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Review

Cyclodextrins and derivatives in drug delivery: New developments, relevant clinical trials, and advanced products

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ABSTRACT

Cyclodextrins (CD) and derivatives are functional excipients that can improve the bioavailability of numerous drugs. Because of their drug solubility improving properties they are used in many pharmaceutical products. Furthermore, the stability of small molecular drugs can be improved by the incorporation in CDs and an unpleasant taste and smell can be masked. In addition to well-established CD derivatives including hydroxypropyl-β-CD, hydroxypropyl-γ-CD, methylated- β-CD and sulfobutylated- β-CD, there are promising new derivatives in development. In particular, CD-based polyrotaxanes exhibiting cellular uptake enhancing properties, CD-polymer conjugates providing sustained drug release, enhanced cellular uptake, and mucoadhesive properties, and thiolated CDs showing mucoadhesive, in situ gelling, as well as permeation and cellular uptake enhancing properties will likely result in innovative new drug delivery systems. Relevant clinical trials showed various new applications of CDs such as the formation of CD-based nanoparticles, stabilizing properties for protein drugs or the development of ready-to-use injection systems. Advanced products are making use of various benefical properties of CDs at the same time. Within this review we provide an overview on these recent developments and take an outlook on how this class of excipients will further shape the landscape of drug delivery.

1. Introduction

A half-century after their first isolation by Villiers and the discovery of their chemical basics by Schardinger, cyclodextrins (CDs) already found applications in drug delivery in the 1950s. As only small amounts of cyclodextrins could be supplied at relatively high production costs, however, they were just rarely used by pharmaceutical industry. Advanced biotechnological manufacturing processes that were established in the 1970s and 1980s paved the way for their large-scale production, increasing interest of pharmaceutical industry that found subsequently various applications for these excipients. CDs exhibit a slightly hydrophobic central cavity where lipophilic drugs or lipophilic moieties of drugs can be incorporated. The complex formation improves the aqueous solubility of drugs, increases their chemical stability, reduces, or prevents irritations or masks their unpleasant tastes or smells (Fenyvesi, Vikmon, & Szente, 2016). Because of these advantages for drug delivery, various CDs and their derivatives have already been registered as pharmaceutical excipients, including α-, β-, γ-CD, hydroxypropyl β-CD (HP-β-CD), hydroxypropyl γ-CD (HP-γ-CD), randomly methylated β-CD (RM-β-CD) and sulfobutylated β-CD (SB-β-CD). Numerous pharmaceutical products containing these excipients are either subject of clinical trials or have already entered the global market. Moreover, various new derivatives, such as CD-based polyrotaxanes, CD-polymer conjugates, or thiolated CDs, are in the pipeline that hold promise to further broaden the applicability of CDs in drug delivery. Within this review, we provide an overview about new developments that are likely game changers, we discuss clinical trial results that are of high scientific relevance, and we highlight successful, approved products giving examples of new developments.

2. Cyclodextrins and derivatives

2.1. Natural cyclodextrins

Cyclodextrins (CDs) are biocompatible and biodegradable materials produced by the enzymatic degradation of starch (Crini et al., 2018; Loftsson, Brewster, & Masson, 2004; Poulson et al., 2022). They consist of six up to 12 (α-1,4)-linked α-D glucopyranose units. Due to the chain conformation of the glucopyranose units, they have the shape of a truncated cone with a slightly hydrophobic central cavity provided by

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the skeletal carbon atoms of glucose and a hydrophilic exterior provided by the hydroxyl groups of glucose (Arruda, Marques, & Soares, 2021; Crini et al., 2018; Davis & Brewster, 2004; Saokham, Muankaew, Jansook, & Loftsson, 2018). Their physicochemical properties are listed in Table 1.

Most prominent are α-, β-, and γ-CD, as illustrated in Fig. 1. In addition to these pharmaceutically approved CDs, larger cyclic oligosaccharides with 9 to 12 glucose units, named as δ-, ε-, κ-, and μ-CDs, respectively, are available. The terminology can be theoretically even continued till ω-CD with 29 repeats (Larsen, 2002).

2.2. Derivatives

Modification of CDs is feasible through the three hydroxyl groups in the anhydroglucose repeats, as illustrated in Figs. 2–4. The -OH in the C-6 position is the most basic and most available for modifications (Fejős, Kalydi, Malanga, Benkovics, & Béni, 2020; Scriba, Konjaria, & Krait, 2023). The hydroxyl in the C-2 position is the most acidic, while the C-3 position is most sterically hindered. CDs can be selectively modified because of these differences in reactivity of the three hydroxyl groups (Köse, Tüysüz, Aksüt, & Uzun, 2022; Wenz, 1994). Nonionic hydrophilic, slightly lipophilic, and ionic CDs are commercially available for various applications (É. Fenyvesi et al., 2016; Puskás, Szente, Szőcs, & Fenyvesi, 2023; Loftsson & Duchêne, 2007; Loftsson, 2021; Jin et al., 2019; Jain, Nowak, & Ravoo, 2022). In most cases, CDs are modified in order to improve their solubility, but there are also good examples of modifications aiming at other goals (Jain et al., 2022; Köse et al., 2022; Morin-Crini et al., 2021; Wenz, 1994).

2.2.1. Substitution reactions

CDs can be derivatized using various substitution reactions. One of the most widely applied methods is converting hydroxyls to other functionalities, resulting in deoxy-functionalized CDs. Another widespread approach is the reaction with hydroxyl groups, leading to the substitution on the oxygen of the hydroxyl moiety (Kasal & Jindřich, 2021; J. Y. Liu, Zhang, & Tian, 2020; Řezanka, 2016; Řezanka, 2019). Monosubstitution and persubstitution of CDs at a specific position (i.e., C-2, C-3, or C-6) are important in order to prevent the formation of different isomers with various degrees of substitution (Řezanka, 2019; Zultanski et al., 2021). Otherwise, these isomers have to be separated via chromatographic methods. Secondary hydroxyls in C-2 and C-3 positions are hardly modified separately (García et al., 2019). Even though C-2 hydroxyl is the most acidic one, attempts to modify it in the presence of an equivalent amount of base resulted in unsatisfying yield and uniformity of the product. The C-3 position is most inaccessible but can be selectively substituted via the inclusion complex method, where the reagent forms a host-guest complex with the CD, and the reactive site is oriented to the C-3 hydroxyl to react with it (Khan, Forgo, Stine, & D'Souza, 1998). Finally, the C-6 position on the primary site is the most accessible and most nucleophilic hydroxyl group, freely available for several substitution reactions. Most monosubstitutions described in the literature aim to modify this hydroxyl group at the primary site. The various products of substitutions are depicted in Fig. 2.

2.2.2. Deoxy cyclodextrins

Mono-6-substituted CDs bear only one functional group per ring; consequently, these derivatives lack the symmetry of the parental CD. For the synthesis of such materials, 6-O-aryl/alkyl-sulfonated CDs are formed in the first step and modified further (Kasal & Jindřich, 2021). Predominantly 6-deoxy-6-halogenated CDs are synthesized because of their high reactivity but the 6-O-aryl/alkyl-sulfonated CDs can also be processed further to target products like mono azides, amines, or thiols (Řezanka, 2019; Řezanka, 2016; Kasal & Jindřich, 2021; J. Y. Liu et al., 2020). These monosubstituted CDs can be directly used (W. Tang & Ng, 2008) or modified further, for example, with click chemistry or oxidation (Kasal & Jindřich, 2021).

Di-6-deoxy-substituted CDs are also synthesized with high selectivity through a protection-selective deprotection step, resulting in di-6-deoxy-6-thiolated α-CD forming intra- and intermolecular disulfides (Kumprecht et al., 2009).

Per-6 modified CDs offer high symmetry and more functionalities than monosubstituted ones. Per-6-halogenated-per-6-deoxy CDs are synthesized in the first step and can be further modified with another substitution reaction, for example, with thiourea, leading to per-6-thiolated CDs (Asim et al., 2020).

Randomly substituted CDs bear several functional moieties in various positions (C-2, C-3, and/or C-6; Zultanski et al., 2021; Řezanka, 2019). The reaction of native CDs with thiourea and the subsequent hydrolysis of the thiouronium anion (Zaman, Bajwa, Saeed, Hussain, & Hanif, 2020) can be improved by a microwave reactor in order to reach a high degree of random thiolation (Hussain Asim et al., 2020; Grassiri, Knoll et al., 2022).

The per-modification of CDs results in the derivatization of all hydroxyl groups. It is mostly used to increase solubility (Řezanka, 2019). A recent study used phosphorous pentasulfide to gain per-deoxy-thiolated β-CD (Kali, Haddadzadegan et al., 2022) in a one-step reaction.

2.2.3. O-substituted cyclodextrins

Among O-substituted CDs, methylated and hydroxypropylated ones are likely the most important derivatives due to their high water solubility and complexing ability. Per-6-O-(*tert*-butyldimethylsilylated) CDs are protected intermediates for selective modification of the C-2 and C-3 positions, followed by a deprotection step (Řezanka, 2019). This method is widely used for per-6 methylation of β-CD (Bálint et al., 2019). A simpler one-pot reaction was recently established to synthesize per-6-methyl β-CD using $CuSO_4$ complexed oligosaccharide (Bucur, Niculaua, Ciobanu, Lungu, & Mangalagiu, 2021). Besides the selective modifications, random substitution of the hydroxyl groups at various positions is also feasible. Among others, randomly methylated β-CD is one of the most prominent methylated derivatives.

The hydroxyl groups of CDs, especially on the primary face, can be utilized for condensation reactions. The most important CDs, modified by condensation reactions, are 2-hydroxypropylated CDs. Among them, 2-hydroxypropyl-β-CD (HP-β-CD) is the most investigated variant due to

Table 1
Physical-chemical parameters of pharmaceutically approved CDs according to Shaokham et al. (Saokham et al., 2018) and Arruda et al. (Arruda et al., 2021).

	Number of glucopyranose units	Degree of substitution	Molecular weight (Da)	Solubility in water (g/L, 25 °C)	Internal diameter (Å)	Internal volume (nm^3)
α-CD	6	–	972	145	4.7–5.3	0.174
β-CD	7	–	1135	18.5	6.0–6.5	0.262
γ-CD	8	–	1297	232	7.5–8.3	0.427
HP-β-CD	7	0.65	1400	>600	6.0	0.262
RM-β-CD	7	1.8	1312	>500	5.8–6.5	0.262
SB-β-CD	7	0.9	2163	>500	6.0–6.5	n.a.
HP-γ-CD	8	0.6	1576	>500	8.0	0.427

HP-β-CD = 2-hydroxypropyl-β-CD, RM-β-CD = randomly methylated-β-CD, SB-β-CD = β-CD sulfobutyl ether sodium salt, HP-γ-CD = 2-hydroxypropyl-γ-CD, n.a = no data available.

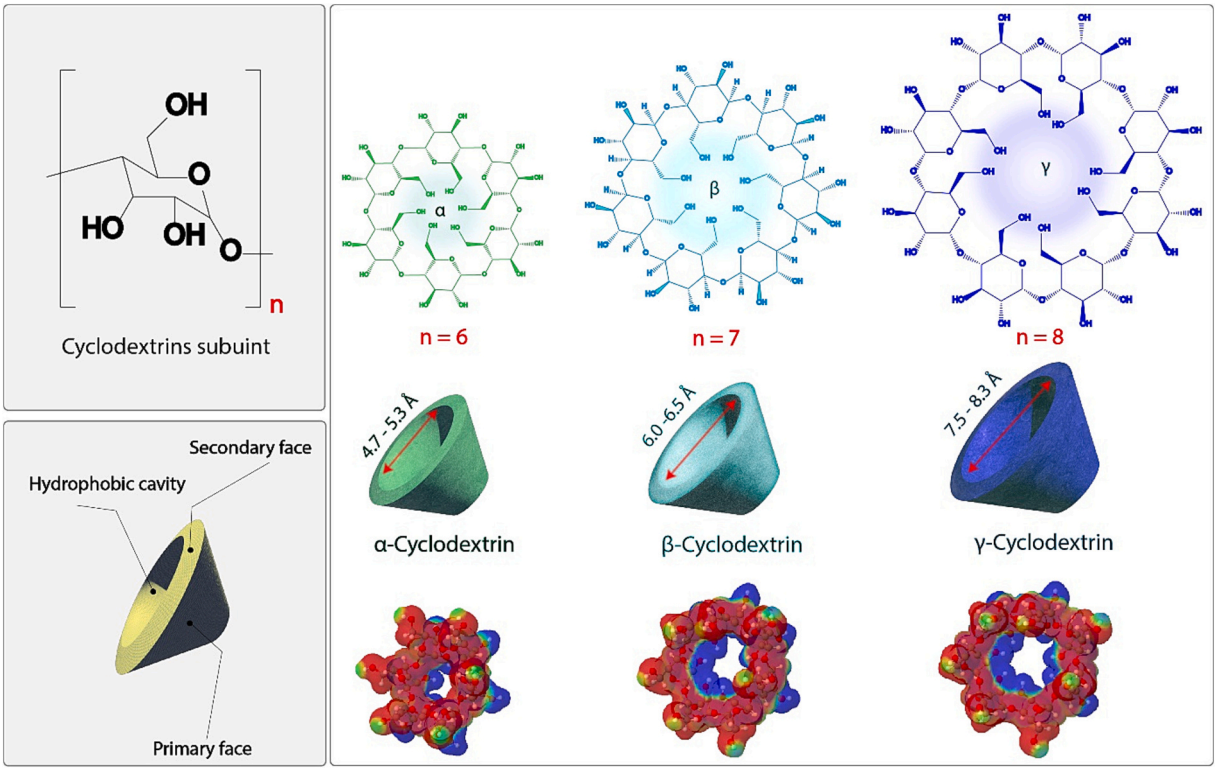

Fig. 1. The structure of the anhydroglucose repeating unit of cyclodextrins (upper left), with a schematic representation of the 3D structure (lower side left) and chemical and 2D structures, as well as computational surface analyses of α-, β-, and γ-cyclodextrins (right-hand side).

its high water solubility, low toxicity, and high complexation profile (D'Aria, Pagano, & Giancola, 2022; Gould & Scott, 2005). Hydroxypropylated CDs are synthesized by a condensation reaction between the native CD and propylene oxide, and the degree of modification can be simply adjusted by the ratio of the reactants (Pitha, Milecki, Fales, Pannell, & Uekama, 1986). Polycondensation reaction of CDs with epichlorohydrin or poly-epoxy compounds results in branched polymeric materials with tunable solubility (Gidwani & Vyas, 2014; Renard, Sebille, Barnathan, & Deratani, 1997).

Regarding the water solubility, which is in many cases the aim of these modifications, random methylation of the hydroxyl groups of β-CD increases its aqueous solubility up to 500 g/L, while hydroxypropylation of the hydroxyl groups in the C-6 position up to above 600 g/L (Saokham et al., 2018). Introducing ionic groups into the CD structure can further increase aqueous solubility.

2.2.4. *Esterification*

A widely used modification method for CDs is their esterification with carboxylic acids, also a kind of O-substitution. This reaction is discussed separately due to the importance of esterification, mostly used to conjugate drugs or targeting moieties to the CDs, to form CD-based surfactants (Schlüter, Bela, Glikman, Braunschweig, & Ravoo, 2020) or to enhance the solubility of some CD-based supramolecular structures (Kato, Hori, & Ito, 2018; Mayumi, Liu, Yasuda, & Ito, 2021). The possible esterification reactions are summarized in Fig. 3. Per-acetylated CDs with high solubility in supercritical carbon dioxide or organic solvents can form host-guest complexes in non-aqueous media (Añibarro et al., 2001; Filardo et al., 2006; Jicsinszky et al., 2015). Esterification of CDs can be achieved by enzymatic transesterification (Pedersen et al., 2005; Putaux et al., 2017; Putaux, Lancelon-Pin, Choisnard, Gèze, & Wouessidjewe, 2022) or chemically, using carbodiimide chemistry or applying the acyl chloride form of the carboxylate (Blaj, Kowalczuk, & Peptu, 2023; Shahiwala, 2020). Another option is to use CDs to initiate the ring-opening polymerization of lactide or ε-caprolactone monomers, resulting in a fully biodegradable macromolecular CD-ester (Blaj, Balan-Porcarasu, Petre, Harabagiu, & Peptu, 2021; Meimoun et al., 2022; Peptu, Blaj, Balan-Porcarasu, & Rydz, 2022).

Polycondensation is achievable by the esterification of CDs with multiple carboxylic acid or anhydride moiety-bearing molecules, such as citric acid, poly(acrylic acid), or pyromellitic dianhydride (Caldera, Tannous, Cavalli, Zanetti, & Trotta, 2017). Depending on the conditions, soluble branched polymers or insoluble gels/nanosponges are formed; both structures are of particular interest for pharmaceutical and environmental applications (Escobar et al., 2023; Garcia-Fernandez et al., 2016; Martel, Ruffin, Weltrowski, Lekchiri, & Morcellet, 2005; Morin-Crini & Crini, 2013).

2.2.5. *Oxidation*

The oxidation of CDs can lead to aldehyde functionalities by opening some anhydroglucose repeating units with $NaIO_4$ (Hoang Thi, Lee, Ryu, Sung, & Park, 2017). The formed aldehydes showed enhanced water solubility (Hoang Thi et al., 2017; Ye et al., 2017). Furthermore, broad-spectrum antimicrobial activity was found for these derivatives (Ye et al., 2017). The aldehyde groups can be subjected to reductive amination, resulting in cationic substructures, that provide high water solubility (Ijaz, Ahmad et al., 2016; Mulazim, Ijaz, Rösch, & Bernkop-Schnürch, 2020) as depicted in Fig. 4. The reductive amination can also be used to form bridged CD derivatives (Marinescu, Doyagüez, Petrillo, Fernández-Mayoralas, & Bols, 2010).

3. Biocompatibility and safety

All parent CDs are 'generally recognized as safe' (GRAS; "European Medicines Agency, Cyclodextrins used as excipients, (EMA/CHMP/495747/2013),"). Because of their small size, however, CDs are to a higher extent osmotic active than polysaccharides. High dosage oral application of CDs that is above 1 g/kg/day can cause diarrhea, or cecal enlargement, while nasal irritation or nasal tissue damage was found

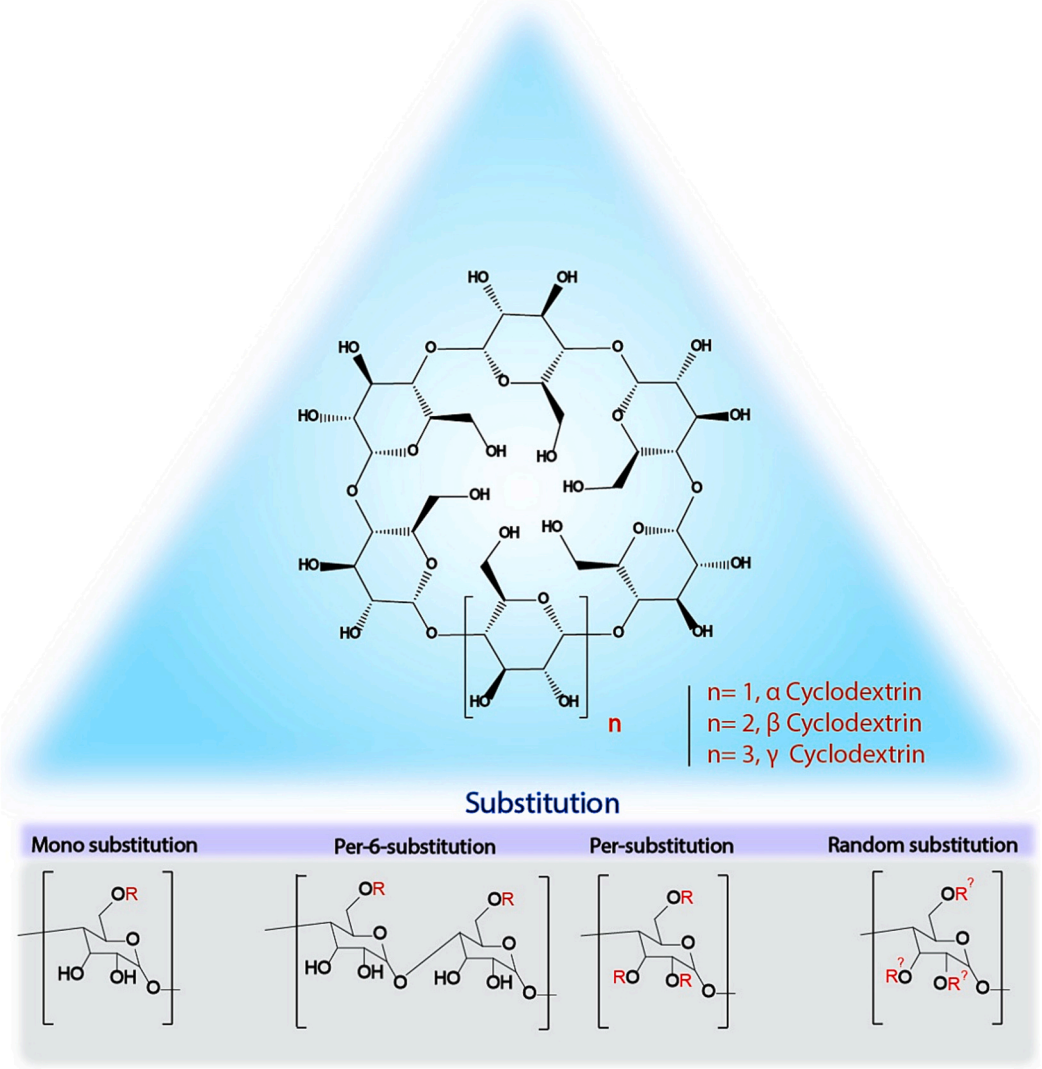

Fig. 2. Synthetic pathways for various substituted CD derivatives, where R is the desired functionality, while $R^?$ is R or H.

only in the case of RM-β-CD at a concentration of 20 %. Ocular application of α- and methylated β-CD causes epithelial toxicity and irritation, respectively, while no such side-effect was detected for β-CD, HP-β-CD, or SB-β-CD. No irritation in the case of rectal application was reported (EMA, 2017; Trotta, Loftsson, Gaud, Trivedi, & Shende, 2022). Even the low cytotoxicity of the various native CDs could increase with their concentration but is also affected by the modification of the CD. Concentrations of 4 % α-CD and 5 % of RM-β-CD, for instance, can be toxic to the corneal epithelium for rabbits ("European Medicines Agency, Cyclodextrins used as excipients, (EMA/CHMP/495747/2013),"). More importantly, CDs show a hemolytic effect. β-CD causes the most serious red blood cell membrane damage, as it extracts cholesterol from the membrane. The HP-β-CD is also used to complex cholesterol in vivo (Hastings, Liu, Hurst, Cox, & Hrynkow, 2022). Among methylated β-CDs, the dimethyl-β-CD presents the highest cholesterol extraction capacity but consequently also the highest hemolytic activity (Kiss et al., 2010). The hemolytic effect of α- and γ-CDs is most probably connected to their inclusion complex formation with membrane lipid constituents, for example, phospholipids (Róka et al., 2015).

4. New developments

4.1. CD-based polyrotaxanes

One of the most intriguing classes of CD-based polymeric materials are polyrotaxanes. These materials consist of polymer chains and threaded ring-shaped molecules, such as CDs (Wenz, Han, & Müller, 2006). Due to the interlocked supramolecular structure, several interesting properties are related to these materials. In order to inhibit the dethreating of CDs from the polymeric axis, stopper molecules are placed at the chain ends, as illustrated in Fig. 5A. These stoppers can also be sensitive to environmental impact, triggering the decomposition of the polyrotaxanes under certain conditions, making this class of materials an interesting tool for various biomedical applications (Zhi Liu, Lin, Purro, & Xiong, 2016; Yoshikawa et al., 2022; Atsushi Tamura & Yui, 2018; Higashi, Iohara, Motoyama, & Arima, 2018). Most polyrotaxanes consist of PEG chains and α-CD. In order to improve the solubility of α-CD, its methylated and hydroxypropylated dergivatives are also used.

4.1.1. Cellular uptake enhancement by polyrotaxanes

Functionalized polyrotaxanes are applied as drug delivery systems enhancing cellular uptake. In particular, anionic carboxylated polyrotaxanes cause strong interaction with membrane proteins. They showed higher cellular internalization than nonionic ones in SR-A-

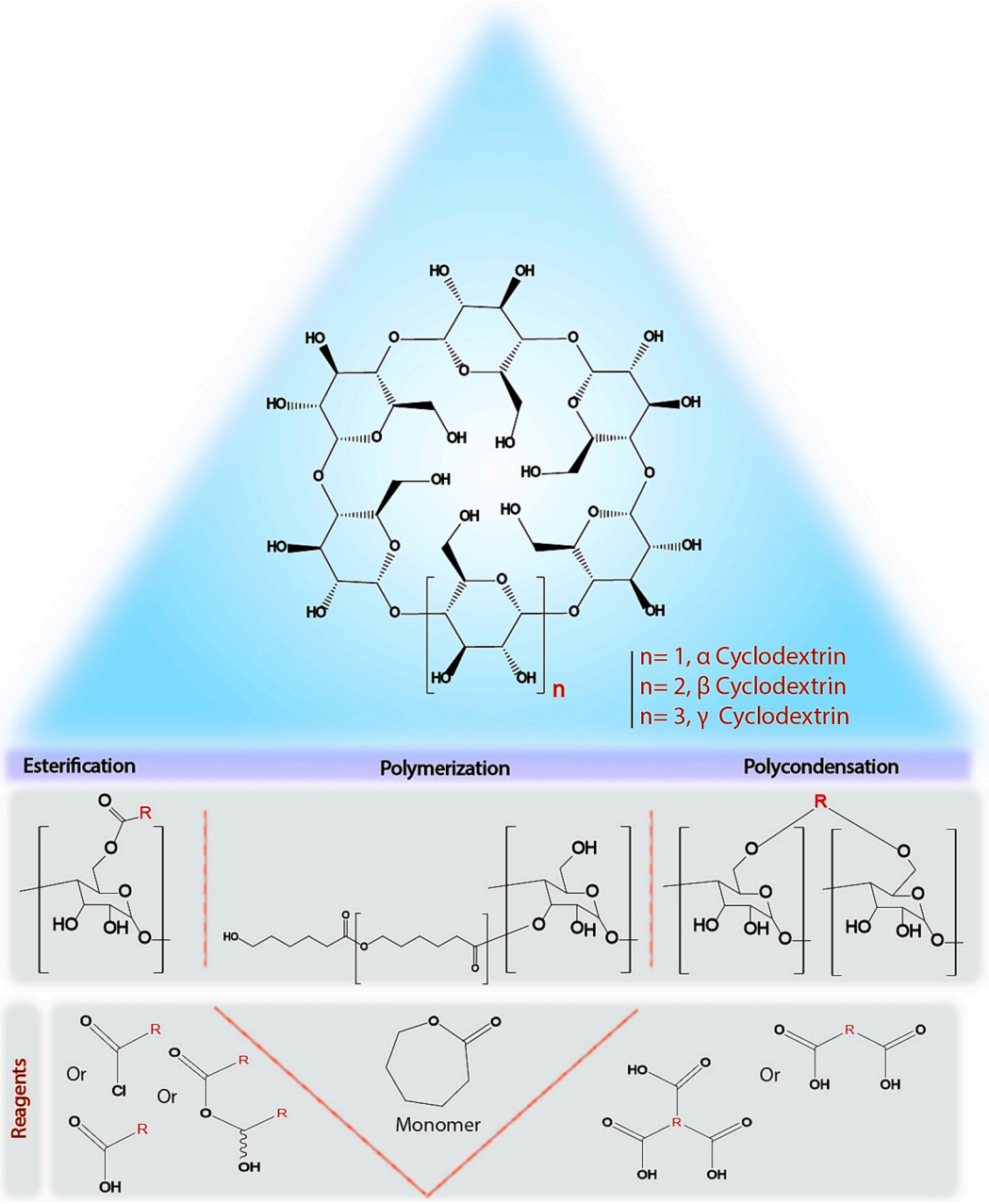

Fig. 3. Schematic representation of the various esterification reactions of CDs, where R is the desired functionality or crosslinker.

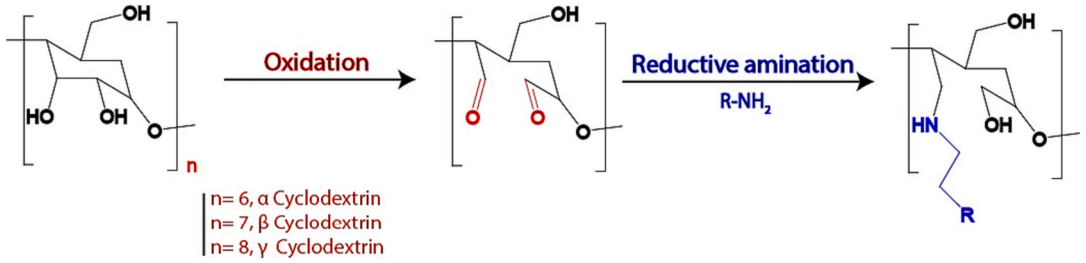

Fig. 4. Schematic reaction pathway of oxidation of CDs followed by reductive amination, where R is the desired functionality.

positive (Matsui et al., 2018) and also, in some cases, in SR-A-negative macrophage-like cells (Zhang, Tamura, & Yui, 2021). By alkyl spacers between the CD and the carboxylic moieties, cellular uptake levels can be varied. Carboxylated and porphyrin-terminated polyrotaxane also resulted in high cellular uptake by HeLa and CT26 cells (Zhang et al., 2020; Y. Zhang et al., 2019). In vivo studies showed that tumor growth was highly inhibited by cisplatin conjugated to the modified CD rings on the polyrotaxane. The polyrotaxane remained in the tumor region for

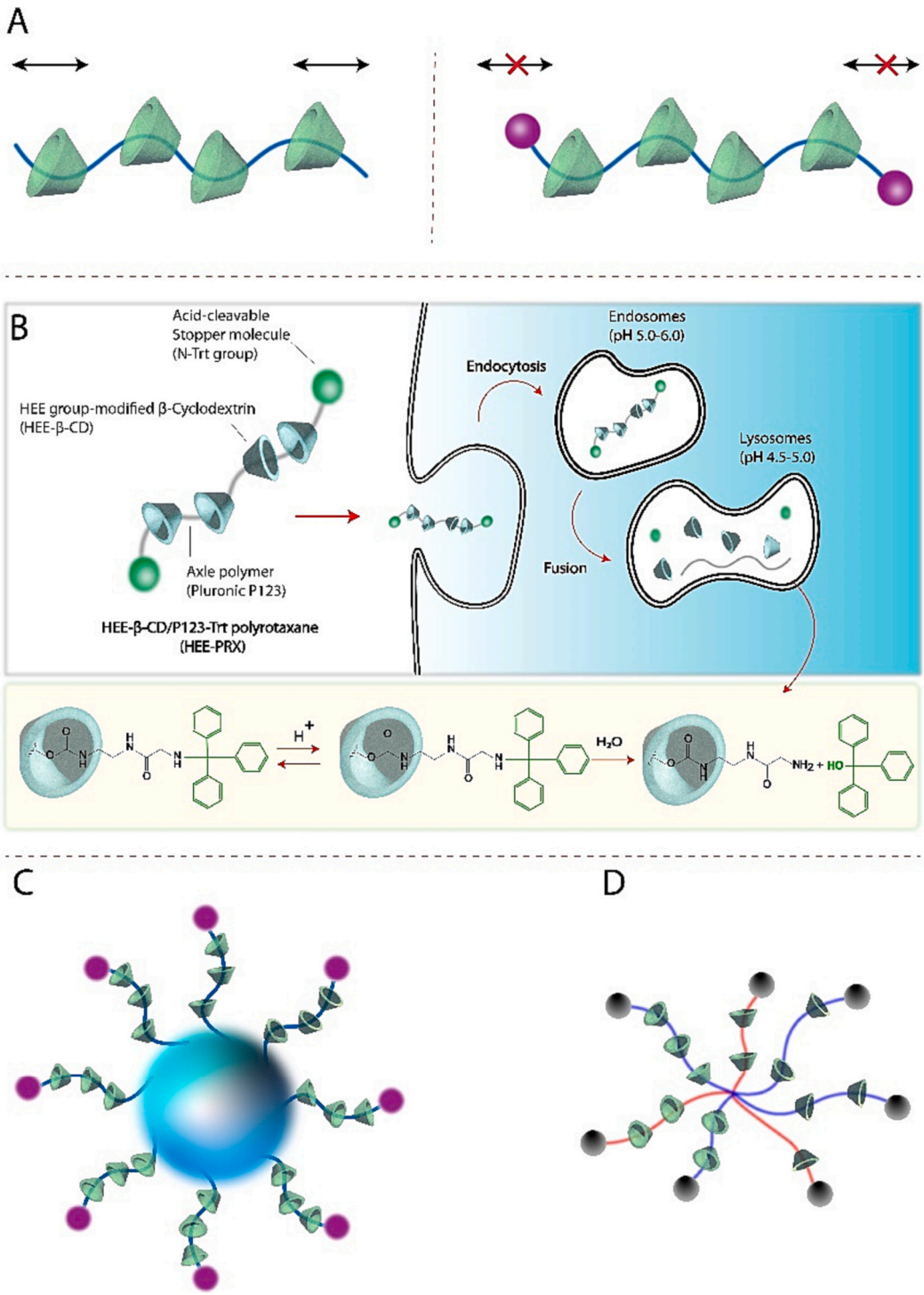

Fig. 5. A: Schematic structure of pseudopolyrotaxanes and polyrotaxanes, B: Illustration of the uptake and intracellular dissociation of acid-sensitive polyrotaxanes, adapted from Tamura et al. (Tamura, Nishida, & Yui, 2016). C: Schematic structure of nanoparticle decorated with polyrotaxane and *D*: *star*-shaped polyrotaxane.

>168 h but was almost entirely removed from other tissues (liver, intestine) within 48 h after intravenous administration. A 1.3-fold longer median survival time compared to free cisplatin was detected in vivo using a xenograft tumor model (Zhang et al., 2020). Camptothecin or polycamptothecin functionalized polyrotaxanes also showed reduced toxicity, prolonged circulation time, enhanced cellular uptake, and sustained anticancer drug release (Bai et al., 2018; Moon et al., 2008). Furthermore, D-α-tocopheryl polyethylene glycol 1000 succinate and 10-hydroxycamptothecin modified polyrotaxane showed high antitumor performance in vivo, effectively suppressing tumor growth and increasing the medial survival time compared to free 10-hydroxycamptothecin (Yi Zhang et al., 2019). Polyrotaxanes with α- and β-CD threaded on PEG and poly(propylene glycol) axes, respectively, were modified with paclitaxel, which showed prolonged blood circulation as well as easy internalization of the conjugates into SH-SY5Y cells without changing the cell morphology. In vivo studies showed high antitumor efficacy of these modified polyrotaxanes (S. Yu et al., 2013; J. Zhang et al., 2018). Ethylene diamine, pentaethylenehexamine, and short linear and branched PEI conjugated cationic PEG/α-CD polyrotaxanes efficiently condensed plasmid DNA. All modified polyrotaxanes showed

high transfection efficiency on various cell lines, especially in case of pentaethylenehexamine conjugated polyrotaxane, which had a 10-fold enhancement compared to PEI25k on HEK293 cells (C. Yang, Wang, Li, Goh, & Li, 2007). Cationic *N*,*N*-dimethylethylene diamine modified PEG-*co*-poly(succinic acid) polyester α-CD polyrotaxane showed high gene loading capacity. The silencing efficiency was similar to Lipofectamine 3000 and branched PEI (25 kDa) and better than PEG-based polyrotaxane (Ghodke, Parkar, Deshpande, Dandekar, & Jain, 2020). Four-arm star PEG with threaded *N*,*N*′-dimethylethylene diamine modified α-CDs provided silencing efficiency also comparable to Lipofectamine 2000 and branched PEI (Kulkarni et al., 2013). Another PEG-based cationic polyrotaxane with poly(aspartic acid) stopper and threaded polycationic α-CDs showed a 2-fold higher cellular internalization in C6 and HepG2 cell lines, using pEGFP-N1 reporter gene (Song et al., 2018). Polymerization of 2-(dimethylamino)ethyl methacrylate from the threaded CDs of the polyrotaxane resulted in polycations with high cell internalization rates and significantly higher transfection efficiency compared to unmodified polyrotaxanes and PEI25k (Wen, Hu, Xu, & Xu, 2016). Monoazidated CD-based polyrotaxane was further modified with octaarginine moieties to trigger cell penetration. Around 2.5-, 3-, and 5-fold higher cellular uptake in case of 5, 8, and 12 octaarginine/polyrotaxane was reached in comparison to the unmodified ones, respectively (Zhang, Tamura, & Yui, 2022). Acid degradable, β-CD-based polyrotaxane, bearing *N*-acetyl-D-galactosamine moieties, showed binding affinity to asialoglycoprotein receptors, increasing with the number of functional groups. Interestingly, an opposite effect was found for cell uptake, as it was higher for polyrotaxanes with a low degree of modification (Ohashi, Tamura, & Yui, 2023). A poly(ε-caprolactone)-*b*-PEG-based polyrotaxane was used for combining chemotherapy with photothermal therapy. Drug-loaded polyrotaxanes eliminated subcutaneous tumors, showed good performance against orthotopic breast cancer, and prevented the formation of lung metastasis (G. Yu et al., 2018). With acid labile stoppers, methylated polyrotaxanes of Pluronic P103 were successfully used as mitochondrial nanodevices for artificial autophagy activation (Nishida, Tamura, Kang, Masuda, & Yui, 2020; Yamada et al., 2019). Furthermore, cationic and anionic/nonionic hydroxypropylated polyrotaxanes showed siRNA uptake in 80–98 % of the total cell population for multiple cell lines (Badwaik et al., 2016). In-chain glutathione (GSH) responsive and acid labile stoppered polyrotaxanes showed more rapid gene accumulation in nuclei than PEI25K (J.-Y. Zhu et al., 2017). In a recent work, a more complex system, adamantane terminated folate functionalized polyrotaxane host-guest complex with CD-polyamidoamine dendrimer conjugate was utilized for siRNA delivery. This complex showed enhanced cellular association and high in vivo antitumor activity (Mohammed et al., 2022). Folate end stoppered PEG based polyrotaxanes also showed better performances in cellular uptake on squamous (Dal Poggetto et al., 2020) and human lung carcinoma cells (Zhou et al., 2012).

4.1.2. Polyrotaxanes in the treatment of Niemann–Pick disease

Niemann–Pick type C disease is a lysosomal metabolic disorder characterized by the accumulation of cholesterol. Due to the high affinity to form a 2:1 host-guest complex with hydrophobic cholesterol molecules, HP-β-CD is a promising candidate for the treatment of this disease (Yergey et al., 2017). Because of the short half-life of HP-β-CD, high concentrations should be frequently administered, causing toxic side effects (Gould & Scott, 2005; Muralidhar et al., 2011). Applying supramolecular structures, such as polyrotaxanes, with threaded HP-β-CD can be beneficial for the treatment of Niemann–Pick type C disease (Egele, Samaddar, Schneider, Thompson, & Wenz, 2019). The threaded CDs are inert in extracellular conditions by applying bioresponsive or cleavable stopper molecules, but the polyrotaxanes decompose in the lysosome, releasing the β-CD derivative directly inside the cell. In the pioneering work of Tamura and Yui, disulfide stoppered Pluronic based hydroxyethyl-β-CD polyrotaxane was disassociated in the lysosome by reduction of disulfides and showed to a lower extent nonspecific interactions with membranes (Tamura & Yui, 2014). With this polyrotaxane, an almost 100-fold higher cholesterol removal from cells was reached than with unthreaded β-CD derivatives. This polyrotaxane improved not only lysosomal cholesterol accumulation but simultaneously impaired autophagy in Niemann–Pick disease (Tamura & Yui, 2015). With an acid-sensitive stopper, as illustrated in Fig. 5B, a 2-(2-hydroxyethoxy)ethyl-β-CD/Pluronic P123 polyrotaxane was also tested as a potential active ingredient to treat Niemann–Pick type C disease (Tamura et al., 2016). High efficacy of cholesterol reduction was observed for an optimized degree of modification, between 4.1 and 5.4 2-(2-hydroxyethoxy)ethyl groups per CD. Weekly subcutaneous administration of such polyrotaxane, in 6- to 9-fold lower concentrations than the unthreaded β-CD derivatives, showed high potency with low toxicity (Tamura & Yui, 2018). Similar Pluronic-based polyrotaxanes with enzyme-degradable trinitrobenzoyl stoppers at the chain ends were also tested with high success both in vitro and in vivo (Collins et al., 2013; Collins et al., 2017). An anionic poly(decamethylene phosphate) based polyrotaxane with threaded HP-β-CD was recently applied in Niemann–Pick C1 cells (Egele et al., 2019). This polyrotaxane was stoppered with end-threaded α-CD, providing simple and effective dissociation of the polyrotaxane and, consequently, rapid release of threaded HP-β-CD. Besides Niemann–Pick disease, the intracellular release of β-CD derivatives can efficiently reduce cholesterol overload in other, for example, RAW264.7 cells (H. Zhu et al., 2022).

4.1.3. Widening the scope of polyrotaxane pharmaceutical applications

Even though the hydrophobic cavities of the CDs are occupied due to the rotaxanation, polyrotaxanes and, more commonly, pseudopolyrotaxanes are also used as drug delivery devices. Pseudopolyrotaxanes of PEGylated insulin with α- and γ-CD show sustained release, controllable with the CD content. An almost 4-fold higher hypoglycemic effect was detected compared to the non-rotaxanated PEG-insulin conjugate (Hirotsu, Higashi, Motoyama, & Arima, 2017). A PEG-poly(L-lactide-*co*-glycolide) based itaconic anhydride functional α-CD pseudopolyrotaxane was used to form micelles for desmethyl naproxen prodrug delivery. The itaconic anhydride moieties lower the intracellular GSH concentration, providing high efficacy of the GSH-sensitive drug (W. Wang et al., 2023).

Pseudopolyrotaxane or polyrotaxane-based self-assembled nanoparticles are similar to nonionic micelles with the advantage of simple dissociation by unthreading of the CDs, which triggers rapid drug release (He & Gu, 2013; Tardy, Dam, Kamphuis, Richardson, & Caruso, 2014; Tonegawa, Tamura, & Yui, 2019). This self-assembly can be triggered by hydrophobic polymer blocks or stoppers (Tonegawa et al., 2019; Zhang, Su, He, & Gu, 2014), as well as partial hydrophobization of the threaded CDs (Tonegawa et al., 2019; Tonegawa, Tamura, Zhang, & Yui, 2020). Supramolecular hydrogels of pseudopolyrotaxanes of various PEG structures with α- and γ-CD are already used for local drug delivery. These hydrogels developed via hydrogen bonding of the threaded CDs (α- and γ-CD) or by forming double strain inclusion complexes of PEG and γ-CD. These hydrogels possess high local effects in vitro and in vivo (Fang, Yang et al., 2022). Recently, a work showed the dependency of the drug-loading efficacy of such gels on the drugs' vapor pressure in some cases, such as salicylic acid, 2-naphthoic acid, salicylamide, paracetamol, (*S*)-(+)-naproxen, and phenothiazin (Kundu, Higashi, Takamizawa, Ueda, & Moribe, 2023). Insulin crosslinked pseudopolyrotaxane hydrogel showed a sustained hypoglycemic effect, as the serum glucose level was recovered 12 h after administration and an increased area under the serum glucose level-time curve (Abu Hashim et al., 2010). The pseudopolyrotaxane-based physical hydrogels also present stabilizing effects for antibodies against thermal and shaking stress (Ohshita et al., 2021). The PEG chains of Soluplus micelle formed polypseudorotaxane with γ-CD, resulted in supramolecular hydrogel. The flurbiprofen loaded gel provided 1.84-fold higher transcorneal permeability coefficient than the free drug, while in vivo studies in rabbits resulted in 21.2-fold higher AUC due to the application of this

supramolecular delivery system (Fang, Wang et al., 2022). Thixotropic pseudopolyrotaxane gel of Tween 80 with α-CD was used for enoxaparin delivery. In vivo studies showed up to 5.53-fold higher AUC values than free drug solution, in rats, and the bioavaibility was depending on the concentration of the added α-CD, (B. Tang et al., 2022). Since methylated polyrotaxanes show thermoresponsive solubility in water, they can be applied as injectable protein carriers in order to prolong the retention time of locally administered proteins (Nishida, Tamura, & Yui, 2018). The lower critical solution temperature of methylated, Pluronic P84-based polyrotaxane was 28.3 °C, and the coacervate droplets underwent acid-induced degradation resulting in pH-triggered drug release at body temperature.

The combination of inorganic nanoparticles and polyrotaxanes leads to promising candidates for therapeutic and theranostic applications (G. Yu et al., 2018). Folate functional pseudopolyrotaxane-modified gold nanorods could be rapidly enriched in the tumor area and show prolonged residence time due to their folate functionalities and morphology. Cisplatin-loaded nanorods show all the advantages of chemotherapy and photothermal therapy (S. Wang et al., 2022). Gold nanoparticles were decorated with PEG moieties and self-assembled by adding α-CD. This nanoparticle was utilized as an injectable therapeutic nanovaccine. In vivo studies showed successful delivery of antigen peptides in antigen-presenting cells, resulting in 4 to 8-fold higher infiltration of antigen-specific cytotoxic T lymphocytes into the tumor tissue (K. Xu et al., 2022). Pseudopolyrotaxane with threaded chlorin e6 modified α-CD was developed as photodynamic theranostic. The polyrotaxane was stable and nontoxic until GSH activation at the tumor site. Higher tumor accumulation and prolonged retention time were detected for this theranostic, and the therapeutic effect was also enhanced (Tong et al., 2016). By introducing pH responsiveness to this system, polylysine with pendant benzimidazole, complexed with HP-β-CD, a positive shift in surface charge is triggered, leading to enhanced cellular internalization (Hu et al., 2022). Pseudopolyrotaxane of PEG and β-CD formed directly on the surface of iron oxide nanoparticles. These superparamagnetic and magnetic-responsive nanoparticles had enhanced loading capacity and rapid acid-triggered release of loaded roxithromycin (Ke et al., 2019).

Some more complex polyrotaxane systems based on nanoparticles (G. Li et al., 2023) or multi-arm star polymers (Cao et al., 2021; Ji et al., 2019), as illustrated in Fig. 5C, are also described. Nitric oxide and clotrimazole loaded α-CD-based polyrotaxane modified mesoporous polydopamine nanoparticles, where the CDs were further modified with pentaethylenehexamine, inhibited the formation of fungal hyphae, and completely eradicated *Candida albicans* (G. Li et al., 2023). *N,N*-Dimethylethylenediamine modified $2/4^{CD}$ 4-arm polyrotaxane showed high efficacy for systemic nucleic acid delivery in vivo (Ji et al., 2019). This *star*-shaped polyrotaxane showed enhanced circulatory half-life and a better pharmacokinetic profile compared to the linear analogue. The pcDNA3.1-GFP-CXCR4 and miR-126 loaded, multi-arm/star polyrotaxane was successfully used to increase adhesion and proliferation, as well as decrease the apoptosis of endothelial progenitor cells in high glucose environments (Cao et al., 2021).

4.2. CD-polymer conjugates

4.2.1. CD-polymer conjugates showing sustained drug release and enhanced cellular uptake

Among CD-polymer conjugates, the *star*-shaped conjugates with a CD core and polymer arms are of particular interest for drug delivery. These conjugates are mainly synthesized using CD as a macroinitiator. Free radical, ring opening, and controlled radical polymerizations, such as atom transfer radical polymerization (ATRP) or reversible addition-fragmentation polymerization (RAFT), are used for syntheses. Biodegradable ε-caprolactone was polymerized using CD as a ring-opening macroinitiator (W. Li et al., 2019; H. Cheng et al., 2019). Further modification with PEG, through disulfide linkage and targeting folic acid moieties, resulted in a micellar structure that can be uptaken by multidrug resistance protein overexpressing tumor cells. Controlled doxorubicin release was triggered by glutathione, reducing the disulfide linkages with this carrier system (W. Li et al., 2019). Poly(ε-caprolactone) decorated β-CD was further modified by poly(2-(dimethylamino) ethyl methacrylate via controlled ATRP, showing a 4.15-fold enhanced transfection efficacy of plasmid DNA in comparison to lipofectamine on RAW264.7 macrophage cells (H. Cheng et al., 2019). Similar β-CD-based star polymer with biodegradable poly(lactic acid)-*b*-PEG decoration showed high encapsulation efficacy for doxorubicin and sustained drug release, depending on PEG chain length (Z. Xu et al., 2015). Moreover, non-biodegradable, mostly acrylic polymers are used to form *star*-shaped CD-based macromolecular structures by using CD as a macroinitiator for reversible deactivation radical polymerization. Butyl acrylate grafted CD was synthesized with a well-defined structure (Chmielarz, Park, Sobkowiak, & Matyjaszewski, 2016). This CD-macroinitiator method was also used to form CD-based star polymers with PEG-methacrylate, and doxorubicin was conjugated to this macromolecule (Jia, Huang, Yang, & Wang, 2017). The star polymer-based micelles showed sustained doxorubicin release and internalization by human cervical cancer HeLa cells. Poly(2-(dimethylamino) ethyl methacrylate grafted β-CD-based star polymer synthesized by ATRP was used to investigate the effect of chain length and degree of modification on the transfection efficacy of these polymers (Xiu, Yang, Zhao, Li, & Xu, 2013). The cytotoxicity of the polymers increased with the degree of modification and the arm lengths, while among star polymers with fixed molecular weights, the one with 21 polymer arms showed the lowest transfection efficiency. Polymerization of polyhexamethylene guanidine hydrochloride via ATRP from CD macroinitiator resulted in a highly effective antibacterial/antiviral material (Pan, Xue, Snow, & Xiao, 2015). *Star*-shaped CD-based polymers can also be synthesized by conjugating the preliminary synthesized polymers to the CD. Among them, PEGylated CDs are the most widely investigated materials due to tunable self-aggregation and triggered cellular responses (Rojas-Aguirre et al., 2019; Rincón-López, Ramírez-Rodríguez et al., 2022; Rincón-López, Martínez-Aguilera, et al., 2022). Further modified, thermoresponsive PEG-*b*-poly(N-isopropyl acrylamide) grafted β-CD showed higher therapeutic efficacy for paclitaxel and doxorubicin than commercial formulations (Fan et al., 2018). Also, PEI can be attached to CD in order to form a dual drug delivery system through ionic and host-guest interactions (Mousazadeh, Bonabi, & Zarghami, 2022).

Another interesting CD-based polymeric material class are polymers with pendant CD moieties. Chitosan-CD conjugates are highly interesting due to the combination of two biobased oligo/polysaccharides, one with the complexing ability of hydrophobes and another with a cationic structure. Recently, carboxymethyl β-CD grafted carboxymethyl chitosan hydrogel was used for oral insulin delivery. Almost 90 % of insulin remained in the hydrogel in the gastric environment, and slow insulin release was achieved. In in vivo studies, up to 12 h of hypoglycemic effect with a peak at 6–7 h was detected (Y. Yang, Liu, Chen, Cheong, & Teng, 2020). In another study, cationic carboxymethyl β-CD grafted trimethyl chitosan nanoparticles were used as a co-carrier for doxorubicin and siRNA. A doxorubicin release of 39 % and 80 % at pH 7.38 and 5.29 after 192 h was detected, respectively. Similarly, siRNA release was 23 % and 71 % at pH 7.38 and 5.29 (Zhang, Yu, Zhu, & Gong, 2021). β-CD grafted quaternized chitosan–hyaluronic acid complex was also used as a skin delivery system, with controlled release of hyaluronic acid (Sakulwech et al., 2022). A β-CD grafted chitosan was applied as a carrier of MUC1 vaccines, where the MUC1 protein was modified with adamantane moieties in order to generate host-guest complex formation with the CD (H. Yu et al., 2022). The vaccine triggered a strong immune response, and the induced antibodies successfully recognized the tumor cells and mediated cytotoxicity against them. A paste formed between doxorubicin loaded β-CD grafted chitosan and gelatin showed controlled drug release in vitro in a simulated tumoral microenvironment and inhibited tumor recurrence in vivo (Xiao, Xu,

Huang, Liu, & Yang, 2022).

Finally, crosslinked CDs presenting 3-dimensional macrostructure are also tested for drug delivery applications (Z. Liu, Ye, Xi, Wang, & Feng, 2021). CDs can be crosslinked via hydroxyl reactive multifunctional species, such as epichlorohydrin, carbnyldiimidazol, epoxy, anhydride, and diisocyanate moieties (Ciesielska et al., 2020; Concheiro & Alvarez-Lorenzo, 2013; Z. Liu et al., 2021). Among the utilized crosslinkers, citric acid is one of the most suitable for pharmaceutical applications because it is generally recognized as safe (Celebioglu & Uyar, 2023). Since most of the crosslinked CDs are insoluble materials, they are mostly used as drug-eluting coatings for medical devices (Concheiro & Alvarez-Lorenzo, 2013) or nanogels (Z. Liu et al., 2021). One of the greatest advantages of these 3-dimensional structures is their great versatility, as the crosslinker can provide tunable swelling, biodegradability, and stimuli responsiveness (Tian, Liu, & Liu, 2021). CD-chitosan-poly(vinyl alcohol-co-acrylic acid) networks, for example,were used as biodegradable carriers for gallic acid (Naeem, Chengqun, Hetonghui, & Z., Weifeng, Z., Yongmei, G., 2023) Crosslinked CD-based metal-organic frameworks (Shen et al., 2022) are suitable materials, even in dentistry, for prolonged drug delivery in the oral cavity (Braga, 2023).

4.2.2. *Mucoadhesive CD-polymer conjugates*

CDs grafted to mucoadhesive polymers give the possibility to form water-soluble delivery systems to complex and immobilize drugs in the mucus gel layer. Chitosan is one of the most used natural mucoadhesive polymers; its cationic structure promotes strong interactions with the anionic substructures of mucus. β-CD grafting on chitosan was used to complex (+)-catechin (Venter, Kotzé, Auzély-Velty, & Rinaudo, 2006). Even though the complex stability of this copolymer with the drug was significantly weaker than that of a free CD, the graft copolymer displayed 12 % stronger mucoadhesive strength than a natural mucoadhesive polymer, pectin. Besides, some short chitosan-*graft*-β-CDs showed prolonged levofloxacin release (Le-Deygen, Skuredina, Mamaeva, Kolmogorov, & Kudryashova, 2023).

A viscosity study investigated the mucoadhesion of β-CD-grafted quaternary ammonium chitosan derivatives. The CD-modified quaternary ammonium chitosans exhibited lower mucoadhesive properties than the polymer without CD grafting, but still, 2.5–3.5-fold higher mucoadhesive properties than poly(acrylic acid; PAA; Sajomsang et al., 2012). Using a citric acid spacer between the quaternary ammonium chitosan and β-CD, besides ionic interactions, hydrogen bonds are formed between the conjugate and the mucus layer. Mucoadhesion was consequently 6.7-fold enhanced, reaching even stronger mucoadhesive properties than unmodified quaternary ammonium chitosan (Chaleawlert-umpon et al., 2011; Sajomsang et al., 2013). The mucoadhesion of α-mangostin loaded β-CD-grafted quaternary ammonium chitosan was investigated. The results showed up to 3-fold higher mucoadhesion in case of loaded chitosan derivative, compared to unloaded one depending on the amount of encapsulated drug (Phunpee et al., 2018). In another study, methylated-β-CD was grafted to quaternary ammonium chitosan through a 10-atom-long spacer. Mucoadhesive strength slightly decreased compared to quaternary chitosan, but dexamethasone, as a hydrophobic model drug, was efficiently complexed with this polymer (Piras et al., 2018). HP-β-CD grafted quaternary ammonium chitosan, as shown in Fig. 6A, displayed an almost 2-fold prolonged residence time on porcine nasal mucosa (Belgamwar, Khan, & Yeole,

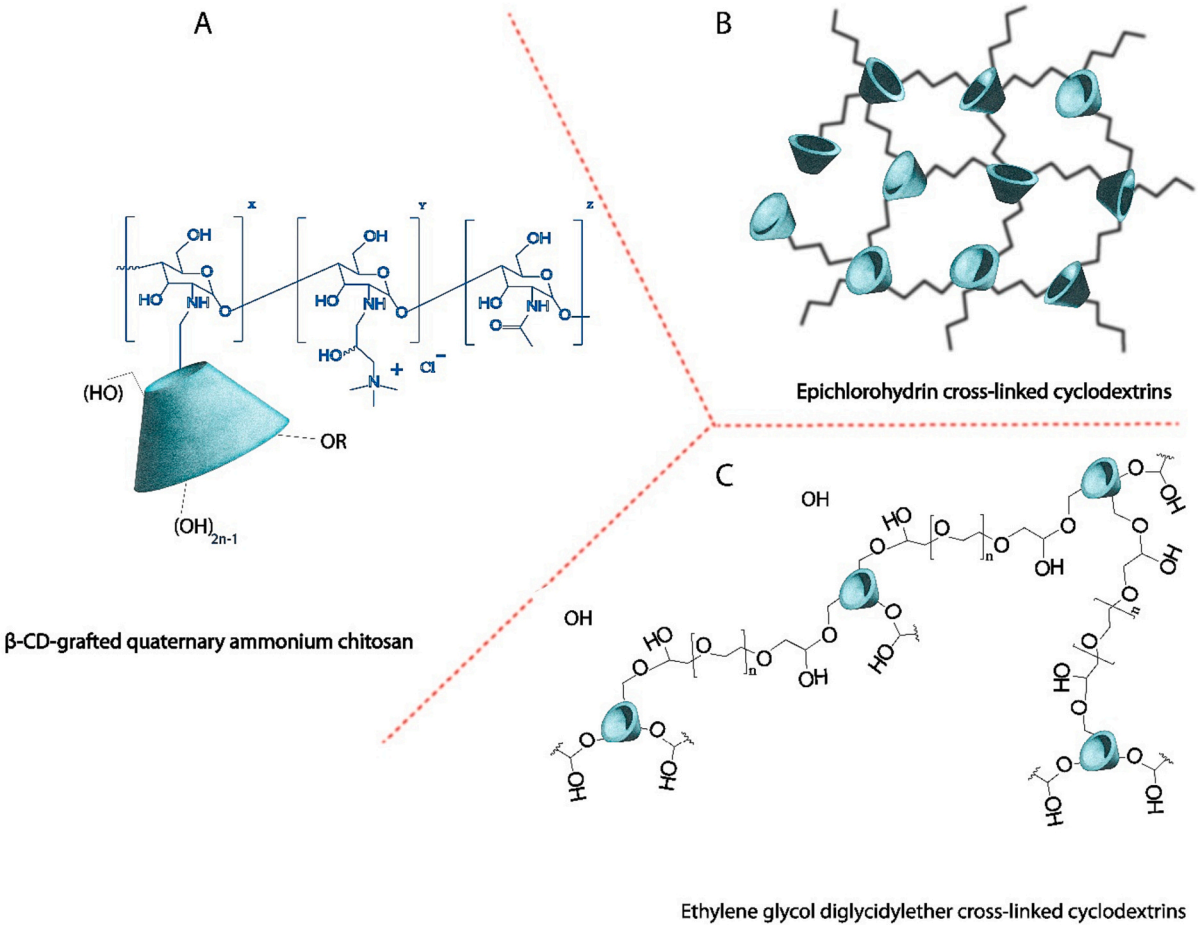

Fig. 6. Schematic representation of (A) β-CD-grafted quaternary ammonium chitosan, as well as (B) epichlorohydrin and (C) ethylene glycol diglycidylether cross-linked CDs.

2018). Thiolated carboxymethyl chitosan-*graft*-β-CD also showed a 5-fold improvement in mucoadhesion, compared to native chitosan on intestinal mouse mucosa due to the formation of disulfide bonds with cysteine-rich substructures of the mucus layer (Prabaharan & Gong, 2008). Furthermore, CD-chitosan conjugates exhibit permeation-enhancing properties (Zou et al., 2022).

Another biodegradable polymer, poly(aspartic acid), was thiolated and functionalized with β-CD in order to generate a mucoadhesive drug delivery system that was characterized by rheological measurements using porcine gastric mucin type II. Compared to thiolated poly(aspartic acid), the synergism parameters did not change significantly after conjugating β-CD, suggesting that mucoadhesion is unaffected by CD grafting (Budai-Szűcs et al., 2018). The formulation showed high complex viscosity, which could contribute to a prolonged mucosal residence time (Gyarmati et al., 2022).

CD can also be modified with non-biodegradable, synthetic mucoadhesive polymers. Native β-CD and HP-β-CD were used as cross-linkers for PAA and applied as a mucoadhesive drug delivery system for diflunisal and fluconazole, showing better complexation in case of HP-β-CD than for the native one (Kutyła, Lambert et al., 2013). This system was also tested on a polydimethylsiloxane surface, mimicking the mucosal layer. Lower mucoadhesion of all the CD cross-linked PAA than Carbopol 934P was found, most probably due to the lower cross-linking density and therefore the longer chain conformation that is responsible for the decreased adhesion (Kutyła, Boehm et al., 2013).

In another study, the mucoadhesive properties of ethylene glycol diglycidylether cross-linked CDs, namely α-CD, β-CD, γ-CD, HP-β-CD, and HP-γ-CD, as illustrated in Fig. 6C, were investigated on porcine vaginal mucosa. In case of homopolymeric CD systems, residence time was mostly around 1–3 h, only in case of HP-β-CD it was almost 6 h. Mixing various CDs into the copolymeric structure increased the residence time reaching >8 h for HP-β-CD/HP-γ-CD 30/20 system (Mennini, Casella, Cirri, Maestrelli, & Mura, 2016).

4.3. Thiolated CDs

4.3.1. Mucoadhesive properties

Since CDs are not mucoadhesive, their benefit for mucosal drug delivery is limited. Via thiolation, however, strong mucoadhesive properties can be introduced, as thiolated CDs form disulfide bonds with cysteine-rich mucus glycoproteins (Mulazim et al., 2020; Kali, Knoll, 2022).

Non-ionic thiolated CD derivatives, depicted in Fig. 7A, were investigated mostly for α- and β-CDs. The per-6-thiolation of α-CD resulted in a thiol content of 4244 ± 402 μmol/g, and this product showed 5.8-fold increased mucus viscosity, compared to native α-CD, indicating strong interactions with mucus glycoproteins (Asim et al., 2020). Mucoadhesion is strongly affected by the degree of thiolation, as

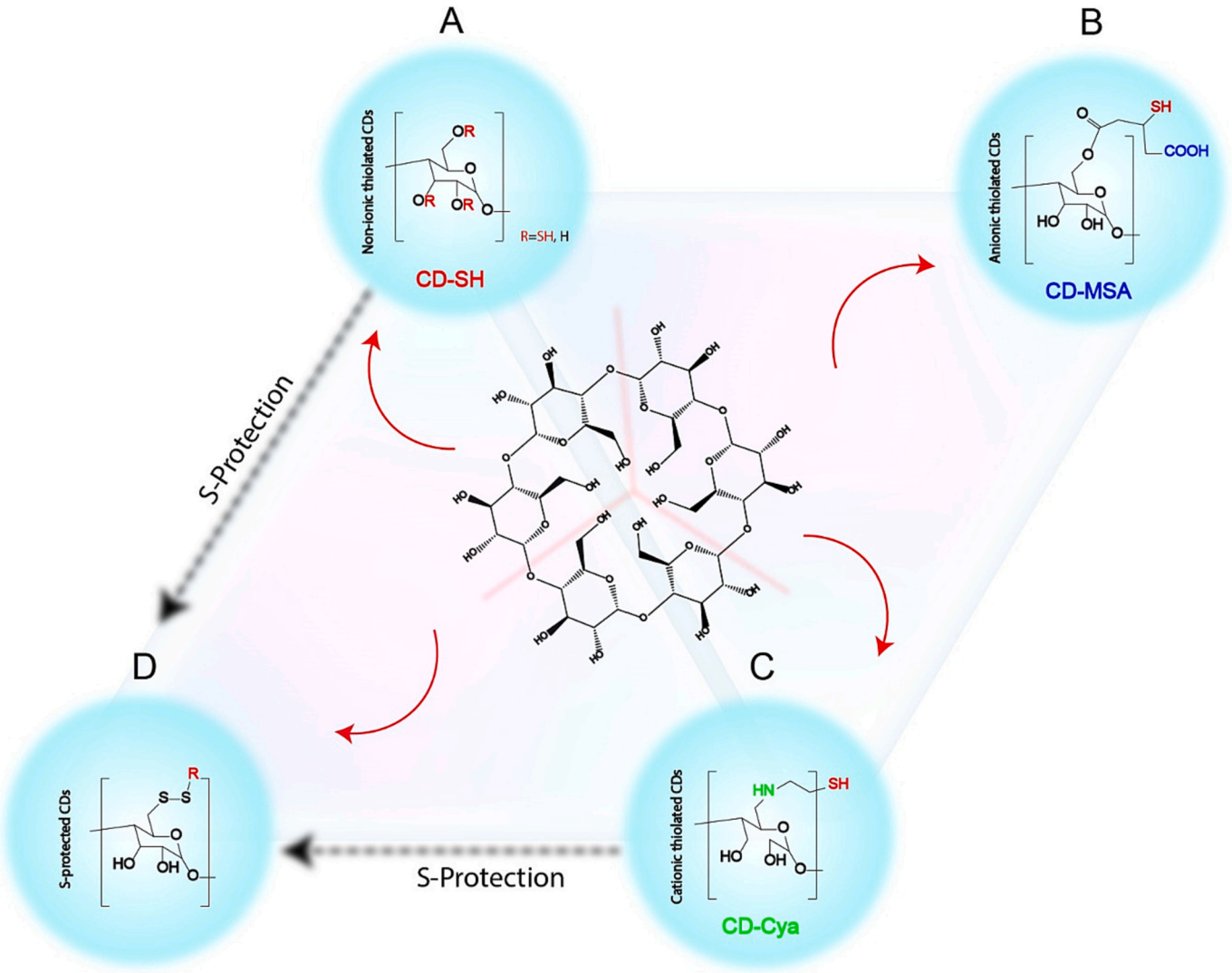

Fig. 7. General structures of the (A) nonionic, (B) anionic, and (C) cationic thiolated CDs, as well as (D) S-protected thiolated CDs.

can be demonstrated by comparing β-CDs with various thiol contents. With a low degree of thiolation (21.625 μmol/g) β-CD-SH showed a 3-fold enhancement in mucoadhesion, determined by tensile studies (Zaman et al., 2020). β-CD with thiol contents of 558.66 ± 78 and 1163.45 ± 96 μmol/g improved the mucoadhesive properties of CD by 39.7- and 46.4-fold, respectively, on porcine intestinal mucosa (Moghadam et al., 2018). The dynamic viscosity of mucus increased up to 7.6-fold by adding tetradeca-thiolated β-CD (Hussain Asim, Nazir, Jalil, Matuszczak, & Bernkop-Schnürch, 2020). In vitro mucoadhesion studies on intestinal, buccal, bladder, and vaginal mucosa resulted in 78.6-, 60.3-, 62.3- and 49.3-fold enhanced mucoadhesion, compared to native β-CD, respectively. For per-thiolated β-CD, an 89-fold increase in mucoadhesion, measured as the retention on porcine intestinal mucosa compared to native β-CD was found (Kali, Haddadzadegan et al., 2022). In vivo studies in rats, illustrated in Fig. 8A, resulted in a 19.4-fold, 2.1-fold, and 4.5-fold higher quantity of per-thiolated β-CD vs. unmodified β-CD in the stomach, duodenum/jejunum, and the ileum 4 h after oral administration, respectively, while after 8 h no native, but 60 % of the initial per-thiolated CD was still present in the small intestine (Kali, Haddadzadegan et al., 2022). In order to increase the water solubility of the thiolated products, HP-β-CD and RM-β-CD were also thiolated. The retention time of thiolated HP-β-CD with thiol content of 975.28 ± 42.01 μmol/g on porcine intestinal mucosa was 11.9-fold increased (Laquintana et al., 2019). Highly water-soluble thiolated 2-methyl-β-CD, with a degree of modification of 67 % showed a 1.6-fold increase in mucus viscosity compared to the corresponding unmodified CD (Grassiri, Cesari et al., 2022). HP-β-CD with a low degree of thiolation (150 ± 50 μmol/g thiol groups) displayed a 2-fold increase in mucus viscosity and a 1.4-fold longer residence time on isolated corneal tissue (Grassiri, Knoll et al., 2022). This thiolated HP-β-CD formed a strong complex with dexamethasone, and in vivo studies in rabbits showed enhanced bioavailability of the drug complexed with thiolated HP-β-CD, as shown in Fig. 8B. These nonionic thiolated CDs showed low cytotoxicity and low hemolytic effect with red blood cells (Kali, Haddadzadegan, 2022; Fürst et al., 2023).

Cationic α-CD-cysteamine conjugates, shown in Fig. 7C, with 558.2 ± 63 and 1143.9 ± 154 μmol/g thiol, showed 23- and 31-fold improved mucoadhesion on porcine intestinal mucosa (Ijaz, Ahmad, Akhtar, Laffleur and Bernkop-Schnürch, 2016). An up to 49-fold and 35-fold improved retention time on porcine intestinal mucosa and porcine buccal mucosa was detected, respectively, depending on the degree of modification (Ijaz et al., 2015). Similar β-CD-cysteamine products with 851.84 ± 107, 1040.44 ± 132, and 1563.72 ± 171 μmol/g free thiol groups also showed this trend (Ijaz, Griessinger et al., 2016). A 6- to 17-fold improvement in mucoadhesion on porcine vaginal mucosa and a 3- to 32-fold improvement on porcine intestinal mucosa could be reached with the various degrees of thiolation. HP-β-CD was decorated with *N*-acetyl cysteine and arginine, which is the major component of most cell-penetrating peptides resulting in a 2-fold increased mucin adsorption and a prolonged gastrointestinal residence time in rats. With complexed insulin, a hypoglycemic effect for 24 h was found for diabetic rats and high bioavailability of around 9 % (S. Li, Liang, Yan, Kawashima, & Sun, 2021). From a safety point of view, however, the cationic character is disadvantageous, increasing toxicity of CD (Fürst et al., 2023).

The mucoadhesion of mercaptosuccinic acid modified α-, β-, and γ-CDs with anionic character (shown in Fig. 7B) was up to 17.8-fold improved compared to native ones (Fürst et al., 2023). Although their cytotoxicity was lower than that of cationic CDs, their mucoadhesion and retention time on porcine intestinal mucosa decreased slightly.

Aqueous solutions of thiolated polymers are barely stable at pH ≥5 and prone to oxidation (Hussain Asim et al., 2020). The thiomers are reacting already on the loose outer mucus gel layer that is quickly removed by the mucus turnover process, lowering the amount of immobilized drug carriers in the mucus gel layer. Less reactive thiomers can be prepared by S-protection through disulfide bonds (Fig. 5D). These disulfides protect the thiols until they get in intimate contact with cysteines of mucus glycoproteins, and new disulfide bonds are formed between them (Iqbal et al., 2012). Nonionic thiolated and thiolated 2-mercaptonicotinic acid (MNA) S-protected γ-CD exhibited 44- and 51-fold improvement in mucoadhesion on porcine intestinal mucosa, respectively (Asim et al., 2018). Cysteamine-modified α-CD was compared with the MNA S-protected analogue. The thiolated α-CD exhibited up to 15-fold, while the S-protected α-CD up to 25-fold improved mucoadhesion, compared to native α-CD. (Ijaz et al., 2017). Utilizing S-protected thiolated α-CD, containing 3804 μmol/g MNA groups, a 38-fold improved mucoadhesion was determined compared to the corresponding unmodified CD (Asim et al., 2019). In vitro mucoadhesion studies on porcine nasal mucosa showed an almost twofold improvement of the mucoadhesion of HP-β-CD, after MNA S-protection.(Racaniello et al., 2021) Recently, short monothiol-PEG was used for the S-protection of γ-CDs. The PEGylated CDs showed enhanced mucoadhesion and also higher mucodiffusion compared to the non- or MNA-protected thiomers (Haddadzadegan, Knoll, Wibel, Kali, & Bernkop-Schnürch, 2023).

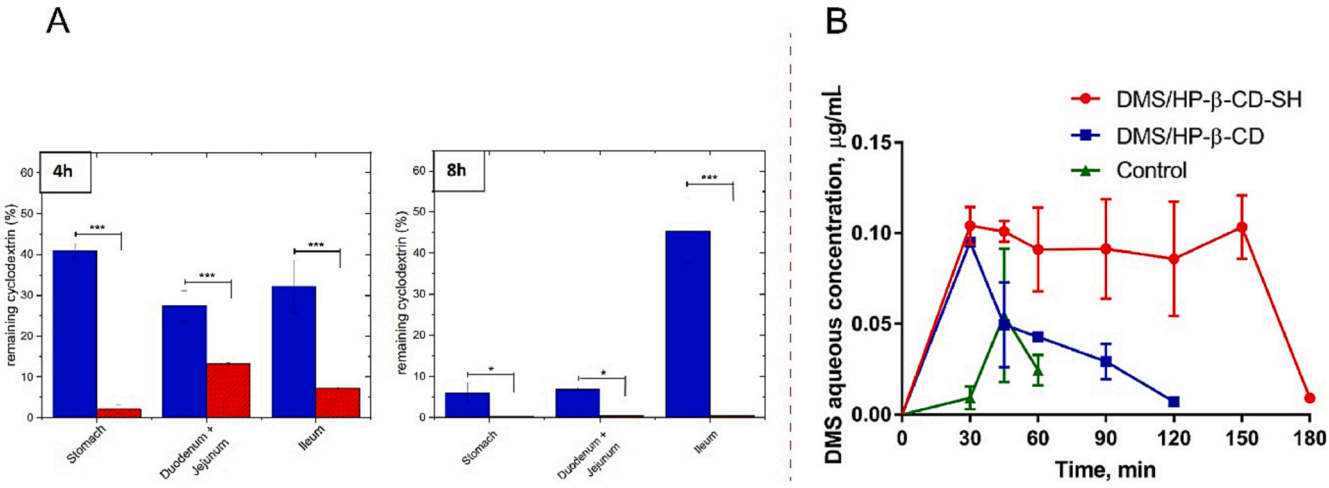

Fig. 8. (A) Percentage and distribution of per-thiolated (blue columns) and native (red columns) β-CD in the gastrointestinal tract of male rats 4 and 8 h after oral administration. (B) Pharmacokinetics of dexamethasone (DMS) in aqueous humour of rabbits after ocular administration of drug/HP-β-CD complex and drug/thiolated HP-β-CD (HP-β-CD-SH) complex. The data are shown as mean ± SD ($n = 4$; ***$P < 0.001$, *$P > 0.01$). Graphs adapted from Kali, Haddadzadegan et al. (2022) and Grassiri, Knoll et al. (2022), respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.3.2. *In situ gelling properties*

Besides their mucoadhesive properties, thiolated CDs are also capable of in situ gelation with other, mostly maleimide or allyl functional macromolecules (Mulazim et al., 2020; Summonte, Racaniello, Lopedota, Denora, & Bernkop-Schnürch, 2021). Solutions of the carrier and drug form a gel at the application site due to external triggers, such as pH, temperature, or oxidative processes. The advantages of in situ gels lie in the sol-gel transition, as the system carries the benefits of both liquid and gel formulations. Michael addition is the most frequently used method for such a hydrogel formation. Maleimide functional water-soluble polymers, such as dextran (Peng et al., 2010; Peng, Tomatsu, Korobko, & Kros, 2010), poly(2-hydroxyethyl methacrylate; Arslan, Aydin, Degirmenci, Sanyal, & Sanyal, 2017), or PEG (Arslan et al., 2017; Arslan, Gevrek, Sanyal, & Sanyal, 2014), form rapidly hydrogels with thiolated β-CDs, as schematically depicted in Fig. 9. The cross-linking reaction can also be achieved using allyl-terminated telechelic polymers (Arslan et al., 2017; Arslan, Gevrek, Sanyal, & Sanyal, 2015). A so-called intelligent property can be added to the gel using thermoresponsive polymeric moieties, as shown in Fig. 9, providing a sustained drug release (Arslan et al., 2017).

The main advantages of these hydrogels are the tunable size, going down to nm-range, and the sustained drug release, without showing a burst at the starting point (Peng, Cui, et al., 2010).

4.3.3. *Permeation and cellular uptake enhancing properties*

Thiolated CDs exhibit permeation-enhancing properties. They interact likely with a cysteine subunit in the active center of protein tyrosine phosphatase, an enzyme responsible for the dephosphorylation of occludin, one of the proteins building up tight junctions (Bernkop-Schnürch, Kast, & Guggi, 2003). Tyrosine phosphatase activity is inhibited by the formation of a disulfide bond, resulting in more phosphorylated occludins and opened tight junctions. Utilizing per-6-thiolated α-CD, the apparent permeability constant of complexed furosemide was 7-fold improved on Caco-2 cell monolayer and 6.5-fold on intestinal mucosa compared to unmodified α-CD. In vivo studies showed a 4.9-fold improved oral bioavailability of furosemide, complexed with per-6-thiolated α-CD vs. native α-CD, due to its mucoadhesive and permeation enhancing properties (Asim et al., 2020). Thiolated β-CD, used for ocular drug delivery, also showed 9.6-, 7.1- and 5.3-fold enhanced permeation of sodium fluorescein on conjunctiva, sclera, and cornea, respectively (Asim et al., 2021). In case of thiolated and arginine-modified HP-β-CD, the synergistic effect of the two penetration-enhancer moieties: cysteine and arginine, was confirmed. The highest permeability across Caco-2 cell monolayer was found for HP-β-CD modified with both cysteine and arginine, compared to unmodified CD or those modified with just one of these moieties (S. Li et al., 2021).

Moreover, methyl-β-CD was shown to enter epithelial cells by fluid-phase endocytosis (Fenyvesi et al., 2014), and this cellular uptake of CDs can be even further improved by the introduction of thiol groups to them. Because of exofacial thiols on the cellular membrane, thiolated CDs can be attached and internalized by forming disulfide bonds with thiol-bearing membrane proteins. Kaplan et al. demonstrated an even 20-fold improved cellular uptake of α-CD by substituting hydroxyl groups with thiol groups (Fig. 10A). Endocytosis was suggested as mode of action as cellular uptake of thiolated α-CD was highly energy dependent. Confocal microscopy results, displayed in Fig. 10B, together

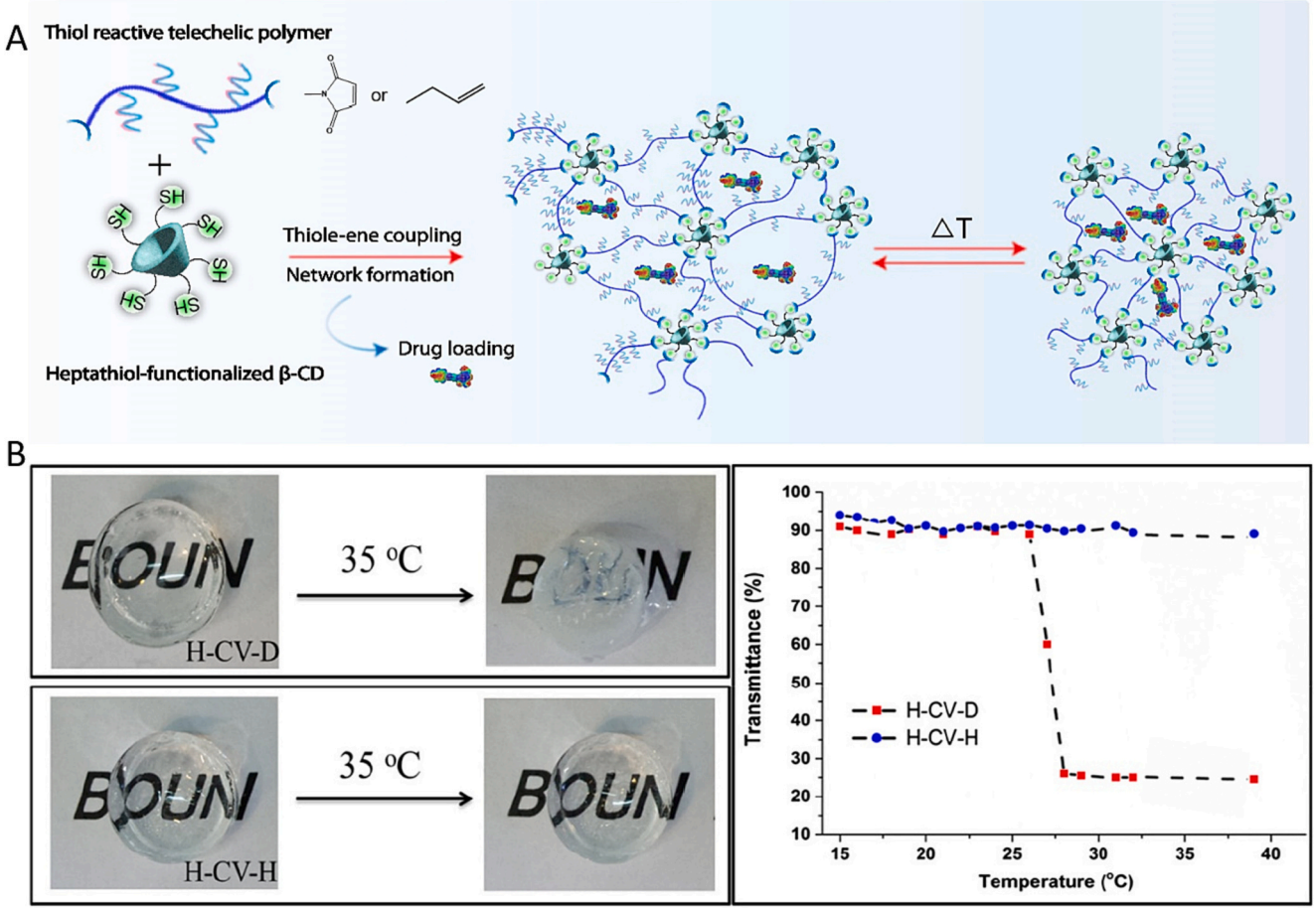

Fig. 9. Schematic illustration of in situ gelation via thiol–ene addition reactions (A) and the thermoresponsive behavior of the clear gels investigated as the change of transmittance upon heating (B); adapted from Arslan et al. (Arslan et al., 2017). H-CV-D and H-CV-H are abbreviations of vinyl end-functional poly(diethylene glycol-methyl ether methacrylate) and poly(2-hydroxyethyl methacrylate) cross-linked thiolated CDs, respectively.

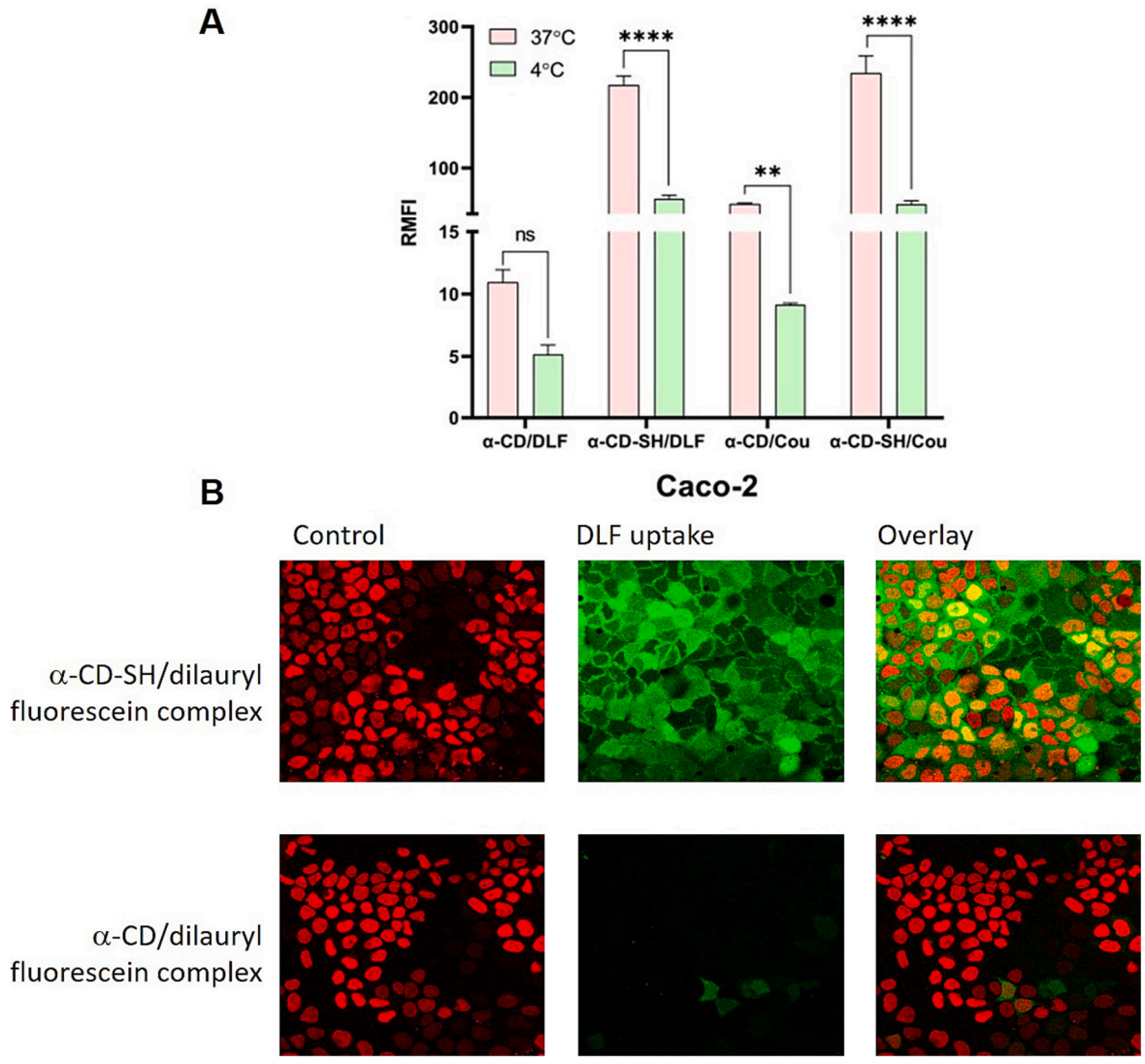

Fig. 10. (A) Analysis of cellular uptake of native (α-CD) and thiolated α-CD (α-CD-SH) labeled with dilauryl fluorescein (DLF) and coumarin-6 (Cou) in Caco-2 cell line at 37 °C (pink columns) and 4 °C (green columns), and (B) visualization of cellular uptake by Caco-2 cells exposed to fluorescently labeled α-CD and α-CD-SH for 3 h using a confocal microscope. The nucleus was stained with NucSpot Live 650. RMFI = relative mean fluorescence intensity values. The figure is adapted from Kaplan et al. (Kaplan et al., 2023). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

with hemolysis studies, showed furthermore that thiolation of α-CD promotes endosomal escape (Kaplan et al., 2023).

Thiolated polymers and nanoparticles can reversibly attach to efflux pumps via disulfide bond formation and inhibit them (Hock et al., 2022). Thiolated β-CD showed high potential for inhibiting P-glycoprotein-mediated efflux in Caco-2 cells. The efflux of the P-glycoprotein substrate rhodamine 123, was 3- and 2-fold lower in the presence of thiolated β-CD than without it or with native CD, respectively (Veider et al., 2023).

5. Clinical trial results

Within the last ten years around fifty clinical trials in that cyclodextrins were used either as drug delivery system or as therapeutic agent such as for decreasing serum cholesterol (NCT01131299) or for treatment of Niemann-Pick disease Type C1 (NCT02912793) were completed. In case of drug delivery CDs were mainly utilized to improve solubility and stability of small molecular drugs. But there were also some clinical trials focusing on other properties of CDs such a tumor targeting with polymeric CDs or the avoidance of di- and oligomerisation of therapeutic proteins.

5.1. Improved drug solubility and stability

Because of the solubilizing and stabilizing properties of CDs for small molecule drugs an improved bioavailability and therapeutic efficacy of these drugs complexed with CDs was shown in numerous clinical trials. In a multicenter, prospective, randomized, double-blind clinical trial, for instance, the antimicrobial efficacy of itraconazole, a water-insoluble triazole antifungal, for treatment of aspergilloma was proven with an oral solution of the drug complexed with HP-β-CD (NCT00005668). Furthermore, the therapeutic efficacy of carbamazepine stable inclusion complexes with HP-β-CD being highly water soluble relative to the non-complexed drug was demonstrated by intravenous infusion every 6 h (NCT01079351). In another study the stabilizing effect of α-CD for sulforaphane, a naturally-occurring phytochemical belonging to the

class of isothiocyanates, being orally administered via acid resistant hydroxypropyl methylcellulose capsules was shown (NCT02055716). A clinical trial comparing the oral bioavailability of different curcumin formulations confirmed the beneficial effect of the solubilizing and stabilizing properties of CD complexes. This clinical trial, however, showed also that the solubility and stability improving properties of CDs are not unique. In fact, an even higher oral bioavailability of curcumin was achieved by incorporating this lipophilic drug in simple polysorbate 80 micelles. The complexation of curcumin with γ-CD improved oral bioavailability 30-fold, whereas it was even 57-fold improved with micelles. The pharmacokinetic profiles are illustrated in Fig. 11 (NCT03530436).

Another concept follows the design of ready-to-use parenteral formulations making use of the drug solubilizing and stabilizing properties of CDs in aqueous media. Diclofenac, for instance, was complexed with HP-β-CD as a solubility enhancer and stabilizer, in a prefilled syringe for self-administered subcutaneous injection. In contrast to oral and rectal formulations, a rapid onset of action in case of acute migraine treatments can be provided with this injection. In a multicenter, phase 2, double-blind, randomized, placebo-controlled, study (EudraCT Registration No. 2017-004828-29) the efficacy, safety and tolerability of this diclofenac in the treatment of an acute migraine attack in 122 subjects could be demonstrated. A significantly higher percentage of patients were pain-free 2 h after injection of this new formulation when compared with placebo. The overall global impression favoured diclofenac complexed with HP-β-CD vs. placebo. There were no adverse events leading to study withdrawal and the majority of treatment-emergent adverse events were mild (Geppetti et al., 2022). This formulation might thus be a valuable option for the acute treatment of migraine attacks.

5.2. Tumor targeting

Linear, CD-based polymers (CDPs) consist of β-CD that has been difunctionalized with a cysteine-containing linker and polyethylene glycol (PEG), as illustrated in Fig. 12. Two molecules of the antitumor drug camptothecin (CPT) were covalently attached per polymer repeat unit via a linker resulting in a neutrally charged, hydrophilic polymer conjugate that self-assembles into water soluble nanoparticles (CRLX101). The lactone-ring of CPT is rapidly opened in vivo causing a loss of its antitumor function. Since the substitution on 20-OH of CPT can essentially reduce the tendency for lactone ring opening, the drug was covalently attached via this site (20-OH) to the CDP (J. Cheng, Khin, Jensen, Liu, & Davis, 2003). CPT solubility increased around 1000-fold due to conjugation. The high molecular mass of CRLX101 (450 kDa) does not allow for first-pass renal clearance, and consequently high levels of circulating nanoparticles are maintained. Furthermore, because of the enhanced permeability and retention (EPR) effect these nanoparticles were supposed to accumulate in the tumor tissue. After CPT release, nanoparticles disassemble into small CD polymer strands allowing renal clearance. In a phase 1 study in patients with refractory solid tumors CRLX101 showed a longer elimination half-life of 43.8 h than free CPT with a half-life of 31.8 h. Tolerability of CRLX101 was also higher than that of free CPT while maintaining similar per-cycle drug exposures (Heidel & Schluep, 2012). In a follow up phase 2 study, CRLX101, supposed to increase the exposure of tumor cells to CPT while minimizing side effects, was tested in non-small cell lung cancer (NSCLC) patients (NCT01380769). After intravenous infusion CRLX101 plasma concentrations increased sharply providing a slow release of CPT from the polymer conjugate. In contrast, unconjugated CPT plasma concentrations increased just gradually. Since volume of distribution and clearance were dose-independent for CRLX101, it was assumed that the polymer-CPT conjugate retained within the vasculature and highly perfused tissues. Despite these encouraging pharmacokinetic data, however, the study did not meet its primary efficacy endpoints and overall survival benefits. The concept likely failed because of an insufficient tumor targeting with these nanoparticles counting on the EPR-effect. Since its introduction in the scientific literature in the 1980s (Matsumura & Maeda, 1986), numerous clinical trials failed by the attempt to target tumors with macromolecular therapeutics and nanoparticles. As so far in not any clinical trial a tumor targeting via the EPR-effect could be shown, the scientific community is meanwhile favouring alternative concepts (Danhier, 2016). Nonetheless, these clinical trials showed that cyclodextrins are suitable and safe building blocks for the design of nanoparticles.

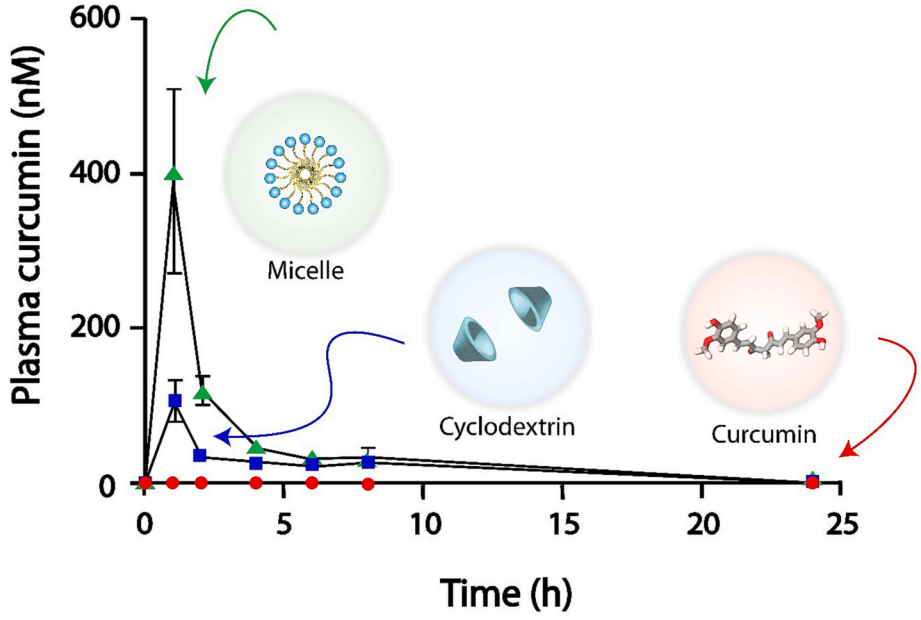

Fig. 11. Pharmacokinetic-study of orally administered curcumin in healthy volunteers over 24 h after oral administration of 207 mg of either micellar curcumin (▲), curcumin/γ-CD complex (■), and submicron-particle curcumin (●). Indicated values are means ± SD ($n = 12$).
(Adapted from Flory et al. (2021).

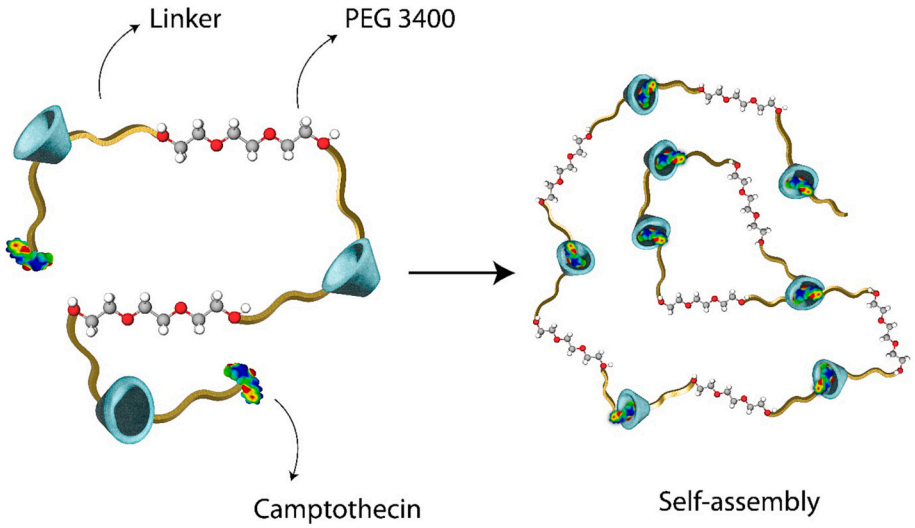

Fig. 12. Structure (left-hand side) and self-assembly (right-hand side) of PEG/CD copolymer-camptothecin conjugate through host-guest interaction between camptothecin and CD; adapted from Gritli et al. (Gritli et al., 2016, chap. 8).

5.3. Avoidance of di- and oligomerisation

Although insulin with a molecular mass of 5.8 kDa is too big to be incorporated in CDs, it forms nonetheless stable complexes. Spectroscopic evaluations showed that HPβCD forms inclusion complexes with the aromatic amino acids such as phenylalanine of this therapeutic protein. These complexes improve the stability of insulin against the formation of di- and hexamers, protect its disulfide bonds and limit its degradation in aqueous media (L. Zhang et al., 2009; Sajeesh & Sharma, 2006; Valentini et al., 2015). As only the monomeric form of insulin binds to its receptor, formulations have to contain just monomers which is the case when insulin concentration is below 0.6 μg/mL. Above this concentration, however, the protein forms di- and hexamers that can be avoided by the formation of complexes with HP-β-CD (Besson, Hernandes, Campos, & d., Morikawa, K. A., Bersani-Amado, C. A., Matioli, G., 2017). This stabilizing effect was utilized for the preparation of polyacrylate hydrogels containing insulin that was complexed with HP-β-CD in a molar ration of 1:5 via coprecipitation. In a randomized, double-blind, prospective clinical trial, the efficacy and safety of this hydrogel was evaluated in patients with grade II pressure ulcers (NCT02418676). Results demonstrated an improved healing of the lesion than the control gel. Complexed insulin showed advantages such as the gradual reduction in the pressure ulcer size and revitalization of the tissue without any necrotic tissue.

6. Approved products

Since the first CD-based pharmaceutical product (Prostarmon E™ sublingual tablets, 1976) entered the market, the number of approved products is continuously increasing. Mostly native and hydroxypropylated CDs are used as excipients, but the number of sulfobutylated CD-based drug delivery systems is also increasing. Among native CDs, β-CD is of highest safety concern. Recently the Food and Drug Administration (FDA) published a list of newly accepted formulations, including 23 CD-based formulations. Most of these novel formulations are based on HP-β-CD (9), but native (5), SBE- (2), or methylated β-CD, together with HP-γ-CD, are also on the list (FDA, 2023). HP-β-CD is used in formulations for all currently available routes and administration

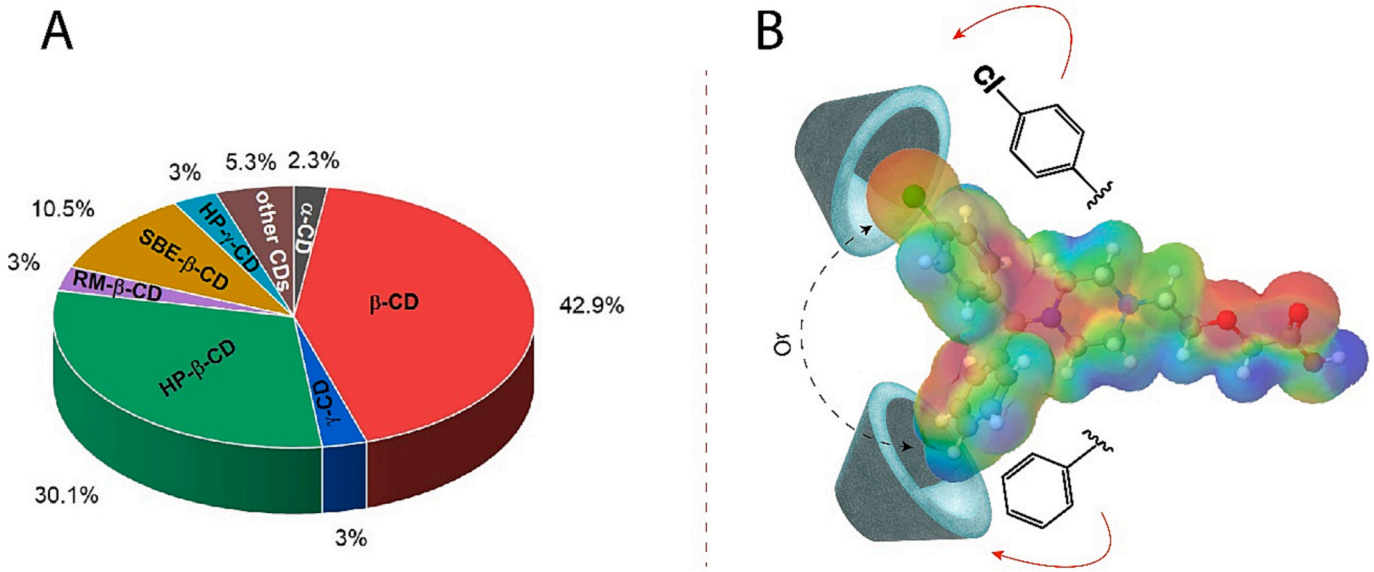

Fig. 13. (A) The percentage of various CDs in marketed formulations based on Puskas et al. (Puskás et al., 2023), (B) schematic structure of cetirizine – β-CD complex.

except nasal, whereas α-CD is currently used just in parental formulations.

An interesting example of pharmaceutical products with CDs showing the multifaceted effect of these excipients is cetirizine, an antiallergic drug. One-day tablets, chewing tablets, and dry syrup formulations containing a drug/β-CD complex are marketed (Puskás et al., 2023). Both chlorophenyl and phenyl rings of cetirizine can form stable complexes with this CD; nonetheless, a 1:1 complex formation could occur, as depicted in Fig. 13 (Ali, Upadhyay, & Maheshwari, 2007; Imtiaz, Muzaffar, & Ali, 2021). The complexation of cetirizine in CD increases drug solubility just up to 20 % but provides higher stability against oxidative degradation of the drug (Paczkowska et al., 2018; Preis, Grother, Axe, & Breitkreutz, 2015). The complexation also offers high patient comfort due to masking of the unpleasant bitter taste of the drug (Lee et al., 2010; Paczkowska et al., 2018; Stojanov & Larsen, 2012; Stojanov, Wimmer, & Larsen, 2011; Szejtli & Szente, 2005).

Another widely used drug/CD complex is that with dexamethasone. This corticosteroid is water-insoluble, with smell, taste, and aftertaste slightly negative for patients (Mitchell & Counselman, 2003). The drug's solubility increases up to 33-fold by forming a 1:1 complex with β-CD (Doile et al., 2008; Schönbeck, Gaardahl, & Houston, 2019). These complexes are thus used as tablets for oral and ointments for topical administration of dexamethasone under the trade name Glymesason® (Loftsson & Duchêne, 2007; Puskás et al., 2023; Rincón-López, Almanza-Arjona, Riascos, & Rojas-Aguirre, 2021) or for ocular drug delivery. (Kristinsson et al., 1996; Loftsson & Stefánsson, 2002; Saari, Nelimarkka, Ahola, Loftsson, & Stefánsson, 2006).

Since prostaglandins, such as prostaglandin E1 and prostaglandin E2, are practically not soluble in water, they are widely used in complex forms with α- and β-CD, as well as their mixtures. The aqueous solubility of the drug can be increased up to 50-fold, while its stability at 40 °C increases from 10-15 % to 90–95 % by the complexation (Inaba, Wakuda, & Uekama, 1984). Several dosage forms, for example, infusions, eye drops, tablets, or sublingual formulations, have been marketed so far (Loftsson & Duchêne, 2007; Puskás et al., 2023). Other formulation approaches addressing the poor solubility of these drugs have some other disadvantages, such as low stability and tolerance (Rodriguez-Aller et al., 2015).

Another good example for successful pharmaceutical products containing a CD are diclofenac/HP-β-CD complexes. Solutions for intravenous or intramuscular administration and eye drops of this CD complexed nonsteroidal anti-inflammatory drug are on the global market (Loftsson, 2021; Loftsson & Duchêne, 2007; Puskás et al., 2023). Diclofenac is almost insoluble below pH 7, but complex formation with HP-β-CD increases its aqueous solubility up to 5-fold (Loftsson, 2021). The increased solubility is particularly important in order to reach the desired therapeutic effect at a low dose due to the high risk of adverse cardiovascular events caused by this drug (Scavone et al., 2016). Furthermore, diclofenac/HP-β-CD complexes, such as Voltaren Ophtha CD eye drops, showed 3-fold lower bovine corneal opacity and permeability and 5-fold higher corneal cell viability compared to pure diclofenac solution (Abdelkader, Fathalla, Moharram, Ali, & Pierscionek, 2018).

Besides these therapeutic applications, β-CD complexed nicotine is used for preventive claims, alleviating the symptoms of nicotine withdrawing and helping smoking cessation (Loftsson & Brewster, 2010; Loftsson & Duchêne, 2007; Puskás et al., 2023; Szejtli & Szente, 2005). Even though nicotine is soluble in water, its solubility is highly pH dependent, and the thermal and oxidative stability of this active ingredient is strongly limited. Nicotine/β-CD complexes are used in lozenges, and chewing gums are marketed under the trade names Nicorex/Nicorette and Nicogum, respectively (Rincón-López et al., 2021; Santus, 1996; Thyresson, Koll, Nilgard, McNally, & Lindell, 2023). Those show higher stabilities against environmental impacts, such as heat and oxidation, and the buccal administration is also favorable over transdermal route due to the higher and faster systemic uptake (Chulurks, Jitapunkul, Katanyutanon, Toochinda, & Lawtrakul, 2021; Hădărugă, Hădărugă, Butnaru, Tatu, & Gruia, 2010; Santus, 1996).

These are just some examples of numerous formulations containing drug/CD complexes demonstrating the versatility of these excipients. A detailed table containing drugs, CDs, trade names, formulations, and providers is summarized in Table 2.

7. Conclusions and outlook

Over the last decades CDs and derivatives have emerged as valuable class of pharmaceutical excipients, that is able to improve the therapeutic efficacy of numerous drugs. Their well-defined ring-shaped structure with both hydrophilic and lipophilic substructures that do not result in surfactant-like properties make them unique among saccharide-based excipients. In addition, they benefit from the small size. 'Small is beautiful.' In comparison to polysaccharides CDs do not form highly viscous hydrogels that are difficult to inject, as chain entanglements and the formation of stable three-dimensional networks can be excluded for them. Moreover, they do not impair vision being advantageous for ocular drug delivery. In contrast to polysaccharides they permeate the mucus gel layer and get in direct contact with the underlying epithelium. As CDs can also reach the unstirred water layer on the epithelial surface, they can enhance the flux of lipophilic drugs across the absorption barrier (Brewster, Noppe, Peeters, & Loftsson, 2007). Despite this small size drugs can nonetheless be incorporated in their core and in some cases even a controlled drug release can be achieved. Accordingly, they are likely the smallest nanocarrier systems in drug delivery.

In contrast to many other classes of excipients for that we have not seen any new developments and introduction of new components since decades, CDs and derivatives are a dynamically growing segment.

In the future, we will likely discover further applications of CDs for drug delivery. Moreover, progress on in silico methods for the simulation of the formation of drug/CD complexes will overcome time- and work-consuming trial-and-error approaches. In addition, new derivatives of CDs will likely broaden the spectrum of this class of excipients and will open the door for numerous further applications. Among them, CD-based polyrotaxanes enhancing cellular uptake via interactions with membrane proteins, CD-polymer conjugates providing controlled drug release and (muco)adhesive properties, and thiolated CDs exhibiting tight junction opening, efflux pump inhibiting, cellular uptake enhancing, and (muco)adhesive properties by the formation of disulfide bonds with endogenous proteins are promising new excipients for drug delivery.

So far, no products containing CD-based polyrotaxanes, CD-polymer conjugates or thiolated CDs, however, have entered the pharmaceutical market. Because of the great potential of these new derivatives and the high added therapeutic value provided by them, it is nonetheless merely a matter of time for the successful commercialization of first products. Since the registration of new excipients is almost as time consuming and costly as that of a new drug, however, likely just a very few of these novel derivatives will end up with their own monograph in the pharmacopeia. They will have to be manufactured in a very efficient and cost-effective manner (i), provide a substantial added value for the therapeutic efficacy of numerous drugs (ii), and will have to be safe for various routes of administration (iii). Recently launched initiatives such as the Novel Excipient Review Pilot Program of the FDA (https://www.fda.gov/drugs/development-approval-process-drugs/novel-excipient-review-pilot-program) that shall foster the development of excipients for scenarios in which excipient manufacturers and drug developers have cited difficulty in using existing excipients, perhaps accelerate this process.

Funding statement

No external funding was applied for this work.

Table 2
Marketed CD formulations according to Puskás et al. (Puskás et al., 2023).

Active pharmaceutical ingredient	Type of CD	Brand name	route of administration	Company
Aceclofenac	β-CD	Aceclofenac-β-Cyclodextrin, Acerap	Oral	Taj Pharm.
Acetaminophen	β-CD	Acetaminophen Chewable Gels	Oral, buccal	7 T Pharma, USA
Acetaminophen	HP-β-CD	Paracetamol	Parenteral, buccal	Uni-Pharma, 7 T Pharma
Ad26.COV2·S	HP-β-CD	Jcovden	Vaccine	J&J
Aluminum Zirconium Trichlorohydrex Gly	β-CD	Secret, Outlast, Olay, Old Spice,Gilette	Dermal	Procter & Gamble,Navajo
Alfaxalone	SBE-β-CD	Phaxan	Parenteral	Drawbridge Pharm., Chemic Labs
Alfaxalone	HP-β-CD	Alfaxan	Parenteral	Jurox, CTD
Allopregnalonone	SBE-β-CD	Zulresso	Parenteral	SAGE Therap
Amiodarone	SBE-β-CD	Nexterone	Parenteral	Baxter
Amlodipine maleate	β-CD	Conjupri	Oral	CSPC Ouyi Pharm, Shijiazhuang
Anagliptin + metformin	α-CD	Metoana Combination Tablets	Oral	Sanwa Kagaku Kenkyusho
Aripiprazole	SBE-β-CD	Abilify	Parenteral	BMS, Otsuka
Azelastine	HP-β-CD	Antalerg	Ocular	Unimed Pharma
Benexate	β-CD	Ulgut, Lonmiel	Oral	Teikoku, Shionogi,Negase
Benzoyl peroxide	γ-CD	Nujevi Acne	Dermal	Nujevi
Betahistine	β-CD	Betahist	Oral	Geno Pharm.
Bilastin	β-CD	Ilaxten	Oral	Menarini Farm. Int.
Biotin and surfactants	HP-β-CD	RegeNail	Nail	Reig Jofre, S.A (Spain)
Brivaracetam	β-CD	Briviact	Oral	UCB Pharma
Bromhexin	β-CD	Bisolvon	Oral	Sanofi
Carbamazepine	SBE-β-CD	Carnexiv	Parenteral	Lundbeck
Carlfilzomib	SBE-β-CD	Kyprolis	Parenteral	Amgen (Onyx), Ono
Cefotiam	β-CD	Pansporin-T	Oral	Takeda
Cefditoren pivoxil	β-CD	Meiact	Oral	Meiji
Cetirizine	β-CD	Zyrtec, WalZyr, Revicet	Oral, buccal	Losan Pharma, UCB Pharma, Sandoz, Walgreen, Sawai Pharm., Nichi-Iko, Takeda
Chloramphenicol	RAMEB	Clorocil	Ocular	Oftalder
Chlordiazepoxide	β-CD	Transilium	Oral	Gador
Chlorpheniramine maleate + acetaminophen	β-CD	Cold Remedy Soothing	Oral	Foshang Dezhong Pharm. (China)
Cholecalciferol	β-CD	Vitamin D3	Oral	Natures Aid (U.K.)
Ciclopirox	HP-β-CD	Dexulac	Nail	Reig Jofre, S.A (Spain)
Ciprofloxacin + Deaxamethasone	HP-β-CD	Kombinil-Duo	Ocular, otic	Promed Exports (India)
Cisapride	HP-β-CD	Prepulsid	Rectal/vaginal	Janssen
Cisapride	β-CD	Propulsid, Coordinax	Rectal/vaginal	Janssen
Cladribine	HP-β-CD	Mavenclad	Oral	Merck
Curcumin extract	γ-CD	Curcumin Extract 45	Oral	Dr. Wolz Zell GmbH (Germany)
Delafloxacin	SBE-β-CD	Baxdela	Parenteral	Melinta
Dexamethasone	β-CD	Glymesason	Oral	Fujinaga
Dextromethorphan	β-CD	Rynathiol	Oral	Synthelabo
Desloratadine	β-CD	Desloratadine	Oral	Northstar Rx
Diclofenac	HP-β-CD	Dyloject, Diclofenac-Solofarm, Ivinak-Solofarm,	Parenteral, ocular	Javelin Pharm.,Vidal
	HP-γ-CD	Voltaren Ophta CD, Voltarol	Ocular	Novartis
Diphenhydramine	β-CD	Stada-Travel	Oral	Stada
Diphenhydramine HCl	HP-β-CD	FirstCare - Children's Allergy Relief	Oral, buccal	FirstCare
Docetaxel	HP-β-CD	Docetaxel Teva Generics	Parenteral	Teva
Estradiol	RAMEB	Aerodiol	Nasal	Servier
Ethinyl estradiol + drospirenone + levomefolate	β-CD	Safyral, Beyaz, Yaz	Oral	Bayer Healthcare
Ethinyl estradiol + drospirenone	β-CD	Yaz, Yasminiq, Gianvi, Rajani, Loryna	Oral	Bayer
Famotidine	β-CD	Famotidine OD Tablets	Oral	Takeda Teva, Taiko
Fenofibrate		Fenofibrate, Fenacor, Fibrate, Lipicard,	Oral	Karalex Pharma, Avinash Health, Taj Pharm.,
	β-CD	Fibrolip, Fenocor, Fibral, Thrombiflo, Lotgl		US Vitamins, Emcure Pharm., Medindia, Torrent, Grandix
Fingolimod	β-CD	Fingolimod beta	Oral	Betapharm
Fingolimod	HP-β-CD	Gilenya	Oral	Novartis
Florbetaben	HP-β-CD	Neuraceq	Parenteral	Piramal Imaging SA
Flunarizine	β-CD	Fluner	Oral	Geno Pharm.
Flupentixol dihydrochloride	β-CD	Fluanxol	Oral	Lundbeck (UK)
Flurbiprofen	β-CD and	Strephen, Strepfen, Strefzap, Strefen,	Buccal	
	HP-β-CD	Flurbiprofen Geiser, Dobendan, FrobenGolmed, Benactivdol		Reckitt (U.K.), Mylan, Fear, Busetti
Fosphenytoin	SBE-β-CD	Sesqient,Cerebyx	Parenteral	Sedor Pharmaceuticals
Garlic Extract	β-CD		Oral	Various
Glucagon	β-CD	Baqsimi	Oral	Eli Lilly
Histamine dihydrochloride	β-CD	Australian dream	Dermal	Nature's Health Connection
Hitchner B1 strain	HP-β-CD	Cevac	Parenteral	Ceva-Phylaxia
Hyaluronic acid		DOLATROX®hcc	Parenteral	Kolinpharma
	HP-β-CD	Vijointhcc	Parenteral	Innventa
Hydrocortisone	HP-β-CD	Dexacort	Buccal	Actavis

(*continued on next page*)

Table 2 (*continued*)

Active pharmaceutical ingredient	Type of CD	Brand name	route of administration	Company
Indomethacin	HP-β-CD	Indocid, Indocyllir	Ocular	Chauvin, Baush & Lomb
Iodine	β-CD	Mena-Gargle	Buccal	Kyushin
Itraconazole	HP-γ-CD	Sporanox, Scemblix, Itrafungol (vet)	Oral, parenteral	Janssen, Eli Lilly, Elanco, Mylan EPD
		Itraconazol Altan	Parenteral	Altan
Lanosterol	HP-β-CD	Lanomax	Ocular	Ventura Labs (US CA)
Lanosterol (0.25 %) + *n*-acetylcarnosine (1 %)	HP-β-CD + RAMEB	LumenPro	Ocular	Heliostatics
Lanosterol (0.25 %) + *n*-acetylcarnosine (1 %)	HP-β-CD + RAMEB	LumenPro	Ocular	Heliostatics
Larotrectinib	HP-β-CD	Vitrakvi	Oral	Bayer
Letermovir	HP-β-CD	Prevymis	Parenteral	Merck
Levocabastine	HP-β-CD	Allergiflash	Ocular	Bausch & Lomb
L-thyroxine sodium	HP-β-CD	Leventa	Oral	Intervet, Merck, Shering Plough
Maropitant	SBE-β-CD	Cerenia	Parenteral	Pfizer Animal Health
Meloxicam	β-CD	Mobitil	Oral, rectal	Med. Union Pharm.
Melphalan	SBE-β-CD	Evomela	Parenteral	Spectrum
Menthol/camphor	β-CD	Pain relief gel	Dermal	MMA Elite,Doctor Hoy's
Mequitazine	β-CD	Zeslan, Nipolazine	Oral	Asahi Kasei, Alfresa
Methyl salicylate	β-CD	Xceptor Pain	Dermal	Xceptor
Methylethylpyridinol	HP-β-CD	Vixipin	Eye drops	Grotex (Russia)
Metronidazole	β-CD	Metrogel, Flagyl, Vandazol, Nidagel	Vaginal	Curatek, Fougera,Tolmar, Malderma Labs
Miconazole	β-CD	MiconaHex-Triz	Dermal	Dechra Veterinary
Midazolam	γ-CD	Ozalin	Oral	Advicenne, Valdepharm
Minoxidil	γ-CD	Alopexy	Dermal	Pierre Fabre
Mitomycin	HP-β-CD	MitoExtra, Mitozytrex	Parenteral	Novartis, SuperGen
Naphasoline hydrochloride	β-CD	Clear eyes	Ocular	Medtech
Nateglinide	β-CD	Nateglinide Tablets	Oral	Teva Takeda
Niacinamide + adenosine	CD	Botanic Heal boH Air Jet Daily Mask Panthenol	Dermal	Cj Olive networks
Nicotine	β-CD	Nicorex,Nicorette	Oral	Pierre Fabre
		Nicogum	Buccal	Pfizer
Nimesulide	β-CD	Nimedex	Oral	Novartis, others
Nitroglycerin	β-CD	Nitropen	Sublingual	Nippon Kayaku
Norfloxacin and Tinidazole	β-CD	Entronor –TZ, Noroxin	Oral	India
Noxamovir	HP-β-CD	Prevymis	Parenteral	Merck
Olmesartan medoxomil	β-CD	Olmetec OD Tablets, Olmesartan OD tables	Oral	Daiichi Sankyo
Olopatadine	HP-β-CD	PrPazeo, Pazeomelph, Opatanol, Olantin	Ocular	Novartis, Alcori
Omeprazol	β-CD	Omebeta, Losamel	Oral	Betafarm, Stada
Oritavancin	HP-β-CD	Kimyrsa	Parenteral	Melinta
Panthenol, Allantoin	HPCD	bdrRe-lax	Dermal	Hanaim Intern.
Perindopril tert.butylamine	HP-β-CD	Perindopril Erbumine	Oral	Sandoz
PGE1	α-CD	Prostavasin	Parenteral	Ono, Schwarz
		Viridal, Alprostadil, Edex, Caverject, Rigidur,	Parenteral	Schwarz, Ferring, Pfizer
		Prostandin 500	Parenteral	Ono
	β-CD	Opalmon	Oral	Ono
	α- + β-CD	Limaprost, Prorenal	Oral	Sawai Pharm., Nichiiko, Sumitomo
PGE2	β-CD	Prostarmon E, Dinoproston- betadex	Sublingual	Ono
Piroxicam	β-CD	Cycladol, Brexin, Flamexin, Pyrodex, Medicam, Flogene	Oral	Chiesi, Ranbaxy, Sun, MMC, Ache
		Brexin	Rectal	Chiesi
porcine circovirus (inactivated)	Sulfolipo-CD	Suvaxin-PCV	Parenteral	Pfizer
Posaconazole	SBE-β-CD	Noxafil	Parenteral	Merck
Pramipexole Dihydrochloride	β-CD	Pramipexole Dihydrochloride	Oral	Endo Pharmaceuticals
Progesterone	HP-β-CD	Lubion	Parenteral	Hikma (Portugal)
Quizartinib	HP-β-CD	Vanflyta	Parenteral	Daiichi Sankyo
Remdesivir	SBE-β-CD	Veklury	parenteral	Gilead Sciences
Rofecoxib	β-CD	Rofizgel	Oral	Wockhardt
		Prosoria, Clarity Clear Skin Essentials Acne	Dermal	
Salicylic acid	CD	Treatment Cream		Nuvothera, Melaleuca
Salicylic acid	HPCD	Age Defying Blemish Treatment, Lipo™ CD-SA	Dermal	Wasatch, Vantage
Solifenacin	β-CD	Solifenacin Succinate OD Tablets	Oral	Japan generic
Tc-99 Teboroxime	HP-γ-CD	CardioTec	Parenteral	Bracco
Televancin	HP-β-CD	Vibativ	Parenteral	Astellas Pharma, Therevance
Thiromersal	β-CD	Vitaseptol	Ocular	Novartis, Europhta
Thyme herb extract (Nerba Thymi vulgaris)	HP-β-CD	Bronchipret	Oral	Bionorica (Germany)
Tiaprofenic acid	β-CD	Surgamyl	Oral	Roussel-Maestrelli
Umbralisib tosylate	HP-β-CD	UKONIQ	Oral	TG Therapeutics, Inc.
Valeriana extract + α-bromoisovaleric acid ethyl ester + phenobarbital + peppermint oil	β-CD	Corvalol	Oral	Farmak (Ukraine)
Voriconazole	SBE-β-CD	Vfend,Voriconazole (vet)	Parenteral	Pfizer,Sandoz

(*continued on next page*)

Table 2 (*continued*)

Active pharmaceutical ingredient	Type of CD	Brand name	route of administration	Company
Voriconazole	HP-β-CD	Vorzu, Voriconazole Synthon	Oral, parenteral	Rhambaxy, Synthon
Ziprasidone	SBE-β-CD	Geodon, Zeldox	Parenteral	Pfizer

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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