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MiniReview

Cyclodextrin-Based Formulations: A Non-Invasive Platform for Targeted Drug Delivery

Chutimon Muankaew[1] and Thorsteinn Loftsson[2]

[1]Faculty of Pharmacy, Siam University, Bangkok, Thailand and [2]Faculty of Pharmaceutical Sciences, University of Iceland, Reykjavik, Iceland

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Abstract: Cyclodextrins (CDs) are recognized as promising pharmaceutical excipients due to their unique ability to form water-soluble inclusion complexes with various poorly soluble compounds. The numerous investigations on CDs and their use in nanomedicine have received considerable attention in the last three decades, leading to the rapid development of new CD-containing formulations that significantly facilitate targeted drug delivery and controlled drug release, with consequent improvements in drug bioavailability. This MiniReview highlights the efficacy and recent uses of CDs for non-invasive drug delivery. Using ophthalmic and nasal drug delivery as examples, an overview of chemical properties, mechanisms of CDs on drug solubilization, stabilization and permeation, along with their toxicological profiles relevant to nasal and ocular administration, are provided and discussed. The recent development and application of CD-based nanocarrier systems for targeted drug delivery are summarized.

Cyclodextrins (CDs) are natural cyclic oligosaccharides that are produced by enzymatic degradation of starch. There are three native CDs designated αCD, βCD and γCD, which are composed of 6, 7 and 8 D-glucopyranose units linked by α-(1, 4) glycosidic, respectively [1]. The molecules are commonly described as truncated cone, bucket-like or donut-shaped, with a hydrophilic outer surface and a relatively hydrophobic inner cavity that allows entrapment of small hydrophobic drug molecules or hydrophobic moieties of larger molecules [2], thereby providing drugs with new physicochemical characteristics without altering their intrinsic properties. Table 1 summarizes the characteristics of different CDs. Natural CDs are preferred for complexation; however, their usability is limited by the small cavity size of αCD, poor aqueous solubility of βCD and low productivity of γCD [3]. Derivatized CDs can be obtained by substituting their hydroxyl groups with desired functional moieties. Methyl-(MeβCD and MeγCD) [4,5], hydroxypropyl-(HPαCD, HPβCD and HPγCD) [6–8] and sulphobutylether (SEBβCD) derivatives [9] are frequently found in pharmaceutical products and have improved solubility and inclusion capacity over natural CDs. Pharmaceutical applications of both natural CDs and their derivatives are common when drug/CD complexes are used to increase drug solubility, improve organoleptic properties [10], enhance drug permeation [11] and increase drug stability, resulting in increased product shelf-life and drug bioavailability [12]. In addition, spontaneous self-assembly of drug/CD complexes into aggregates can lead to innovative drug delivery systems, such as CD-containing liposomes and microspheres as well as micro- and nanoparticles [13]. Polymerized CDs (e.g. Epi-αCD and Epi-βCD) have also been synthesized to enhance the self-assembly ability of CDs, and to strengthen their interactions with drugs and biological membranes [14]. Compared with other pharmaceutical excipients, CDs have been shown to reduce the toxicity of several drugs and are biocompatible [15–17]. As a result, they are appealing for use in the development of pharmaceutical formulations, including the reformulation of existing drug products.

Non-invasive drug delivery routes, such as topical and transmucosal administration, achieve painless systemic and local therapeutic effects, and are an attractive alternative to oral and injectable routes of drug delivery. The unique advantages of topical and transmucosal delivery approaches are their ease of use, avoidance of first-pass metabolism that subsequently reduces fluctuations in drug levels and elimination of systemic effects [18]. Recently, there has been growing interest in non-invasive ocular drug delivery and intranasal drug delivery research. However, the complexity of biological membranes is an enormous challenge for effective drug delivery systems, for instance, the presence of microvilli, and double layer of mucus on the nasal epithelium that can clear drugs from the nasal cavity [19]. The eye cornea is covered with an aqueous tear film that is highly impermeable to hydrophobic drugs. The nasal and ocular routes of delivery are also hampered by the volume that can be delivered, which is approximately 25–250 μl to the nasal cavity and 30 μl to the eye [20].

The ocular drug bioavailability in conventional eyedrops is very poor, being less than 5–10% of drug administered.

Author for correspondence: Chutimon Muankaew, Faculty of Pharmacy, Siam University, 38 Petchkasem Road, Phasi Charoen District, Bangkok 10160, Thailand (e-mail chutimon.mua@siam.edu).

Table 1.
Chemical structure and physical properties of natural cyclodextrins and some of their derivatives found in drug delivery systems [88,94].

Name of CDs	n[1]	Substituted (R)	M.W.[2]	Solubility (mg/ml)	Inner cavity diameter (Å)	Surface tension (mN/m)
α-cyclodextrin (αCD)	6	H	972	145	4.5–5.3	71.0
β-cyclodextrin (βCD)	7	H	1135	18.5	6.0–6.5	71.0
γ-cyclodextrin (γCD)	8	H	1297	232	7.5–8.3	71.0
Hydroxypropyl-α-cyclodextrin (HPαCD)	6	$-CH_2-CHOH-CH_3$	1180	≥600	4.5–5.3	65.3
Dimethyl-β-cyclodextrin (DMβCD)	7	$-CH_3$	1331	≥500	5.8–6.5	62.0
Randomly methylated-β-cyclodextrin (RMβCD)	7	$-CH_3$	1312	≥500	5.8–6.5	54.8–57.5
Hydroxypropyl-β-cyclodextrin (HPβCD)	7	$-CH_2-CHOH-CH_3$	1400	≥600	5.8–6.5	54.8–57.5
Sulphobutylether-β-cyclodextrin (SBEβCD)	7	$(CH_2)_4-SO_3Na$	2163	≥500	5.8–6.5	70.8
Hydroxypropyl-γ-cyclodextrin (HPγCD)	8	$-CH_2-CHOH-CH_3$	1576	≥500	7.5–8.3	–[3]
Epichlorohydrin-carboxymethyl-α-cyclodextrin (Epi-αCD)	6	Epichlorohydrin	55,000	≥500	–	–
Epichlorohydrin-β-cyclodextrin (Epi-βCD)	7	Epichlorohydrin	112,000	≥500	–	71.0

[1]n is defined as the number of D-glucopyranose subunits forming the CD molecule.
[2]Molecular weight in Dalton (Da).
[3]The value has not been reported, but the decreased surface tension was mentioned in the literature.

Hydrophilic drugs and mucociliary clearance mechanisms are the main factors limiting the bioavailability of drug after nasal administration. Hence, the appropriate concentration of drug at targeted sites is the primary parameter for achieving therapeutic effects of drugs. Despite the presence of several ocular barriers, transcorneal permeation is the main route of drug absorption [21]. The topical delivery of drug, primarily in eyedrops form, is an effective way to treat anterior segment diseases of the eye, owing to the direct access of the target site [22].

Many studies have demonstrated that colloidal drug delivery system using small molecule drugs has increased permeability into the back of the eye [23,24]. Intranasal delivery is also an attractive strategy; nasal mucosa has a large surface area with a high degree of vascularization, providing rapid drug absorption and high bioavailability [25]. The mechanism of drug absorption through nasal mucosa includes paracellular and transcellular transportation. Nasal drug delivery, in particular, enables systemic drug administration, delivers drugs to specific site of action and allows direct transportation of drugs to the brain by bypassing the blood–brain barrier [26]. Furthermore, this non-invasive drug delivery route has significant impact on the therapeutic outcome [27], due to improved patient compliance and better suitability for self-administration, compared with invasive routes of administration. Importantly, the treatment can be immediately stopped to minimize adverse effects. In this context, CDs can serve as solubilizers, stabilizers or permeation enhancers. Their nano-sized self-aggregates can be developed into specialized drug delivery systems [28]. The design of effective CD-based formulations relies on the understanding of (1) physicochemical properties of drugs of interest and any other ingredients used, (2) the drug's pharmacokinetic profiles, (3) the biochemical characteristics of target sites, and (4) relevant clinical requirements. Here, some theoretical considerations for the application of CDs in drug delivery systems, and the general aspects of their toxicity are reviewed. This article emphasizes recent developments and applications of CD-based nanomedicines for topical ocular and nasal administration. The interesting findings resulting from the use of CDs, proving their efficiency and high bioavailability, will be summarized.

Inclusion Complex Formation and Self-Aggregates

Cyclodextrins already have a long history of use in the pharmaceutical industry due to their fascinating ability to form water-soluble inclusion complexes. CDs can accommodate a wide range of drug molecules, including proteins and peptides, into their central cavity. The main forces involved in the inclusion complex formation are weak non-ionic interactions, such as van der Waal forces, hydrophobic bonding and hydrogen bonding between the CD's cavity and drug molecules [29]. CD inclusion complex formation is a dynamic equilibrium process, whereby the drug molecules continuously associate and dissociate from the CD cavity. The most common stoichiometry of the complexes is 1:1 (i.e. one drug molecule forms a complex with one CD molecule), and the equilibrium is expressed in terms of the stability constant or affinity constant, $K_{1:1}$ (M^{-1}) [30]. Determination of a Higuchi phase-solubility diagram [31] is typically used to observe the formation complexes, and is obtained by plotting the observed drug solubility against increasing concentrations of CD. Complexes of 1:1 stoichiometry form linear diagrams from which $K_{1:1}$ can be calculated from the slope, according to the equation:

$$K_{1:1} = \text{slope}/S_0(1 - \text{slope}),$$

where S_0 is the intrinsic solubility of the drug in the absence of CD. There are two main types of phase-solubility diagrams: A type, the solubility of drug increases as a function of CD concentration, and B type in which the solubility of complexes is limited. $K_{1:1}$ values of drug/CD complexes generally range from 100 to 20,000 M^{-1} [32]. However, the values obtained for the same complex may vary depending on the

environmental condition. For example, the presence of water-soluble polymers in the aqueous complexation media might increase the value of $K_{1:1}$ [33] and addition of chaotropic agents (e.g. urea) might decrease $K_{1:1}$ [34]. A more accurate method to describe and compare the solubilizing properties of CDs is to determine the complexation efficacy (CE):

$$CE = S_0 \times K_{1:1} = \text{slope}/(1 - \text{slope}).$$

The self-assembly of natural CD molecules in aqueous solutions has been investigated for decades. All natural CDs have a tendency to form aggregates that are driven by intermolecular hydrogen bonds of hydroxyl groups, allocated at the hydrophilic edge of the CD molecules. This phenomenon is assumed to be the reason why the colligative properties of CDs deviate from ideality [35]. The size of aggregates ranges from <20 nm to larger than 200 nm, and their mass percentage is <1%. The aggregate formation is concentration-dependent, but the aggregates are unstable and easily collapse upon the addition of chaotropic solutes (e.g. urea, sodium chloride), media dilution and increased temperature [35]. Different shapes of aggregates, such as rods, worm-like structures, discs and sheets, are observed. Derivatives, such as HPβCD and sulphobutylether βCD (SBEβCD), have less tendency to form aggregates due to the additional centres of hydrogen bond formation, compared to the native CDs [36]. The interactions between inclusion complexes and non-inclusion complexes have been reported to associate with CD complex aggregates [37]. The existence of CD inclusion complexes with trans-β-carotene, to form self-aggregates in aqueous solution, was observed by light scattering and NMR spectroscopy [38]. The result suggested a micelle-like structure of the CDs with a hydrophobic core and hydrophilic surface. Recently, a series of amphiphilic CDs have been fabricated providing the supramolecular self-assemblies with high drug encapsulation efficiency and interesting functions [39], for example stimuli-responsive nanosystems of azobenzene and αCD [40]. This phenomenon can be a useful property for drug delivery, owing to the increased solubility, permeability and controlled release of drugs.

Toxicity of Cyclodextrins

Safety is a major concern when selecting excipients for drug formulations. Natural CDs and their derivatives are listed as inactive ingredients and accepted as excipients in pharmaceutical products by the USFDA [41]. CD toxicity is dependent on administration routes. Natural CDs are well tolerated and non-toxic when administered orally. αCD and βCD are both resistant to human amylase but are readily metabolized by microflora in the gastrointestinal tract and excreted intact in faeces [42], whereas γCD is digested by this enzyme. Parenterally administered CDs are rapidly eliminated from the body without undergoing metabolism.

αCD, βCD and some of their derivatives are unsafe when administered intravenously because they can recrystallize and accumulate in kidney tissue, subsequently causing nephrotoxicity [43]. The natural αCD and βCD are more toxic than their more water-soluble derivatives. Hydroxypropyl- and sulphobutylether CDs are recognized as safe and used in parenteral solutions whereas methylated CDs that possess surface activity are of more limited usage [44]. The cytotoxicity of RMβCD on buccal mucosa was evaluated using MTT assay and indicated that 10% RMβCD produced inflammatory effects depending on the time exposure whereas 2% and 5% RMβCD are safe to use in buccal drug delivery systems [45]. Although methylated CDs are corrosive to tissues, some commercial products contain RMβCD, such as eyedrops (Clorocil®) [46] and nasal sprays (Aerodil®) [47].

Learoy-Lechat *et al.* [48] investigated the interaction of cholesterol with CDs and found that MeβCD was able to extract cholesterol and triglycerides, whereas native CDs had less effect in aqueous environments. γCD is reported to have less selectivity of lipid extraction compared to the other native CDs. Kiss *et al.* [49] have shown that increased cholesterol extraction from cell membranes is dependent on the number of methyl groups in the βCD molecules, whereas ionic substitution of the methyl group reduces the level of extraction. Unlike surfactants, CDs form lipid complexes outside the membranes rather than penetrating their lipid bilayers. αCD and βCD are also reported to affect the unfolding temperature and aggregation tendency of some proteins [50]. The *in vivo* haemolytic activity of CDs is said to be negligible although it is observed *in vitro*, and explained by low CD concentration after parenteral administration. However, Tengumnuay *et al.* [51] observed that 1.25% DMβCD was irritating to rat nasal mucosa after perfusion for 30 min. In addition, a rather mild and reversible opening of the nasal mucosa tight junctions of the nasal mucosa has been observed. Regarding the cytotoxicity of CD-based polymers, such as Epi-αCD, the authors showed that Epi-αCD has no toxic effect up to 100 mM and no haemolytic effect [52]. The pre-clinical toxicity studies, tolerability and toxicity studies of CD-containing formulations are shown in table 2. Overall, the natural CDs and their hydrophilic derivatives are considered to be safe for direct application on membrane surfaces.

The Role of Cyclodextrins in Drug Delivery

Cyclodextrins as solubilizers.

The most common application of CDs in drug formulations is to increase the apparent solubility of poorly water-soluble drugs via inclusion complex formation. The inclusion complex formation depends on the chemical structures and physicochemical properties of both guest and CD molecules. The drug must possess a lipophilic moiety of suitable size capable of entering the somewhat hydrophobic CD cavity [53]. Several reports have suggested that CDs demonstrate greater solubility enhancement towards the unionized form of a given drug compared with ionized form, due to its higher affinity for entering the CD cavity [33]. In accordance with the Biopharmaceutical Classification System (BCS), CDs effectively increase the solubility of BCS class II (high permeability and low solubility) and sometimes class IV (low permeability and

Table 2.
The pre-clinical toxicity studies of some selected CDs and their tolerability/toxicity studied in topical ocular and nasal drug formulations.

Types	Species	Route	LD50 or NOEL/NOAEL	Tolerability/Toxicity
αCD	Rat	IV	LD50: 1000 mg/kg	***Corneal:*** 40 mg/ml αCD in 0.025% cyclosporine eyedrops reduce corneal toxicity [95]. >4% caused erosion in cornea of rabbits. ***Nasal mucosa:*** Partially reversible cilio-inhibition observed at 5% concentration [96].
βCD	Rat	IV	LD50: 788 mg/kg	***Nasal mucosa:*** 1.5% does not cause tissue damage [97].
		Oral	LD50: >5000 mg/kg	
	Dog	Oral	LD50: >5000 mg/kg	
γCD	Rat	IV	LD50: >3750 mg/kg	***Corneal:*** Eyedrops containing γCD are well tolerated [98]. ***Nasal mucosa:*** 1–10% do not demonstrate significant cilio-inhibitory effect [96].
		Oral	LD50: >8000 mg/kg	
MβCD	Rat	Oral	LD50: >8000 mg/kg	***Corneal:*** 5% and 12.5% DMβCD are not suitable vehicle for ophthalmic formulations [99]. ***Nasal mucosa:*** Irreversible cilio-inhibition was found at 10% DMβCD [96]. 2–5% concentration of RMβCD has minor toxic on nasal morphology and effectively enhanced nasal absorption. 20% concentration of RMβCD did not show any toxicity [100,101].
		IH	LC50: >2950 mg/m^3/4 hr	
	28-days rat	Oral	NOEL/NOAEL: 300 mg/kg/day	
SBEβCD	52-weeks dog	Oral	NOEL/NOAEL: 500 mg/kg/day	***Corneal:*** Decrease the eye irritation [102]. ***Nasal mucosa:*** Reduce local irritation and enhance drug absorption [103].
	90-days rat	Oral	NOEL/NOAEL: 3600 mg/kg/day	
HPβCD	1-year rat	Oral	NOEL/NOAEL: 500 mg/kg/day	***Corneal:*** Well tolerated in rabbit eye and not toxic to the corneal epithelium at 12.5% concentration [99]. ***Nasal mucosa:*** 10% does not demonstrated significant cilio-inhibitory effect [96].
	1-month dog	Oral	NOEL/NOAEL: 2250 mg/kg/day	

low solubility) drugs, thus moving the drugs from their original classes to BCS Class I (high permeability and high solubility) [54]. In general, CDs cannot improve the bioavailability of BCS Class III (low permeability and high solubility) drugs. Also, CDs can only be used as solubility enhancers for high- to medium-potency drugs and only if the drug has a high CE, because the optimum drug bioavailability is frequently obtained with a minimum amount of CD exploited [37,55].

Cyclodextrins as permeation enhancers.

The application of CDs in pharmaceutical products is not limited to drug solubilization. CDs are also known to enhance drug permeation through biological membranes, but only under specific conditions, and the mechanism is not clearly understood. CDs are very large hydrophilic molecules that cannot pass through lipophilic biological membranes [56]. It has been suggested that the increase in drug availability at the membrane barrier surface, as well as solubilization of membrane lipid components, is due to the absorption enhancement mechanisms of CDs [28]. In general, the outermost layer of membranes is covered with an unstirred water layer (UWL), mucus on nasal membranes and tear fluid layers on the eye surface, and this layer is considered to be the rate-limiting barrier to the topical drug delivery of lipophilic drugs [57]. The drug must possess adequate lipophilicity that it can diffuse through lipophilic biomembranes. Additionally, the drug must have enough aqueous solubility in the UWL to partition into a lipophilic layer, as the rate of drug permeation from the surface is proportional to the concentration gradient of dissolved drug, according to Fick's first law. The lipophilicity of drug is commonly expressed in terms of log $K_{octanol/water}$ (i.e. the logarithm of the drug partition coefficient between water and n-octanol). The relationship between the apparent partition coefficient (P_{app}) and the UWL or membranes has been explained elsewhere [58,59].

Cyclodextrins will effectively enhance lipophilic drug permeation through biomembranes when the UWL is the major hindrance, and the effective permeability will depend on the concentration of CDs. Increased CDs result in increased UWL permeability, due to a decrease in the apparent UWL thickness, but decreased membrane permeability, owing to a reduction in the fraction of free drug molecules [60]. The work carried out by Miller and coworkers [61] demonstrated that the use of appropriate CD concentrations reduces the UWL effect on the P_{app} of progesterone. Their results suggest that HPβCD effectively shrinks the UWL, and facilitates drug transport to the membrane when the drug concentration at the membrane surface is equal to the concentration of drug in the

bulk (i.e. the chemical potential of drug is equal on both sides of the membranes). Other studies have implied that the optimal CD-based formulations are achievable when using minimum amount of CD sufficient to solubilize the drugs [62,63].

In terms of ocular and nasal drug delivery, due to the corneal and nasal epithelium cells being tightly packed together, nanoparticles cannot simply diffuse across the epithelium layers. This is because of the restriction caused by the gap between the epithelium tight junction beneath the mucus layers, which is <0.1 nm [64], except in certain pathological conditions, for example vascular inflammation. Therefore, increasing the residence time and improving the diffusion of drugs across the mucus layers are the main strategies used to deliver nanoparticles. CDs have been used for enhancing the mucus-penetrating properties of drugs; unfortunately, natural CDs lack mucoadhesive properties [65]. Other biodegradable and biocompatible polymers, such as poly(lactic-co-glycolic acid) (PLGA), polyethylene oxide (PEO), chitosan and thiolated polymers, are incorporated into the formulations in order to improve the mucoadhesiveness.

Cyclodextrins as stabilizers of colloids.

In dispersed systems, CDs serve as stabilizers and true carriers that augment the availability of drug molecules to the targeted sites. The evidence that CDs form aggregates, or micelle-like structures, with surfactant-like effects, led to the idea of surfactant-free formulations [66]. Publications on CDs acting as surface-active complexes have already been reported by several researchers. Inoue *et al.* [67] reported the stabilizing ability of three natural CDs, with the βCD inclusion complex showing the best stabilizing effect. They explained that at high concentrations, CD complexes have a contact angle <90°, precipitated at o/w interface resulting in a stable emulsion. Mathapa and Paunov [68] investigated Pickering emulsions formulated with CDs. They proposed that self-assembled CDs formed microparticles at the surface of emulsion droplets. Makhlof *et al.* [69] successfully employed CDs as protective stabilizers for preparing indomethacin nanocrystals, and they revealed that the network formation of CDs contributed to the uniform particle size of drug nanocrystals. Interestingly, many studies observed that CDs have the capability to stabilize the liquid formulation of proteins [70,71]. This ability is attributed to the binding between CD and hydrophobic residues on proteins, inhibiting protein aggregation. In dried protein formulations, CDs can serve as lyoprotectants, providing excellent physical stability of lyophilized cakes and preventing crystallization of amorphous complexes [72].

Cyclodextrins as controlled-release modifiers.

One of the functions of CDs in drug delivery is to optimize the drug release in accordance with the therapeutic purposes. Simple media dilution is a major driving force of drug release from CD complexes. In the human body, drug–protein binding, competitive binding and drug separation from complexes to targeted tissues can cause rapid drug release from CD complexes [73]. CDs can serve as immediate-, delayed- or prolonged-release carriers. For example, Bibby *et al.* [74] demonstrated that the incorporation of CDs into buccal patches containing buprenorphine increased the amount of drug released from the polymer matrix. Nonetheless, many studies have shown that CDs restrict the release of drug from polymeric drug delivery systems. Controlled-release mechanisms of CDs have been studied intensively in oral drug delivery systems, but only a few referred to topical or nasal drug formulations. Hydrophilic CDs typically provide a fast release of drug in contrast to hydrophobic CDs, which impede the drug release [75]. However, the release behaviour in the drug delivery system deviates from this basis depending on the type of CD, materials presented in formulations, encapsulation efficiency and drug properties.

The release rate of doxorubicin from micelles triggered by the presence of βCD was studied by Wang *et al.* [76]; they observed rapid release profiles with increasing βCD concentrations. Vafaei *et al.* [77] fabricated multivesicular liposomes containing CDs for ocular drug delivery and reported that HPβCD demonstrated sustained-release behaviour of drug from liposomes, whereas αCD showed an increased release rate from the same system. The burst release followed by delayed release of drugs was observed when utilizing amphiphilic βCD [78] or chitosan-grafted βCD nanoparticles [79]. The former result could be explained by improvements in drug solubility, whereas the latter could be attributed to the diffusion of the remaining drug in the hydrophobic core, in addition to weakened hydrogen bonds among chitosan. The affinity of drug to CD cavity is one of the mechanisms that govern drug release behaviour. High drug loading of SBEβCD nanoparticles showed a sustained release, with small quantities of anti-Alzheimer's drug, due to a high affinity of drug and SBEβCD [80]. Machín *et al.* [81] observed that the diffusion coefficient of drug from CD hydrogels inversely correlated with drug/CD affinity.

Cyclodextrin-Based Nanocarriers for Targeted Ocular and Nasal Drug Delivery

CDs have been investigated as nanocarriers for drug delivery due to their self-assembling ability and biocompatibility. Structurally tailored CDs have led to special nanoarchitectures, such as nanospheres, nanomicelles, nanoparticles and nanogels, with either water-soluble or insoluble drugs being loaded into the hydrophilic and hydrophobic parts of the CD units. The publication analysis performed by Lim Chin *et al.* [82] indicated that about 22% of the total development in the context of nanosuspensions focused on ophthalmic and nasal drug delivery. The nano- and micro-sized carriers from drug/CD complex aggregates, using natural CDs, were developed by Loftsson and coworkers [83]. They discovered that aggregates behave like nanoscale-dispersed systems, which gradually break into smaller complex aggregates and maintain high drug concentrations in tear fluid, with consequent improvements of patients' therapeutic outcome.

CD/chitosan nanoparticles, with particle sizes ranging from 200 to 500 nm [84,85], and prepared using the ionotropic gelation method, have been used for topical and transmucosal

Table 3.
Some examples of non-invasive cyclodextrin-based formulations studied for targeted drug delivery systems.

Targets	Systems	Drug examples	Cyclodextrins	~Size (nm)	Physical forms	Finding results [Ref.]
Ocular	CD/Chitosan nanoparticles	Naringenin	SBEβCD	446.4	Colloid dispersions	The systems prolong residence time and significantly increase bioavailability in rabbits' aqueous humour [104].
	CD/PLGA nano- and microspheres	Dexamethasone sodium phosphate	HPγCD, γCD	4.44–21.53 μm	Suspensions	The systems significantly increase the entrapment efficacy and diminish the release of the drug [105].
	CD-based nanogel	Dexamethasone	HPβCD, γCD	2.23–119	Colloid dispersions (Eyedrops)	Provide sustained release of drug for at least 6 h in the tear fluid [106].
	CD-based nano- and microparticles	Dexamethasone	HPβCD, HPγCD, γCD	n.d.	Suspensions (Eyedrops)	Well tolerated, improve visual acuity and decrease macular thickness in patients with DME [107].
		Disulphiram	HPβCD	183	Colloid dispersions (Eyedrops)	AUC and mean corneal residence time increased by 1.45 times and 1.44 times [108].
Nasal	CD/Albumin nanoparticles	Tacrine HCl	HPβCD, SBEβCD	0.33–300	Colloid dispersions	NPs show high entrapment of drug and good adhesion to nasal mucosa [80].
	CD/Chitosan nanoparticles	Dopamine	SBEβCD	214–1 μm	Suspensions	The NP carriers slow down the autoxidation process of dopamine and provide controlled release of the drug [109].
	CD-based nano- and microparticles	Insulin	βCD, SBEβCD, CMβCD	198–340	Colloid dispersions (Nasal drops)	Increase loading capacity and encapsulation efficacy, CD contents affect the release rate and cumulative release of insulin [110].
	CD/PLGA nanoparticles	Bovine serum albumin	bis-CD	n.d.	Colloid dispersions	Increasing entrapment efficacy up to 83.5% and showing burst effect followed by continuous release [111].

CMβCD = carboximethyl-βCDl, bis-CD = ethylenediamino or diethylenetriamino bridged bis(βCD); n.d. = no data available from the author.

administration. Trapani *et al.* [86] suggested that CD/chitosan encapsulation efficiency corresponds to the concentrations of the two polymers used, the viscosity of the chitosan solution and the drug to polymer ratio. Based on the solubilizing effects of anionic CDs (e.g. SBEβCD and carboxymethyl-βCD [CMβCD]) and the mucoadhesive effect of chitosan, a cationic polymer, the resulting nanoparticles have been found to be more stable, prolong the residence time on the membrane surface and increase the permeability of drugs through biomembranes. CD-based hydrogels have also been investigated and described in the literature. Li *et al.* [87] reported the first hydrogel formed by directly cross-linking poly(ethylene glycol)s (PEG) and αCD; the resulting system created a microenvironment which CD–drug affinity controlled drug release. Gref *et al.* [88] developed CD-based nanogels by applying the lock and key mechanism. This interpenetrating network spontaneously forms at room temperature or under mild conditions by mixing aqueous solutions of βCD polymer and modified dextran polymer. The results showed high production yields of 95%, and stable nanoassemblies with a diameter of approximately 200 nm. Their nanogels displayed a drug-loading capacity of up to 5% dry weight and sustained drug release behaviour. Fundueanu *et al* [89]. have scrutinized starch/CD microspheres obtained by cross-linking with epichlorohydrin for the nasal delivery of antiproteases. The obtained microspheres increase the stability of the drug and provide good adhesive properties, allowing the drug to adhere to the nasal mucosa. Other studies showed that the formation of CD and drug complexes, in both thermo-reversible gels and *in situ* nasal insert, leads to an increased viscosity and a gradual absorption of drug from the formulations [90,91]. Hyperbranched CDs have been explored for enhancing insulin transport across the nasal mucosa, with a high insulin-loading content, and an *in vivo* reduction in blood glucose concentration, being observed [92]. The application of nanofibres, produced by electrospinning a mixed solution of polyvinyl alcohol and HPβCD, for ophthalmic drug delivery has been investigated by Sun *et al.* [93]. In rabbits, they observed a significant improvement in half-life in rabbits compared to voriconazole ophthalmic solution. Example of non-invasive, CD-based drug delivery systems that have recently been studied for targeted ocular and nasal drug delivery are listed in table 3.

As seen from table 3, CD-containing formulations have significant potential to improve drug bioavailability by increasing drug loading, and overcoming the static and dynamic barriers at the surface of target sites. In comparison with other non-invasive drug delivery systems, CD-based drug delivery systems prevent better the physical and chemical instability of drugs that are associated with liposomes and nanosuspensions. This requires small amount of surfactants, along with reduced permeation enhancer, which consequently eradicates the uncomfortable feeling during application. It is unnecessary to utilize special devices and techniques (e.g. iontophoresis) because the formulations are easily applied at the site of their target tissue. Considering the economic impact of using CDs, they improve clinical efficacy and patient compliance and in that way reduce the cost of drug administration. The manufacturing cost is more affordable, and refined formulations known as super generic drug formulations are attained. However, we should bear in mind that these new formulations are not bioequivalent with the conventional formulations due to bioavailability differences.

Concluding Remarks

Cyclodextrins and their derivatives have great versatility for the development of new formulations. Understanding the basic chemistry of CDs including the formation of their inclusion complexes, their limitations and self-assembled aggregates of CDs contribute towards the success and effectiveness of their pharmaceutical applications. The formulations comprising CDs are biodegradable, show favourable toxicological profiles and reduce the use of surfactants and organic solvents in dosage forms. As addressed in the literature, several diverse assemblies of CDs, such as nanoparticles, nanoemulsions and nanogels, are making it possible to allow targeted drug delivery to specific sites in minimally invasive pathways. The use of CDs in nanotechnology for non-invasive drug delivery is shedding light on the improvements in and broadening our knowledge of topical, ocular and transmucosal drug delivery technologies. Until now, many nanomedicines have been successfully formulated into non-invasive drug delivery systems. The literatures describe the pharmacokinetic behaviour of these formulations although data based on studies in human beings are still insufficient. Considering the potential of CDs in drug delivery, it is certain that CDs will continue to play a significant role in drug delivery and development.

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