REVIEW ARTICLE

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An update on cyclodextrins as drug vehicles for antimicrobial applications

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ABSTRACT

Cyclodextrins belong to cyclic oligosaccharides comprised of α-(1,4) linked glucopyranose groups. Their interesting supramolecular cavity-like structure can host active molecules providing a breeding ground for drug delivery systems. Cyclodextrins, due to their unique functional structure, can produce host-guest complexes with active ingredients, such as drugs, peptides, proteins, etc.; the complexes resulted from intramolecular interactions leading to stable molecules vehicles. Moreover, cyclodextrins are already applied in pharmaceutical industry applications since they can induce the solubility of lipophilic compounds and provide bioavailability and excellent safety profile and stability. In this review, the basic background for cyclodextrins and their current applications in the antimicrobial field are discussed. Besides, the antibacterial and antifungal-applications in the pharmaceutical field attract most researchers because of microbes' resistance. Regarding this, the most recent cyclodextrin inclusion complexes with antimicrobial and antifungal drugs are summarized in this article.

1. INTRODUCTION

Over the last decades, solid dispersion (SD) technology has been utilized to improve oral bioavailability via the enhancement of poorly soluble drug solubility [1,2]. Besides, given that most of the active molecules are lipophilic with low aqueous solubility, their delivery in the form of amorphous SDs seems to be advantageous [3]. Except for oral bioavailability, SDs have also been applied for maximizing ocular bioavailability, as well [4]. SDs have been defined as the systems were one or more active molecules are dispersed in an inert carrier produced by various methods, melting, dissolution, or combination of them and others [5]. Solvent evaporation, electrospinning, spray drying, and hot melting, cyclodextrin complexation, as well as kneading [6-10], are commonly used techniques. Cyclodextrin (CD) complexes belong to the most handful of SDs categories [2,11].

2. CYCLODEXTRINS

CDs belong to the family of cyclic oligosaccharides comprised of glucopyranose units. Other names of CDs are Schardinger sugars or cycloamylose dextrins. Vielliers in 1891 was the first who discovered CDs which at that time were named as "cellulosing" [12]. Some years later, Schardinger, who has been considered as the "founding father" of CD chemistry, describes the preparation and separation methods of CDs. In contrast, recently, Loftsson and coworkers have significantly contributed to the development of the CD field [13-17].

The most common CDs are α, β, and γ, constituted by 6, 7, and 8 glucopyranose units (**Figure 1**), respectively. However, except for them, δ-, ζ-, ξ- and even η-CD (9-12 units) have been confirmed. Their structure mimics doughnut ring exists as a truncated cone (**Figure 2**); the outer part of the cone presents hydrophilic nature resulted from the hydroxyl groups of the glucopyranose units while the inner cavity is apolar. The truncated shape is the result of the rotation of the primary hydroxyl groups located at the end of the cavity reducing the size of the cavity toward the side of the secondary hydroxyls regarding the C2 and C3 carbon atoms of the glucose units located to the edges of the cavity [18]. The main property of CDs is their ability to form host-guest complexes leading to stable complexes; one or two guest molecules can be entrapped by one, two, or three CDs. The formation of the complexes can be easily detected by phase solubility studies [2,19]. It is generally accepted that

the complex formation issued by various mechanisms [20] such as;

a. van der Waals interactions between the CD cavity and the hydrophobic unit of the guest molecules [21],
b. hydrogen bonding between the polar functional groups of the guest molecules and the hydroxyl groups of the CD [21],
c. release of high energy water molecules from the cavity during the complexation
d. release of strain energy into the ring structure system of the CD [22].

Also, CDs due to the presence of the hydroxyl groups can be easily functionalized, providing derivatives such as hydroxypropyl-β-CD, sulfobutylether-β-CD [23], and others. These derivatives present more excellent solubility in water or improved properties. Asides from these, CDs can be used to graft polymers resulting in multifunctional drug carriers [24].

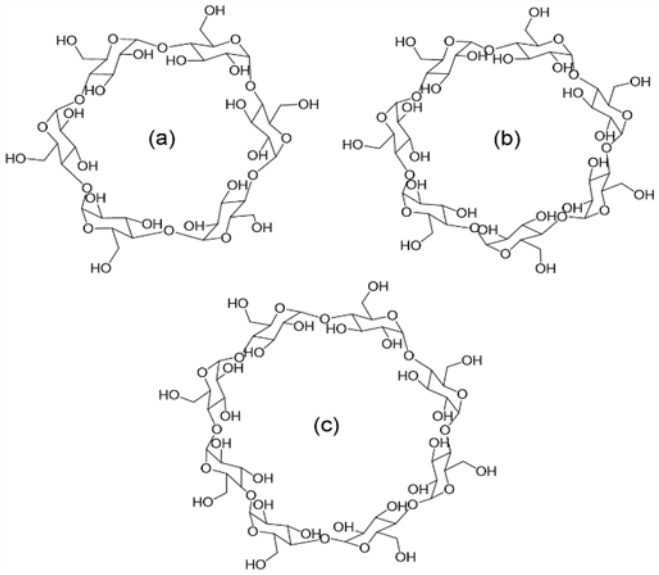

Figure 1. *The most common cyclodextrins structures (a) α-CD, (b) β-CD and (c) γ-CD*

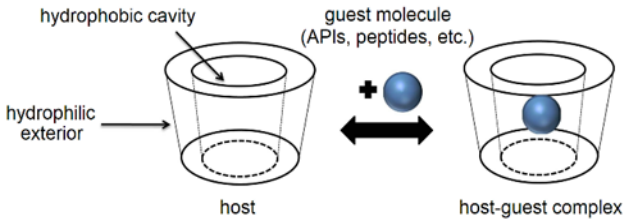

Figure 2. *Cyclodextrin structure and complexation mechanism (host-guest complex) APIs= Active pharmaceutical ingredients*

The natural CDs (α-, β-, γ-) are not toxic but present limited water solubility [25]. **Table 1** summarizes basic properties of natural CDs. This limitation can be overcome via their functionalization with;

a. propylene oxide leading to hydroxypropylated CDs,
b. monochloroacetic acid resulting in carboxymethylated CDs
c. methyl iodide methylated CDs and
d. 4-butane sultone resulting in sulfobutylether CDs [26].

Table 1. *Physicochemical properties of α-, β-, γ- CDs*

Properties	α-CD	β-CD	γ- CD
Glucose units	6	7	8
Cavity diameter (Å)	4.7-5.3	6.0-6.5	7.0-8.3
Cavity height (Å)	7.9	7.9	7.9
Cavity volume (Å)	174	262	427
Crystal shape	hexagonal lattice	monocyclic par-allelograms	quadratic prism
$\log P_{oct/water}$ [1]	-13	-14	-17
MW [2] (g/mol)	973	1135	1297
F_{oral} [3]	0.02	0.006	<0.01

[1] *logarithm of the calculated octanol/water partition coefficient*
[2] *molecular weight*
[3] *fraction of the absorbed CD amount when orally administered to rats*

2.1. Preparation and Characterization Methods

For the preparation of CD complexes with various active ingredients, several preparation methods have been proposed through literature. Commonly used methods are freeze-drying, physical mixing, kneading, co-precipitation, solvent evaporation, and supercritical process [27-31]. The developed complexes to be characterized, are analyzed using Fourier-Transformed Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), scanning electron microscopy (SEM), and x-ray diffractometry (XRD) [2]. In further, the successful complexation is examined via various physicochemical methods. In detail, numerous spectroscopic methods as fluorescence spectroscopy, Ultra-violet/visible spectroscopy aqueous phase solubility studies, and nuclear magnetic resonance (NMR) spectroscopy are reported to detect the complexation between drug and CDs [32-34].

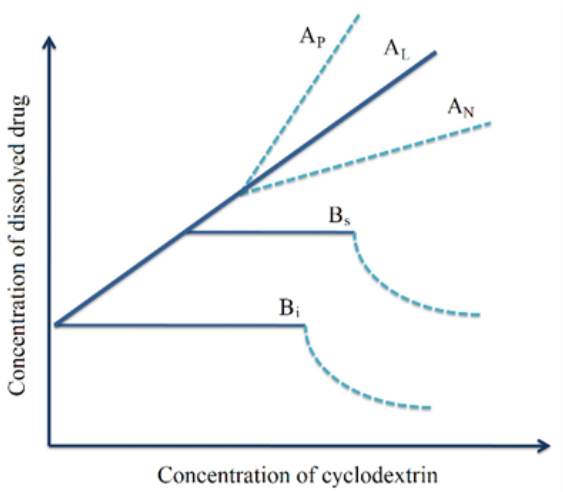

Figure 3. *Phase-solubility profiles acquired through Higuchi and Connors methods [33].*

The phase solubility studies, according to the molecule solubility in moles/L plotted against the molar CD concentration, is one of the most common and easy methods utilized. Although these studies do not prove the formation of the inclusion complexes, describe how the increment of CD concentration affects drug solubility. Five main profiles have been identified (**Figure 3**). Generally, A-type profiles are acquired from water-soluble CD derivatives (i.e., HP-β CD) while B-type from natural CDs. First, A-type phase (AL, AP, AN) solubility profiles are obtained when drug solubility of the drug-enhanced by enhancing CD

concentration through the complexation between the hydrophilic drug and CD. AL profile is acquired when the complex is first-order regarding CD and first or higher-order in respect of the drug resulting in 1:1, 2:1, or 3:1 drug/CD complexes. AP profile identifies the complexes with the first order of drug, but a second or higher order of CD. AN profile is difficult to be examined, but the variance from linearity could be associated with various changes, according to Jansook et al. [26]. The B-type profiles specify the formation of complexes with low solubility in the water media [17].

3. CYCLODEXTRIN BASED ANTIMICROBIAL SYSTEMS

Currently, physicians and researchers from the health sciences field are quite aware of the antimicrobial resistance; the ability of microbes to resist the effects of medications [35]. Both microbe and fungi resistance represents a major clinical challenge to clinicians since they can resist certain medications leading to severe complications of the patients' life [35-37]. Thus, this research field based on antimicrobial systems is a developing one. The researchers either focus on new active ingredients or other administration routes. Besides, most of the antimicrobial ingredients are lipophilic, limiting their oral use. Except, oral administration, the ocular and parenteral routes are widely utilized for the delivery of antimicrobial drugs. Consequently, the use of CDs as a matrix for the delivery of such drugs could be very promising. There are several marketed products based on CD complexes and various active ingredients. In 1976, the first marketed product was developed via prostaglandin E2 and β-CD in the form of sublingual tablets [19]. More specifically, in the case of antimicrobial pharmaceutical field, a known marketed product is the intravenous solution of Voriconazole (VRC) and Sulfobutylether-β-CD complex, supplied by Pfizer under the brand name Vfend®.

3.1. Cyclodextrins-Antibacterial Drug Complexes

An oral drug formulation based on tebipenem pivoxyl (TP) has been proposed. Tebipenem pivoxil-β-cyclodextrin (TP-β-CD) complex was prepared, and the physicochemical properties were changed. The inclusion of TP-β-CD was confirmed using DSC (thermal method) as well as infrared and Raman spectroscopy (spectral method). Due to the inclusion complexation, there has been an increase in solubility and chemical solid-stability. Biologically primary effects of TP and β-CD interactions decreased TP permeability through Caco-2 cell using efflux effect inhibition and enhanced antibacterial activity. The pharmaceutical formulation showed a great opportunity for the treatment of resistant bacterial infections [38].

The formation of the β-CD inclusion complex with levofloxacin was studied using fluorescence spectroscopy in pH 7.4 buffer solution. It was revealed that a 1:1 inclusion complex of β-CD with levofloxacin was developed, as the ^{1}H NMR and IR methods depicted. The complex formation between levofloxacin and gadolinium (III) ion was examined in aqueous solutions with and without β-CD. The stability and stoichiometry constants of the complexes were reported, and the concentration distribution of some complexes has been measured as a function of pH. The effect of β-CD on dissociation constants, Ka of levofloxacin, and stability constants of levofloxacin-gadolinium (III) complexes were checked. Also, gadolinium (III) distribution in human blood was showed with computer simulation [39].

The main complication of hernia repair is mesh-infection. Bacterial infections can develop in textile structures, after knitted mesh implantation. Sanbhal et al. prepared polypropylene (PP) mesh materials, which were modified with β-CD and hexamethylene diisocyanate and then loaded with levofloxacin for the treatment of hernia mesh-infection. First, oxygen plasma was able to provide surface roughness, and then hexamethylene diisocyanate was suitably grafted onto surfaces of PP fibers. Afterward, the CD was grafted onto the hexamethylene diisocyanate modified polypropylene meshes, and levofloxacin HCL loaded into the CD. A sustained drug release was obtained between surfaces of aqueous environment and meshes. In further, samples showed sustained antibacterial activities against both Gram-positive and negative bacteria for 10 and 7 days, respectively. The complexes demonstrated a burst release after 6 hours, followed by a sustained release for 48 hours. The modified mesh was the most stable between all specimens and provided more sustained drug release, which is essential for future clinical treatments [40].

Aytaç et al. modified pharmaceutical-grade CDs (HP-β-CD, M-β-CD, and HP-γ-CD) were used for complexation with linalool. These CDs were acquired due to their higher solubility in comparison with natural CDs. Their higher water solubility could induce their successful electrospinning to nanofibrous structures. They prepared nanofibers based on the CD/linalool-inclusion complex using an electrospinning apparatus. The high mass of linalool (45-89%) was loaded into the nanofibers because of CD complexation. Besides, the thermal stability of linalool increased due to the CD inclusion complexation. The complexes demonstrated very high antibacterial activity against Gram-positive (*S. aureus*) and Gram -negative (*E. coli*) bacteria. CD complexes were dissolved entirely in water in two seconds. The produced CD based nanofibers confer high linalool loading capacity, the effective antibacterial activity of linalool, and enhanced shelf life [41].

Szabó et al. studied moxifloxacin (MOX) and β-CD complexation to enhance its antibacterial property. This inclusion complexation was examined with NMR, mass spectrometry, affinity capillary electrophoresis, DSC, and FTIR techniques. The antimicrobial test showed that the MOX inclusion complex offers slightly improved activity against *Enterococcus faecalis* and Methicillin-resistant *Staphylococcus aureus* (MRSA) [42].

Masood et al. prepared roxithromycin (ROX) encapsulated in the cavity of β-CD and HP-β-CD formulations, to enhance ROX poor solubility. In further, blank and ROX loaded poly (lactic-co-glycolic acid) nanoparticles were prepared. The nanoparticles were capable of inhibiting the growth of multidrug-resistant Gram-negative and Gram-positive bacteria compared to the HP-β-CD-ROX/PLGA NPs and β-CD-ROX/PLGA NPs [43].

He et al. produced rifampicin (RFP) HP-β-CD complexes to form a molecular inclusion complex (MRICD) with excellent stability and solubility. The complex was prepared using a solid-state grinding technique without any water revealing a greater dissolution rate of than free RFP.

Moreover, the complex showed enhanced antibacterial activity and improved the physical properties of RFP [44].

Choi et al. investigated the complexation effect of mono-6-deoxy-6-aminoethylamino-β-cyclodextrin (Et-β-CD) on the bioavailability and solubility of ciprofloxacin which is used to treat bacterial infections. The complexes were characterized using DSC, FE-SEM, FT-IR, T1 relaxation, DOSY NMR spectroscopy, 2D NOESY, and molecular modeling tests. The solubility of the ciprofloxacin complex was improved by seven-time when compared to pure ciprofloxacin. The antibacterial activity of the ciprofloxacin complex against *Staphylococcus aureus* was increased, demonstrating growth inhibition. The results of this study suggested that the induced oval-shaped cavity of Et-β-CD may be used for other guest molecules besides ciprofloxacin [45].

Taha et al. aimed to load antibiotics onto hip implants for preventing infection risk after a total hip replacement. They modified the surface of hydroxyapatite (HA) coated titanium implant material (Ti-HA) with poly CD for loading tobramycin and rifampicin. They achieved a sustained drug delivery. A strong efficacy against both Enterobacter cloacae and *Staphylococcus aureus* was achieved because of dual-antibiotic loading. The antibacterial coating (polyBTCA/ Me-β-CD) for an HA-coated titanium prosthesis provided an enlarged therapeutic spectrum [46].

3.2. Cyclodextrins-Antifungal Drug Complexes

Li et al. prepared fluconazole (HFlu) loaded inclusion complexes with β-CD and HP-β-CD via the co-precipitation technique. The 1:1 stoichiometry for both CD complexes was achieved according to phase solubility and fluorometric studies. These preparations were characterized by DSC-TGA and ESI-MS spectra analyses. Finally, Flu-HP-β-CD showed higher stability than for HFlu-β-CD [47].

Orgován et al. aimed to quantify acid-base and CD-complex formation equilibria of fluconazole. ^{1}H-NMR pH titrations exhibited protonation levels in the acidic and the highly basic region (log K1= 11.96). The structure and stability of its complexes with β-CD (2-hydroxy) propyl-β-CD and sulfobutyl ether-β-CD were studied by NMR methodologies. The CD complexes of fluconazole are of average stability. Two isomeric complexes of comparable stability were formed between the β-CD and fluconazole [48].

Oral VRC is used for patients with kidney failure due to concerns about CD accumulation. Siafaka et al. compared two different preparation methods for the improvement of the dissolution rate of VRC. Poly(ε-caprolactone) (PCL) electrospun fibers were developed with an electrospinning process, and β-CD complexes were prepared with an inclusion complexation method. The formulations were loaded with various concentrations of VRC. PCL nanofibers were characterized based on morphology. β-CD complexes were evaluated for phase solubility. An improved VRC solubility was found for all formulations, whereas inhibition of fungi proliferation was also revealed [2]. Kim et al. studied the effects of IV VRC formulated using sulfobutylether β-cyclodextrin (SBECD) in patients with kidney failure. An observational study was conducted on 25 adult invasive aspergillosis patients treated with IV VRC. Even in patients with renal insufficiency after VRC treatment, no significant impairment of kidney function was observed in any patient. IV VRC formulated with SBECD did not cause an increase in the incidence of serious adverse events, including nephrotoxicity in hematological patients with CrCl<50 mL/min [49]. According to another study, VRC was incorporated in SBECD for renal function. The impact of long-term use of intravenous VRC on renal function is indefinite. Their retrospective study of data proved that the worsening of renal function was notably connected with a total dose of IV VRC (≥400 mg/kg), recommending that a higher cumulative dosage of IV VRC is a risk factor for renal dysfunction [50].

Sun et al. used the electrospinning technique to prepare VRC incorporated polyvinyl alcohol (PVA)/HP-β-CD blended nanofibers for ocular application. HP-β-CD content increased drug solubility. The nanofibers presented bead-free mean fiber diameters of 307±31 nm, and VRC was released in a sustained profile. The proton nuclear magnetic resonance was practiced to analyze the molar proportion of HP-β-CD/VRC in the nanofibers. The nanofibers remarkably improved the bioavailability and increased the half-life of VRC in rabbit tears when compared with a VRC solution. VRC nanofibers were found promising for ophthalmic drug delivery [51]. Vass et al. conducted a study to evaluate electrospinning as an alternative process of the dilution injection dosage form. High-speed electrospinning with a new continuous cyclone collection was applied to produce a formulation of VRC using sulfobutylether-β-cyclodextrin (SBE-β-CD). SBE-β-CD worked as a 'quasi-polymer,' and it could be electrospun despite its low molecular weight. The crystalline form of VRC in fibers was not detected according to DSC and XRD methods. Also, it was determined by energy dispersive spectroscopy and Raman mapping measurements that the VRC in the amorphous form in the fibers showed a proper distribution. According to Reconstitution tests with ground fiber powder, a clear solution formed later 30 seconds (similar to Vfend®). With this study, it has been proved that aqueous high-speed electrospinning, is an economically viable manufacture alternative compared to freeze-drying [52].

Herrera et al. used a co-precipitation method for preparation inclusion complexes based on β-CD and antimicrobial drugs. These preparations were characterized by entrapment efficiency (EE), thermal analysis, X-ray diffraction, 1H NMR spectroscopy, and water sorption. They also evaluated for drug release and antifungal activity. EE% was found between 66-91%. High relative humidity was affected by drug release. These complexes also showed antifungal activity on *B. cinereal*. For this reason, these preparations could be used in antifungal packaging [53].

Econazole nitrate (ECN) is a weakly basic drug with low water solubility resulting in low bioavailability. The ECN/ CD complex was used to increase the solubility of the drug in the aqueous medium. Jansook et al. conducted a study to determine the effect of CD inclusion complex and pH adjustment on ECN solubility. The solubility of this drug in acidic solutions containing α-CD was higher under the same conditions than aqueous γ-CD solutions. The presence of the ECN/CD complex was confirmed using proton nuclear magnetic resonance spectroscopy. Autoclaving increased the

drug stability of ECN/CD complexes. To create nanoparticles and microparticles, γ-CD complexes can self-assembled, while α-CD complexes are at a negligible level of self-assembly. ECN/α-CD has been shown to increase antifungal activity against filamentous fungi [54].

Eleamen et al. used a freeze-drying method for preparing a complex of HP-β-CD and 6CN10 (a poorly water-soluble 2-aminothiophene derivative). The complexes were characterized by infrared/Raman spectroscopy, thermal analysis, scanning electron microscopy, and X-ray diffraction. The water solubility of 6CN10 with HP-β-CD improved more than 29 times. The antifungal activity against *Cryptococcus neoformans* presented the better performance of the complex (46.66 µg/mL) compared to the free drug (166.66-333.33 µg/mL). This study provided useful complexation with low soluble compounds and HP-β-CD [55].

Gontijo et al. produced CDs with ellagic acid. Caco-2 cell lines cultivated in a Transwell® insert were contaminated with *Candida albicans* to promote an *in vitro* model. Characterization studies of complexes and microbial effects were evaluated. Ellagic acid exhibited the ability to defeat the *Candida albicans* invasion. Poor absorption and poor water solubility of ellagic acid probably limited this ability. Ellagic acid/hydroxypropyl-β-CD did not improve the antifungal activity. Poor water solubility was improved with HP-β-CD complexation. This formulation presented a promising antifungal activity [56].

Propiconazole nitrate incorporated inclusion complexes prepared by the freeze-drying method. The preparations were characterized by 1H-NMR, 2D Roesy NMR, and DSC. The complexes with sulfobutylether-β-CD had the highest association constant values, and the inclusion efficiency was close to 100%. Antifungal activity, in silico docking and molecular dynamics simulations, were evaluated. For all complexes showed similar results on *Candida spp*. The complexes were also evaluated for cytotoxicity, and the β-CD complex was showed higher cytotoxicity than other complexes [57].

Teodoro et al. were prepared gallic acid CDs (GA/HP-β-CD) by spray drying to enhance gallic acid (GA) solubility for the management of *Candida albicans* biofilm. Complexes were characterized by drug loading, SEM, and DSC and were tested on *Candida albicans* biofilm. The drug loading % was found approximately 10%. Inclusion complexes were confirmed with SEM and DSC tests. The developed complex kept the antimicrobial activity of the pure GA while it was found effective on *Candida albicans* biofilms of 24 and 48h. Besides, the *in vivo* results showed an anti-inflammatory activity of GA/HP-β-CD [58].

4. CURRENT STATUS OF CYCLODEXTRIN COMPLEXES IN PHARMACEUTICAL APPLICATIONS

CD complexes included in about 40 marketed pharmaceutical applications worldwide, in addition to many foods, toiletry, and cosmetic products [59]. CD complexes are all found in one or more pharmaceutical products in Japan, the USA, or Europe: Cefotiam hexetil hydrochloride (Pansporin T, Japan), Benexate hydrochloride (Ulgut, Lonmiel, Japan), Omeprazole (Omebeta, Europe), Piroxicam (Brexin, Europe), Cisapride (Propulsid, Europe), Itraconazole (Sporanox, Europe, USA), Mitomycin (Mitozytres, USA), 17b -Estradiol (Aerodiol, Europe), Voriconazole (Vfend, Europe, USA), Ziprasidone maleate (Geodon, Zeldox, Europe, USA), Diclofenac sodium (Voltaren, Europe) [60].

The biopharmaceutical classification system (BCS) divides oral drugs into 4 cases based on their solubility and gastrointestinal permeability. CD complexes mostly studied to improve oral bioavailability of Class II drugs (poor aqueous solubility - good permeability) and Class IV drugs (poor aqueous solubility - poor permeability) [59]. The complexes of these drugs with CDs could mask undesirable properties. CD carriers such as nanosystems (nanosponges, nanofibers, dendrimers, metallic nanoparticles, quantum dots, nanoemulsions), liposomes, micelles, micro rods, niosomes, and siRNA may hide the undesired characteristics of drugs, thus improving their bioavailability [61,62].

CD has been extensively applied in gene therapy, nanomedicine therapy, cell therapy, chemotherapy, and immunotherapy. Studies have shown that numerous anti-cancer drugs, with properties such as instability, lack of physicochemical properties, or poor water solubility, have limited application in pharmaceutical applications [62]. Also, α-CD and β-CD are not degraded by pancreatic amylases enzymes and human salivary. Thus, CD-drug complexes remain unspoiled in the upper GI tract until they reach the colon. In this state, CD complexes of anti-cancer drugs serve as a hopeful system by improving both solubility and the availability of anti-cancer drugs at the colon site [63]. Also, the versatile nature of CDs may be used to defeat the limitations of ophthalmic topical delivery systems. CDs provide an attractive way to increase the solubility of wettable and poorly soluble drugs, to enhance their permeability and retention on ocular surfaces. CD has the potential to develop conventional eye drops to offer more excellent permeability, safety, effectiveness, and stability in the topical ocular delivery of the posterior and anterior segments [64]. A review has presented regarding applications of CDs in medical textiles. It was about the release/deposition of the drug onto/from a textile underlayer to the dermis, with CD complexes. Therapeutic textile fabrics with controlled drug release give an alternative with great medical potential, given both their numerous biopharmacological advantages. The use of CD-based medical textile fabrics applies to antimicrobial, anti-psoriasis, antiallergic (atopic and contact dermatitis), or venous insufficiency at the level of the dermis [65].

5. CONCLUSION

In this review, an update on CDs as drug vehicles for antimicrobial applications was presented. Overall, CDs as drug vehicles promote a promising approach for antimicrobial applications due to its ability to increase stability and the water solubility of antimicrobial drugs by inclusion complexation. Antimicrobial tests in some studies have shown that the inclusion complex offers more improved activity than pure drugs. In conclusion, research over the past few years has led to the development of CD as an antimicrobial drug carrier material. The antimicrobial drug/CD complexes may have many advantages over the conventional antimicrobial drug delivery systems. Further

technological and research advancements are expected to widen the importance of CDs in antimicrobial applications.

AUTHOR CONTRIBUTIONS

Concept: EÖB, KE, NÜO, PIS; Design: EÖB, KE, NÜO, PIS; Supervision: NÜO, PIS; Materials: EÖB, KE, NÜO, PIS; Data Collection and/or Processing: EÖB, KE, NÜO, PIS; Analysis and/or Interpretation: EÖB, KE, NÜO, PIS; Literature Search: EÖB, KE, NÜO, PIS; Writing: EÖB, KE, NÜO, PIS; Critical Reviews: NÜO, PIS.

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CONFLICT OF INTEREST DECLARATION

The authors declare no conflict of interest.

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