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Review

# Cyclodextrins in topical drug formulations: theory and practice

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**Abstract**

Cyclodextrins are cyclic oligosaccharides with a hydrophilic outer surface and a somewhat lipophilic central cavity. Cyclodextrins are able to form water-soluble inclusion complexes with many lipophilic water-insoluble drugs. In aqueous solutions drug molecules located in the central cavity are in a dynamic equilibrium with free drug molecules. Furthermore, lipophilic molecules in the aqueous complexation media will compete with each other for a space in the cavity. Due to their size and hydrophilicity only insignificant amounts of cyclodextrins and drug/cyclodextrin complexes are able to penetrate into lipophilic biological barriers, such as intact skin. In general, cyclodextrins enhance topical drug delivery by increasing the drug availability at the barrier surface. At the surface the drug molecules partition from the cyclodextrin cavity into the lipophilic barrier. Thus, drug delivery from aqueous cyclodextrin solutions is both diffusion controlled and membrane controlled. It appears that cyclodextrins can only enhance topical drug delivery in the presence of water. 

*Keywords:* Cyclodextrin; Permeability; Drug delivery; Topical

## 1. Introduction

It is generally recognized that the bioavailability of topically applied drugs is very low. Consequently various approaches have been developed in order to enhance the bioavailability of topically applied drugs (Smith and Maibach, 1995a; Finnin and Morgan, 1999; Hadgraft, 1999). For example, it is possible to enhance the bioavailability by employment of an innocuous chemical or physical means to reversibly improve the solubility of the drug in the barrier, e.g. stratum corneum, and facilitate diffusion of the drug through the barrier (Smith and Maibach, 1995b). Chemical enhancers, such as fatty acids, alcohols, amines and amides, are absorbed into the barrier where they alter the overall solvent potential of the barrier. At the same time the enhancers may disrupt the ordered lipid structure within the barrier thereby

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lowering its viscosity. These physicochemical changes will facilitate drug partition from a topically applied formulation into the barrier as well as diffusion of drug molecules through the barrier. Some physical enhancers, such as ultrasound, decrease the barrier function through wave energy that is absorbed into the barrier (Mitragotri et al., 1995). Other physical techniques, such as iontophoresis, enhance permeability of ionized drug molecules by applying small electrical current across the barrier (Chang and Banga, 1998). Several other techniques have been applied in order to enhance bioavailability of topically applied drugs, almost all of which provoke physicochemical, biochemical or metabolic changes within the barrier, such as skin (Finnin and Morgan, 1999; Hadgraft, 1999). However, through formation of supersaturated drug solutions it is possible to improve drug delivery into the skin surface without affecting the skin barrier (Smith and Surber, 1999; Iervolino et al., 2001). Supersaturated solutions are inherently unstable and are, conse-

Table 1
Cyclodextrins in topical formulations for dermal and transdermal drug delivery; release and permeability studies

| Drug | Cyclodextrin | Reference |
|---|---|---|
| Acitretin | RMβCD | (Loftsson et al., 1995) |
| Alkannin | HPβCD | (Chen et al., 1996) |
| Beclomethasone diproprionate | γCD | (Uekama et al., 1985) |
| 4-Biphenylylacetic acid | βCD, DMβCD, HPβCD | (Arima et al., 1990a, 1996) |
| Capsaicin analog | HPβCD | (Lee et al., 1997) |
| Dexamethasone acetate | βCD, HPβCD | (Lopez et al., 2000) |
| 17β-Estradiol | HPβCD | (Loftsson et al., 1991) |
| Ethyl 4-biphenylyl acetate | βCD, DMβCD, HPβCD | (Arima et al., 1990b, 1998) |
| Hydrocortisone | βCD, HPβCD, MLβCD, RMβCD, CMβCD | (Loftsson et al., 1991; Loftsson and Sigurdardottir, 1994; Loftsson et al., 1994a; Sigurdardottir and Loftsson, 1995; Preiss et al., 1995; Chang and Banga, 1998; Masson et al., 1999) |
| Ibuprofen | HPβCD | (Iervolino et al., 2000, 2001) |
| Indomethacin | βCD, DMβCD, DEβCD[a] | (Okamoto et al., 1986; Kawahara et al., 1992) |
| Ketoprofen | HPβCD | (Batzdorf and Mullergoymann, 1993) |
| Liarozole | HPβCD | (Vollmer et al., 1993) |
| Lidocaine | HPβCD, DMβCD, SBEβCD | (Dollo et al., 1998) |
| Loteprednol etabonate | DMβCD | (Loftsson and Bodor, 1994) |
| Melantonin | HPβCD | (Lee et al., 1998) |
| Methyl paraben | HPβCD | (Tanaka et al., 1995) |
| Miconazole | αCD, HPβCD | (Tenjarla et al., 1998) |
| Naproxen | βCD | (Celebi et al., 1993) |
| Piribedil | RMβCD | (Legendre et al., 1995) |
| Piroxicam | HPβCD | (Doliwa et al., 2000) |
| Prednisolone | βCD, γCD | (Uekama et al., 1987) |
| Prostaglandin E1 | αCD , βCD, CMEβCD[b] | (Adachi et al., 1992; Uekama et al., 1992; Adachi et al., 1993; Yuzuriha et al., 1999) |
| S-9977 | RMβCD | (Legendre et al., 1995) |
| Shikonin | HPβCD | (Chen et al., 1996) |
| Sulfanilic acid | βCD, DMβCD | (Okamoto et al., 1986) |
| Testosterone | HPβCD | (Loftsson et al., 1991) |
| Tolnaftate | βCD, βCD-polymer | (Szeman et al., 1987) |
| Tretinoin | βCD, HPβCD, DMβCD | (Amdidouche et al., 1994; Montassier et al., 1998) |

[a] DEβCD = diethyl βCD
[b] CMEβCD = *O*-carboxymethyl-*O*-ethyl-βCD

Table 2
Cyclodextrins in topical formulations for ocular drug delivery; release and permeability studies

| Drug | Cyclodextrin | Reference |
|---|---|---|
| Acetazolamide | HPβCD | (Loftsson et al., 1994c, 1996) |
| Anandamides | HPβCD | (Pate et al., 1996; Jarho et al., 1996b) |
| Cannabinoids (various) | HPβCD | (Pate et al., 1998) |
| Cyclosporin | αCD | (Kanai et al., 1989; Sasamoto et al., 1991; Cheeks et al., 1992) |
| Dehydroepiandrosterone | HPβCD | (Kearse et al., 2001) |
| Dexamethasone | HPβCD | (Usayapant et al., 1991; Loftsson et al., 1994b; Kristinsson et al., 1996; Gavrilin et al., 1999) |
| Diclofenac | HPβCD | (Reer et al., 1994) |
| Diclofenac sodium | HPβCD, RMβCD | (Reer et al., 1994) |
| Dipivefrine | SBEβCD | (Jarho et al., 1997) |
| Fluorometholone | HPγCD | (Morita et al., 1996) |
| Hydrocortisone | HPβCD | (Davies et al., 1997; Bary et al., 2000) |
| Pilocarpine | αCD, βCD, HEβCD[a], HPβCD, SBEβCD | (Reddy et al., 1996; Siefert and Keipert, 1997) (Freedman et al., 1993) |
| Prostaglandins | HPβCD | (Freedman et al., 1993; Järvinen et al., 1994; Keipert et al., 1996; Siefert and Keipert, 1997) |
| Talidomide | HPβCD | (Wheeler, 1991) |
| Δ9-Tetrahydrocannobinol | αCD, βCD, HPβCD, γCD | (Siefert et al., 1999; Green and Kearse, 2000; Kearse and Green, 2000) |

[a] HEβCD = (hydroxyethyl)-βCD

quently, of limited value as drug delivery formulations. Thus, there is a certain demand for stable formulation techniques that can be applied in order to enhance bioavailability of topically applied drugs, and which do not affect the barrier. This is especially true in the case of topically applied ophthalmic drugs.

There are numerous studies of the effects of cyclodextrins on topical drug availability (Tables 1 and 2). These studies show that, depending on the vehicle composition, cyclodextrins can either increase or decrease drug permeability through biological barriers. Furthermore, hydrophilic cyclodextrins, and their drug complexes, are only able to permeate into biological membranes with considerable difficulty. These and other observations indicate that cyclodextrins do enhance drug permeability without causing physicochemical changes within the barrier (Rajewski and Stella, 1996; Uekama et al., 1998; Loftsson and Järvinen, 1999; Matsuda and Arima, 1999; Masson et al., 1999; Stella et al., 1999). In this present review we focus primarily on recent findings on the effects of cyclodextrins on topical drug delivery. Based on the physicochemical and biological properties of cyclodextrins we attempt to explain the mechanism of cyclodextrin enhancement of drug delivery and their potential as permeation enhancers.

## 2. Cyclodextrins and their properties

Enzymatic hydrolysis of starch usually results in formation of glucose, maltose, and a long range of linear and branched dextrins. However, a number of different microorganisms and plants produce certain enzymes, called cyclodextrin glucosyltransferases (CGTs), which degrade starch through an intramolecular chain splitting reaction. The cyclic products formed are called cyclodextrins. Previously only small amounts of cyclodextrins could be generated and high production costs prevented their industrial applications. Now most of the CGT genes have been cloned making low-cost CGTs available for large-scale production of cyclodextrins.

Cyclodextrins are cyclic oligosaccharides, consisting of (α-1,4)-linked α-D-glucopyranose units,

with a somewhat lipophilic central cavity and a hydrophilic outer surface. Due to the chair formation of the glucopyranose units, the cyclodextrin molecules are shaped like a truncated cone rather than a perfect cylinder. The hydroxyl functions are orientated to the cone exterior with the primary hydroxyl groups of the glucose residues at the narrow edge of the cone and the secondary hydroxyl groups at the wider edge. The central cavity is lined by skeletal carbons and ethereal oxygens, which give it a lipophilic character. Cyclodextrins can contain more than 15 glucopyranose units per ring. However, the most abundant natural cyclodextrins are α-cyclodextrin (αCD), β-cyclodextrin (βCD) and γ-cyclodextrin (γCD), containing six, seven, and eight glucopyranose units, respectively. Of these three cyclodextrins βCD appears to be the most useful pharmaceutical complexing agent because of its complexing abilities, low cost and other properties.

Cyclodextrins are chemically stable in aqueous alkaline solutions but are susceptible to hydrolytic cleavage under strong acidic conditions (Bender and Komiyama, 1978; Hirayama et al., 1992). However, cyclodextrins are more resistant towards acid-catalyzed hydrolysis than comparable linear dextrins and the hydrolytic rate decreases with decreasing cavity size. Some starch degrading enzymes, such as certain α-amylases, are able to cleave the glycosidic bonds, but again at much slower rate than in the case of linear cyclodextrins and at decreasing rate with decreasing cavity size (Irie and Uekama, 1997). The rate of both the non-enzymatic and enzymatic hydrolysis is decreased when the cavity is occupied by appropriate drug molecule.

The natural cyclodextrins, in particular βCD, have limited aqueous solubility, and their complex formation with lipophilic compounds frequently results in precipitation of solid cyclodextrin complexes. In fact, the aqueous solubility of the natural cyclodextrins is much lower than that of comparable linear or branched dextrins. 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). In addition, βCD form intramolecular hydrogen bonding between the secondary hydroxyl groups which reduces the number of hydroxyl groups capable of forming hydrogen bonds with the surrounding water molecules (Szejtli, 1988). Random substitution of the hydrogen bond forming hydroxy groups, even by hydrophobic moieties such as methoxy or ethoxy functions, will result in a dramatic increase in aqueous solubility. The random substitution of the cyclodextrin molecule transforms the crystalline cyclodextrins into amorphous mixtures of isomeric derivatives. For example, (2-hydroxypropyl)-βCD (HPβCD) is obtained by treating a base-solubilized solution of βCD with propylene oxide, resulting in an isomeric system that has an aqueous solubility well in excess of 60% (w/v) (Pitha et al., 1986). The number of isomers generated based on random substitution is very large. Statistically, there exist about 130,000 possible heptakis (2-hydroxypropyl)-βCD isomers, and given that introduction of 2-hydroxypropyl function also introduces an optical active center, the total number of isomers, is even much greater (Loftsson and Brewster, 1996). About 100 different cyclodextrin derivatives are commercially available as fine chemicals. However, only relatively few of those derivatives have gone through toxicological evaluations and are available as bulk chemicals for pharmaceutical applications. Cyclodextrin derivatives currently used in drug formulations include HPβCD, randomly methylated βCD (RMβCD), sulfobutylether βCD (SBEβCD), maltosyl βCD (MLβCD) and (2-hydroxypropyl)-γCD (HPγCD). The aqueous solubility of these derivatives is usually 50–70% (w/v). All of these five derivatives, as well as the natural αCD, βCD and γCD, can be used in topical drug formulations.

In an aqueous environment, cyclodextrins form inclusion complexes with many lipophilic drug molecules through a process in which water molecules located inside the central cavity are replaced by either the whole drug molecule, or more frequently, by some lipophilic structure of the molecule (Fig. 1). Since water molecules located inside the lipophilic cyclodextrin cavity cannot satisfy their hydrogen-bonding potential, they are of higher enthalpy than bulk water molecules located in the aqueous environment (Bergeron, 1984). The main driving force for complex forma-

tion, at least in the case of βCD and its derivatives, appears to be release of these enthalpy-rich water molecules from the cyclodextrin cavity which lowers the energy of the system. However, other forces, such as van der Waals interactions, hydrogen bonding, hydrophobic interactions, release of structural strains and changes in surface tension, may also be involved in the drug/cyclodextrin complex formation (Loftsson and Brewster, 1996). No covalent bonds are involved in the complex formation and drug molecules located within the cavity are in a very dynamic equilibrium with free drug molecules out in the solution. In aqueous solutions drug/cyclodextrin complexes are constantly being formed and broken at rates very close to the diffusion controlled limits (Stella and Rajewski, 1997). Both cyclodextrins and drug/cyclodextrin complexes do possess some surface activity in aqueous solutions and they are known to form loosely connected aggregates or micelles (Szente et al., 1998; Angelova et al., 1999).

Once included in the cyclodextrin cavity, the drug molecules may be released through complex dilution, by replacement of the included drug by some other suitable molecule such as the skin lipids or, if the complex is located in close approximation to a lipophilic biological membrane such as the skin surface, the drug may be transferred to the matrix for which it has the highest affinity.

Various methods have been applied to preparation of cyclodextrin complexes (Hirayama and Uekama, 1987; Hedges, 1998; Loftsson et al., 1999b). In solution, the complexes are usually prepared by addition of an excess amount of the drug to an aqueous cyclodextrin solution. The suspension formed is equilibrated (for periods of up to one week at the desired temperature) and then filtered or centrifuged to form a clear drug/cyclodextrin complex solution. For preparation of the solid complexes, the water is removed from the aqueous drug/cyclodextrin solutions by evaporation or sublimation, e.g. spray drying or freeze-drying. Other methods can also be applied to prepare solid drug/cyclodextrin complexes including kneading and slurry methods, co-precipitation, neutralization, and grinding techniques (Loftsson, 1999).

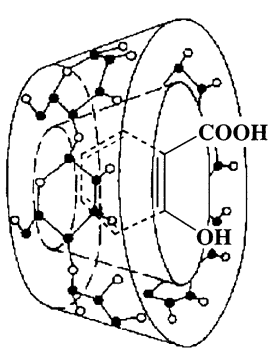


Fig. 1. Schematic drawing of an aspirin/βCD complex.

In some cases the complexation efficiency is not very high, and therefore, relatively large amounts of cyclodextrin are needed to complex small amounts of a given drug. To add to this difficulty, various vehicle constituents, such as surfactants, lipids, organic solvents, buffer salts, and preservatives, often reduce the efficiency. However, it is possible to enhance the efficiency through formation of multicomponent complex systems (Redenti et al., 2000). For example, water-soluble polymers are known to enhance the complexation efficacy of a wide variety of guest molecules, through stabilization of the drug/cyclodextrin complex, and to increase the aqueous solubility of the natural cyclodextrins (Loftsson, 1998).

The toxicological profile of cyclodextrins has recently been reviewed (Irie and Uekama, 1997; Thompson, 1997). In general, orally administered cyclodextrins are practically non-toxic, due to lack of absorption from the gastrointestinal tract. Furthermore, a number of safety evaluations have shown that HPβCD, SBEβCD, MLβCD, γCD and HPγCD appear to be suitable in parenteral as well as oral formulations. However, the lack of available toxicological data will, more than anything else, hamper pharmaceutical applications of cyclodextrins.

## 3. Cyclodextrins as drug penetration enhancers

Cyclodextrin molecules are relatively large (MW ranging from almost 1000–2000) with hydrated outer surface, and under normal condi-

tions, cyclodextrin molecules and their complexes will only permeate lipophilic biomembranes with considerably difficulty. For example, only 0.02% of topically applied radiolabeled HPβCD was absorbed into intact hairless mouse skin under occlusive conditions during a 24-h period but in the same study about 24% of HPβCD was absorbed into stripped skin (Tanaka et al., 1995). Stratum corneum is the main barrier to percutaneous absorption of HPβCD and other cyclodextrins. Penetration enhancers which decrease the barrier properties of stratum corneum will enhance penetration of hydrophilic cyclodextrins into skin (Arima et al., 1990b; Adachi et al., 1993). Lipophilic cyclodextrins, such as DMβCD (heptakis(2,6-di-O-methyl)-βCD) and RMβCD, are probably absorbed to somewhat greater extent into skin, but still the absorption is negligible. For example, in vivo study in rats showed that less than 0.2% of topically applied radiolabeled DMβCD was excreted in the urine and blood samples indicated that only about 0.3% of the dose was absorbed through the skin during the 24-h study period (Gerlóczy et al., 1988). Other biomembranes are slightly more permeable towards cyclodextrins (Irie and Uekama, 1997; Merkus et al., 1999). In one human study 2.5–4% of nasally administered DMβCD was recovered in the urine (Reeuwijk et al., 1993). In rats less than 10% of orally administered DMβCD was absorbed (Szatmári and Vargay, 1988). Other more hydrophilic cyclodextrins are absorbed to a much lesser extent. For example, when the parent cyclodextrins were administered orally at a dose of 500 mg/kg to rats in vivo, the cumulative amounts of intact cyclodextrin excreted into the urine were $1.95 \pm 0.25$, $0.45 \pm 0.12$, and $0.38 \pm 0.16$% of the dose for αCD, βCD, and γCD, respectively (Irie and Uekama, 1997). When radiolabelled HPβCD was administered orally to rats about 3% of the radiolabel was excreted in the urine (Gerlóczy et al., 1990). There were some indications that, due to degradation of radiolabeled HPβCD in the gastrointestinal tract, the reported bioavailability was an overestimation. No intact HPβCD could be detected in the plasma or urine after oral administration of HPβCD to human volunteers (Szathmary et al., 1990). Thus, it is highly unlikely that cyclodextrins act as conventional topically applied chemical penetration enhancers, that is by penetrating into the barrier.

Since the hydrophilic cyclodextrins can only penetrate the intact skin with considerable difficulty, and since cyclodextrin complexes are in a dynamic equilibrium with molecules in their environment, it is generally believed that the hydrated drug/cyclodextrin complexes are unable to permeate lipophilic biological membranes such as skin and the eye cornea (Loftsson and Bodor, 1995; Rajewski and Stella, 1996; Uekama et al., 1998).

Cyclodextrins are able to interact with some lipophilic components of the skin and cornea. For example, pure aqueous buffer solutions of βCD, RMβCD, HPβCD have been shown to be able to extract lipids from the stratum corneum (Legendre et al., 1995; Vitória et al., 1997). Other studies have shown that the natural αCD, βCD, and γCD can cause skin irritation and that this irritation is related to their abilities to extract lipids from the skin (Irie and Uekama, 1997). It is also known that, in a Caco-2 model, lipophilic cyclodextrins, such as DMβCD, do increase permeability of hydrophilic compounds (Hovgaard and Brønsted, 1995; Tötterman et al., 1997). Based on these observations some investigators have suggested that cyclodextrin enhanced drug permeability through biomembranes, such as skin and eye cornea, is due to their ability to extract lipophilic components from the membrane (Duchêne and Wouessidjewe, 1996; Siefert and Keipert, 1997; Vitória et al., 1997). However, other investigators have pointed out that both pre- or post-application of hydrophilic cyclodextrins, under more normal conditions where the skin lipids have to compete with lipophilic vehicle constituents for a space in the cyclodextrin cavity, does not affect the skin barrier (Arima et al., 1996, 1998) and that hydrophilic cyclodextrins do not, in general, enhance the permeability of water-soluble drugs through skin or cornea, at least not under physiological conditions (Loftsson and Stefánsson, 1997; Siefert and Keipert, 1997). In addition, a number of studies using various of biomembrane, under several different experimental conditions, have shown that excess cyclodextrin, i.e. more than

needed to solubilize a given lipophilic drug in an aqueous vehicle, results in decreased drug penetration through the membrane (Loftsson and Sigurdardottir, 1994; Sigurdardottir and Loftsson, 1995; Cho et al., 1995; Kublik et al., 1996; Jarho et al., 1996b; Chang and Banga, 1998; Masson et al., 1999; Loftsson, 2000; Zuo et al., 2000). Cyclodextrins are also able to alleviate local drug irritation after topical application (Amdidouche et al., 1994; Järvinen et al., 1995; Suhonen et al., 1995; Jarho et al., 1996a). Thus although cyclodextrins are able, under some specific conditions, to extract lipophilic components of biological membranes it is highly unlikely that the main mechanism of cyclodextrin enhanced transdermal or transcorneal drug delivery is disruption of the barrier.

Some biomembranes, such as the nasal mucosa, present both physical and metabolic barrier to drug absorption and it is known that cyclodextrin can reduce or prevent enzymatic degradation of drugs (Loftsson and Brewster, 1996; Sigurjonsdottir et al., 1999; Lopez et al., 2000). However, since little or no enzymatic activity exists within the skin barrier (stratum corneum), or at the skin surface, and since cyclodextrins only penetrate the barrier with considerable difficulty, it is highly unlikely that this drug stabilizing property of cyclodextrins will have any significant effect on topical drug delivery to the skin. Tear fluid, on the other hand, contains wide variety of enzymes which can effect topical drug delivery to the eye (Baeyens and Gurny, 1997). These enzymes have been used to activate topically applied ophthalmic prodrugs (Lee and Bundgaard, 1992).

The effect of several different cyclodextrins, i.e. RMβCD, HPβCD, carboxymethyl-βCD (CMβCD) or MLβCD, on the flux of hydrocortisone from aqueous vehicles containing hydrocortisone/cyclodextrin complexes through hairless mouse skin has been investigated (Loftsson and Sigurdardottir, 1994; Sigurdardottir and Loftsson, 1995; Masson et al., 1999). The hydrocortisone concentration was kept constant, but the cyclodextrin concentration was increased from 0 to 25% (w/v). When hydrocortisone was in suspension, an increase in the cyclodextrin concentration resulted in increased hydrocortisone flux through the skin. In contrast, when all hydrocortisone was in solution, an increase in the cyclodextrin concentration led to decrease in the flux. In all cases maximum flux through the hairless mouse skin was obtained when just enough cyclodextrin was added to the vehicle to keep all hydrocortisone in solution (Fig. 2). In pure aqueous cyclodextrin solutions saturated with drug the concentration of free drug is constant and equal to the aqueous solubility of the drug. In pure aqueous solutions which are not saturated with drug the concentration of free drug decreases with increasing cyclodextrin concentration. It is apparent that there is no direct relationship between either the amount of free drug concentration (Fig. 2A) or the total amount of drug in the aqueous vehicle (Fig. 2B) and the drug flux through skin. Similar

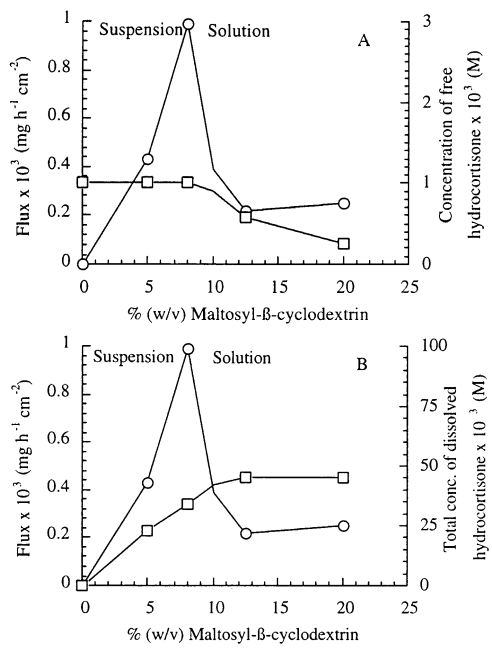


Fig. 2. The effect of the maltosyl-β-cyclodextrin (MLβCD) concentration on the flux (○) of hydrocortisone through hairless mouse skin. The hydrocortisone concentration was kept constant at 0.045 M. (A): the flux in relation to the amount of free hydrocortisone (□) in the donor phase; (B): the flux in relation to the total amount of dissolved hydrocortisone (□) in the donor phase. The donor phase consisted of aqueous hydrocortisone suspension at MLβCD concentrations below 8% (w/v) but hydrocortisone solution at higher MLβCD concentrations. (Sigurdardottir and Loftsson, 1995).

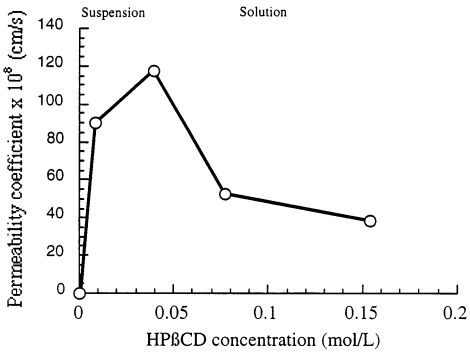


Fig. 3. Permeability of arachidonylethanolamide through isolated rabbit cornea as a function of HPβCD concentration. The vehicle consisted of 0.5 mg/ml suspension or solution of the drug in water containing 0–1.155 M HPβCD. (Jarho et al., 1996b).

observations were made when the effect of HPβCD concentration on the in vitro corneal permeability of arachidonylethanolamide was investigated (Jarho et al., 1996b). Maximum corneal permeability was observed when just enough cyclodextrin was added to dissolve the drug in the aqueous vehicle (Fig. 3).

## 4. Theoretical considerations

In general, drugs permeate biomembranes, such as skin and the eye cornea, by passive diffusion. Under such conditions there is a net flux of drug molecules from a donor phase, trough the membrane, to the receptor phase (Fig. 4). According to Fick's first law the driving force for the diffusion is the concentration gradient (or more correctly, the chemical potential gradient) of drug molecules across the membrane (Eq. (1)):

$$J = \frac{K_{(m/d)} D_m}{h_m} \Delta[D], \quad (1)$$

where $J$ is the drug flux across the membrane, $K_{(m/d)}$ is the drug partition coefficient between donor phase and membrane, $D_m$ is the drug diffusion coefficient within the membrane, $\Delta[D]$ is the difference in drug concentration between the donor phase ($[D]_d$) and the receptor side of the membrane, and $h_m$ is the thickness of the membrane.

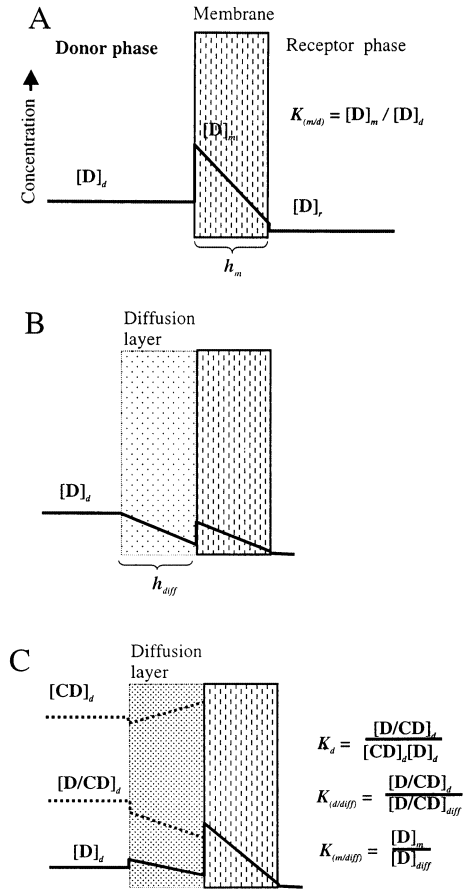


Fig. 4. Schematic representations of steady-state permeability of a drug through a membrane. (A): The drug flux through a membrane when the drug concentration at the membrane surface is the same as in the bulk of the donor phase. In this case Eq. (1) or Eq. (2) will apply. (B): The drug flux through a membrane when a diffusion layer exists at the membrane surface. Here the properties of the diffusion layer are the same as those of the donor phase. Eq. (3) will apply. (C): The drug flux from an aqueous donor phase when the drug is in a cyclodextrin complex. The properties of the diffusion layer can be different from those of the donor phase. Eq. (4) will apply.

Under in vivo conditions the drug concentration in the receptor phase ($[D]_r$), e.g. the blood stream, aqueous humor in the eye, or fat tissue, will generally be much lower than the drug concentration in the donor phase. Eq. (2) will apply under such sink conditions ($\Delta[D] \approx [D]_d$), but only if the membrane is fully uniform:

$$J = \frac{K_{(m/d)} D_m}{h_m} [D]_d. \quad (2)$$

Eq. (2) applies when $[D]_d >> [D]_r$ (i.e. under sink conditions) and when the membrane is fully uniform. Examples of such uniform membranes are artificial membranes used for drug release studies (Moeckly and Matheson, 1991; Pefile et al., 1998). Biological membranes, such as skin and cornea, are not uniform membranes. The skin consists of three main layers: stratum corneum, viable epidermis and dermis. However, since in dermal drug delivery the main diffusion barrier, is the outermost layer of the skin, stratum corneum, Eq. (2) will apply under most experimental conditions.

Several mathematical models have been developed to explain transdermal drug delivery (Potts and Guy, 1991; Lien and Gao, 1994; Cronin et al., 1999; Edwards and Langer, 1999; Smith and Surber, 1999). In these models the drug permeability is to some extent proportional to lipophilicity of the drug but inverse proportional to the molecular weight or molecular volume of the drug. Thus it is assumed that the drug permeability is primarily stratum cornea lipid lamella limited transport (Potts and Guy, 1995). $K_{(m/d)}$ increases with increasing lipophilicity of the drug and $D_m$ will decrease with increasing molecular weight. Other models have also accounted for possible drug transport through aqueous routes in appendages, such as hair follicles and sweat ducts (Edwards and Langer, 1999).

These mathematical models do not take into the account the donor phase composition. In praxis drug permeability is highly dependent on the physicochemical properties of the drug vehicle, i.e. donor phase. Frequently, the drug vehicle contains some permeation enhancers. Conventional enhancers will affect lipid structure of the stratum corneum and, thus, both drug partition into stratum corneaum and drug diffusitivity in the stratum corneum will be affected (Smith and Maibach, 1995b; Kirjavainen et al., 1999; Fujii et al., 2000). Excipients commonly used in topical vehicles, such as propylene glycol and ethanol, can be absorbed into the membrane where they act as chemical permeation enhancers (Berner and Liu, 1995). The chemical potential of the drug in the donor phase will also affect drug permeability through the membrane. If the barrier function of a membrane is unaffected by the donor phase composition the permeability will increase with increasing chemical potential. The value of $K_{m/d}$ is at its maximum when the chemical potential of the drug in the donor phase is at its maximum and then the drug molecules will have maximum tendency to leave the donor phase and go into the membrane. This is the situation when the donor phase is saturated by the drug. Consequently, if the drug concentration is constant the transmembrane flux should decrease with increasing drug solubility in the donor phase. However, if the drug diffusivity within the membrane is very high or if the drug concentration in the donor phase is low then a diffusion barrier will be formed in the donor phase (Flynn and Yalkowsky, 1972; Lee and Lippold, 1998). Close to the membrane surface a thin diffusion layer will be formed where the donor phase drug concentration decreases towards the membrane surface (Fig. 4B). Under such conditions the flux will depend on the diffusion constant of the drug in the donor phase ($D_{diff}$), thickness of the diffusion layer ($h_{diff}$) and properties of the membrane (Eq. (3)):

$$J = \frac{K_{(m/d)} D_m D_{diff}}{h_m D_{diff} + h_{diff} K_{(m/d)} D_m} [D]_d. \quad (3)$$

Addition of cyclodextrins to an aqueous vehicle will often result in increased solubility of lipophilic drugs, without any major effect on biological membranes. In aqueous drug solutions, when the drug concentration is constant and below saturation, transdermal (Loftsson et al., 1995; Sigurdardottir and Loftsson, 1995) and transcorneal (Jarho et al., 1996b) flux will decrease with increasing cyclodextrin concentration (Figs. 2 and 3). Thus flux will decrease as the chemical potential of the drug decreases. In saturated solutions the chemical potential is constant. The flux from an aqueous vehicle, which is saturated with the drug, will increase with increasing cyclodextrin concentration if the drug is solublized by cyclodextrin (Figs. 2 and 3).

The former observation would be consistent with conditions as shown in (Fig. 4A). However the latter observation can only be explained by

postulating an aqueous diffusion barrier. Under such conditions the drug flux through the aqueous barrier will increase as the total concentration of drug, i. e. concentration of free drug and drug in cyclodextrin complex, increases.

Eq. (4) describes the flux of lipophilic water-insoluble drugs from aqueous cyclodextrin solution through a membrane (Masson et al., 1999). When the donor phase does not contain any cyclodextrin the solubility of the drug in the donor phase is negligible. Drug flux from such donor phase through the membrane can therefore be ignored from the equation. The transmembrane flux will then depend on four parameters: a constant ($P_m/K_d$) which is the membrane permeability divided by the stability constant of the drug/cyclodextrin complex in the donor phase, a constant ($M_{\frac{1}{2}}$) which is equal to the cyclodextrin concentration in the donor phase when the flux is half the maximum flux, the cyclodextrin concentration in the donor phase ($[CD]_d$) and the concentration of the complex in the donor phase ($[D/CD]$). Experimental data for the flux of hydrocortisone through hairless mouse skin has been fitted to this equation (Masson et al., 1999).

$$J = \frac{D_m K_{(m/diff)} D_{diff} K_{(d/diff)} [D/CD]}{D_m K_{(m/diff)} h_{diff} + D_{diff} K_{(d/diff)} K_d h_m [CD]} = \frac{(P_m/K_d)[D/CD]}{M_{1/2} + [CD]}. \quad (4)$$

Drug can be absorbed into the skin by aqueous pathway through hair follicles, sweat duct (Illel et al., 1991; Meidan et al., 1998) or intracellular aqueous pores in the stratum corneum (Li et al., 1998; Sznitowska et al., 1998). Furthermore, there is some evidence of drug transport through aqueous pores in the cornea (Hamalainene et al., 2000). A kinetic barrier to drug transport can also be present at the interface between aqueous phase and a lipophilic phase (Guy and Honda, 1984). Cyclodextrin complexation can increase drug flux through such aqueous pores (Preiss et al., 1994) or barriers. Eq. (4) can then be used to describe the net flux of a drug from the aqueous vehicle through the membrane.

## 5. The vehicle effects

Since cyclodextrins enhance topical drug bioavailability by affecting the diffusion process at the aqueous barrier exterior, cyclodextrins should not have penetration enhancing effect in a non-aqueous environment. Furthermore, based on this theory diffusion controlled drug release rate from non-aqueous vehicles will be unaffected or even hampered by cyclodextrins. There are relatively few reports on the effects of cyclodextrins on drug release from non-aqueous vehicles. Uekama and coworkers have investigated the effects of vehicle composition on the in vitro release rate of corticosteroids (Uekama et al., 1998). They have concluded that the release rate from water-containing ointments is markedly increased by hydrophilic cyclodextrins, whereas in other ointments (fatty alcohol, propylene glycol or macrogol base) the same cyclodextrins retard drug release. For example, in hydrophilic ointments HPβCD increased the flux of ethyl 4-biphenylyl acetate through hairless mouse skin but decreased the flux from non-aqueous propylene glycol based vehicle (Arima et al., 1998). In another study both βCD and HPβCD reduced the amount of hydrocortisone, which was released from petrolatum-based vehicle or w/o cream (water-in-oil emulsion) formulations but enhanced the release from both o/w cream (oil-in-water emulsion) and hydrogel formulation (Preiss et al., 1994). Both cyclodextrins enhanced hydrocortisone permeability from o/w cream and hydrogel into the dermis of excised human skin but reduced the permeability from the non-aqueous petrolatum based vehicle (Preiss et al., 1995). These observations are in agreement with the proposed mechanism of cyclodextrin-enhanced permeability.

In a diffusion controlled model the concentration gradient of dissolved drug over the diffusion layer is the main driving force for the drug delivery to the surface of the barrier. The availability of dissolved drug in the aqueous vehicle is crucial for effective drug delivery. Thus, for maximum delivery the drug/cyclodextrin complex must be solubilized in the aqueous vehicle. For example, the permeability of ethyl 4-biphenylyl acetate from hydrophilic ointment through rat skin in

vivo was enhanced by cyclodextrin complexation in the order of βCD < DMβCD ≤ HPβCD (Arima et al., 1990c). The improvement could be correlated with the improved solubility, but not with the observed decrease in diffusivity upon complexation of the drug. In other words, the concentration gradient over the diffusion layer was more important than the size of the diffusing species. Hydrophilic βCD derivatives, such as HPβCD, do form more water-soluble complexes and, thus give frequently better enhancement than the parent βCD. However, as previously mentioned excess cyclodextrin, more than needed to solubilize the lipophilic drug in the vehicle, will decrease the drug availability in the aqueous vehicle. Methods that solubilize drug/CD complexes will improve drug availability in βCD containing vehicles (Loftsson et al., 1999a). For example, hydrophilic polymers are known to be able to solubilize βCD and its complexes (Loftsson and Friðriksdóttir, 1998). Thus, enhanced drug availability in βCD containing o/w cream formulations can be obtained by including hydrophilic polymers in the complexation medium during preparation of the drug/βCD complexes (Fig. 5).

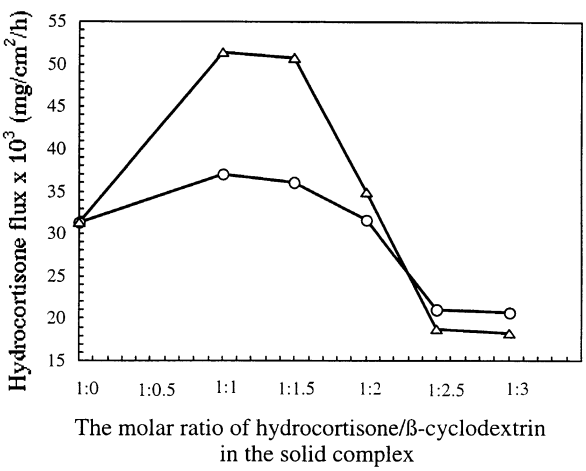


Fig. 5. The effect of the hydrocortisone/βCD molar ratio on the hydrocortisone release from o/w cream through a semipermeable cellophane membrane. The hydrocortisone concentration was kept constant at 2.8 mg/ml but the βCD concentration was varied. (○): no polymer was added to the complexation media when the complex powder was prepared; (△): 0.25% (w/v) sodium carboxymethylcellulose was present in the aqueous complexation media during preparation of the complex powder. (Loftsson, 1999).

Cyclodextrins enhance drug permeability by increasing drug availability at the barrier exterior. Conventional penetration enhancers enhance drug permeability by causing some physicochemical changes within the barrier. Thus, combining cyclodextrins with the conventional enhancers should result in an additive effect. This is exactly what has been observed. Unsaturated glycerol monoether extract from shark-liver-oil consists of a mixture of saturated and unsaturated fatty alcohol ethers of glycerol, which enhance drug permeability through biological membranes by penetrating into the membranes where the acids change the barrier structure (Loftsson et al., 1997). In one study the effects of both HPβCD and a glycerol monoether extract on transdermal delivery of testosterone, from o/w cream through hairless mouse skin, was investigated (Loftsson et al., 1998). About 60% increase in the testosterone flux was observed when HPβCD was added to the cream, about 40% increase was observed when the extract was added to the cream but about 80% increase in the flux was observed when both HPβCD and the extract were added to the cream. A comparable effect was observed when the conventional penetration enhancer HPE-101 (1-[2-(decylthio)-ethyl]azacyclopentane-2-one) and CMβCD were used to enhance transdermal delivery of prostaglandin $E_1$, although it this case CMβCD also enhanced dermal delivery of the lipophilic penetration enhancer HPE-101 (Adachi et al., 1992, 1993). Also in iontophoresis hydrophilic cyclodextrins such as HPβCD have synergistic effect on the transdermal delivery of lipophilic water-insoluble drugs (Chang and Banga, 1998).

Finally, it has been suggested that cyclodextrins deliver drugs preferably via the skin appendages (Preiss et al., 1995). This proposed diffusion route would be in agreement with the aqueous diffusion layer model and, if proven to be correct, would give opportunity for a site-specific drug delivery within the skin. However, this transappendageal route of cyclodextrin enhanced drug delivery has to be studied further.

## 6. Conclusion

In general, cyclodextrins can only enhance topical drug delivery in the presence of water. Cyclodextrins solubilize lipophilic water-insoluble drugs in the aqueous vehicle systems and deliver the drug molecules to the barrier surface. At the surface the drug molecules partition from the cyclodextrin cavity into the lipophilic barrier. Thus, drug delivery from aqueous cyclodextrin solutions is both diffusion controlled and membrane controlled. Only insignificant amounts of the hydrated cyclodextrin molecules and drug/cyclodextrin complexes are able to penetrate into the lipophilic biological barriers, such as intact skin.

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