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The Effect of Cyclodextrin on the Action of Drugs and Their Release in the Body

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Abstract

In some cases, in order to overcome the immune mechanisms or faster drug absorption, various routes are considered for drug administration. Regarding the physicochemical properties of many drugs, it is possible that they interact with certain molecules in the body and cause severe toxicity. On the other hand, degradation by enzymes, drug uptake by macrophages and performance reduction are among the factors that can design a unique route for drug administration. Also, the application of many useful pharmaceutical formulations is faced with restrictions due to some undesirable properties such as insolubility, poor physiochemical properties, toxicity, allergy and inflammation after administration. Since a drug redesigning process is a time-consuming, costly and complex process, attempts are being made to establish connections and interactions between drug molecules and specific carriers of bio-materials so that it reduces the undesirable properties of these molecules. Oligo-/polysaccharides such as Cyclodextrins (CDs) are promising biomaterials possessing the multi-functions and high safety and used as targeting ligands, pharmaceutical excipients, gelatinizers, etc. in the pharmaceutical fields. Regarding the hydrophilic property of the outer surface and the hydrophobic property of the inner surface, the application of cyclodextrins to create complex Drug/CDs can lead to a huge development in targeted delivery of many drugs from different administration routes. In general, increased solubility, stability, safety and bioavailability of drug molecules are among the most common applications of CDs.

Keywords: Cyclodextrin; Drug Delivery; Complex Drug/CDs; Drug Administration

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1. Introduction

Recently, active pharmaceutical ingredients (APIs) have been extending from low molecular weight compounds to proteins or nucleic acids. As a result, advanced pharmaceutical techniques are required to develop the drugs including proteins or nucleic acids. For instance, improvements of solubility, stability, and/or blood retention are required to develop protein drugs. In the case of nucleic acids, improvements of their transfer efficiencies to target tissues and cells are necessary. To achieve these techniques, various biomaterials such as polymers, sugars, liposome, micelle, and nanosphere are utilized. Oligo-/polysaccharides such as Cyclodextrins (CDs) are promising biomaterials possessing the multi-functions and high safety and used as targeting ligands, pharmaceutical excipients, gelatinizers, etc. in the pharmaceutical fields [1,2].

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The cyclodextrins (CDs) have been known for over 100 years. They were first discovered in 1891 by Villiers, a French scientist. Villiers has named this product "cellulosine" because the substance appeared to be resistant at acid hydrolysis and did not have reducing properties [3]. In the second stage (from 1930s to the 1970s), the structures of α- and β-CDs were first determined by X-ray diffraction in 1942, followed by the γ-CD structure in 1948. At the same time, structures of some inclusion complexes of CDs were determined and in 1961, the natural existence of δ-, ζ-, ξ-, and even η-CD was reported. The first patent in CDs was reported in 1953 (Freundenberg, Cramer, & Plieninger, 1953) and the first fundamental review on CDs and derivatives was published by French (1957). Until the end of the 1960s, the CD structure, physical and chemical properties, methods of preparation, and corresponding inclusion complexes have been investigated in detail by many authors such as Higuchi and Connors, 1965; Cramer, Saenger, & Satz, 1967 [3].

Summarizing the literature until the end of 1960s, CDs were considered to be promising molecules, particularly because of their industrial potential, but they remained as expensive substances (fabrication in small quantities) and their utilization in products for human use questionable because of unknown potential toxic effect. Following the last period from the 1970s until present, after adequate toxicological studies, CDs are today used as successful "new" pharmacological excipients [3]. Every year, CDs are the subject of approximately 1000 additional research articles and abstracts, with a large number in the pharmaceutical branch, and many CDs and derivatives are included in the Handbook of Pharmaceutical Excipients. Considering the price of β-CD, while in 1970 1 kg costed about 2000 euros, today it is only several euros (~400-450 euros) per kilogram. Thus, a large number of CD derivatives are produced industrially and used in the manufacture of drug carriers, cosmetics, or in catalysis, agricultural, and food industries [3].

2. Cyclodextrins

Cyclodextrins (CDs) are cyclic oligosaccharides containing six (α-CD), seven (β-CD) or eight (γ-CD) α-1,4-linked glycopyranose units, with a hydrophilic hydroxyl group on their outer surface and a hydrophobic cavity in the center. Owing to lack of free rotation about the bonds connecting the glucopyranose units, the cyclodextrins are not perfectly cylindrical molecules but are toroidal or cone shaped. Based on the architecture, the primary hydroxyl groups are located on the narrow side of the torus while the secondary hydroxyl groups are located on the wider edge [1, 4-6]. Structure and conformation of natural cyclodextrins shown in Figure 1.

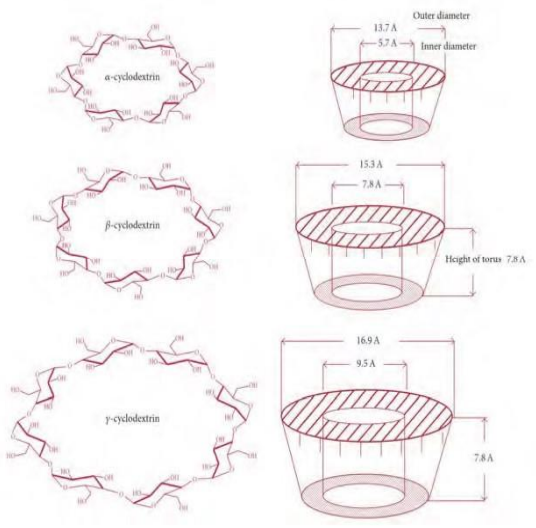

Figure 1. Structure and conformation of natural cyclodextrins[7].

The most common cyclodextrins are α-cyclodextrin(αCD), β-cyclodextrin(βCD) and γ-cyclodextrin(γCD) which consist of six, seven and eight glucopyranose units respectively. But due to steric factors, cyclodextrins having fewer than six glucopyranose units cannot exist, cyclodextrins containing nine, ten, eleven, twelve and thirteen glucopyranose units, which are designated δ-, ε-, ζ-, η- and θ-cyclodextrin, respectively have been reported [4]. The chemical and physical properties of the four most common cyclodextrins are given in Table1[4].

Table 1. Characteristics/properties of CDs [3].

Characteristics	Type of cyclodextrin		
	α-CD	β-CD	γ-CD
Number of glucopyranose units	6	7	8
Molecular weight (g/mol)	972	1135	1297
Solubility in water at 25°C (%, w/w)	145	18.5	233
$[\alpha]_D$ 25°C	150 ± 5	162.5 ± 5	177.4 ± 5
Internal diameter (Å)	4.7–5.3	6.0–6.5	7.5–8.3
External diameter (Å)	14.6	15.4	17.5
Volume of the cavity (Å^3)	174	262	427
Approx. cavity volume in 1 mol CD (mL)	104	157	256
Cristal forms (from water)	Hexagonal plates	Monoclinic parallelograms	Quadratic prisms
Cristal water (wt %)	10.2	13.2–14.5	8.13–17.7
Diffusion constant at 40°C	3.443	3.224	3.000
Hydrolysis by *A. oryzae α-amylase*	Negligible	Slow	Rapid
pK (by potentiometry) at 25°C	12,332	12,202	12,081

CDs are capable of forming inclusion complexes with many drugs by taking up a whole drug molecule, or some part of it, into the cavity [1]. Such molecular encapsulation will affect many of the physicochemical properties of drugs, such as their aqueous solubility and rate of dissolution. Among the various approaches, preparation of inclusion complexes with cyclodextrin have proven to be successful in enhancing the solubility of poorly water soluble drugs I, II [2, 4, 7]. The formation of inclusion complexes with a wide variety of guest molecules is one of the most interesting properties of cyclodextrins. Molecular encapsulation may occur both in solid and in solution state. In solid state, guest molecules can be enclosed within the cavity or may be aggregated to the outside of the cyclodextrin molecule and in solution state; there is equilibrium between complexed and non-complexed guest molecules. A guest molecule experiences changes in the physicochemical properties when it gets incorporated within the cyclodextrin cavity. Changes in the physicochemical properties provide methods to characterize whether guest molecules are really included in the cyclodextrin cavity [4]. Some of cyclodextrin derivatives are shown in Table 2.

Table 2. Some of the cyclodextrin derivatives [8].

Cyclodextrin	Abbreviation	R	n
Carboxymethyl-β-cyclodextrin	CM-β-CD	CH_2C0_2H or H	5
Carboxymethyl-ethyl-β-cyclodextrin	CME-β-CD	CH_2C0_2H, CH_2CH_3 or H	5
Diethyl-β-cyclodextrin	DE-β-CD	CH_2CH_3 or H	5
Dimethyl-β-cyclodextrin	DM-β-CD	CH_3 or H	5
Glucosyl-β-cyclodextrin	G_1-β-CD	Glucosyl or H	5
Hydroxybutenyl-β-cyclodextrin	HBU-β-CD	$CH_2CH(CHCH_2)OH$ or H	5
Hydroxyethyl-β-cyclodextrin	HE-β-CD	CH_2CH_20H or H	5
Hydroxypropyl-β-cyclodextrin	HP-β-CD	$CH_2CHOHCH_3$ or H	5
Hydroxypropyl-γ-cyclodextrin	HP-γ-CD	$CH_2CHOHCH_3$ or H	6
Maltosyl-β-cyclodextrin	G_2-β-CD	Maltosyl or H	5
Methyl-β-cyclodextrin	M-β-CD	CH_3 or H	5
Random methyl-β-cyclodextrin	RM-β-CD	CH_3 or H	5
Sulfobutylether-β-cyclodextrin	SBE-β-CD	$(CH_2)_4S0_3Na$ or H	5

In the cell biology fields, CDs at higher concentration induce hemolysis and decrease the integrity of the mucosal epithelial cells and extract cholesterol, phospholipids, and proteins from biological membranes, which are useful for investigating the function of caveolae, lipid rafts, and cholesterol transporter. However, the interactions between CDs and proteins or nucleic acids are negligible, resulting in a limitation to utilize CDs as drug carriers for these drugs [1]. They

are widely used in the pharmaceutical, food, textile, and home-based consumer products owing to its binding capacity for small molecules with phenyl rings. However, native CDs typically do not form viable complexes with hydrophilic molecules, or macromolecules, and most commonly used CD form β-CD has poor water solubility which limits their complexation abilities. Moreover, β-CD cannot be injected intravenously as they are known to complex with cholesterol, thereby leading to nephrotoxicity. To overcome these potential problems of native CDs, several structural modifications have been explored [6].

3. Drug delivery with Cyclodextrin

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) [9]. Owing to the remarkable ability of CDs to form inclusion complexes with a variety of drug molecules, numerous applications have been developed in the drug delivery field using almost all routes of administration [3]. Equilibrium binding of a drug with a cyclodextrin to form a 1:1 inclusion complex is shown in Figure 2. This section is mainly concerned with applications of cyclodextrins in oral and sublingual, ocular, nasal, dermal, parenteral, rectal and other novel drug delivery systems site-specific drug targeting and nanoparticles [10].

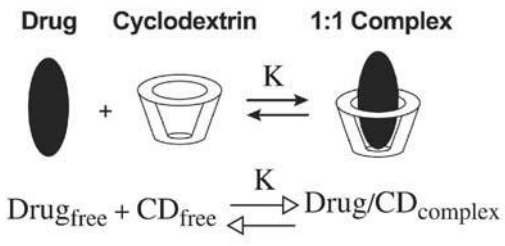

Figure 1. Equilibrium binding of a drug with a cyclodextrin to form a 1:1 inclusion complex [8].

3.1 Oral drug delivery

Applications of CDs in oral drug delivery include improvement of drug bioavailability due to increased drug solubility, improvement of rate and extent of dissolution, and/ or stability of the drug at the absorption site, eg, the gastrointestinal tract (GIT) or in formulation, reduction of drug- induced irritation, and taste masking. CD complexation was found to decrease local drug irritation and also modify the time of drug release during GI transit. CDs enhance the mucosal drug permeability mainly by increasing the free drug availability at the absorptive surface. CD complexation can provide better and uniform absorption of low-soluble drugs with poor and erratic absorption and also enhance the drug activity on oral administration CD complexation increased the anthelmentic activity of albendazole and provided a high plasma concentration of the active metabolite. CD complexation increased the absorption of poorly water-soluble drugs, delivered via buccal or sublingual mucosa. Complexation can also mask the undesirable taste of drugs [11].

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 [9]. At present, oral administration of inclusion complexes of CDs with many poorly water-soluble drugs is possible because of the natural α- and β-CDs, unlike γ-CD (very large cavity) are not hydrolyzed by human saliva [3]. CDs (α-CD, β-CD, γ-CD) and their derivatives [sulfated-α-CD, sulfated-β-CD, carboxymethyl-β-CD (CM-β-CD), and 2-HP-β-CD] have been utilized in oral hygiene products to bind large sized malodorous compounds residing in the mouth (organic acids, amines, amino acids) [3]. The effect of cyclodextrins on oral drug absorption can be explained in the context of the Biopharmaceutics Classification System. The Biopharmaceutics Classification System categorises drugs according to their aqueous solubility and ability to permeate the intestinal mucosa [9, 10].

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 to reduce local drug irritation and increase the rate of drug absorption [9, 10]. 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 [9, 10]. 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 [9,10]. FDA Biopharmaceutics classification system of orally administered drugs is shown in Table 3.

Table 3. FDA Biopharmaceutics classification system of orally administered drugs [9, 10].

FDA class	Drug Properties Aqueous solubility	Permeability	Rate-determining step (RDS) to drug absorption*	Effect of cyclodextrin complexation
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
***RDS of drug delivery from the aqueous exterior into the body.**				

Very important characteristics of CDs and derivatives for oral delivery purposes stems from their ability to modify the bioavailability of drugs by increasing the time period of drug release and the drug dissolution rate whereas at the same time CDs may decrease local GI tract irritation or bitter taste of drugs[3]. Following interactions are possible in order to eliminate the bitter taste [3]:

1) The formation of a "host–guest" complex CD molecule (with bad tasting), impeding its reaction with the taste buds.
2) The interaction of the CDs with the so-called gatekeeper proteins localized in the taste bud paralyzing them.

The relative safety, efficacy in terms of complexation, cost, and acceptance in pharmacopeias are some important factors to be considered in selecting a CD for drug complexation [11].

Sublingual drug delivery is one of the most efficient ways to bypass hepatic first-pass metabolism. 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 [9,10]. In case of lipophilic compounds, the aqueous solubility and dissolution rate of a drug is usually the rate-limiting step for drug absorption. The increased bioavailabilities achieved by cyclodextrins are due to the increased aqueous solubility and drug resolution rate. In addition to this, they also act as conventional penetration enhancers. There are some basic differences between sublingual and oral administration of cyclodextrin containing formulation. The drug must be released from the inclusion complex before it can be absorbed. This can be a problem for sublingual application due to the small volume of aqueous saliva and the relatively short residence time. The dissolved drug is removed from the buccal area within few minutes after administration, therefore not allowing enough time for the drug to be released from cyclodextrin complex. One limitation in the use of cyclodextrin in sublingual administration is the effect of cyclodextrins on formulation bulk [9,10]. Some examples of the use of CDs in oral delivery is shown in Table 4.

Table 4. Some examples of the use of CDs in oral delivery [3, 9-11].

CD derivatives	Active molecules	Drugs
α-CD	Peptides	-
β-CD	Nicotine Polyphenols and chlorogenic acid Peptides Flavonoid dioclein Cilostazol Flurbiprofen Gefitinib Piroxicam Efavirenz	Ketoprofen Griseofulvin Terfenadine Tolbutamide Piroxicam (Class I) Glibenclamide (Class II) Spironolactone (Class II) Acyclovir (Class III)
γ- CD	Peptides Cilostazol	Digoxin (Class II) Spironolactone (Class II)
CM-β-CD	Lactic acid and succinic acid	-
HP-β-CD	Peptides Triclosan Cilostazol Efavirenz Andragrapholide Gefitinib Diclofenac Paclitaxel	Albendazole Ketoprofen Phenytoin (Class II) Gliclazide Tolbutamide (Class II) Amylobarbitone Flutamide Rutin Clomipramine Testosterone Miconazole (Class II) Spironolactone (Class II) Diphenhydramine HCl (Class III) Danazole Flutamide
DM-β-CD	Peptides Cilostazol	Tacrolimus Diphenhydramine HCl (Class III) Cyclosporin A (Class IV) α-Tocopherylnicotinate (Class II) Spironolactone (Class II) Carbamazepine (Class II)
ME-β-CD	-	Phenytoin
M-β-CD	-	Albendazole
SBE7–β-CD		Spiranolactone (Class II) Danazole Glibenclamide (Class II)
E-βCD	-	Phenytoin (Class II)
GluβCD	-	Phenytoin (Class II)
MalβCD	-	Phenytoin (Class II)

3.2 Ocular 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 water soluble to be able to penetrate this aqueous diffusion barrier to reach the corneal surface. 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 [9]. In the ophthalmology field, drug formulations are gener- ally applied to the surface of the eye for two purposes: (1) to provide intraocular treatment throughout the cornea for diseases like glaucoma and (2) to treat

the outside of the eye for infections (conjunctivitis, blepharitis, keratitis sicca). Eye-drops are the conventional drug dosage forms for 90% of currently used ophthalmic formulations [3].

The possible advantages in ocular use of cyclodextrins are the increase in solubility and stability and avoidance of incompatibilities of drugs such as irritation and discomfort. One of the pre requisites for a new vehicle to be used in ophthalmic preparations is that it is not irritating to the ocular surface, because irritation causes reflex tearing and blinking, which results in a fast washout of the instilled drug. Hydrophilic cyclodextrins, especially 2-hydroxy propyl-βcyclodextrin and sulfo butyl β-cyclodextrin, have been shown to be nontoxic to the eye and are well tolerated in aqueous eye drop formulations [10, 11]. Since only the free drug can permeate biological membranes, ophthalmic delivery of drugs can be limited by the dissociation of drug/CD complexes in the precorneal area due to the limited dilution in this area. The dissociation of drug/CD complexes depends more on the binding of drugs to precorneal proteins, absorption by corneal tissue, and displacement of drugs from CD complexes by precorneal fluid components. The ability of CDs to decrease membrane lipophilicity by interacting with the lipophilic compounds of epithelium was indicated by the reduction in the bioavailability of highly lipophilic pilocarpine prodrugs on addition of CDs [3, 11].

Another major problem with eye drops is its inability to sustain high local concentration of drugs. The administration of ophthalmic drugs in gels and in polymer matrix has been shown to increase the contact time of the drugs with the cornea, a situation which increases their ocular bioavailability. However, patient acceptance of such delivery systems is unsatisfactory. Conversely, eye drops with low viscosity appears to be the most acceptable delivery form of ophthalmic drugs. Hydrophilic cyclodextrins do not penetrate tight biological barriers such as the eye cornea but enhance the ocular bioavailability of lipophilic drugs by keeping the drugs in solution and increasing their availability at the surface of the corneal barrier. The cyclodextrin increases the dose to solubility ratio of water soluble drugs [10]. In this context, CDs may represent an alternative approach to increase the solubility and corneal permeability of drugs. Indeed, the inclusion complexes of ophthalmic drugs with CDs were found to increase the drug aqueous solubility without affecting their chemical structure and/or activity. Consequently, CDs may be useful in the formulation of ophthalmic suspension by complexation with a large number of ophthalmic drugs [3, 9]. Some examples of the use of CDs in ocular delivery is shown in Table 5.

Table 5: Some examples of the use of CDs in ocular delivery[3, 11].

CD derivatives	Drugs
α-CD	Acetazolamide Cyclosporine Pilocarpine
β-CD	Pilocarpine
HP-β-CD	Acetazolamide Hydrocortisone Dipiverfrin Arachidonylethanolamide Dexamethasone Dexamethasone acetate Diclofenac Ethoxyzolamide Pilocarpine Pilocarpine prodrugs
SBE-β-CD	Dipiverfrin Pilocaprine
M-β-CD	Diclofenac Ethoxyzolamide

3.3 Nasal Drug Delivery

CDs are effective excipients in nasal drug delivery. CDs improve nasal drug absorption either by increasing aqueous drug solubility and/or by enhancing nasal drug permeability [11]. The nasal route is another effective way to bypass first-pass metabolism. 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. The lipophilic cyclodextrins acts as penetration enhancers, especially in nasal delivery of peptides. The methylated cyclodextrin derivatives increase the bioavailability [3, 9, 10]. Application of CD solution directly onto the mucosa (nasal, buccal) is regarded as safe for hydrophilic and natural CDs in a wide range of concentrations while for methylated CD derivatives, the application time and the concentration should be controlled [3].

Nasal preparations must be critically evaluated for their possible effect on the nasal mucociliary functions, which are known to defend the respiratory tract against dust, allergens and bacteria. Most of the cyclodextrins are removed from the cavity by the nasal mucociliary system, that transport cyclodextrins to esophagus and to the gastro intestinal tract finally. The local toxicity of cyclodextrins after nasal administration is very low. In the case of the nasal preparations containing the complexes of steroids with cyclodextrins, the effects of the cyclodextrins on the nasal epithelial membranes seem to be of minor importance for absorption enhancement, because the cyclodextrins would lose their abilities to interact with the membranes when their cavities are

occupied by steroids [3, 10]. In conclusion, CDs may improve the drug bioavailability and help bypassing the nasal barrier [3].

3.4 Dermal drug delivery

Dermal drug delivery has gained popularity in the past decade. Many drugs have been successfully formulated by this route. The transdermal drug transport and release is restricted by the stratum corneum which represents the main barrier toward the administration of active compounds by this route. Therefore, many methods to increase drug absorption have been tested[3]. Four different approaches have been proposed to enhance drug delivery through the skin[3]:

1) Enhancement in the release of drugs from the transdermal pharmaceutical preparation bases.
2) Improvement of drug retention in the skin or of the flux of drug through the skin.
3) Increase in the tissue targeting (localized drug delivery).
4) A combination of (1), (2), and (3).

The main barrier for dermal drug absorption through the skin is the outer most layer stratum corneum. Penetration enhancers like alcohols, fatty acids etc. are used to decrease its barrier properties [9, 10]. Cyclodextrins have a significant safety margin in dermal application and can be used to optimize the transdermal delivery of drugs intended either for local or systemic use. They also improves the solubility and stability of drugs in the topical preparations, enhances the transdermal absorption of drugs, sustains the drug release from the vehicle and avoids undesirable side effects associated with dermally applied drugs [10]. CDs, by enhancing apparent drug solubility, enhance the drug thermodynamic activity in vehicles and thus cause enhancement of drug release from vehicles. The enhancement of drug release from vehicles by CDs in turn enhances the dermal drug absorption by improving the drug availability at the lipophilic absorptive barrier surface (ie, skin). Although the drug partition coefficient (eg, a lipophilic drug) may be decreased on complexation with CDs (eg, with hydrophilic CDs), the increased drug solubility and thermodynamic activity in vehicles can lead to increased drug permeability through skin, eg, increased skin permeability of dexamethasone by HP-β-CD [11]. The cyclodextrins enhance drug delivery through aqueous diffusion barriers, but not through lipophilic barriers like stratum corneum. A suitable vehicle must be selected so that cyclodextrins fully exert their functions [10, 11]. If the drug release is from an aqueous based vehicle or if an aqueous diffusion layer at outer surface of skin is a rate determining factor, then cyclodextrins can acts as penetration enhancers. But if drug penetration through the lipophilic stratum corneum is the main rate determining factor then cyclodextrins are unable to enhance the drug delivery [3, 10]. Hydrophilic CDs improve the release rate of lipophilic drugs from hydrophilic aqueous vehicles [11]. The enhancement of drug release can be ascribed to an increase in solubility, diffusibility and concentration of the drug in the aqueous phase of the ointment through water-soluble complex formation [3, 10]. also, the free drug fraction at the barrier surface depends on the drug dissolution rate, relative magnitude of the stability constants of the CD complexes with the drug and the competing agent at the absorption site, and the drug absorption rate constant [11]. In ointments, as with suppositories, the drug in its cyclodextrin complex may be displaced by some components of the ointment, depending on the magnitude of the stability constant of the complex. Thus, an optimized release of the drug from the preparation containing its cyclodextrin complex may be obtained by using a vehicle in which the complex is barely dissociated and maintains a high thermodynamic activity. Generally, cyclodextrins do not enhance drug delivery from non-aqueous vehicles [3, 10].

Briefly CDs, by increasing solubility, facilitate drug incorporation into formulation and thus increase the drug concentration in the formulation. CDs may alleviate drug-induced skin irritation by lowering the extent of free drug resulting from inclusion equilibrium. Hydrophobic CDs can modulate drug release from vehicles. Though only insignificant amounts of CDs and drug/CD complexes can penetrate into biological barriers because of their size and hydrophilicity, CDs may interact with some of the skin components. It was reported that the free CDs released on complex dissociation, due to their ability to remove some membrane surface components, can modify the membrane transport properties and thus can facilitate absorption of drugs, especially water-soluble drugs. CDs, the safer solubilizing agents with bioadaptability and multifunctional characteristics, have been evaluated for formulation of poorly water-soluble cosmetic materials. Other CD applications in cosmetics include masking of smell and stench, stabilization of cosmetic materials (eg, loyal jelly and antiplasmin drugs), assisting in preparation of stable emulsion and suspension, inhibition of foaming caused by amphiphilic materials, and powderization of oily materials. The ability of CDs to increase stability (against light and oxygen) and solubility of sparingly water-soluble molecules made them useful in the formulation of cosmetic products [11].

3.5 Parenteral Drug Delivery

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. Sometimes it is possible to alleviate these side effects by designing a water-soluble prodrug of the lipophilic water insoluble drug [9]. CD derivatives such as amorphous HP-β- and SBE-β-CDs have been widely investigated for parenteral use on account of their high aqueous solubility and minimal toxicity. HP-β-CD with much higher aqueous solubility allows parenteral administration of various drugs with no significant toxicity problems and hence is more often used in parenteral formulations. Applications of CDs in parenteral delivery are solubilization of drugs, reduction of drug irritation at the site of administration, and stabilization of drugs unstable in the aqueous environment [11]. 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. However, because cyclodextrins are rapidly eliminated in the urine cyclodextrins can increase renal clearance of lipophilic water-insoluble drugs. 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 [9].

3.6 Rectal drug delivery

Rectal drug delivery stands for a very important system for a large number of patients, for example, children, infants, patients with nausea, swallowing, or vomiting. However, the main problems encountered in the administration of drugs by rectal route are generally considered to be the following ones[3]:

1) the majority of drugs are poorly absorbed through the rectal mucosa,
2) restrictive absorbing surface area,
3) inefficient dissolution due to the small fluid present in the rectum,
4) drug metabolism into the rectal mucosa and microorganisms.

In order to overcome these disadvantages, many studies have been conducted consisting in the use of absorption enhancers, mixed micelle and polymers, surfactants, etc. However, the most important factor in rectal absorption is the release and the stabilizing effects of drugs from suppository bases, which inhibits the bioconversion of drugs in the rectum [3].

Applications of CDs in rectal delivery include enhancing drug absorption from a suppository base either by enhancing drug release from the base or by increasing drug mucosal permeability, increasing drug stability in the base or at the absorption site, providing sustained drug release, and alleviating drug-induced irritation. Drug release from the suppository base is important in rectal absorption because of the high viscosity of rectal fluids [11]. The release of drugs from suppository bases is one of the important factors in the rectal absorption of the drugs, since the rectal fluid is small in volume and viscous compared to gastrointestinal fluid. In general, hydrophilic cyclodextrins enhance the release of poorly water-soluble drugs from oleaginous suppository bases because of the lesser interaction of the resultant complexes with the vehicles. The complexation of lipophilic drugs with hydrophilic cyclodextrins makes them insoluble in hydrophobic vehicles, the complex existing as well-dispersed fine particles in the vehicles. This manipulation not only enhances drug dissolution at an interface between the molten bases and the surrounding fluid but also inhibits the reverse diffusion of the drugs into the vehicles [10]. The CD complex, once released from the base, mostly releases the free drug for absorption. The competing sites for the free drug released at the absorption site are CD cavity, suppository base, and the rectal mucosa. The extent of drug diffusion into these sites depends on drug's partition coefficient, magnitude of the stability constant of the drug/CD complex, and the relative lipophilicity of the competing sites. In the case of lipophilic drugs with a high partition coefficient, there might be some back diffusion of the released free drug into the lipophilic base. Since a part of drug may get absorbed as the CD complex, the partition coefficient of the complex also becomes important, eg, rectal absorption of a part of EBA as HP-β-CD complex [11].

4. Conclusion

The application of many useful pharmaceutical formulations is faced with restrictions due to some undesirable properties such as insolubility, poor physiochemical properties, toxicity, allergy and inflammation after administration. Since cyclodextrins are found to extend the performance of drug molecules, drug encapsulation in CDs can reduce many undesirable properties of the drugs. In this paper, a study was conducted on some of the applications of natural and synthetic cyclodextrins in drug delivery via different routes of administration including ocular, inhaler, injection, oral, dermal and anal administration methods.

It seems that a wide range of applications in various fields of drug delivery can be performed using CDs due to their ability to create a complex with a large

number of pharmacological agents. Studies on humans and animals have shown that CDs could be used to improve drug delivery to almost any type of pharmaceutical formulation. In general, increased solubility, stability, safety and bioavailability of drug molecules is considered one of the most common applications of CDs.

Through creating an appropriate interaction with poorly soluble drugs, CDs increase their solubility. This phenomenon is based on CDs ability to encapsulate drugs inside them and the formation of a dynamic and non-covalent complex. Other features of CDs in improving the solubility include their ability to form and stabilize supersaturated medicinal solutions. An increased solubility often leads to an increase in the dissolution rate. This helps improve oral bioavailability of many drugs. Another feature of CDs is its ability to camouflage the undesirable physical properties of drug molecules.

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