REVIEW ARTICLE

Cyclodextrin Complexes: An Approach to Improve the Physicochemical Properties of Drugs and Applications of Cyclodextrin Complexes

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Abstract

Inclusion complexes have various applications in different fields of drug delivery and pharmaceutical industry due to their ability of complexation with guest molecules and enhancement of the physicochemical properties of guest molecules. Cyclodextrins and their derivatives have the ability to encapsulate the bioactive compounds into its cavity and protect these from the environmental conditions, improve the solubility, bioavailability, and other properties also. The aim of this review is to highlight the advantages of cyclodextrins in the enhancement of physicochemical properties of drugs (such as solubility, stability, bioavailability, permeability, and others), different methods for production and various characterization techniques used for evaluation of complexes. Applications of cyclodextrin complexes in pharmaceutical and other fields are also explained here with examples. Thus cyclodextrins, because of their continuing ability to find several novel applications in drug delivery, are expected to solve many problems accompanied with the delivery of different novel drugs through various delivery routes.

Key words: Applications, Bioavailability, Cyclodextrins, Inclusion complexes, Solubility, Stability

INTRODUCTION

The main goal of oral drug delivery systems is to modulate the solubility of active pharmaceutical ingredients (APIs) that improve the absorption of the drug and its bioavailability also. With the development of technologies in discovery and development of new chemical entities (NCEs), a large number of new entities have been discovery with large molecular size and higher degree of lipophilicity. About 40% of the NCEs in the pipeline and 60% of newly developed APIs are associated with low aqueous solubility which leads to poor absorption and bioavailability. The problem of low solubility is mainly related to the BCS Class-II and IV drugs. These drugs show low absorption often lead to inconsistent *in vitro in vivo* correlation and poor bioavailability. Dissolution step is the rate-limiting factor for the absorption of BCS Class II drugs whereas dissolution and permeability both are rate-limiting factor for BCS Class IV drugs. Pharmaceutical researchers are constantly working on various approaches for the enhancement of drug solubility and dissolution of BCS Class II drugs which improve the therapeutic responses and overcome the toxic effects related to the higher dose.[1-8]

For the enhancement of solubility and dissolution, pharmaceutical scientists have been used various approaches such as particle size reduction, i.e., micronization and nanoformulations,[9] salt formation,[10] prodrug and drug derivatization,[11] cosolvency,[12] use of surfactants,[13] cyclodextrin complexes,[14] change in crystal habit or cocrystals,[6] self-emulsifying drug delivery systems,[15] solid dispersions,[16] etc. Each technique has its own merits and demerits regarding solubility enhancement and selection of suitable one is mainly depends on the type of drug, polymers,

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therapeutic, and targeted delivery of drug which to be obtained.[17-19]

These common approaches have been commonly used for enhancement of solubility, bioavailability, and other physicochemical properties of drugs by researchers. These approaches have their own merits and demerits depending on the selection of drug, polymer, properties, stability, technology transfer from lab to industrial scale, etc. Among these, solid dispersions have been generally used for the improvement of oral bioavailability of poorly water-soluble drugs.[20,21] However, the major disadvantage of this approach is that solid dispersionslack physical stability and revert back to the crystalline state on storage.[22,23] Inclusion complexes can be easily developed as a viable and fruitful alternative for solid dispersions and other techniques for the development of solid state forms to improve the pharmaceutical characteristics.

INCLUSION COMPLEXES

First time in 1886, Mylius saw the unusual complexations between hydroquinone and several volatile compounds within the inclusion complexes and also observed that one molecule was entrapped into another molecule without any

Table 1: Different compounds used as adductors to prepare the coordination compounds

Adductors	Structure of inclusion compounds
Polymolecular inclusion compounds	
Urea	In the absence of a guest component, urea crystallizes in a tetragonal arrangement. The structure is relatively open with low Vander wall forces acting between the molecules. In the presence of suitably sized guest molecule, it assembles in the form of hexagonal arrangement forming a channel such as void space having the channel diameter of approximately 5Å, around the guest, and the coordination producing a denser structure than the tetragonal arrangement.[31]
Thiourea	This is a sulfur analog of urea and forms hexagonal channel-like complexes with a channel diameter of 7 Å due to a larger size of sulfur atom.[31]
Deoxycholic acids	The deoxycholic acid forms a network around the guest molecule interact through Vander wall forces. An inclusion compound of deoxycholic acid with fatty acids orient in the end-to-end arrangement within the open channels of the deoxycholic crystals, in which it is characterized by whole number ratios such as four molecules of deoxycholic acid to one of C4-C8 acid, six to one of C9-C14 acid, and eight to one of C15-C29 acid.[32]
Hydroquinone	Six hydroquinone molecules are joined by hydrogen bonding to form a large open structure which may be visualized as consisting of two interpenetrating “cups,” each cup formed by three hydroquinone molecules with a cavity in between, which forms a channel for the accommodation of guest molecules.[33]
Water	The water clathrate framework resembles the ice lattice in that each oxygen atom is hydrogen bonded to four other oxygen atoms. The hydrogen bonds in ice have a length of 2.76 Å, virtually the same as in the clathrate (2.76 Å). The water molecules in clathrates are joined in the rings of five.[27]
Monomolecular inclusion compounds	
Cyclodextrins	These are, composed of 5 or more α-D-glucopyranoside units linked by α1-4 linkages, as in amylose (a fragment of starch). Typical cyclodextrins contain a number of glucose monomers ranging from 6 to 8 units in a ring, creating a cone shape. Thus, denoting: α–cyclodextrin (six sugar ring molecule), β-cyclodextrin (seven sugar ring molecule), and γ-cyclodextrin (eight sugar ring molecule) enclosing the cavity of about 6, 8, and 10 Å, respectively, in which the guest molecule is enclosed.[27]
Macromolecular inclusion compounds	
Zeolites	They contain two tight hexagons, each with six silicon and aluminum atoms, along with their associated oxygen atoms, facing each other and forming a flat prism. Eight such prisms are joined together to form an oval cavity of approximately 11 Å. There are 5 × 1021 such cavities /in^2.[34]
Silica Gel	Silica gels are composed of three dimensional networks of silica atoms in the same spatial relationships the hydrogen-bonded oxygen atoms of water. The silica gels are formed by crystallization of the silicon-oxygen atoms around the guest molecule.[27]

chemical bonding. The term "inclusion compounds" was first time given by Schlenk and previously also known by some other names such as "occlusion compounds, adducts, and clathrates." Inclusion compound is the complex of one guest molecule with the host molecule. The hydrophobic drug substance is entrapped into the host molecule, and this complexation is characterized by the presence of non-covalent interactions between drug and host molecule. The essential criteria of this technique are the size of the guest molecule, i.e., size of the guest molecule should be equivalent to the host molecule, so that guest molecule entrapped into the cavity of host molecule and formed a stable complex with desired physiochemical properties. The stereochemistry and polarity of both the host and guest molecules conclude whether inclusion can arise or not. The two components produce a combination of considerable strength due to the total dispersion forces between the two components. The inclusion complex configuration does not take place by ionic, covalent or coordinate covalent bonds but relatively dependent on dispersion forces.[24-26]

Various classifications have been proposed for the inclusion complexes by the researchers. Frank classified the inclusion complexes into polymolecular, monomolecular, and macromolecular on the basis of organization and their structures in complexes as summarized here in the Table 1.[27] Harris categorized the host molecules into hard hosts and soft host on the basis of the stability of the host molecule.[28] Steed and Atwood classified these compounds into cavitands and clathrands on the basis of the topological relationship between host and guest.[29] Dyadin and Terekhova proposed different types of inclusion complexes such as crypto-clathrates, tubulatoclathrates and intercalator clathrates on the basis of structure, and shape of the host's cavity.[30]

CYCLODEXTRINS

A French scientist Antoine Villiers isolated potato starch by bacterial digestion in 1891 and described this experimental outcome material as dextrin and named as "cellulosine."[35] In 1903, Franz Schardinger discovered two crystalline compounds α-dextrin and β-dextrin and Villiers' "cellulosine" also identifies as β-dextrin and presently, these are also known as α-cyclodextrin (α-CD) and beta-cyclodextrin (β-CD).[36,37] In 1935, Freudenberg *et al*. identified another compound known as γ-cyclodextrin (γCD).[38] In 1976, the first time a formulation of cyclodextrin and prostaglandin (Prostarmon-E™ sublingual tablets) was marketed by Japan. In 1977, Piroxicam/β-CD (Brexin® tablets) pharmaceutical product was to be the first formulation which was marketed in Europe and itraconazole/2-hydroxypropyl-βCD oral solution (Sporanox®) was the first US-approved product.[39] A detailed historical background about the development of cyclodextrin formulation was briefly explained by some researchers.[24,25] Nowaday's, various types of cyclodextrin (such as α-CD, β-CD, γ cyclodextrin [γ-CD], and their derivatives) have been used by the researcher for improvement of the physicochemical properties of drugs.[14,40,41] Cyclodextrins have various pharmaceutical applications which make them a valuable tool for enhancing the physicochemical properties of drugs and removing undesirable effects related to the drug molecule. Cyclodextrins have the capabilities to encapsulate the guest molecule into its cavity and improve the solubility, stability, and release profile of the drugs. Different types of cyclodextrins (such as α-CD, β-CD, γ-CD, and their derivatives) based on their size, number of units and molecular weight have been used for modulating the physicochemical properties are mainly based on their cavity size, ability to encapsulate the guest molecule and improvement of properties of drugs. Summarized details related to the types of cyclodextrins have discussed here and their applications.[42]

α-CD

CDs are mainly classified based on the number of glucose units present in their structure, i.e. 6-glucose units molecules are called as α-CD.[43]

Weak hydrogen bonding is present between 2-OH and 3-OH groups on the outer edge, and this interaction is weak in α-CD and the strongest in γ CD. In α-CD, 3-OH group acts as a donor and 2-OH acts as acceptor, whereas in β- and γ-CD, the bonding switches between 3-OH (acceptor) and 2-OH (donor). CDs are amphipathic structures in which 3-OH and 2-OH groups are displayed on the wider rim and 6-OH groups on the narrower rim. The molecular cavity of cyclodextrins is surrounded by hydrophilic groups whereas inner part is hydrophobic which is covered by ether like anomeric oxygen atoms. The cavity size of α-CD is insufficient to entrap the drugs into its cavity.[44-46] α-CDs are the most efficient in extracting phospholipids.

β-Cyclodextrin (β-CD)

β-CD has been generally used in the initial stages of pharmaceutical applications due to easily accessible and suitable cavity size for a wide range of drugs.[46] The cavity size of β-CD is more suitable than other CDs to encapsulate a wide range of molecules.[47,48] The use of β-CD on drug solubility, bioavailability, safety, stability, and as a carrier in drug formulation may be attained by the formation of inclusion complexes with drug molecules; in fact, the use of β-CD already has a long history in pharmacy.[49,50] β-CD consists of seven glucopyranose residues and is only moderately soluble in water because of intermolecular hydrogen bonding. Modified CDs with alkylated hydroxyl groups, such as randomly methylated-β-cyclodextrin (M-β-CD) break up this hydrogen bonding network and are considerably more water soluble. Alkylated CDs are also less toxic than the parent β-CD.[51] β-CD has a hydrophilic outer surface and a lipophilic central cavity to accommodate a variety of

lipophilic drugs,[39] resulting in increased solubility of the incorporated drug, enhanced permeation for macromolecular drugs,[52] and inhibition of certain protease activities.[53,54]

γ-CD

γ-CD possesses large internal cavity size and also have the advantage to encapsulate the bigger molecules which cannot be entrapped by the α- and β-CD s.[42]γ- CD has the highest aqueous solubility than other natural cyclodextrins because of its noncoplanar and flexible structure.[55] This property makes it good host for enhancement of solubility of poor water-soluble drugs which further explains its applications in other industries.[47] γ-CD has low bioavailability because it cannot permeate through the biological membranes easily and digested rapidly in the gastrointestinal tract and also excreted through the urine in unchanged form after parental administration.[56-60] High water solubility, larger cavity size, and most favorable toxicological profile make the γ-CD a better candidate to enhance the properties of drugs.[42] Recently, Saokham and Loftsson presented a detailed summary of γ-CD about formulation, physicochemical properties, toxicological profile, and applications in different areas.[61]

ADVANTAGES OF CYCLODEXTRIN COMPLEXES

CDs have emerged as complexing agents in the researcher's armamentarium to modulate the various physicochemical properties of drugs and also a better choice of contemporary drug pipelines. Low toxicity and different cavity sizes of cyclodextrins make it an important tool for enhancement of solubility and bioavailability of drugs. Various advantages of cyclodextrin complexes for enhancement of physicochemical properties (such as solubility, bioavailability, taste masking, permeability, and stability) of drugs have been discussed here and in Table 2.[14,40]

Improvement of solubility and dissolution rate

During oral drug administration, water solubility of drug is a very important property for absorption of drug and also has the potential to good bioavailability. The bioavailability of BCS Class II and IV drugs can be enhanced by increasing the solubility and dissolution rate. The cyclodextrin complexes have the ability to solubilize the drugs by forming the non-covalent complexes in solution.[14] Miletica *et al*. formulated the cyclodextrin complexes of Voriconazole, an antifungal drug, with hydroxypropyl-β-cyclodextrin (HPBCD) and 2-O-methyl-β-cyclodextrin by spray drying and results revealed that dissolution rate and solubility of inclusion complexes would be higher than pure drug.[62] Rodriguez-Aller *et al*. prepared the cyclodextrin complexes of latanoprost, practically insoluble prostaglandin, with different cyclodextrins for ocular administration and among all cyclodextrin complexes, latanoprost propylamino-β-CD formulation showed the higher solubility and lower irritation the commercial latanoprost formulation used as a reference.[63] Braithwaite *et al*. formulated the cyclodextrins of three vitamins cholecalciferol, ascorbic acid, and α-tocopherol with different cyclodextrins and observed for the improved solubility and efficacy of vitamins.[64] Xu *et al*. synthesized the inclusion complexes of nateglinide with sulfobutyl ether β-CD and found higher aqueous solubility as compared to free drug.[65]

Bioavailability enhancement

Oral bioavailability of a drug mainly depends on the solubility and permeability in the gastrointestinal tract. Higher solubility in the gastrointestinal fluids and good permeability of drugs through the gastrointestinal membrane of drugs lead to the better oral bioavailability of the formulation. The ultimate goal for the development of pharmaceutical solid dosage forms is to enhance the bioavailability of the drugs. Cyclodextrin complexes also have the property to increase the solubility and bioavailability of the APIs. Cyclodextrin complexes of glimepiride were prepared to demonstrate for the enhancement of oral bioavailability and therapeutic efficacy.[66] Ozdemir and Erkin formulated the inclusion complexes of sulfamethoxazole with β- CD and *in vivo* studies on six healthy volunteers showed the higher bioavailability as compared to pure.[67] Holm *et al*. studied the effect of cyclodextrin concentration on the oral bioavailability of danazol and cinnarizine in rats. Pharmacokinetic studies showed that bioavailability of danazol decreased with increase in the concentration of CD whereas there was no significant effect on bioavailability of cinnarizine with change in concentration of CD. The study suggested that the concentration of CDs should affect the bioavailability of some compounds whereas others had no effect on their bioavailability with change in concentration of CDs.[68] Desai *et al*. formulated the cyclodextrin inclusion complex based orally disintegrating tablets of eslicarbazepine acetate and *in-vivo* studies showed 2 times higher bioavailability than marketed formulations.[69]

Higher stability against hydrolysis and thermal

Stability is the main parameter which should be kept in the mind of the researchers during the development of pharmaceutical formulations. Various types of stability studies of need to be determined which would modulate the shelf life of the formulation.[70] Cyclodextrin complexes protected the host compound by shielding it and reduced the effect of heat, light or oxygen on the formulation and also may improve the stability of the entrapped drug in the complexes.[71] Many researchers formulated and analyzed the inclusion complexes of many APIs and found in the enhancement of different types of stability of the complexes as compared to pure drug and physical mixtures.

Table 2: Various pharmaceutical advantages of cyclodextrin complexes

Drugs	Cyclodextrins	Pharmaceutical Application	Ref.
Voriconazole	HP-β-CD and 2-O-methyl-β-cyclodextrin	Enhance solubility, dissolution rate, and chemical stability	[62]
Glimepiride	HP- β-CD, β-CD	Enhancement in dissolution rate increased the duration of action and improvement of therapeutic efficacy of the drug	[66]
Latanoprost	propylamino-β-CD	Higher stability, solubility, and ocular tolerance	[63]
Nateglinide	sulfobutyl ether β-cyclodextrin	Higher aqueous solubility	[65]
Sulfamethoxazole	β-CD	Enhance bioavailability and dissolution rate	[67]
Eslicarbazepine acetate	β-CD	Faster onset of action and higher bioavailability	[69]
Polylactic acid	β-CD	Improve the thermal expansion stability	[72]
Chimonanthus praecox	β-CD	Enhancement of antioxidant activity and thermal stability	[73]
Famotidine	Carboxymethyl β-CD	Improvement of chemical stability, oral bioavailability, and bitter taste	[75]
Astaxanthin	HP- β-CD	Storage stability and antioxidant activity	[76]
Catechin	β-CD	Protection of antioxidants, higher storage stability against temperature, oxygen, and light	[51]
α-tocopherol	β-CD	Higher antioxidant activity and better UV-light stability.	[77]
Rhein	HP- β-CD	Improvement in photostability	[78]
Nootkatone	β-CD, HP- β-CD	Superior enhancement solubility and photostability	[80]
13-cis-retinoic	α-CD, HP- β-CD	HP- β-CD showed lesser photodegradation in an aqueous medium as compared to α-CD	[81]
Isradipine	β-CD	Enhance solubility and photostability	[82]
Cetirizine dihydrochloride	β-CD	Enhance bitter taste and organoleptic properties	[83]
Prostaglandin E1	α-CD, β-CD, CME-β-CD	Enhance topical drug delivery in the presence of water	[101]

α-CD: α-cyclodextrin, β-CD: β-cyclodextrin, UV: Ultraviolet

Thermal stability

Stability studies at high temperature describe the thermal stability of the formulations. Few studies about the thermal stability of cyclodextrins complexes have been reported in the literature. Improvement in the thermal stability of polylactic acid-β-cyclodextrin inclusion complex composite films (PLA-IC-CFs) was observed as compared to the pure PLA composite films because the presence of cyclodextrin complexes in composite films.[72] Another study showed the enhancement of thermal stability of *Chimonanthus praecox* extract by formulating inclusion complexes with β-cyclodextrin.[73]

Chemical stability

During the development of new product, chemical stability should be kept in mind to prevent degradation in the presence of different excipients. In 2017, Popielec and Loftsson published a very informative review article regarding the effects of cyclodextrin complexes on the chemical stability of drugs.[74] In another study, inclusion complexes of famotidine were formulated with carboxymethyl-β-cyclodextrin and pronounced enhancement effect on chemical stability in acidic environment of the drug.[75] Improvement in the chemical stability of Voriconazole was also observed by formulating inclusion complexes with cyclodextrin.[62]

Storage stability

Stability studies at different conditions are performed to estimate the shelf life and storage stability of the drugs. Enhancement in the storage stability of the drug is mainly correlated with the shelf life performance of the formulation.[17] Yuan *et al*. formulated the inclusion complexes of astaxanthin with HPBCD and found the better storage stability of inclusion complexes as compared to the native astaxanthin. The enhancement in the storage stability of the astaxanthin due to inclusion complexes also improved the antioxidant activity of the formulation.[76] The formation of inclusion complexes of catechin with β-CD s showed the higher storage stability and provided more protection against temperature, oxygen, and light.[51]

Photostability

Photostability of the drugs is also a fundamental property for the development of new product because photo-degradation may lead to produce toxic products and also reduce the bioavailability of the drugs. Cyclodextrin complexes also improve the photostability of the light sensitive drugs. Enhancement in the stability of α-tocopherol against UV-light was observed by the formation of cyclodextrin complexes. Inclusion complexes of α-tocopherol with β-CD showed higher antioxidant activity and photostability with the help of electro spinning.[77] In a similar study, inclusion complexes of Rhein were formulated with HP-β-CD and observed in the improvement of photostability.[78] Photostability study of flavonoids and geraldol was investigated with β-CD and modified β-CD and found that modified β-CD formed stronger complexes with flavonoids and geraldol as compared to β-CD and also showed higher photostability.[79] Inclusion complexes of Nootkatone (A volatile sesquiterpene with grapefruit like flavor) were formulated with β-CD and HP-β-CD and found that β-CD had superior enhancement for solubility and photostability as compare with HP-β-CD.[80] 13-cis-Retinoic, a high photosensitive compound, showed an increase in the photostability and solubility by formation of cyclodextrin complexes with α-CD and HP-β-CD. Complexes with HP-β-CD showed lesser photo-degradation of 13-cis-Retinoic acid in aqueous medium as compared to α-CD.[81] The complexes of isradipine were prepared with β-CD which enhances the solubility and photostability of the inclusion complex as compared to raw isradipine.[82]

Reduce odors and tastes

Some other organoleptic properties (such as odor and taste) of drugs may also be improved by formation of cyclodextrin complexes. Bitter taste drugs partially or completely encapsulate into the cyclodextrin complexes and precipitate the bitter taste and odor. Bitter taste of drug cetirizine di-hydrochloride was successfully masked by formation of complexes with β-cyclodextrin and this helped in improvement in organoleptic properties and patient compliances toward the product.[83] A comparative study on taste masking capacities of HP-β-CDs and maltodextrins with different APIs was performed and results obtained from e-tongues indicated good taste masking effect of both types of cyclodextrins, but maltodextrins showed some better effect than cyclodextrins.[84] Guo *et al*. also evaluated property of HP-β-CD for masking of bitter taste for 13 drugs by formulating inclusion complexes.[85] Precipitation in the bitter taste of amino acids and hydrolyzed soy proteins was analyzed by formation of inclusion complexes with α-CD.[86]

Permeability enhancement

Permeability of drugs through biological membranes is the most important parameter for determining the oral bioavailability of formulations. Various studies reported in the literature related to cyclodextrin complexes showed that the permeability of drugs was increased or decreased through biological barriers.[87-91] Cyclodextrins increase the drug solubility at the absorption site which may enhance the permeability without changes in the physicochemical properties of the drugs. Some observations indicated that drug permeability of drugs can be enhanced through the barriers using penetration enhancers. Cyclodextrins complexes with penetration enhancers have the additive effect on the permeability of drug the membrane barriers.[26,92-97] Loftsson *et al*. studied the permeability study of testosterone through transdermal delivery from o/w cream through hairless mouse skin using 2-hydroxypropyl-β-cyclodextrin and glycerol mono ether, a penetration enhancer. HP-β-CD showed about 60% increase in testosterone flux whereas extract showed only 40% increase when added to the cream. About 80% increase on the flux was observed when both HP-β-CD and extract were added to the cream.[98] Similar type of comparable effects were observed on the transdermal delivery of prostaglandin E1 using CM-β-CD and a conventional penetration enhancer HPE-101(1-[2- (decylthio)-ethyl]azacyclopentane-2-one) and found that CM-beta-CD also enhanced dermal delivery of the lipophilic penetration enhancer HPE-101.[99-101] The results of another study showed that enhancement in the corneal permeation of timolol maleate was observed by addition of HPBCD and other permeability enhancers whereas decrease in the corneal permeability of drug was observed by addition of both bioadhesive polymer (chitosan, hyaluronic acid, and alginate) and permeability enhancers (HP-β-CD and other) in the formulation.[102] Permeability of paclitaxel was improved by formulating the inclusion complexes with 2-hydroxyproply-β-cyclodextrin and further encapsulating these into the poly(anhydride) nanoparticles and found about 500 times higher drug loading and about 12-fold higher permeability as compared to control formulation.[103] The permeability of cyclodextrins can be increased of water soluble drugs by direct action on mucosal membrane and the drug absorption and bioavailability also enhanced.[104,105]

METHODS FOR CYCLODEXTRIN COMPLEXES FORMATION

Cyclodextrin complexes have attracted the researcher minds for the development of inclusion complexes due to advantages accompanied with these formulations. Various technologies have been used for the synthesis of cyclodextrin complexes formation and discussed here with suitable examples.

Kneading method

In kneading method, the guest substance was dissolved in the solvent and slurry of cyclodextrin added to the solution in mortar pestle and dried at room temperature. The complexes were obtained in solid form and dried

under vacuum. In this method, cyclodextrin complexes with modified physicochemical properties were obtained because the guest molecule entrapped into the cyclodextrin, but this method is suitable for bulk production.[106,107] Inclusion complexes of Ibuprofen were formulated with cyclodextrins by this method and a significant improvement in the solubility and bioavailability was observed. Cyclodextrin complexes of these drugs were formulated by this method and improvement in different physicochemical properties was observed. The inclusion complex formation of cyclodextrins by kneading method has been described by encapsulation of ibuprofen,[108] Omega-3 fatty acids in thymol essential oil,[109] and European anchovy (*Engraulis encrasicolus* L.) oil.[110,111]

Coprecipitation method

Coprecipitation is used for the formation of cyclodextrin complexes of hydrophobic drugs. The guest molecule or hydrophobic drugs were dissolved in organic phase and host molecules were dissolved in aqueous phase. Organic phase solution was dissolved in the aqueous phase solution with proper agitation. The solution was cooled and complexes were washed with organic solvent and dried at 50°C.[112-114] Coprecipitation method was used for encapsulation of drugs such as oxaprozin[115] and trans-anethole (major component of anise and fennel essential oils).[111,116] A performance of inclusion complexes of fenbufen and ibuprofen with β-cyclodextrin was compared by two different methods such as coprecipitation and freeze-drying methods.[117]

Solvent evaporation method

In this technique, guest and host molecules were dissolved separately into the miscible solvents and molecular dispersion was obtained by mixing these solutions. Then, finally evaporated the solvent under vacuum at 45°C and dried mass was passed through the sieve, the solid powdered inclusion complex was collected. This technique is simple and economic and used for both on laboratory and industrial scale. It is considered to be very efficient and alternative of spray drying method.[118] In another study, cyclodextrin complexes of norfloxacin formulated by solvent evaporation method showed higher solubility and dissolution rate as compared to other methods such as physical trituration and kneading methods.[119]

Freeze-drying or lyophilization

This technique is the most suitable technique for the formulation of cyclodextrin complexes of thermolabile and water-soluble drugs and may also have used at large scale production.[120] In this method, drug and polymer were dissolved in a suitable solvent with proper stirring after that the solution was freeze-dried. The solvent was evaporated under the vacuum, and good quality of cyclodextrin inclusion complexes was obtained.[113,121] Many essential oils (such as cinnamon, clove,[122] estragole,[123] black pepper oil,[124] thymol,[109] Kamebakaurin,[125] and chloramphenicol)[126] were encapsulated by the formation of inclusion complexes with cyclodextrins.[111]

Spray drying

Spray dryer can also be used for the formulation of inclusion complexes. In this technique, host and guest molecules were dissolved in common solvent and dried by spray drying technique. Different size of inclusion complexes was obtained by checking the size of atomizer or spray nozzle and other parameters such as sample feeding rate and inlet temperature. For volatile substances, this method reduced the losses and not appropriate for highly volatile or thermolabile substances.[42] Inclusion complexes of Voriconazole with cyclodextrin were formulated by spray drying method and showed higher solubility, dissolution rate, and chemical stability as compared to pure drug.[62] This technique was also used for encapsulated of folic acid in cyclodextrin.[111]

CHARACTERIZATION OF CYCLODEXTRIN COMPLEXES

Structure and properties of cyclodextrin complexes can be characterized by various techniques. Some techniques have been discussed here, are used to evaluate the type of interactions between host and guest molecules, their structure, ability of host to entrap the guest into its cavity, dissolution behavior, thermal analysis, and others properties.

Entrapment efficiency

Entrapment efficiency evaluates about the amount of drug entrapped into the host molecules. Higher entrapment efficiency signifies the more amount of drug entrapped in the host molecule. Entrapment efficiency in cyclodextrin complexes mainly depends on the size of the guest molecules and cavity size of host molecules.[127]

FTIR analysis

FTIR spectra indicate the type of intramolecular or intermolecular interaction between drug and polymer. Drug, polymer, physical mixture, and formulation were evaluated in the range of 4000–400 cm^{-1}. Shifting in the peaks toward higher or lower wavenumber in inclusion complexes indicated the formation of H-bonding between drug and cyclodextrin[128] and also indicated that drug was covered into the cavity of polymer of inclusion complex formation.[129]

Differential scanning calorimetry analysis

The thermal behavior of drugs such as melting point and heat change formulation was studied by DSC. Changes in the melting point during the formation of inclusion complexes indicated the entrapment of the guest molecules into host molecules. The thermogram obtained from DSC during thermal analysis also explained the crystal behavior endothermic or exothermic reaction and formation of new compound.[65]

XRD analysis

XRD technique performs structural analysis based on the spreading of X-rays on the samples. XRD allowed the examination of the solid state structure of material and more advanced technique confirmed the formation of inclusion complexes. Change in intensity and shifting of the peaks indicated the formation of new solid structure.[65,130,131]

Dissolution studies

Dissolution studies are used to evaluate the variations in aqueous solubility of drug during with time in a suitable dissolution medium. The outcomes from solubility studies indicated the performance of the inclusion complex when compared to pure drug. It showed that the evident between drug and polymer complexes presented higher concentrations of dissolved drug from the dissolutions of the samples and it reached the maximum dissolution.[131]

Scanning electron microscopy (SEM):

The surface morphology of different formation was examined by scanning electron microscope. The SEM experiments were conducted to visualize the changes in the surface morphology of drug/polymer. It displayed the size and shape of the inclusion complexes and also confirmed the surface morphology of inclusion complexes.[65]

APPLICATIONS OF CYCLODEXTRINS IN DIFFERENT AREAS

Entrapments of drugs in cyclodextrin complexes alter the physicochemical properties of guest molecules by temporarily locked in the host cavity give rise to beneficial benefits to the guest molecules such as modification in physicochemical properties, controlled release of drug, reduced local, and systemic toxicity.[26,87,132,133] Some recent applications of cyclodextrin complexes related to the pharmaceutical, food, chemical, and other fields have been discussed here.

Cyclodextrins and pharmacy

Cyclodextrin complexes have emerged as a productive approach to improve the physicochemical properties of drugs and drug delivery systems in the pharmaceutical field. Availability of many pharmaceutical formulations in market using cyclodextrins as a functional excipient, demonstrate the utility of the CDs. 100 years after their discovery, with the development of new modified polymers and technologies cyclodextrins are still regarded as novel excipients of unexplored possibilities.[39,134]

Cyclodextrins and nanotechnology

Cyclodextrins complexes with nanosystems have emerged as promising platforms for drug-specific construction of the oral delivery nanosystems able to optimize the desired physicochemical properties and pharmacokinetic parameters; without a compromise on safety. Various studies focused on some recent and encouraging advances in the application of cyclodextrin nanosystems for oral drug delivery.[135-138]

Cyclodextrin in oral drug delivery

Improvement of oral bioavailability of poorly aqueous soluble drugs is the most challenging step for the scientists in formulation and development of dosage forms. Cyclodextrins have unique structures with versatile physicochemical properties which lead to enhance the solubility, stability, and bioavailability of drugs in the gastrointestinal tract. Through the various reported studies, cyclodextrin complexes highlighted the concept of cyclodextrin and its derivatives in enhancing solubility and bioavailability of BCS Class-II drugs.[87,139]

Cyclodextrin in nasal drug delivery

Nasal drug delivery offers a better approach for systemic administration of drugs by avoiding first-pass metabolism or degradation in liver and gastrointestinal tract. Cyclodextrin complexes improve the absorption of drugs through nasal mucosa and increase their solubility and nasal absorption. Various studies related to nasal drug absorption had been reported in the literature with different cyclodextrins and results demonstrated the safety and non-toxicity of cyclodextrins. CDs are able to improve the drug bioavailability, but due to the barrier function of free CDs sometimes disturb the nasal mucociliary functions. Therefore, the concentration and application circumstances of CDs should be considered before nasal administration. Me-β-CDs were primarily found to be beneficial excipients on nasal drug delivery systems.[140-145]

Cyclodextrin in topical drug delivery

Cyclodextrins are available in different size and their hydrophilic outer surface allow only insignificant amount

of cyclodextrins and drug/cyclodextrin complexes able to penetrate through the lipophilic biological membrane. Cyclodextrins increase the topical drug delivery by enhancing the drug availability at the barrier site. The drug molecules partitioned from the cyclodextrin complexes at the lipophilic barrier and absorption of drug from aqueous solution took place by both diffusion controlled and membrane controlled. It was also observed that cyclodextrins only enhanced the topical drug delivery in the presence of water. With the help of penetration enhancers cyclodextrin enhanced the physicochemical and biological properties through topical route. The natural cyclodextrins and their derivatives are used in topical and oral formulations, but only α-CD and the hydrophilic derivatives of β- and γ-cyclodextrin can be used in parenteral formulations.[101] β-CD, applied under occlusion condition onto the skin surface in humans, does not cause irritation or allergenic reaction.[146] Skin compatibility with CDs, both natural and a wide range of derivatives, has been reported by other researchers.[147] In general, all types of CDs can be used in skin and mucosal formulations safely and without risk of irritation; even methylated CDs in low concentrations can be safely applied. Only for aqueous solution/suspension containing high concentration of CDs there is some possibility that methylated CD will interact with the stratum corneum lipids (cholesterol and triglycerides) and temporarily affect the membrane integrity.[148,149]

Cyclodextrin in ocular drug delivery

In general, the permeability of the drug through the membrane (i.e., cornea, conjunctiva, and sclera) is the rate-limiting step for the ocular drug delivery system. For better ocular drug delivery, the drug should be both hydrophilic and lipophilic in nature.[150-152] Cyclodextrins complexes increase the aqueous solubility of some lipophilic drugs without altering the molecular structure and increase the ability to permeate through the biological membranes. Hydrophilic cyclodextrins, especially 2-hydroxypropyl-β-cyclodextrin and sulfobutyl-β-cyclodextrin, are nontoxic to the eye and are well tolerated in aqueous eye drop formulations.[26,153-157]

Cyclodextrins and their capacity to form inclusion complexes

Several studies have shown that, on complexation, it the most hydrophobic part of the host molecule that is preferentially incorporated into the cavity of the cyclodextrin and the encapsulated molecules are oriented in such a way as to maximize the contact between their hydrophobic parts and the apolar cyclodextrin cavity.[158]

Cyclodextrins and their tendency to form aggregates

In recent years, it has been observed that in pharmaceutical applications other types of cyclodextrin complexes such as non-inclusion complexes are also participate in cyclodextrin solubilization of poorly soluble drugs. There are some indications that formation of CD/drug complex aggregates might play an important role in cyclodextrin enhancement of drug bioavailability. The cyclodextrin aggregates present the ability to form complexes, and nanosized aggregates, and nanotube-type host/guest architectures can be envisaged.[24,139,159]

Biomedical applications and biomedicine

At present, the field of medicine is closely concerned with CD inclusion complexes. The best known example is that containing the active compound sugammadex (Bridion): It is a modified γ-CD used as an antidote to certain curare-like muscle relaxants and has been used in anesthesia since 2008.[160] Actually, CDs are perceived as dream molecules for the development of applications in biomedicine and nanomedicine, such as nanoparticles for drug delivery, innovative biosensors for molecular diagnosis and medical imaging, gene therapy, or tissue engineering. Surface grafting or thermo fixation of cyclodextrin such benefit can be achieved by medical devices such as catheters, prosthesis, vascular grafts, and bone implants.[161]

Cyclodextrins and food

Nowadays, in the food industry, the research is increased into the new compounds with high added value in the fortification of traditional products. An antioxidant compound of lipophilic nature is the most promising in food technology.[162] In the literature review, the host/guest molecules complexes in the antioxidant activity they form the different and identical complexation. Natural or modified cyclodextrins are used for the antioxidant compounds and show the bioavailability in the presence of cyclodextrins.[51]

Controlled release of fragrances and aromas

In the chemical industry fragrance and flavor is a large innovative sector in industry.[163] Fragrance is used for consumer products such as personal care products, perfumes, deodorants, and laundry detergents. Encapsulation techniques using CDs are used for improving the efficiency of odorant and aroma substances. Most of the additives in many consumer products are toxic and non-biodegradable. The main advantages of CDs are not only their ability to encapsulate a guest in their cavity to form an inclusion complex but also their no toxicity.[164]

Textiles and cosmetotextiles

Chemical finishing is critical for giving textiles new functionalities and making them appropriate for special applications, such as antimicrobial resistance, flame

retardancy, and others. Textile finishing is critical step for the improvement of appearance and performance. CD is considered as a promising reagent in textile finishing. Cosmetotextiles also meet an increasing demand on the market. Neither cosmetics nor textiles, the microencapsulated ingredients on cosmetotextiles ensure their slimming, hydrating, or perfuming progressive effect on the skin. The cosmetic and textile industries are at the forefront of the research on this topic.[165]

Cyclodextrin-based supramolecular architectures

Indeed, the understanding and the design of supramolecular systems require a detailed characterization with respect to stoichiometry, affinity, structure, heterogeneity, and supramolecular dynamics. Recently, fluorescence correlation spectroscopy has been proposed to the study of the dynamics of different systems.[166-168]

Cyclodextrins and click chemistry

CDs can be used in the click reaction in carbohydrate chemistry for drug discovery and for the generation of various glycoconjugates (glycopeptides, glycodendrimers, etc.). In future, it is believed that CDs will play a very important role in this new developments.[167-169]

Cyclodextrins and sugar-based surfactants

Carbohydrate-based surfactants are today an important class of amphiphilic compounds. The growing interest in such compounds is due to inter alia, their preparation from renewable raw materials, their ready biodegradability and biocompatibility, as well as other more basic reasons of practical, economic, and environmental order. When the complexes of cyclodextrins with carbohydrate-based surfactants considerably increase, their performance and potential applications also spread. The use of these new systems is promising.[167,170,171]

Cyclodextrins and membranes

Membrane technology has spread to reach many domains including separation, purification, and fraction enrichment. This is due to the ability of membranes to work in continuous processes and because they are modular, energy-efficient, and environmentally friendly. It is known that the incorporation of complexing sites in membranes leads to the facilitation of the transport of certain species as compared to others and to the improvement of membrane performance.[172,173]

Cyclodextrins and remediation

Our group described recent developments in the use of cross linked CD-based polymers as complexing polymeric matrixes for pollutant removal by oriented-adsorption processes. From the year 2000 to the present day, numerous researchers have investigated CD materials and polymers for applications that concern complexation of pollutants from the environment. Polymerized cyclodextrin used in various fields such as biomedical, gene delivery, and pharmaceutical is increasing day by day.[168,174,175]

CONCLUSIONS

Various types of solubility enhancement techniques have been used by the researchers for improving the oral bioavailability and other physicochemical properties of the APIs. Among these techniques, cyclodextrin inclusion complexes are useful as carriers and solubilizing agents that have enjoyed widespread attention and use in the pharmaceutical industry. 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. Cyclodextrin complexes are popular among the researchers because of their ability to increase the solubility and bioavailability of the drugs and also used as drug carrier for delivering the drug in different drug delivery systems such as oral, ocular, topical, and nasal. From the literature, studies on both humans and animals have shown that cyclodextrins can be used to improve the drug delivery from almost any type of drug formulations. Cyclodextrins have the ability to form complexes with a large number of compounds and this helps to tailor the solubility and dissolution rate of the molecule and also enhance the bioavailability and permeability through the biological membranes, to increase the various types of stabilities (such as thermal, chemical, storage, and photostability) from light, heat, and other environmental conditions and to decrease the other properties such as taste and odor also. These properties have resulted in the growing importance of the applications of cyclodextrins in pharmaceutical industry and other fields such as food, agriculture, cosmetic, textiles, and fragrance industries. Addition of cyclodextrin complexes with other existing formulations construct a new class of novel drug delivery systems such as liposome, microspheres, osmotic pump, peptide delivery, nanoparticles, and site specific prodrugs.

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