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Review Article

CYCLODEXTRIN AS SOLUBILIZER AND TARGETING AGENT FOR DRUGS

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ABSTRACT

Natural cyclic oligosaccharides called cyclodextrins (CDs) improve the bioavailability of drugs by the formation of inclusion complexes involving small and macromolecules of poorly soluble compounds in water. CDs act as a solubilizer and targeting agent for drugs with low water solubility, enabling them to effectively target specific cells. Where poorly water-soluble compounds interact with the hydrophobic cavity of CDs to enhance their solubility. CDs are effective drug delivery agents because of their essential function as processing complex carriers. Various ligands can be utilized to modify the surface of cyclodextrin to actively target drugs. It is possible to consider it to have amphiphilic characteristics by enduring a chemical transformation with long aliphatic chains, and a variety of amphiphilic CDs can produce nanoparticles without the usage of surfactants. CD-nanocarriersact as cargo with solubilizers for drugs and a targeting agent for specific receptors present in specific cells and release the drug. CDs have many applications, including the reduction of drug-induced gastrointestinal discomfort, avoiding interactions between drug-drug and drug-excipient, and transforming drug products that are liquid into microcrystalline solid powders. Because of their biocompatibility and biodegradability, CDs have outstanding properties that make them particularly useful in the pharmaceutical and cosmetic industries.

Keywords: Cyclodextrins, Inclusion complex, Solubilizer, Targeting agent, Nanoparticle, Nanocarrier

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INTRODUCTION

Cyclodextrins (CDs) are the products of the starch breakdown performed by the enzyme glucosyl transferase [1]. The articles for the current review were sourced from specialized databases.(Range of years: 2000-2024) such as Elsevier, Pubmed, and Ovid using the keywords Cyclodextrin Solubilty. Other selections include articles from Springer, information from Internet sources, and Online published articles from Nature Medscape. Google Scholar may be a viable addition as a search option for cyclodextrin searches. CDs are cyclic oligosaccharides that occur naturally and resemble a cone in their shape. On the inside of the cavity, they show hydrophobic characteristics and have a hydrophobic coating on the outside [2]. It is possible to increase the bioavailability of drugs by utilizing cyclodextrins that are soluble in water [3]. This is accomplished by forming inclusion complexes with sections of large compounds and tiny molecules that have poor aqueous solubility [4]. Hydrophobic interactions inside cavity-containing molecules, such as in aqueous solutions CDs, can significantly enhance the solubility of drugs. The resulting drug is both chemically and physiologically accessible [5]. Patients can be given pharmaceutical drugs that aren't very water-soluble or chemically stable using CDs. This makes it possible for more drugs to be given to patients [6]. As a consequence of this, CDs have the potential to convert molecules that possess biological activity but do not have the physiochemical features of drugs into drugs that have the required therapeutic effect [7]. CDs take on the role of hosts by allowing a portion of a drug molecule to be placed inside their core cavities to facilitate drug-containing inclusion complex formation [8]. Because of this modification, the Drugs' physiochemical characteristics will be altered. For instance, by generating a Drug-CD inclusion complex, the product's aqueous solubility, physical and chemical stability, and distribution of the drug across biological membranes may all be enhanced [9]. During the process of complex formation, there is no creation or destruction of covalent bonds, and the drug particles that are bound inside the CD inclusion complex are present in a dynamic equilibrium with the drug compounds that are free in aqueous solutions [10] [fig. 1].

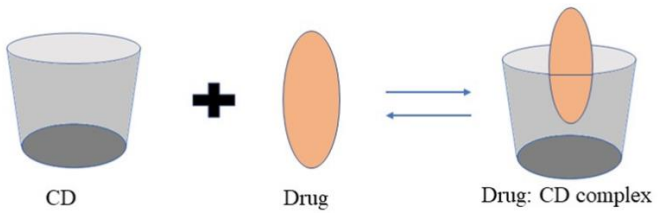

Fig. 1: Bucket shape CD forms inclusion complex

In recent years, a strategy that is possible for the development of unique, optimized systems is the combination of CD derivatives [fig. 2] with nanomaterials. This technique has emerged as an affordable option [11]. It has been illustrated in research that CDs can reduce the toxicity of various drugs and be biologically compatible when compared to other pharmaceutical excipients. For this reason, they have the potential as components in new drug compositions, including the modification of current medicinal products [12, 13].

Cyclodextrin acts as a solubilizer

CDs are practical functional excipients that have grabbed a lot of interest and are frequently used [14]. The pharmacological perspective is based on the ability of these components the interact with weakly water-soluble drugs and drug molecules, resulting in an enhancement in their apparent water solubility [15]. The capability of CDs to develop dynamic inclusion complexes formed through non-

covalent interactions in a solution determines the process for this solubilization [16, 17]. The ability to design aggregates and related domains and additional solubilizing properties may include the capability of CDs for producing and stabilizing supersaturated drug solutions, in addition to the capability of non-inclusion-based complex formations. These additional solubilizing qualities can be found in some solubilizers. The oral bioavailability of Biopharmaceutics Classification System (BCS) Class II and IV category of drugs can be improved by the enhancement in solubility [18], which can also increase the rate of dissolution [19]. Based on its capacity to mask undesired physicochemical characteristics, there are now several cyclodextrin-based products available in the market. The use of CD as solubilizers, kinetic and thermodynamic methods, and parameters for cyclodextrin-mediated drug solubilization [20]. CDs are a class of cyclic oligosaccharides that are composed of glucopyranose units that are connected by α-(1, 4) bonds. The natural CDs that are commonly utilized are α, β, and γ-CD, which are composed of 6, 7, and 8 glucopyranose units, respectively [21] [fig. 3]. CD particles possess a distinct configuration featuring a cavity that exhibits hydrophobic properties, while its exterior displays hydrophilic characteristics, which enables the encapsulation of a guest molecule [22] [fig. 4].

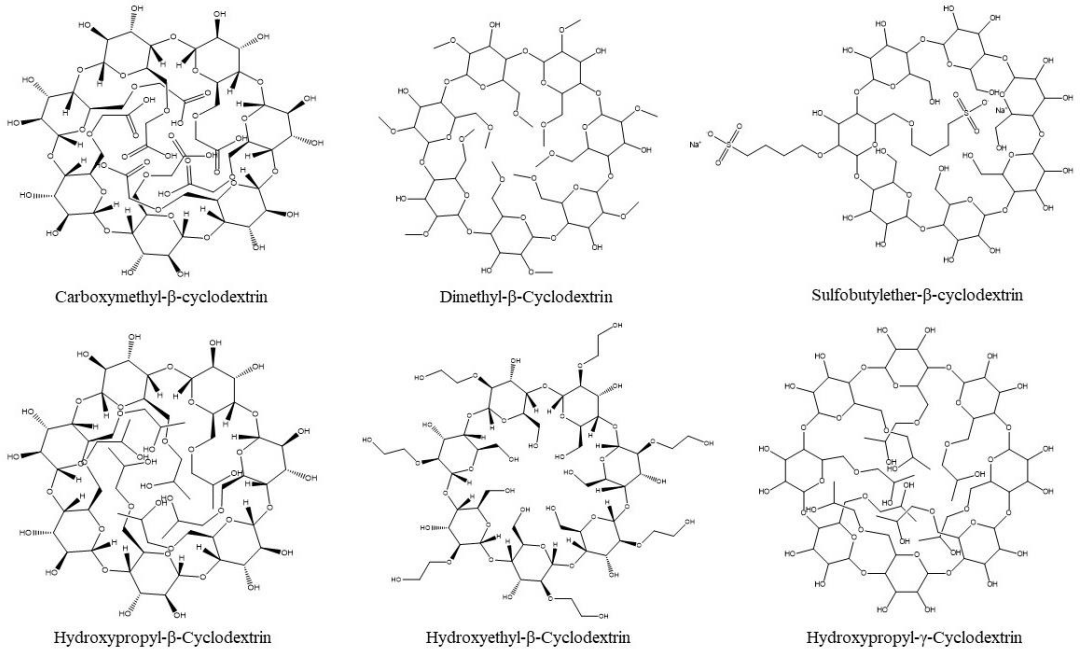

Fig. 2: Derivatives of CDs for enhancement of solubility

Alpha-cyclodextrin (α-CD)

α-CD is composed of six glucose units [23] and is utilized in the chiral separation process in addition to its role as a complexing agent in the production of food, cosmetics, and agricultural chemicals [24]. It is allowed to be used as an inert ingredient in non-food pesticide products, and it is utilized as a carrier, stabilizer, absorbent, and encapsulating agent for food additives, flavorings, and vitamins. Inertness to light and heat, stability in alkaline and acid solutions [25], and a water solubility that is only moderately affected are some of the functional features of α-CDs [26, 27]. It is also referred to as cyclohexaamylose or cyclomaltohexaose. α-CD is a soluble dietary fibre that does not absorb water and is made from corn starch. The dissolution rate of α-CD in water is 13 g/100 ml when the temperature is at room temperature, which is 77° Fahrenheit. The solubility of α-CD in water increases when the temperature is turned up to 140° Fahrenheit. Molecules that are resistant to water, such as α-CD [28]. Due to this characteristic, α-CD has the ability to encase fat molecules within its structure, preventing fat from being absorbed by the body. There is a possibility that α-CD can function as a drug transporter through the cornea [29]. In addition, α-CD may directly disrupt membrane structures, in particular in the lipoidal epithelial cell layers, which results in a destabilization of the barrier and an increase in both its own and the drug's permeability. This is especially true in the case of the lipoidal epithelial cell layers [30].

Beta-cyclodextrin (β-CD)

The cyclic oligosaccharide known as β-CD is comprised of seven glucose units that are bonded together as α-(1, 4) isomers [31]. It is safe to consume, non-toxic, non-hygroscopic, chemically stable, and easy to separate into its parts [32]. β-CD is used as a complexing agent in the drug delivery process because of its ability to produce an inclusion complex with a drug molecule [33]. β-CD complexes amplify the bioavailability, aqueous solubility, and dissolution rate of the pharmaceuticals they are combined with, making them an efficient method for the administration of drugs that are only moderately soluble in water [34]. β-CDs have found applications not only in the pharmaceutical industries and textiles but also in food technology, agriculture, environmental protection, biological and chemical analysis, color cosmetics, and the cosmetics industry [35]. β-CDs are extensively utilized in the pharmaceutical industry because of their ability to improve drug stability and solubility through complex formation in the solid state. This ability is the primary reason for the widespread usage of β-CDs in the pharmaceutical industry [36]. β-CD is by far the most common type of cyclodextrin, and for a good reason: not only is it inexpensive, but it's also simple to produce and gentle on the skin. A molecule can be housed in the hydrophobic cavity of the β-CD molecule, which has the shape of a hollow truncated cone. This can be accomplished through a mechanism known as a host-guest of inclusion complex [37]. β-CD can be utilized to great efficiency to achieve the task of removing cholesterol from cell membranes. Several studies have demonstrated that when cells are subjected to β-CDs, the cholesterol that is normally found within the cells is removed [38]. Although β-CDs can be easily dissolved in water and the solubility of β-CD is not as good as that of its derivative, hydroxypropyl-β-CD [39] (fig. 4) carboxy, which is a cyclodextrin that has been hydroxypropylated. According to the studies that have been published, the use of hydroxypropyl-β-CD[40], which is a derivative of β-CD with higher

water solubility and increased safety, is often utilized to increase the solubility of hydrophobic drugs [41]. Table 1 displays the various derivatives of natural CDs that are at one's disposal. The significant role of β-CD is that it acts as a host in inclusion complexes with the guest molecules. There is a stoichiometric component to the molecular processes that make up the inclusion complex. CDs can change the physicochemical characteristics of the active compound without changing the characteristics that are inherent to the active molecule because they are able to incorporate the guest molecule within the internal cavity of the CDs as a host at a ratio of 1:1 [34]. This allows the CDs to alter the physicochemical characteristics of the active molecule. Changes in the dissolving rate, solubility, stability, and bioavailability of particular pharmacological compounds are among the things that fall under this category [42].

Gamma-cyclodextrin (γ-CD)

γ-CD is a cyclic alpha-(1, 4)-linked oligosaccharide that is composed of eight glucose units[43]. In the food industry, it is utilized as a carrier, flavor adjuster, and stabilizer [44]. Moreover, it has been granted permission for use as a non-active component in non-food pesticide formulations. Hydrolyzed starch syrups undergo a reaction with the enzyme cyclodextrin-glycosyl transferase, which results in the formation of the product [45]. Because the inner surface of the torus-shaped molecule is less polar than its outer surface, γ-CD, like other CDs, exhibits the ability to create inclusion complexes with a wide range of organic compounds [46]. γ-CD is soluble quite quickly in water and dimethyl sulfoxide; however, it is not soluble very well in methanol [47]. The non-coplanar structure of γ-CD leads to the high solubility of the drug [48].

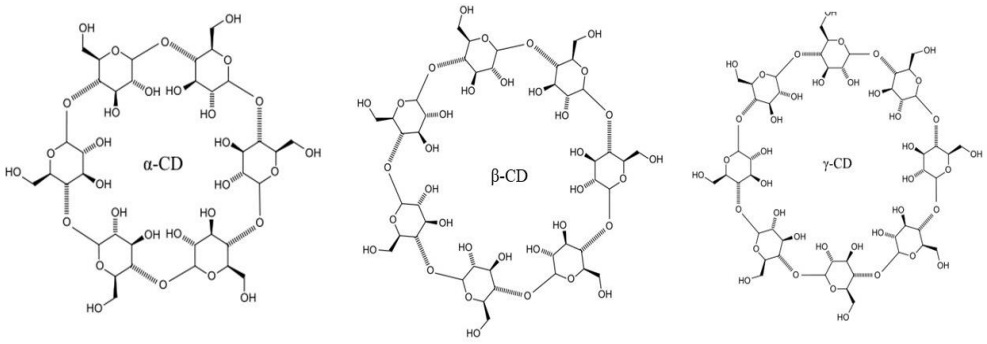

Fig. 3: Different types of CDs (α, β, and γ)

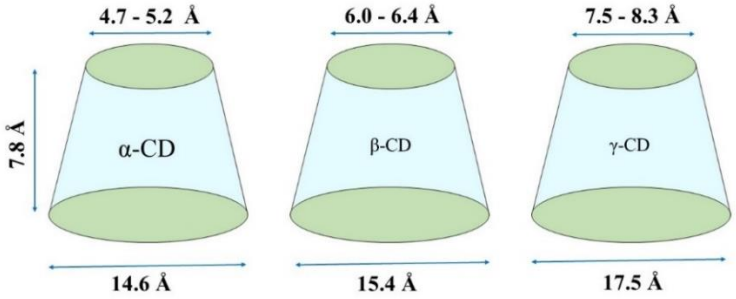

Fig. 4: Dimensions of different CDs α-CD, β-CD, and γ-CD (height, inner cavity diameter, outer diameter)

Table 1: Cyclodextrins and its derivatives

Cyclodextrins	Substituted (R)	Number of D-glucopyranose subunits	References
α-Cyclodextrin	H	6	[48, 49]
β-Cyclodextrin	H	7	[46, 47, 49]
γ-Cyclodextrin	H	8	[45, 47, 49]
Carboxymethyl-β-Cyclodextrin	CH_2CO_2H or H	7	[42, 45, 48]
Carboxymethyl Ethyl-β-Cyclodextrin	CH_2CO_2H, CH_2CH_3 or H	7	[47, 48, 50, 51]
Diethyl-β-Cyclodextrin	CH_2CH_3 or H	7	[47, 49, 50]
Dimethyl-β-Cyclodextrin	CH_3 or H	7	[43, 46, 48, 50]
Sulfobutylether-β-cyclodextrin	(CH2)4-SO3Na	7	[43, 45, 49, 51]
Hydroxypropyl-β-Cyclodextrin	$CH_2CHOHCH_3$ or H	7	[46, 47, 50, 51]
Hydroxyethyl-β-Cyclodextrin	CH_2CH_2OH or H	7	[48, 49, 51]
Methyl-β-Cyclodextrin	CH_3 or H	7	[47, 49, 51]
Hydroxypropyl-γ-Cyclodextrin	$CH_2CHOHCH_3$ or H	8	[45, 51]

CD Application as a solubilizer in formulation

CDs are becoming an increasingly attractive choice for use as a functional excipient. From a pharmaceutical perspective, this is a result of the fact that these compounds, through interaction, have the potential to raise the apparent water solubility of drugs and therapeutic candidates that have a low level of water solubility. It has been found that the drug's unionized form exhibits a higher tendency to penetrate the CD cavity, which results in a more significant solubility increase by CDs [20]. In the BCS, drugs that are currently classified in the Class II category (high permeability and poor solubility) and even or sometimes the Class IV category (low permeability and low solubility) have the potential to be moved to the Class I category (high permeability and high solubility) as a

result of the solubility increases brought about by CDs [49]. The utilization of CDs does not enhance the bioavailability of drugs that fall into the BCS Class III category (which is characterized by low permeability and high solubility). In addition, CDs are only useful when used for a solubility-increasing capacity for drugs ranging from medium to high potency if the drug also possesses a high complexation enhancer. This is due to the fact that the highest possible level of drug bioavailability is typically accomplished with the least amount of CD that is exploited [4, 50].

CD in carbonic anhydrase inhibitor

Glaucoma can be treated with both topical and systemic carbonic anhydrase inhibitors (CAIs), which work by lowering the pressure inside the eye [51]. The poor water solubility properties of CAI agents reduce the body's ability to absorb drugs, which in turn leads to insufficient therapeutic efficacy. Researchers formulated a novel aqueous CAI eye drop that makes use of self-assembled drug-CD nanoparticles to increase and prolong drug delivery to the eye [52]. Certain CDs, such as hydroxypropyl derivatives of β and γ-CD (HP-β-CD and HP-γ-CD), sulfobutylether β-CD (SBE-β-CD) and randomly methylated β-CD (RM-β-CD) among others, have had their molecular structures altered to make them more soluble in order to enhance their biological and physiochemical capabilities [53](fig. 4). The incorporation of water-soluble polymers, such as hydroxypropyl methylcellulose (HPMC), sodium carboxy-methylcellulose, and polyvinylpyrrolidone can enhance βand γ-CD solubilization. HPMC is the most effective at increasing CAI solubilization by β and γ-CD [54]. Ophthalmic Dorzolamide is a CAI which is widely used to treat Glaucoma. Dorzolamide have poor aqueous solubility when it comes to the formulation of eye drops and it can lead to the irritation of the eye as well as other potential adverse effects. The greatest affinity of Dorzolamide was found with RM-β-CD and γ-CD [55]. HPMC performed the best in terms of mucoadhesion and stability done on Dorzolamide-CD complexes; by the formation of this complex, the solubility of the drug enhanced and led to the maximum concentration and therapeutic activity to the eye after topical administration [56].

CD in anti-inflammatory drugs

Inflammation is a biological process that is triggered whenever the immune system identifies a potential danger [57], such as a virus, damaged cells, or poisonous substances. This may result in the release of inflammatory chemicals [58]. HP-β-CD is an effective carrier used with anti-inflammatory drugs for the treatment of atherosclerosis by a reduction in plasma triglyceride levels and inflammatory cytokines, as well as an increase in the amount of HDL cholesterol in the plasma, which was accomplished by the reprogramming of macrophages [59, 60]. The activation of the terminal complement pathway and a reduction in the expression of particular receptors on monocytes provided evidence that HP-β-CD interacted with cholesterol crystals to reduce the accumulation of triglycerides. After administration of the HP-β-CD, there was also a reduction in the levels of cytokines that promote inflammation. The effect was analyzed using data from other deposits, such as monosodium urate crystal, but it was ineffective; this indicates that the effect is selective for cholesterol crystals [61]. α-CD inhibits complement-mediated inflammation brought on by cholesterol crystals in a manner that is comparable to that of HP-β-CD [62]. For example, the anti-inflammatory drug Nimesulide is used for the formation of an inclusion complex with β-CD as a carrier by the use of a Supercritical Anti-Solvent process [63]. The utilization of β-CD as a carrier in Supercritical Anti-Solvent coprecipitation has been found to be efficacious in enhancing the solubility of active ingredients, thereby improving their bioavailability. The dissolution rate of drugs was observed to increase upon the inclusion of Supercritical Anti-Solvent complexes. Moreover, the creation of inclusion complexes based on CD facilitated a substantial reduction in the number of carriers, reaching a molar ratio of Nimesulide-β-CD [64].

CD in anti-diabetic drugs

Diabetes is a chronic condition that impairs your body's ability to turn the nutrients in meals into fuel that it can use [65]. When there is an increase in the amount of sugar in the blood, the pancreas will respond by producing more insulin [66]. The complexation of a diabetes drug that had poor water solubility with β-CD in the presence of HPMC will improve the drug's water solubility as well as its bioavailability [67]. Various techniques, such as the kneading method, can be used to produce 1:1 and 1:2 molar ratios of drug-CD complexes. Cyclodextrin contributed to the increased solubility of the drug [68]. Repaglinide is an oral antidiabetic drug, and it is poorly soluble in water. Researchers synthesized Repaglinide formulation by the inclusion of complex formation with β-CD, RM-β-CD, and HP-β-CD. Upon formation of the inclusion complexes the solubility of Repaglinide gets increased by the presence of β-CD, as well as its derivatives, RM-β-CD and HP-β-CD [69]. Repaglinide-β-CD complexes were found to be more successful at lowering blood sugar levels when compared to pure drug powder and tablets sold commercially [70].

CD in intranasal drugs

Nasal drug delivery is a promising approach for the systemic distribution of high-potency drugs with low oral bioavailability because of the extensive gastrointestinal breakdown and the high hepatic first-pass effect. CDs are utilized to enhance the nasal absorption of these drugs by either enhancing their water solubility or increasing their nasal absorption. This is accomplished by increasing the surface area of the nasal mucosa. The safety of nasal absorption enhancers, specifically dimethyl-β-CD and RM-β-CD, has been adopted through toxicological studies on their local effects on the nasal mucosa. The study found that the toxicity of methylated β-CDs was lower in the release of marker compounds adhering to nasal administration. The likelihood of systemic toxicity following the administration of nasal CD is considered low, given the administration of low doses and the absorption of only minimal quantities. CDs' mechanism of action is elucidated by their interaction with the nasal epithelial membranes and their capacity to temporarily interrupt tight junctions. Intranasal administration of Midazolam has attracted a lot of attention because it is a convenient method that eliminates the need for needle sticks [71]. However, the low quantity of Midazolam and high acidity of the intravenous formulation make it less than optimal for delivery through the nasal passages. To produce Midazolam, a buffer solution consisting of sulfobutylether and β-CD (SBE-β-CD) was mixed with water [72]. The nasal formulation is quite comparable to the intravenous form in terms of absorption rate, serum levels, and clinical sedative effect. There were no major detrimental effects that were observed [42, 73].

CD for targeting disease

It is possible to connect several distinct ligands to the surface of CD in order to target the delivery of drugs [74]. Because of the adaptability of CDs, they are increasingly being used in the drug delivery processes of many routes, including oral, nasal, transdermal, parenteral, and rectal administration [75].

CD in gaucher disease

The buildup of fat in the body, most noticeably in the liver and spleen, is the root cause of Gaucher disease [76]. Chaperones that can get the endogenous mutant enzyme to fold and move around normally could be a good option for Gaucher disease treatment involving enzyme replacement and substrate reduction, which both have a lot of drawbacks [77, 78]. It is conceivable to enhance the regulated delivery of chaperones to macrophages by forming ternary complexes between the chaperones, a trivalent mannosylated β-CD easily binds to the receptors present in the macrophage, which is known as macrophage mannose receptor [79]. This formation of the β-CD inclusion complex is useful for the delivery of chaperones in a macrophage mannose receptor. The macrophage mannose receptor easily engulfs the delivery route, and it can easily release the chaperones in the Gaucher disease [38, 80].

CD in prostate cancer

The growth of cancerous cells in the tissues of the prostate is the defining characteristic of the condition known as prostate cancer [81]. The prostate-specific membrane antigen (PSMA) is a protein found in the plasma membrane of prostate cancer cells that

expresses itself and has been revealed to have potential as a therapeutic target [82]. Using β-CDin the cancer cells has been modified to have dipeptide-like urea arms, which is a well-known model of a selective ligand against PSMA; researchers were able to make a drug delivery and targeting system for prostate cancer cells that works with the formation of β-CD inclusion complex. The CD-drug complex can directly target prostate cancer cells [83]. Normal prostate cells exhibit extremely low levels of PSMA (non-tumoral cells). When combined with β-CD, which has been functionalized with a PSMA ligand, the anticancer drug doxorubicin can cause prostate tumoral cells to be more susceptible to its lethal effects. There is optimistic reason about the potential of this method for selectively delivering medicines to prostate cancer cells [84].

CD in HIV

The human immunodeficiency virus (HIV) is a pathogen that impairs the functionality of the immune system, which results in the progression of AIDS (acquired immunodeficiency syndrome) [85, 86]. The patient's ability to adhere to a daily dosing schedule is the single most important factor in determining whether or not antiretroviral preexposure prophylaxis (PrEP) will be effective in preventing HIV transmission [87]. The combination of β-CD and nelfinavir resulted in sustained plasma concentrations that exceeded the protein-adjusted threshold necessary to inhibit viral replication and prohibit the drug penetration into organs critical for HIV-1 transmission [88]. Upon the formation of the inclusion complex, there is the enhancement of the effectiveness of extended PrEP administration utilizing β-CD in conjunction with Nelfinavir via a nanofluidic implant [89].

CD in Alzheimer's disease

Alzheimer's disease is a neurological condition that, over time, gradually destroys a person's cognitive ability [90]. Curcumin (CUR) is beneficial in the treatment of Alzheimer's disease because of its antioxidant and anti-inflammatory effects [91]. Because of its low solubility and high volatility, CUR has only a limited range of applications [92]. To analyze and contrast administration, researchers synthesized hydroxypropyl-β-CD-encapsulated CUR complexes (CUR-HP-β-CD inclusion complexes) [93, 94]. The study revealed that CUR in CUR-HP-β-CD inclusion complexes is stable *in vitro*, even at high concentrations of the compound. In the meantime, CUR-HP-β-CD inclusion complexes revealed improved cellular absorption of CUR in cell lines. In the CUR-HP-β-CD inclusion complex CUR is shown to have cytotoxicity reduction properties and antioxidant effects. CUR-HP-β-CD inclusion complexes are used as a carrier for drug delivery of CUR for usage in Alzheimer's disease [95-97].

CONCLUSION

Because of the passage of time, high throughput screening processes have evolved into routine practice in the pharmaceutical industry to locate potentially useful drug treatments. However, many potentially useful ideas for drugs have not been developed because of their poor solubility. As a consequence of this, formulators today require a greater variety of formulations and, as a direct consequence of this, excipients in order to meet the ever-increasing demands placed on modern pharmaceuticals. In this context, CDs provide a significant amount of value; these derivatives of starch are powerful solubilizers that make it possible for liquid forms of drugs to be taken orally or injected intravenously. In addition, they can enhance the oral bioavailability of solids by enhancing the dissolving rate, which in turn increases the molecule's apparent solubility. This is accomplished by improving the apparent solubility of the compound Even though the formation of inclusion complexes is the fundamental process connected to the potential solubilization of CDs, the effects of non-inclusion complexation and supersaturation may also play significant roles under specific situations [Not only are CDs utilized in the design of formulations and the early testing of drug molecules, but numerous CDs, including α-CD, β-CD, γ-CD, HP-β-CD, RM-β-CD, and SBE-β-CD, have evolved into indispensable resources for the formulation process the use of CD as a solubilizer in pharmaceuticals appears to have a bright future, particularly in light of the numerous CD-containing formulations that are already available on the market and the relatively recent introduction of several new CD-containing products this subfield of research is still going strong as a result of the expanding use of well-known CDs and the development of novel derivatives

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AUTHORS CONTRIBUTIONS

Conceptualization:-Kalvatala Sudhakar, Aditya Narayan Singh, Bimlesh Kumar, and Narendra Pandey; Data curation:-Kalvatala Sudhakar, Aditya Narayan Singh, Bimlesh Kumar, Narendra Pandey, Saurabh Singh, Dileep Singh Baghel; writing-review and editing:-Aditya Narayan Singh, Dileep Singh Baghel, Bimlesh Kumar, Narendra Kumar Pandey, Saurabh Singh, Kalvatala Sudhakar, R Narayana charyulu. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTERESTS

Declared none

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