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Introduction And General Outline Of Cyclodextrin As A Pharmaceutical Aid

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A B S T R A C T :

Cyclodextrins are practical functional excipients that are widely used and appreciated. Cyclodextrin's tendency to interact with medications and drug candidates that aren't very water soluble, increasing their apparent solubility in water. The capacity of cyclodextrin to create non-covalent dynamic inclusion complexes in solution is the basis for this solubilization mechanism. Drug/CD complex enhances the penetration of drug through biological membrane due to its increased water solubility. To increase the absorption of drug, cyclodextrin is added in optimized amount into pharmaceutical preparations. Solubility of cyclodextrin is affected by pharmaceutical excipients like polymers, surfactants, preservatives as well as their physical and chemical properties.

Objectives: This review's goal is to draw attention to the benefits of cyclodextrins in improving the physicochemical characteristics of medications (such as solubility, stability, bioavailability, permeability, and others), as well as the various production processes and characterization techniques used to assess complexes.

Methods: The numerous uses of cyclodextrins in industrial products, technologies, analytical and chemical processes, and recent industrial advancements are compiled in this article through a thorough literature search conducted on numerous scientific databases, Google, and the websites of numerous related pharmaceutical industries and patenting authorities worldwide.

Results and conclusion: Cyclodextrins are anticipated to address several issues related to the delivery of various unique medications via a variety of delivery routes due to their ongoing capacity to discover numerous innovative uses in drug delivery.

Keywords: Cyclodextrin; complex; solubility; properties; applications

1. Introduction

Cyclodextrins have been used as medicinal excipients for more than a century, despite the fact that they are usually thought of as a novel class. However, cyclodextrins could only be manufactured in limited quantities until 1970, and their high production costs hindered their extensive use in pharmaceutical formulations. The manufacturing of cyclodextrin has dramatically improved as a result of biotechnological developments, reducing the cost of production. As a result, very pure cyclodextrins and their derivatives are now accessible [1]. Because cyclodextrins interact with drug molecules to form inclusion complexes, they are useful in pharmacological dosage forms [2].

Structure and physicochemical properties

Cyclodextrins are R-D-glucopyranose cyclic (R-1,4)-linked oligosaccharides with a hydrophilic outer surface and a comparatively hydrophobic interior cavity. Cyclodextrins are toroidal or cone-shaped molecules rather than precisely cylindrical ones. Secondary hydroxyl groups are placed on the narrow side of the torus while the primary hydroxyl groups are on the broader side in cyclodextrin structure. With six, seven, and eight glucopyranose units, respectively, R-cyclodextrin, â-cyclodextrin, and γ-cyclodextrin are the most prevalent cyclodextrins [3].

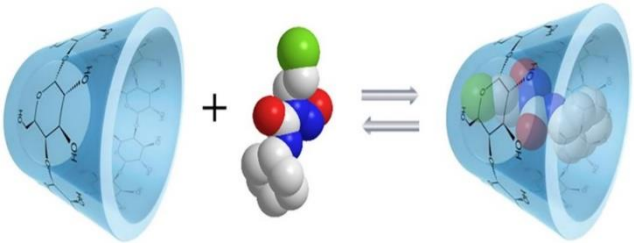

Fig. 1 – Cyclodextrin inclusion complex

A lipophilic center chamber and a hydrophilic outer surface characterize these bucket-shaped [33–35] cyclic oligosaccharides, which are made up of (a-1-4)-linked a-D glucopyranose units. Carbon and oxygen from the glucose residue forms the lining of cavity which makes the molecule lipophilic. Primary hydroxyl groups at the narrow edge of the cone and secondary hydroxyl groups at the wider edge forms the hydrophilic outer lining of molecule [4]. Cyclodextrins (CDs) are safe and stable in water and some organic solvents [5]. It is reported that have high stability in alkaline condition with pKa 12.1 to 13.5 [6]. CDs are very susceptible to acid hydrolysis at low pH, which makes ring opening and the formation of different linear oligosaccharides and glucose units [7]. Urea crystallizes in a tetragonal configuration when there is no guest component present. With less Vander wall forces operating between the molecules, the structure is comparatively open. When a guest molecule of the right size is present, it forms a channel, such as a void space, around the guest in a hexagonal pattern with a channel diameter of around 5Å [8].

- Cyclodextrins are non-reducing
- The only byproduct of methylation followed by hydrolysis is 2,3,6-trimethyl glucose, while glucose is the only byproduct of acid hydrolysis of cyclodextrin.
- The result for glucose residue is integrally multiplied by the molecular weight.
- Neither formaldehyde nor formic acid are produced by periodate oxidation [19].

2. Cyclodextrin complex formation

By allowing a drug molecule or, more commonly, just the lipophilic part of the medicinal moiety to enter their central cavity, cyclodextrins in aqueous solution can form inclusion complexes with a variety of medications [10]. The "host" molecule is the dissolved cyclodextrin, and the "driving force" behind the complex formation is the suitable "guest" molecule that replaces the high-enthalpy water molecules. The host: guest ratio is typically 1:1. This is what "molecular encapsulation" is all about. No covalent bonds are broken or created at the time of inclusion complex formation. In order to achieve an apolar–apolar connection and reduce cyclodextrin ring strain, more hydrophobic guest molecules in the solution displace water molecules, creating a more stable lower energy state. [11] Any non-aqueous solvent can be present during inclusion complexation, as well as in a co-solvent system. Cyclodextrins has a significant impact on the guest molecules' physicochemical characteristics. These characteristics include improving the solubility of highly insoluble guests, stabilizing labile guests against the damaging effects of heat, UV light, and oxidation, controlling volatility and sublimation, physically isolating incompatible compounds, chromatographic separations, altering taste by masking off flavors and offensive odors, and regulating the release of medications and flavors. As a result, cyclodextrins find application in the food [12], pharmaceutical [13], cosmetic [14], environmental protection [15], bioconversion [16], packaging, and textile industries [17]. It is possible to separate the resulting inclusion complexes as stable amorphous or microcrystalline materials. [18]

3.1. Preparation method

Cyclodextrin inclusion complex is formed when a single drug molecule interacts with cyclodextrin molecule and get trap into the cyclodextrin cavity. Formation of non-covalent forces, including van der Walls forces and hydrophobic contacts makes the complex very stable. In theory, it is reported that, only drug molecule needs to trap perfectly into cyclodextrin cavity for the complex formation. Consequently, one-to-one molar ratios are not always reached, particularly in case of high or low molecular weight guest molecules.

2.1.1. Solution Dynamics

Only the cyclodextrin crystal's surface molecules are accessible for complexation when it is in its crystalline form. More cyclodextrin molecules are made accessible in solution. Heating makes both the cyclodextrin and the guest more soluble, which raises the likelihood that a complex will form. When the guest component is present in soluble form or in finely distributed particles, complexation proceeds more quickly.

3.1.2. Temperature effect

Cyclodextrin complexes are affected by temperature in multiple ways. Although heating can make a complex more soluble, it can also cause it to become unstable. Since each guest has a different level of heat stability, most complexes begin to break down between 50 and 60 ◦C, but some are stable at higher temperatures, particularly if the guest is tightly bound or the complex is extremely unsolvable.

3.1.3. Use of solvents

The solvent most frequently employed for complexation processes is water. The number of molecules available for complexation increases with the Cyclodextrin's solubility in the solvent. If solvent-free compounds are sought, the solvent must be readily extracted. When a guest has multiple components, one of them could behave both as a solvent and as a visitor. Since not every visitor dissolves easily in water, complexity can be either extremely slow or impossible. In these situations, it is preferable to dissolve the visitor using an organic solvent. The solvent should readily evaporate and not form a strong combination with the cyclodextrin.

3.1.4. Effect of water

The solubility of both cyclodextrin and guest increases with increasing water content, facilitating complexation. However, the cyclodextrin and the visitor may become so diluted as the water content rises that they are less likely to come into contact than they are in a more potent mixture. As a result, it is preferable to maintain a low enough water content to guarantee complexation proceeds quickly enough. Instead of associating with cyclodextrin, certain high molecular weight substances, including oils, prefer to associate with themselves. In these situations, improved dispersion and separation of the oil molecules or isolation of the oil molecules from one another will be possible with the use of more water along with good mixing.

3.1.5. Volatile guests

During complexation, volatile guests may be lost, particularly if heat is applied. Refluxing the volatile guests back into the mixing vessel or employing a sealed reactor are two ways to avoid this with extremely volatile guests [19,20].

3.2. Methods for cyclodextrin complex formation

3.2.1. Kneading method

The guest material was dissolved in the solvent using the kneading process, and with the help of mortar and pestle, cyclodextrin slurry was mixed before being allowed to dry at room temperature. After being solidified, the complexes were vacuum-dried [21].

3.2.2. *Co-precipitation method*

Co-precipitation is utilized to create hydrophobic medicinal cyclodextrin complexes. The organic phase was used to dissolve the hydrophobic medications or guest molecules, whereas the aqueous phase was used to dissolve the host molecules. Organic phase solution was dissolved in the aqueous phase solution with proper agitation. After cooling the solution, the complexes were cleaned with an organic solvent and allowed to dry at 50°C [22-24].

3.2.3. Solvent evaporation method

This method involved dissolving the host and guest molecules independently in the miscible solvents, then combining the solutions to create molecular dispersion. Solvent from the solid powdered inclusion complex was evaporated at 45°C under vacuum and a screen was used to run the dried bulk. It considered as very efficient substitute for spray drying process [25].

3.2.4. Freeze-drying of Lyophilization method

This method works best for creating cyclodextrin complexes of medications that are both water-soluble and thermolabile. This approach involved dissolving the medication and polymer in an appropriate solvent while stirring, and then freeze-drying the mixture. After the solvent was removed using a vacuum, high-quality cyclodextrin inclusion complexes were produced [26-30].

3.2.5. Spray drying method

This method involved dissolving the host and guest molecules in a common solvent and using the spray drying technique to dry them. By examining the size of the atomizer or spray nozzle as well as additional variables like sample feeding rate and inlet temperature, different sizes of inclusion complexes were produced [31].

4. Characterization of cyclodextrin complex

Numerous methods can be used to describe the structure and characteristics of cyclodextrin complexes. Methods for assessing the kind of interactions between host and guest molecules, their structure, the host's capacity to trap the guest in its cavity, dissolving behavior, temperature analysis, and other characteristics have been covered here.

4.1. Entrapment efficiency

The amount of drug entrapped in the host molecules is measured by entrapment efficiency. The size of the host molecules' cavity and the guest molecules' size are the primary determinants of entrapment efficiency in cyclodextrin complexes. More drug entrapment in the host molecule is indicated by a higher entrapment efficiency [32] .

4.2. FTIR Analysis

The kind of intramolecular or intermolecular interaction between a drug and a polymer is indicated by FTIR spectra. The evaluation of the drug, polymer, physical combination, and formulation took place between 4000 and 400 cm−1. When peaks in inclusion complexes shifted toward higher or lower

wavenumbers, it meant that an H-bond had formed between the drug and cyclodextrin [31] and that the drug had been covered into the cavity of the polymer that formed the inclusion complex [34] .

4.3. Differential scanning calorimetry analysis

DSC investigated the thermal behaviour of medications, including melting point and heat change formulation. Entrapment of the guest molecules into host molecules was revealed by changes in the melting point during the formation of inclusion complexes. The DSC thermogram acquired during thermal analysis also clarified the endothermic or exothermic reaction and novel chemical synthesis in the crystal [35] .

4.4.XRD analysis

The X-ray spreading on the samples is the basis for the structural investigation carried out by the XRD technique. XRD made it possible to examine the material's solid state structure, and more sophisticated methods verified that inclusion complexes had formed. The peaks' movement and change in strength suggested the development of a new solid structure [35-37] .

4.5. Dissolution studies

Dissolution studies are performed to assess how a drug's aqueous solubility changes over time in an appropriate dissolution media. The results of solubility tests showed how well the inclusion complex performed in comparison to the medication in its pure form. From the sample dissolutions, it demonstrated that the drug-polymer complexes had larger concentrations of dissolved drug and reached the maximum dissolution [37] .

4.6. Scanning electron microscopy (SEM)

Several formations' surface morphologies were investigated using a scanning electron microscope. To see the changes in the drug or polymer's surface morphology, SEM studies were carried out. It demonstrated the inclusion complexes' dimensions and forms and validated their surface morphology [35]

4.7. Infra-Red (I R) spectroscopy

Describes how stretching vibrations of the absorbance bands cause them to shift to lower frequencies, increase in intensity, and broaden the band group that participates in the cyclodextrin-active drug complex's hydrogen bond formation.

4.8. Thin Layer chromatography

Describes how an active drug's RF values significantly decrease, which aids in determining when complex formation is complete.

4.9. Electrochemistry [38]

4.9.1. Polarography
Describes the distribution of electrons in an aqueous solution of a complexed electroactive guest molecule that is distinct from that in the aqueous solution's non-complexed condition.

4.9.2. Conductivity
Inclusion complex formation with cyclodextrins has a significant impact on conductivities.

4.9.3. Polarimetry
Because beta CD is naturally optically active, a polarimetric investigation serves as a supporting instrument for the complex development.

4.10. pH-Potentiometric Titration

Practical method: the pKa value of an acidic medicine molecule is typically raised when the active ingredient has a prototropic action, whereas those of basic ones are typically reduced by attaching to cyclodextrin [39] .

4.11. Spectroscopy [38]

4.11.1. Nuclear Magnetic Resonance (NMR)
Refers concrete proof that a medication can be added to a cyclodextrin cavity in solution.

4.11.2 . Electron Spin Resonance (ESR)
Effective method for examining inclusion complexation in aqueous solutions containing radicals.

4.11.3. Ultraviolet/Visible (UV/VIS)
Defined by a shift in a drug's absorption spectra.

4.11.4. ***Fluorescence spectroscopy***
Defined by a shift in the drug's excitation and emission wavelengths.

4.11.5. Circular Dichroism (CD)
Defined by modifications to the drug's and complex's circular dichroism (CD) spectra.

5. Absorption, distribution, metabolism and toxicity

In the gastrointestinal tract, bacteria to produce oligosaccharides, monosaccharides, and gases like hydrogen, carbon dioxide, and methane mostly break down CDs. They also have a very low oral bioavailability (<4%) [40]. The creation of inclusion complexes can slow down the rate at which CDs degrade in the gastrointestinal tract [41]. Although CDs are resistant to β-amylases, α-amylases hydrolyse them gradually [42]. CDs can influence tissue permeability and, thus, drug bioavailability through topical routes such the nasal, rectal, dermal, and ocular, depending on their amount [43].
Following absorption, CDs spread to a variety of organs and tissues, such as the liver, kidney, bladder, adrenal gland, and others. [44,45] Of all tissues, the kidney has the highest concentration of CDs. [46] CDs are eliminated rapidly (t1⁄2 = 2 h in humans). After intravenous administration, unaltered in urine without tubular reabsorption [47]. There is no CD build up in patients with typical levels of excretion. [49] Generally speaking, CDs have a somewhat good toxicological profile, especially when compared to other excipients such organic solvents, polymers, and surfactants. CDs can produce reversible diarrhoea and cecal hypertrophy in animals at high dosages (more than 1000 mg/kg/day), and to a lesser extent in humans as well [52]. When given intravenously, β-CD exhibits more haemolytic activity than either α-CD or γ-CD. Additionally, its limited water solubility causes it to crystallize in the kidneys, which has a nephrotoxic impact. Three naturally occurring CDs (α-CD, β-CD, and γ-CD) as well as a few chemically modified CDs (HP-β-CD, 2,6-di-O-methyl-β-CD, and SBE-β-CD) can be utilized in oral formulations, according to many safety investigations [50] .

6.Phase- solubility diagram [54]

The complexes' stoichiometry and the numerical values of their stability constants are their two most crucial properties. The following general equilibrium is reached if m drug molecules (D) combine with n CD molecules (CD) to create a complex (Dm/CDn):

$$m \cdot D + n \cdot CD \xleftrightarrow[K_{m:n}]{} DM/\ CDn \quad (1)$$

where, $K_{m:n}$ is reported as the stability constant for the drug–CD complex.

Stoichiometry of drug-CD complex and the value of stability constant is determined with the help of Phase- solubility diagram. Phase- solubility diagram defines the solubility of drug as a function of total amount of CD added to the complexation medium.

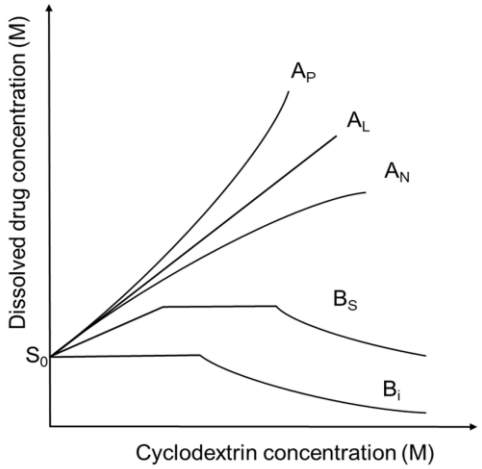

Fig. 1 – Phase solubility diagram

The complex is first order with regard to the CD (n = 1 in Equation 1) and first or higher according to linear phase-solubility diagrams (AL-type) order in relation to the medication (m≥1). The apparent drug solubility (S_{tot}) in this instance will be determined by:

$$Stot = S_0 + m[D_m/\ CD] \quad (2)$$

Where, S_0 represents the drug's inherent solubility in the aqueous complexation medium.

The following equation will yield the slope of the linear phase-solubility diagram if one drug molecule and one CD molecule create a water soluble complex (i.e., a 1:1 complex):

$$\text{Slope} = S_0 K_{1:1} / (S_0 K_{1:1} + 1) \quad (3)$$

The stability constant for the complex is $K_{1:1}$. Since the slope in this instance is always smaller than unity, $K_{1:1}$ can be calculated using the following formula.

$$K_{1:1} = \text{Slope}/S_0(1 - \text{Slope}) \quad (4)$$

The following equation will give the slope of the linear phase-solubility diagram in the event that a 2:1 drug–cyclodextrin complex forms:

$$Slope = [(2S_0 \Lambda 2K_{2:1}) /(S_0 K_{2:1}) + 1] \quad (5)$$

Here, $K_{2:1}$ represents the complex's stability constant. The linear phase-solubility diagram's slope in this instance is consistently less than two. According to AP-type phase-solubility diagrams, a positive departure from linearity indicates the creation of a higher-order complex with regard to CD. Curve fitting using a quadratic model can be used to investigate the system's stoichiometry. A 1: 2 drug–CD combination could be suggested by a good fit to this model:

$$S_{tot} = S_0 + K_{1:1} S_0[CD] + K_{1:1} K_{1:2} S_0[CD] \Lambda 2 \quad (6)$$

Where, the concentration of free CD is denoted by [CD].

Phase-solubility tests are conducted in drug-saturated media, most frequently drug-saturated aqueous CD solutions, and it should be underlined once more that these solutions are not optimal. It is common practice to analyse drug–CD complexes using NMR or other spectrophotometric analyses of diluted aqueous CD solutions or under "ideal" circumstances. It is difficult to use results from such circumstances to explain complexation events in less-than-ideal circumstances. The majority of aqueous medication formulations also include excipients that can affect the drug complexation, including buffer salts, polymers, and preservatives. Therefore, the composition of the aqueous complexation media used in drug formulation should be very similar to that of the finished formulation.

7.Cyclodextrin and drug degradation [51]

Drugs' chemical breakdown can be slowed down or perhaps accelerated by CD complexation. A reaction's observed first-order rate constants (K_{obs}) asymptotically approach a minimum value for the stabilizing impact (inhibition) or a maximum value for the destabilizing effect (catalysis) when the concentration of CD increases due to saturation kinetics. For a given CD concentration, the weighted average of the first-order rate constants for the degradation of the free (Kf) and bound (Kc) drug is the value of K_{obs}.

$$K_{obs} = K_f F_f + K_c F_c \quad (7)$$

Where f_c is the fraction of drug in complex and f_f is the fraction of free drug. $K_{1:1}$ can be found using the concentration dependency of K_{obs} [20,55]. The following equations are found if we assume that just a 1:1 drug–CD complex is being formed:

$$-d / dt = K_{obs}[D]t = (k_f + K_c K_{1:1}[CD])[D_t] \quad (8)$$

It can be presumed that $[CD] = [CD]_T$[2], if the total CD concentration is significantly higher than the total drug concentration ($[CD]_T \geq 10 \cdot [D]_T$).

$$K_{obs} = (K_f + K_c K_{1:1}) /(1 + K_{1:1}[CD]_t \quad (9)$$

8.The effect of temperature

The temperature dependence of the stability constant (K) of the CD complex can be used to determine the thermodynamic parameters for CD complexation, such as the standard free energy change (DG°), the standard enthalpy change (DH°), and the standard entropy change (DS°) [52].

$$\Delta G° = -RT \ln K \quad (10)$$

where T is the temperature in Kelvin and R is the gas constant. ΔH° is derived from K's temperature dependence:

$$\ln K = [(-\Delta H° / R) \times (1 / T)] + cons\tan t \quad (11)$$

The following equation is then used to get ΔS°.

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad (12)$$

While the ΔS°might be either positive or negative, the complex creation is nearly invariably linked to a comparatively significant negative ΔH°. [53,54,55] Furthermore, the complex formation is mostly unaffected by the chemical characteristics of the drug molecules that are the guests. The correlation between substrate polarizability and binding constants implies that van der Waal's forces play a significant role in the development of complexes [56]. It is reasonable to assume that the water molecules located within the CD cavity have a higher energy than those in the bulk media and do not have the whole complement of hydrogen bonds due to the comparatively hydrophobic environment of the cavity. According to this viewpoint, the release of these " ΔH°-rich" molecules could be a motivating factor.

9.Recent advance in the field of cyclodextrin

9.1. Nanocarriers

CDs can be added to nanostructured networks to create carriers that hold various medications. They are able to collaborate and develop novel systems, which lead to an abundance of uses [57]. In many fields, nanotechnologies are becoming more and more well-liked as therapeutic instruments. Polymeric nanoparticles that are both biocompatible and biodegradable are a very potential alternative for medication delivery systems. The solubility and complexing capabilities of CDs can be improved by adding polymers that are water-soluble to drug/CD inclusion complexes [58]. Their other benefits include great stability and controlled drug-release patterns. Polymeric nanoparticles can be chemically altered to enhance particular features and maximize their potential for use such as medication delivery agents. Furthermore, in besides controlling the rate at which guest molecules are released, CD-based Nano carriers may additionally regulate cell contacts, shield an encapsulated medication, and even improve delivery smoother [58,59]. Despite being poorly soluble in water, CD polymers show interest as Nano carriers for anticancer medications [60]. Additionally, cationic or anionic groups can be added to CD polymers to improve their drug loading capabilities. The potential of CD Nano assemblies to enhance the pharmacological profile of medications is another significant benefit [59]. It is crucial that a drug's pharmacological activity has been achieved at the intended location, has the right concentration, and prevents nonspecific absorption. It is possible to create multidimensional systems by attaching several CDs to polymers [57]. Making covalent or non-covalent bonds makes it feasible. When CDs and polymers are combined, new molecular structures are produced. These formulations provide an additional means of releasing active ingredients. Treatment for cancer may employ a targeted delivery method based on polymeric nanoparticles serving as drug carriers. When an anti-cancer medication is encapsulated in CD polymer-based nanoparticles, the tumour location, organ, and cell are more precisely targeted [61]. A common feature of many cytotoxic chemotherapy medications is their restricted water solubility. By circumventing both cellular and noncellular resistance systems, nanoparticles improve the selectivity of cancer cells and lessen their harmful effects on healthy tissues [62]. Furthermore, studies have indicated that cyclodextrin-based nanoparticles used as drug carriers may have a greater effect on tumour cells compared to the free drug itself. They can be identified by their controlled anti-cancer drug release in vivo, their ability to inhibit the proliferation of tumour cells, or their potential for local treatment of inoperable tumours [62].

9.2. 3D Printing using cyclodextrin

Cyclodextrins may also be employed as excipients in tablets that are 3D printed in the future. One technique that can create customized goods is 3D printing. The creation of tablets with CDs added as a sensor to determine whether the tablet is being consumed is another possibility for future growth [63]. Thus far, efforts have been made to investigate the potential of utilizing CDs in the production of customized, or dispersible, instant released carbamazepine printlets. Using 3D printing through semisolid extrusion, HP-β-CD was utilized to create an or dispersible, instantly released formulation. This CD was used to create carbamazepine printlets, which need to be released quickly and dosed appropriately. Furthermore, by controlling the complex's formulation size, porosity, and dosage using 3D printing, the soluble filler HP-β-CD makes it feasible to create a customized, quickly released API [64].

9.3. Cyclodextrin as pharmaceutical excipients

CDs may be used as excipients in a variety of pharmaceutical medicines. Cyclodextrins αCD, β-CD and γ-CD were classified as food additives and generally regarded as safe (GRAS) according to the FDA. Cisapride suppositories and cetirizine tablets in Europe include β-CD. While γ-CD utilized as an excipient in minoxidil solution, derivatives of β-CD can be found in intravenous voriconazole (SBE-β-CD), intravenous and oral solutions of itraconazole (HP-β-CD), and nasal spray (RM-β-CD). Now, CDs are not covered by the European Commission's guideline on excipients in human medicine labels and leaflets [65].

9.4. Clinical trial using cyclodextrin

The effectiveness of active ingredients is being improved and enhanced by a very large number of ongoing clinical trials and research on CD characteristics. This clinical trial's purpose was to ascertain how oral α-CD, a soluble fiber derived from corn, affected the total cholesterol level in a population without diabetes. The final findings show that αCD seems to be well tolerated by healthy people and show improvements in glucose-related metrics along with a little decrease in tiny LDL particles [66]. Clinical trials are being conducted to examine the effects of a new oral midazolam formulation (γ-CD midazolam) on preoperative anxiety and sedation levels in paediatric anaesthesia. Thirty minutes after the premedication medication is administered, the sedation score is tested as part of the study, and the response is examined [70]. Another clinical trial employing sugammadex, a modified γ-CD derivative, aims to determine whether patients experience less respiratory depression and surgical residual paralysis soon after tracheal

extubation [67].

10.Different routes of administration of drugs with cyclodextrin

A variety of formulations, such as tablets, parenteral solutions, ointments, eye drops, suppositories, and vaginal suppositories, are approved for the use of CD inclusion complexes [68]. Complexed medications can be administered by ocular, nasal, cutaneous, or rectal delivery, although oral formulations are the most common because they have minimal mucous and eye irritation, low local toxicity, or convenient availability.

10.1. Oral route of administration

The oral route of administration is a widely used technique, mostly due to the patient's easier accessibility [69]. While adding CDs has enhanced the solubility of numerous poorly soluble compounds meant for oral ingestion, like acyclovir, nimesulide, meloxicam, or coenzyme Q10, this strategy has certain drawbacks. One major challenge is the rise in formulation volume brought on by the cyclodextrin molecule's comparatively large size and weight.

10.2. Ocular drug delivery

Eye medication delivery is a practical method of administration for eye illnesses [70]. When CDs are added to drug administration, there is an increase in both ocular absorption and corneal penetration (pilocarpine). Additionally, they increase the effectiveness of medications that are not very soluble in water, like dexamethasone or acetazolamide. By retaining hydrophobic molecules in solution and transporting them to the corneal epithelium, CDs serve as transporters. The aqueous stability and bioavailability of their bound medications are enhanced by CD complexation. Compared to the free medication, these HP-β-CD complexes with zinc diethyldithiocarbamate and disulfiram exhibit greater permeability through the cornea and less adverse effects, such as cataract formation. Because CDs interact with biological membranes, they also have the advantage of increased drug bioavailability as compared to traditional penetration enhancers like benzalkonium chloride. Additionally, CDs can lessen the ocular irritation caused by medications like pilocarpine.

10.3. Dermal application

Both local and systemic effects can be obtained with transdermal system distribution. When the medication enters the systemic circulation directly, the first pass effect is removed [71]. By raising the drug's thermodynamic activity in the vehicle, CDs seem to enhance the cutaneous route of delivery. Additionally, CDs' capacity to absorb stratum corneum lipids enhances penetration. Sunscreens may benefit from inclusion complexes that exhibit enhanced wettability, stability, and even photostability. However, because of their large molecular weight, CDs might not be able to pass through biological membranes. Only trace amounts of hydrophilic substances, which are accessible to the free drug, can pass through the skin or the gastrointestinal mucosa (lipophilic biological membranes). Actually, too many CDs may lessen the amount of medication penetration across membranes. Following their formation of inclusion complexes with β-CD, the cutaneous corticoids betamethasone and beclamethasone dipropionate also exhibit increased release from hydrophilic bases, such as ointments. Following complexation with β and HP-β-CD, indomethacin administered in a hydrophilic basis (hydroxyethylcellulose hydrogels) showed improved anti-inflammatory effects, indicating that CDs may enhance the dermal absorption of NSAIDs [72].

10.4. Nasal drug delivery

The nasal mucosa is also a desirable route for administering drugs because of its facile accessibility and wide vascularity, among other factors [73]. More thorough and quicker drug absorption is also made feasible by the endothelium membrane's porous nature, vast surface area, and high overall blood flow. Additionally, hepatic first-pass metabolism is not included, which is significant. Despite avoiding the blood-brain barrier, medication molecules are able to enter the central nervous system. Since the drug-CD complex has a higher overall lipophilicity than the molecule alone, adding CD improves the stability of active pharmaceutical ingredients (API). This solution has been used to enable the nasal administration of granisetron and midazolam. Additionally, CDs could be utilized to enhance the nasal absorption of peptides like insulin or calcitonin, which is given in cases of postmenopausal osteoporosis.

10.5. Rectal route of administration

Rectal delivery can be enhanced by CD complexes. Since this method circumvents first-pass metabolism, it may be a viable substitute for parenteral or oral administration in situations when the oral route is not feasible [74]. Numerous patients, including young children, those who have difficulty swallowing, those who experience nausea or vomiting, and others, may find this method of administration to be highly beneficial and significant. For the delivery of protein peptide drugs, the rectal route is also suitable.

11.Toxicity and safety consideration [75]

The growing use of cyclodextrins (CDs) in the food, pharmaceutical, and environmental remediation sectors, among others, emphasizes how crucial it is to fully comprehend their safety and toxicity profiles. Although cyclodextrins are generally thought to be safe, especially when taken orally, their safety depends on a number of variables, such as the kind of cyclodextrin, the dosage, the mode of administration, and the guest molecules that they form

complexes with. A thorough evaluation of cyclodextrins' toxicological profiles is crucial as they are included into increasingly intricate formulations, particularly in the pharmaceutical and biomedical industries. Because native cyclodextrins are largely eliminated unaltered in the feces and are not well absorbed in the gastrointestinal tract, they typically have little toxicity when taken orally. For example, regulatory bodies have approved γ-cyclodextrin as generally recognized as safe (GRAS) for usage in pharmaceuticals and food items. However, toxicity issues could surface if cyclodextrins are given by other methods, such parenterally (e.g., intramuscular or intravenous injection). Particularly when given parenterally, β-cyclodextrin has been linked to nephrotoxicity, particularly at large dosages. Its build-up in the kidneys, where it can harm renal cells, is mostly to blame for this toxicity. The use of β-cyclodextrin in parenteral medication formulations is severely
limited by this. It is well known that methylated cyclodextrins have a stronger interaction with cell membranes than native CDs, which can cause cytotoxicity and membrane rupture. Applications involving direct contact with cells or tissues, including topical formulations or drug delivery systems, are especially concerned about this cytotoxic effect. Additionally, the type of cyclodextrin being employed determines toxicity. When taken orally, α-cyclodextrin is thought to be less hazardous than β-cyclodextrin. α-cyclodextrin has been added to food products as a dietary fiber since studies on its oral toxicity have revealed that people can tolerate it well, even at high dosages. The type of guest molecules that cyclodextrins form inclusion complexes with determines their toxicity in addition to the cyclodextrin molecule itself. The risk of drug toxicity may also grow as guest compounds' bioavailability increases. By retaining a drug in a solubilized condition, for instance, cyclodextrins can greatly improve absorption; but, if the dosage is not appropriately managed, this may result in drug concentrations that surpass therapeutic thresholds, which could have harmful effects. Additionally, cyclodextrins have the ability to change how medications are distributed throughout the body, which may result in a greater build-up in particular tissues and exacerbate drug-induced toxicity there. The inclusion complex may dissociate more quickly in acidic environments, like the stomach, causing a rapid release of the medication that may irritate the area or have other harmful effects. On the other hand, the drug may release more slowly in surroundings that are more basic or neutral, which could delay therapeutic benefits or result in uneven drug distribution. In summary, cyclodextrins have proven to be safe and efficient excipients for a variety of uses, particularly in the food and drug delivery industries. However, their toxicological profiles need to be carefully taken into account, especially when employing more delicate ways of administration like parenteral delivery.

12.Challanges and considerations in cyclodextrin-drug formulations [75]

Considering all of the advantages that cyclodextrins provide in medication formulations, a number of problems need to be addressed in order to optimize their use in clinical settings. The specific cyclodextrin type used, the administration method, and the length of exposure can all have a substantial impact on the safety profile of cyclodextrin–drug complexes ain, especially when used in large quantities or for extended periods of time. In certain investigations, β-cyclodextrin has been linked to nephrotoxicity, especially when given in large quantities. This finding emphasizes how crucial it is to carefully choose the right cyclodextrin derivative depending on the patient demographic and the particular treatment scenario. The way cyclodextrins interact with biological membranes is another difficulty because it can lead to cytotoxicity and membrane rupture. Since methylated and other highly substituted cyclodextrins have a greater affinity for lipid membranes, this problem is especially pertinent to them. Concerns about cytotoxicity may arise because highly substituted cyclodextrins, like hydroxypropyl-β-cyclodextrin, may interact with lipid membranes more strongly.

13.Applications and their uses [76]

From a microscopical perspective, the guest molecule is microencapsulated since it is encircled by a cyclodextrin derivative. This may result in favourable modifications to the guest molecules' physical and chemical characteristics.

- Stabilization of materials that are susceptible to light or oxygen
- A change in the guest molecules' chemical reactivity
- Fixation of very volatile substances
- Enhancement of the compounds' solubility.
- Converting liquid materials into powders
- Disguising an unpleasant taste and odour
- Cyclodextrins' catalytic function with foreign molecules.

Because of these properties, cyclodextrins or their derivatives can be used in food and toilet products, analytical chemistry, agriculture, and the pharmaceutical industry.

13.1. Cosmetics, personal care and toiletry

Another area that requires the use of cyclodexytrin is cosmetic preparation, principally for the controlled release of aromas from inclusion compounds, which limits the volatility of detergents, room fresheners, and perfumes. In this industry, preservation, fragrance control, and process optimization following solidification of a liquid constituent are the primary benefits of cyclodextrins. Paper towels, tissues, underarm shields, toothpaste, skin creams, and liquid and solid fabric softeners are a few examples of applications.

13.2. Food and flavours

In food compositions, cyclodextrins are employed to express or preserve flavour. They combine with a range of compounds, including as lipids, flavours, and colours, to produce inclusion complexes. Complexation with cyclodextrins offers a possible substitute for the traditional encapsulation technologies employed for flavour protection, as the majority of natural and artificial flavors are volatile oils or liquids. Additionally, cyclodextrins are employed as process aids, such as for removing cholesterol from foods like milk, butter, and eggs. Cyclodextrins were reported to enhance the texture of meat products

and pastry. Their capacity to stabilize flavors during prolonged storage and to lessen bitterness, bad smells, and bad tastes leads to other uses. Cyclodextrins serve as molecular encapsulates, preserving flavor through a variety of demanding freezing, thawing, and microwave food processing techniques. For almost 20 years, cyclodextrins have been permitted for use in food applications in Japan as "modified starches," helping to stabilize fish oils and cover up fresh food odors. When CDs are complexed with sweeteners like aspartame, the flavor is stabilized and enhanced. It has also been asserted that CDs enhance the flavor of alcoholic beverages like beer and whisky. The most common application of CD in process aids is the elimination of cholesterol from animal products, including dairy and eggs.

13.3. Pharmaceuticals

Enhancing medication distribution via biological membranes is one of cyclodextrins' special qualities. Cyclodextrins are known to function as genuine carriers by retaining hydrophobic drug molecules in solution and transporting them to the biological membrane's surface, such as the skin, mucosa, or cornea, where they partition into the membrane. Cyclodextrins increase medication availability at the biological barrier's surface, hence acting as penetration enhancers. In addition to being non-irritating, cyclodextrins have several benefits, including stabilizing active ingredients, lowering medication molecule volatility, and covering up unpleasant odors and harsh flavors. Cyclodextrins have a wide range of uses in the pharmaceutical industry. For instance, adding - or -cyclodextrin makes a number of poorly water-soluble compounds more soluble in water. In certain instances, this leads to enhanced bioavailability, which heightens the pharmacological impact and permits a decrease in the dosage of the medication. Cyclodextrins are used to make compounds more stable by making them more resistant to metal salts, heat, light, oxidation, and hydrolysis. In addition to protecting the stomach mucosa when taken orally, cyclodextrins that include irritating ingredients can also lessen skin damage when used topically.

13.4. Agriculture and chemical industries

Numerous agricultural compounds, such as pheromones, growth regulators, insecticides, fungicides, herbicides, and repellents, combine with cyclodextrins to produce complexes. Cyclodextrins can be used to prolong seed germination. Grain treated with cyclodextrins inhibits some of the amylases that break down the seeds' starch supply. At first, the plant develops more slowly, but this is eventually more than made up for by better plant growth that results in a crop that is 20–45% greater [77]. The expression of cyclodextrin glucanotransferases (CGTases) in plants is a recent phenomenon. Cyclodextrins are frequently employed in the chemical industry to remove or detoxify waste materials, catalyse reactions, assist in a variety of processes, and separate isomers and enantiomers. Cyclodextrins are frequently employed in gas chromatography (GC) and high performance liquid chromatography (HPLC) for the separation of enantiomers. Because of their steric effects, CDs also increase enantioselectivity, which is important for biocatalytic processes. In environmental science, cyclodextrins can be very important for the solubilisation of organic pollutants, the enrichment and removal of organic pollutants, and the removal of heavy metals from the soil, water, and atmosphere. The characteristic of CDs' increased solubility is utilized to assess the restoration of soil.

13.5. Adhesives, coating and other polymer

Certain hot melts and adhesives become tackier and adherent when cyclodextrins are added. Additionally, they provide blowing agents and additives that work with hot melt systems. In associative thickening emulsion-type coatings, like paints, the interaction between polymer molecules tends to increase viscosity; CDS can be employed to reverse this unwanted effect.

13.6. Packing and textile industry

Cyclodextrins are also becoming more and more popular in the textile finishing industry. By using cyclodextrins, fabrics can be given new qualities. Wacker-Chemie covalently bonded a reactive CD derivative with monochlorotriazinyl (MCT) substituents to the fiber in order to permanently impart the adaptable qualities of cyclodextrins to textiles. Excellent textile finishing was offered to cottons, mixed materials, and woollens with this replacement CD. Additionally, CDs are woven into the textiles to capture and cover up aromas from cigarette smoke and perspiration. In order to improve the fabric's absorption of dye and decrease the quantity of dye lost in wastewater, CDs are also used to colour textiles. Fluorescent dye binding to polyester fiber was increased threefold by using hydrophobic tosyl derivative of b-cyclodextrins. Additionally, CDs are quite important to the packing sector. Fresh items are wrapped in a water-absorbing sheet coated with a cyclodextrin inclusion complex that contains volatile and oily antibacterial chemicals and a natural resin binder. After a week of storage at room temperature, it was discovered that a food packaging bag made with CD containing ethylene-tetracyclo-3-dodecane copolymer and hinokitol had no odour and good antifungal qualities, which was helpful for food packaging materials.

14.Conclusion

Researchers have employed a variety of solubility enhancement strategies to improve the APIs' oral bioavailability and other physicochemical characteristics. Cyclodextrin inclusion complexes are one of these methods that work well as carriers and solubilizing agents and have been widely used in the pharmaceutical sector. Cyclodextrins encapsulate the guest molecule into its cavity and these complexes have the characteristics to modulate the physicochemical properties and alleviate the unwanted properties of drug molecules in various drug delivery systems. Because they can improve the solubility and bioavailability of medications and can be utilized as drug carriers, cyclodextrin complexes are well-liked by researchers for administering the medication via several drug delivery methods, including topical, nasal, ocular, and oral. The CD's propensity to mix with a variety of medicinal compounds and create inclusion complexes has been credited with all of its benefits. This CD-drug interaction is of the host-guest type, meaning that the

drug molecule (guest) partially or fully fits into the host's lipophilic cavity to form a complex. The physiochemical and pharmacological characteristics of the drug molecule can be altered by this one interaction alone, leading to improved water solubility, increased bioavailability, improved stabilization of the drug under light, heat, and oxidizing conditions (i.e., preventing the drug from deteriorating in these sources), and decreased volatility. As a result, all of these enhancements to the medication's properties show how promising the CD is as the most cutting-edge drug delivery method. CDs have been utilized in pharmaceuticals for decades, but in recent years, a wide range of additional uses for CDs has surfaced outside of improving the solubility and stability of different medications. CDs can be used as a penetration booster. The medications' ability to pass across cellular membranes is aided by the hydrophobic CDs. CDs assist in delivering sustained release preparations that can be given through a variety of channels. The best way to address the several problems associated with medicine administration is to use CDs' ability to compound with different medications. Because of these characteristics, cyclodextrin uses in the pharmaceutical business as well as other industries including food, agriculture, cosmetics, textiles, and fragrance are becoming more and more significant. A new class of innovative drug delivery methods, including liposomes, microspheres, osmotic pumps, peptide delivery, nanoparticles, and site-specific prodrugs, are created by combining cyclodextrin complexes with other already-existing formulations.

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