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"A Short Review on Cyclodextrin Inclusion Complexes: Synthesis, Characterization and Their Applications"

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ABSTRACT

The supramolecular chemistry gives broad idea of intermolecular interactions where covalent bonds are not likely to form between the interacting species. Thus, interactions have been performed by host-guest interaction. Among the host molecule cyclodextrin seems to be the most promising to form the inclusion complexes with various guest molecules with suitable polarity and dimensions. Among the various types of cyclodextrins, α-cyclodextrin is not suitable for many drugs and γ-cyclodextrin is expensive. Most suitable and widely used cyclodextrin is β-cyclodextrin as it is readily available and the size of cavity is suitable for a wide range of guest molecules. The reported behavior of inclusion complexes had been used to improve the aqueous solubility, bioavailability, stability of unstable drugs, reduction of the unwanted side effects and smell or bad taste can also be masked of a drug molecule. If a drug is hydrophilic, the dissolved drug molecule will not partition from the aqueous exterior into a lipophilic bio membrane and then permeate the membrane. Screening approaches to drug development have led to an increasing number of lipophilic water-insoluble drugs whose medical usefulness is hampered by their insolubility in water.

Keywords: Inclusion Complex, β-Cyclodextrin, Superamolecular Chemistry.

I. INTRODUCTION

Cyclodextrins were first described by Villiers in 1891. Schardinger laid the foundation of the cyclodextrin chemistry in 1903–1911 and identified both α- and β-cyclodextrin. Many drugs are able to form an inclusion complex with CDs, being trapped entirely or at least partially into their slightly apolar cavities [1-3]. Such an encapsulation affects many of the physiochemical properties of drugs such as its solubility, rate of dissociation etc. CDs can increase the water solubility of some contaminations, reduce their toxicity and catalyze their decomposition by forming inclusion complex [4, 5]. Although the interaction of host and guest molecules are very important to study the inclusion complexes, but the methods to obtain the direct information are very rare. In the solution phase, some information can be obtained by nuclear magnetic resonance (NMR) spectroscopy [6]. In solid State, X-Ray single crystal analysis is a specific method in providing the information and gives significant results [7]. Sometimes NMR cannot completely distinguish the complex signals and the results of crystallographic studies are not being same as that in solution phase. In this type of a situation commonly ab-initio and density functional theory (DFT) calculations are very much useful. However, the calculations of inclusion complex are very difficult due to its large size and more number of atoms contained. The formation of inclusion complex with a wide variety of guest molecules is one of the most interesting properties of CDs. There are various methods available to synthesize the inclusion complex [8]. The schematic representation of β-cyclodextrin is shown in Figure1.

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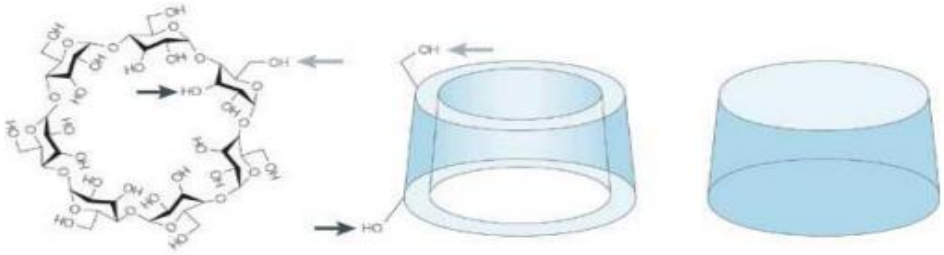

Figure1: Schematic representations of β-cyclodextrin. The black and grey arrows point to primary and secondary hydroxyl groups (Davis and Brewster 2004).

II. PREPARATION OF INCLUSION COMPLEXES

In the β conformation intramolecular hydrogen bonds appear between hydroxyl groups which prevent the formation of hydrogen bond with surrounding molecules resulting in poor water solubility (Muller and Brauns 1986). Chemical Properties of cyclodextrin molecules are given in Table 1.

Table 1: Chemical Properties of cyclodextrin

Property	α-Cyclodextrin	B- Cyclodextrin	γ- Cyclodextrin
Number of glucopyranose units	6	7	8
Molecular Weight	972	1135	1297
Solubility in water [g/100mL]	14.5	1.8	23.3
Outer Diameter(Å)	14.6	15.4	17.5
Cavity Diameter(Å)	4.9	6.0-6.3	7.5-8.0
Cavity Volume(Å)	174	262	427

The great significance of CDs both in research and applications stands in their ability to selectively form inclusion complexes with other molecules and ions (Dodziuk 2006). This formation of the inclusion complex is the outcome of the equilibrium between the CD molecules, the free guest and the supramolecules of inclusion. Figure 2 represents inclusion of a guest within a cyclodextrin host to form a complex.

Free guest + free CD ⟷ CD/guest complex

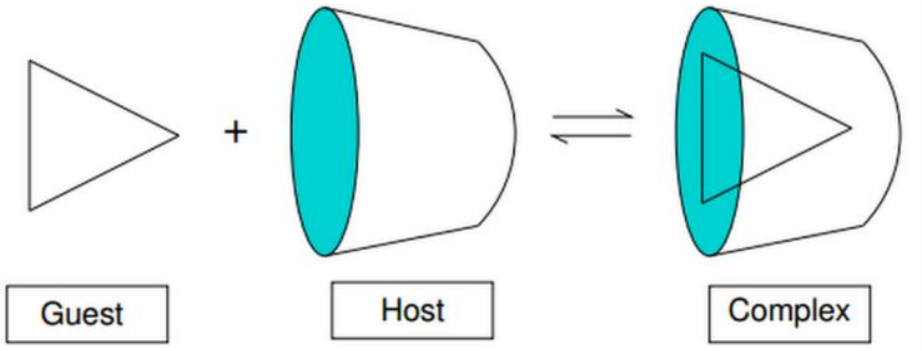

Figure 2: Inclusion of a guest within a cyclodextrin host to form a complex.

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1.1 Approaches for making of Inclusion Complexes

(i) Physical blending method

A solid physical mixture of drug and CDs are prepared simply by mechanical trituration. In laboratory scale CDs and drug are mixed together thoroughly by trituration in a mortar and passes through appropriate sieve to get the desired particle size in the final product. In industry scale, the preparation of physical mixtures is based on extensive blending of the drug with CDs in a rapid mass granulator usually for 30 minutes. These powdered physical mixtures are then stored in the room at controlled temperatures and humidity conditions [9].

(ii) Kneading method

This method is based on impregnating the CDs with little amount of water or hydro alcoholic solutions to be converted into a paste. The drug is then added to the above paste and kneaded for a specified time. The kneaded mixture is then dried and passed through a sieve if required [10]. Parik et al. [11] have reported the dissolution enhancement of nimesulide using complexation method. In laboratory scale kneading can be achieved by using a mortar and pestle [12-14].

(iii) Co-precipitation technique

This method involves the co-precipitation of drug and CDs in a complex. In this method, required amount of drug is added to the solution of CDs. The system is kept under magnetic agitation with controlled process parameters and the content is protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex. Moyano et al. [15] have studied the solid-state characterization and dissolution characteristics of gliclazide-β-cyclodextrin inclusion complexes. This technique leaves a drug-CD solution in very close conditions to the saturation and through abrupt changes of temperature with addition of organic solvents.

(iv) Solution/solvent evaporation method

This method involves dissolving of the drug and CDs separately in to two mutually miscible solvents, mixing of both solutions to get molecular dispersion of drug and complexing agents and finally evaporating the solvent under vacuum to obtain solid powdered inclusion compound. Generally, the aqueous solution of CDs is simply added to the alcoholic solution of drugs. The resulting mixture is stirred for 24 hours and evaporated under vacuum at 45 ºC. The dried mass was pulverized and passed through a sieve.

(v) Neutralization precipitation method

This method is based on the precipitation of inclusion compounds by neutralization technique and consists of dissolving the drug in alkaline solutions like sodium/ammonium hydroxide and mixing with an aqueous solution of CDs. The resultant clear solution is then neutralized under agitation using hydrochloric acid solution till reaching the equivalence point. A white precipitate is being formed at this moment, corresponding to the formation of the inclusion compound. This precipitate is filtered and dried. Doijad et al. [16] have studied the enhancement of solubility of piroxicam by complexation with β-cyclodextrin.

(vi) Milling/Co-grinding technique

A solid binary inclusion compounds can be prepared by grinding and milling of the drug and CDs with the help of mechanical devices. Drug and CDs are mixed intimately and the physical mixture is introduced in an oscillatory mill and grinded for suitable time. Alternatively, the ball milling process can also be utilized for preparation of the drug-CD binary system. The ball mill containing balls of varied size is operated at a specified

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speed for a predetermined time, and then it is unloaded, sieved through a 60-mesh sieve. This technique is superior to other approaches from economic as well as environmental stand point in that unlike similar methods it does not require any toxic organic solvents [17].

(vii) Atomization/Spray drying method

Spray-drying is a common technique used in pharmaceuticals to produce a dry powder from a liquid phase. Another application is its use as a preservation method, increasing the storage stability due to the water elimination [18]. This method represents one of the most employed methods to produce the inclusion complex starting from a solution. The mixture pass to a fast elimination system propitiate solvent and shows a high efficiency in forming complex. Besides, the product obtained by this method yield the particles in the controlled manner which in turn improves the dissolution rate of drug in complex form. Vozone et al. [19] have developed complexation of budesonide in cyclodextrins and particle aerodynamic characterization of the complex solid form for dry powder Inhalation.

(viii) Lyophilization/ Freeze drying technique

In order to get a porous, amorphous powder with high degree of interaction between drug & CD, lyophilization/freeze drying technique is considered as a suitable [20]. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug and CD at reduced pressure. Thermolabile substances can be successfully made into complex form by this method. The limitations of this technique are long time process and yield poor flowing powdered product.

(ix) Microwave irradiation method

This technique involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. The drug and CD in definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a round bottom flask. The mixture is reacted for short time of about one to two minutes at 60 ºC in the microwave oven. After the reaction completes, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed free drug and CD. The precipitate so obtained is separated using whatman filter paper, and dried in vacuum oven at 40 ºC for 48 hrs. Deshmukh et al. [21] have developed inclusion complexes of ziprasidone hydrochloride with β-cyclodextrin and hydroxypropyl β-cyclodextrin to design the fast dissolving formulation using various superdisintegrants. Microwave irradiation method is a novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of the product [22].

(x) Supercritical antisolvent technique

This method was introduced in the late 1980s [23]. Since the first experiences of Hannoy et al in 1879, a number of techniques have been developed and patented in the field of supercritical fluid-assisted particle design. In the supercritical fluid antisolvent technique, carbon dioxide is used as anti-solvent for the solute but as a solvent with respect to the organic solvent. The use of supercritical carbon dioxide is advantageous as its low critical temperature and pressure makes it attractive for processing heat-labile pharmaceuticals. Supercritical particle generation processes are new and efficient route for improving bioavailability of pharmaceutically active compounds [24].

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1.2 Methods for investigating the inclusion complexes

The complexation depends largely on the dimensions of the cyclodextrins and the particular sterical arrangement of the functional groups of the molecules, which leads to a relatively hydrophilic outside and a hydrophobic inside cavity of the molecule. Inclusion complexes formed between the guest and cyclodextrin molecules can be characterized both in the solid and solution state by the following techniques:

(A) Inclusion complexation in the solid state characterized by

(i) Thermo-analytical methods

Thermo-analytical methods [9, 25-28] determine whether the guest substance undergoes some change before the thermal degradation of cyclodextrin. The change of the guest substance may be melting, evaporation, decomposition, oxidation or polymorphic transition. The change of the guest substance indicates the complex formation. The effect of cyclodextrins on the thermogram obtained by DTA and DSC were observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks. Changes in the weight loss were evaluated to provide supporting evidence for the formation of inclusion complexes. The nature of the drug and cyclodextrins used and method of preparation of complex have been found to influence the above finding considerably. If the interaction between the drug and the excipient is weak, the shift in the endothermic peak is very small.

(ii) Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy [27, 29,30] is used to study the microscopic aspects of the raw material (cyclodextrin and the guest substances, respectively) and the product obtained by co-precipitation/evaporation [10, 31,32].The difference in crystallization state of the raw material and the product seen under electron microscope indicates the formation of the inclusion complexes. SEM analysis is performed to investigate the morphologies of pure drug and carriers and their combinations.

(iii) X-ray diffractiometry analysis

Powder X-ray diffractiometry [9,26] may be used to detect inclusion complexation in the solid state. When the guest molecules are liquid since liquid have no diffraction pattern of their own, then the diffraction pattern of a newly formed substance clearly differs from that of uncomplexed cyclodextrin. This difference of diffraction pattern indicates the complex formation [10, 33,34]. When the guest compound is a solid substance, a comparison has to be made between the diffractogram of the assumed complex and that of the mechanical mixture of the guest and cyclodextrin molecules [32]. Comparison of the diffractogram is only possible if the cyclodextrin as well as the guest molecules are treated under identical conditions as that of the assumed complex because cyclodextrin inclusion complex preparation processes such as freeze drying and grinding, may change the crystallinity of the pure substances and this may lead to different diffraction patterns [27, 35].

(iv) Infra-Red (IR) spectroscopy

Infra-Red spectroscopy is used to estimate the interaction between cyclodextrin and the guest molecules in the solid state [27,28]. Cyclodextrin bands often change only slightly upon complex formation and if the fraction of the guest molecules encapsulated in the complex is less than 25%, bands which could be assigned to the included part of the guest molecules are easily masked by the bands of the spectrum of cyclodextrin [25,34,36-38]. Infra-red spectral studies give information regarding the involvement of hydrogen in various functional groups. This generally shifts the absorbance bands to the lower frequency, increases the intensity and widens the

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band caused by stretching vibration of the group involved in the formation of the hydrogen bonds. Hydrogen bond at the hydroxyl group causes the largest shift of the stretching vibration band. It has been observed that cleavage of the hydrogen bonding due to inclusion complexation results in the shift of absorbance bands to higher frequency.

(B) Inclusion complexation in solution state characterized by

(i) Nuclear Magnetic Resonance (NMR) spectroscopy

The most direct evidence for the inclusion of a guest into a cyclodextrin cavity in solution is obtained by 1H NMR spectroscopy [28,34]. 1H NMR may also be used to determine the direction of penetration of guest molecules into the cyclodextrin cavity [37,38].The H-3 and H-5 atoms of cyclodextrin, which are directed towards the interior of the cyclodextrin will show a significant up field shift if inclusion does indeed occur and the H-1, H-2 and H-4 atoms, located on the exterior of the cavity will show only marginal upfield shifts. The spectrum of the guest molecule may also be changed upon inclusion complex formation [39-42]. A similar method to investigate inclusion complex formation is ^{13}C-NMR spectroscopy [43]. It is often used to gain insight into the inclusion modes of inclusion complexes in aqueous solution. The cyclodextrin induced change in the ^{13}C chemical shift result predominantly from the electrical environment effect of the cyclodextrin cavity and in general ^{13}C inclusion shift may be mainly divided into hydrophobic and van der Waals interaction shifts [40].

(ii) Electron Spin Resonance (ESR)

Electron Spin Resonance [44] is a useful method to investigate inclusion complexation with radicals in aqueous solutions. The hyperfine coupling constant of radicals is known to be sensitive to the polarity of the medium. If the hyperfine coupling constant alters, the movement of a radical to an environment less polar than water is indicated and confirms the inclusion complex formation.

(iii) Ultraviolet/Visible (UV/VIS) Spectroscopy

The complexation causes a change in the absorption spectrum of a guest molecule [9,28,45]. During the spectral changes, the chromophore of the guest is transferred from an aqueous medium to the non-polar cyclodextrin. These changes must be due to a perturbation of the electronic energy levels of the guest caused either by direct interaction with the cyclodextrin, by the exclusion of solvating water molecules or by a combination of these two effects [36]. Small shifts are observed on the UV spectra of the included guests, the method is often used to detect inclusion complexation [46-48]. Hypsochromic or bathochromic shift or increase in the absorptivity without change in the λmax has been considered as evidence for interaction between cyclodextrin and the drug in the formation of the complex.

(iv) Fluorescence Spectroscopy

When fluorescent molecules in aqueous solution are included in cyclodextrins, fluorescence spectra may be influenced which indicates the formation of inclusion complexes [47]. The inclusion complex formation generally leads to the change of excitation and emission wavelength of the drug [49]. The effect of inclusion between 1,8-dihydroxyanthraquinone with α-CD, β-CD and γ-CD on the fluorescence spectra of the drug was studied which indicates that the inclusion complex formation leads to the change of excitation and emission wavelength of the drug. A red shift from 571 to 595 nm of the emission band was observed along with an increase in the intensity of emission when 1, 8-dihydroxyanthraquinone complexed with γ-CD by hyrodgen

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bond formation [47]. The fluorescence emission spectra confirmed that the solubility of the complex formed using β-CD and γ-CD was more than that of plain drug. Binding of the chromophore in a monomeric form with β-CD and γ-CD was also confirmed. The spectral change was maximum in γ-CD, less in β-CD and none in α-CD indicating that the substrate was included inside the cavity completely in case of γ-CD due to larger cavity size, and partly into the β-CD cavity and no inclusion in case of α-CD [49].

1.3 Chemistry of Inclusion Complex

The field of "inclusion complex" holds considerable promise in the study of reactivities of guest molecules and the way in which this reactivity is governed by the environment. Based on size selective complexation properties of CDs, the better the fit of guest molecules inside the cavity, the more stable the complex will be. The stability of the complex is inversely proportional to the polarity of the guest molecule [50,51]. Several hypotheses have been proposed for the driving forces for the CD inclusion complexation, including Vander Waals interactions, hydrogen bonding between the polar functional groups of the guest molecules, the hydroxyl groups of CDs, release of high-energy water in the cavity in the complex formation, hydrophobic interactions between the hydrophobic moiety of the guest molecules or the CD cavity and release of strain energy in the ring frame of the cyclodextrin. Among those forces, hydrophobic interactions are frequently considered as the main driving force for the complexation in aqueous media between hosts containing hydrophobic (apolar) cavities and non polar guest molecules. New cyclodextrin-based technologies are constantly being developed and, thus, 100 years after their discovery cyclodextrins are still regarded as novel excipients of unexplored potential.

1.4 Pharmaceutical applications of inclusion complex

CDs and their derivatives have received a lot of attention in the field of pharma sciences for the past few years. Many articles have already been published regarding the interaction of host-guest moiety and increased number of reviews have been dedicated to their application in pharmaceutical sciences [52-54]. CDs and their derivatives have well-known effects on drug solubility and dissolution, bioavailability, safety and stability, and their applications in different areas of drug delivery have been also reported. However, the cavity size of β-CD depends upon the complexation of guest with host molecule many physiochemical properties have been changed.

CDs have mainly been used as complexing agents to increase the aqueous solubility of poorly water-soluble drugs and to increase their bioavailability and stability. In addition, CDs have been used to reduce or prevent gastrointestinal or ocular irritation, reduce or eliminate unpleasant smells or tastes, prevent drug-drug or drug-additive interactions, or even to convert oils and liquid drugs into microcrystalline or amorphous powders.

(i) Enhancement of solubility

CDs increase the aqueous solubility of many poorly soluble drugs by forming inclusion complexes with their apolar molecules or functional groups. The resulting complex hides most of the hydrophobic functionality in the interior cavity of the CD while the hydrophilic hydroxyl groups on the external surface remain exposed to the environment. The net effect is that a water-soluble CD drug complex is formed [55].

(ii) Enhancement of bioavailability

When poor bioavailability is due to low solubility, CDs are of extreme value. Preconditions for the absorption of an orally administered drug are its release from the formulation in dissolved form. When drug is complexed with CD, dissolution rate and, consequently, absorption are enhanced. Reducing the hydrophobicity of drugs

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by CD complexation also improves their percutaneous or rectal absorption. In addition to improving solubility, CDs also prevent crystallization of active ingredients by complexing individual drug molecules so that they can no longer self-assemble into a crystal lattice [56].

(iii) Improvement of stability

CD complexation is of immense application in improving the chemical, physical and thermal stability of drugs. For an active molecule to degrade upon exposure to oxygen, water, radiation or heat, chemical reactions must take place. When a molecule is entrapped within the CD cavity, it is difficult for the reactants to diffuse into the cavity and react with the protected guest [57].

(iv) Prevention of incompatibility

Drugs are often incompatible with each other or with other inactive ingredients present in a formulation. Encapsulating one of the incompatible ingredients within a CD molecule stabilizes the formulation by physically separating the components in order to prevent drug-drug or drug-additive interaction [58].

(v) Odor and taste masking

Unpleasant odor and bitter taste of drugs can be masked by complexation with CDs. Molecules or functional groups that cause unpleasant tastes or odors can be hidden from the sensory receptors by encapsulating them within the CD cavity. The resulting complexes have no or little taste or odor and are much more acceptable to the patient.

Of course pharmacy is not the only field in which cyclodextrin have found so much applications. In the field of analytical chemistry, cosmetics, agriculture, biochemical and food industry CDs have prooved their usefulness too. In the analytical chemistry cyclodextrins and inclusion complexes can be used in high pressure liquid chromatography (HPLC), gas chromatography, spectroscopy and electrophoresis. Cyclodextrin complexation have been successfully applied to rapid analysis of various drugs by HPLC.

III. CONCLUSION

A survey of literature related to use of cyclodextrin molecule for obtaining inclusion complex with various practically insoluble available drugs was conducted in order to characterize their formation by various techniques in solid state and solution phase or to study their applicability in the field of pharmaceutical sciences and analytical sciences. CDs have mainly been used as complexing agents to increase the aqueous solubility of poorly water-soluble drugs, and to increase their stability and bio-availability. In addition, they can be used to reduce or prevent gastro-intestinal or ocular irritation, eliminate unpleasant smells or tastes, prevent drug-drug or drug-additive interactions, or even to convert oils and liquid drugs into micro crystalline or amorphous powders. Literature revealed that inclusion complex synthesis is based on size selective complexation properties of CDs, the better the fit of guest molecules inside the cavity, the more will be the stability which is inversely proportional to polarity of guest molecule. Complexation of cyclodextrin molecule with various drugs is applied very well in both the fields pharmaceutical as well as non pharmaceutical.

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