This was observed for compounds such as itraconazole where the extremely low aqueous solubility (≈1 ng/mL at pH 7) gave artifactually low permeabilities and fluxes even though the bioavailability and fraction absorbed in man is quite high if the drug is adequately formulated/solubilized.

5. Cyclodextrins in Buccal, Sublingual, and Modified-Release Formulations

Five of the drugs listed in table IV were formulated as cyclodextrin-containing sublingual or buccal formulations and tested either in humans or animals. Although the BCS was originally developed for solid oral dosage forms, this system can be extended to other types of delivery systems.[149] Since the volume of saliva is only about 5mL, the maximum D : S ratio for buccal or sublingual delivery will only be about 5mL instead of 250mL for oral drug delivery. Consequently, drugs that are assigned as class I when given orally could be assigned to class II when given sublingually or buccally. For example, 17β-estradiol is a lipophilic (log $K_{(octanol/water)}$ 4.0), water-insoluble (C_S = 10 μg/mL) drug, but it is highly potent (dose about 0.1 mg) and thus would be indicated as a class I drug (D : S 10mL) if it could be given orally. However, 17β-estradiol undergoes first-pass metabolism and thus sublingual delivery of the drug appears to be a feasible alternative. As stated, this would necessitate the reclassification of the compound as class II (assuming a high P value). Importantly, cyclodextrin complexation of the drug increases its solubility and lowers the D : S ratio to <1mL, making buccal delivery of 17β-estradiol possible.[89,90,149]

Cyclodextrins have also been used to obtain sustained or site-specific drug release. For example, lipophilic and somewhat water-insoluble cyclodextrins, such as ethylated β-cyclodextrin and triacetyl-β-cyclodextrin, have been used to obtain sustained drug release.[106,150] Cyclodextrins have also been used in osmotic pumps for controlled drug delivery[151,152] and in matrix tablets to prevent solubility-dependent drug release.[153,154] Finally, drug-cyclodextrin conjugates have been used to obtain colon-specific drug delivery[155] or sustained plasma levels.[156]

6. Conclusions

Hydrophilic cyclodextrins and drug/cyclodextrin complexes do not permeate the gastrointestinal mucosa, so cyclodextrins are unable to have direct effects on drug permeability through the mucosa. However, cyclodextrins can have an indirect effect on drug permeability through the mucosa by increasing availability of dissolved drug molecules at the aqueous mucosal surface (i.e. by

increasing C_{Aq}). For solid dosage forms, hydrophilic cyclodextrin is selected based on its price, toxicologic profile, complexation efficacy regarding drug being formulated, and aqueous solubility of the drug/cyclodextrin complex. Lipophilic cyclodextrins, such as the methylated β-cyclodextrins, are able to permeate mucosa and are known to enhance drug delivery through biologic membranes by reducing barrier function of the membranes (i.e. by increasing both C_{Aq} and P).[157] However, these cyclodextrins have somewhat limited utility in oral delivery because they are potentially toxic in the systemic circulation and presently the recommended maximum daily dose is therefore low.

Class I drugs are relatively water-soluble (have relatively high C_S value) and their absolute bioavailability is ≥90%. These drugs permeate easily through the aqueous diffusion layer and possess sufficient lipophilicity to partition into and then permeate through the gastrointestinal mucosa. Thus, hydrophilic cyclodextrins are not able to improve their bioavailability. However, cyclodextrins are able to reduce or prevent gastrointestinal irritation of some class I drugs, such as the NSAIDs. Furthermore, in some cases cyclodextrins can increase the dissolution rate of class I drugs with somewhat limited aqueous solubility, resulting in faster drug absorption and more rapid onset of drug action.

Class II drugs have limited aqueous solubility, resulting in dissolution-rate limited oral absorption. However, once in solution these drugs permeate biologic membranes relatively easily resulting in ≥90% absolute bioavailability. Thus, low C_S hampers their dissolution. The drug permeation through the aqueous diffusion layer adjacent to the mucosal surface will also be slow as a result of low C_S. Water-soluble cyclodextrin complexes of these drugs will increase their apparent C_S value, enhance their diffusion to the mucosal surface and increase their C_{Aq} value, leading to enhanced oral bioavailability.

Class III drugs are water-soluble but do not easily permeate biologic membranes as a result of, for example, their size (MW >500Da) and/or extent of hydration (number of hydrogen donors and acceptors). These drugs have a high C_S value (leading to high C_{Aq} value) but low P value. Consequently, formation of hydrophilic drug/cyclodextrin complexes will not enhance their oral bioavailability but will, if anything, reduce the ability of dissolved drug molecules to partition from the aqueous exterior into the gastrointestinal mucosa.

Class IV drugs are water-insoluble and do not permeate lipophilic biologic membranes. These can, for example, be water-insoluble zwitterions or relatively large lipophilic molecules. Hydrophilic water-insoluble compounds like zwitterions do not readily form cyclodextrin complexes and hydrophilic cyclodextrins are therefore not likely to improve their oral bioavailability. However, cyclodextrins are able to improve aqueous solubility of some large lipophilic molecules, leading to increased drug availability at the mucosal surface (i.e. increased C_{Aq} value). This will frequently lead to increased oral bioavailability, although the absolute drug bioavailability will likely be much lower than 90%.

Acknowledgment

Financial support from the University of Iceland Research Fund is gratefully acknowledged. The authors have provided no information on conflicts of interest that are directly relevant to the content of this review.

References

1. Dressman J, Butler J, Hempenstall J, et al. The BCS: where do we go from here? Pharm Tech North Am 2001; 25 (7): 68-76
2. Lipinski CA, Lombardo F, Dominy BW, et al. Experimental and computatorial approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 2001; 46: 3-26
3. Duchêne D, editor. New trends in cyclodextrins and derivatives. Paris: Editions de Santé, 1991
4. Duchêne D. Cyclodextrins and their industrial uses. Paris: Editions de Santé, 1987
5. Szejtli J. Cyclodextrin technology. Dordrecht: Kluwer Academic Publisher, 1988
6. Frömming KH, Szejtli J. Cyclodextrins in pharmacy. Dordrecht: Kluwer Academic Publishers, 1994
7. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins: 1. Drug solubilization and stabilization. J Pharm Sci 1996; 85 (10): 1017-25
8. Rajewski RA, Stella VJ. Pharmaceutical applications of cyclodextrins: 2. *In vivo* drug delivery. J Pharm Sci 1996; 85 (11): 1142-68
9. Irie T, Uekama K. Pharmaceutical applications of cyclodextrins: III. Toxicological issues and safety evaluation. J Pharm Sci 1997; 86 (2): 147-62
10. Stella VJ, Rajewski RA. Cyclodextrins: their future in drug formulation and delivery. Pharm Res 1997; 14 (5): 556-67
11. Uekama K, editor. Cyclodextrins in drug delivery in Adv. Drug Deliv Rev 1999; 36 (1): 1-141
12. D'Souza VT, Lipkowitz KB, editors. Cyclodextrins: introduction. Chem Rev 1998; 98 (5): 1741-2
13. Lennernäs H. Human intestinal permeability. J Pharm Sci 1998; 87: 403-10
14. van de Waterbeemd H. The fundamental variables of the biopharmaceutics classification system (BCS): a commentary. Eur J Pharm Sci 1998; 7: 1-3
15. Yoshida F, Topliss JG. QSAR model for drug human oral bioavailability. J Med Chem 2000; 43: 2575-85
16. Amidon GL, Lennernäs H, Shah VP, et al. A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res 1995; 12: 413-20
17. Löbenberg R, Amidon GL. Modern bioavailability, bioequivalence and biopharmaceutics classification system: new scientific approaches to international regulatory standards. Eur J Pharm Biopharm 2000; 50: 3-12
18. Hörter D, Dressman JB. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. Adv Drug Deliv Rev 2001; 46: 75-87
19. US FDA, Center for Drug Evaluation and Research: The biopharmaceutics classification system (BCS) guidance [online]. Available from URL: www.fda.gov/cder/OPS/BSC_guidance.htm [Accessed 2004 Oct 18]
20. Yu LX, Amidon GL, Polli JE, et al. Biopharmaceutics classification system: the scientific basis for biowaiver extensions. Pharm Res 2002; 19: 921-5
21. Yazdanian M, Briggs K, Jankovsky C, et al. The 'high solubility' definition of current FDA guidance on biopharmaceutical classification system may be too strict for acidic drugs. Pharm Res 2004; 21: 293-9
22. Szejtli J. Cyclodextrins and their inclusion complexes: Akademiai Kiadó, Budapest; 1982
23. Uekama K, Hirayama F, Irie T. Cyclodextrin drug carrier systems. Chem Rev 1998; 98: 2045-76
24. Thompson DO. Cyclodextrins-enabling excipients: their present and future use in pharmaceuticals. Crit Rev Ther Drug Carrier Syst 1997; 14: 1-104

25. Evaluation of certain food additives and contaminants, WHO Technical Report Series No. 909. Geneva: World Health Organization, 2002
26. Uekama K. Recent aspects of pharmaceutical application of cyclodextrins. J Incl Phenom Macroc Chem 2002; 44: 3-7
27. Bergeron RJ. Cycloamylose-substrate binding. In: Attwood JL, Bavies JED, MacNicol DD, editors. Inclusion compounds. London: Academic Press, 1984: 391-443
28. Liu L, Guo Q-X. The driving forces in the inclusion complexation of cyclodextrins. J Incl Phenom Macroc Chem 2002; 42: 1-14
29. Connors KA. Population characteristics of cyclodextrin complex stabilities in aqueous solution. J Pharm Sci 1995; 84: 843-8
30. Connors KA. The stability of cyclodextrin complexes in solution. Chem Rev 1997; 97: 1325-57
31. Rao VM, Stella VJ. When can cyclodextrins be considered for solubilizing purposes? J Pharm Sci 2003; 92: 927-32
32. Loftsson T, Magnúsdóttir A, Másson M, et al. Self-association and cyclodextrin solubilization of drugs. J Pharm Sci 2002; 91: 2307-16
33. Loftsson T, Másson M, Brewster ME. Self-association of cyclodextrins and cyclodextrin complexes. J Pharm Sci 2004; 93: 1091-9
34. Loftsson T. Effects of cyclodextrins on chemical stability of drugs in aqueous solutions. Drug Stability 1995; 1: 22-33
35. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersion. Eur J Pharm Biopharm 2000; 50: 47-60
36. Serajuddin AT. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems and recent break-through. J Pharm Sci 1999; 88: 1058-66
37. Corrigan OI, Stanley CT. Dissolution properties of phenobarbitone-β-cyclodextrin systems. Pharm Acta Helv 1981; 56: 204-8
38. Corrigan OI, Stanley CT. Mechanism of drug dissolution rate enhancement from β-cyclodextrin-drug systems. J Pharm Pharmacol 1982; 34: 621-6
39. Loftsson T, Másson M, Sigurjónsdóttir JF. Methods to enhance the complexation efficiency of cyclodextrins. STP Pharma Sci 1999; 9: 237-42
40. Loftsson T, Másson M. The effects of water-soluble polymers on cyclodextrins and cyclodextrin solubilization of drugs. J Drug Del Sci Tech 2004; 14: 35-43
41. Krishnamoorthy R, Mitra AK. Complexation of weak acids and basis with cyclodextrins: effects of substrate ionization on the estimation and interpretation of association constants. Int J Pharm Advances 1996; 1: 330-43
42. Redenti E, Szente L, Szejtli J. Cyclodextrin complexes of salts of acidic drugs: thermodynamic properties, structural features, and pharmaceutical applications. J Pharm Sci 2001; 90: 979-86
43. Redenti E, Szente L, Szejtli J. Drug/cyclodextrin/hydroxy acid multicomponent systems: properties and pharmaceutical applications. J Pharm Sci 2000; 89: 1-8
44. Loftsson T, Sigurdsson HH, Másson M, et al. Preparation of solid drug/cyclodextrin complexes of acidic and basic drugs. Pharmazie 2004; 59: 25-9
45. Loftsson T, Matthíasson K, Másson M. The effects of organic salts on the cyclodextrin solubilization of drugs. Int J Pharm 2003; 262: 101-7
46. Li P, Tabibi E, Yalkowsky SH. Combined effect of complexation and pH on solubilization. J Pharm Sci 1998; 87: 1535-7
47. Loftsson T, Masson M. Cyclodextrins in topical drug formulations: theory and practice. Int J Pharm 2001; 225: 15-30
48. Loftsson T, Sigfússon SD, Sigurdsson HH, et al. The effects of cyclodextrins on topical delivery of hydrocortisone: the aqueous diffusion layer. STP Pharma Sci 2003; 13: 125-31
49. Matsuda H, Arima H. Cyclodextrins in transdermal and rectal delivery. Adv Drug Deliv Rev 1999; 36: 81-99
50. Legendre JY, Rault I, Petit A, et al. Effects of β-cyclodextrins on skin: implications for the transdermal delivery of piribedil and a novel cognition enhancing-drug, S-9977. Eur J Pharm Sci 1995; 3: 311-22
51. Vitória M, Bentley B, Renata F, et al. Characterization of the influence of some cyclodextrins on the stratum corneum from the hairless mouse. J Pharm Pharmacol 1997; 49: 397-402
52. Arima H, Miyaji T, Irie T, et al. Possible enhancing mechanism of the cutaneous permeation of 4-biphenylylacetic acid by β-cyclodextrin derivatives in hydrophilic ointment. Chem Pharm Bull 1996; 44: 582-6
53. Arima H, Miyaji T, Irie T, et al. Enhancing effect of hydroxypropyl- β-cyclodextrin on cutaneous penetration activation of ethyl 4-biphenylyl acetate in hairless mouse skin. Eur J Pharm Sci 1998; 6: 53-9
54. Irie T, Wakamatsu K, Arima H, et al. Enhancing effects of cyclodextrins on nasal absorption of insulin in rats. Int J Pharm 1992; 84: 129-39
55. Moffat AC, Osselton MD, Widdop B, editors. Clarke's analysis of drugs and poisons. 3rd ed. London: Pharmaceutical Press, 2004
56. Luengo J, Aránguiz T, Sepúlveda J, et al. Preliminary pharmacokinetic study of different preparations of acyclovir with β-cyclodextrin. J Pharm Sci 2002; 91: 2593-8
57. Evrard B, Chiap P, DeTullio P, et al. Oral bioavailability in sheep of albendazole from a suspension and from a solution containing hydroxypropyl-β-cyclodextrin. J Control Release 2002; 85: 45-50
58. García JJ, Bolás F, Torrado JJ. Bioavailability and efficiency characteristics of two different oral liquid formulations of albendazole. Int J Pharm 2003; 250: 351-8
59. Castillo JA, Palomo-Canales J, Garcia JJ, et al. Preparation and characterization of albendazole β-cyclodextrin complexes. Drug Dev Ind Pharm 1999; 25: 1241-8
60. Fathy M, Sheha M. *In vitro* and *in vivo* evaluation of an amylobarbitone/hydroxypropyl-β-cyclodextrin complex prepared by a freeze-drying method. Pharmazie 2000; 55: 513-7
61. Wong JW, Yuen KH. Improved oral bioavailability of artemisinin through inclusion complexation with β- and γ-cyclodextrins. Int J Pharm 2001; 227: 177-85
62. Teixeira LR, Sinisterra RD, Vieira RP, et al. Inclusion of benzaldehyde semicarbazone into β-cyclodextrin produces a very effective anticonvulsant formulation. J Incl Phenom Macroc Chem 2003; 47: 77-82
63. Puglisi G, Santagati NA, Ventura CA, et al. Enhancement of 4-biphenylacetic acid bioavailability in rats by its β-cyclodextrin complex after oral administration. J Pharm Pharmacol 1991; 43: 430-2
64. Puglisi G, Ventura CA, Spadaro A, et al. Differential-effects of modified β-cyclodextrins on pharmacological activity and bioavailability of 4-biphenylacetic acid in rats after oral administration. J Pharm Pharmacol 1995; 47: 120-3
65. Hatanaka H, Komada F, Mishima Y, et al. Improved bioavailability of para-boronophenylalanine by cyclodextrin complexation. J Pharm Sci 1993; 82: 1054-7
66. El-Gindy GA, Mohammed FA, Salem SY. Preparation, pharmacokinetic and pharmacodynamic evaluation of carbamazepine inclusion complexes with cyclodextrins. STP Pharma Sci 2002; 12: 369-78
67. Brewster ME, Anderson WR, Meinsma D, et al. Intravenous and oral pharmacokinetic evaluation of a 2-hydroxypropyl-β-cyclodextrin-based formulation of carbamazepine in the dog: comparison with commercially available tablets and suspensions. J Pharm Sci 1997; 86: 335-9
68. Betlach CJ, Gonzalez MA, McKiernan BC, et al. Oral pharmacokinetics of carbamazepine in dogs from commercial tablets and a cyclodextrin complex. J Pharm Sci 1993; 82: 1058-60
69. Choudhury S, Nelson KF. Improvement of oral bioavailability of carbamazepine by inclusion in 2-hydroxypropyl-β-cyclodextrin. Int J Pharm 1992; 85: 175-80
70. Koester LS, Bertuol JB, Groch KR, et al. Bioavailability of carbamazepine: β-cyclodextrin complex in beagle dogs from hydroxypropylmethylcellulose matrix tablets. Eur J Pharm Sci 2004; 22: 201-7
71. Fekkes D, Tuiten A, Bom I, et al. Pharmacokinetics of the b-carboline norharman in man. Life Sci 2001; 69: 2113-21
72. Hirayama F, Usami M, Kimura K, et al. Crystallization and polymorphic transition behavior of chloramphemicol palmitate in 2-hydroxypropyl-β-cyclodextrin matrix. Eur J Pharm Biopharm 1997; 5: 23-30
73. Tokumura T, Tsushima Y, Kayano M, et al. Enhancement of bioavailability of cinnarizine from its β-cyclodextrin complex on oral administration with DL-phenylalanine as a competing agent. J Pharm Sci 1985; 74: 496-7
74. Järvinen T, Järvinen K, Schwarting N, et al. β-Cyclodextrin derivatives, SBE4-b-CD and HP-b-CD, increase the oral bioavailability of cinnarizine in beagle dogs. J Pharm Sci 1995; 84: 295-9
75. Tokumura T, Nanba M, Tsushima Y, et al. Enhancement of bioavailability of cinnarizine from its β-cyclodextrin complex on oral administration with DL-phenylalanine as a competing agent. J Pharm Sci 1986; 75: 391-4
76. Yoo SD, Yoon BM, Lee HS, et al. Increased bioavailability of clomipramine after sublingual administration in rats. J Pharm Sci 1999; 88: 1119-21
77. Miyake K, Irie T, Hirayama F, et al. Improved solubility and oral bioavailability of cyclosporin A by hydrophilic cyclodextrin complexation. In: Torres Labandeira JJ, Vila-Jato JL, editors. Proceedings of the Ninth International Symposium on Cyclodextrins; 1998 Jun 3; Santiago de Compostela. Dordrecht: Kluwer Academic Publishers, 1999: 293-6

78. Miyake K, Arima H, Irie T, et al. Enhanced absorption of cyclosporin A by complexation with dimethyl-β-cyclodextrin in bile duct-cannulated and -non-cannulated rats. Biol Pharm Bull 1999; 22: 66-72
79. Jain AC, Aungst BJ, Adeyeye MC. Development and *in vivo* evaluation of buccal tablets prepared using danazole-sulfobutylether 7β-cyclodextrin (SBE 7) complexes. J Pharm Sci 2002; 91: 1659-68
80. Badawy SIF, Ghorab MM, Adeyeye CM. Characterization and bioavailability of danazol-hydroxypropyl-β-cyclodextrin coprecipitates. Int J Pharm 1996; 128: 45-54
81. Liversidge GG, Cundy KC. Particle-size reduction for improvement of oral bioavailability of hydrophobic drugs: 1. Absolute oral bioavailability of nanocrystalline danazol in beagle dogs. Int J Pharm 1995; 125: 91-7
82. Badawy SIF, Ghorab MM, Adeyeye CM. Bioavailability of danazol-hydroxypropyl-β-cyclodextrin complex by different routes of administration. Int J Pharm 1996; 145: 137-43
83. Corvi Mora P, Cirri M, Allolio B, et al. Enhancement of dehydroepianhydrosterone solubility and bioavailability by ternary complexation with α-cyclodextrin and glycine. J Pharm Sci 2003; 92: 2177-84
84. Uekama K, Fujinaga T, Hirayama F, et al. Improvement of the oral bioavailability of digitalis glycosides by cyclodextrin complexation. J Pharm Sci 1983; 72: 1338-41
85. Le Corre P, Dollo G, Chevanne F, et al. Influence of hydroxypropyl-β-cyclodextrin and dimethyl-β-cyclodextrin on diphenhydramine intestinal absorption in a rat *in situ* model. Int J Pharm 1998; 169: 221-8
86. Ricevuti G, Mazzone A, Pasotti D, et al. Pharmacokinetics of dipyridamole-β-cyclodextrin complex in healthy volunteers after single and multiple doses. Eur J Drug Metab Pharmacokinet 1991; 16: 197-201
87. Stracciari GL, Malvisi J, Anfossi P, et al. Pharmacokinetics of dipyridamole-β-cyclodextrin complex in dogs. Arch Int Pharmacodyn 1989; 300: 7-13
88. Savolainen J, Frosberg M, Taipale H, et al. Effect of aqueous solubility and dissolution characteristics on oral bioavailability of entacapone. Drug Dev Res 2000; 49: 238-44
89. Loftsson T, Gudmundsson JA, Árnadóttir RO, et al. Sublingual delivery of 17β-estradiol from cyclodextrin containing tablets. Pharmazie 2003; 58: 358-9
90. Fridriksdóttir H, Loftsson T, Gudmundsson JA, et al. Design and *in vivo* testing of 17β-estradiol-HPbCD sublingual tablets. Pharmazie 1996; 51: 39-42
91. Hoon TJ, Dawood MY, Khan-Dawood FS, et al. Bioequivalence of 17β-estradiol hydroxypropyl-β-cyclodextrin complex in postmenopausal women. J Clin Pharmacol 1993; 33: 1116-21
92. Miyaji T, Inoue Y, Acarturk F, et al. Improvement of oral bioavailability of fenbufen by cyclodextrin complexation. Acta Pharm Nord 1992; 4: 17-22
93. Géczy J, Bruhwyler J, Scuvée-Moreau J, et al. The inclusion of fluoxitine into γ-cyclodextrin increases its bioavailability: behavioral, electrophysiological and pharmacokinetic studies. Psychopharmacology 2000; 151: 328-34
94. Zuo Z, Tam YK, Diakur J, et al. Hydroxypropyl-β-cyclodextrin-flutamide inclusion complex: II. Oral and intravenous pharmacokinetics of flutamide in the rat. J Pharm Pharm Sci 2002; 5: 292-8
95. Savolainen J, Järvinen K, Taipale H, et al. Coadministration of a water-soluble polymer increases the usefulness of cyclodextrins in solid dosage forms. Pharm Res 1998; 15: 1696-701
96. Jayachandra Babu R, Pandit JK. Enhancement of dissolution rate and hypoglycemic activity of glibenclamide with β-cyclodextrin. STP Pharma Sci 1995; 5: 196-201
97. Aggarwal S, Singh PN, Mishra B. Studies on solubility and hypoglycemic activity of gliclazide β-cyclodextrin-hydroxypropylmethylcellulose complexes. Pharmazie 2002; 57: 191-3
98. Sridevi S, Chauhan AS, Chalasani KB, et al. Enhancement of dissolution and oral bioavailability of gliquidone with hydroxy propyl-β-cyclodextrin. Pharmazie 2003; 58: 807-10
99. Uekama K, Udo K, Irie T, et al. Improvement of dissolution and absorption characteristics of indomethacin by water-soluble α-cyclodextrin-epichlorohydrin polymer. Acta Pharm Suec 1987; 24: 27-36
100. Jambhekar S, Casella R, Maher T. The physicochemical characteristics and bioavailability of indomethacin from β-cyclodextrin, hydroxyethyl-β-cyclodextrin, and hydroxypropyl-β-cyclodextrin complexes. Int J Pharm 2004; 270: 149-66
101. Zhao Q, Zhou H, Pesco-Koplowitz L. Pharmacokinetics of intravenous itraconazole followed by itraconazole oral solution in patients with human immunodeficiency virus infection. J Clin Pharmacol 2001; 41: 1319-28
102. Barone JA, Moskovitz BL, Guarnieri J, et al. Enhanced bioavailability of itraconazole in hydroxypropyl-β-cyclodextrin solution versus capsules in healthy volunteers. Antimicrob Agents Chemother 1998; 42: 1862-5
103. Ahn HJ, Kim KM, Choi JS, et al. Effects of cyclodextrin derivatives on bioavailability of ketoprofen. Drug Dev Ind Pharm 1997; 23: 397-401
104. Tenjarla S, Puranajoti P, Kasina R, et al. Preparation, characterization, and evaluation of miconazole-cyclodextrin complexes for improved oral and topical delivery. J Pharm Sci 1998; 87: 425-9
105. Otero-Espinar FJ, Anguiano-Igea S, García-Gonzales N, et al. Oral bioavailability of naproxen-β-cyclodextrin inclusion compound. Int J Pharm 1991; 75: 37-44
106. Fernandes CM, Ramos P, Falcão AC, et al. Hydrophilic and hydrophobic cyclodextrins in a new sustained release oral formulation of nicardipine: in vitro evaluation and bioavailability studies in rabbits. J Control Release 2003; 88: 127-34
107. Chowdary KPR, Kamalakara RG. Controlled release of nifedipine from mucoadhesive tablets of its inclusion complexes with β-cyclodextrin. Pharmazie 2003; 58: 721-4
108. Emara LH, Badr RM, Abd Elbary A. Improving the dissolution and bioavailability of nifedipine using solid dispersions and solubilizers. Drug Dev Ind Pharm 2002; 28: 795-807
109. Uekama K, Ikegami K, Wang Z, et al. Inhibitory effect of 2-hydroxypropyl-β-cyclodextrin on crystal-growth of nifedipine during storage: superior dissolution and oral bioavailability compared with polyvinylpyrrolidone K-30. J Pharm Pharmacol 1992; 44: 73-8
110. Wang Z, Hirayama F, Uekama K. *In-vivo* and *in-vitro* evaluations of modified-release oral dosage form of nifedipine by hybridization of hydroxypropyl-β-cyclodextrin and hydroxypropylcellulose in dogs. J Pharm Pharmacol 1994; 46: 505-7
111. Choi H-G, Kim D-D, Jun HW, et al. Improvement of dissolution and bioavailability of nitrendipine by inclusion in hydroxypropyl- β-cyclodextrin. Drug Dev Ind Pharm 2003; 29: 1085-94
112. Savolainen J, Järvinen K, Matilainen L, et al. Improved dissolution and bioavailability of phenytoin by sulfobutylether-β-cyclodextrin (SBE)7m-β-CD) and hydroxypropyl-β-cyclodextrin (HP-b-CD) complexation. Int J Pharm 1998; 165: 69-78
113. Uekama K, Otagiri M, Irie T, et al. Improvement of dissolution and absorption characteristics of phenytoin by a water-soluble β-cyclodextrin-epichlorohydrin polymer. Int J Pharm 1985; 23: 35-42
114. Tanino T, Ogiso T, Iwaki M. Effect of sugar-modified β-cyclodextrins on dissolution and absorption characteristics of phenytoin. Biol Pharm Bull 1999; 22: 298-304
115. Woodcock BG, Acerbi D, Merz PG, et al. Supermolecular inclusion of piroxicam with β-cyclodextrin: pharmacokinetic properties in man. Eur J Rheumatol Inflamm 1993; 12: 12-28
116. McEwen J. Clinical pharmacology of piroxicam-β-cyclodextrin: implications for innovative patient care. Clin Drug Invest 2000; 19 Suppl. 2: 27-31
117. Elkheshen SA, Ahmed SM, Al-Quadeib BT. Inclusion complexes of piroxicam with β-cyclodextrin derivatives in comparison with the natural β-cyclodextrin, 2nd communication: *in vitro* and *in vivo* drug availability. Pharm Ind 2002; 64: 708-15
118. Kimura E, Bersani-Amado CA, Sudo LS, et al. Pharmacokinetic profile of piroxicam β-cyclodextrin, in rat plasma and lymph. Gen Pharmacol 1997; 28: 695-8
119. Deroubaix X, Stockis A, Allemon AM, et al. Oral bioavailability of CHF1194, an inclusion complex of piroxicam and β-cyclodextrin, in healthy-subjects under single-dose and steady-state conditions. Eur J Clin Pharmacol 1995; 47: 531-6
120. Hashimoto N, Fujioka T, Hayashi K, et al. Renin inhibitor: relationship between molecular structure and oral absorption. Pharm Res 1994; 11: 1443-7
121. Lin H-S, Chan SY, Low KSY, et al. Kinetic study of a 2-hydroxypropyl- β-cyclodextrin based formulation of all-trans-retinoic acid in Sprague-Dawley rats after oral or intravenous administration. J Pharm Sci 2000; 89: 260-7
122. Chavanpatil M, Dawre FD, Shakleya DS, et al. Enhancement of oral bioavailability of rofecoxib using β-cyclodextrin. J Incl Phenom Macroc Chem 2002; 44: 145-9

123. Miyake K, Arima H, Hirayama F, et al. Improvement of solubility and oral bioavailability of rutin by complexation with 2-hydroxypropyl- β-cyclodextrin. Pharm Dev Technol 2000; 5: 399-407

124. Arcari M, Brambilla A, Brandt A, et al. Nuovo complesso di inclusione tra la silibina e la b-ciclodextrina: velocità di sissoluzione *in vitro* e assorbimento *in vivo* in confronto a formulazioni tradizionali. Boll Chim Farm 1992; 131: 205-9

125. Seo H, Tsuruoka M, Hashimoto T, et al. Enhancement of oral bioavailability of spironolactone by β- and γ-cyclodextrin complexation. Chem Pharm Bull 1983; 31: 286-91

126. Kaukonen AM, Lennernäs A, Mannermaa JP. Water-soluble β-cyclodextrins in pediatric oral solutions of spironolactone: preclinical evaluation of spironolactone bioavailability from solutions of β-cyclodextrin derivatives in rats. J Pharm Pharmacol 1998; 50: 611-9

127. Soliman OAE, Kimura K, Hirayama F, et al. Amorphous spirolactone-hydroxypropylated cyclodextrin complexes with superior dissolution and oral bioavailability. Int J Pharm 1997; 149: 73-83

128. Arima H, Yunomae K, Miyake K, et al. Comparative studies of the enhancing effects of cyclodextrins on the solubility and oral bioavailability of tacrolimus in rats. J Pharm Sci 2001; 90: 690-701

129. Pitha J, Harman SM, Michel ME. Hydrophilic cyclodextrin derivatives enable effective oral administration of steroidal hormones. J Pharm Sci 1986; 75: 165-7

130. Stuenkel CA, Dudley RE, Yen SSC. Sublingual administration of testosterone-hydroxypropyl-β-cyclodextrin inclusion complex simulates episodic androgen release in hypogonadal men. J Clin Endocrinol Metab 1991; 72: 1054-9

131. Vakily M, Pasutto FM, Daneshtalab M, et al. Inclusion complexation of heptakis (2,6-di-O-ethul)-β-cyclodextrin with tiaprofenic acid: pharmacokinetic consequences of a pH-dependent release and stereoselective dissolution. J Pharm Sci 1995; 84: 1014-9

132. Veiga F, Fernandes C, Teixeira T. Oral bioavailability and hypoglycemic activity of tolbutamide/cyclodextrin inclusion complexes. Int J Pharm 2000; 202: 165-71

133. Kimura K, Hirayama F, Arima H, et al. Effects of aging on crystallization, dissolution and absorption characteristics of amorphous tolbutamide-2-hydroxypropyl-β-cyclodextrin complex. Chem Pharm Bull (Tokyo) 2000; 48: 646-50

134. Uekama K, Horiuchi Y, Kikuchi M, et al. Enhanced dissolution and oral bioavailability of α-tocopheryl esters by dimethyl-β-cyclodextrin complexation. J Incl Phenom 1988; 6: 167-74

135. Ventura P, Panini R, Montosi G, et al. Ursodeoxycholic acid complexation with 2-hydroxypropyl-β-cyclodextrin increases ursodeoxycholic acid biliary excretion after single oral administration to rats. Pharmacology 2001; 62: 107-12

136. Panini R, Vandelli MA, Forni F, et al. Improvement of ursodeoxycholic acid bioavailability by 2-hydroxypropyl-β-cyclodextrin complexation in healthy volunteers. Pharmacol Res 1995; 31: 205-9

137. Amselem S, Friedman D, Yogev A, et al. Formulation development for a zidovudine chemical delivery system: 2. Towards oral and non-parenteral dosage forms. Int J Pharm 1995; 125: 31-43

138. Goodman Gilman A, Rall TW, Nies AS, et al., editors. The pharmacological basis of therapeutics. New York: McGraw-Hill, 1992

139. Ahuja N, Singh A, Singh B. Rofecoxib: an update on physicochemical, ISSN pharmaceutical, Pharmacodynamic and pharmacokinetic aspects. J Pharm Pharmacol 2003; 55: 859-94

140. Kobayashi Y, Ito S, Itai S, et al. Physicochemical properties and bioavailability of carbamazepine polymorphs and dihydrate. Int J Pharm 2000; 193: 137-46

141. Popovic J, Mikov M, Jakovljevic V. Pharmacokientics of carbamazepine derived from a new tablet formulation. Eur J Drug Metab Pharmacokinet 1995; 20: 297-300

142. Anderson PO, Knoben JE, Troutman WG, editors. Handbook of clinical drug data. 9th ed. Stamford: Appelton & Lange, 1999

143. Kann J, Krol G, Raemsch K, et al. Bioequivalence and metabolism of nitrendipine administered orally to healthy volunteers. J Cardiovasc Pharmacol 1984; 6 Suppl. 7: S968-73

144. Veiga M-D, Ahsan F. Hydroxypropyl gamma cyclodextrin as a solubilizer and dissolution enhancing agent: the case of tolbutamide - a poorly water-soluble drug. In: Torres Labandeira JJ, Vila-Jato JL, editors. Proceedings of the Ninth International Symposium on Cyclodextrins; 1998 Jun 3; Santiago de Compostela. Dordrecht: Kluwer Academic Publishers, 1999: 321-4

145. Peeters J, Neeskens P, Tollenaere JP, et al. Characterization of the interaction of 2-hydroxypropyl-β-cyclodextrin with itraconazole at pH 2, 4, and 7. J Pharm Sci 2002; 91: 1414-22

146. Brewster ME, Verreck G, Chun I, et al. The use of polymer-based electrospun nanofibers containing amorphous drug dispersions for the delivery of poorly water-soluble pharmaceuticals. Pharmazie 2004 May; 59 (5): 387-91

147. Benet LZ, Øie S, Schwartz JB. Design and optimization of dosage regimens; pharmacokinetic data. In: Hardman JG, Limbird LE, Molinoff PB, et al., editors. Goodman & Gilman's the pharmaceutical basis of therapeutics. New York: McGraw-Hill, 1996: 1752

148. Miyake K, Hirayama F, Uekama K. Solubility and mass and nuclear magnetic resonance spectroscopic studies on interaction of cyclosporin A with dimethyl-α- and β-cyclodextrins in aqueous solution. J Pharm Sci 1999; 88: 39-45

149. Loftsson T. Cyclodextrins and the biopharmaceutics classification system. J Incl Phenom Macroc Chem 2002; 44: 63-7

150. Lemesle-Lamache V, Wouessidjewe D, Chéron M, et al. Study of β-cyclodextrin and ethylated β-cyclodextrin salbutamol complexes, *in vitro* evaluation of sustained-release behavior of salbutamol. Int J Pharm 1996; 141: 117-24

151. Zannou EA, Streng WH, Stella VJ. Osmotic properties of sulfobutylether and hydroxypropyl cyclodextrins. Pharm Res 2001; 18: 1226-31

152. Stella VJ, Rao VM, Zannou EA. The pharmaceutical use of Captisol®: some surprising observations. J Incl Phenom Macroc Chem 2002; 44: 29-33

153. Koester LS, Xavier CR, Mayorga P, et al. Influence of β-cyclodextrin complexation on carbamazepine release from hydroxypropyl methylcellulose matrix tablets. Eur J Pharm Biopharm 2003; 55: 85-91

154. Rao VM, Haslam JL, Stella VJ. Controlled and complete release of a model poorly water-soluble drug, prednisolone, from hydroxypropyl methylcellulose matrix tablets using (SBE) (7M)-β-cyclodextrin as a solubilizing agent. J Pharm Sci 2001; 90: 807-16

155. Yano H, Hirayama F, Kamada M, et al. Colon-specific delivery of prednisolone-appended α-cyclodextrin conjugate: alleviation of systemic side effect after oral administration. J Control Release 2002; 79: 103-12

156. Hirayama F, Kamada M, Yano H, et al. Prolonged plasma levels of ketoprofen after oral administration of its α-cyclodextrin conjugate/ethylcellulose dispersion in rats. J Incl Phenom Macroc Chem 2002; 44: 159-61

157. Marttin E, Verhoef JC, Merkus FWHM. Efficiency, safety and mechanism of cyclodextrins as absorption enhancers in nasal delivery of peptide and protein drugs. J Drug Target 1998; 6: 17-36

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