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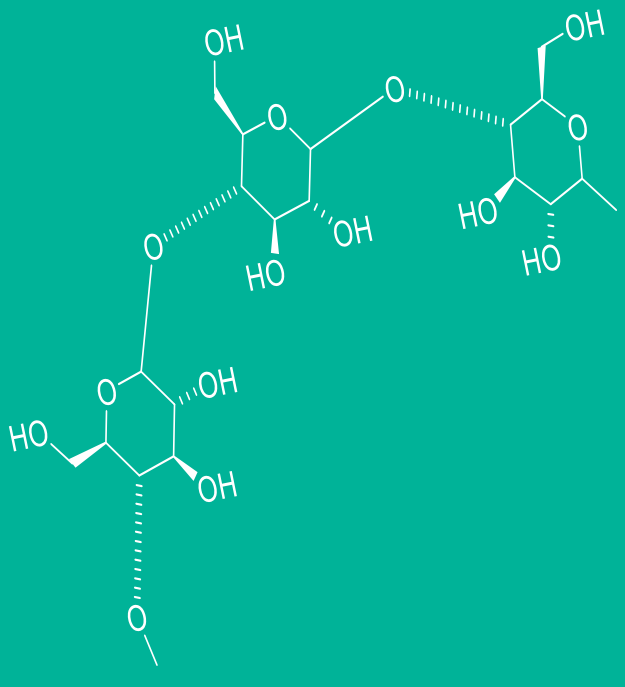
Cyclodextrins

Solubilization and stabilization excipients

for improved efficacy and safety of your product



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ADVANTAGES

Cyclodextrins (CDs) are oligosaccharides used as complexing agents to increase the water solubility of lipophilic compounds and bio-availability of medicinal products.

Due to their cyclic structure, cyclodextrins can form inclusion complexes when they interact with hydrophobic drug substances; as a result, they demonstrate higher aqueous solubility than that of comparable acyclic saccharides.

Cyclodextrins are made up of six, seven or eight dextrose units, forming α-, β-, and γ-Cyclodextrins respectively, with different cavity sizes. Cavity size is the major determinant for the suitability of cyclodextrins in complexations.

VIO Chemicals offers high quality soluble α-, β-, and γ-Cyclodextrins for pharmaceutical applications.

BENEFITS

The mechanism for the increased solubility of cyclodextrins is rooted in their ability to form non-covalent dynamic inclusion complexes in solution. High solubility can lead to high dissolution rates and greater oral bioavailability and stability of biopharmaceuticals with high or low permeability and low solubility, BCS Class II and IV drug substances.

Cyclodextrins can also lower the free concentration of the drug and therefore affect significantly the pharmacokinetics and pharmacodynamics of the active substance.

In addition, cyclodextrins can reduce or prevent gastrointestinal and ocular irritation, reduce or eliminate unpleasant smells or tastes, prevent pre-systemic drug-drug or drug-additive interactions within a formulation or help to convert oils and liquid drugs into microcrystalline or amorphous powders.

FEATURES

- High aqueous solubility of drug substances
- Formation of inclusion complexes
- Bio-adaptability and multi-functional properties
- Permeability through the biological membranes

APPLICATIONS

Cyclodextrins have multiple applications. A great number of different pharmaceutical products containing cyclodextrins are currently on the market worldwide, mostly tablets, aqueous parenteral solutions, nasal sprays and eye drop solutions.

Examples of the use of cyclodextrins in medicines on the European market are β-CD in Cetirizine tablets and Cisapride suppositories, and γ-CD in Minoxidil solution. Examples of the use of β-CD derivatives are SBE-β-CD in the intravenous antimycotic Voriconazole, and HP-β-CD in the antifungal Itraconazole, intravenous and oral solutions. In Germany and Japan there are infusion products on the market, containing Alprostadil (PGE1) with α-CD.

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α-Cyclodextrin (α-CD), EP, USP/NF

- CAS No: 10016-20-3
- Empirical formula: $C_{36}H_{60}O_{30}$
- Molecular weight: 972.84

TEST	SPECIFICATION
Appearance	white or almost white, amorphous or crystalline powder
Solubility	freely soluble in water, slightly soluble in propylene glycol, practically insoluble in anhydrous ethanol and in methylene chloride
Identification Specific optical rotation HPLC Reaction with Iodine solution	 +147 to +152 (dried substance) (1% w/v in CO_2 –free water) has to confirm with reference material positive
Reducing sugars	max. 0.2%
pH	5.0 to 8.0
β-CD content	max. 0.25%
γ-CD content	max. 0.25%
Sum of impurities other than β– CD and γ-CD	max. 0.5%
Light absorbing impurities	NMT 0.10 between 230-350 nm NMT 0.05 between 350-750nm (1% w/v in CO_2-free water)

TEST	SPECIFICATION
Assay	97.0 - 102.0% dried substance (EP) 98.0 - 101.0% on anhydrous basis (USP/NF)
Clarity of solution	clear
Loss on drying Water	max. 11% (EP) max. 11% (USP/NF)
Sulfated ash	max. 0.1%
Residual solvents	limits according to EP, USP/NF, ICH Q3C
Microbiological analysis: TAMC, TYMC, specific microorganisms (USP/NF)	tests and limits may vary depending on the use of the material
Storage conditions	in an airtight container

Examples of API formulations containing α-CD, currently on the market*: Alprostadil (PGE), Cefotiam hexetil HCl,

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β-Cyclodextrin (β-CD), EP, USP/NF

- CAS No: 7585-39-9
- Empirical formula: $C_{42}H_{70}O_{35}$
- Molecular weight: 1134.98

TEST	SPECIFICATION
Appearance	white or almost white, amorphous or crystalline powder
Solubility	sparingly soluble in water and in propylene glycol, practically insoluble in anhydrous ethanol and in methylene chloride
Identification	
Specific optical rotation	+160 to +164 (dried substance) (1% w/v in CO_2 –free water)
HPLC	has to confirm with reference material
Reaction with Iodine solution	positive
IR (USP/NF)	has to confirm with reference material
Reducing sugars	max. 0.2%
pH	5.0 to 8.0
α-CD content	max. 0.25%
γ-CD content	max. 0.25%
Sum of impurities other than α– CD and γ-CD	max. 0.5%
Light absorbing impurities	NMT 0.10 between 230-350 nm NMT 0.05 between 350-750nm (1% w/v in CO_2-free water)

TEST	SPECIFICATION
Assay	98.0 - 101.0% dried substance (EP) 98.0 - 102.0% on anhydrous basis (USP/NF)
Colour and clarity of solution	clear and colourless
Loss on drying Water	max. 16% (EP) max. 14% (USP/NF)
Sulfated ash	max. 0.1%
Residual solvents	limits according to EP, USP/NF, ICH Q3C
Microbiological analysis: TAMC, TYMC, specific microorganisms (USP/NF)	tests and limits may vary depending on the use of the material
Storage conditions	in an airtight container

Examples of API formulations containing β-CD, currently on the market*: Benexate, Cetirizine, Lodine, Nicotine, Nimesulde, Omeprazole, Piroxicam, Tiaprofenic acid

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γ-Cyclodextrin (γ-CD), EP, USP/NF

- CAS No: 17465-86-0
- Empirical formula: $C_{48}H_{80}O_{40}$
- Molecular weight: 1297.12

TEST	SPECIFICATION
Appearance	white or almost white, amorphous or crystalline, hydroscopic powder
Solubility	freely soluble in water, very slightly soluble in propylene glycol, practically insoluble in anhydrous ethanol and in methylene chloride. When dissolved in water, it forms a colloidal dispersion over time.
Identification Specific optical rotation HPLC IR	 +174 to +180 (dried substance) (1% w/v in CO2 –free water) has to confirm with reference material has to confirm with reference material
Reducing sugars Reducing substances	max. 0.2% (EP) max. 0.5% (USP/NF)
pH	5.0 to 8.0
α-CD content	0.5%
β-CD content	0.5%
Sum of impurities other than α-CD and β-CD	0.5 %

TEST	SPECIFICATION
Assay	97.0 - 102.0% dried substance (EP) 98.0 - 102.0% dried substance (USP/NF)
Colour and clarity of solution	clear Abs at 420 nm, NMT 0.20 (10% w/v in CO_2-free water)
Loss on drying	max. 11.0%
Sulfated ash	max. 0.1%
Residual solvents	limits according to EP, USP/NF, ICH Q3C
Microbiological analysis: TAMC, TYMC, specific microorganisms (USP/NF)	tests and limits may vary depending on the use of the material
Storage conditions	in an airtight container

Compared with α- and β-Cyclodextrins, γ-Cyclodextrin has a larger internal cavity, which leads to higher water solubility and greater bioavailability of the drug substance.

Examples of API formulations containing γ-CD, currently on the market*: Minoxidil

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Hydroxypropyl-β-Cyclodextrin (HP-β-CD), EP, USP/NF

- CAS No: 94035-02-6
- Empirical formula: $C_{42}H_{70}O_{35}(C_3H_6O)x$, x=7·MS
- Molecular weight: -

TEST	SPECIFICATION
Appearance	white or almost white, amorphous or crystalline powder
Solubility	freely soluble in water and in propylene glycol
Identification IR Clarity of solution	 has to confirm with reference material Clear and colourless
Conductivity	max. 200µS·cm^{-1} (10% w/v in CO2 –free water)
β-CD content	max. 1.5%
Propylene glycol	max. 2.5%
Propylene oxide	NMT 0.0001% (USP/NF)
Other single impurity	max. 0.25% (USP/NF)
Sum of other impurities	max. 1%

TEST	SPECIFICATION
Assay—Molar substitution (MS)	0.40 - 1.50
Loss on drying	max. 10.0%
Residual solvents	limits according to EP, USP/NF, ICH Q3C
Microbiological analysis: TAMC, TYMC, specific microorganisms, BET, sterility (USP/NF)	tests and limits may vary depending on the use of the material
Storage conditions	in an airtight container

Examples of API formulations containing HP-β-CD, currently on the market*: Aripiprazole, Cisapride, Hydrocortisone, Indomethacin, Levosimendan, Mitomycin, Posaconazole (POS) and Florfenicol (veterinary drug)

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Sulfobutyl-ether-β-Cyclodextrin sodium (SBE-β-CD), EP, USP/NF

- CAS No: 182410-00-0
- Empirical formula: $C_{42}H_{70-n}O_{35}.(C_4H_8SO_3Na)_n$
- Molecular weight: 2163 when n=6.5

TEST	SPECIFICATION
Appearance	white or almost white, hydroscopic powder
Solubility	freely soluble in water, practically insoluble in anhydrous ethanol and in methylene chloride
Identification IR Reaction of Sodium HPLC	 has to confirm with reference material positive has to confirm with reference material
Reducing sugars	max. 0.05%
pH	5.0-7.5 (EP) / 4.0-6.8 (USP)
β-CD content	max. 0.1%
1,2λ⁶-oxathiane-2,2-dione (EP) 1,4-Butane Sultone (USP/NF)	max. 0.5ppm
4-hydroxybutane-1-sulfonic acid	≤0.1% (EP) ≤0.09 (USP/NF)
4,4'-oxydi(butane-1-sulfonic acid) (EP) Bis(4-sulfobutyl) ether disodium (USP/NF)	≤0.05%

TEST	SPECIFICATION
Assay	98.0 - 102.0% anhydrous substance (EP) 95.0 - 105.0% on anhydrous basis (USP/NF)
Clarity of solution	clear and colourless
Chlorides	max. 0.12% (corresponding to 0.20 % expressed as sodium chloride)
Water	max 10.0%
Average degree of substitution (DS)	5.9 - 6.6 (EP) 6.2 - 6.9 (USP/NF)
Residual solvents	limits according to EP, USP/NF, ICH Q3C
Microbiological analysis: TAMC, TYMC, specific microorganisms, BET (USP/NF)	tests and limits may vary depending on the use of the material
Storage conditions	in an airtight container

* Information published in Nature Reviews Drug Discovery 3, 1023-1035 (2004).

SBE-β-CD has been designed to maximize safety and optimize interaction with drug molecules to improve the solubility, stability, bioavailability or lessen volatility, irritation, smell or taste of the drug. For β-CD, which itself has a relatively low aqueous solubility, substitution of any of the hydrogen bond-forming hydroxyl groups, even by lipophilic functions, results in a dramatic improvement in the aqueous solubility of the SBE-β-CD derivative.

Examples of API formulations containing SBE-β-CD, currently on the market: Carfilzomib, Voriconazole, Ziprasidone maleate, Posaconazole, Itraconazole and Maropitant (veterinary drug)*, Remdesivir

Products which are subject to patent protection are currently not offered or made available in countries where patents are in force. No orders or deliveries are possible prior to the expiry date of valid patents.

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