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Cyclodextrins in drug delivery

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Cyclodextrins are a family of cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. Cyclodextrin molecules are relatively large with a number of hydrogen donors and acceptors and, thus, in general they do not permeate lipophilic membranes. In the pharmaceutical industry cyclodextrins have mainly been used as complexing agents to increase aqueous solubility of poorly soluble drugs, and to increase their bioavailability and stability. Studies in both humans and animals have shown that cyclodextrins can be used to improve drug delivery from almost any type of drug formulation. However, the addition of cyclodextrins to existing formulations without further optimisation will seldom result in acceptable outcome. Currently there are ~ 30 different pharmaceutical products worldwide containing drug/cyclodextrin complexes on the market.

Keywords: absorption, bioavailability, cyclodextrin, drug delivery, formulation, solubilisation, stabilisation

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1. Introduction

All drugs must possess some degree of aqueous solubility to be pharmacologically active, and most drugs need to be lipophilic to be able to permeate biological membranes via passive diffusion. How water-soluble a given drug needs to be is determined by its potency (i.e., the dosage size) and type of formulation. For example, in an aqueous eye drop formulation the dose should be soluble in < 50 µl (i.e., one drop) of water, but in a parenteral formulation the dose should preferably be soluble in < 5 ml of water, corresponding to solubility > ~ 15 mg/ml for a medium potent drug (i.e., dose of ~ 1 mg/kg) [1]. Oral absorption of drugs with solubilities < 0.1 mg/ml is likely to be dissolution limited [2]. On the other hand, if a drug is too water soluble (and/or too hydrophilic) the dissolved drug molecule will have little tendency to partition from the aqueous exterior into a lipophilic biomembrane (e.g., the eye cornea or gastrointestinal mucosa) and then to permeate the membrane. High-throughput screening approaches to drug development have led to an increasing number of lipophilic water-insoluble drug candidates [3] or drugs whose clinical usefulness is hampered by their insolubility in water. These drugs are classified as Class II (i.e., poorly soluble/highly permeable) or Class IV (i.e., poorly soluble/poorly permeable) drugs according to the Biopharmaceutics Classification System [4]. In general, formulation techniques that increase the apparent aqueous solubility of Class II and Class IV drugs without decreasing their lipophilicity will enhance their absorption through biological membranes. These techniques include particle size reduction, salt formation, solid dispersion, melt extrusion, spray drying and complexation, as well as drug solutions in microemulsions, liposomes, and non-aqueous solvents. The following is a review of cyclodextrins and their place in drug delivery.

2. Cyclodextrins

Cyclodextrins are natural cyclic oligosaccharides that were discovered > 100 years ago [5], but only recently did highly purified cyclodextrins become available as pharmaceutical excipients. Worldwide ~ 30 different pharmaceutical products

Table 1. Some examples of marketed products containing cyclodextrin.

Drug	Formulation	Trade name	Company
α-Cyclodextrin			
Alprostadil (PGE_1)	Intravenous solution	Prostavasin	Ono (Japan)
Cefotiam hexetil HCl	Oral tablet	Pansporin T	Takeda (Japan)
β-Cyclodextrin			
Benexate HCl	Oral capsule	Ulgut	Teikoku Kagaku Sangyou (Japan)
Dexamethasone	Dermal ointment	Glymesason	Fujinaga (Japan)
Nicotine	Sublingual tablet	Nicorette	Pharmacia (Sweden)
Nitroglycerin	Sublingual tablet	Nitropen	Nihon Kayaku (Japan)
Piroxicam	Oral tablet	Brexin	Chiesi (Italy)
Tiaprofenic acid	Oral tablet	Surgamyl	Roussel-Maestrelli (Italy)
2-Hydroxypropyl-β-cyclodextrin			
Cisapride	Suppository	Propulsid	Janssen (Belgium)
Indomethacin	Eye drop solution	Indocid	Chauvin (France)
Itraconazole	Oral and intravenous solutions	Sporanox	Janssen (Belgium)
Mitomycin	Intravenous solution	Mitozytrex MitoExtra	SuperGen (USA) Novartis (Switzerland)
Randomly methylated β-cyclodextrin			
17β-Oestradiol	Nasal spray	Aerodiol	Servier (France)
Chloramphenicol	Eye drop solution	Clorocil	Oftalder (Portugal)
Sulfobutylether β-cyclodextrin			
Voriconazole	Intravenous solution	Vfend	Pfizer (USA)
Ziprasidone maleate	Intramuscular solution	Geodon, Zeldox	Pfizer (USA)
2-Hydroxypropyl-γ-cyclodextrin			
Diclofenac sodium	Eye drop solution	Voltaren ophtha	Novartis (Switzerland)

PGE_1: Prostaglandin E1.

containing cyclodextrins are on the market (**Table 1**). In the pharmaceutical industry cyclodextrins have mainly been used as complexing agents to increase aqueous solubility of poorly soluble drugs, and to increase their bioavailability and stability. In addition, cyclodextrins can, for example, be used to reduce gastrointestinal drug irritation, convert liquid drugs into microcrystalline or amorphous powder, and prevent drug–drug and drug–excipient interactions. A number of books and review articles have been published on the pharmaceutical applications of cyclodextrins [6-18].

2.1 Structure and properties

Cyclodextrins are cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. They consist of (α-1,4-)-linked α-D-glucopyranose units with a lipophilic central cavity (**Figure 1**). Due to the chair formation of the glucopyranose units, cyclodextrin molecules are shaped like cones with secondary hydroxy groups extending from the wider edge and the primary groups from the narrow edge. This gives cyclodextrin molecules a hydrophilic outer surface, whereas the lipophilicity of their central cavity is comparable to an aqueous ethanolic solution [8]. The most common natural cyclodextrins consist of six (α-cyclodextrin), seven (β-cyclodextrin) and eight (γ-cyclodextrin) glucopyranose units. Although the natural cyclodextrins and their complexes are hydrophilic, their aqueous solubility is rather limited, especially that of β-cyclodextrin. This is thought to be due to relatively strong binding of the cyclodextrin molecules in the crystal state (i.e., relatively high crystal lattice energy) [9]. Random substitution of the hydroxy groups, even by hydrophobic

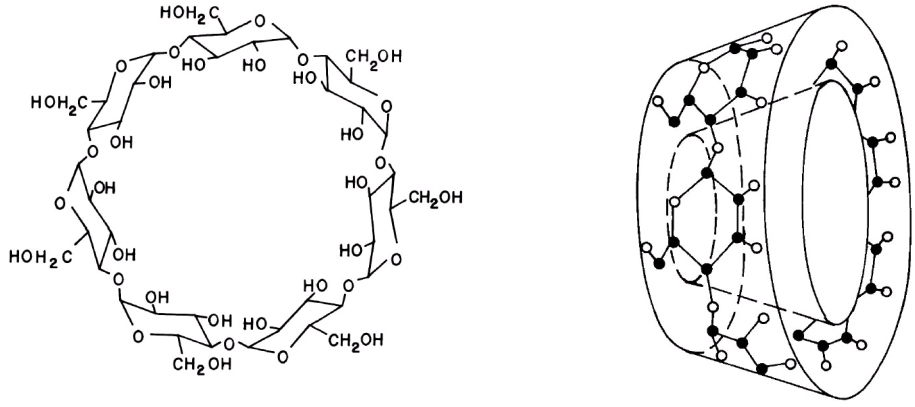


Figure 1. The chemical structure and the conical shape of the β-cyclodextrin molecule. Used with permission from LOFTSSON T, BREWSTER ME: Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization. *J. Pharm. Sci.* (1996) **85**:1017-1025 © (1996) Wiley-Liss, Inc., A Wiley Company.

Table 2. Cyclodextrins that can be found in marketed pharmaceutical products.

Cyclodextrin	Substitution*	MW (Da)	Solubility in water (mg/ml)‡	Applications
α-Cyclodextrin	-	972	145	Oral, parenteral, topical
β-Cyclodextrin	-	1135	18.5	Oral, topical
2-Hydroxypropyl-β-cyclodextrin	0.65	1400	> 600	Oral, parenteral, topical
Randomly methylated β-cyclodextrin	1.8	1312	> 500	Oral§, topical
β-Cyclodextrin sulfobutyl ether sodium salt	0.9	2163	> 500	Oral, parenteral, topical
γ-Cyclodextrin	-	1297	232	Oral, parenteral§, topical
2-Hydroxypropyl-γ-cyclodextrin	0.6	1576	> 500	Oral, parenteral, topical

*Average number of substituents per glucopyranose repeat unit. ‡Solubility in pure water at ~ 25°C. §In very limited amounts.
MW: Molecular weight.

moieties such as methoxy functions, will result in dramatic improvements in their solubility (**Table 2**). The main reason for the solubility enhancement is that the random substitution transforms the crystalline cyclodextrins into amorphous mixtures of isomeric derivatives. 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.

Cyclodextrin molecules are relatively large (molecular weight ranging from almost 1000 to > 2000 Da) with a large number of hydrogen donors and acceptors, and are consequently poorly absorbed through biological membranes. The natural α- and β-cyclodextrin, unlike γ-cyclodextrin, cannot be hydrolysed by human salivary and pancreatic amylases [19,20], but all three are subjected to fermentation by the intestinal microflora. Hydrophilic cyclodextrins are nontoxic at low to moderate oral dosages [11,15]. The natural cyclodextrins and their derivatives are used in topical and oral formulations, but only α-cyclodextrin and the hydrophilic derivatives of β- and γ-cyclodextrin can be used in parenteral formulations. γ-Cyclodextrin forms visible aggregates in aqueous solutions and, thus, is not well suited for parenteral formulations [21]. Due to its nephrotoxicity, β-cyclodextrin cannot be used in parenteral formulations. 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 [11]. Presently, oral administration of methylated β-cyclodextrin is limited by its potential toxicity. Cyclodextrin monographs can be found in several Pharmacopoeias. For example, α-cyclodextrin and β-cyclodextrin are listed in the US Pharmacopeia, European Pharmacopeia and the Japanese Pharmacopeia. γ-Cyclodextrin will soon be included in the US Pharmacopeia and subsequently in the European Pharmacopeia as well. A monograph for 2-hydroxypropyl-β-cyclodextrin has recently appeared in the European Pharmacopeia. β-Cyclodextrin and γ-cyclodextrin are also listed in the 'generally regarded as safe' list of the FDA for use as food additives.

2.2 Complex formation and drug solubility

In aqueous solutions cyclodextrins are able to form inclusion complexes with many drugs by taking up a drug molecule, or more frequently some lipophilic moiety of the molecule, into

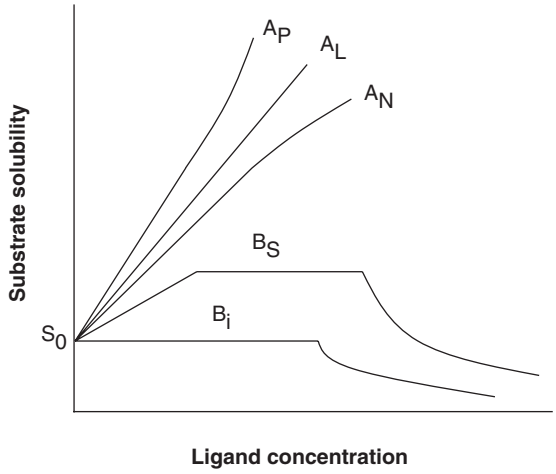


Figure 2. Phase-solubility profiles and classification of complexes according to Higuchi and Connors [26]. S_0 is the intrinsic solubility of the substrate (the drug) in the aqueous complexation medium when no ligand (cyclodextrin) is present.

the central cavity. No covalent bonds are formed or broken during the complex formation, and drug molecules in the complex are in rapid equilibrium with free molecules in the solution. The driving forces for the complex formation include release of enthalpy-rich water molecules from the cavity (i.e., water molecules that cannot have a full compliment of hydrogen bonds), electrostatic interactions, van der Waals' interactions, hydrophobic interactions, hydrogen bonding, release of conformational strain and charge-transfer interactions [9,22]. The physicochemical properties of free drug molecules are different from those bound to the cyclodextrin molecules. Likewise, the physicochemical properties of free cyclodextrin molecules are different from those in the complex. In theory, any methodology that can be used to observe these changes in additive physicochemical properties may be utilised to determine the stoichiometry of the complexes formed and the numerical values of their stability constants [23-25]. These include changes in solubility, chemical reactivity, ultraviolet/visible light (UV/VIS) absorbance, fluorescence, drug retention (e.g., in liquid chromatography), p*K*a values, potentiometric measurements and chemical stability, nuclear magnetic resonance (NMR) chemical shifts and effects on drug permeability through artificial membranes. Furthermore, because complexation will influence the physicochemical properties of the aqueous complexation media, methods that monitor these media changes can be applied to study the complexation; for example, measurements of conductivity changes, determinations of freezing point depression, viscosity measurements and calorimetric titrations. However, only few of these methods can be applied to obtain structural information on drug/cyclodextrin complexes.

Higuchi and Connors [26] have classified complexes based on their effect on substrate solubility as indicated by phase-solubility profiles (**Figure 2**). A-type phase-solubility profiles are obtained when the solubility of the substrate (i.e., drug) increases with increasing ligand (i.e., cyclodextrin) concentration. When the complex is first order with respect to ligand and first or higher order with respect to substrate then A_L-type phase-solubility profiles are obtained. If the complex is first order with respect to the substrate, but second or higher order with respect to the ligand then A_P-type phase-solubility profiles are obtained. A_N-type phase-solubility profiles can be difficult to interpret. The negative deviation from linearity may be associated with cyclodextrin-induced changes in the dielectric constant of the aqueous complexation media, changes in complex solubility or self-association of cyclodextrin molecules [24]. B-type phase-solubility profiles indicate formation of complexes with limited solubility in the aqueous complexation medium. In general, the water-soluble cyclodextrin derivatives form A-type phase-solubility profiles, whereas the less soluble natural cyclodextrins frequently form B-type profiles. Most drug/cyclodextrin complexes are thought to be inclusion complexes, but cyclodextrins are also known to form non-inclusion complexes and complex aggregates capable of dissolving drugs through micelle-like structures [27,28]. The phase-solubility profiles do not verify formation of inclusion complexes. They only describe how the increasing cyclodextrin concentration influences drug solubility. To distinguish between inclusion and non-inclusion complexes, experimental results from phase-solubility studies have to be compared with other experimental results from, for example, UV/VIS, fluorescence and NMR studies [27,28]. The most common type of cyclodextrin complex is the 1:1 drug/cyclodextrin complex (D/CD) in which one drug molecule (D) forms a complex with one cyclodextrin molecule (CD):

$$D + CD \overset{K_{1:1}}{\leftrightarrow} D/CD \qquad (1)$$

Under such conditions an A_L-type phase-solubility diagram, with slope less than unity, would be observed, and the stability constant ($K_{1:1}$) of the complex can be calculated from the slope and the intrinsic solubility (S_0) of the drug in the aqueous complexation media (i.e., drug solubility when no cyclodextrin is present):

$$K_{1:1} = Slope/[S_0(1 - Slope)] \qquad (2)$$

The value of $K_{1:1}$ is most often between 50 and 2000 M^{-1} with a mean value of 129, 490 and 355 M^{-1} for α-, β- and γ-cyclodextrin, respectively [12,29-31]. For 1:1 drug/cyclodextrin complexes the complexation efficiency (CE) can be calculated from the slope of the phase-solubility diagram:

$$CE = [D/CD]/[CD] = S_0 \cdot K_{1:1} = Slope/(1 - Slope) \qquad (3)$$

When selecting cyclodextrin or complexation conditions during formulation work it can frequently be more convenient to compare the CE than $K_{1:1}$ values. The most common stoichiometry of higher order drug/cyclodextrin

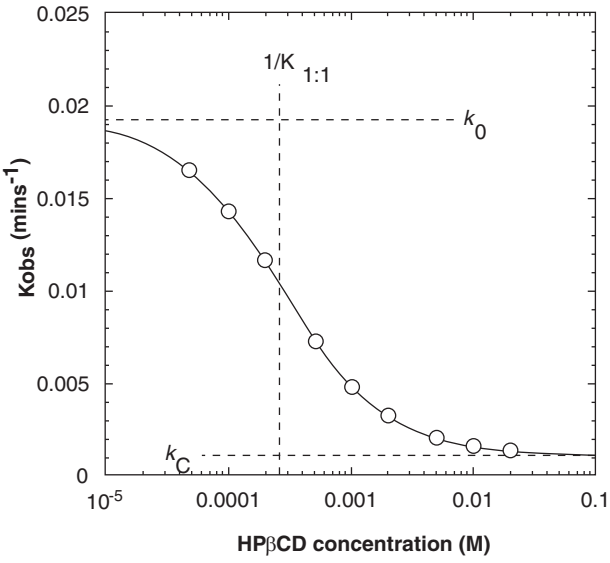


Figure 3. Results from a kinetic study of the effect of cyclodextrin on drug stability. Degradation of chlorambucil in HPβCD solution (10 mM NaH2PO4/NaOH buffer, pH 7.5, 30 °C).
HPβCD: 2-Hydroxypropyl-β-cyclodextrin.

complexes is the 1:2 drug/cyclodextrin complex resulting in A_P-type phase-solubility diagram. Consecutive complexation is assumed where the 1:2 complex is formed when one additional CD molecule forms a complex with an existing 1:1 complex [24]:

$$D/CD + CD \overset{K_{1:2}}{\leftrightarrow} D/CD_2 \qquad (4)$$

The stoichiometry of the system can be probed by curve fitting of the diagram with a quadratic model:

$$S_{tot} = S_0 + K_{1:1}S_0[CD] + K_{1:1}K_{1:2}S_0[CD]^2 \qquad (5)$$

Here [CD] represents the concentration of free cyclodextrin, but it is customary to plot the total amount of dissolved drug (S_{tot}) against the total amount of cyclodextrin in solution ($[CD]_{tot}$), assuming that the extent of complexation is low (i.e., [CD] ~ $[CD]_{tot}$). The value of $K_{1:2}$ is frequently between 10 and 500 M^{-1}, or significantly lower than that of $K_{1:1}$.

Various methods can be applied to prepare D/CD complexes, including the solution method, the co-precipitation method, neutralisation method, the slurry method, the kneading method and the grinding method [23,32]. In most cases presence of at least some water is essential for successful complex formation. In solution, cyclodextrin complexes are usually prepared by the addition of excess amount of drug to an aqueous cyclodextrin solution. The suspension formed is equilibrated at the desired temperature (which may require periods of ≤ 1 week) and then filtered or centrifuged to form clear D/CD complex solution. For preparation of solid complexes, the water is removed from the aqueous D/CD solution by evaporation (e.g., spray drying) or sublimation (e.g., lyophilisation).

For a variety of reasons, such as isotonicity of parenteral formulations and formulation bulk of solid dosage forms, it is important to include as little cyclodextrin as possible in a pharmaceutical formulation. Various methods have been applied to enhance the complexation efficacy [33]. These include addition of polymers to the complexation media [34], drug ionisation and salt formation [35,36], addition of hydroxy carboxylic acids to the complexation media [37], addition of volatile acids or bases to the complexation media [38], addition of organic salts [39], and addition of cosolvents [40]. However, even under the best conditions, cyclodextrin complexation will result in over fourfold increase in the formulation bulk of solid dosage forms [33]. Rao and Stella [31] have shown how the feasibility of using cyclodextrins in dosage forms can be calculated from few simple experiments.

2.3 Drug stability

Stability issues can limit the feasibility of a pharmaceutical formulation. This is especially true for aqueous formulations of drugs that are prone to hydrolysis or oxidation. The reaction rates can be affected by inclusion of the drug, and especially inclusion of its chemically labile moiety, into the cyclodextrin cavity.

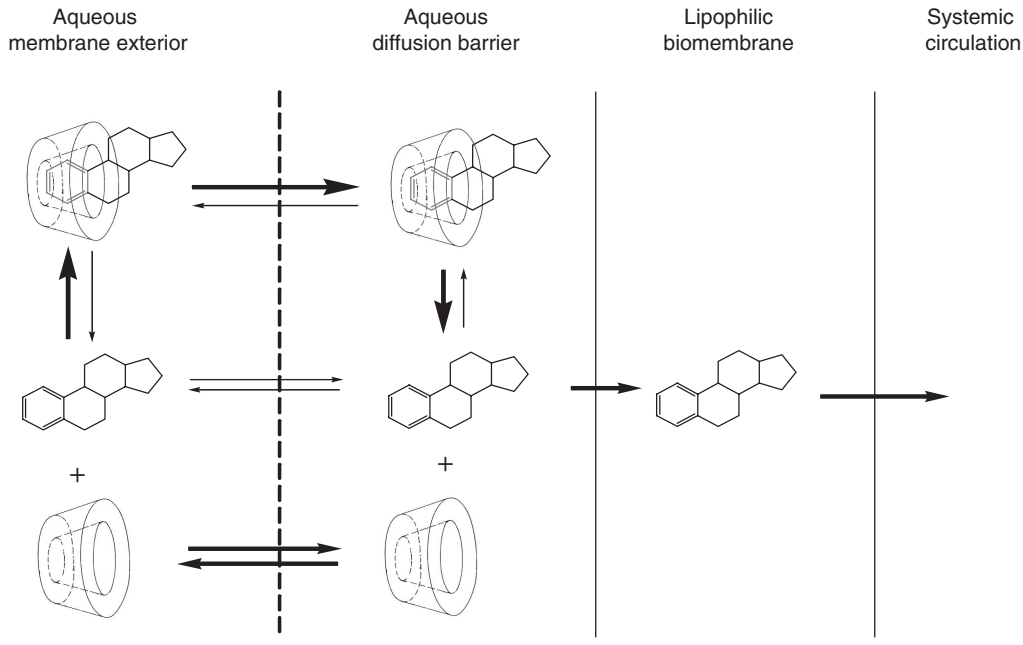
In cyclodextrin solutions the observed degradation rate for a chemically unstable compound, forming 1:1 complex, will be the weighted average of the degradation rates of the free drug and drug in cyclodextrin complex. In first-order and pseudo-first-order reactions, such as hydrolysis or oxidation, the stabilising (or catalytic) effect will depend on three parameters: the cyclodextrin concentration, the stability constant of the complex and the degradation rate constant for the drug degradation within the cyclodextrin cavity (k_C). These parameters can be determined by fitting degradation data obtained at several cyclodextrin concentrations to Equation 7:

$$\begin{array}{ccc} & \overset{K_{1:1}}{} & \\ D + CD & \leftrightarrow & D/CD \\ k_0 \downarrow & & \downarrow k_c \\ \text{Degradation products} & & \end{array} \qquad (6)$$

$$k_{obs} = (k_0 + k_c K_{1:1}[CD]) / (1 + K_{1:1}[CD]) \qquad (7)$$

Where k_{obs} is observed rate constant for the reaction and k_0 is the rate constant for the reaction in pure aqueous solution. An example of such kinetic study, of chlorambucil degradation in aqueous 2-hydroxypropyl-β-cyclodextrin solution, is shown in **Figure 3** [41]. Through nonlinear fitting of Equation 7, the values for $K_{1:1}$ (3836 ± 89 M^{-1}, mean ± standard deviation), k_o and k_C can be obtained (k_o/k_C = 17). From **Figure 3** it can be seen that 50% of the maximum stabilising effect is obtained when the cyclodextrin

Table 3. The effect of cyclodextrin complexation on drug bioavailability after nonparenteral administration.



FDA class*	Drug properties		RDS to drug absorption¶	Effect of cyclodextrin complexation
	Aqueous solubility‡	***Permeability§***		
I	Highly soluble	Highly permeable	(Good bioavailability)	Can decrease absorption
II	Poorly soluble	Highly permeable	Aqueous diffusion	Can enhance absorption
III	Highly soluble	Poorly permeable	Membrane permeation	Can decrease absorption
IV	Poorly soluble	Poorly permeable	Aqueous diffusion and membrane permeation	Can enhance absorption

*FDA Biopharmaceutics Classification System of orally administered drugs. ‡Intrinsic solubility of the drug in the aqueous membrane exterior. §Passive drug permeation through lipophilic biomembrane such as the gastrointestinal mucosa. ¶RDS of drug delivery from the aqueous exterior into the body.
FDA: Food and Drug Association; RDS: Rate-determining step.

concentration is equal to $1/K_{1:1}$. In many of the older publications the values of k_C and $K_{1:1}$ were obtained by linear fitting to Equation 8 [42]:

$$1/(k_0 - k_{obs}) = 1/(k_0 - k_c) + 1/K_{1:1}\,(k_0 - k_c)\,1/[CD] \quad (8)$$

However, because the nonlinear method is less sensitive to experimental errors than the linear one, it frequently gives more accurate results [43,44]. Many studies have shown that the stability of chemically labile drugs and compounds such as steroid esters [45], alkylating anticancer agents [46-49], prostaglandins [50-52], prodrugs [53,54] and various other drug compounds [9,42] can be improved through formulation with cyclodextrins. Most of these studies have been focused on drug stability in aqueous solutions, but cyclodextrins have also been shown to stabilise drugs in solid dosage forms [55,56]. The photochemistry of cyclodextrin inclusion complexes has been studied [57] and the effect of complexation on photostability of drugs has been investigated [58]. These studies have shown that cyclodextrin complexation can affect the light absorption properties of the inclusion compound and primary and secondary photochemical reactions, and that the effect can be either stabilising or destabilising. In general, these effects are modest and may depend on the type of cyclodextrin used and on the experimental conditions, such as the irradiation wavelength. Finally, cyclodextrins can also increase physical stability of drugs. For example, evaporation of volatile compounds can be significantly reduced through complex formation [32], and cyclodextrins have been used to prevent aggregation and to reduce denaturation in peptide and protein formulations [59-61].

Cyclodextrins can sometimes have a destabilising effect on drugs through direct catalysis or, for example, by enhancing drug solubility in aqueous drug suspensions [9,42]. Frequently, the catalytic effect is associated with deprotonisation of the hydroxy groups located at the rim of the cyclodextrin cavity [62-64]. In this way cyclodextrins

behave like carbohydrates and other polyhydric alcohols with adjacent hydroxy groups [63]. In this case the catalytic effect will mainly be observed under basic conditions and will increase with increasing pH.

2.4 Drug delivery through biological membranes

The chemical structure of cyclodextrins (i.e., the large number of hydrogen donors and acceptors), their molecular weight (i.e., > 970 Da) and their very low octanol/water partition coefficient (approximately log $P_{o/w}$ between -3 and 0.00 [65]) are all characteristics of compounds that do not readily permeate biological membranes [4,66]. In fact, experiments have shown that only negligible amounts of hydrophilic cyclodextrins and drug/cyclodextrin complexes are able to permeate lipophilic membranes such as skin and gastrointestinal mucosa [11,67]. Only the free form of the drug, which is in equilibrium with the drug/cyclodextrin complex, is capable of penetrating lipophilic membranes [68]. Cyclodextrins are able to extract lipophilic components from biomembranes such as the stratum corneum [69,70], but both pre- and postapplication of hydrophilic cyclodextrins does not affect, for example, the skin barrier [71,72]. Cyclodextrins do not, in general, enhance permeability of hydrophilic water-soluble drugs through lipophilic biological membranes [73,74], and numerous studies have shown that excess cyclodextrin will reduce drug permeability through biological membranes [73]. The physicochemical properties of the drug (e.g., its solubility in water), the composition of the drug formulation (e.g., aqueous or non-aqueous) and physiological composition of the membrane barrier (e.g., presence of an aqueous diffusion layer), will determine whether cyclodextrins will enhance or hamper drug delivery through a biological membrane (**Table 3**). Most biological membrane barriers (or biomembranes) are lipophilic with an aqueous exterior, which forms a structured water layer at the membrane surface frequently referred to as unstirred diffusion layer. If drug permeation through the aqueous diffusion layer is the rate-limiting step of drug permeation through the barrier, cyclodextrins can frequently enhance the permeation. However, cyclodextrins are in most cases unable to enhance drug permeation through a lipophilic membrane barrier and excess cyclodextrin (more than is needed to dissolve the drug) will hamper drug permeation through the membrane. In other words, cyclodextrins will enhance drug delivery through aqueous diffusion-controlled barriers, but can hamper drug delivery through lipophilic membrane-controlled barriers [74]. However, there is one exception: lipophilic cyclodextrins, such as the methylated β-cyclodextrins, are able to permeate mucosa and are known to enhance drug delivery through biological membranes, such as through the nasal mucosa, by reducing barrier function of the membranes [75].

Cyclodextrins can, at least in theory, enhance drug bioavailability by stabilisation of 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 stabilising effect [76]. In general, drug stabilisation associated with cyclodextrin complexation plays only a very minor role when it comes to drug delivery through biological membranes. It is their solubilising effect that is usually related to improved drug delivery. However, as cyclodextrins can both enhance and hamper drug delivery through biological membranes it is of utmost importance to optimise cyclodextrin-containing drug formulations with regard to drug delivery from the formulations [73]. Too much or too little cyclodextrin can result in less than optimum drug bioavailability.

3. Formulation with cyclodextrins

It is important for a pharmaceutical formulator to know the advantages and limitations of each excipient used during design of a product. Excipients are selected based on the physicochemical properties of the drug (e.g., solubility, stability), type of delivery (e.g., tablet, parenteral solution) and desired pharmacokinetics (e.g., instant release, sustained release). The following is a brief overview of the use of cyclodextrins in various formulations, with the main emphasis on the effects of cyclodextrins on aqueous solubility and drug permeability through biological membranes. However, cyclodextrins are also able to increase the physical and chemical stability of drugs in the various formulations (i.e., increasing the shelf-life of the pharmaceutical product) as well as to reduce local drug irritation.

3.1 Oral drug delivery

Drug absorption from immediate-release tablets in the gastrointestinal tract consists of a series of rate processes including drug dissolution in the aqueous gastrointestinal fluids, permeation of the drug molecules from the intestinal fluid through an aqueous diffusion layer immediately adjacent to the mucosal surface, and permeation through the mucosa. The effect of cyclodextrins on oral drug absorption can be explained in the context of the Biopharmaceutics Classification System (**Table 4**) [77]. The Biopharmaceutics Classification System categorises drugs according to their aqueous solubility and ability to permeate the intestinal mucosa (**Table 3**). A given drug substance is considered 'highly soluble' when the highest dose strength is soluble in ≤ 250 ml water over a pH range of 1.0 – 7.5, and 'highly permeable' when the extent of oral absorption in humans is determined to be ≥ 90% of an administered dose (in solution). For an immediate-release tablet, ≥ 85% of the labelled amount of drug substance must dissolve within 30 min [2,4,301]. Class I drugs are relatively water soluble 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. In general, hydrophilic cyclodextrins are not able to improve bioavailability of Class I drugs. However, cyclodextrin can be used

Table 4. Some examples of cyclodextrins in oral formulations, tested *in vivo* in humans and/or animals, and the effect of the cyclodextrin complexation on the absolute bioavailability compared with identical cyclodextrin-free formulation.

Drug	Cyclodextrin	Formulation	Species	F_{rel}*	Ref.
Class I					
Piroxicam	βCD	Tablet, capsule and oral suspension	Human, rat, rabbit	≤ 1.4	[128-131]
Class II					
Carbamazepine	DMβCD	Oral powder and solution, tablet	Rabbit, dog, rat	≤ 5.6	[132-136]
Digoxin	γCD	Tablet	Dog	5.4	[137]
Glibenclamide	βCD, SBEβCD	Capsule containing powder	Dog, rat	≤ 6.2	[138,139]
Miconazole	HPβCD	Aqueous suspension	Rat	2.3	[140]
Phenytoin	E-βCD, GluβCD, MalβCD, SBEβCD, HPβCD	Suspension, capsule containing powder	Rat, dog	≤ 5	[141-143]
Spironolactone	βCD, γCD, DMβCD, SBEβCD, HPβCD	Oral solution and powder	Rat, dog	≤ 3.6	[144-146]
Tolbutamide	βCD, HPβCD	Suspension, oral powder	Rabbit, dog	≤ 1.5	[147,148]
α-Tocopheryl nicotinate	DMβCD	Capsule containing powder	Dog	~ 70	[149]
Class III					
Acyclovir	βCD	Oral suspension	Rat	1.1	[150]
Diphenhydramine HCl	DMβCD, HPβCD	Solution	Rat	≤ 0.9	[151]
Class IV					
Cyclosporin A	DMβCD	Oral suspension	Rat	4.7	[152,153]

*F_{rel} (i.e., the 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).

AUC: Area-under-curve; βCD: β-Cyclodextrin; γCD: γ-Cyclodextrin; DMβCD: Dimethyl-β-cyclodextrin; E-βCD: β-Cyclodextrin epichlorohydrin polymer; F_{rel} : Relative bioavailability; GluβCD: Glucosyl-β-cyclodextrin; HPβCD: 2-Hydroxypropyl-β-cyclodextrin; MalβCD: Maltosyl-β-cyclodextrin; SBEβCD: Sulfobutylether-β-cyclodextrin sodium salt.

to reduce local drug irritation and increase the rate of drug absorption. Class II drugs have limited aqueous solubility, resulting in dissolution-rate limited oral absorption. However, once in solution these drugs permeate biological membranes relatively easily, resulting in ≥ 90% absolute bioavailability. Thus, low aqueous solubility hampers their dissolution rate. The drug permeation through the aqueous diffusion layer adjacent to the mucosal surface will also be slow due to their low aqueous solubility. Water-soluble cyclodextrin complexes of these drugs will enhance their diffusion to the mucosal surface leading to enhanced oral bioavailability. Class III drugs are water soluble, but do not easily permeate biological membranes due to, for example, their size and/or extent of hydration. 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 readily permeate lipophilic biological membranes. These can, for example, be water-insoluble zwitterions or relatively large lipophilic molecules. Hydrophilic water-insoluble compounds such as zwitterions do not readily form cyclodextrin complexes and, thus, hydrophilic cyclodextrins are 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. This will frequently lead to increased oral bioavailability.

3.2 Sublingual drug delivery

Sublingual drug delivery is one of the most efficient ways to bypass hepatic first-pass metabolism [78]. However, in order to enter into the systemic circulation the drug must dissolve in the saliva. Due to the small volume of saliva in the mouth, the therapeutic dose has to be relatively small and usually dissolution enhancers must be applied.

In sublingual formulations the complexation of poorly water-soluble drugs with cyclodextrins has been shown to increase the bioavailability of various lipophilic drugs. For example, 2-hydroxypropyl-β-cyclodextrin has been shown to increase the bioavailability of 17β-oestradiol [79,80], androstenediol [81], clomipramine [82] and danazol [83]. In the case of lipophilic compounds, the aqueous solubility and dissolution rate of a drug is usually the rate-limiting step for drug

absorption and, after dissolution, the drug readily penetrates through mucosal membranes. Thus, in most studies, the increased bioavailability achieved by cyclodextrins is likely to be due to increased aqueous solubility and drug dissolution rate. However, interactions between cyclodextrins and sublingual mucosa (i.e., cyclodextrins acting as conventional penetration enhancers) cannot be excluded.

From a toxicological point of view the use of cyclodextrins in sublingual formulations is closely related to other forms of oral administration. The large hydrophilic cyclodextrin molecules do not permeate across the sublingual mucosa and, thus, they are eventually swallowed. However, there are some basic differences between sublingual administration and oral administration of cyclodextrin-containing formulations. As discussed earlier, the drug must be released from the inclusion complex before it can be absorbed. This can be a problem for sublingual applications due to the small volume of aqueous saliva and the relatively short residence time. The dissolved drug is removed from the buccal area within a few minutes after administration; therefore, not allowing enough time for the drug to be released from the cyclodextrin complex.

One limitation in the use of cyclodextrins in sublingual administration is the effect of cyclodextrins on formulation bulk. For example, in the development of sublingual formulations of Δ^9-tetrahydrocannabinol (THC) for the treatment of various medical conditions, the complexation of THC with 2-hydroxypropyl-β-cyclodextrin and randomly methylated β-cyclodextrin was studied. The result showed that the estimated therapeutic dose (1 mg) of THC could form a water-soluble complex with 400 mg of 2-hydroxypropyl-β-cyclodextrin, but formulation bulk of 400 mg is considered too large for sublingual administration. However, the complexation efficiency of randomly methylated β-cyclodextrin with THC was much higher and, thus, the same amount of THC (1 mg) could form a soluble complex with 25 mg of randomly methylated β-cyclodextrin, which made the development of sublingual THC formulations possible [201]. Results from *in vivo* absorption studies showed that sublingual administration of randomly methylated β-cyclodextrin containing THC formulation increases the bioavailability of THC compared with oral administration [84].

3.3 Nasal drug delivery

The nasal route is another effective way to bypass the hepatic first-pass metabolism [85]. Because of the good permeability properties of nasal mucosa, the nasal route has also been studied as a possible administration route for systemic delivery of peptides. However, in order to enter the systemic circulation the drug has to dissolve in the aqueous nasal fluids. In nasal formulations, cyclodextrins are normally used to increase the aqueous solubility of lipophilic drugs. However, lipophilic cyclodextrins can also interact with biological membranes, acting as penetration enhancers, especially in nasal delivery of peptides [75]. Numerous studies have demonstrated that methylated cyclodextrins in particular are efficient absorption enhancers, and this is one reason why they are the most commonly studied cyclodextrins in nasal drug delivery [86]. The first cyclodextrin-based nasal formulations contained steroidal hormones and peptides [76,87-89]. The results were very promising and the most effective cyclodextrins, methylated cyclodextrin derivatives, increased, for example, the bioavailability of progesterone threefold compared with suspension of the same compound [90]. For example, nasal bioavailability of insulin in rats was increased from ~ 0 to 100% by including methylated cyclodextrins in the formulation [91]. However, much lower insulin bioavailability after nasal administration was later observed in human studies and it is well known that there are large interspecies differences associated with nasal drug delivery [86]. Recently, promising results from nasal delivery of dihydroergotamine [92], midazolam [93], acyclovir [94] and heparins [95] have been reported. Only insignificant amounts of cyclodextrins are absorbed from the nasal cavity. Most cyclodextrins are removed from the cavity by the nasal mucociliary system, which transports cyclodextrins to the oesophagus and ultimately into the gastrointestinal tract. The local toxicity of cyclodextrins after nasal administration is very low. The acute histological effects of the lipophilic methylated cyclodextrins, for example, were close to physiological saline when studied in rats [96]. In addition, the local toxicity of dimethyl-β-cyclodextrin, indicated by ciliary beat frequency, has been shown to be very mild compared with other absorption-enhancing agents and preservatives (e.g., benzalkonium chloride) used in nasal formulations [97].

The amount of cyclodextrins that can be used in nasal formulations is limited by the fact that only 25 – 150 µl of liquid can be sprayed into each nostril [85]. The oestradiol nasal spray Aerodiol® (Servier, France) represents the successful use of cyclodextrins in nasal applications; each spray delivers 70 µl of solution, which contains 150 µg of oestradiol dissolved in aqueous randomly methylated β-cyclodextrin solution.

3.4 Pulmonary drug delivery

Pulmonary administration of drugs is usually intended for local treatment of diseases (i.e., to treat asthma, chronic obstructive pulmonary disease or other lung diseases) [98]. However, pulmonary drug delivery is also an attractive route for systemic drug delivery. Drug degradation in the gastrointestinal tract and first-pass metabolism can be circumvented by administration via the lungs. Lungs have a large surface area, the blood flow to the lungs is high and the enzymatic activity in the lungs is relatively low, all of which generate good conditions for effective drug absorption. However, pulmonary drug delivery can be limited by low aqueous solubility and slow drug dissolution. Insoluble particles are removed from the lungs by the mucociliary clearance in the upper airways and by macrophages in the alveoli [98]. Cyclodextrins can be of value in pulmonary delivery by increasing the solubility, stability and dissolution rate of water-insoluble and chemically unstable drugs. This can lead to decreased clearance, increased drug absorption and faster onset of drug action. Furthermore, by forming drug/cyclodextrin

Table 5. Current marketed drug formulations [154] compared with cyclodextrin formulations (unpublished results and [155]).

	Commercial product	Cyclodextrin formulation
Diazepam intravenous solution (Roche)		
Diazepam	5 mg/ml	5 mg/ml
Propylene glycol	40%	
Ethyl alcohol	10%	
Sodium benzoate/benzoic acid	5%	
Benzyl alcohol	1.5%	
Water for injection	~ 43%	~ 93%
HPβCD		6%
Sodium chloride		0.6%
Phenytoin intravenous solution (Parke–Davis)		
Phenytoin sodium	50 mg/ml	50 mg/ml
Propylene glycol	40%	
Alcohol	10%	
Sodium hydroxide	adjust pH to 12	adjust pH to 11
Water for injection	~ 43%	~ 75%
HPβCD		20%

HPβCD: 2-Hydroxy-β-cyclodextrin.

complexes, a liquid drug can be converted to a solid form, two incompatible drugs can be mixed in a dry powder formulation, bad smells and/or tastes can be reduced, and local drug irritation in the lungs can be reduced.

Cyclodextrins are more readily absorbed from the lungs than from the gastrointestinal tract and this limits the number of cyclodextrins that can be included in pulmonary formulations but, in general, cyclodextrins that are considered safe for parenteral administration are also considered safe for pulmonary administration [11,99]. Among the cyclodextrins used in pharmaceutical products, γ-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin and sulfobutylether β-cyclodextrin are considered to be the safest for parenteral administration. However, the number of studies dealing with the toxicity or local effects of cyclodextrins on lung cells is very limited. A 72-h treatment with aqueous 0.1 – 1% 2-hydroxypropyl-β-cyclodextrin solutions did not have any significant effect on growth of CRL7272 human lung cells *in vitro* [100]. The toxicity of natural cyclodextrins, 2-hydroxypropyl-β-cyclodextrin and randomly methylated β-cyclodextrin was also studied recently with Calu-3 pulmonary epithelial cell line *in vitro* [101]. The results showed that cyclodextrins are well tolerable in Calu-3 cells and decreased the cell viability only at the high cyclodextrin concentrations.

The number of studies dealing with pulmonary applications of cyclodextrins is also very limited. Studies have been performed using premetered dry powder inhalers, which emit the dose from a pierced blister or capsule [102]. The respirable fraction of salbutamol from Diskhaler® (GlaxoSmithKline) has been increased by complexation with γ-cyclodextrin and dimethyl-β-cyclodextrin [104], and the respirable fraction of beclomethasone dipropionate from Microhaler® has been increased by 2-hydroxypropyl-β-cyclodextrin complexation [104]. Furthermore, the absorption of intratracheally administered drugs has been shown to increase in the presence of various cyclodextrins [105-107]. A recent study with budesonide also showed that cyclodextrin complexes could be used in an inhalation powder without lowering the pulmonary deposition of the drug [108].

3.5 Injectable formulations

Injectable formulations of lipophilic water-insoluble drugs frequently consist of mixtures of water, organic cosolvents and surfactants. Limitations in using organic solvents in injectable formulations include possible drug precipitation, pain, inflammation and haemolysis on injection [109]. Sometimes it is possible to alleviate these side effects by designing a water-soluble prodrug of the lipophilic water-insoluble drug. However, a prodrug will change the pharmacokinetics of the parent drug. For example, due to the gradual metabolism of the prodrug to form the active drug, the onset time of the drug (i.e., the time required for the drug to reach minimum effective plasma concentration) will be delayed [110,111]. Organic solvents and surfactants can be replaced by isotonic aqueous cyclodextrin solutions (**Table 5**). Numerous studies have shown that unlike prodrugs these aqueous cyclodextrin vehicles containing the active drug will in general not alter the intrinsic pharmacokinetics of a drug [10,12]. On parenteral administration, especially after intravenous injection, the drug is both rapidly and quantitatively released from the cyclodextrin complex upon dilution, competitive replacement, and binding of drug molecules to plasma proteins and tissue [113]. However, because cyclodextrins are rapidly eliminated in the urine cyclodextrins can increase renal clearance of lipophilic water-insoluble drugs [112]. Finally, the hydrophilic cyclodextrin derivatives, such as 2-hydroxypropyl-β-cyclodextrin and sulfobutylether β-cyclodextrin, are relatively non-toxic compared with organic solvents and surfactant formulations. Furthermore, as they have a minimal effect on the intrinsic pharmacokinetics of drugs, cyclodextrin-containing formulations are increasingly being used during *in vitro* and *in vivo* screening of new pharmacologically active compounds.

3.6 Ophthalmic drug delivery

In ophthalmology local drug administration in the form of topically applied low viscosity aqueous eye drop solutions is preferred. The outermost layer of the eye cornea is a lipophilic epithelium and, thus, drugs must be somewhat lipophilic to be able to permeate through the cornea into the eye. However, attached to microvilli at the corneal surface is an aqueous layer of ~ 8 μm thick and, thus, topically applied drugs must be

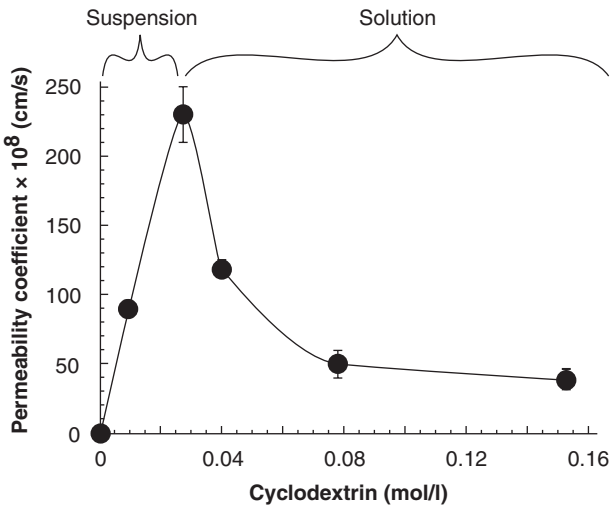


Figure 4. The permeability coefficient of arachidonylethanolamide through the isolated cornea of pigmented rabbits as a function of 2-hydroxypropyl-β-cyclodextrin concentration. The vehicle consisted of 0.5 mg/ml of the drug in suspension or solution containing from 0.000 to 0.155 mol/l cyclodextrin. Approximately 0.03 mol/l cyclodextrin was needed to dissolve 0.5 mg/ml of the drug. Modified from JARHO P, URTTI A, PATE DW, SUHONEN P, JÄRVINEN T: Increase in aqueous solubility, stability and in vitro corneal permeability of anandamide by hydroxypropyl-b-cyclodextrin. *Int. J. Pharm.* (1996) **137**:209-217 [156].

water soluble to be able to penetrate this aqueous diffusion barrier to reach the corneal surface [113]. In addition, only one eye drop, or 0.03 – 0.05 ml, can be applied to the eye, which means that in aqueous eye drop solution the drug dose must be soluble in < 0.05 ml of the aqueous formulation. The average tear volume is only 7 µl and any excess liquid is rapidly spilled onto the skin or drained through the nasolacrimal duct into the nose. In addition, continuous secretion of tear fluid limits the contact time of topically applied drugs with the eye surface. Consequently, < 5% of a topically applied drug is absorbed into the eye [114,115]. Through cyclodextrin solubilisation it is possible to increase the dose-to-solubility ratio, making it possible to apply drugs topically that previously could only be given by systemic delivery [115,116]. For example, acetazolamide is a carbonic anhydrase inhibitor that is used to treat glaucoma with oral daily dose as high as 1000 mg. The aqueous solubility of acetazolamide in pure water is 0.7 mg/ml, but in 20% (weight/volume) aqueous 2-hydroxypropyl-β-cyclodextrin solution it is 7 mg/ml. Addition of water-soluble polymers to the aqueous cyclodextrin solution increases the solubility even further. Thus, it is possible to obtain topically effective acetazolamide eye drop solution through cyclodextrin solubilisation of the drug [117].

Cyclodextrin solubilisation of the drug will increase the amount of dissolved drug at the lipophilic membrane surface (i.e., enhance drug delivery through the aqueous diffusion barrier), but excess cyclodextrin (i.e., more than is needed to dissolve the drug) will decrease the ability of the drug molecules to partition into the lipophilic barrier. Thus, excess cyclodextrin can result in decreased drug delivery through the cornea (**Figure 4**). Cyclodextrins have also been used to reduce ophthalmic drug irritation and to increase chemical stability of drugs in aqueous ophthalmic formulations [115,118].

3.7 Dermal drug delivery

It is generally believed that the main barrier to drug absorption, into and through the skin, is the outermost layer of the skin: the stratum corneum. Penetration enhancers used in dermal drug formulations, such as fatty acids and alcohols, penetrate into stratum corneum and temporary decrease its barrier properties. However, only negligible amounts of topically applied hydrophilic cyclodextrins are able to penetrate into the stratum corneum and they have negligible effect on its barrier properties [10,67,68,73]. Numerous studies have shown that excess cyclodextrins do, like in the case of ophthalmic drug delivery (**Figure 4**), decrease drug delivery through excised skin [73]. Cyclodextrins enhance drug delivery through aqueous diffusion layers (i.e., aqueous diffusion barriers), but not through lipophilic barriers such as the stratum corneum. If the drug release is from an aqueous-based vehicle or if an aqueous diffusion layer at the outer surface of the skin is a rate-determining factor in dermal drug delivery, then cyclodextrins can act as penetration enhancers (**Table 3**). However, if drug penetration through the lipophilic stratum corneum is the main rate-determining factor then cyclodextrins are unable to enhance the delivery [74]. It appears that cyclodextrins do enhance hydrocortisone delivery from an unstirred aqueous donor phase through hairless mouse skin, but have no effect on hydrocortisone delivery from a well-stirred donor phase [74,119]. In general, cyclodextrins do not enhance drug delivery from non-aqueous vehicles [68]. For example, it has been shown that both β-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin reduce the amount of hydrocortisone released from non-aqueous petrolatum-based vehicles and from w/o cream (water-in-oil emulsion), but enhance the release from both o/w cream (oil-in-water emulsion) and a hydrogel formulation [120]. When applied to excised human skin, cyclodextrins enhanced hydrocortisone delivery from the o/w cream, but reduced the delivery from the non-aqueous petrolatum-based vehicle [121]. As cyclodextrins enhance dermal delivery of drugs by increasing the amount of drug at the surface of the stratum corneum, and conventional penetration enhancers enhance drug delivery by decreasing the barrier function of the stratum corneum, it is possible to obtain an additive effect by combining the two types of enhancers [122,123]. For example, in one study the effects of both 2-hydroxypropyl-β-cyclodextrin and a conventional penetration enhancer (i.e., glycerol monoether extract) on transdermal delivery of testosterone, from o/w cream through hairless mouse skin, was investigated *in vitro* [124]. An ~ 60% increase in the testosterone flux was obtained when cyclodextrin was added to the cream, an ~ 40% increase occurred when the

extract was added to the cream, but an ~ 80% increase in the flux was observed when both cyclodextrin and the extract were added to the cream.

Cyclodextrins have also been used to reduce permeability of compounds into skin. For example, addition of an excess of 2-hydroxypropyl-β-cyclodextrin to a vehicle containing the UV-absorbing compound oxybenzone (a common sunscreen) (more than needed to solubilising the compound) reduced significantly transdermal permeation of the compound [125]. In addition, studies have indicated that complexation of the sunscreen enhances its photoprotective effects by preventing permeation of the sunscreen into skin [126].

4. Expert opinion and conclusion

Recent advances in drug development, such as high-throughput screening, have increased the number of drug candidates whose clinical usefulness is hampered by their insolubility in water. Furthermore, the usefulness of a number of drugs and drug candidates is hampered by their chemical or physical instability, or local irritation after administration. Cyclodextrins can alleviate many of these undesirable drug properties. Worldwide there are currently ~ 30 different cyclodextrin-containing pharmaceutical products on the market in ~ 14 different types of formulations, including different types of tablets (i.e., conventional, chewing and sublingual tablets), oral capsules, parenteral solutions, suppositories, nasal sprays, eye drop solutions and dermal products. In these products cyclodextrins are used to replace organic solvents in parenteral and topical formulations, to enhance oral bioavailability of Class II and some Class IV drugs, to reduce gastrointestinal irritation and to increase dermal availability of drugs. Furthermore, studies in both humans and animals have shown that cyclodextrins can be used to improve drug delivery from almost any type of drug formulation, but not all. The outcome of a cyclodextrin formulation is highly dependent on the physicochemical properties of the drug being formulated. In addition, the pharmaceutical formulator has to possess a good knowledge of the physicochemical properties of cyclodextrins and their complexes to be able to apply this new technology successfully in drug delivery. The addition of cyclodextrins to existing formulations, without further optimisation, will seldom result in acceptable outcome.

We still lack deeper knowledge of the forces involved in the complex formation. Recent studies have shown that cyclodextrins form both inclusion and non-inclusion complexes, and that those complexes coexist in aqueous solutions. It has also been shown that cyclodextrins form aggregates in aqueous solutions and that those aggregates are able to act as solubilisers in a micellar-like fashion. However, we do not know the exact structures of these non-inclusion complexes and aggregates, nor do we know how they influence drug delivery from cyclodextrin-containing drug formulations. Novel cyclodextrin derivatives for site-specific drug delivery and gene delivery are being synthesised and tested in animals, as well as derivatives in which cyclodextrins are being used as pro-moieties in prodrugs intended for colon drug delivery. In addition, pharmacologically active cyclodextrin derivatives have recently been designed and shown to be clinically effective drugs. Thus, functionality of cyclodextrins will increase rapidly in the coming years.

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