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Research Article

Cyclodextrin: A Novel Excipient for Drug Development

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ABSTRACT

Cyclodextrin's (CDs) are very important excipient in the recent drug development for the pharmaceutical industry due their ability to complex formation and their wide characteristics. Basically, Cyclodextrin's are large molecules which contain number of hydrogen donors and acceptors; thus, they generally do not permeate lipophilic membrane. Mainly Cyclodextrin's are used to enhance the drugs solubility, bioavailability, stability and safety of drug molecules. Because of its supramolecular structure, they carried out chemical reactions that involve intra-molecular interactions. According to structure CDs are three types like α, β and γ cyclodextrin's. Cyclodextrin's can improve the solubility of poorly water soluble drugs through complex formation. Complex formation takes place by several techniques like kneading, co-precipitation method, dry mixing, sealing, slurry-complexation, spray-drying, freeze-drying etc. Because of its various characteristics it is applied in pharmaceutical industry, cosmetics, foods and biotechnology industry. The objective of review article is to describe properties, structure, types, inclusion complex formation and application of cyclodextrin.

Keywords: Cyclodextrin's, structure, types, methods and applications.

INTRODUCTION

Cyclodextrins are oligosaccharides, which consists of six member α-Cyclodextrin, seven member β-Cyclodextrin, eight member γ-Cyclodextrin or more glycopyranose units which is linked by α-(1, 4) bonds. They are also called as cycloamyloses, cyclomeltoses and Schardinger's dextrins. They are prepared by the intra-molecular transglycosylation reaction from the disintegration of starch by cyclodextrin glucanotransferase (CGTase) enzyme[1]. It is assumed that 7 member β-cyclodextrin is less soluble in water (at 25^0 C, 18 mg/ cm^3), the 6-member α-cyclodextrin is better soluble in water (at 25^0 C, 140 mg/ cm^3), and the 8-member γ-cyclodextrin attains the highest solubility in water (at 25^0 C, 220 mg/ cm^3). But also, denoted that a freshly prepared γ-cyclodextrin solution which is far below the saturation level that can always become turbid after few hours or days. If β-cyclodextrin is attached substituent, the solubility increases unlimitedly[2]. All types of drugs should have some degree of aqueous solubility, so they called as pharmacologically active drug and most drugs need to lipophilic so they have ability to permeate biological membranes via passive diffusion. It is considered that oral route is the simplest, safest and most preferred route for drug administration because it has several advantages like versatility, patient compliance, and greater solubility, bitter taste masking ability, better bioavailability and ease of ingestion[5]. It is very important thing that Cyclodextrins are synthesized by degradation processes, which can be possible by development of carbohydrate chemistry, with a special emphasis on Cyclodextrins[6]. If a drug has too much lipophilicity, the dissolved drug molecule having little tendency to partition from the aqueous exterior into the lipophilic membrane (e.g. the eye cornea or gastrointestinal mucosa) and then they can permeated from the membrane. Several screening processes are employed to drug development to increase the solubility of lipophilic water insoluble drug candidates or some other water insoluble drugs.

Cyclodextrins comprises of three industrially prepared major and several rare and minor oligosaccharides. The three major types of Cyclodextrins are basically crystalline, homogenous, non hygroscopic substances. They are like macro-ring built up from glycopyranose units. The α-cyclodextrin comprises of six glycopyranose units, it is also called as Schardinger's α dextrin, cyclomeltohexaose, cyclohexaglucan, cyclohexaamylose, α-CD, ACD, C6A. The β-cyclodextrin of seven such units, it is also called as Schardinger's β dextrin, cyclomeltoheptaose, cycloheptaglucan, cycloheptaamylose, β-CD, BCD, C7A. The γ-cyclodextrin of eight such units, it is also called as Schardinger's γ dextrin, cyclomeltootaose, cyclooctaglucan, cyclooctaamylose, γ-CD, GCD, C8A[2].Cyclodextrins formed during bacterial digestion of cellulose. These cyclic oligosaccharides consists α-(1, 4)-linked α-D-glycopyranose units. It contains a lipophilic central cavity and hydrophilic outer surface. Basically, Cyclodextrins are shaped like a truncated cone rather than a perfect cylinder. This is due to the chair conformation of the glycopyranose units[4,11]. The lipophilic characteristics is due to the central cavity is lined by the skeletal carbon and ethereal oxygen of the glucose residues. Primary hydroxyl groups of sugar residues are

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situated at the narrow edge of the cone and the secondary hydroxyl groups are situated at the wider edge. This lower aqueous solubility is due to relatively strong intermolecular hydrogen bonding in the crystal state, which can be improved by substitution of any of the hydrogen bond forming hydroxyl group, even by lipophilic methoxy functions[11]. Cyclodextrins interacted with hydrophobic drug molecules to form inclusion complexes which can improve the aqueous solubility of the drug molecule[3]. The structure of different types of cyclodextrin are mentioned in figure 1, 2 and 3.

Properties[1,5,6,7]

- Main three types of Cyclodextrins are α-Cyclodextrin, β-Cyclodextrin, γ-Cyclodextrin; they are called as first generation or parent Cyclodextrins.
- They are most accessible, lowest price and generally the most useful excipient.
- Derivatives of Cyclodextrins prepared from the parent Cyclodextrins. The preparation processes are aminations, esterification or esterification of primary and secondary hydroxyl groups of the Cyclodextrins.
- Cyclodextrins are frequently used as building blockers for the construction of supramolecular complexes.
- All derivatives have a changed hydrophobic cavity volume, their modified structure can improve the solubility, stability against light or oxygen and help to control the chemical activity of guest molecules.
- Production of cyclodextrin derivatives requires regioselective reagents, optimization of reaction conditions and a good separation of products.
- Drugs which have bitter tastes can mask the bitter taste if it forms an inclusion complex with an appropriate cyclodextrin.
- In poor water soluble drugs, Cyclodextrins used to improve the solubility and dissolution through complex formation. It also improves drug efficacy and potency and reduces the drug toxicity.

Advantages[11,12,13]

- Cyclodextrins can protect drugs from biodegradation.
- Cyclodextrins can increase product's shelf-life.
- It has very low toxicity.
- They don't have pharmacological activities.
- It is therapeutically inert.
- It is non-irritating.
- Thermally stable up to 300°C.
- Different molecular size of drugs can be entrapped due to different cavity diameter of Cyclodextrins.
- Complex formation can be very easily done.

Limitations[6]

All drugs cannot form complex with Cyclodextrins, for complex formation drugs should have certain characteristics, they are-

- There molecular weight should be between 100-400
- Melting point of the guest substance should be below 250°C.
- Solubility of those substances in water is less than 10 mg/ml.
- Guest molecule should not contain less than five considered rings.

Toxicity

Safety profile and toxicology of three parent cyclodextrin and their derivatives have been studied[39]. They are only able to permeate lipophilic biological membranes, such as the eye cornea. The randomly methylated α- Cyclodextrin does not readily permeate lipophilic membranes. So, it interacts more readily with membranes than the hydrophilic derivatives. After some toxicological studies it has been reported that orally administered Cyclodextrins are non-toxic. Toxicological studies also reported that β-cyclodextrin, 2-Hydroxy propyl-β-Cyclodextrin, Sulphobutylether β-Cyclodextrin, Sulphated β-Cyclodextrin and Maltosyl β-Cyclodextrin are safe even when administration done parenterally. α-Cyclodextrin, β-Cyclodextrin and Methylated β-Cyclodextrin are not suitable for Parenteral administration[1,6,14,15]. Cyclodextrins which are orally administered may cause reversible diarrhea at high doses (>1000 mg/kg/day). The entire three parent Cyclodextrins are accepted as food additives and they 'generally recognized as safe (GRAS). Both α-Cyclodextrin and β-Cyclodextrin can show renal toxicity when they administered parenterally. These products are not indicated for new-born babies and also infants under 2 years old, and for the patient with renal impairment[3].

Types of cyclodextrins

According to Hydrophilicity-

Hydrophilic cyclodextrins

These type of Cyclodextrins used in the modification of release of poorly water soluble drugs and enhance the drug absorption. β-Cyclodextrins are widely used because it is easy to available but it has several limitations like it has low solubility and nephrotoxicity[5]. Hydroxy propyl-β-Cyclodextrins have high water solubility. So, they are mainly used in Parenteral preparation, they are amorphous and have lower haemolytic activities[5,17].

Hydrophobic cyclodextrins

This type of Cyclodextrins forms during substitution of ethyl, acetyl or longer acyl groups on hydroxyl groups of Cyclodextrins[5]. Several hydrophobic Cyclodextrins like ethylated and acetylated β-Cyclodextrins can be used as prolonged-release type carriers for water soluble drugs like diltiazem hydrochloride etc[16].

According to The Structure

α-Cyclodextrin

Properties[1, 6]

- Irritating after intramuscular injection.
- Binds with some lipids.
- It can produce eye irritation.
- 2-3 % absorption takes place after oral administration.
- No metabolism observed in the upper intestinal tract.
- Cleavage is only done by the intestinal flora of caecum and colon.
- Excretion after oral administration to rats- 60% as CO_2, 26-33% as metabolite incorporation, 7-14 % as metabolites in feces and urine, mainly excreted unchanged by renal route after intravenous injection with half-life 25 minutes.

β-Cyclodextrin

Properties[1,6]

- Less irritating than α-cyclodextrin after intramuscular injection.
- It binds with cholesterol.
- 1-2% absorbed in the upper intestinal tract after oral administration.
- No metabolism observed in upper intestinal tract.
- Metabolism done by bacteria in caecum and colon.
- β-Cyclodextrin is most commonly used cyclodextrin in pharmaceutical industry so it is the best studied cyclodextrin in humans.
- Used in high doses may cause toxicity. So, it is not recommended.
- Side effects- Bacterial degradation and fermentation in colon can result gas production and diarrhea.

γ-Cyclodextrin

Properties[1,6]

- It can show insignificant irritation after intramuscular injection.
- Rapid and complete degradation by intestinal enzymes to glucose in the upper intestinal tract (even at high doses, e.g. 10-20 g/kg).
- 0.1% absorption (almost no) after oral administration.
- No metabolization after intravenous administration practically.
- This is very low toxicity forming Cyclodextrin, rather than other parent Cyclodextrins.
- It has less complex forming abilities than β-Cyclodextrin and other water soluble β-Cyclodextrin derivatives.
- When it form complex it has limited solubility in aqueous solutions, which makes the solution unclear (opalescence).

Inclusion complex formation

Most important characteristics of cyclodextrin is their ability to form inclusion complexes (host-guest complexes), with various types of solid, liquid and gaseous compounds by a molecular complex formation. The guest molecule is held within the cavity of the cyclodextrin host molecule. Complex formation will be properly done if the fitting between the host cavity and guest molecule is perfectly done[1,33]. The inner lipophilic cavity of cyclodextrin molecule gives a microenvironment into which appropriate size of non-polar moieties can enter to form inclusion complex[1,34]. The inner cavity of the cyclodextrin is hydrophobic; within it the hydrophobic guest is attached to form a complex which is usually 1:1 complex[37]. One important thing is that no covalent bonds are formed during formation of the inclusion complex[1,35]. The force required for the complex formation is obtained from the release of enthalpy-rich water molecules from the cavity[1]. The most important thing is that binding of guest molecules within the host cyclodextrin is not fixed or permanent. Inclusion complex can affect the physicochemical properties of the guest molecules as they are temporarily locked or caged within the host cavity which gives modifications to guest molecules[1,36].

The inclusion complex formation of Cyclodextrins with a guest molecule depends upon two key factors. One is steric, which is depends upon the relative size of the cyclodextrin to the size of the guest molecule or certain functional groups present within the guest. If the guest is having wrong size related to the host, it will not properly fits into the cyclodextrin cavity. Another one is thermodynamic interactions between the different components of the system (cyclodextrin, solvent, and guest). For a complex formation, energetic driving force pulls the guest into the cyclodextrin[1]. There are two types of complexes, one is inclusion and another one is non-inclusion complexes[11].

There are several instrumental techniques available to characterize the complex formation. For example, Phase solubility, High performance liquid chromatography (HPLC), Circular dichroism, Nuclear Magnetic Resonance (NMR), X-ray powder diffraction (XRPD), Differential scanning calorimetry (DSC), Thermogravimetric analysis (TGA), UV-Vis spectroscopy, Fourier Transform Infrared Spectroscopy (FTIR) and FT-Raman Spectroscopy.

Techniques of Cyclodextrin Complex Formation

Kneading [5,6,38,18]

Kneading technique is almost similar to the wet granulation technique; in this process conventional kneaders are used, like low and high shear mixtures. The complex formation takes place by wetting the physical mixer in a mortar with a minimum volume of water and subsequently kneading continuously with a pastel to obtain a paste. After preparation of the paste, it is dried under vacuum at room temperature. Then the dried powder is sieved through appropriate sieve and stored in a desccicator.

Co-precipitation[6]

Co-precipitation method is widely used method in the laboratory. Inclusion complex of guest molecule of poor aqueous soluble drugs with β-cyclodextrin is prepared by in this method. At fast the guest molecule or the drug is dissolved in minimum quantity organic solvent like acetone. Cyclodextrin is dissolved in water and the guest is added in very minute quantity while stirring the cyclodextrin solution. Cyclodextrin and guest molecule mixture is cooled to room temperature while stirring[6]. Then precipitates are formed. The precipitates can be collected by decanting, centrifugation or filtration[1]. Then it is dried and stored at 25°±2°C and relative humidity of 40-50 %. Sometime the precipitate can be washed with water or other water-miscible solvent such as methanol, ethyl alcohol or acetone.

Dry mixing[6]

In dry mixing the guest molecule or substance is added within the cyclodextrin. They are mixed thoroughly; as a result complex will form. Advantages of this dry mixing are no water or other solvents are needed. But it have several disadvantages like insufficient mixing cannot produce proper complex and it can prolong mixing time. The mixing time depends upon the guest characteristics. In this process washing step is needed. The process is performed under ambient temperature.

Sealing[6]

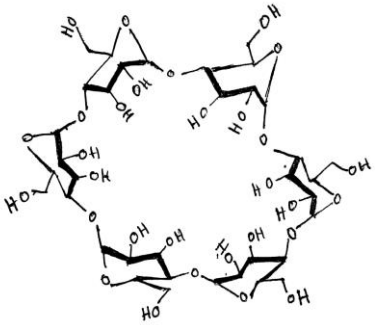

Figure 1: α- Cyclodextrin structure.

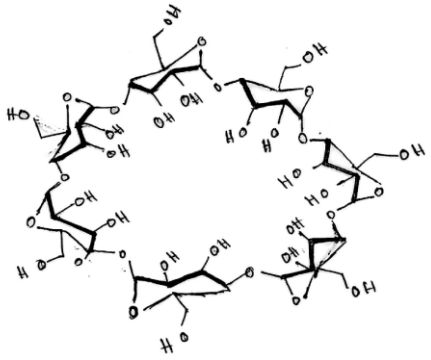

Figure 2: B-cyclodextrin structure.

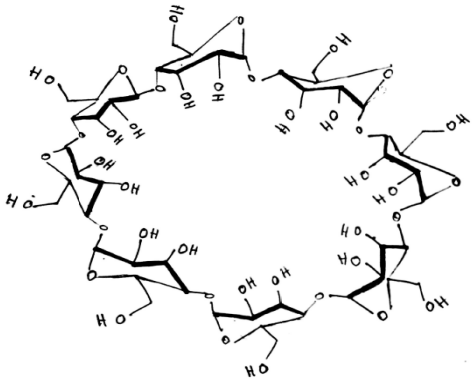

Figure 3: γ-Cyclodextrin structure.

Cyclodextrin-guest complex can be formed by grinding with definite amount of physical mixtures of guest and cyclodextrin. Then the mixture is taken in to a glass container which will be sealed, that's why it is called as sealing method. And then the glass container is stored in 60-90℃ temperature. The conformation about the guest-cyclodextrin complex formation is done by Infrared (IR) Spectrum and powder X-Ray Diffraction.

Slurry-complexation[6]

In this type of process, it is very necessary to dissolve the cyclodextrin to form a complex[1]. Suspension of cyclodextrin in water is formed up to 40-45 % w/w concentration and stirred[6]. The aqueous phase will be saturated with cyclodextrin in the solution[1] and precipitates are formed. The process is carried out under ambient temperature. In some cases heat applied in small amount can improve the complexation but care should be taken because too much heat can destabilize the complex. The formation of complex is depending upon the characteristics of the guest and the r.p.m of stirring.

Spray drying[6]

In this process cyclodextrin dissolved in 200 ml alkalinized solution, the used solution is alkalinized with 25 % aqueous ammonia (final pH 9.5). Then the guest is dissolved in 100 ml of 96 % ethyl alcohol. Both freshly prepared solutions are mixed and sonicated. Then the final mixture solution is spray dried to get the complexes[6]. Then the final mixture solution is spray dried to get the complex.

Freeze-drying (lyophilization[6]

In this method the physical mixture of guest and cyclodextrin is wetted with the minute quantity of buffer solution and then kneading process can form a homogenous suspension which is then freeze dried. The final product then pulverized and sieved through an appropriate sieve. This process is very time consuming. It is used for heat labile guests. But in this process excessive amount of cyclodextrin is needed because of the low solubility of hydrophobic guest in guest in aqueous solution.

Name of other techniques that are used for complexation with cyclodextrins are- Solvent Evaporation[6], Neutralization[6], Paste Complexation[1], Damp Mixing[1], Extrusion[1] etc.

Applications

In pharmaceutical technology

- Bioavailability enhancement[8], active stabilization, odor or taste masking[8], irritation reduction and material handling benefits[6].
- Enhancement of drugs aqueous solubility[8], minimization of toxic effects, reduction of tissue irritation and lesser or no precipitation of drug in the physiological pH[6].
- Stabilization of light or oxygen sensitive substances[1].
- Modification of the chemical reactivity of guest molecules[1].
- Fixation of very volatile substances[1].
- Modification of liquid substances to powders is possible[1].
- Catalytic activity of Cyclodextrins with guest molecules[1].

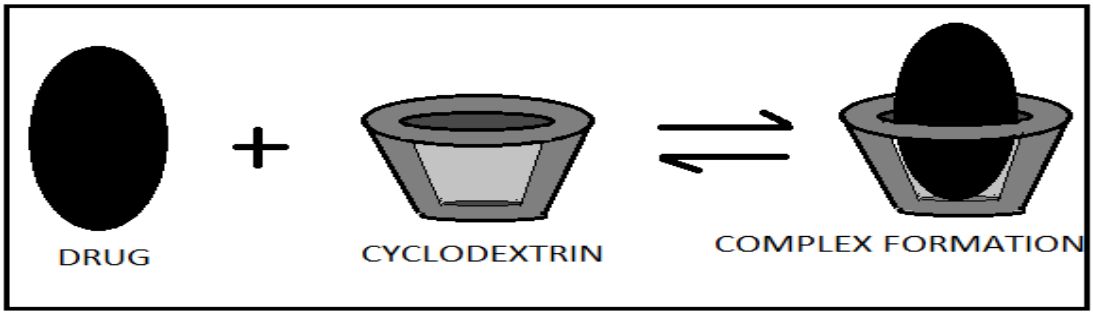

Figure 4: Drug-Cyclodextrin complex formation.

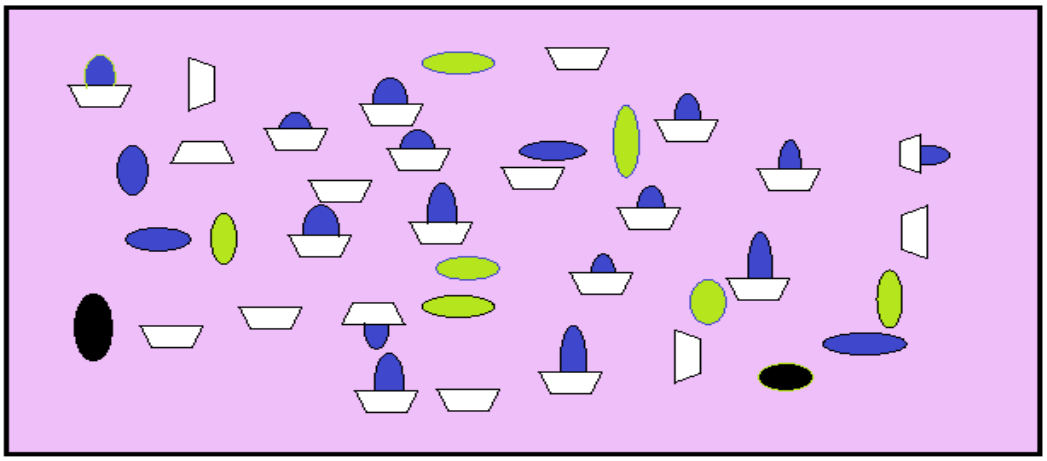

Figure 5: Inclusion and Non-inclusion Complex Formation.

Free drug molecule

Drug in an inclusion complex

Drug in a non inclusion complex

Empty cyclodextrin molecule

Drug -cyclodextrin inclusion complex

- Masking pigments or the color of substance[1].
- Protection against degradation of various substances by micro organisms[1].

In food industry

- It can protect lipophilic food components that are sensitive to oxygen, light or heat.
- Protection can convert the liquid food ingredients to solid powders.
- It can mask unpleasant taste and odors.
- Controlled release of food ingredients.
- Maintains the food quality during storage.
- B-Cyclodextrin can remove cholesterol from milk, to produce dairy products low in cholesterol[1,9,32].

In biotechnological field[6]

- Cyclodextrins and its derivatives can enhance the solubility of complexed substrates in aqueous media; also it can reduce their toxicity without damaging the microbial cells or the enzyme.
- It can use into the microbial transformation processes in the fermentation medium.

In cosmetics and personal care[6]

- It is used in deodorant sticks and is able to complex perspiration malodors.
- Minimize or prevent skin irritation.
- It can increase or decrease the absorption of various compounds into skin.
- Eliminate undesired odor.
- It can increase the physical and chemical stability of guest molecules by protecting against decomposition.

Role of cyclodextrins when used with chemotherapeutic agents

Poor aqueous solubility and rate of dissolution can affect the formulation and development process of drugs and also can alter therapeutic application[4,10]. Poorly soluble drugs which belong to BCS Class II or Class IV of Biopharmaceutical Classification System, administration through different routes are very challenging process[4,19]. Most of the cytotoxic anticancer drugs belong to the BCS Class IV (low solubility, low permeability)[4,24]. Cyclodextrin complex formation came into existence and presented a great interest[4,25,26]. Combined approach of cyclodextrin and nanotechnology has emerged as a novel plan to improve such formulation problems[4,23,24,25]. Chemotherapy for cancer has limited therapeutic effect, very low aqueous solubility (hydrophobicity), degradation in gastrointestinal fluids, insufficient in vitro

Different routes of administration[11, 31]

Name of Cyclodextrin	Routes of Administration									
	Oral	Dermal	Topical	Sublingual	Rectal	Buccal	Eye drops	I.M	I.V	Nasal spray
α-Cyclodextrin	Yes	No	No	No	No	No	No	No	Yes	No
β-Cyclodextrin	Yes	Yes	Yes	Yes	No	No	No	No	No	No
γ-Cyclodextrin	No	No	No	No	No	No	No	No	Yes	No
2-Hydroxy Propyl β-Cyclodextrin	Yes	No	No	No	Yes	Yes	Yes	No	Yes	No
Randomly Methylated β-Cyclodextrin	No	No	No	No	No	No	Yes	No	No	Yes
Sulfobutylether -β-Cyclodextrin	No	No	No	No	No	No	No	Yes	Yes	No
2-Hydroxy Propyl γ-Cyclodextrin	No	No	No	No	No	No	yes	No	Yes	No

solubility (half-life), low bioavailability, short in vivo stability (half-life), affinity for intestinal and liver cytochromic P450 (CYP 3A4) and P-glycoprotein (P-gp) in the intestinal barrier, poor intestinal permeability and dose depended side effects are several problems related to cancer treatment[4,26]. Toxic effects due to lack of selectivity and short blood circulation time are also major problems[4,27]. Because of the narrow therapeutic index of some anti-cancer drugs, they damage not only cancer cells but also damage the normal and healthy tissue is a major challenge. Multidrug resistance are formed due to increase efflux pumps such as P-glycoprotein (P-gp) in the cell membranes which can carried most of anti-cancer drugs out of the cell, is also major problem[4,28,29]. This is necessary to develop such formulations, which combines safety, efficacy and convenience. Cyclodextrin have several characteristics to overcome such drawbacks of anti-cancer drugs. Encapsulation process of cyclodextrin complexed drug into carriers increases the drug loading capacity and entrapment efficiency. It can prolong the existence of the drug in the systemic circulation. It can reduce toxicity and provides controlled sustained or targeted release. CDs can produce a valuable product. Drug-Cyclodextrin complex can lower aggregation. It can improve ADME [Absorption, Dissolution, Metabolism, Excretion] properties, toxicity related problems[4,30].

CONCLUSION

Complex formation of Cyclodextrins with a wide variety of organic compounds improves the apparent solubility of the guest molecule, and also increases the stability of compound in the presence of light, heat and oxidizing conditions and decrease volatility of compound. The complex formation techniques of CDs with drugs are used for preparation of a new class of novel drug delivery systems like liposomes, microspheres, nano particle and targeted drug delivery system. CDs plays a very important role in Parenteral and topical formulations because it replaces the use of organic solvents. It can enhance the bioavailability of BCS Class II and some BCS Class IV drugs. It can also reduce gastrointestinal irritation and can increase dermal availability of drugs. Research process on both human and animal have shown that CDs also play very important role in the anti-cancer treatment; it can improve the delivery of anti-cancer drugs. lodextrins can be used to improve drug delivery from almost any type of drug formulation. As a conclusion it plays a remarkable role for drug development in pharmaceutical industry.

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