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SULFOBUTYLETHER B-CYCLODEXTRINE (SBE-B-CD): A BREAKTHROUGH FOR SOLUBILITY ENHANCEMENT

[1*]Prathamesh P. Walke and [2]Dr. Swaroop R. Lahoti

[1]Research Scholar, [2]Professor Dept. of Pharmaceutics,
Department of Pharmaceutics, Maulana Azad Educational Trust Y. B. Chavan College of Pharmacy, Rauzabaugh, Dr. Rafique Zakeria Marg Aurangabad, Maharashtra, India.

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***Corresponding Author**
Mr. Prathamesh P. Walke
Research Scholar,
Department of Pharmaceutics, Maulana Azad Educational Trust Y. B. Chavan College of Pharmacy, Rauzabaugh, Dr. Rafique Zakeria Marg Aurangabad, Maharashtra, India.

ABSTRACT

More than 40% of medications have poor bioavailability, and a key contributing factor to this is the low water solubility of the API. A number of poorly soluble lipophilic medications can combine with oligosaccharides like cyclodextrins (CDs) to produce water-soluble inclusion complexes. Consequently, CDs are employed to improve the bioavailability and water solubility. Depending on whether the parent, or natural, CDs have six, seven, or eight glucopyranose units, they are referred to as alpha, beta, or gamma CDs respectively. Many derivatives with better features are found in addition to these parent CDs. One of the most recently developed and specially modified derivatives of CD is sulfobutylether-β-cyclodextrin (SBE-β-CD), a compound whose structure is logically designed to enhance interaction and increase safety while enhancing the solubility and stability of active components SBE-β-CD's physico-chemical characteristics offer the perfect medium for solubilizing medications with limited water solubility by nature. An examination of the literature indicates that there are numerous reviews on CDs; however, there isn't a review specifically on SBE-β-CD. For this reason, we focused our evaluation on the qualities, safety concerns, research, patents, and regulatory elements of SBE-β-CD.

KEYWORDS: Cyclodextrins, Solubility, Dissolution, Bioavailability, Glucopyranose unit.

INTRODUCTION

Any dosage form's intrinsic attribute is its solubility, which means that internal modifications might enhance the active compound's properties. Conversely, dissolution is an extrinsic feature of a drug product, meaning that external modification might enhance the nature or qualities of the active ingredient. A pharmacological product's solubility can be described in terms of both quantitative and qualitative factors.

The amount of solute particles needed to create a saturated solution is known as quantitative solubility.

The process of mixing two phases to create a homogenous solution is known as qualitative solubility.[1]

The following is the Lipinski rule, which shows that an active chemical is either weakly or non-aqueously soluble in water

1. An active substance containing five or more carbon atoms.
2. Log P has a value of two or more than two.
3. The compound's molecular weight is more than 500 Daltons.[2]

Together with water solubility, permeability is another crucial aspect of oral bioavailability. In the mid-1990s, the Biopharmaceutical Classification System (BCS) was used to classify drug molecules according to their water solubility and membrane permeability.[3]

Table 1: BCS Classification.[4]

Class	Solubility	Permeability	Absorption pattern	Rate limiting step in absorption	Examples
I	High	High	Well Absorb	Gastric emptying	Diltiazam
II	Low	High	Variable	Dissolution	Acotiamide
III	High	Low	Variable	Permeability	Insulin
IV	Low	Low	Poorly Absorb	Case by case	Taxol

The analytical composition of a saturated solution stated as a percentage of a specified solute in a designated solvent is known as solubility, according to IUPAC. Solubility can be expressed in units of concentration, molality, mole fraction, mole ratio, and other units.[5]

Table 2: Definitions of solubility.[6]

Definition	Number of solvent parts needed to make one solute portion
Very soluble	NMT 1
Freely soluble	1 to 10
Soluble	10 to 30
Sparingly soluble	30 to100
Slightly soluble	100 to 1000
Very slightly soluble	1000 to 10000
Insoluble	More than 10000

Dissolution

A solid that is dispersed in a liquid dissolve in two stages: the first is the formation of solute molecules from the solid phase through an interfacial interaction between the liquid and solid phases, and the second is the diffusion-driven movement of these molecules from the point of entry into the mass media.

The detailed procedure for dissolution is explained by the Noyes-Whitney equation[8]

$dm/dt = D \times A / h (S - C_b)$

Where,

D: Solute Diffusion coefficient

A: Effective surface area of the dispersed solid (surface area of the particles exposed to the solvent)

h : Diffusion boundary layer thickness

S: Saturation solubility (i.e. the equilibrium solubility)

Cb: Solute concentration in bulk medium at time "t"

The Noyes-Whitney equation is a model that assumes

1. The medication dissolves evenly on all of the particle surfaces,
2. The sphere-shaped particles
3. The diffusion boundary layer's thickness remains constant.
4. Particle size has no bearing on the saturation solubility or the diffusion boundary layer's thickness.

Techniques of Solubility Enhancement[10]

There are numerous methods for making poorly soluble medications more soluble. Several methods to increase the solubility include:

I. PHYSICAL MODIFICATIONS

1. Particle size reduction

a. Micronization

b. Nanosuspension

2. Modification of the crystal habit

a. Formation of Polymorphs

b. Pseudo-polymorphs

3. Drug distribution within carriers

a. Eutectic blend

b. Solid dispersions

c. Solid solutions

4. Inclusion Complexation

a. Complexing agents are applied

5. Solubilization by surfactants

a. Microemulsions

b. Self micro-emulsifying drug delivery systems

II. CHEMICAL MODIFICATION

1. pH control

2. Salt formation

III. MISCELLANEOUS METHODS

COMPLEXATION

Complexation is an alliance of two or more molecules to create an entity that is not bound with a well specified stoichiometry. It requires relatively weak forces such as hydrophobic interactions, hydrogen bonds, and London forces.[11]

Table 3: List of Complexing Agents.

Sr. No.	Types	Examples
1	Coordination	Hexamine cobalt(III) chloride
2	Chelates	EDTA, EGTA
3	Metal-Olefin	Ferrocene
4	Inclusion	Cyclodextrins, Choleic acid
5	Molecular Complexes	Polymers

Inclusion complexes

Together with a companion molecule like cyclodextrine, the medicine forms an inclusion complex. The medication is contained by non-covalent intermolecular forces within the partner molecule's cavities. The resulting formulation enhances the bioavailability and solubility of the poorly soluble pharmaceuticals. Two of the most significant variables to consider when designing drug-cyclodextrin inclusion complexes are lipophilicity and drug molecular size. Drug-cyclodextrin inclusion complexes might be made using either spray drying or coprecipitate. Figure 1 illustrates the formation of drug-cyclodextrin inclusion complex.

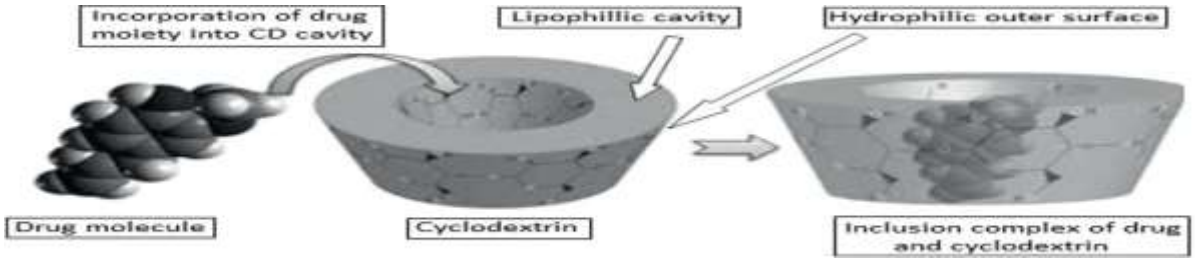

Figure 1: Drug-Cyclodextrin Inclusion Complex.

ADVANTAGES

1) Cyclodextrins enhance the bioavailability and solubility of poorly soluble medications.
2) Aqueous stability is facilitated by cyclodextrins.
3) Gradual release.
4) Less toxicity.
5) Ignoring smell or taste.
6) Formulation versatility.

DISADVANTAGES

1) Designing of a dosage form and medication loading could be restricting variables.
2) Expanding the production process can present difficulties.
3) The effects of production complexity on costs.
4) Possible allergic responses in those who are sensitive.
5) Limited suitability for specific medicinal compounds.
6) Potential modification of medication pharmacokinetics.

Approaches for making of inclusion complexes[13]

1) Physical blending method

To achieve the required size of particles in the final product, CDs and medication are fully combined in a mortar by trituration and then passed through an appropriate sieve in a laboratory setting. On an industrial scale, creating physical combinations involves thoroughly mixing the medication and CDs in a fast mass granulator for around half an hour.

2) Kneading method

The visitor is dissolved in an appropriate vehicle that is room temperature and contains the necessary amount of CD. After that, the thick slurry is kneaded in a mortar for around an hour. To obtain the complex powder, the powder was dried in a hot air oven, then ground and sieved.[14]

3) Co-precipitation technique

After dissolving the CD in the water, swirl the mixture before adding the visitor. If the visitor is able to withstand the increased warmth, heating will degrade 20% more CD. Before a precipitate forms, the CD and guest solution must be cooled while being stirred. Using filtering, centrifugation, or decanting, the precipitate can be gathered and then cleaned. The scale-up is this method's primary drawback. The solid-state characterisation and dissolving properties of the gliclazide-β-cyclodextrin Moyano et al. have looked into inclusion complex.

4) Solution/solvent evaporation method

To the aqueous solution of CD, a solution with poor aqueous solubility guest in an appropriate organic solvent is added. The mixture is then agitated for 30 minutes at a temperature of between 40 and 50 0C, during which time turbidity begins to form in the mixture. The solution is then filtered, and the moist solid is left in the air or oven to eliminate any remaining solvent.

5) Neutralization precipitation method

Done by dissolving the drug in an alkaline solution, such as sodium/ammonium hydroxide, and then combining it with an aqueous CD solution. Next, agitation is used to neutralize the clear solution with a hydrochloric acid solution until the equivalence point is achieved. At this point, a white precipitate and the inclusion compound are starting to develop. After filtering, this precipitate is dried. Doijad et al.'s[17] research examined how complexing

piroxicam with beta-cyclodextrin improved its solubility. The drawback of this method is that it may cause drugs that are sensitive to alkaline and acidic breakdown to occur.

6) Milling/Co-grinding technique

After meticulously mixing the drug and CDs, the physical mixture is put into an oscillation mill and processed for an appropriate length of time. After operating at a predefined speed for a predetermined amount of time using balls of varying sizes inside, the ball mill is unloaded and sieved via a 60-mesh sieve. This method is better than other procedures from an environmental and economic perspective because it doesn't use any hazardous organic solvents, in contrast to similar techniques.[18]

7) Spray drying method

In the following technique the guest and cyclodextrin both are dissolved in suitable vehicle and spray dried in spray dryers. This method represents among the most employed methods to produce the inclusion complex starting from a solution. Vozone et. al.[19] have created budesonide complexation in cyclodextrins as well as particle aerodynamic characterisation of the solid complex for inhaling dry powder.

8) Lyophilization / Freeze drying technique

In this method guest is added to aqueous solution of cyclodextrin while mixing with a magnetic stirrer. After 24 hours of agitation, the resulting solution is frozen by keeping it in a repository at 50 to 60°C and is lyophilized in a freeze-dryer for 24 hours. This technique works well for converting thermolabile materials into complicated forms. It involves combining the medication and carrier molecules molecularly in a shared solvent as an alternative to solvent evaporation.[20]

9) Microwave irradiation method

In a round-bottom flask, the medication and cyclodextrin are dissolved in a solution of organic solvent and water according to a predetermined ratio. At 60º C, the combination responds in the microwave oven for one to two minutes only. After the reaction is complete, a suitable amount of solvent mixture is added to the reaction mixture above in order to remove any leftover, uncomplexed free drug and CD. The precipitate that results is separated with Wattmaan filter paper and dried in a vacuum oven at 40º C for 48 hours. Deshmukh et al.[21] created inclusion complexes of ziprasidone hydrochloride with beta-cyclodextrin and

hydroxypropyl beta-cyclodextrin using a range of super disintegrants to produce a fast-dissolving formulation.

10) Ultra sonication

1:1 molar ratio of drug and β-cyclodextrine was added in 2:8 ratio of hydroalcoholic solution i.e. ethanol and water. Mixture was treated with 60 watt Ultra Sonicator for specific time at different amplifications.

CYCLODEXTRIN

The cyclodextrins (CD) are cyclic oligosaccharides which are having a hydrophilous outer surface and a lipophilic interior chamber. The molecules of cyclodextrin have several hydrogen donors and acceptors and are comparatively big. Cyclodextrins find extensive application as "molecular cages" in the food, agricultural, pharmaceutical, and cosmetic sectors. They can be engaged as complexing agents in the pharma firm to increase the stability and bioavailability of poorly soluble drug as well as their aqueous solubility.

The three main CDs are torus-shaped macro-rings composed of glucopyranose units that are crystalline, homogenous, and non-hygroscopic.

1) The α-CD, comprises of six glucopyranose units.
2) The β-CD, comprises of seven glucopyranose units.
3) The γ-CD, comprises of eight glucopyranose units.[22,23]

Table 4: Properties of cyclodextrins.[24]

Cyclodextrin	α-CD	β-CD	γ-CD
No. of Glucopyranose units	6	7	8
Molecular weight	972	1135	1297
Solubility in water (g/100 ml)	14.5	1.85	23.2
pKa	12.33	12.2	12.08
Height (nm)	0.79	0.79	0.79
Cavity volume (nm)	0.174	0.262	0.472
Cavity volume (ml) Per 1 mol Per 1 g	1040.1	1570.14	256

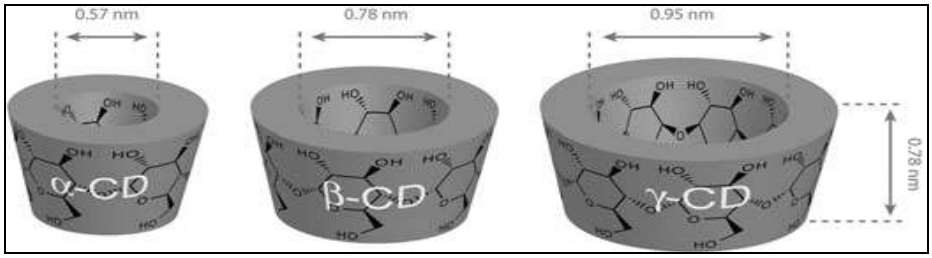

Figure 2: Representation of the geometry and dimensions of α-, β-and γ-CDs.[25]

History of Cyclodextrins

A. Villiers, a French scientist, separated bacterial digest from starch in 1891. Villiers called the substance "cellulosine" and it was a dextrin. The Austrian microbiologist Franz Schardinger subsequently identified the two crystalline compounds—α-dextrin and β-dextrin—that he had obtained from a bacterial breakdown of potato starch. He recognized Villiers' "cellulosine" as β-dextrin. Nowadays, these materials are often known as cyclodextrins (α- and β-cyclodextrins; CD and β-CD, respectively), or less commonly, cyclomaltodextrins.[26]

Table 5: Historical milestones in Cyclodextrins science.[27]

Historical period	Investigator	Event or achievement
1891	A. Villiers	The identification of alpha and beta cyclodextrins and the groundbreaking investigation of their chemical makeup
1903–1911	F. Schardinger	Isolation of bacteria responsible for CD synthesis; first attempted to distinguish between different Cyclodextrin
1930s	-	Maltose units bound via α -1,4-glycosidic linkages are found to be building blocks for CD molecule; first isolation of pure CDs
1935 1936	K. Freudenberg	γ -CD is discovered CD cyclic structure is disclosed
1940s	F. Cramer	Idea of inclusion complex formation is suggested
1948	K. Freudenberg W. Borchert	γ -CD structure is clarified Structures of α-, β- and γ -CD are determined by X-ray diffraction
1950s	D. French F. Cramer	Discovery of CDs with larger rings Study of inclusion complexation properties of CDs
1953	K. Freudenberg F. Cramer H. Plieninger	First patent on CDs
1957	D. French	First fundamental review on CDs containing first misinformation on toxicity of β-CD
1965	T. Higuchi	Development of a mathematical model describing

	K. Connors	inclusion complexation mechanism
1975	M. Furue	First publication on CD polymers
1976	Ono Pharmaceutical Co.	Release of the first medicine, prostarmon E, from CD
1980s	U. Brauns B. Müller J. Pitha	Beginning of industrial application of CDs in food and cosmetics HP β-CD is patented in Europe and the USA
1981	J. Szejtli	The first cyclodextrin book is published, and the First International Cyclodextrin Symposium is arranged.
1983	K. Miyajima	First suggestion of self-association of parent CDs
1991	V. Stella R. Rajewski	SBE β -CD is patented
1990s	A. Harada M. Kamachi	Intensive research activity on CD catenanes and rotaxanes
2000s	M. Bonini A. Coleman G. Gonzalez-Gaitiano T. Loftsson L. Szente	Intensive research activity on CD aggregation

β-Cyclodextrin: Structure and properties.

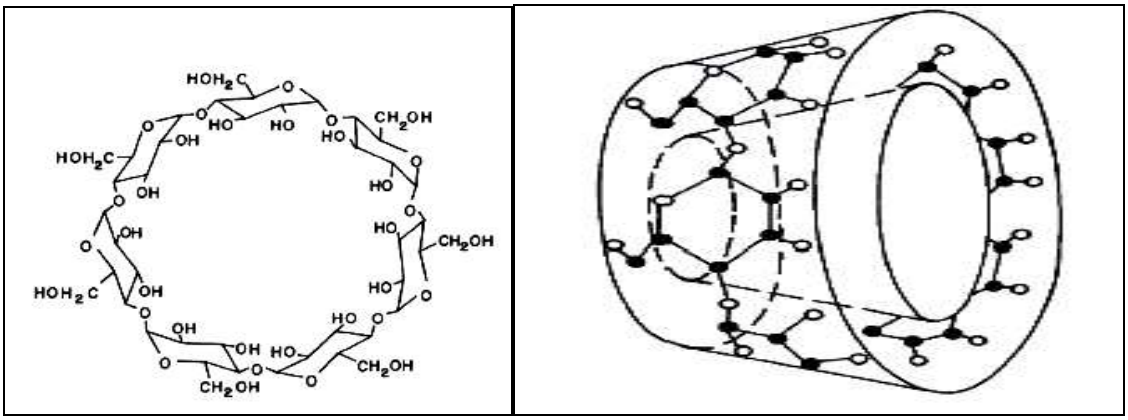

Figure 3: The chemical structure of β-cyclodextrin molecule.[28]

The structures of cyclodextrin are as follows: It is made up of α-D-glucopyranose units that are (α-1,4)-linked and have a hydrophobic inner cavity (fig 1). Cyclodextrin molecules have a cone like structure with secondary hydroxyl owing to the chair formation of the glucopyranose units, groups emanating from the wider edge and primary groups from the small edge. Because of this, the external surface of cyclodextrin molecules is hydrophilic, but the lipophilicity of their core cavity is similar to that of an aqueous ethanolic solution. Unlike γ-Cyclodextrine, the natural α-Cyclodextrine and β-Cyclodextrine are not hydrolyzable by human salivary or pancreatic amylases; nonetheless, the intestinal micro flora ferments all three at low to moderate oral dosages, hydrophilic cyclodextrins are thought to be

cytotoxic.[24,29] For parenteral formulations, α-cyclodextrin and its hydrophilic derivatives β- and γ-cyclodextrin can be used; for topical and oral formulations, native cyclodextrin and its derivatives are used. Due to its tendency to form visible aggregates in aqueous solution, γ-cyclodextrin is not well suited for parenteral formulations.[30] A selection of the notable β-cyclodextrin derivatives in the pharmaceutical sector are shown in Table 6.

Table 6: Pharmaceutical derivatives of β-cyclodextrin.[31]

Cyclodextrin	Character
2-Hydroxypropyl- β-CD	Introducing hydroxypropyl group at OH group
Sulfobutylether β-CD	Introducing sulfobutylether group to β-CD
Randomly methylated β-CD	Substitution of -OH with -CH_3
Branched β-CD	Glucosyl or maltosyl group
Methyl β-CD	Methylation β-CD at Hydroxyl group
Amino β-CD	Amination of β-CD at primary OH group
Polymer-Modified β-CD	Chemical linking or polymers like PVA and PEG

Sulfobutylether β-cyclodextrin: (SBE-β-CD)

SBE-β-CD is a specially modified cyclodextrin that is patent protected. Its chemical structure was thoughtfully engineered to optimize interaction and increase safety while enhancing the solubility, stability, and administration of active substances.[32]

Definition

SBE-β-CD, an anionic derivative of β-cyclodextrin, is kept apart from the hydrophobic cavity by a sodium sulfonate salt and a butyl ether spacer group. At positions 2, 3, and 6, a sulfobutylether (SBE) substituent is added to one or more glucopyranose units in the cyclodextrin structure.[32]

History of SBE-β-CD

Scientists at the University of Kansas' Higuchi Biosciences Center designed and first developed SBE-β-CD specifically for use in medication formulation and development. Six FDA-approved products—including Pfizer's VFENDIV and Onyx Pharmaceuticals' KYPROLIS®—have been made possible by this innovative technology. Over fifty SBE-β-CD-enabled products are in the clinical development stage right now. SBE-β-CD, also known as sulfo-butyl ether (SBE), is a combination of polyanionicβ-cyclodextrin derivatives of sodium sulfonate salt attached to the lipophilic cavity by a butyl-ether group. Evaluations of the mono, tetra, and hepta-substituted preparations led to the selection of SBE-β-CD as the cyclodextrin preparation with the highest favorable safety profile and drug association

qualities. Parenterally administered SBE-β-CD has proven harmless, in sharp contrast to unmodified β-cyclodextrin's nephrotoxicity.[32]

The low water solubility of these pharmaceuticals can be effectively solubilized thanks to the physical and chemical features of SBE-β-CD. This chiral molecule has a molecular weight of around 2163 and is made up of seven α-D glucopyranose units. (molecular formula $C_{42}H_{70-n}O_{35}(C_4H_8SO_3Na)_{nxH2O}$ n¼ 6.6]; Fig. 4).[33]

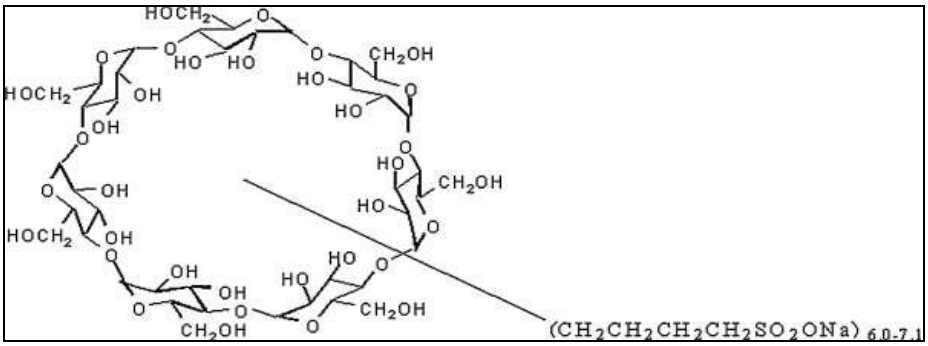

Figure 4: Structural formula of sulfobutylether-β-cyclodextrin sodium salt.[33]

Solubility

Cyclic sugar SBE-β-CD has a hydrophilic envelope and a sizable hydrophobic cavity. Many different chemicals have poor associations with the hydrophobic core. The combination formed by SBE-β-CD and the research chemical leads to a significant increase in water solubility.[32,33,34]

Table 7: Comparison of relevant physico-chemical properties of HP-β-CD& SBE-β-CD.[35]

Properties	HP-β-CD	SBE-β-CD
Crystallinity /amorphousness	Amorphous	Amorphous
Color	white	white
Administration route (typical examples)	Oral, nasal, suppository, intramuscular, intravenous, and ophthalmic	Inhalation, nasal, ophthalmic, subcutaneous, intramuscular, and oral
Acceptable DS according to pharmacopoeia	2.8 to10.5	6.2 to 6.9
Charge	Neutral	Polyanionic (Na^+ salt)
Suitability for taste masking	Suitable	Not suitable due to salty taste

Non-Clinical studies of SBE-β-CD

Pharmacology in Animal Models[36,37,38]

1. Investigations revealed that SBE-β-CD has no impact on both somatic and autonomic functions of anesthetized cats, nor on the cardiovascular systems of dogs and cats.
2. Rats' respiration, urine pH, or flow rates were not impacted by SBE-β-CD. At 500 mg/kg IV, rat urine showed slight increases in potassium and sodium and a greater increase in chlorine. These aren't regarded as clinically significant affects on renal function, though.
3. As a result, SBE-β-CD showed no pharmacological effect in several test systems.

Pharmacokinetics in Animal Models[39]

A 14 C-labeled SBE-β-CD side chain is being used to study the pharmacokinetics and metabolism of the drug in mice, rats, rabbits, and dogs.

1. HPLC and MS was employed to analyze urine samples, and the results showed that there had been no metabolic modifications to SBE-β-CD after in-vivo treatment.
2. In every researched species, SBE-β-CD is eliminated by the kidneys at a pace that aligns with their glomerular filtration rate (GFR).
3. Renal excretion of unmetabolized material is the method by which SBE-β-CD is excreted.
4. Following IV delivery of [14C]-SBE-β-CD, radioactivity was disseminated throughout all bodily tissues.
5. The absence of radioactivity in brain tissue indicates that SBE-β-CD is unable to pass through the blood-brain barrier.
6. Urine is the major route of excretion.
7. There was no evidence of retention in any tissue.

Toxicology in Animal Models

There was no clinical evidence of toxicity in dogs at daily doses up to 1500 mg/kg.

Clinical studies of SBE-β-CD

Clinical Pharmacokinetics[40,41]

1. In subjects with normal renal function, exposure data (Cmax and AUC) show that after 10 days of twice daily treatment, there is no accumulation of SBE-β-CD.
2. An injectable drug that has a renal clearance (Cl) rate of 120 mL/min, which is comparable to GFR and is entirely removed by the kidneys.
3. The average distribution volume at steady state (Vss) was 208 mL/kg, which is comparable to human extracellular fluid.

4. No radioactivity was found in the feces; 95% of the radioactivity was recovered and entirely removed in the urine.
5. Additionally, mass spectrometry examination of the urine samples confirmed that there had been no metabolic alterations to SBE-β-CD, confirming the absence of hepatic or metabolic involvement in its clearance.

Safety Studies[42,43,44]

1. Eighteen healthy male subjects were randomized to voriconazole plus SBE-β-CD or placebo for 10 days seven adverse events were reported in three of nine subjects, none of which were considered serious or related to SBE-β-CD.
2. In a different multiple dose safety study, the investigator determined that rare adverse events were related to the treatment; three subjects reported abnormal vision at the low SBE-β-CD dose (96 mg/kg day 1, 48 mg/kg multiple dose); one subject reported abnormal vision in the mid-dose group (96 mg/kg day 1, 64 mg/kg multiple dose); and one other subject reported abnormal vision, headache, and eye pain in the high dose group (96 mg/kg day 1, 80 mg/kg multiple dose).
3. Neither the Phase 1 trials of the intravenous formulation of voriconazole incorporating SBE-β-CD nor the studies looking at the effects of SBE-β-CD alone revealed any detrimental effects of SBE-β-CD on renal function in normal volunteers.
4. There were also no changes in other laboratory measurements such as blood pressure, ECG, and clinical pathology to suggest any systemic effects of single or multiple doses of SBE-β-CDin healthy volunteers.

Updates of research work on various drug-SBE-β-CD inclusion complex

- Abhijeet Kulkarni, *et.al,*[45] demonstrated how the SBE-β-CD complexation impacts the pH stability, solubility, and dissolution of the poorly soluble polyphenol chrysin (CHR) using the freeze-drying method. Phase solubility revealed the 1:1 stoichiometry. The creation of the inclusion complex was verified through analysis using FTIR, DSC, PXRD, and SEM. Additionally, the CHR/SBE-β-CD combination exhibited ~108 times quicker dissolution and better solubility than CHR.
- Jingna Xu *et.al,*[46] demonstrated an exclusive inclusion combination of nateglinide (NTG) with SBE-β-CD, which was synthesized by freeze-drying in an attempt to improve its properties. A phase solubility analysis was performed to find the stoichiometry and stability constant. These methods were then used to describe the solid inclusion complex:

1H, 2D, NMR, PXRD, SEM, DSC, and FT-IR. The results showed that nateglinide formed an inclusion complex with a stoichiometry of 1:1 by partially embedding from the secondary face into the SBE-β-CD cavity. The NTG-SBE-β-CD inclusion complex demonstrated increased water solubility in comparison to free NTG, suggesting potential therapeutic applications.

- Takayuki Furuishi, *et.al*,[47] investigated the effect of CD derivatives on the solubility of clozapine. We investigated the synergistic effect of water-soluble polymers and SBE-β-CD on clozapine solubility. Among these polymers were propylene glycol alginate (PGA), polyvinyl alcohol, sodium alginate, carboxymethylcellulose sodium salt, and hydroxypropyl methylcellulose. NMR revealed the production of a ternary complex including clozapine, SBE-β-CD, and PGA. It was found that the combination of PGA and SBE-β-CD increased the solubility of clozapine.
- Annalisa Cutrignelli, *et.al*[48] showcased a recently created curcumin soluble inclusion complex with SBE-β-CD that was produced employing a number of methods in both the solution and solid states. It was identified using phase solubility tests, Job's plot method, FTIR, NMR, DSC, and SEM. The data clearly show that curcumin combines with SBE-β-CD to generate an SBE-β-CD–Drug complex, which has an apparent 1455 M−1 formation constant. Moreover, SBE-β-CD significantly increases curcumin's water solubility at 25◦C (from 0.56 to 102.78 µg/mL), and lyophilization is the most effective way to prepare the complex for solid state extraction. In conclusion, an in vitro experiment using the human liver cancer cell line HepG-2 demonstrated that complexation significantly enhances curcumin's antioxidant and anticancer effects.
- Ashwinkumar Jain, *et.al*,[49,50] in this HPMC and polycarbophil were combined with danazol-β-SBE complex to create a mucoadhesive controlled release formulation. The mixture was then compacted into tablets. When comparing tablets containing polycarbophils to those containing hydroxypropylmethyl cellulose, there was an increase in mucoadhesion. The danazol-SBE-β-CD complex given intraperitoneally and the danazol-SBE-β-CD (in matrix) buccal tablets had absolute bioavailabilities of 64% and 25%, respectively, according to in vivo bioavailability tests conducted on dogs. These values are significantly higher than the 1.8% found for the commercial formulation Danocrine.
- Noratiqah Mohtar *et.al*,[51] investigated the solubility of fisetin, a flavonoid that occurs naturally, by complexing it with three distinct cyclodextrin types. SBE-β-CD showed the

highest complexation efficiency and preserved the in vitro antioxidant activity of offisetin. The amount of solubilized fisetin in the complex increased 5.9-fold in comparison to the water-only system as 20% v/v ethanol was added to the water. A twofold increase in the fine particle fraction (FPF) was noted when the fisetin-SBE-β-CD complex solution was sprayed dried with ethanol present, as opposed to the powder produced from the complex solution containing water alone. This implied that a dry powder inhaler may be used to inhale the powder with improved aerosolization properties. Fisetin-SBE-β-CD was successfully combined to create an inhalable dry powder with improved aqueous solubility. Large doses of fisetin may be therapeutically delivered to the deep lung region with the use of the dry powder.

- J. Savolainen *et.al,*[52] investigated the phenytoin inclusion complexation with SBE-β-CD and HP-β-CD to improve the medication's low water solubility and poor oral bioavailability. The formation of 1:1-complexes is revealed by AL type diagrams for both SBE-β-CD and HP-β-CD, which show that phenytoin's solubility increased in proportion to CD concentration. Phenytoin solid inclusion complexes with SBE-β-CD and HP-β-CD were prepared by freeze-drying. In vitro phenytoin dissolution rate was increased by phenytoin: HP-β-CD physical combination and inclusion complexes. Phenytoin formulations based on CDs raised peak plasma concentration by approximately 1.6 times and bioavailability (AUC0–24 h) by almost two times when compared to plain phenytoin. This study found that the increased bioavailability of phenytoin in the presence of CDs was due to a higher level of substance.
- Sutthilug Sotthivirat, *et.al,*[53] demonstrate that Prednisolone (PDL), a medication that is somewhat soluble in water, is released completely and continuously from controlled porosity osmotic pump pellets (CP-OPP) with the integration of SBE-β-CD. The addition of SBE-β-CD significantly improved PDL release from the CP-OPPs as compared to the coated pellet formulation that used lactose instead of SBE-β-CD. The molar ratio of SBE-β-CD to PDL, the microporous membrane's thickness, and the osmotic pressure differential across the membrane all affect PDL release profiles.
- Jian Wu, *et.al,*[54] Chitosan was ionic gelated with tripolyphosphate in the presence of cyclodextrins to create docetaxel-SBE-β-CD/chitosan nanoparticles. The outcomes showed that in vitro tests on release and rat small intestine absorption of docetaxel/SBE-β-CD /chitosan nanoparticles and docetaxel-SBE-β-CD inclusion complexes performed well. The docetaxel/SBE-β-CD /chitosan nanoparticles dramatically decreased the

clearance and raised the AUC0→t in the pharmacokinetics research. In comparison to the pure docetaxel formulation, the oral relative bioavailability of the docetaxel-SBE-β-CD /chitosan nanoparticles was as high as 1447.53%.

- Colin S. Goodchild, *et.al,*[55] Alphaxalone, a neuroactive steroid anesthetic, is poorly soluble in water. It was developed in 1972 with the nonionic surfactant component Cremophor EL and was marketed under the name Althesin (ALTH). The product was a flexible, short-acting IV anesthetic that was used in clinical settings in many different countries between 1972 and 1984. Because of a hypersensitive reaction to Cremophor EL, its clinical use was stopped. Three anesthetics were compared in this study: propofol, an alphaxalone preparation made with Cremophor EL, and a novel alphaxalone aqueous solution dissolved in 7-sulfobutyl-ether-β-cyclodextrin (SBE-β-CD), a water-soluble molecule with a lipophilic cavity that facilitates drug solubilization in water. Alloxalone provided fast-onset anesthesia in both formulations (PHAX and ALTH) at the same dosage. The anesthetic action of alphaxalone was not affected by the use of SBE-β-CD as a drug-solubilizing excipient; however, in PHAX, alphaxalone's therapeutic index was increased in comparison to ALTH. PHAX has a higher safety margin when compared to the propofol lipid formulation and the alphaxalone formulation found in Cremophor EL (ALTH).
- Ankitkumar S. Jain, *et.al,*[56] investigated SBE-β-CD's ability to form an inclusion complex with the low-water-soluble anti-epileptic drug carbamazepine using the spray-drying method. The creation of an inclusion complex between carbamazepine and SBE-β-CD was confirmed by DSC, IR, and NMR investigations, despite XRD testing suggesting that the inclusion complex was amorphous. Molecular modeling studies showed a good correlation with experimental results and indicated multiple mechanisms of interaction between carbamazepine and sulfobutylether-β-cyclodextrin. The inclusion complex's in vitro solubility profile was noticeably higher than that of powdered carbamazepine alone. The carbamazepine/SBE-β-CD combination showed significantly more anti-epileptic effect ($p < 0.01$) when given orally compared to the carbamazepine suspension.
- Samuel F. Lockwood, *et.al,*[57] studied the capacity of SBE-β-CD (Na), like the brand Captisol1, to raise crystalline astaxanthin's aqueous water solubility. Astaxanthin is a commercially significant oxygenated carotenoid, it is composed of 3,30-dihydroxy-β, β-carotene-4, and 40-dione. When crystalline astaxanthin and captisol were complexed, the crystalline astaxanthin's apparent water solubility increased by about 71 times, reaching a

concentration of around 2 mg/mL. The present study has demonstrated that crystalline astaxanthin can be more soluble in water. This development is expected to be profitable when crystalline astaxanthin is introduced into mammalian cell culture systems. Previously, these systems relied on liposomes or hazardous organic solvents to introduce carotenoids into aqueous solution.

- Michelle P. McIntosh, *et.al,*[58] has documented the etomidate synthesis in an aqueous solution and its evaluation in vivo using SBE-β-CD as a solubilizing agent. In addition to evaluating the phase-solubility behavior of etomidate as a function of SBE-β-CD concentration, accelerated solution stability studies were conducted using 2 mg/mL etomidate in a 5%w/v SBE-β-CD solution. Amidate, a commercial etomidate drug produced using propylene glycol as a cosolvent, was compared with the SBE-β-CD etomidate formulation given intravenously to dogs. The results suggest that the SBE-β-CD formulation is a promising clinical medicine product with a decreased side-effect profile.
- Ramsharan Singh, *et.al,*[59] compared the stability of the recently approved Captisol (SBE-β-CD)-stabilized propylene glycol-free melphalan injection (EvomelaTM) with that of the commercially available propylene glycol-based melphalan injection. The products were compared using both the admixture solutions prepared from ordinary saline in infusion bags and the reconstituted solutions in vials. It was demonstrated that the melphalan formulation made with Captisol technology was far more stable than the melphalan hydrochloride that was reconstituted with propylene-glycol-based diluents.

Marketed drug products containing SBE-β-CD:[27,60] β-CD is the most widely used CD-containing medicinal formulation, according to a comparative review of over 30 currently known formulations (Fig.6). This is because it is inexpensive to produce and is easy to make. β-CD do have certain disadvantages, though, most notably its comparatively lesser aqueous solubility. β-CD's limited solubility in water makes it inappropriate for parenteral delivery. A general solution to this issue was discovered by substituting numerous β-CD hydroxyl on the molecule's two rims. Furthermore, as in comparison with there parent CDs, some derivatives, such 2-hydroxypropyl (HP-β-CD) and sulfobutylether (SBE-β-CD), have better toxicological profiles. Owing to these benefits, substituted CDs account for approximately one-third of all CD-containing medications; conversely, a high tolerance in human body provided new opportunities for the development of more efficient injectable formulations.

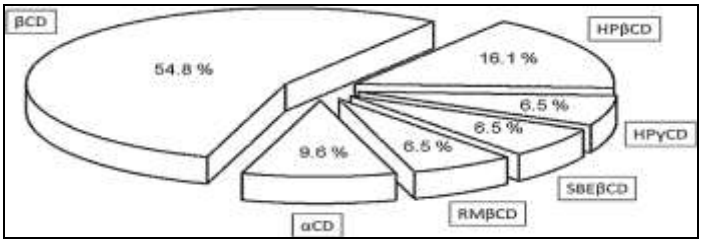

Figure 6: Distribution of cyclodextrins in pharmaceutical products that are sold.

Table 9: Marketed drug products containing SBE-β-CD.[60]

Brand Name	Drug	Category	ROA	Drug: SBE-β-CD Ratio
DEXOLVE	Voriconazole	Antifungal	IV	1:2.6
KYPROLIS	Carfilzomib	Anticancer	IV	1:16.6
NEXTERONE	Amiodarone.HCl	Antiarrhythmic	IV	1:3
GEODON	Ziprasidone(mesylate)	Antipsychotic	IM	1:2.8
CERENIA	Maropitant (citrate)	Anti-Nausea	IV	1:1.4
ABILIFY	Aripiprazole	Antipsychotic	IM	1:4.1
NOXAFIL	Posaconazole	Antifungal	IM	1:7.2

SBE-β-CD in Patents

1. **Formulations containing Amiodarone and SBE-β-CD:** Gerold L. *et.al,*[61] They reveal the aqueous parenteral formulations that contain SBE-β-CD and amiodarone, an antiarrhythmic drug. The formulation yields appropriate quantities of amiodarone suited for parenteral administration and can be made in acidic, neutral, or slightly basic media. Amiodarone in the SBE-β-CD formulation is available as a reconstituted powder or in liquid form. Furthermore, solutions with an amiodarone concentration of more than 200 mg/mL can be made. Water can be added to solutions to make them dilutable or non-dilutable in room temperature or under usual clinic circumstances.

2. **Formulations containing Propofol and SBE-β-CD:** Diane O. Thompson, *et.al,*[62] Using sulfobutylether-β-cyclodextrin as a solubilizing and complexing excipient, they created a genuine aqueous solution rather than a propofol (anesthetic) suspension. Compared to known emulsion type propofol formulations, this formulation reduces injection pain and the allergic response and microbiological contamination problems usually associated with propofol parenteral formulations. Unlike emulsion-type preparations of tranquil hypnotics, the liquid formulation can be sterile filtered. To create a solid formulation, the liquid formulation can be dried in any way, such as lyophilization.

3. **DPI Formulation containing SBE-β-CD:** James D. Pipkin, *et.al,*[63] They offered an inhalable dry powder formulation with an active ingredient and SBE-β-CD. Rather than

acting as an absorption enhancer, the SBE-β-CD functions as a carrier. The SBE-β-CD-containing particles separate from the active agent-containing particles in the throat or buccal cavity after being released from the DPI device, and the active agent-containing particles then go farther into the respiratory system. DPI can deliver drugs with a positive, neutral, or negative electrostatic charge when SBE-β-CD is utilized as the carrier.

4. **Formulations containing Clopdogrel and SBE-β-CD:** Rebecca L. Wedel, *et.al*,[64] Their innovation offers compositions that contain SBE-β-CD and clopidogrel, either as a free base or as a salt that is amenable to pharmaceuticals. The SBE-β-CD facilitates the solubility and stability of clopidogrel in aqueous solutions. Clopidogrel is more stable against degradation by hydrolysis, thermal degradation, and photolysis. Clopidogrel is more stable against degradation by hydrolysis, thermal degradation, and photolysis. Clopidogrel containing SBE-β-CD is available as a liquid, solid, or powder that can be reconstituted. It is possible to make concentrated liquid compositions as well as ready-to-use ones. The compositions presented here offer significant pharmacokinetic, pharmacodynamic, and/or therapeutic advantages over a tablet composition administered peroraly. They can be supplied parenterally or perorally.

5. **Composition comprising an RNA polymerase inhibitor and cyclodextring for treating viral infection:** N. Lawson *et.al*,[66] The composition of the present invention consists of cyclodextrin, compound 1 or a salt of it that is appropriate for use in pharmaceuticals, and optionally a pH-adjusting agent. The pharmacological formulations reported treat viral infections from multiple families, including Arenaviridae, Coronaviridae, Filoviridae, Flaviviridae, and Paramyxoviridae, by combining an RNA polymerase inhibitor with cyclodextrin. By acting as a solubilizer, cyclodextrin improves the inhibitor's stability and bioavailability. To maximize the stability and solubility of the formulation, an optional pH-modifying agent may be included. These formulations, which are appropriate for parenteral administration and target viral replication, present a viable therapeutic option in situations where supportive care is the only available choice.

Regulatory status

The status of CDs in terms of regulation is always changing. Extensive safety and clinical trials proving the excellent systemic safety profile of SBE-β-CD support its regulatory acceptance. Drug Master Files (DMF) Type IV and V are kept up to date with the FDA. Type IV DMF contains CMC data specifically related to Captisol production. Furthermore, the

USP N.F. monograph SBE-β-CD has been granted by USP. After reviewing the data package, many FDA divisions approved the use of SBE-β-CD in clinical investigations. Currently, six commercial products use SBE-β-CD. The FDA has classified it as generally recognized as safe (GRAS) under specific circumstances, and it is included in the USP/NF, JPC, and European and US Pharmacopoeias (USP/NF).[32,65]

CONCLUSION

SBE-β- CD which is one of the uniquely modified latest derivatives of CD serves as a better alternative for solving the problem of poor aqueous solubility. Non-clinical and clinical studies confirm the safety of SBE-β- CD. Many formulations are successfully developed and marketed by complexing the drug with SBE-β- CD reveals regulatory acceptance of it. Though parent β-CD is used very frequently in the formulations but new trends suggest the use of derivatives of it increased a lot.

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