Yashfeen Journal of Health Innovation & Practice
ISSN Online: 2959-5800

Research Article

CYCLODEXTRINS, THEIR PROPERTIES AND USES OF B-CYCLODEXTRIN IN DIFFERENT INDUSTRIES: A REVIEW

Fahmeed Nasir [*]

Abstract

Cyclodextrins are a family of cyclic oligosaccharides composed of α-(1,4) linked glucopyranose subunits. All cyclodextrins are produced due to the transformation of starch by the bacteria e.g. Bacillus macerans. This whole procedure comprises of 4 phases. There are three basic types of cyclodextrinsnamely Alpha, beta and gamma cyclodextrins. Upon I.V injection the alpha-cyclodextrin is the most irritatating. There is a directly effect of temperature on solubility of cyclodextrins as the temperature increases the solubility increases. All cyclodextrins are heat stable and are non hygroscopic in nature. These are chemically stable compounds and are hydrolyzed by cyclodextringlucosyltransferase (CGT-ase) the enzyme used to produce cyclodextrins.Complexes are typically formed with organic compounds and these complex formations are either reversible or irreversible.Among all three types beta cyclodextrins and their derivatives are widely used in different industries due to their some distinguished properties e.g. most accessible, the lowest-priced, less irritating, and diameter etc. The major industrial uses of beta cyclodextrins and their derivatives includes in cosmetology, in food industry, in laundry, as deodorants, tobacco industries, decrease in undesirable effects, increase solubility, prolonged release of active ingredients.

Keywords: Cyclodextrins, cyclodextrin glucosyltransferase (CGT-ase), complex formations.

Introduction:

Cyclodextrins are cyclic oligomers of a-Dglucopyranose. These are produced by the transformation of starch. Bacterias play an important role in their production. The most common example of these bacterias is *Bacillus macerans.* When cyclodextrins were dicoverd, the common concideration was “these are poisonous substances” but later on it was proved by the researchers that the cyclodextrins are non toxic and also helpful in various walks of life as they protect flavours, vitamins and natural colours.(Jeang, Lin, & Hsieh, 2005)

The preparation process of CDs consists of four principal phases:
Phase I: Production of cyclodextrin glucosyltransferase enzyme (CGT-ase) by the culturing of microorganism.
Phase II: Separation, concentration and then purification of the enzyme from the fermentation medium;
Phase III: Enzymatical conversion of pre hydrolyzed starch in mixture of cyclic and acyclic dextrins.

[*] *Sr. Lecturer Yashfeen College of Pharmacy.*

Corresponding author:
Fahmeed Nasir
Email Address: fahmeed.nasir@yes.edu.pk

Phase IV: Separation of CDs from the mixture, their purification and crystallization.

The simple role of CGT-ase enzyme is to degrade the starch and production ofintramolecular reactions without the water participation. There are basicthree types of CD's. These are alpha- (6 glucose units), beta- (7 glucose units), and gamma- cyclodextrin (8 glucose units). The subunit of the structures (glucose) is rigid, the cyclodextrin molecule possesses a cavity, even in the absence of a guest. The dimensions of the cavitiesare always comparable to the molecular dimensions of many simple organic molecules. In structure the inner part which is known as interior is hydrophobic and outer part which is known as exterior is hydrophilic. The good solubility of cyclodextrins is due to exterior hydrophilic part. The exterior part of the CD's can be easily modified. (ATWOOD, COLEMAN, & ZHANG, 1989)

α -Cyclodextrin

α-Cyclodextrinare relatively irritating after i.m. injection. It can binds some lipids. Some eye irritation can be observed after oral absorption that is between 2 and 3%. DimensionalStructure of α-Cyclodextrin is given in figure 1.(Del Valle, 2004)

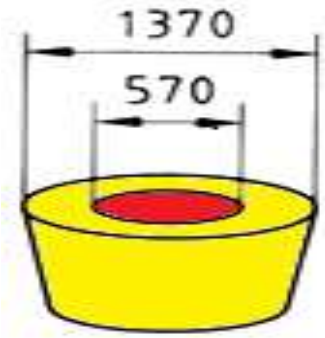

Figure 1. Representation of structure of α-Cyclodextrin in picometer.

Outer ring diameter is 1370pm and inner ring diameter is 570pm

β-Cyclodextrin

β-Cyclodextrinare less irritating than α-cyclodextrin after i.m. injection. It can bind with cholesterol. After oral administration a very small amount (1–2%) is absorbed in the upper intestinal tract nut no metabolism occurin the upper intestinal tract. It is metabolizedby bacteria in caecum and colon. DimensionalStructure of β-Cyclodextrin is given in figure 2. (Del Valle, 2004)

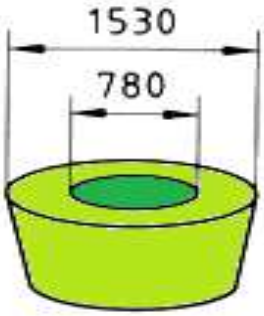

Figure 2. Representation of structure of β-Cyclodextrin in picometer.

Outer ring diameter is 1530pm and inner ring diameter is 780pm

γ-Cyclodextrin

The main properties are: insignificant irritation after i.m. injection; rapidly and completely degraded to glucose in the upper intestinal tract by intestinal enzymes (even at high daily dosages, e.g. 10–20 g/kg); almost no (0.1%) absorption after oral administration; practically no metabolism after i.v. administration; probably the least toxic cyclodextrin, at least of the three natural cyclodextrins. Actively promoted as food additive by its main manufactures; complexing abilities, in general, less than those of β -cyclodextrin and the water soluble β-cyclodextrin derivatives; its complexes frequently have limited solubility in aqueous solutions and tend to aggregate in aqueous solutions, which makes the solution unclear (opalescence). Dimensional Structure of γ-cyclodextrin is given in figure 3.(Del Valle, 2004)

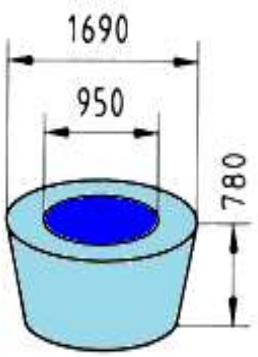

Figure 3. Representation of structure of γ-Cyclodextrin in picometer.

Outer ring diameter is 1690pm and inner ring diameter is 950pm. Height of outer ring is 780pm.

Production of cyclodextrins (α, β, γ-cyclodextrins).

At the initial level cyclodextrin glucosyl transferase (CGT-ase) enzyme is produced by culturing of microorganism *Bacillus macerans*. In the second step liquefaction of the starch is done at temperature. Now in the third step cool the mixture. In the fifth step CGT-ase enzyme is added to the starch solution. In the last step 1-decanol, Toulene and cyclohexadecenol is added to the conversion mixture for the production of **α** –CD (Figure 4), **β**-CD (Figure 5) and γ-CD (Figure 6) respectively.

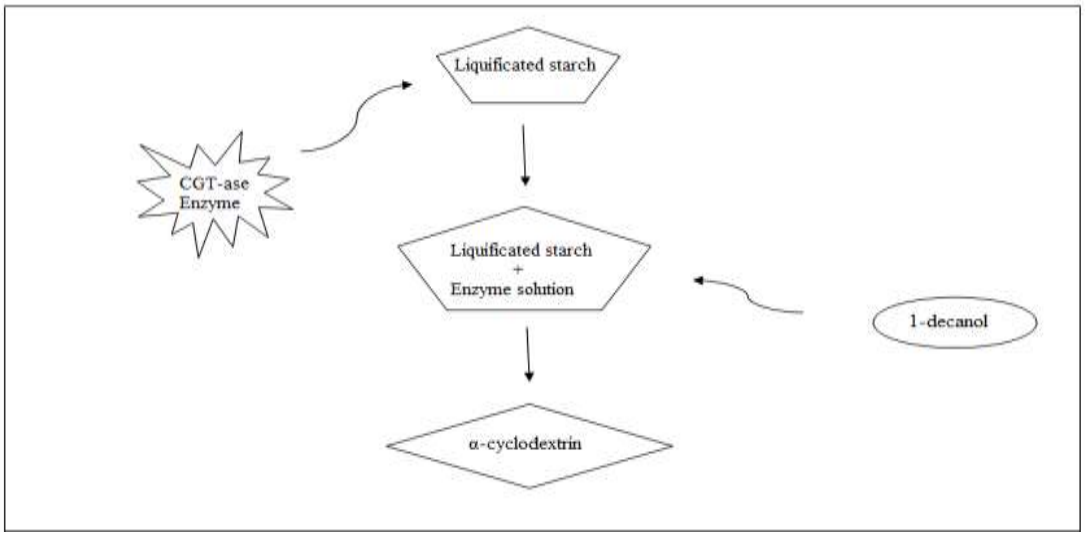

Figure 4.Schemic diagram of the production of α-cyclodextrin

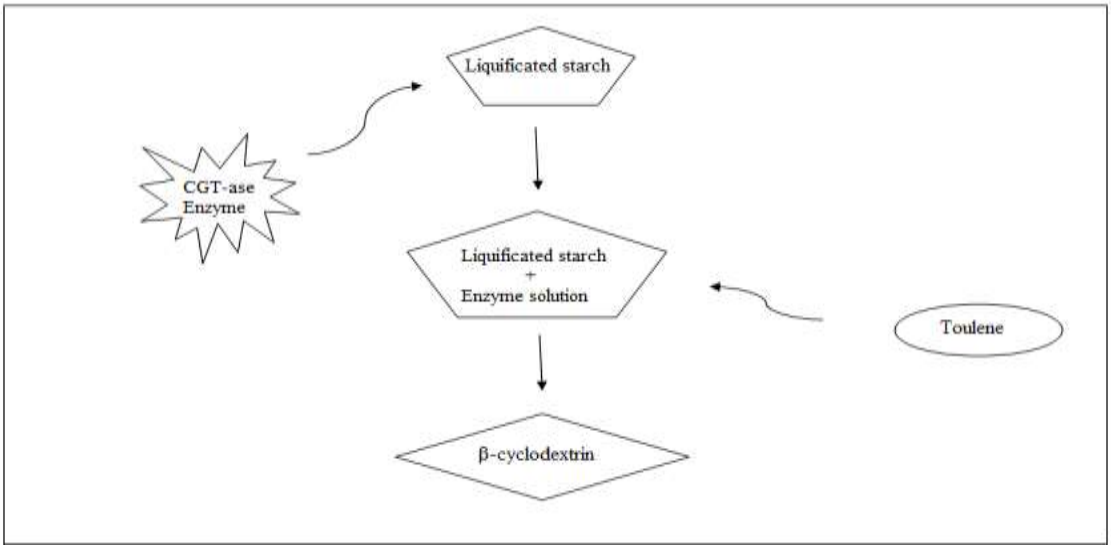

Figure 5.Schemic diagram of the production of β-cyclodextrin

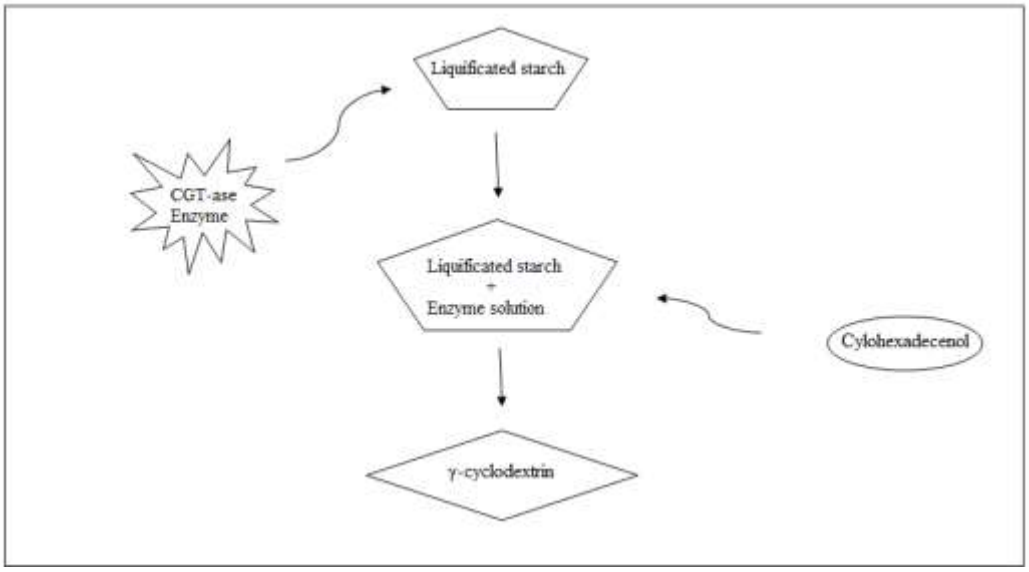

Figure 6.Schemic diagram of the production of γ-cyclodextrin

General properties of Cyclodextrins (α, β, γcyclodextrins):

Solubility of cyclodextrins.

The solubility of all cyclodextrins increases as the temperature increases. At room temperature solubility of α, β, γ-cyclodextrins is 12.8g, 1.8g, and 25.6 g respectively and it is measured in grams per 100ml. If the guest have higher solubility in water then the complexation of guest and cylodextrin increases the solubility of cyclodextrin and If the guest have no or slightly less solubility in water then the complexation of guest and cylodextrin decreases the solubility of cyclodextrin. The solubility of the complex is also due to the polar or ionic group of the guest molecule extending out of the cavity and the hydroxyl groups in the cyclodextrin forming new interactions. All cyclodextrins have different solubilities. The solubility of complex formation is also varies. There are so many factors which are still understood affect the solubility of a complex.

Thermal stability.

Cyclodextrins are heat stable. In the differential scanning calorimetry when heating α, β, γ-cyclodextrins two peaks are observed. The first one is due to dehydration of the water that is included in the crystal structure while the second is due to melting of the crystal and thermal degradation of the cyclodextrin at about 300 °C. Although the peak values are observed to be very similar, there are no endotherms or exotherms between these two sharp peaks.

Hygroscopicity.

Hygroscopic property is not shown by cylcodextrins. When cyclodextrins are dried and placed in an environment where they can absorbed water from that environment, a little amount of water can be absorbed. The equilibrium will be achieved in about 24 hours and cyclodextrins will contain about 10 to 14% of water. This quatity is depends upon humidity and temperature conditions. Starch also shows almost the same quantity. All cyclodextrins remain pourable and powder at the equilibrium moisture.

Chemical stability.

Cyclodextrins are hydrolyzed by strong acids such as HCl or H_2SO_4. The temperature Concentration of the acid and directly affacts the rate of hydrolysis as the rate of hydrolysis increases when the concentration and the temperature increases. (French, Pazur, Levine, & Norberg, 1948) There is no effect of weak acids on the hydrolysis of cyclodextrins. Only β-cyclodextrins is hydrolyzed by citric acid but at the temperature above 50°C and molar was concentration 0.5. Additionally, bases don't hydrolyze cyclodextrins. No signs of the cyclodextrins' hydrolysis were discovered despite multiple syntheses carried out at temperatures of 65 °C or higher and sodium hydroxide concentrations of 0.1 molar or higher.

Enzymatic stability.

The same enzyme that makes cyclodextrins also hydrolyzes them. This enzyme is called cyclodextrin glucosyltransferase. The same enzyme that breaks down starch into cyclodextrins can also break down cyclodextrins into oligosaccharides. The enzyme also carries out alpha amylase activities with water as the acceptor and transglycosylase reactions with oligosaccharides as the acceptor. Neither beta amylases nor glucose amylases can hydrolyze cyclodextrins. For these enzymes, hydrolysis cannot begin unless a reducing end group is present. Since cyclodextrins are closed circular molecules, hydrolysis cannot begin because there is no reducing end group accessible. Cyclodextrins can be hydrolyzed by a variety of alpha amylases. (French et al., 1948). The fungal alpha amylases hydrolyze cyclodextrins more easily than the bacterial amylases. The degree to which cyclodextrins are susceptible to alpha amylase hydrolysis varies as well. Starch and gamma cyclodextrin hydrolyze equally easily. Compared to starch, beta and alpha cyclodextrin hydrolyze more slowly. Compared to alpha cyclodextrin, beta cyclodextrin is more prone to enzymatic hydrolysis. Because they lessen or completely stop enzymatic hydrolysis, complex formation and chemical modification of the cyclodextrins also have an impact on hydrolysis.

Toxicology and metabolism.

Because both beta and alpha cyclodextrin are resistant to pancreatic and salivary amylases, they pass through the digestive system and into the colon. The enzymes generated by the intestinal flora hydrolyze beta cyclodextrin in this colon. The cyclodextrin is broken down in the colon together with other starch hydrolysate when the ring is opened. Colonic enzymes has no effects on the hydrolysis of alpha cyclodextrin (French et al., 1954; Hedges, Shieh, & Sikorski, 1995), whereas gamma cyclodexrin is hydrolyzed by the pancreatic and pancreatic amylases. As a result similarly to stomach, it is completely metabolized and absorbed and hydrolyzed.

Complexation.

Organic substances including aliphatic compounds, phenyl derivatives, conjugated rings, and heterocyclic compounds can form complexes. Complex formation is influenced by a number of factors, including dipole-dipole interaction, hydrophobic contact, and van der Waal forces.

These forces are just strong enough to create a stable complex; they are not strong enough to allow the guest molecule to be freed from the complex and used for its original purpose. The molecule's shape is a crucial component in the creation of complexes. When a hydrophobic group or a guest molecule contacts with the cylodextrin cavity walls, complexation takes place. Stronger binding occurs when the hydrophobic group makes greater contact with the cavity.

The degree to which a guest molecule penetrates the cyclodextrin cavity may be restricted by certain side chains on the molecule, but a sufficient number of guests usually penetrate the cavity to the extent necessary to form a stable combination. Ionic or polar groups don't interact with the hydrophobic cyclodextrin cavity walls. There are two methods to accomplish complexation: the first involves the hydrophobic part of the molecule interacting with the cavity walls, and the second involves the polar or ionic groups protruding from the cavity. The hydroxyl groups on the cyclodextrin's rim will frequently engage with polar or ionic groups to establish hydrogen bonds, which will boost the guest's binding to the cyclodextrin.

In complexation, a molecule's form matters more than its molecular weight. Multiple cyclodextrin molecules can form complexes with larger molecules, while multiple small molecules may form complexes with a single cyclodextrin molecule.

One guest molecule and one cyclodextrin molecule often form an inclusion complex. Consequently, unlike other forms of encapsulation where many molecules are encased in a film generated by the encapsulating material, the guest molecule is isolated from other molecules. There is a benefit to this seclusion in many cases. Contact with other molecules that might react with the guest molecule is avoided by isolation. Certain compounds are stabilized upon direct contact with the cyclodextrin walls, preventing oxidation by light or heat.(Hedges et al., 1995)

Production of Complexes.

The procedure of creating cyclodextrin complexes is straightforward. Water is used to combine the guest and cyclodextrin. The only tools required in the lab are a hot plate with stirrer and a beaker. The guest to be complexed determines the variation in water volume. The complex can be collected by filtration or centrifugation and dried in an oven if a dry complex is required. There is a way to use less water. Any type of mixing tool can be utilized, and depending on the tool and the material to be complexed, different amounts of time will need to be spent mixing.

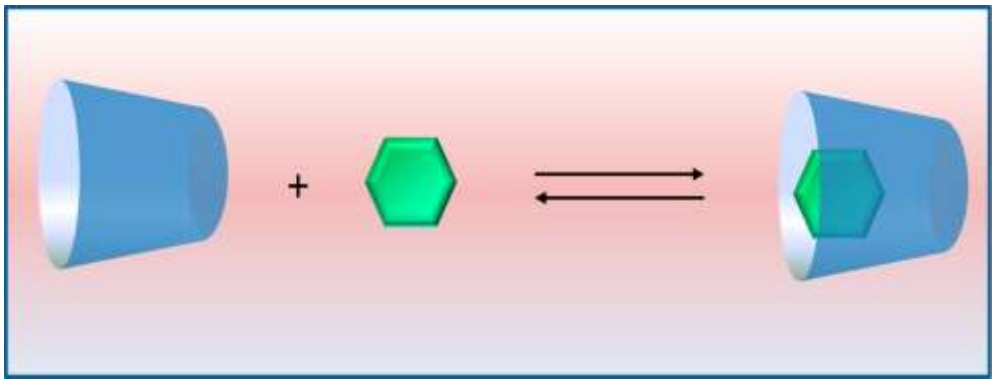

Figure 7.Schematic illustration of reversible host−guest complex formation (blue: cyclodextrin; green: guest compound or analyte).

Factors influencing inclusion complex formation

Type of CD can influence the formation as well as the performance of drug/CD complexes.(Castillo et al., 1999; Díaz, Llanos, & Bernad, 1999; P Mura, Faucci, Parrini, Furlanetto, & Pinzauti, 1999) For complexation, the cavity size of CD should be suitable to accommodate a drug molecule of particular size.(Akasaka, Endo, Nagase, UEDA, & KOBAYASHI, 2000; Arias-Blanco, Moyano, Perez-Martinez, & Gines, 1998; P Mura, Adragna, et al., 1999; Nagase et al., 2001; Ueda et al., 1999) Compared with neutral CDs, complexation can be better when the CD and the drug carry opposite charge but may decrease when they carry the same charge. (Jain & Adeyeye, 2001; Nagase et al., 2001)

A change in the pH of the solution can alter the complex constant in the case of ionisable pharmaceuticals, as the presence of charge may be important in drug/CD complexation. Ionic drug forms often have lower complex-forming abilities than nonionic forms..(Kim et al., 1998; Tros de Llarduya, Martín, Goni, & Martinez-Oharriz, 1998) but in the case of mebendazole, the un-ionized form was less included in HP-β-CD than the cationic form.(Díaz, Bernad, Gracia-Mora, & Llanos, 1999)

Drug/CD complexation can be impacted by temperature variations. The majority of the time, a rise in temperature was found to have a negative impact on the apparent stability constant of the drug/CD complex. This effect was attributed to the potential reduction of drug/CD contact forces, including van der Waals and hydrophobic forces.(Jain & Adeyeye, 2001; Zarzycki & Lamparczyk, 1998) Temperature variations, however, might not have much of an impact if the drug/CD interaction is mostly entropy driven, meaning that it results from the inclusion complexation that releases hydrated water molecules surrounding the charges of the guest and host molecules.(Nagase et al., 2001)

Drug/CD complexation may be impacted by the preparation technique, such as co-grinding, kneading, solid dispersion, solvent evaporation, co-precipitation, spray drying, or freeze drying. The type of medication and CD determine a method's efficacy.(P Mura, Adragna, et al., 1999; Palmieri, Galli-Angeli, Giovannucci, & Martelli, 1997) In many cases, spray drying,(Moyano, Arias, Gines, Perez, & Rabasco, 1997; Palmieri et al., 1997; Palmieri, Wehrlé, & Stamm, 1993) and freeze drying(Castillo et al., 1999), were found to be most effective for drug complexation. (Díaz, Llanos, et al., 1999)

Regardless of the physiochemical characteristics of the drug, the polymers or ion pairing agents enhance the pharmacological and biological qualities of drug/CD complexes by their direct involvement in drug complexation.(Cappello, Carmignani, Iervolino, La Rotonda, & Saettone, 2001; Faucci & Mura, 2001; Granero, De Bertorello, & Longhi, 2002; Loftsson, Guo¯ mundsdóttir, & Frio¯ riksdóttir, 1996; Tondare, 2011) Certain additives may compete with drug molecules for CD cavities and thus decrease the apparent complex stability constant, eg, additives with positive and negative hydrotropic effect.(Tokumura et al., 1986). Simultaneous complexation and salt formation with hydroxy carboxylic acid (HA) significantly increased the CD solubilizing power for a sparingly water-soluble amine type drug by forming drug/ CD/HA multicomponent systems.(Redenti, Szente, & Szejtli, 2000) Co-solvents can improve the solubilizing and stabilizing effects of CDs, eg, use of 10% propylene glycol in development of an oral itraconazole preparation containing 40% of HP-β-CD.(Li, Zhao, & Yalkowsky, 1999)

Occasionally, co-solvents can impede drug complexation by competitive inclusion. For example, the solubilizing efficacy of HP-β-CD for itraconazole was reduced when 10% propylene glycol was present. Propylene glycol promoted itraconazole absorption and precipitation in GI fluids and formulation upon dilution by offering a higher percentage of the free drug. Reduced intrinsic solubility of the drug in comparison to the dilution concentration line at a specific HP-β-CD concentration was stated to be the cause of the higher percentage of

free drug in the presence of co-solvent..(Miyake et al., 1999)

Characteristics of Cds (Paola Mura, 2014)

Characteristics	α	β	γ
no. of glucose units	6	7	8
Molecular weight	972	1135	1297
solubility in water, g 100 mL-1 at room temp	14.5	1.85	23.2
cavity diameter, Å height of torus, Å	4.7±5.3	6.0±6.5	7.5±8.3
height of torus, Å	7.9 ± 0.1	7.9 ± 0.1	7.9 ± 0.1
diameter of outher periphery, Å	14.6 ± 0.4	15.4 ± 0.4	17.5 ± 0.4
approx volume of cavity, $Å^3$	174	262	427
crystal forms (from water)	hexagonal plates	monoclinic parallelograms	quadratic prisms
crystal water, wt %	10.2	13.2-14.5	8.13-17.7
diffusion constant at 40 °C	3.443	3.224	3.000
Vmax value, min-1	5.8	166	2300

Table 1. Characteristics of α, β, γ-cyclodextrins

Cyclodextrin Derivatices(Duchene & Wouessidjewe, 1992)

The majority of derivatives of cyclodextrin are quite soluble in water, whereas some are not soluble at all.

Water-soluble derivatives.

One of the earliest known water-soluble derivatives is methyl cyclodextrin. Either both C2 secondary and C6 primary hydroxyl groups (dimethyl cyclodextrins) or all C2, C3, and C6 hydroxyls (trimethyl cyclodextrins) are involved in cyclodextrin methylation.In comparison to 1.85 for the mother product, the water solubility of the beta-cyclodextrin derivatives is 57 and

31g/100ml for dimethyl and trimethyl, respectively. Methylated cyclodextrins' reduced solubility with rising temperatures is a drawback, nevertheless.

Since hydroxypropylation does not provide a selective replacement like methylation does, hydroxypropyl cyclodextrins are essentially different compounds. A diversity of products with varying degrees of substitution is produced as the reaction progresses due to fluctuations in the hydroxyl reactivity. The result is that amorphous compounds are obtained since crystallization is impossible due to the presence of so many different forms of hydroxypropyl cyclodextrin in the same reaction product. In addition to their chemical makeup, hydroxypropyl cyclodextrins have an amorphous shape that contributes to their high water solubility. Since their dissolution is endothermic, the solubility does not decrease as the temperature rises. Because of the resultant solution's viscosity, it is challenging to ascertain their precise water solubility. At 25°C, it is, nevertheless, greater than 50 g/lOO ml.

Because of the viscosity of the resulting solution, it is challenging to pinpoint their precise water solubility. However, at 25°C, it is greater than 50 g/lOO ml.

Other derivatives.

Similar to methylation, ethylation of cyclodextrins yields distinct compounds, namely di- and triethyl cyclodextrins, which have extremely low water solubility at 25°C. The solubility of carboxymethyl ethyl cyclodextrin varies with pH: it is nearly constant (1 to 1.5g/100ml) below pH 2.5, significantly increases above pH 4 (lOg/lOOml), and becomes freely soluble at pH > 6. Low molecular weight cyclodextrin polymers (between 3000 and 6000) dissolve easily in water, whereas molecular weight polymers (beyond 10,000) only cause swelling and insoluble gel formation.

Uses of Beta Cyclodextrins:

Cosmetics, Toiletories and personal uses:

The process of ethylation, akin to methylation, yields distinct byproducts, namely triethyl and di-cyclodextrins, which have extremely low water solubility at 25°C. Carboxymethyl ethyl cyclodextrin's solubility varies with pH: it is nearly constant (1 to 1.5g/100ml) below pH 2.5, significantly increases (lOg/lOOml) above pH 4, and is freely soluble at pH > 6. While cyclodextrin polymers with molecular weights exceeding 10,000 can only expand in water and form insoluble gels, those with molecular weights between 3000 and 6000 are easily soluble in water.(Chaudhary & Patel, 2013)

In this industry, stabilization, odor control, improved process when a liquid ingredient is turned into a solid, flavor delivery and protection in lipsticks, water solubility, and increased oil thermal stability are the main advantages of cyclodextrins. Other uses for it include underarm shields, paper towels, tissues, liquid and solid fabric softeners, toothpaste, and skin treatments. (József Szejtli, 1998)

Long-term stabilization of fragrance against evaporation and oxidation is achieved through the use of CD-complex perfumes in skin products like talcum powder. Additionally, the product's antibacterial activity has been enhanced. In the process of making bath preparations, fragrance is encased in CD, and the inclusion compound that results is combined with calcium phosphate to preserve the fragrance (Singh, Sharma, & Banerjee, 2002)

When CD-complex perfumes are used in skin treatments like talcum powder, they preserve the smell over time against evaporation and oxidation loss. The product's antibacterial efficiency is additionally enhanced. To stabilize the aroma when making bath preparations, the fragrance is encased in CD and the inclusion compound that results is combined with calcium phosphate.

(Trinh et al., 1999).

Odors in washed objects can be concealed by using CDs in laundry and dishwashing detergent mixes. Through cyclodextrin complexation, CDs used in silica-based toothpastes improve the availability of triclosan, an antibacterial. This process nearly triples the availability of triclosan. (Trinh et al., 1999)

In order to minimize the adverse effects of the formulation, cyclodextrins are employed in sunscreen lotion manufacture in a 1:1 ratio (sunscreen/hydroxypropyl b-CD). This is because the cavity of the CD inhibits the contact between the UV filter and the skin. Similarly, the efficacy and shelf life of self-tanning emulsions and creams are enhanced by the addition of CD. An additional benefit is that the tan seems more natural than the typical dihydroxy acetone product's yellow and reddish hue.(Scalia, Villani, & Casolari, 1999).

As deodorants:

To absorb lingering and disagreeable odors, they can be used as a deodorant to liquid body deodorants or breath fresheners (fish, garlic, cigarettes, alcohol) (Duchene & Wouessidjewe, 1992)

In food industry:

species is frequently utilized in Japanese cooking, although certain species have odd smells that might overpower the flavor. These odor-causing nitrogen-containing substances can be found in cyclodextrins. The use of cyclodextrins has the masking effect of improving the odor of fish paste goods. Fish that has been dipped in a cyclodextrin solution and left raw has less of an odor. The distinctive mutton smell can also be lessened by adding cyclodextrin. You can cook rice with β-cyclodextrin to get rid of the bad smell that develops while it's being stored.(Duchene & Wouessidjewe, 1992)

The removal of caffeine from tea is another application for cyclodextrins' ability to trap substances in the food business. In this case, cross-linked cyclodextrin polymers appear to be more useful than β-cyclodextrin.

Tobacco industry

Cyclodextrins are used in the to lower the amounts of tar and nicotine in cigarette smoke. They can contribute to the cellulose or make up a larger portion of the filter. (Duchene & Wouessidjewe, 1992)

In laundering

Cyclodextrins are used in the to lower the amounts of tar and nicotine in cigarette smoke. They can make up the majority of the filter or be added to the cellulose as an addition.(Duchene & Wouessidjewe, 1992)

Transformation of Liquids into Solids

Usually, when it comes to extremely volatile liquids like essential oils that are employed to flavor industrial meals, this change is studied. β-cyclodextrin has the ability to trap oils such as dill, coriander, marjoram, sage, raspberry, lemon, cinnamon, carrot, aniseed, orange, thyme, peppermint, sweet cumin, celery, garlic, onion, tarragon, caraway, basil, bay leaf, and mustard.[61]Fragrance compounds can also be encapsulated using hydroxypropyl β-cyclodextrin or natural β-cyclodextrin. The resulting microcrystalline complexes are practically odorless powders that are not hygroscopic. There is 6 to 15% fragrance content, while 8 to 10%

is more common. When they are dry, they are stable and shielded from oxidation. Aroma inclusion complexes kept in sealed containers at room temperature lose less than 5% of their active component content after two years, according to stability testing. (Duchene & Wouessidjewe, 1992)

Improvement in Stability

A guest molecule enclosed in a cyclodextrin cavity often has some degree of protection against oxygen, light, and heat from the surrounding environment.When heated during industrial food processing, spices that have been incorporated and turned into a powder by cyclodextrins show good stability. It is feasible to use fewer amounts of included flavors than natural ones since the inclusion of fruit flavors yields the same outcome. Moreover, these flavors last longer than those of the liquid product.(Duchene & Wouessidjewe, 1992)

Intriguingly, the unstable liposoluble vitamins A, D, E, and K may be made more stable. The vitamin D3/β-cyclodextrin complex, which has significantly increased resistance to oxidation, is the vitamin inclusion that has been studied the most. Pyrethroids are another type of substance that is part of cyclodextrin and is mostly used to increase stability. In the human environment, they are great pesticides. They have a strong knock-down action on insects, which renders them harmless to mammals. Their susceptibility to oxygen and UV radiation is a drawback. They can be made more stable by adding them to betacyclodextrin. Another pesticide is methylparathion. It is a contact toxin that breaks down quickly while not being flammable. (J Szejtli, Bolla-Pusztai, Szabo, & Ferenczy, 1980)

Decrease in Undesirable Side Effects

Similar to how a guest molecule inside a cyclodextrin's cavity might lessen the attack from external causes, it can also shield the surrounding medium from the host molecule's unfavorable side effects. Applications in the pharmaceutical industry may find this particularly intriguing. Non-steroidal anti-inflammatory drugs, for example, frequently have an adverse effect on the stomach mucosa. It has been shown that adding phenylbutazone to beta-cyclodextrin lessens its irritability. Nevertheless, not all anti-inflammatory medications provide this sort of outcome, and flufenamic acid or indomethacin do not lessen irritancy.(Duchene & Wouessidjewe, 1992)

The unpleasant taste that some medications, including pirprofen, produce is another type of adverse drug reaction. Because of its incorporation into beta-cyclodextrin, the irritation to the throat mucous membrane is lessened. Both ibuprofen and flurbiprofen yield the same outcome. Cosmetic items can also irritate certain people, particularly due to the scents they contain and the emulsifying chemicals that are sometimes added to the mix to increase the perfumes' irritability. This kind of negative effect can be significantly reduced by including them in a cyclodextrin. (Duchene & Wouessidjewe, 1992)

Sometimes the only thing sought after is the hiding of an unpleasant odor. Cyclodextrins are used in cosmetics to lessen the smell of mercaptan, which is an ingredient in permanent hair treatments. Similarly, the smell of this antiseptic may be covered up by adding iodine to cyclodextrins, which allows you to utilize it in tooth decay prevention preparations.(Duchene & Wouessidjewe, 1992)

Enhancement of solubility

Cyclodextrins are able to incorporate hydrophobic molecules and provide them hydrophilic properties with ease since they are comparatively hydrophobic inside their cavity and hydrophilic outside. Therefore, dissolving agents such as cyclodextrins and their hydro soluble derivatives can be used. This phenomenon is being studied to see whether it can be used to boost the absorption of insoluble compounds via different membranes, or if it can be used to

capitalize on the inherent benefits of a liquid product. Recall that the most prevalent natural cyclodextrin, beta-cyclodextrin, is the least soluble, and that this affects the rise in solubility in part due to the cyclodextrin's solubility. The hydroxypropyl β-cyclodextrins seem to have a significant role in the market of the future among the hydrosoluble derivatives. The solubility of free flurbiprofen is quite poor, and it was significantly enhanced by beta-cyclodextrin. Melphalan (L-phenylalanine mustard), an anticancer medication used to treat multiple myeloma and ovarian and breast cancer, is one example of a medication that has become more water soluble.In a similar vein, adding insoluble fungicides to cyclodextrins can ease their application. (József Szejtli, 1988)

Lotions for the face and eyes have straightforward formulas in the field of cosmetology. They are mostly made of water, generally with trace quantities of water-soluble astringent chemicals, and are clear and faintly colored. Nonetheless, some lotions include ingredients that are liposoluble. Micellar solubilization is the most generally utilized procedure to maintain a clear preparation; nevertheless, the lotion's irritating action may be exacerbated by the presence of surfactant. This disadvantage can be mitigated by using an inclusion.Cyclodextrin and certain of its derivatives may include vitamin E, which is used to cleanse and whiten burnt complexions.(Duchene & Wouessidjewe, 1992) In the same way, isopropylmyristate can be added to face lotion after incorporation. Precipitations are avoided in the food business by adding P-cyclodextrin to canned citrus items or bamboo shoots. After beta-cyclodextrin is added, sweetening agents (chalcone and dihydrochalcone), which precipitate readily upon cooling, cease to do so. After beta-cyclodextrin is added, sweetening agents (chalcone and dihydrochalcone), which precipitate readily upon cooling, cease to precipitate. (Duchene & Wouessidjewe, 1992)

Prolonged Release of Active Ingredient:

Cyclodextrins are frequently utilized to speed up an ingredient's release from a particular form and increase its water solubility. Nevertheless, the most widely used cyclodextrin, beta-cyclodextrin, only dissolves in water at a rate of 1.85 g/100 ml and may also incorporate water-soluble molecules, provided that they are less hydrophilic than water. Under these circumstances, hydrophilic products added to insoluble derivatives of beta-cyclodextrin, such ethyl cyclodextrins, may release their constituents more slowly.

Transformation of Gases into Solids

Gases and other tiny molecules can be mixed with a-cyclodextrin to solidify them. Because ethylene is a highly powerful hormone-like agent for plants, its presence in cyclodextrin is quite intriguing for the agricultural sector. The intracellular synthesis of ethylene is somewhat linked to the ripening process of fruits and the abscission of leaves. An aqueous medium can be used to manufacture the inclusion compound. (Duchene & Wouessidjewe, 1992)

Increased absorption through biological membranes.

The primary goal of using cyclodextrins in pharmaceuticals is frequently to make an active component more bioavailable. The derivatives of cyclodextrins do not directly improve absorption.Examples of how adding acyclodextrin to a drug has increased its bioavailability in pharmacy are numerous, but mostly focused on animal studies. The following active components are available for oral administration: digoxin, spironolectone, phenytoin, bacetohexamide, diazam, and ketoprofin. Methylcyclodextrins and other water-soluble derivatives provide comparable outcomes. Trimethyl P-cyclodextrin, for instance, more than triples the bioavailability of ketoprofen and twice that of ibuprofen. There are instances where the rise in bioavailability makes it feasible to suggest a reduction in the dosage given. It is also possible to achieve increased bioavailability for various routes of administration, including sublingual, ophthalmic, cutaneous, and rectal.(Duchene & Wouessidjewe, 1992)

REFERENCES

- Akasaka, H., Endo, T., Nagase, H., UEDA, H., & KOBAYASHI, S. (2000). Complex formation of cyclomaltononaose δ-cyclodextrin (δ-CD) with macrocyclic compounds. *Chemical and pharmaceutical bulletin*, *48*(12), 1986-1989.
- Arias-Blanco, M. J., Moyano, J. R., Perez-Martinez, J. I., & Gines, J. M. (1998). Study of the inclusion of gliclazide in α-cyclodextrin. *Journal of pharmaceutical and biomedical analysis*, *18*(1-2), 275-279.
- ATWOOD, J. L., COLEMAN, A. W., & ZHANG, H. (1989). *and SIMON G. BOTT Department of Chemistry, University of Alabama, Tuscaloosa, AL 35487, USA (Received: 1 February 1988).* Paper presented at the United States-Japan Seminar on Host-Guest Chemistry: Proceedings of the US-Japan Seminar on Host-Guest Chemistry, Miami, Florida, USA, 2–6 November 1987.
- Cappello, B., Carmignani, C., Iervolino, M., La Rotonda, M. I., & Saettone, M. F. (2001). Solubilization of tropicamide by hydroxypropyl-β-cyclodextrin and water-soluble polymers: in vitro/in vivo studies. *International journal of pharmaceutics*, *213*(1-2), 75-81.
- Castillo, J., Palomo-Canales, J., Garcia, J., Lastres, J., Bolas, F., & Torrado, J. (1999). Preparation and characterization of albendazole β-cyclodextrin complexes. *Drug development and industrial pharmacy*, *25*(12), 1241-1248.
- Chaudhary, V., & Patel, J. (2013). Cyclodextrin inclusion complex to enhance solubility of poorly water soluble drugs: A review. *International Journal of Pharmaceutical Sciences and Research*, *4*(1), 68.
- Del Valle, E. M. (2004). Cyclodextrins and their uses: a review. *Process biochemistry*, *39*(9), 1033-1046.
- Díaz, D., Bernad, M. J. B., Gracia-Mora, J., & Llanos, C. M. E. (1999). Solubility, 1H-NMR, and molecular mechanics of mebendazole with different cyclodextrins. *Drug development and industrial pharmacy*, *25*(1), 111-115.
- Díaz, D., Llanos, C. M. E., & Bernad, M. J. B. (1999). Study of the binding in an aqueous medium of inclusion complexes of several cyclodextrins involving fenoprofen calcium. *Drug development and industrial pharmacy*, *25*(1), 107-110.
- Duchene, D., & Wouessidjewe, D. (1992). Industrial uses of cyclodextrins and their derivatives. *Journal of coordination chemistry*, *27*(1-3), 223-236.
- Faucci, M. T., & Mura, P. (2001). Effect of Water-Soluble Polymers on Naproxen Complexation with Natural and Chemically Modified B-Cyclodextrins. *Drug development and industrial pharmacy*, *27*(9), 909-917.
- French, D., Levine, M. L., Norberg, E., Nordin, P., Pazur, J. H., & Wild, G. M. (1954). Studies on the Schardinger Dextrins. VII. Co-substrate Specificity in Coupling Reactions of Macerans Amylase1, 2. *Journal of the American Chemical Society*, *76*(9), 2387-2390.
- French, D., Pazur, J., Levine, M. L., & Norberg, E. (1948). REVERSIBLE ACTION OF macerans AMYLASE1. *Journal of the American Chemical Society*, *70*(9), 3145-3145.
- Granero, G., De Bertorello, M., & Longhi, M. (2002). Solubilization of a naphthoquinone derivative by hydroxypropyl-beta-cyclodextrin (HP-beta-CD) and polyvinylpyrrolidone (PVP-K30). The influence of PVP-K30 and pH on solubilizing effect of HP-beta-CD. *Bollettino Chimico Farmaceutico*, *141*(1), 63-66.
- Hedges, A. R., Shieh, W. J., & Sikorski, C. T. (1995). Use of cyclodextrins for encapsulation in the use and treatment of food products.
- Jain, A. C., & Adeyeye, M. C. (2001). Hygroscopicity, phase solubility and dissolution of various substituted sulfobutylether β-cyclodextrins (SBE) and danazol–SBE inclusion complexes. *International journal of pharmaceutics*, *212*(2), 177-186.

- Jeang, C.-L., Lin, D.-G., & Hsieh, S.-H. (2005). Characterization of cyclodextrin glycosyltransferase of the same gene expressed from Bacillus macerans, Bacillus subtilis, and Escherichia coli. *Journal of Agricultural and Food Chemistry, 53*(16), 6301-6304.
- Kim, Y., Oksanen, D. A., Massefski, J. W., Blake, J. F., Duffy, E. M., & Chrunyk, B. (1998). Inclusion complexation of ziprasidone mesylate with β-cyclodextrin sulfobutyl ether. *Journal of pharmaceutical sciences, 87*(12), 1560-1567.
- Li, P., Zhao, L., & Yalkowsky, S. H. (1999). Combined effect of cosolvent and cyclodextrin on solubilization of nonpolar drugs. *Journal of pharmaceutical sciences, 88*(11), 1107-1111.
- Loftsson, T., Guo¯ mundsdóttir, T., & Frio¯ riksdóttir, H. (1996). The influence of water-soluble polymers and pH on hydroxypropyl-β-cyclodextrin complexation of drugs. *Drug development and industrial pharmacy, 22*(5), 401-405.
- Miyake, K., Irie, T., Arima, H., Hirayama, F., Uekama, K., Hirano, M., & Okamoto, Y. (1999). Characterization of itraconazole/2-hydroxypropyl-β-cyclodextrin inclusion complex in aqueous propylene glycol solution. *International journal of pharmaceutics, 179*(2), 237-245.
- Moyano, J., Arias, M., Gines, J., Perez, J., & Rabasco, A. (1997). Dissolution Behavior of Oxazepam in Presence of Cyclodextrins: Evaluation of Oxazepam-Dimeb Binary Systemxs. *Drug development and industrial pharmacy, 23*(4), 379-385.
- Mura, P. (2014). Analytical techniques for characterization of cyclodextrin complexes in aqueous solution: A review. *Journal of pharmaceutical and biomedical analysis, 101*, 238-250.
- Mura, P., Adragna, E., Rabasco, A., Moyano, J., Perez-Martinez, J., Arias, M., & Gines, J. (1999). Effects of the host cavity size and the preparation method on the physicochemical properties of ibuproxam-cyclodextrin systems. *Drug development and industrial pharmacy, 25*(3), 279-287.
- Mura, P., Faucci, M., Parrini, P., Furlanetto, S., & Pinzauti, S. (1999). Influence of the preparation method on the physicochemical properties of ketoprofen–cyclodextrin binary systems. *International journal of pharmaceutics, 179*(1), 117-128.
- Nagase, Y., Hirata, M., Wada, K., Arima, H., Hirayama, F., Irie, T., . . . Uekama, K. (2001). Improvement of some pharmaceutical properties of DY-9760e by sulfobutyl ether β-cyclodextrin. *International journal of pharmaceutics, 229*(1-2), 163-172.
- Palmieri, G. F., Galli-Angeli, D., Giovannucci, G., & Martelli, S. (1997). Inclusion of methoxybutropate in β-and hydroxypropyl β-cyclodextrins: comparison of preparation methods. *Drug development and industrial pharmacy, 23*(1), 27-37.
- Palmieri, G. F., Wehrlé, P., & Stamm, A. (1993). Inclusion of vitamin D2 in β-cyclodextrin. Evaluation of different complexation methods. *Drug development and industrial pharmacy, 19*(8), 875-885.
- Redenti, E., Szente, L., & Szejtli, J. (2000). Drug/cyclodextrin/hydroxy acid multicomponent systems. Properties and pharmaceutical applications. *Journal of pharmaceutical sciences, 89*(1), 1-8.
- Scalia, S., Villani, S., & Casolari, A. (1999). Inclusion Complexation of the Sunscreen Agent 2-Ethylhexyl-p-dimethylaminobenzoate with Hydroxypropyl-β-cyclodextrin: Effect on Photostability. *Journal of pharmacy and pharmacology, 51*(12), 1367-1374.
- Singh, M., Sharma, R., & Banerjee, U. (2002). Biotechnological applications of cyclodextrins. *Biotechnology advances, 20*(5-6), 341-359.
- Szejtli, J. (1988). *Cyclodextrin technology* (Vol. 1): Springer Science & Business Media.
- Szejtli, J. (1998). Introduction and general overview of cyclodextrin

chemistry. *Chemical reviews, 98*(5), 1743-1754.

- Szejtli, J., Bolla-Pusztai, E., Szabo, P., & Ferenczy, T. (1980). Enhancement of stability and biological effect of cholecalciferol by ß-cyclodextrin complexation. *Pharmazie, 35*(12), 779-787.
- Tokumura, T., Nanbas, M., Tsushima, Y., Tatsuishi, K., Kayano, M., Machida, Y., & Nagai, T. (1986). Enhancement of bioavailability of cinnarizine from its β-cyclodextrin complex on oral administration with dl-phenylalanine as a competing agent. *Journal of pharmaceutical sciences, 75*(4), 391-394.
- Tondare, A. (2011). *Enhancement of Solubility and Dissolution of Gliclazide by Complexation with Hydroxypropyl β-Cyclodextrin.* Rajiv Gandhi University of Health Sciences (India).
- Trinh, T., Lucas, J. M., Bartolo, R. G., Dodd, M. T., Buckner, R. Y., & Kajs, T. M. (1999). Compositions for reducing body odor: Google Patents.
- Tros de Llarduya, M., Martín, C., Goni, M., & Martinez-Oharriz, M. (1998). Solubilization and interaction of sulindac with polyvinylpyrrolidone K30 in the solid state and in aqueous solution. *Drug development and industrial pharmacy, 24*(3), 295-300.
- Ueda, H., Wakamiya, A., Endo, T., Nagase, H., Tomono, K., & Nagai, T. (1999). Interaction of cyclomaltononaose (δ-CD) with several drugs. *Drug development and industrial pharmacy, 25*(8), 951-954.
- Zarzycki, P., & Lamparczyk, H. (1998). The equilibrium constant of β-cyclodextrin–phenolphtalein complex; influence of temperature and tetrahydrofuran addition. *Journal of pharmaceutical and biomedical analysis, 18*(1-2), 165-170.