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Review

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Cyclodextrins as Drug Carrier Molecule: A Review

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Abstract

The cyclodextrins have a wide range of applications in different areas of drug delivery and pharmaceutical industry due to their complexation ability and other versatile characteristics. The most common pharmaceutical application of cyclodextrin is to enhance the solubility, stability, safety and bioavailability of drug molecules. The purpose of this review is to discuss and summarize some of the findings and applications of cyclodextrin (CD) and their derivatives in different areas of drug delivery. This article highlights the molecular structure, properties like complexation, solubility etc. of cyclodextrins and focuses on its use for parenteral, oral, ophthalmic and nasal drug delivery. Other routes including dermal, rectal, sublingual and pulmonary delivery are also briefly addressed. The objective of this contribution is to focus on the potential use of chemically modified cyclodextrins as high-performance drug carriers in drug delivery systems with emphasis on the more recent developments. Thus cyclodextrins, because of their continuing ability to find several novel applications in drug delivery, are expected to solve many problems associated with the delivery of different novel drugs through different delivery routes.

Keywords

Cyclodextrins • Drug formulation • Drug delivery • Complexation • Novel delivery systems

1. Introduction

To be pharmacologically active, all drugs must possess some degree of aqueous solubility, and most drugs should be lipophilic to permeate the biological membranes via

passive diffusion. The water solubility of any drug is determined by its potency and its type of formulation [1]. If a drug is hydrophilic, the dissolved drug molecule will not partition from the aqueous exterior into a lipophilic bio membrane and then permeate the membrane. High-throughput screening approaches to drug development have led to an increasing number of lipophilic water-insoluble drugs whose clinical usefulness are hampered by their insolubility in water. The effect of cyclodextrin on drug solubility, dissolution, bioavailability, safety, stability and its use as excipients in drug formulation are discussed in this article. Also some focus is given on various factors influencing inclusion complex formation of cyclodextrin [2]. The findings and applications of cyclodextrin (CD) and their derivatives in different areas of drug delivery, particularly in parenteral, oral, ophthalmic, nasal, dermal, rectal, sublingual, pulmonary and other novel drug delivery systems are explained in detail.

2. Cyclodextrin

Cyclodextrins (CD) 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. Cyclodextrins are widely used as "molecular cages" in the pharmaceutical, agrochemical, food and cosmetic industries [3]. In the pharmaceutical industry they are used as complexing agents to increase the aqueous solubility of poorly soluble drugs and to increase their bioavailability and stability [4]. In addition, cyclodextrins can be used to reduce gastrointestinal drug irritation, convert liquid drugs into microcrystalline or amorphous powder, and prevent drug–drug and drug–excipient interactions etc.

2.1 Structure and properties

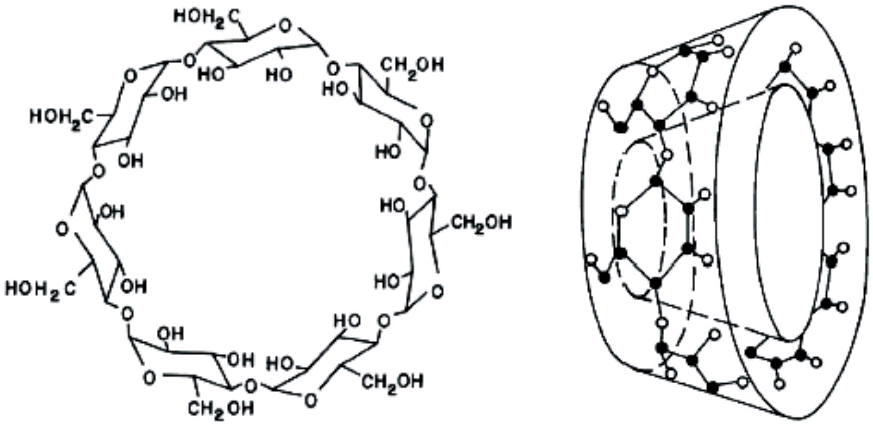

Fig. 1. The chemical structure of β-cyclodextrin molecule

Cyclodextrin consists of (α-1,4)-linked α-D-glucopyranose unit with a lipophilic central cavity and the structures are as shown in fig.1. Due to the chair formation of the glucopyranose units, cyclodextrin molecules are shaped like cones with secondary hydroxyl 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. The naturally occurring cyclodextrins are α, β and γ types containing 6, 7 and 8 glucopyranose units respectively. They have limited aqueous solubility due to the strong intermolecular hydrogen bonding in the crystal state. Substitution of the H-bond forming -OH group has improved their solubility [5]. The various derivatives that have gained pharmaceutical interest include hydroxyl propyl derivatives of β, γ and methylated β-cyclodextrins, sulfo butyl ether β-cyclodextrin etc.

The natural α-CD and β-CD, unlike γ-CD cannot be hydrolyzed by human salivary and pancreatic amylases; though all three are subjected to fermentation by the intestinal micro flora. Hydrophilic cyclodextrins are considered nontoxic at low to moderate oral dosages [6, 7]. The natural cyclodextrin and its 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. The γ-cyclodextrin forms visible aggregates in aqueous solution and is not well suited for parenteral formulations [8]. 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. Presently, oral administration of methylated β-cyclodextrin is limited by its potential toxicity. Some of the pharmaceutically important derivatives of β-cyclodextrin are enumerated in tab.1.

Tab. 1. Pharmaceutical derivatives of β-cyclodextrin

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

2.2 Complex formation and drug solubility of cyclodextrin

In aqueous solutions, cyclodextrins are able to form inclusion complexes with many drugs by taking up the drug molecule or some lipophilic moiety of the molecule, into the central cavity. No covalent bonds are formed or broken during complex formation, and the drug molecules in 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, hydrogen bonding, Vander Waals interaction, charge transfer interaction etc. [9]. The physicochemical properties of free cyclodextrin molecule differ from those in complex. The stoichiometry of the complexes formed and the numerical value of their stability constants can be determined by observing the changes in physicochemical properties like solubility, chemical reactivity, UV/VIS absorbance, drug retention, chemical stability, effects on drug permeability through artificial membranes etc [10]. The formation of the inclusion complex between omeprazole (OME) and methyl-β-cyclodextrin (MβCD) has been studied and the stoichiometry of the complexes was found to be 1:1 mol:mol OME:cyclodextrin and the value of K_s was higher for OME:MβCD than for OME:βCD inclusion complexes [11].

2.3 Phase-solubility diagram

Higuchi and Connors [12] have classified complexes based on their effect on substrate solubility and it is indicated by the phase-solubility profiles as shown in Fig. 2. A-type phase-solubility profiles are obtained when the solubility of the substrate (i.e. drug) increases with increasing ligand (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 profile is 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 profile is obtained. It is difficult to interpret the A_N-type phase-solubility profile. 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. B-type phase-solubility profiles indicate formation of complexes with limited solubility in the aqueous complexation medium.

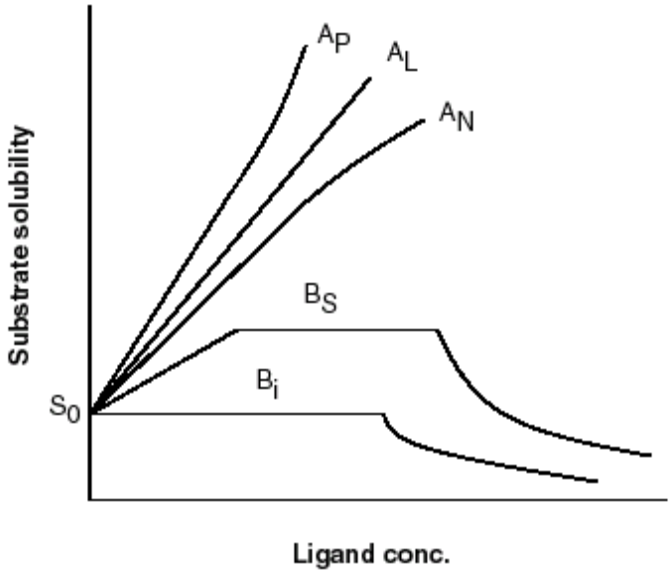

Fig. 2. Phase-solubility profiles

In general, the water-soluble cyclodextrin derivatives form A-type phase solubility profiles, whereas the less soluble natural cyclodextrin forms B-type profiles. Most of the drug/cyclodextrin complexes are thought to be inclusion complexes, but cyclodextrins are also known to form non-inclusion complexes and the complex aggregates are capable of dissolving drugs through micelle-like structures [13]. The phase-solubility profiles only describe how the increasing cyclodextrin concentration influences the drug solubility. The most common type of cyclodextrin complexes is the 1:1 drug/cyclodextrin (D/CD) complex where one drug molecule (D) forms a complex with one cyclodextrin molecule (CD) and is given in eq. 1.

Eq. 1. $$D + CD \xleftrightarrow{K_{1:1}} D/CD$$

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 [14, 15]. Under such conditions, for an A_L-type phase-solubility diagram with slope less than unity, the stability constant ($K_{1:1}$) of the complex can be calculated from the slope and the intrinsic solubility (s_o) of the drug in aqueous complexation media (i.e, drug solubility when no CD is present) and is given in eq. 2.

Eq. 2. $$K_{1:1} = \frac{\text{Slope}}{S_0\,(1 - \text{Slope})}$$

For 1:1 drug/CD complexes the complexation efficiency (CE) can be calculated from the slope of the phase-solubility diagram (eq. 3) by

Eq. 3. $$CE = \frac{[D/CD]}{[CD]} = S_0 \cdot K_{1:1} = \frac{\text{Slope}}{S_0\,(1 - \text{Slope})}$$

The most common stoichometry of higher order D/CD complexes is the 1:2 D/CD complex resulting in A_p-type phase soluability diagram. Consecutive complexation is assumed where 1:2 complex (eq. 4) is formed when one additional cyclodextrin molecule forms a complex with an existing 1:1 complex. The value of $k_{1:2}$ frequently lies between 10–500 μ^{-1} and is lower than that of $k_{1;1}$(50–2000 μ^{-1}).

Eq. 4. $$D/CD + CD \xleftrightarrow{K_{1:2}} D/CD_2$$

The various methods that are used to prepare D/CD complexes include solution method, co-precipitation method, neutralisation method, slurry method, kneading method, grinding method etc [16] and water is essential for the successful complex formation. In solution, the cyclodextrin complexes are prepared by addition of excess amount of drug to an aqueous cyclodextrin solution. The suspension formed is equilibrated at desired temperature and then centrifuged to form clear D/CD complex solution. For preparation of solid complexes water is removed from the aqueous D/CD complex by evaporation or sublimation. 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. The complexation efficiency can be enhanced by various methods [17] and are shown in tab. 2.

Tab. 2. Methods that enhances the complexation efficiency

Effect	Consequences
Drug ionization	Unionized drugs do usually form more stable complexes than their ionic counterparts. However, ionization of a drug increases its apparent intrinsic solubility resulting in enhanced complexation.
Salt formation	It is sometimes possible to enhance the apparent intrinsic solubility of a drug through salt formation.
Complex-in-complex	It is sometimes possible to increase the apparent intrinsic solubility of a drug through formation of metal complexes.
The acid/base ternary complexes	It has been shown that certain organic hydroxy acids (such as citric acid) and certain organic bases are able to enhance the complexation efficiency by formation of ternary drug/cyclodextrin/acid or base complexes.
Polymer complexes	Water-soluble polymers form a ternary complex with drug/cyclodextrin complex thereby increasing the observed stability constant of the drug/cyclodextrin complex. This observed increase in the value of the constant increases the complexation efficiency.
Solubilization of cyclodextrin aggregates	Organic cations and anions are known to solubilize uncharged D/CD complexes that have limited aqueous solubility. This will enhance the complexation efficiency during preparation of solid drug/cyclodextrin complex powder.
Combination of two or more methods	Frequently the complexation efficiency can be enhanced even further by combining two or more of the above mentioned methods. For example drug ionization and the polymer method or solubilization of the cyclodextrin aggregates by adding both polymers and cations or anions to the aqueous complexation medium.

2.4 Non conventional cyclodextrin complexes

It has been assumed that the mechanism where by cyclodextrin exert their effects, especially their augmentation solubility is via the formation of non covalent dynamic inclusion complexes. This model regards D/CD interactions as discrete phenomenon and ignores the possible interactions of these complexes with one another. These non conventional cyclodextrin complexes gain more importance in the aspects of drug solubilization by means of molecular aggregation.

2.5 Drug stability

The feasibility of a pharmaceutical formulation can be limited by stability issues, especially for aqueous formulation of drugs that are prone to hydrolysis or oxidation. The reaction rates can be affected by inclusion of the chemically liable moiety of the drug 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 stabilizing effect will depends on three

parameters like the cyclodextrin concentration, the stability constant of the complex and the degradation rate constant for the drug degradation within the cyclodextrin cavity. Many studies have shown that stability of chemically liable drugs like steroid esters, alkylating anti cancer agents, prostaglandins, prodrugs and various other compounds can be significantly improved through formulation with cyclodextrin. The studies also revealed that cyclodextrin can increase the physical stability of various drugs. For example, evaporation of volatile compounds can be significantly reduced through complex formation. The cyclodextrin will also reduce denaturation in peptide and protein formulations.

Cyclodextrin can sometimes have a destabilizing effect on drugs through direct catalysis, for example, by enhancing drug solubility in aqueous drug suspensions. The catalytic effect is associated with deprotonisation of the hydroxyl groups located at the rim of the cyclodextrin cavity. This catalytic effect is mainly observed under basic conditions and increases with increasing pH.

2.6. Drug Delivery through biological membrane

The cyclodextrin do not readily permeate the biological membranes due to its chemical structure, molecular weight and very low octanol/water partition coefficient. Only the free form of drug, which is in equilibrium with the D/CD complexes are capable of penetrating lipophilic membranes. Cyclodextrins, in general, do not enhance permeability of hydrophilic water-soluble drugs through lipophilic biological membranes. 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 the cyclodextrins will enhance or will hamper drug delivery through a biological membrane. The cyclodextrins will enhance drug delivery through aqueous diffusion-controlled barriers, but can hamper drug delivery through lipophilic membrane-controlled barriers [18].

Cyclodextrins can also enhance the drug bioavailability by stabilization of drug molecules at the bio-membrane surface. For example, the cyclodextrin-enhanced insulin bioavailability after nasal administration is partly due to this stabilizing effect [19]. In general, drug stabilization 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 optimize cyclodextrin-containing drug formulations with regard to drug delivery from the formulations [20]. Too much or too little cyclodextrin can result in less than optimum drug bioavailability.

3. Cyclodextrin effects on important drug properties in formulation

3.1 Effect on Drug Solubility and Dissolution

The cyclodextrin has been playing a very important role in formulation of poorly water-soluble drugs by improving the apparent drug solubility and dissolution through inclusion complexation or solid dispersion. It act as hydrophilic carriers for drugs with inadequate molecular characteristics for complexation, or as tablet dissolution enhancers for drugs with high dose, with which use of a D/CD complex is difficult [21]. The various applications of cyclodextrin as solubilizing agents are summarized in tab.3. Among the various

commercially available cyclodextrins, methylated cyclodextrin with a relatively low molar substitution appears to be the most powerful solubilizers. The reduction of drug crystallinity on complexation or solid dispersion with cyclodextrins also contributes to the cyclodextrin increased apparent drug solubility and dissolution rate [22]. Cyclodextrins, as a result of their ability to form in-situ inclusion complexes in dissolution medium, can enhance drug dissolution even when there is no complexation in the solid state [23]. The studies showed that the formation of complexation of CP-β-CD with the antibiotics significantly improve the water solubility. The solubility of the antibiotics linearly increase with the concentration of CP-β-CD and the values of the association constant $K_{1:1}$ of the butyl paraben/CP-β-CD and triclosan/CP-β-CD complexes were 3800 M^{-1} and 3082 M^{-1} respectively [24].

Tab. 3. Examples of CD enhanced solubility and dissolution

CD	Drugs
β-CD	Nimesulide, Sulfomethiazole, Lorazepam, Ketoprofen, Griseofulvin, Praziquantel, Chlorthalidon, Exodolac, Piroxicam, Itraconazole, Ibuprofen
α-CD	Praziquantel
γ-CD	Praziquantel, Omeprazole, Digoxin
HP-β-CD	Albendazole, DY-9760e, ETH-615, Levemopamil HCl, Sulfomethiazole, Ketoprofen, Griseofulvin, Itraconazole, Carbamazepine Zolpidem, Phenytoin, Rutin
DM-β-CD	Naproxen, Camptothesin
SBE-β-CD	DY-9760e, Danazol, Fluasterone, Spiranolactone
RM-β-CD	ETH-615, Tacrolimus
Randomly acetylated amorphous-β-CD	Naproxen

3.2 Effect on Drug Bioavailability

The cyclodextrin enhances the bioavailability of insoluble drugs by increasing its drug solubility, dissolution and drug permeability. This is achieved by making the drug available at the surface of the biological barrier, e.g., skin, mucosa, or the eye cornea, from where it partitions into the membrane without disrupting the lipid layers of the barrier [25]. In such cases, it is important to use just enough cyclodextrin to solubilize the drug in the aqueous vehicle since excess may decrease the drug availability [26, 27]. It was found that the addition of polymers can further enhance the drug permeability from aqueous cyclodextrin solutions. In the case of water-soluble drugs, cyclodextrins increase the drug permeability by direct action on mucosal membranes and enhance drug absorption and bioavailability [28].

It was reported that cyclodextrins, because of their ability to remove cholesterol, may increase membrane fluidity and induce membrane invagination through a loss of bending resistance and results in cell lysis. On the other hand, removal of phospholipids, especially phosphatidyl choline and sphingomyelin from the outer half of the membrane bi layer by cyclodextrin causes bi layer imbalance. Labile drug stabilization by cyclodextrins [29, 30] and their ability to ameliorate drug irritation, and thus improve drug contact time at the absorption site in nasal, ocular, rectal and transdermal delivery are some other important

factors that contribute to the cyclodextrin-improved bioavailability. α-CD improved the rectal bioavailability of morphine by inhibiting the drug's upward movement from areas impacted by first pass metabolism.

3.3 Effect on Drug Safety

Cyclodextrins have been used to ameliorate the irritation caused by drugs [31]. The increased drug efficacy and potency, caused by cyclodextrin-increased drug solubility, may reduce drug toxicity by making the drug effective at lower doses. The studies showed that the β-CD enhanced antiviral activity of ganciclovir on human cytomegalo virus clinical strains and the resultant increase in the drug potency has reduced the drug toxicity [32]. The toxicities associated with crystallization of poorly water-soluble drugs in parenteral formulations can often be reduced by formation of soluble D/CD complexes. Further cyclodextrin entrapment of drugs at the molecular level prevents their direct contact with biological membranes and thus reduces their side effects and local irritation with no drastic loss of therapeutic benefits [33].

3.4 Effect on Drug Stability

Cyclodextrins can improve the stability of several labile drugs against dehydration, hydrolysis, oxidation and photodecomposition and thus increase the shelf life of drugs. Tab.4 summarizes the effects of cyclodextrin on drug stability. It was reported that cyclodextrin-induced enhancement of drug stability may be a result of inhibition of drug interaction with vehicles and inhibition of drug bioconversion at the absorption site. By providing a molecular shield, cyclodextrin complexation encapsulates labile drug molecules at the molecular level and thus insulates them against various degradation processes. SBE-β-CD showed greater stability enhancement of many chemically unstable drugs than other cyclodextrins [34]. The stabilizing effect of cyclodextrins depends on the nature and effect of the included functional group on drug stability and vehicle.

The cyclodextrins were reported to have improved the photostability of trimeprazine [35] and promethazine [36]. They also enhanced the solid state stability and shelf life of drugs [37]. The physical stability of viral vectors for gene therapy and the formulations containing sucrose and cyclodextrins were stable for 2 years when stored at 20°C has been reported [38]. Since the hydrolysis of drugs encapsulated in cyclodextrins is slower than that of free drugs [39], the stability of the D/CD complex, plays a significant role in determining the extent of protection [40, 41]. Under specific conditions, cyclodextrin complexation may accelerate drug degradation depending on the type of cyclodextrins. Structural changes in drug molecules on cyclodextrin complexation can also accelerate drug degradation [42].

Tab. 4. Effect of CD on drug stability

Drug	CD	Effect
Promethazine	HP-β-CD, DM-β-CD	Photostability
2-ethylhexyl p-(dimethylamino)benzoate	HP-β-CD	Photostability
Glibenclamide	β-CD	Shelf life with unaffected dissolution rates for 4 years
Diclofenac sodium	β-CD	Thermal stability in solid state
Quinaril	β-CD, HP-β-CD	Stability against intramolecular cyclization in solid state
Doxorubicin	HP-β-CD, HP-γ-CD	Stability to acid hydrolysis and photodecomposition
Acyl ester prodrugs of Ganciclovir	HP-β-CD	Stability against hydrolysis
Digoxin	γ-CD	Stability against hydrolysis
Rutin	HP-β-CD	Stability against hydrolysis
Camptothesin	RDM-β-CD	Stability against hydrolysis
Melphalan and Carmustine	SBE-β-CD, HP-β-CD	Stability against hydrolysis
Paclitaxel	γ-CD, HP-γ-CD, HP-β-CD	Stability against hydrolysis
Spiranolactone	SBE-α-CD, SBE-β-CD, HP-β-CD, γ-CD, β-CD	Deacylation or degradation
Flutamide	β-CD	Photoreactivity

4. Cyclodextrin based drug delivery

On the basis of the multifunctional characteristics of cyclodextrins, this section is mainly concerned with the latest applications of cyclodextrins in oral, rectal, sublingual, ocular, nasal, pulmonary, dermal and other novel drug delivery systems like liposomal, microspheres, osmotic pump, peptide and protein delivery, site-specific drug targeting and nanoparticles.

4.1 Oral drug delivery

4.1.1 Controlled Release in Oral Delivery

There has been a growing interest in developing the rate or time controlled type oral preparations, because an appropriate drug release from the dosage forms is of critical importance in realizing their therapeutic efficacy. From the viewpoint of the optimization of pharmacotherapy, drug release should be controlled in accordance with the therapeutic purpose and the pharmacological properties of active substances. The drug release-time profiles after oral administration can be mainly classified into two categories as rate-controlled type and time-controlled type (delayed release type).

Tab. 5. Pharmaceutical applications of various CD derivatives in the formulation of modified release preparations

Derivative	Drug	Summary
Diethyl-β-CD	Diltiazem	Sustained release for oral use
	Buserelin acetate	Sustained release for subcutaneous use
	Nitroglycerin	Sustained release for percutaneous use
	Isosorbide dinitrate	Sustained release
	Tiaprofenic acid	Delayed release
Triacetyl-β-CD	Flufenamic acid	Prolonged release for oral use
Peracylated-β-CD (TB- β-CD)	Molsidomine	Sustained release for oral use
	Salbutamol	Prolonged release for oral use
	Captopril	Sustained release
A1-β-CD-sulfate	Recombinant human basic fibroblast growth factor	Sustained release for oral use; enhanced stability
O-carboxymethyl-O-β-CD	Molsidomine	Delayed release
	Diltiazem HCl	

A. Rate controlled release

The rate-controlled type is further classified into three types as immediate release, prolonged release and modified release types. On the basis of this knowledge, various cyclodextrin derivatives have been used in order to modify drug release in oral preparations. A combination of cyclodextrins and other carrier materials is useful to optimize the release rate of drugs.

Immediate Release: As the dissolution rate of the poorly water-soluble drugs is mainly responsible for both the rate and extent of oral bioavailability of the drugs, various hydrophilic materials are used to attain the immediate release formulation. The hydrophilic cyclodextrins have been extensively applied to enhance the oral bioavailability of steroids, cardiac glycosides, non steroidal anti inflammatory drugs, barbiturates, anti-epileptics, benzodiazepines, anti diabetics, vasodilators etc [43, 44]. Also, the immediate release formulations of analgesics, antipyretics, coronary vasodilators etc., are very useful in emergency situations. These improvements are mainly due to the increase in solubility and wettability of the drugs through the formation of inclusion complexes. The stabilizing effect of cyclodextrins on labile drugs is also responsible for the improvement of oral bioavailability.

Prolonged Release: Most of the slow-release preparations have been aimed at achieving the zero-order or pH-independent release of drugs to provide a constant blood level for a longer period of time. This kind of formulation has many advantages such as reducing the frequency of dosing, prolonging the drug efficacy and avoiding the toxicity associated with the administration of a simple plain tablet. For this purpose, hydrophobic cyclodextrins

such as alkylated and acylated derivatives are useful as slow-release carriers for water-soluble drugs.

Modified Release: This involves the release of drug in a different physical state. The conventional formulation of nifedipine, a typical calcium-channel antagonist, must be dosed either twice or three times daily, because of the short elimination half-life due to the considerable first-pass metabolism. Moreover, it has some pharmaceutical problems such as low oral bioavailability due to poor aqueous solubility and a decrease in dissolution rate during the storage due to the crystal growth [45]. Therefore, the release rate of nifedipine must be modified in order to obtain a more balanced oral bioavailability with prolonged therapeutic effect. The pharmaceutical applications of various cyclodextrin derivatives in the formulation of modified release preparations are shown in tab.5.

B. Delayed Release

An enteric preparation can be classified as time-controlled release, since the drug is preferentially released in the intestinal tract. Hydrophobic excipients having a weak acidic group are preferable because they are less soluble in water at low pH and soluble in neutral and alkaline regions due to the ionization of the acidic group. Under the control of this pH dependence, the delayed release dosage form which passes from the stomach into the higher pH environment of the upper small intestine would experience increased drug release. For this purpose, 6-*O*-(carboxy methyl)-*O*-ethyl-β-cyclodextrin was developed to exhibit pH dependent solubility for use in selective dissolution of the drug/cyclodextrin complex. The modifications of the drug release site and time profile by cyclodextrins are mentioned in tab.6

Tab. 6. Modification of the Drug Release Site and Time Profile by CDs

Aim	Use of CD	Release Pattern
Enhanced dissolution and absorption of poorly water-soluble drugs	HP-β-, DM-β-, SB-β-, and branched-β-CDs	Immediate release
Sustained release of water soluble drugs	Ethylated β-CDs, acylated β-CDs	Prolonged release
More balanced oral bioavailability with prolonged therapeutic effects	Simultaneous use of different CDs and/or other excipients	Modified release
Enteric acid protection of drugs	CME-β-CD	Delayed, pH-dependent release
Colon-targeting	Drug/CD conjugate	Site-specific release

Presently, the commercial viability of cyclodextrin-based oral formulations has been established. The cyclodextrins are supposed to act only as carrier materials and thereby helps to transport the drug through an aqueous medium to the lipophilic absorption surface in the gastrointestinal tracts. Therefore, such applications have been successful when the rate-limiting step in drug absorption is dissolution of the drug itself and not absorption

across the gastrointestinal tracts. 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 delivery [46] can be explained as in tab.7.

Tab. 7. The pharmaceutical application of cyclodextrins in oral drug delivery

Drugs	CD	Increased Effect
Ketoprofen, Griseofulvin, Terfenadine	β-CD	Bioavailability
Albendazole, Ketoprofen, Phenytoin, Gliclazide	HP-β-CD	Solubility and dissolution rate
Spiranolactone	SBE7-β-CD	Solubility and dissolution rate
Tacrolimus	DM-β-CD	Solubility and dissolution rate
Albendazole	M-β-CD	Solubility and dissolution rate
Phenytoin	ME-β-CD	Solubility and dissolution rate
Terfanidine, Tolbutamide	β-CD	Intensity or duration of therapeutic activity
Tolbutamide, Amylobarbitone	HP-β-CD	Intensity or duration of therapeutic activity
Flutamide	HP-β-CD	Permeability
Digoxin	γ-CD	Gastrointestinal stability
Rutin	HP-β-CD	Gastrointestinal stability
Clomipramine, Testosterone	HP-β-CD	Sublingual bioavailability
Danazole	SBE7-β-CD, HP-β-CD	Buccal bioavailability

Tab. 8. FDA Biopharmaceutics classification system of orally administered drugs

FDA class	Drug Properties	
	Aqueous solubility	Permeability
I	Highly soluble	Highly permeable
II	Poorly soluble	Highly permeable
III	Highly soluble	Poorly permeable
IV	Poorly soluble	Poorly permeable

The FDA Biopharmaceutics classification system categorizes drugs according to their aqueous solubility and ability to permeate the intestinal mucosa as shown in tab.8. In general hydrophilic cyclodextrins are not able to improve bioavailability of class I drugs. However they are used to reduce local drug irritation and to increase the rate of drug absorption. Class II drugs have limited solubility resulting in dissolution rate limited oral absorption, thus aqueous solubility hampers dissolution rate. Water soluble cyclodextrin

complexes of these drugs will enhance their diffusion to the mucosal surface leading to enhanced oral bioavailability [47].

Tab. 9. Examples of cyclodextrins in oral, sublingual and buccal formulations and its clinical and bioavailability studies

Drug	CD	Formulation	Species	Relative Bioavailability
Class 1				
Piroxicam	βCD	Tablet, capsule and oral suspension	Human, rat, rabbit	≤ 1.4
Class II				
Carbamazepine	DMβCD	Oral powder and solution, tablet	Rabbit, dog, rat	≤ 5.6
Digoxin	γCD	Tablet	Dog	5.4
Glibenclamide	βCD, SBEβCD	Capsule containing powder	Dog, rat	≤ 6.2
Miconazole	HPβCD	Aqueous suspension	Rat	2.3
Phenytoin	E-βCD, GluβCD, MalβCD, SBEβCD, HPβCD	Suspension, capsule containing powder	Rat, dog	≤ 5
Spironolactone	βCD, γCD, DMβCD, SBEβCD, HPβCD	Oral solution and powder	Rat, dog	≤ 3.6
Tolbutamide	βCD, HPβCD	Suspension, oral powder	Rabbit, dog	≤ 1.5
α-Tocopheryl nicotinate	DMβCD	Capsule containing powder	Dog	~ 70
Class III				
Acyclovir	βCD	Oral suspension	Rat	1.1
Diphenhydramine HCl	DMβCD, HpβCD	Solution	Rat	≤ 0.9
Class IV				
Cyclosporin A	DMβCD	Oral suspension	Rat	4.7

Class III drugs are water soluble but do not readily permeate biological membranes due to their size and extent of hydration. Consequently formation of hydrophilic drug by cyclodextrin complexes will not enhance their oral bioavailability, but reduce the ability of the dissolved drug molecules to partition from the aqueous exterior into the gastro intestinal mucosa. Class IV drugs are water soluble and do not readily permeate lipophilic biological membranes. Hydrophilic water insoluble compounds such as zwitter ions do not

readily form cyclodextrin complexes and hence do not improve their oral bioavailability. However cyclodextrins are able to improve aqueous solubility of some large lipophilic molecules leading to increased drug availability at mucosal surface that will lead to increased oral bioavailability. Tab.9 shows the examples of cyclodextrins in oral, sublingual and buccal formulations and its clinical and bioavailability studies.

4.2. Rectal drug delivery

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. In comparison with the parent cyclodextrins, the methylated cyclodextrins significantly enhance the rectal absorption of hydrophobic drugs, which are anti inflammatory agents, such as flurbiprofen [48], carmofur and biphenyl acetic acid [49] from the oleaginous suppository. The superior effect of the methylated cyclodextrins can be explained by the faster release of the drugs together with the lowering affinity of the complexed drugs to the oleaginous suppository base [50].

4.3 Sublingual drug delivery

Sublingual drug delivery is one of the most efficient ways to bypass hepatic first-pass metabolism [51]. In this method the drug enters the systemic circulation by dissolving in the mucosa. In the sublingual formulations the complexation of poorly water soluble drugs with cyclodextrin has been shown to increase the bioavailability of various lipophilic drugs. For example, 2-hydroxy propyl-β-CD has been shown to increase the bioavailability of 17β-oestradiol [52], androstenediol [53], clomipramine [54] and danazol [55]. 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 with in 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. For example, the development of sublingual formulation of Δ^9-tetrahydrocannabinol (THC), the complexation of THC with 2-hydroxypropyl-β-CD and methylated β-CD was studied. Results from studies showed that the estimated therapeutic dose (1mg) of THC could form a water soluble complex with 400 mg of 2-hydroxy propyl-β-CD, but formulation bulk of 400 mg is considered too large for sublingual

administration. The same amount of THC (1 mg) could form a soluble complex with 25 mg of randomly methylated β-cyclodextrin. Thus sublingual administration of randomly methylated β-CD containing THC formulation increases bioavailability of THC compared with oral administration [56].

4.4. Ocular drug delivery

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 [57]. 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 [58]. Hydrophilic cyclodextrins, especially 2-hydroxy propyl-β-cyclodextrin and sulfo butyl-β-cyclodextrin, have been shown to be nontoxic to the eye and are well tolerated in aqueous eye drop formulations.

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. For example, acetazolamide is a carbonic anhydrase inhibitor used to treat glaucoma. Its aqueous solubility in pure water is 0.7 mg/ml, but in 20% (w/v) aqueous 2-hydroxy propyl-β-CD solution, it is 7 mg/ml. Addition of water-soluble polymers to the aqueous cyclodextrin solution increases the solubility further [59]. Cyclodextrin solubilization of the drug will increase the amount of dissolved drug at lipophilic membrane surface but excess will decrease the drug delivery through cornea [60]. Thus, cyclodextrins are used to decrease ophthalmic drug irritation [61] and to increase the chemical stability of drugs in aqueous ophthalmic formulations [62].

4.5 Nasal Drug Delivery

The nasal route is another effective way to bypass first-pass metabolism [63]. 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. For example, the nasal bio availability of insulin in rats was increased from about 0-100% by including methylated cyclodextrins in formulations [64]. Promising results from nasal delivery of dihydroergotamine [65], midazolam [66] heparins [67] and ondansetron [68] have also been reported.

Nasal preparations must be critically evaluated for their possible effect on the nasal muco-ciliary 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 muco-

ciliary 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.

4.6 Pulmonary drug delivery

Pulmonary administration of drugs is usually intended for local treatment of diseases. Drug degradation in the gastro intestinal tract and first-pass metabolism can be avoided by administration through lungs. There will be effective drug absorption in the lungs because of its large surface area, good blood supply and low enzymatic activity. However, pulmonary drug delivery can be limited by low aqueous solubility and slow drug dissolution. Insoluble particles are removed from the lungs by the muco-ciliary clearance in the upper airways and by macrophages in the alveoli [69]. Cyclodextrins can increase the solubility, stability and dissolution rate of water insoluble and chemically unstable drugs, thereby leading to decreased clearance, increased drug absorption and faster onset of drug action. By forming D/CD complexes, a liquid drug can be converted to a solid form, two incompatible drugs can be mixed in dry powder formulation, bad smells and tastes can be reduced and local irritation in lungs can be reduced. Among the cyclodextrins, the γ–CD, 2-hydroxy propyl-β-CD and sulfo butyl ether β-CD are considered to be safest for parenteral administration. The cyclodextrins are well tolerable in calu-3-cells and have decreased cell viability only at high concentration. The cyclodextrin complexes could also be used in an inhalation powder without lowering the pulmonary deposition of the drug.

4.7 Dermal drug delivery

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 [70]. 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. 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. 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. For instance, the in vitro release rate of corticosteroids from water-containing ointments is markedly increased by hydrophilic cyclodextrins, whereas in other ointments the cyclodextrins retard the drug release. 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. 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. Cyclodextrins have also been used to reduce permeability of compounds into skin [71, 72]. It has been indicated that complexation of sunscreen enhances its photo protective effects by preventing permeation of the sunlight into the skin.

4.8 Novel Drug delivery

The cyclodextrins due to their ability either to form complex drugs or to act as functional carrier materials in pharmaceutical formulations can serve as potential candidates for efficient and precise delivery of required amounts of drugs to a targeted site for a necessary period of time. They have applications in the design of some novel delivery systems like liposomes, microspheres, osmotic pump, peptide and protein delivery, specific site targeting and nanoparticles. They have to be released and to execute their therapeutic effects. For example, chemical drug delivery, colon specific drug delivery, brain drug delivery or brain targeting etc. The study suggested that various release-controlled preparations can be designed by employing CD conjugates in combination with other carriers with different releasing properties [73].

4.8.1 Cyclodextrin in liposomal drug delivery

The main purpose of the liposomal drug delivery is to combine the advantages of cyclodextrin such as increased drug solubility with the advantages of liposome such as drug targeting. Liposomes entrap hydrophilic drugs in the aqueous phase and hydrophobic drugs in the lipid bi layers and retain drugs en route to their destination with a pre-determined rate [74, 75]. By forming water soluble complexes, CD would allow insoluble drugs to accommodate in the aqueous phase of vesicles, thereby potentially increasing the drug-to-lipid mass ratio levels, enlarges the range of insoluble drugs amenable for encapsulation, allows drug targeting and reduce drug toxicity [76]. Problems associated with intravenous administration of CD complexes such as their rapid removal into urine and toxicity to kidneys, especially after chronic use, can be avoided by their entrapment in liposomes [77].

Complexation with CD can also improve the stability of liposomes, eg, most stable liposomal formulations of metronidazole and verapamil were obtained by direct spray drying of lipid, drug and HP-β-CD mixture [78]. Inclusion complexation can greatly increase the chemical stability of labile drugs in multilamellar liposomes. Multilamellar DRV liposomes containing a riboflavin/γ-CD complex provided optimal protection to the photosensitive drug. Similarly, multilamellar liposomes containing indomethacin/HP-β-CD inclusion complex showed increased stability of the hydrolysable drug. Complexation with CD increases the liposomal entrapment of nifedipine by reducing its interaction with lipid bilayers and also improved the liposomal stability in plasma.

Liposomal entrapment of prednisolone was higher when incorporated as HP-β-CD complex than as free drug. Selection of CD can also have a significant effect on the amount of drug associated with vesicles, e.g., HP-β-CD, with a more lipophilic interior and

considerably higher aqueous solubility incorporated higher drug amounts in vesicles than β-CD. However, HP-β-CD, as a result of its ability to get entrapped in higher amounts in the vesicles, also showed a higher velocity of destabilizing effect on vesicles than β-CD [79].

4.8.2 Cyclodextrin in microspheres

The role of cyclodextrins in microsphere preparation was first studied by Loftsson [80]. Nifedipine release from chitosan microspheres was slowed down on complexation with HP-β-CD in spite of the improved drug-loading efficiency. It is highly unlikely for CD molecules to diffuse out of the microspheres, even with a low stability constant, the complex must first release the free drug that can permeate out of the microspheres. Hence the observed slow nifedipine release from the microspheres was reported to be due to lesser drug availability from the complex and also due to formation of hydrophilic chitosan/CD matrix layer around the lipophilic drug that further decreases the drug matrix permeability. Sustained hydrocortisone release with no enhancement of its dissolution rate was observed from chitosan microspheres containing its HP-β-CD complex. The sustained hydrocortisone release was reported to be due to formation of a layer adjacent to the interface by the slowly dissolving drug during the dissolution process that makes the microsphere surface increasingly hydrophobic [81].

Study of in vivo release behavior of β-CD from β-CD/poly acrylic acid (PAA) microspheres, prepared by a water/oil solvent evaporation technique, indicated a high encapsulating efficiency (99%) with potential covalent binding of the CD [82]. β-CD caused no alteration of the in vitro release kinetics of dyes, phenolphthalein and rhodamine B from the microspheres. The reasons suggested for the unaltered release kinetics were rapid hydration of the polymer matrix because of limited crosslinking, perturbation of dye/β-CD complex by oil, organic solvent residues or conformational changes and reduction of β-CD complexing ability on covalent binding with PAA due to steric hindrance of its cavity.

HP-β-CD acted as a promising agent for stabilizing lysozyme and bovine serum albumin during primary emulsification of poly (d,l-lactide-co-glycolide) (PLGA) microsphere preparation. The stabilizing effect was reported to be a result of increased hydrophilicity of the proteins caused by shielding of their hydrophobic residues by HP-β-CD. It also increased its recovery from water/oil emulsion by preventing the adsorption of the protein to PLGA [83]. The CD were also used to modulate peptide release rate from microspheres, eg, HP-β-CD co-encapsulation in PLGA microspheres slowed down insulin release rate. Microspheres, prepared by spray drying of a water/oil emulsion containing the CD provided constant insulin release up to 45 days without initial burst and maintained the peptide stability during the entire release phase. The slowing down of overall release rate of the peptide was reported to be due to its decreased matrix diffusivity caused by its higher apparent molecular weight and size on complexation. Co-encapsulation of the CD also reduced the apparent particle size of the microspheres.

All PVA/CD microspheres, prepared by crosslinking of an acidified aqueous mixture solution of PVA and CD (α-, β-, or γ-CD) with gluteraldehyde, displayed good affinity for different drugs like diclofenac, indomethacin, metronidazole and propranolol. The amount of CD linked in microspheres was in the order β- > γ-> α-CD and the dimensions of the microspheres with γ-CD were much higher than those with α- or β-CDs.

4.8.3 Cyclodextrin in osmotic pump tablet

Osmotically controlled oral drug delivery systems are available in various designs to control the drug release based on the principle of osmosis. Osmotic tablets offer many advantages like zero-order delivery rate, improving patient compliance, a high degree of in vitro-in vivo correlation and they are simple in operation. In the 1970s, the elementary osmotic pump (EOP) was introduced. Oral osmotic pump tablets generally consist of a core including the active agent, an osmogent and other common excipients, coated with semi permeable membrane. A delivery orifice drilled through the coating, provides a passage way for drug release by hydrostatic pressure created from the core osmogent when exposed to an aqueous environment.

The rates of drug release from osmotic pump depends on the drug solubility and the osmotic pressure of the core, hence, these systems are suitable for delivery of drugs with moderate water solubility [84]. The push-pull osmotic tablets were developed in the 1980s and were used to deliver drugs having low to high water solubility [85]. Drugs such as oxybutynin chloride, nifedipine and glipizide are based on this technology. These pumps are in the form of a two layer tablet with a drug and a push layer. When the system comes in contact with an aqueous environment, both layers absorb water. The lower part, which does not have an orifice swells and pushes the drug through the orifice as a solution or suspension in the upper chamber [86]. However, this system has some disadvantages; firstly, laser drilling technology should be employed to drill the orifice next to the drug compartment. Secondly, lag time for drug release from osmotic pumps after coming in contact with the aqueous media is long.

In contrast to push–pull osmotic system, EOP tablets are prepared by a simple technology without any lag time for drug release however an EOP system requires that the drug to be in solution in order to be delivered in a controlled predictable manner. If the drug is insoluble, an EOP will not function properly. There are several techniques which can be used to solubilize drugs. Solubilization by cosolvents, crystal modification, prodrug formation and complexation can individually or in combination be extremely valuable means for solubilization of drugs [87]. One approach to overcome pharmaceutical solubility problems is complexation.

Okimoto et al. has investigated poorly water soluble drugs such as testestrone, prednisolone, chlorpromazine, indometacin and naproxen complexation utilizing (SBE) 7m-β-CD in osmotic tablets [88]. It has been reported that Sulfo butyl ether (SBE) 7m-β-CD could serves both as a solubilizer and osmotic agent. The possibility of improving the solubility and dissolution rate of lovastatin by complexation with β-CD in the EOP tablets was also investigated. The results confirmed that dissolution rate of lovastatin β-CD were greatly enhanced and this system has suitable solubility behavior in EOP tablet formulations [89].

4.8.4 Cyclodextrin in Peptide and Protein Delivery

Advances in biotechnology have accelerated the economical, large-scale production of therapeutically active peptide-and protein-based drugs used to combat poorly controlled diseases, making them more readily available for therapeutic use. This rapid progress in molecular biology, however, has not been matched by the progress in the formulation and development of delivery systems for peptide and protein drugs [90]. There are

considerable hurdles to be overcome before practical use can be made of therapeutic peptides and proteins because of chemical and enzymatic instability, poor absorption through biological membranes, rapid plasma clearance, peculiar dose-response curves and immunogenicity. Many attempts have been made to address these problems by chemical modifications or by co-administration of adjuvants to eliminate undesirable properties of peptides and proteins. Cyclodextrin complexation seems to be an attractive alternative to these approaches [91].

Cyclodextrins can recognize not only the size and shape but also the chirality of amino acids. However, molecules of many peptides and proteins are too hydrophilic and bulky to be wholly included in the cyclodextrin cavity and the topological constraints of the peptide backbone may reduce the formation of inclusion complexes. Thus their interaction with cyclodextrins could be only local; that is, accessible hydrophobic side chains may form inclusion complexes with cyclodextrins. Such interaction possibly affects the overall three-dimensional structure of peptides and proteins or inhibits their intermolecular association and thus changes their chemical and biological properties.

The systemic delivery of peptide and protein based drugs via various mucosal routes is receiving extensive scrutiny as an alternative to the oral and parenteral routes. The trans-mucosal delivery has advantages of being non inversive and of bypassing gastrointestinal and hepatic clearances. Among them the peptide delivery through nasal mucosa seems to be most successful and practical. However, even with the intranasal route of delivery, the nasal epithelium presents both a physical and a metabolic barrier to the absorption of peptides and proteins. Therefore, the use of absorption-promoting agents is necessary to achieve sufficient intranasal absorption of most peptides and proteins. The potential of cyclodextrins, especially the methylated cyclodextrins, as nasal absorption enhancers has been demonstrated for luteinizing hormone-releasing hormone agonists, insulin, adreno corticotropic hormone analogue, calcitonin, granulocyte colony-stimulating factor, insulin-like growth factor-I etc. The absorption enhancement afforded by cyclodextrins can be attributed primarily to their ability to reduce the physical and metabolic barriers to these peptides and proteins. The limited systemic bioavailability of peptides and proteins is partly due to the existence of a substantial enzymatic barrier in the epithelial cells. Cyclodextrins can protect peptides and proteins against enzymatic as well as chemical degradation [92].

4.8.5 Cyclodextrin in Site-specific Delivery

Recently, intensive efforts have been made to design systems able to deliver drugs more efficiently to specific organs, tissues, cells etc. Cyclodextrin complexes are in equilibrium with guest and host molecules in water, the degree of dissociation being dependent on the magnitude of stability constant. This property of the complex is a desirable quality, because the complex dissociates to free cyclodextrin and drug at the absorption site, and only the drug in free form enters into systemic circulation. A typical example is the application of 2-hydroxy propyl-β-cyclodextrin to the chemical delivery system. On the other hand, the inclusion equilibrium is disadvantageous when drug targeting is to be attempted, because the complex dissociates before it reaches the organs or tissues to which it is to be delivered. One method to prevent this dissociation is to bind a drug covalently to cyclodextrins [93]. In this section, recent results on site-specific delivery using cyclodextrins are described, although there are presently very few reports from this area.

Chemical Delivery System: When a drug is covalently coupled to 1-methyl-1,4-dihydro nicotinic acid through enzymatically labile linkage, its lipophilicity increases and allows selective delivery of drug molecules into the brain across the blood-brain barrier. After the entry into the brain, the dihydro pyridine moiety is oxidized by oxido reductase to 1-methyl pyridinium cation. Thus, the polar drug/1-methyl pyridinium derivative is trapped in the brain due to the presence of the blood-brain barrier. Subsequently, the parent drug is released from the prodrug by action of second enzymes. This is an essential concept of Bodor's chemical delivery system and is applied to brain targeting of drugs such as steroids, anti tumor agents and calcium channel antagonist [94].

Brain Targeting: The blood-brain barrier, characterized by the endothelial cells of cerebral capillaries having tight continuous circumferential junctions, restricts the passage of polar drugs to the brain and thus obstructs the specific delivery of potential neuro pharmaceuticals to the brain. One of the strategies to overcome this transport problem is to prepare prodrugs with high lipophilicity that pass through the blood-brain barrier [95].

Colon Targeting: Colon targeting is essentially classified as a delayed release with fairly long lag time, because the time required reaching the colon after oral administration is expected to be about 8 h in man. When a cyclodextrin complex is orally applied, it readily dissociates in the gastrointestinal fluid, depending on the magnitude of the stability constant. This indicates that cyclodextrin complex is not suitable for colon-specific delivery as the drug is released, because of the dilution and competitive inclusion effects, before it reaches the colon. One of the advantages of the cyclodextrin-drug conjugate is that it can survive passage through stomach and small intestine, but the drug release will be triggered by enzymatic degradation of cyclodextrins in the colon [96]. Cyclodextrin-based colon-targeting prodrugs can be characterized as follows: In the case of ester type conjugates, drug release is triggered by the ring-opening of cyclodextrins, which consequently provides the site-specific drug delivery in the colon. On the other hand, the amide conjugates do not release the drug even in the cecum and colon, despite the ring-opening of cyclodextrins. The amide linkage of the small saccharide-biphenyl acetic acid conjugates may be resistant to the bacterial enzymes and poorly absorbable from the intestinal tracts due to high hydrophilicity. Therefore, the ester type conjugate is preferable as a delayed release-type prodrug which can release a parent drug selectively in cecum and colon.

4.8.6 Cyclodextrins in Nanoparticles

Nanoparticles are considered more stable than liposomal delivery systems. However, a major drawback is associated with the drug loading capacity of polymeric nanoparticles. Cyclodextrins are used for this reason to improve water solubility and sometimes the hydrolytic or photolytic stability of drugs for better loading properties [97]. D/CD complexes act to solubilize or stabilize active ingredients within the nanoparticles, resulting in increased drug concentration in the polymerization medium and increased hydrophobic sites in the nanosphere structure when large amounts of CD are associated to the nanoparticles. The antiviral agent saguinavir was complexed to HP-β-CD to increase saquinavir loading into poly alkyl cyano acrylate nanoparticles by providing a soluble drug reservoir in the polymerization medium that is the basis of nanoparticle formation [98, 99].

Incorporation of the steroidal drugs hydrocortisone and progesterone in complex with β-CD and HP-β-CD reduced the particle size for solid lipid nanoparticles (SLNs) below 100 nm. HP-β-CD addition in the polymerization medium of poly ethyl cyano acrylate (PECA) nanospheres improved the subcutaneous absorption of metoclopramide in rats. PECA nanospheres with HP-β-CD provided the highest drug concentration and enhanced drug absorption compared with those with dextran or with drug solution. However, in addition to drug absorption from subcutaneous sites, HP-β-CD also enhanced the drug elimination by enhancing the drug absorption to reticulo endothelial tissues [100, 101]. Progesterone complexed to HP-β-CD or DM-β-CD was loaded into bovine serum albumin (BSA) nanospheres. Dissolution rates of progesterone were significantly enhanced by complexation to CD with respect to free drug [102].

In another approach, CD properties of complexation were combined with those of chitosan. Complexation with CD was believed to permit solubilization as well as protection for labile drugs while entrapment in the chitosan network was expected to facilitate absorption. Chitosan nanoparticles including complexes of HP-β-CD with the hydrophobic model drugs triclosan and furosemide, were prepared by ionic crosslinking of chitosan with sodium tri poly phosphate (TPP) in the presence of CD. Nanoparticles were then prepared by ionotropic gelation using the obtained drug HP-β-CD inclusion complexes and chitosan. Cyclodextrin and TPP concentration largely affected particle size but the zeta potential remained unchanged with different parameters. On the other hand, drug entrapment increased upto 4 and 10 times by triclosan and furosemide respectively. The release profile of nanoparticles indicated an initial burst release followed by a delayed release profile lasting up to 4 h [103]. The HP-β-CD inclusion complex with insulin was encapsulated into the nanoparticles resulting in a pH dependent release profile. The biological activity of insulin was demonstrated with enzyme linked immunosorbent assay (ELISA). Cyclodextrin complexed to insulin encapsulated into mucoadhesive nanoparticles was believed to be a promising candidate for oral insulin delivery [104].

5. Conclusions

Cyclodextrins are useful functional excipients that have enjoyed widespread attention and use in the pharmaceutical industry. Studies in both humans and animals have shown that cyclodextrins can be used to improve the drug delivery from almost any type of drug formulations. The bioadaptability and multi-functional characteristics of cyclodextrins, makes them capable of alleviating the undesirable properties of drug molecules in various routes of administration through the formation of inclusion complexes. The knowledge of different factors that can influence complex formation inorder to prepare economically drug/cyclodextrin complexes with desirable properties are necessary. However, additions of cyclodextrins to existing formulations without further optimization will seldom result in acceptable outcome. This article outlines the current application of natural and chemically modified CD in the design of advanced dosage forms. Since CD are able to extend the function of pharmaceutical additives, the combination of molecular encapsulation with other carrier materials will become effective and a valuable tool in the improvement of drug formulation. Moreover, the most desirable attribute for the drug carrier is its ability to deliver a drug to a targeted site. The conjugates of a drug with CD can be a versatile means of constructing a new class of novel drug delivery systems like liposome, microspheres, osmotic pump, peptide delivery, nanoparticle and site specific prodrugs.

Thus, there is a scope for a vibrant future in the research and development of cyclodextrin based drug delivery systems.

Authors' Statement

Competing Interests

The authors declare no conflict of interest.

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