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Advances in cyclodextrins: Enhancing drug solubility, stability, and bioavailability for therapeutic applications

M Jude Jenita
Department of Chemistry, Government College of Engineering, Theni, Tamil Nadu, India

Abstract
Cyclodextrins (CDs) represent a versatile class of carrier molecules that significantly enhance the pharmacokinetic profiles of therapeutic drugs. These cyclic oligosaccharides are capable of forming inclusion complexes with water-insoluble compounds, making them highly valuable in the fields of medicine and pharmacology. Due to their unique structural properties, cyclodextrins are extensively utilized in the pharmaceutical industry, particularly in drug delivery systems. Their primary role in medicine is to improve the solubility, stability, safety, and bioavailability of active pharmaceutical ingredients (APIs). This article provides a comprehensive review of the chemical structure, solubility, complexation behavior, and therapeutic applications of cyclodextrins, focusing on their use as active pharmaceutical ingredients in the treatment of various diseases, including viral infections, metabolic disorders, and cardiovascular conditions. The review also explores the structural characteristics, applications, and derivatives of cyclodextrins in drug delivery, highlighting their potential to revolutionize therapeutic interventions.

Keywords: Cyclodextrins, inclusion complex, cholesterol, antibiotic, veterinary medicine, drug delivery

Introduction

Cyclodextrins have been recognized as important excipients in the pharmaceutical industry for over a century. This crystalline material, known as CDs, was initially identified by the French scientist Villiers as being produced by bacteria (Bacillus macerans) during the breakdown of starch. All medications need to be somewhat soluble in water to be pharmacologically active, and most drugs need to be lipophilic to diffuse through biological membranes passively. The water solubility of a medicine is determined by its potency and formulation type [1]. When a hydrophilic medication is dissolved, it will not transform into a lipophilic biomembrane and penetrate from the outer watery layer. High-throughput screening methods in drug development have uncovered a growing number of lipophilic, water-insoluble medicines, limiting their therapeutic value due to their insolubility in water [2]. Due to their unique structure, CDs can accommodate small to medium-sized organic molecules, making them highly versatile for various scientific fields, particularly in the pharmaceutical industry where they are used as carriers for drug transport and solubility. This study explores the impact of cyclodextrin on solubility, stability, bioavailability, safety, and its use as an excipient in medication formulation. CDs are widely utilized in the food, chemical, pharmaceutical, drug delivery, and cosmetic industries, and can be found in over-the-counter drugs like pills, ointments, and eye drops. Furthermore, the study also delves into the factors influencing the development of cyclodextrin inclusion complexes.

Cyclodextrin

Cyclodextrins (CD) are cyclic oligosaccharides with a hydrophilic exterior and a lipophilic center. Due to their abundance of hydrogen donors and acceptors, cyclodextrin molecules are typically too large to pass through lipophilic membranes. They are commonly used as "molecular cages" in the food, cosmetic, agrochemical, and pharmaceutical industries [3]. An enzyme known as cyclodextrin glycosyltransferase converts starch into cyclodextrins. Although there has been a report of a chemical synthesis, it is considered too laborious for cyclodextrin manufacturing on a commercial scale. The three primary cyclodextrins produced by the enzyme are alpha, beta, and gamma, which include α-D-glucopyranosyl units connected in six, seven, and eight positions, respectively. Several types of bacteria produce the enzymes necessary to create cyclodextrins (CD). No documentation exists of any fungus or other organisms generating cyclodextrin glucosyltransferase (CGTase). There are variations in the proportion of α-, β-, and γ-cyclodextrins generated by the enzymes derived from these bacteria. The result typically consists of a combination of two or three cyclodextrins. A second or third cyclodextrin also begins to accumulate as the reaction progresses. Once the reaction is complete, β-cyclodextrin might have been the first cyclodextrin created, but over time, other types, like beta-cyclodextrin, may have accumulated in larger amounts. These cyclodextrins are used in the pharmaceutical industry as complexing agents to enhance the bioavailability, stability, and water solubility of medications that are poorly soluble [4]. Furthermore, cyclodextrins can be used to prevent interactions between pharmaceuticals and excipients, alleviate gastrointestinal discomfort caused by medications, and convert liquid medications into amorphous or microcrystalline powder.

1. Structure and properties

Each α-D-glucopyranose unit in cyclodextrin has a lipophilic core cavity and is linked by α-1, 4 bonds. Figure 1 illustrates these structures. Cyclodextrins are shaped like toroids with larger and smaller pores, which expose the solvent's secondary and primary hydroxyl groups, respectively. They are made up of six to eight glucopyranoside units. Because of this shape, the inside of the toroids can hold other hydrophobic molecules, as it is less hydrophilic than the surrounding watery environment.

On the contrary, the outside is hydrophilic enough to make cyclodextrins (or their complexes) soluble in water [5]. The physical and chemical properties of the guest molecule change significantly when inclusion compounds are formed, especially in terms of its solubility in water. Hydrophilic cyclodextrins are considered safe when taken orally in small to moderate amounts [6, 7]. Parenteral formulations are limited to the use of α-cyclodextrin and its hydrophilic derivatives, β- and γ-cyclodextrin. Formulations for topical and oral usage include natural cyclodextrin and its derivatives. γ-cyclodextrin clumps visibly in aqueous solution, hence parenteral formulations are not a good fit for it [8]. Parenteral formulations cannot contain β-cyclodextrin due to its nephrotoxicity. When administered through injection, lipophilic cyclodextrin derivatives, such as methylated cyclodextrins, are hazardous. They enter the bloodstream after being partially absorbed by the digestive system. Empirical computational techniques have been used to apply theoretical concepts to the structural analysis of various cyclodextrins.

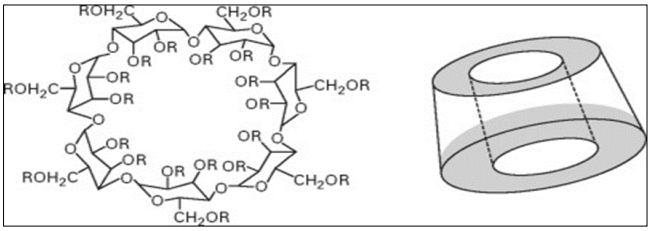

Fig 1: The β-cyclodextrin molecule's chemical composition

A wide variety of symmetric and non-symmetric structural shapes have been discovered. Although semiempirical methods have been used to explore molecular geometries, the results obtained are questionable because the methods used may not accurately describe hydrogen bonding. While symmetric structures with intramolecular hydrogen bonds at the rim have been found, the global minimum, a closed form with two hydrogen bond rings, has not yet been experimentally tested, most likely due to experimental challenges.

2. Cyclodextrin's drug solubility and Complex formation

Cyclodextrins contain a central cavity that can encapsulate a lipophilic component or a drug molecule to form inclusion complexes with various pharmaceuticals in water-based solutions. The drug molecules reach a balance with the free molecules in the solution during the complex formation process, without forming or breaking covalent bonds. The development of the complex is propelled by several mechanisms, such as Vander Waals interaction, hydrogen bonding, charge transfer contact, and the release of high-enthalpy water molecules from the cavity [9]. The physicochemical properties of cyclodextrin are different in its complexed and free forms. Determining the stoichiometry of complex formation and the numerical values of its stability constants is possible by observing changes in various physicochemical properties. These properties include solubility in alcohol, chemical reactivity, UV/VIS absorbance, drug retention, chemical stability, and effects on drug permeability through artificial membranes [10]. One study examined the development of an inclusion complex between methyl-β-cyclodextrin (MβCD) and omeprazole (OME). The complexes were found to have a stoichiometry of 1:1 mol: mol OME: cyclodextrin [11], and OME: MβCD had a higher Ks value than OME: βCD inclusion complexes.

3. Phase-solubility diagram

The phase-solubility profiles depicted in Figure 2 demonstrate how complexes are categorized by Higuchi and Connors [12] based on their impact on substrate solubility.A-type phase-solubility profiles occur when the concentration of the ligand (cyclodextrin) increases, resulting in improved solubility of the medication or substrate. An AL-type phase-solubility profile is produced when the complex exhibits first-order behavior concerning the ligand and first-order or higher-order behavior concerning the substrate. An AP-type phase-solubility profile is observed when the complex has a substrate order of one and a ligand order of two or higher. The characteristics of an AN-type phase-solubility profile are more challenging to comprehend.

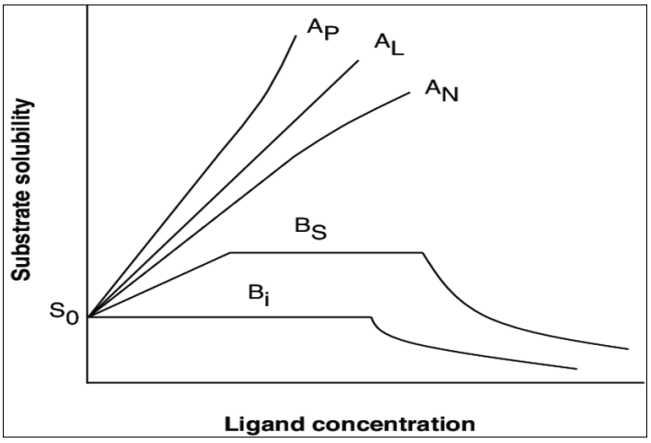

Fig 2: Phase-solubility profiles

The deviation from linearity may be due to several factors, such as the self-association of molecules caused by cyclodextrin, changes in complex solubility, or variations in the dielectric constant of the complexation medium. In the aqueous complexation medium, limited solubility complexes are formed, as shown by B-type phase-solubility profiles. Water-soluble cyclodextrin derivatives create A-type phase solubility profiles, while the less soluble native cyclodextrin produces B-type phase solubility profiles. Cyclodextrins can form non-inclusion complexes, yet most drug/cyclodextrin complexes are thought to be inclusion complexes due to the ability of the complex aggregates to dissolve medications through micelle-like structures [13]. Medication solubility is only affected by increasing the cyclodextrin concentration, as explained by the phase-solubility profiles. The most common type of cyclodextrin complex is a 1:1 drug/cyclodextrin (D/CD) complex, in which one drug molecule (D) binds to one cyclodextrin molecule (CD).

The impact of cyclodextrin on important medication properties during formulation

1. Impact of medication bioavailability

Drug permeability, dissolution, and solubility are all enhanced by cyclodextrin, which also increases the bioavailability of insoluble medicines. By delivering the medication to the surface of biological barriers such as the skin, mucosa, or cornea of the eye, cyclodextrin helps the

medication enter the membrane and partition without interfering with the barrier's lipid layers [14]. It is important to use the right amount of cyclodextrin to dissolve the medication in the aqueous medium, as using too much could reduce the medication's availability [15, 16]. Additionally, with the addition of polymers, there was an additional increase in the drug's permeability from aqueous cyclodextrin solutions. For water-soluble medications, cyclodextrins improve drug absorption and bioavailability by directly affecting mucosal membranes to increase drug permeability [17]. Studies have shown that cyclodextrins can remove cholesterol from membranes, which increases membrane fluidity and promotes membrane invagination by reducing bending resistance. However, cyclodextrins also remove phospholipids, such as phosphatidylcholine and sphingomyelin, from the outer half of the membrane bilayer, leading to an imbalance in the bilayer.

2. Effect on drug stability

Cyclodextrins can extend the shelf life of many unstable medications by increasing their resistance to oxidation, hydrolysis, dehydration, and photodecomposition. Table 1 provides a summary of cyclodextrin's impact on medication stability. According to certain theories, cyclodextrin enhances drug stability by preventing drug interaction with vehicles and inhibiting drug bioconversion at the absorption site

Table 1: CD's effect on the stability of pharmaceuticals

Drug	CD	Effect
Promethazine	HP-β-CD, DM-β-CD	Photostabilities
Glibenclamide	β-CD	Four years of unaltered dissolution rates during the shelf life.
Diclofenac sodium	β-CD	When a material is solid, thermal stability.
Quinaril	β-CD, HP-β-CD	Resistance to intramolecular cyclization in the solid state stability.
Doxorubicin	HP-β-CD, HP-γ-CD S	Resilience against photodecomposition and acid hydrolysis.

In cyclodextrin complexation, labile drug molecules are encased by cyclodextrins, acting as a molecular shield to protect them from various degradation processes. When compared to other cyclodextrins, Sulfobutylether β-CD demonstrated a higher level of stability enhancement for various chemically unstable medications [18]. The stabilizing effect of cyclodextrins depends on the type of additional functional group and its influence on the stability of the drug and the vehicle. Studies have shown that cyclodextrins improved the photostability of promethazine [19] and trimeprazine [20]. They also increased the stability and shelf life of medications in the solid state [21]. It's important to note that structural changes to drug molecules during cyclodextrin complexation can lead to accelerated drug degradation.

Cyclodextrins: Emerging medicines

1. Medicinal cyclodextrins-antiviral activity

1.1. Influenza treatment and prevention

The presence of a specific molecule in a virus's membrane makes it vulnerable to disruption by cyclodextrins, which can trap cholesterol. Cholesterol is typically found in lipid rafts, which are small areas of the membrane. Using RAMEB (randomly methylated β-cyclodextrin) to reduce cholesterol levels has been shown to cause structural changes in the viral membrane and disrupt lipid rafts, ultimately affecting influenza viral particles [22].

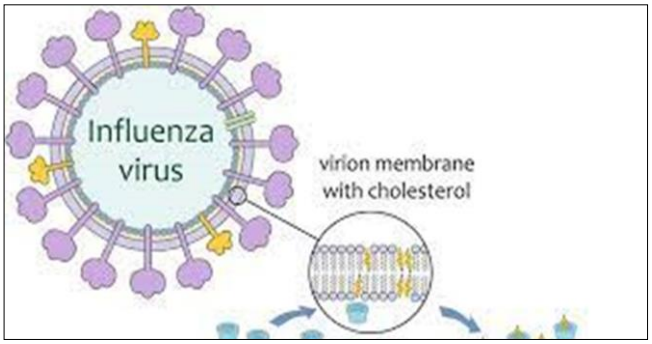

Fig 3: Diagrammatic illustration of the RAMEB's suggested mode of action against influenza virus particles. RAMEB damages the integrity of the viral envelope by sequestering membrane cholesterol

Analysis under a microscope reveals perforations in the viral envelope. Additionally, research has shown that RAMEB-induced cholesterol depletion significantly reduces the infectivity of influenza A (H1N1 strain) virus particles *in vitro* [23]. Although RAMEB is not yet approved for human use, these preliminary findings have opened up the possibility of utilizing other cyclodextrins for preventing influenza in humans. Moreover, the antiviral properties of cyclodextrins have laid the groundwork for a new influenza vaccine developed by a Japanese research team. This vaccine, which is delivered through the nose, is more patient-friendly compared to traditional injections currently available on the market.

1.2. The Dengue Virus's Interactions

The depletion of cholesterol induced by RAMEB in Flaviviridae viruses has been shown to affect both the entry and replication of these viruses within cells [24]. This discovery holds great promise for the treatment of diseases caused by this viral family, such as the Japanese encephalitis virus (JEV) and the dengue virus (DEN). Several studies have investigated the potential therapeutic uses of cyclodextrins for treating dengue, a disease that is widespread in tropical and subtropical regions. When tested *in vitro* using a monocyte cell model, RAMEB treatment led to a significant decrease in infection rates [25]. It is believed that this decrease is due to the virus particles' inability to deliver genetic material into infected cells. Additionally, when RAMEB is present in Aedes aegypti and Aedes albopictus mosquitoes, which transmit the Asian tiger virus, it can disrupt the virus's life cycle [26]. RAMEB reduces the synthesis of NS1 (non-structural protein 1), altering how the virus metabolizes its proteins inside mosquito cells.

2. Antiparasitic activity

2.1. Leishmanicidal cyclodextrins

Global warming is a threat to the spread of leishmaniasis, a neglected tropical disease found in tropical regions of Africa, the Middle East, and Central and South America [27, 28]. HPβCD, which can be used in injectable formulations and can sequester cholesterol, is a promising option for treating leishmaniasis. In a study on mice infected with

Leishmania donovani (a specific research strain), those given an aqueous solution of HPβCD Bimolecular injection showed a 21% reduction in liver infection compared to the control group. Research suggests that RAMEB effectively reduces the infectiousness and ability of L. donovani to infect the host's immune cells, supporting its potential as a new leishmanicidal medication. Additionally, RAMEB is patented for leishmanicidal purposes, and dosages between 20 and 500 mg/kg of body weight are feasible. The drug can be administered orally, via inhalation, or through implantation.

2.2. Anti-malaria sulphated cyclodextrins

The most common medication for treating malaria, a tropical hemorrhagic fever caused by Plasmodium protozoa parasites, is becoming less effective against an increasing number of malaria strains [29]. This makes the illness clinically challenging. Anionic saccharides are effective in preventing parasite entry into target cells, particularly erythrocytes and hepatocytes. In the quest for novel drugs, anionic cyclodextrins containing sulfate substituents were created and examined as potential antimalarial drugs. The results imply that the size of the cyclodextrin ring is not an important factor in the action, as derivatives of all the parent cyclodextrins (α-, β-, and γ-CDs) suppressed parasite reproduction [30]. The degree of substitution appears to be the primary determinant of each cyclodextrin derivative's potency of activity against malaria parasites. The sodium version of poly-sulfated β-cyclodextrin demonstrated the highest efficacy among all the chemicals examined, with an average sulphation degree of 16.9 sulfate groups (per CD molecule). The IC50 value of this derivative against P. falciparum was found to be 2.4 ± 0.3 µM. The results showed that CD compounds with sulphation levels between 0.8 and 1.7 were fully ineffective. The investigation's findings point to 16.9-sulphated-β-CD as a possible novel treatment for malaria, but a complete safety profile examination is still needed before this medication is successfully introduced into clinical practice.

3. Cyclodextrins in heart conditions

Atherosclerosis is a condition that affects the walls of arteries and is the main cause of peripheral vascular disease, heart attacks, and strokes. It progresses as plaques made of cholesterol-rich lipids build up in vulnerable areas of the arteries. It is believed that oxidized cholesterol in these plaques forms a blockage that prevents the body from naturally eliminating the lipid build-up [31]. The discovery that HPβCD can solubilize different forms of cholesterol has provided hope for preventing the accumulation of atherosclerotic plaque. Although HPβCD does not reduce total cholesterol levels in the blood, studies on mice *in vivo* showed that it is well tolerated at doses of 13 mg/day for four weeks [32]. By dissolving cholesterol deposits in artery walls and reprogramming macrophages to convert cholesterol into soluble oxysterols, HPβCD has been shown to prevent atherosclerosis in a series of *in vivo* tests on mice without affecting plasma cholesterol levels. HPβCD also has an anti-inflammatory effect on excised human atherosclerotic carotid plaques by controlling complement-related genes within the plaque cells and reducing complement component C5, a pro-inflammatory protein [33]. Furthermore, research has been conducted on the role of α-CD in preventing cardiovascular diseases. Since α-CD is already approved as a dietary supplement, the study focused on administering a daily dose of 6 mg of α-CD orally for 12 weeks to 75 healthy participants. However, no significant positive changes in the participants' blood lipid profiles were observed. This is likely due to the almost complete lack of absorption of α-CD when taken orally.

Biomedical technology using cyclodextrins

1. Cryopreservement of sperm

Stallion semen cryopreservation typically involves using egg yolk for dilution. However, cholesterol-loaded HPβCD can be used as an alternative. The HPβCD•cholesterol complex not only provides cholesterol to the medium in a water-soluble form but also improves the survivability and mobility of semen after thawing [34]. Similar methods using cyclodextrins can be used to cryopreserve goat sperm. To minimize the loss of membrane cholesterol during cryopreservation, excess RAMEB•cholesterol complex is added to the sperm dilution media before freezing. Fluorescence microscopy confirmed a 30% decrease in membrane cholesterol loss, although the reproductive rate did not increase despite the spermatozoa being more resilient to cold shock. The sperm of various mammal species, including buffalo bulls, boars, and Markhoz (Angora) bucks (Capra hircus), can be cryopreserved using the RAMEB•cholesterol complex. Pure HPβCD and RAMEB can be used to enhance sperm motility and viability after thawing in chicken sperm preservation [35, 36]. However, it was observed that adding cholesterol in addition to cyclodextrins seemed to be harmful, as shown by the reduced motility of chicken sperm supplemented with HPβCD•cholesterol complex, as well as the apoptosis and damage to the spermatozoa's acrosomes and cell walls of those treated with RAMEB•cholesterol.

2. Biomimetic corneal implants

Five million or so people worldwide suffer from corneal blindness. Multiple factors contribute to the origins, such as corneal dystrophies having a hereditary origin [37] and hyperkeratinization linked to ophthalmic infections or minor eye traumas [38]. A second human cornea that was obtained from volunteer organ donors after death is transplanted to replace the damaged cornea as part of the procedure. Immune rejection is a risk in allograft corneal transplantation, in addition to the constraints brought on by the small number of donors. To achieve sufficient transparency, mechanical resilience, and biocompatibility, biomimetic artificial corneas would be the best course of action.

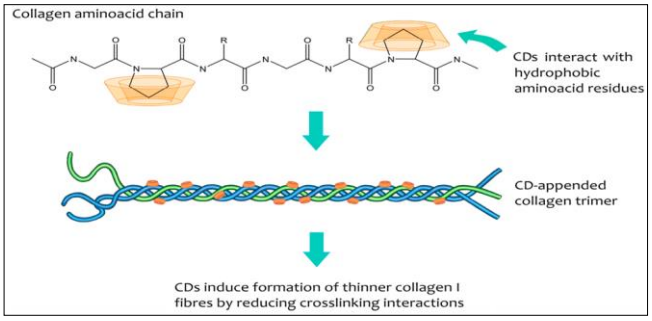

Fig 4: This illustrates the expected mode of action for cyclodextrins' *in vitro* regulation of collagen synthesis

The structure of collagen can be bioengineered to resemble that of the cornea by using cyclodextrins to aid in its growth *in vitro*. Due to their thinner size compared to other connective tissues, the cornea's collagen fibrils are unique in that they guarantee transparency. The process of crosslinking is halted when cyclodextrins are introduced to collagen during fibrinogenesis because of their interactions with the hydrophobic amino acid residues in collagen [39]. Natural cyclodextrins can be utilized to create mechanically robust, transparent corneal substitutes that control the self-assembly of type I collagen during vitrification. Immersion investigations on the collagen/β-CD cornea demonstrate that these biomimetic corneal substitutes have an ultrastructure similar to the original cornea and are robust enough to support re-epithelialization and host tissue integration. The process is already protected by a patent, and these materials show great potential as corneal biomimetic posters."During their synthesis, CDs are thought to interact with the hydrophobic residues of single-chain amino acids. However, the exact mechanism of inclusion remains unknown. Trimer formation occurs when the amino acid chains link and these trimers then come together to form fibrils [40]. The presence of cyclodextrins leads to the formation of thin fibrils and type I collagen by reducing the crosslinking between the different trimers that make up the fibrils."

Cyclodextrin-Drug combinations usable in veterinary medicine

1. Advantages for anti-bacterial therapy with inclusion complexes (CD–Antibiotic)

The discovery of antibiotics in the history of medicine marked a pivotal moment that has saved many lives, both human and animal. However, different bacterial species are rapidly acquiring antibiotic resistance today. Antibiotics such as beta-lactams, macrolides, and glycopeptides depend on time, while aminoglycosides and fluoroquinolones depend on concentration to be effective in treating animal infections.

Table 2: A brief description of the antibacterial drug inclusion complexes used in veterinary medicine

Compound in Action	Spectrum of Activity	Treated Species	CD Type	Characterization	Stoichiometry Guest: Host
Enrofloxacin	Escherichia coli, Proteus, Klebsiella, Pasteurella multocida, Pseudomonas, Rickettsia, Actinobacillus pleuropneumonia, Haemophilus parasuis, Streptococcus suis, Mannheimia haemolytica, and Haemophilus somni are among the bacteria that cause blood clots.	every kind of animal	γ-CD	FT-IR, ^{1}H-NMR, SEM, UV spectroscopy, HPLC, Dissolution Studies	1:1
Norfloxacin	Mycoplasma, Gram-negative (colibacilli, Salmonella spp., Pasteurella spp.), and Gram-positive (staphylococci, streptococci, etc.)	pigs, poultry, sheep, goats, and cattle	β-CD	DSC, TGA, FT-IR, XRD, SEM, NMR spectrometry, HPLC, Dissolution Studies	1:1
Amoxicillin	Upper respiratory tract infections are caused by gram-positive bacteria, specifically streptococcal bacteria.	every animal species	HP-β-CD	MDS, IMC, MM, HPLC	1:1
Florfenicol	Mycoplasma, Gram-negative cocci, and Gram-positive bacilli	pigs, sheep, and cattle	HP-β-CD	SEM, XRD, DSC, FT-IR, ^{1}H-NMR	1:1

Prolonged administration times for some antibiotics and the requirement for high concentrations for others can lead to extremely high residual concentrations with prolonged half-lives [41]. The presence of antibiotic residues in food products and the environment poses a serious risk to the health of both humans and animals. Additionally, the emergence of superbug bacteria, which are resistant to multiple antibiotic classes, makes these medications less effective as therapies. It's important to note that the bactericidal activity of enrofloxacin is concentration-dependent, and its limited water solubility restricts its therapeutic effects. Studies have shown that the combination of enrofloxacin with certain compounds can significantly enhance its antibacterial activity. For example, when enrofloxacin was complexed with γ-CD or 2-hydroxypropyl-β-CD (HP-β-CD), it exhibited increased solubility and stability, which resulted in the reduction of antibiotic dosage, shorter treatment duration, and improved therapeutic efficacy. Thermal studies also indicated that the presence of β-CD increased the stability of norfloxacin.

2. Benefits of inclusion complexes of CD-Antifungal in antifungal therapy

Fungal infections, known as dermatophytoses, are uncommon in animals and are typically seen in dogs and cats. Dermatophytes are fungi that can penetrate below the skin and feed on keratin. When humans and other animal species come into contact with these organisms that have adapted to live in animals, they can be transmitted [42]. The genera of dermatophytes most significant for veterinary treatment are Microsporum, Trichophyton, and Epidermophyton. Itraconazole is a triazole antifungal compound complexed with CDs that is commonly used to treat fungal infections in companion animals. Traditional itraconazole therapy has been associated with intestinal, renal, liver, and cardiac problems in carnivores. The FDA in the USA has approved an inclusion complex that combines itraconazole and HP-β-CD to treat pet dermatophytosis [43]. This generic drug has significantly better absorption and bioavailability in cats and dogs than regular itraconazole. Additionally, the inclusion complex has been shown to have a stronger antifungal effect than fluconazole or ketoconazole, and it is safer, more affordable, and more convenient to use than the new triazoles.

Table 3: An overview of the antifungal drug inclusion complexes used in veterinary medicine

Compound in Action	Spectrum of Activity	Treated Species	CD Type	Characterization
Flucytosine	Candida species, Aspergillus species, and filamentous fungi such as Cryptococcus neoformans	cat and dog	β-CD HP-β-CD	UV–VIS, ^{1}H-NMR, Dissolution Studies, DSC, SEM, FT-IR, XRD
Itraconazole	Microsporum canis, Trichophyton species, T. terrestre, Microsporum gypseum, and Cryptococcus neoformans, and C. gattii.	Small mammals, dogs, horses, birds, and reptiles.	β-CD HP-β-CD	FT-IR, DSC, UV Dissolution Studies and Spectroscopy
Sulconazole nitrate	Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, and Microsporum canis and Malassezia furfur	dog	β-CD	^{1}H-NMR, DSC, TGA, SEM, XRD

Cyclodextrins's Use in Pharmaceutical Applications

Cyclodextrins are utilized in almost all drug delivery systems due to their multifunctional properties. They have been employed in various research studies and commercial products for drug delivery.

1. Oral drug delivery

Oral drug delivery is the most preferred method of administering medication due to its many benefits, including ease of consumption, non-invasiveness, adaptability, increased stability, and patient compliance [44]. Many medications on the market have low solubility in water. Hydrophilic cyclodextrins are commonly used to enhance the oral bioavailability and solubility of poorly soluble medications. On the other hand, hydrophobic cyclodextrins are often used to modify or delay the release of medications.

2. Nasal drug delivery

The hepatic first-pass metabolism can be avoided by using the nasal route for drug delivery due to the high permeability of the nasal mucosa. For the drug to be absorbed through the nasal mucosa, it must dissolve in nasal secretions. Cyclodextrin is commonly used to increase the solubility of lipophilic medications in nasal preparations. Additionally, lipophilic cyclodextrin can enhance permeability by interacting with biological membranes, especially when delivering peptides through the nasal route [45, 46]. However, most cyclodextrins are removed from the nasal cavity through the nasal mucociliary system and end up in the gastrointestinal tract. Cyclodextrins generally show minimal local toxicity upon nasal delivery.

Table 4: Pharmaceutical products on the market that contain cyclodextrin complexes

Name of Trade	Form of dosage	Cyclodextrin (CD)	pharmacological active ingredients (APIs)
Pansporin T	Tablet	α - CD	Cefotiam hexetil HCl
Caverjext Dual	Intravenous fluid solution	α - CD	Alprostadil
Meiact	Tablet	β - CD	Cephalosporin
Omebata	Tablet	β - CD	Omeprazole
Surgamyl	Tablet	β - CD	Tiaprofenic acid
Stadatravel	Tablet Chewable	β - CD	Diphenhydramine& chlortheophylline
Nicorette	Tablet Sublingual	β - CD	Nicotine
Lonmiel	Capsule	β - CD	Benexate HCl

3. Pulmonary drug delivery

The goal of delivering medication to the lungs is usually to treat local illnesses. By administering drugs through the lungs, it's possible to avoid first-pass metabolism and breakdown in the gastrointestinal tract. The lungs have a large surface area, healthy blood flow, and minimal enzymatic activity, which allows for effective drug absorption. However, pulmonary medication delivery may be hindered by delayed drug dissolution and low water solubility. Insoluble particles in the lungs are cleared by macrophages in the alveoli and the mucociliary clearance in the upper airways [47]. It has been found that cyclodextrins only significantly impair cell viability at high concentrations in all 3 cells. These complexes can be used as an inhalation powder without reducing the medication's deposition in the lungs.

4. Dermal drug delivery

The outermost layer of the skin, called the stratum corneum, acts as a barrier preventing medications from entering the body through the skin. To reduce this barrier, various permeation enhancers are used. Cyclodextrins, when applied topically, are a safe option and can be used to enhance the transdermal delivery of medications that are meant to have a local or systemic effect. Although they do not improve the distribution of drugs through lipid barriers like the stratum corneum, they do enhance it through aqueous diffusion layers [48]. During the delivery of drugs through the skin, cyclodextrins can act as a permeation enhancer when the drug is released from water-based vehicles or when the release rate is influenced by an aqueous diffusion layer at the skin's outer surface.

Conclusions

The versatility and multifunctional properties of cyclodextrins (CDs) make them invaluable in mitigating the unfavourable characteristics of therapeutic molecules across various delivery platforms through the formation of inclusion complexes. The incorporation of cholesterol by HP-β-CD and other CD derivatives expands their clinical applications, notably in the treatment of viral and parasitic diseases such as leishmaniasis and malaria. Cyclodextrins hold significant promise in the pharmaceutical industry, with their use extending to drug delivery, HIV treatment, space research, healthcare, and even cosmetics. Their efficacy is further demonstrated by the successful

formulations available in the veterinary market. In gene therapy, cyclodextrins continue to garner interest, especially in non-viral delivery methods, which offer a solution to the challenges posed by viral gene delivery. These innovative formulations have markedly improved the properties of previously poorly soluble medicinal compounds by enhancing solubility, bioavailability, distribution, and elimination while minimizing side effects and simplifying dosage, treatment duration, and handling. As a result, the study and development of cyclodextrin-based drug delivery systems hold a promising future, poised to make significant advancements in therapeutic interventions.

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