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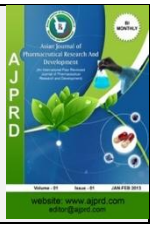

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Review Article

Beta-Cyclodextrin As An Excipient In Drug Formulation

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A B S T R A C T

After its discovery nearly 30 years ago, (2-Hydroxy –propyl) Beta –Cyclodextrin, a highly soluble derivative of Beta –Cyclodextrin, has been an authorized excipients of drug formulation in both the US and European pharmacopoeia. It is recommended for use in oral and parenteral formulations as a solubilizer and stabilizer. The majority of medications taken by mouth have low aqueous solubility and dissolution rates. Beta-Cyclodextrin that has been chemically modified Dynamic complex formation used to enchance the Low aqueous solubility, slow dissolution rate, and reduced drug stability. Cyclodextrin form inclusion complexes with appropriately sized guest molecules to improve aqueous solubility, physical chemical stability, and bioavailability of drugs. Cyclodextrin is a group of compounds made up of glucose monomers arranged in a donut form. They are non-reducing, crystalline cyclic oligosaccrides with a truncated core that produces a hydrophilic outer surface. Cyclodextrin and its derivatives have become common modalities for increasing oral bio availability and absorption rate as a result of these effects. Cyclodextrin has been positioned as an effective facilitating and usable excipients. This article discusses the widespread use of Cyclodextrin as excipients in drug formulations as well as recent Cyclodextrin developments.

Key Words: Beta –Cyclodextrin, Cyclodextrin, Drug Formulation

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INTRODUCTION

Cyclodextrin are cyclic oligosaccharide-based on molecular cages in the form of a cup. They are new excipients that contain glycopyranose units and exhibit amphoteric properties, such as a lipophilic central cavity and a hydrophilic outer surface[1 2]Cyclodextrins are a homologous group of cyclic glucans made up of alpha 1, 4 glucose units bound together[2]. [3]They are produced by the action of Cyclodextrin glucano transferase on staphylococcus aureus. Because of their ability to form inclusion complexes with a wide range of drugs, Cyclodextrin can significantly improve pharmaceuticals' aqueous solubility[3]. [4]Formulators faces ongoing solubility problems, as approximately 40% of marketed drugs are labeled as practically insoluble. As most drugs in production indicate, there are little chances of change in the coming decades.

ADVANTAGES

1. CDs aid in the aqueous solubility of certain medications that are poorly soluble in water.
2. CDs help to improve drug bioavailability by increasing dissolution.
3. Drugs' chemical, physical, and thermal stability are improved by CDs complexation
4. CDs inclusion complexation reduces the irritancy of the drug moiety, which can irritate the stomach, skin, or eyes.
5. Drugs' unpleasant odour and bitter taste are masked by CDs.
6. Using CDs to transform oily or sticky liquids into microcrystalline or amorphous powders improves material handling properties.
7. CDs aid in the reduction of drug-related side effects.
8. CDs have also been used in the development of novel pharmaceutical applications[4].

TYPES OF CYCLODEXTRINS

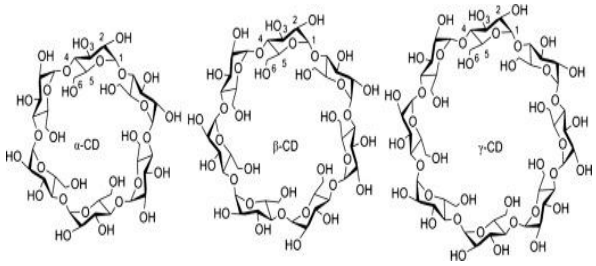

Figure 1: structure of Cyclodextrin

α -Cyclodextrin: six membered sugar ring molecule

β -Cyclodextrin: seven membered sugar ring molecule

γ -Cyclodextrin: eight membered sugar ring molecule[5]

Cyclodextrin History:

A Willers, a French scientist, isolated bacterial digest from starch in 1981. (Villers et al 1891, Loftson et.al., 2007). Villers called the substance Cellusion Later, an Australian microbiologist, Franz Schardinger, identified two crystalline compounds, alpha-dextrin and beta-dextrose, he isolated from a bacterial digest of potato starch.

CDs' structure:

CDs are cyclic oligosaccharides made from starch by bacilli (Bacillus macerans and B circulans) that contain cycloglycosyl transferase amylases. Three main types of CDs are generated depending on the exact reaction conditions and CD, which each contain six to eight dextrose units. CDs are ring molecules with no free rotation at the level of bonds between glycopyranose units they are cone-shaped. The properties of CDs can be modified by substituting different functional groups on the CDs ring. Substituting the hydroxyl group of CD by chemical and enzymatic reactions by variety of substituting groups like hydroxypropyl–, methyl–, carboxyalkyl–, thio–, tosyl–, amino–, maltosyl–, glucosyl–, and sulfobutyl –ether–groups to β–CD can increase the solubility. Solubility of nonpolar solutes occurs due to the nonpolar nature (lipophilic) of the internal cavity of CDs rather than cylindrical[6,7,8]. [9]The active molecule is incorporated into a hollow tapered cavity with a depth of 0.79 nm on CDs. Main hydroxyl groups are on the narrow side, while secondary hydroxyl groups are on the broader side[9. 10]The polar structure (hydrophilic) of the CDs' external component, on the other hand, aids in the solubilization of the CDs and drug in aqueous solution.Nature CDs are commonly soluble in certain polar, aprotic solvents, but insoluble in most organic solvents due to these characteristics.Despite the fact that CDs are more soluble in certain organic solvents than in water, inclusion complexes do not form in nonaqueous solvents.Although inclusion complexes do not form in nonaqueous solvents because the guest molecule's affinity for the solvent is greater than its affinity for water.CDs can be hydrolyzed by strong acids including hydrochloric acid and sulfuric acid[10].[11]Cyclodextrin and its derivatives are commonly used as solubilizer, lubricants, and adhesive. A drug delivery system is intended to effectively and precisely deliver the appropriate amount of drug to the desired site for the required period of time.To overcome the undesirable properties of drug molecules, various carrier materials are constantly being created.Cyclodextrins are one of the most versatile aids in pharmaceutical science.These come with a variety of distribution options[11].

Cyclodextrin Synthesis

The synthesis of Cyclodextrin is relatively easy and requires the use of a series of readily available enzymes to treat ordinary starch.CGTases (Cyclodextrin glycosyltransferases) and -amylase are commonly used.After liquefying the starch with heat or -amylase, CGTase is applied to complete the enzymatic conversion.CGTases can synthesise all types of Cyclodextrin, so the end product is a mixture of the three main types of cyclic molecules, in ratios that are strictly dependent on the enzyme used[12]. [13]Each CGTase has its own unique synthesis ratio.Purification of the three different forms of Cyclodextrin takes advantage of the molecule's different water solubility.The less water soluble -CD can be easily recovered by crystallisation, while the more water soluble and -CDs are normally filtered using costly and time consuming chromatography techniques.Alternatively, during the enzymatic conversion process, a "complexing agent" may be added: such agents (usually organic solvents like toluene, acetone, or ethanol) form a complex with the Cyclodextrin output[13] [14]Treatment of starch with Bacillus macerans amylase yields a crude Cyclodextrin mixture that was difficult to purify because it also contained many other linear and branched dextrin, as well as small quantities of proteins and other impurities. The biotechnological developments of the 1970s resulted in significant improvements in their development. By incorporating the drug molecule, or more generally a lipophilic moiety of the molecule, into the central cavity, Cyclodextrin may form dynamic molecular inclusion complexes with a variety of drugs[14].

During the development of the drug/Cyclodextrin complex, no covalent bonds are formed or broken. The release of enthalpy-rich water molecules from the cavity is one of the driving forces that leads to the creation of inclusion complexes. Vander Walls interaction, electrostatic interaction, hydrophobic interaction, hydrogen bonding Charge transfer interaction and conformational strain release[15], [16,17]Both the armed forces. The stability constant (k1;1) for most drug molecules is between 50 and 2000 mol-1, with mean values of 129,490 and 355 mol-1 for alpha beta and gamma Cyclodextrin, respectively[16,17], [18,19,20,21]Complex D+CD D/CD. The concentration of free drug is constant and equal to the drug's apparent intrinsic solubility in water. When a medication is encapsulated in Cyclodextrin, its psychiological properties, such as aqueous solubility and chemical stability, are altered. The Cyclodextrin molecule forms a hydrophilic shield around the drug molecule's relevant lipophilic moiety.

This would increase the drug's apparent aqueous solubility, and Cyclodextrin will also shield chemically labile drug molecules from corrosive environments. As a result, drug hydrolysis, degradation, racemization, and enzymatic decomposition are reduced or even prevented.[18, 19, 20, 21]

Approaches for Making Inclusion Complexes

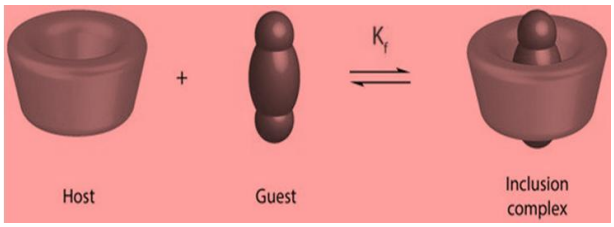

Figure 2: Inclusion complex

Physical Blending Method:

To obtain the desired product, the method involves homogeneous mixing of the physical mixture of drug and CD, followed by passing the mixture through a suitable sieve.

Kneading Method:

The drug and CD are grinded with extreme trituration for about 30 minutes in this process. To achieve a pasty consistency, the mixture is kneaded with hydro alcoholic solution. The mass is then dried for 1 hour at 40°C, deposited overnight in vacuum desiccators, and sieved to obtain the desired product [22].

Solvent Evaporation Method:

The molecular dispersion process, also known as the solid dispersion method, entails stirring an alcoholic drug solution and an aqueous CD solution to achieve a molecular dispersion, accompanied by evaporation of the solvent under vacuum until dried mass is produced. To obtain the complexed product the dried mass is pulverised and sieved[23].

Spray Drying Method:

A popular technique involving the preparation of a monophasic solution of drug and Cyclodextrin in a suitable solvent system, usually ethanol: water 50% v/v.The resulting mixture is then stirred at room temperature for 24 hours to achieve equilibrium, after which the solvent is sprayed out.The drug's interaction with the body is sufficient and efficient

Freeze Drying Technique

This technique is also known as lyophillisation and is used to create a porous, amorphous powder. A magnetic stirrer is used to disperse a stoichiometric volume of medication and CDs in a hydro alcoholic solution. The resulting solution is frozen and lyophilised under reduced pressure in a freeze dryer after agitating for a set amount of time. This technique works well with thermolabile compounds.[24]

***Microwave Irradiation Technique*:**

This method involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. This is a novel method for industrial scale preparation which requires a shorter reaction time and higher aim product[25,26] .

Melting:

This method involves melting excess amount of guest followed by mixing with powdered CD. The drug-CD mixture is cooled and the excess amount of guest is then removed by carefully washing with weak complex forming solvent or by sublimation under vaccum[27]

Supercritical Anti-solvent Technique:

Carbon dioxide is used as an anti-solvent for the solute but as a solvent for the organic solvent in this technique. After dissolving the drug and CD in a suitable solvent, the solution is fed through a nozzle into a pressure vessel containing supercritical fluid anti-solvent. The anti-solvent quickly diffuses into the liquid solvent as the carrier when the solution is sprayed.

High Pressure Homogenization Method:

In this technique, drug and CD in an appropriate solvent are mixed together and the passed through a high-pressure homogenizer causing the disintegration of particles and dispersion throughout the product. The eventual solution was filtered and evaporated to dry Because of the peculiar nature of their arrangement. Cyclodextrin can form host-guest complexes with hydrophobic molecules. As a result of their multifunctionality, CDs can be used in almost every drug delivery system, including oral, ocular, and novel drug delivery system.[28,29]

Application of Cyclodextrin:

Because of the peculiar nature of their arrangement, Cyclodextrin can form host-guest complexes with hydrophobic molecules. As a result of their multifunctionality, CDs can be used in almost every drug delivery system, including oral, ocular, and novel drug delivery systems. [30]

Cyclodextrin in Oral Drug Delivery:

Nearly 40% of the new chemical entities currently being discovered are poorly water soluble drugs, thus to enhance their efficacy is a challenging task in drug development. The most common pharmaceutical application of CDs in oral drug delivery includes enhanced drug solubility in aqueous solutions thus resulting in an enhanced dissolution and bioavailability, and stability of the drug at the absorption site or in formulation, reduction of drug induced irritation, and taste making. Aside from that, CDs could be used as modified release carriers for water-soluble drugs including proteins and peptides. By preparing solid dispersion, the drug's solubility was successfully increased to 9.69 mg/ml at pH 6.8 with -CD inclusion complex, compared to 2.09 mg/ml for pure drug. The hydrophobic properties of Cyclosporine A limit its use in asthma inhalation therapy. Complex formation with maltosyl-CD, on the other hand, not only decreased the effective drug dose but also increased the therapeutic safety margin when Cyclosporine was inhaled. Repaginate, an anti-diabetic medication, with HPCD using the lyophillisation technique revealed an increased solubility of the drug. Drugs' bitter taste and odour can be masked by creating an inclusion complex with the drug[31,32,33,34,35,.

Cyclodextrin in Ophthalmic Drug Delivery

For topical administration into the eye, a variety of drug formulations are available in the form of suspensions, eye drops, ointments, gels, and solid inserts. However, the

majority of these formulations are linked to negative side effects such as eye irritation, blurred vision, and pain. When formulating drugs for ocular delivery, drug solubility and stability must also be taken into account.[36,37]

CDs, in particular, the following are some of the advantages of using CDs in ocular formulations:

i. Drug release is sustained.

ii. Improving drug solubilization and chemical stability.

iii. Increased medication permeability in the eyes.

iv. Less fatigue and pain from ophthalmic drugs.

This drug delivery system enhances both the drug solubility in aqueous eye drops and the drug permeability via the rabbit cornea by combining the drug zinc-diethyldithiocarbamate with HP—CD complexation, as well as the addition of polymers and penetration enhancers. Indomethacin, a water-insoluble anti-inflammatory compound, was given an aqueous ocular delivery system[38].

Cyclodextrin in Transdermal Drug Delivery

The topical availability of drugs is determined by the drug's ability to dissolve in the vehicle (base) and permeate the skin barrier in order to have an effect.The majority of medications, however, fail to fulfill this one-of-a-kind amphiphillic nature criterion. Hence, formulations require incorporation of excipients like permeation enhancers, solubilizer etc. that can overcome the problems of either or both of the transport processes (i.e. dissolution into vehicle and diffusion across skin)The main limitation of this route is to overcome the stratum cornium, the outermost skin barrier In order to achieve therapeutic concentrations and to improve the drug flux, permeation enhancers are used to optimize drug permeation through the skin. CDs play an important role in dermal drug delivery, both locally and systemically.

The following are some of the advantages of using CDs in Transdermal drug delivery:

i. Improved drug release and/or permeation.

ii. Drug stabilization in the formulation or at the absorption site

iii. Improved lipophilic drug solubilization

iv. Reduction of local inflammation caused by drugs.[39]

Nasal Drug Delivery

Drugs with high potency can be delivered systemically through the nasal mucosa. Due to extensive gastro-intestinal breakdown and a high hepatic first-pass effect, this novel approach is useful for drugs with poor oral bioavailability. Nasal delivery of lipophilic drugs is possible if they can be dissolved in the dosage form. CDs are non-toxic and stable, making them useful excipients for nasal drug delivery because they can improve drug absorption by improving aqueous solubility, drug permeability, or both. Through the rapid and reversible development of inclusion complexes, hydrophilic CDs increase membrane permeability by solubilizing certain basic lipids from biological membranes. Aside from that, they can reduce nasal toxicity and serve as a carrier for long-term drug release through the nasal mucosa. HP—CDs and methylated -CDs have mostly been used as solubilizer and absorption enhancers in pharmaceuticals.[40]

Cyclodextrin in Liposomal Drug Delivery

The main goal of liposomal drug delivery is to combine the benefits of CDs, like improved drug solubility, with the benefits of liposome's, like drug targeting. A novel drug delivery design takes advantage of the properties of drug "containers" such as Cyclodextrin and liposome to incorporate them into a single system, avoiding the issues that both systems have. The idea is to entrap water-soluble Cyclodextrin drug inclusion complexes in liposome, allowing insoluble drugs to be accommodated in the aqueous phase of vesicles. The development of a new delivery mechanism with enhanced therapeutic efficacy of the local anesthetic, prilocaine, has been investigated using a combined approach focused on Cyclodextrin complexation and loading in liposome (PRL). In comparison to formulations containing, respectively, free PRL in the lipophilic phase or PRL hydrochloride in the aqueous vesicle core. Cyclodextrin complexation not only allowed for efficient encapsulation of PRL base in the aqueous vesicle core, but also increased the anesthetic effect period and reduced the initial lag time. Curcumin is a water-insoluble compound with anti-inflammatory properties[41].

Cyclodextrin in Microspheres

CDs may be used as a polymer in microspheres, which can increase the therapeutic effectiveness of the medication and patient compliance. The ability of CDs to stabilize -chymotrypsin after encapsulation in Poly (lacticco-glycolic) acid (PLGA) microspheres was investigated using the solid-in-oil-in-water (s/o/w) method. The findings indicate that MCD may be effective excipients for improving efficiency. The stabilizing effect was attributed to the proteins' increased hydrophilicity, which was caused by HP—CD shielding their hydrophobic residues. Spray drying was used to make theophylline chitosan/-Cyclodextrin microspheres with a long release time. Within 8 hours the microspheres showed a prolonged release trend, with a release rate of 60.20 percent (pH 6.8).

Cyclodextrin in Nanoparticles

Because of their low drug loading and entrapment performance, Nanoparticles' protection and efficacy are restricted. CDs aided in the design of Nanoparticles by increasing drug loading potential and facilitating the spontaneous creation of Nanocapsules or Nanospheres from amphiphillic CDs diester nanoprecipitation. As a result, the best option for providing targeted drug delivery and enhance owing to side effects associated with the solubilizer used and the drug's propensity to precipitate in aqueous media.. Amphiphillic Cyclodextrin Nanoparticles have emerged as a promising alternative formulation for injectable paclitaxel administration that is both safe and efficientcing[42]

Recommendations for the Guidelines:

The European Commission Guideline on Excipients in the Label and Box Leaflet of Pharmaceutical Products for

Human Use currently excludes cyclodextrins. Despite the fact that Cyclodextrin have a low oral supply, high doses may induce reversible diarrhea and cecal enlargement in animals, and thus to some degree in humans. Cyclodextrin can cause allergic reactions depending on the amount consume at high systemic exposure Cyclodextrin can cause Nephrotoxicity in animals. There has been no evidence of these effects in humans to date, but data in children under the age of two is scarce[3]In items containing Cyclodextrin as excipients, safety information in the box leaflet is desirable. The safety aspect of Cyclodextrin is complicated due to their complex behavior[43]

Table:1 Approved pharmaceutical products:

Drug/Cyclodextrin	Trade name	Indication	Formulation	Company/country
PGE2/□ CD	Prostarmon E	Induction of labor	Sublingual tablet	Ono, Japan
PGE1/□ CD20 µg/amp	Prostavasin .Edex	Chronic arterial occlusive disease erectile disfunction	Intraarterial inj intracavern inj.	Ono, Japan, Schwarz, Germany
PGE1/□ CD	Prostandin 500	Controlled hypotension during surgery	Infusion	Ono, Japan
OP-1206/□ CD	Opalmon	Buerger's disease	Tablet	Ono, Japan
Piroxicam/□ CD	Cicladol, Brexin	Anti-inflammatory, analgesic	Tablet, sachet, and suppository	Masterpharma, Chiesi, Italy
Garlic oil/□ CD	Xund, Tegna, Allidex Garlessence	Antiartherosclerotic	Dragees Bipharm,	Hermes Germany Pharmafontana, H, CTD, USA
Benexate/□ CD	Ulgut, Lonmiel	Antiulcerant	Capsules	Teikoku, Japan Shionogi, Japan
Iodine/□ CD	Mena-Gargle	Throat disinfectant	Gargling	Kyushin, Japan
Dexamethasone, Glyteer/□ CD	Glymesason	Analgesic anti-inflammatory,	Ointment Fujinaga	, Japan
Nitroglycerin/□ CD	Nitropen	Coronary dilator	Sublingual tablet	Nippon Kayaku, Japan
Cefotiam-hexetil/□ CD	Pansporin T	Antibiotics	Tablet	Takeda, Japan
Cephalosporin (ME 1207)/□ CD	Meiact	Antibiotics	Tablet	Meiji Seika, Japan
Tiaprofenic acid/□ CD	Surgamyl	Analgesic	Tablet	Roussel-Maestrelli, Italy
Diphenhydramine.HCl chlortheophylline+□ CD	Stada-Travel	Travel sickness	Chewing tablet	Stada, Germany
Chlordiazepoxide/□ CD	Transillium	Tranquilizer	Tablet	Gador, Argentina
Piroxicam/□ CD	Flogene	Anti-inflammatory analgesic for pediatric use	, Liquid	Aché, Brasil
Hydrocortisone/HP□ CD .	Dexacort	Mouth wash against aphta, gingivitis, etc	Liquid	Island
Itraconazole/HP□ CD	Sporanox	Esophageal candidiosis	Liquid	Janssen, Belgium
Cloramaphenicol/ methyl □ CD	Clorocil	Eye drop, , antibiotic agent	Liquid	Oftalder Portugal
Cisapride/□ CD Prepulsid	Coordinax	Gastrointestinal mobility stimulant	Rectal suppository	Janssen, Belgium
Nimesulide/□ CD	Mesulid Fast Nimedex	Nonsteroid anti-inflammatory	Oral sachet	Novartis (LPB), Italy
Nicotine/□ CD	Nicorette Nicogum		Sublingual tablet chewing gum	Pharmacia Upjohn, Sweden, Pierre Fabre, France
Dextromethorphan/□ CD	Rynathisol	Antitussive		Synthelabo, Italy
Omeprazole/□ CD	Omebeta	Proton pump inhibitor	Tablet	Betapharm, Germany
Mitomycin/HP□ CD	MitoExtra Mitozytrex	Anti-inflammatory	Infusion	Novartis, Switzerland
Diclofenac Na/HP□ CD	Voltaren ophtha	Nonsteroid anti-inflammatory	Eye drop	Novartis, Switzerland
Cetirizine/□ CD	Cetirizin	Antiallergic		Losan Pharma, Germany
Ziprasidone mesylate/ sulphobutyl □ CD	Zeldox, Geodon	Antischizophenic	i.m. inj.	Pfizer, USA
Voriconazole sulfobutyl-□ CD	VFEND®	Antimycotic	i.v. inj	/. Pfizer, USA
Tc-99 Teboroxime/HP□ CD	Cardiotec	Radioactive imaging agent	i.v. inj	. Bracco, USA
17-□-Estradiol/Me□ CD	Aerodiol	Nasal spray	Liquid	Servier, France

CONCLUSION:-

The Proposed Review on Cyclodextrin looks at its utility as a useful functional excipients that has gotten a lot of attention and is widely used in the pharmaceutical industry. Cyclodextrin bioadaptability and multifunctional characteristics allow it to mitigate the undesirable properties of drug molecules in various routes of administration by forming inclusion complexes.

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