CYCLOLAB

The Cyclodextrin Company

Dexolve™

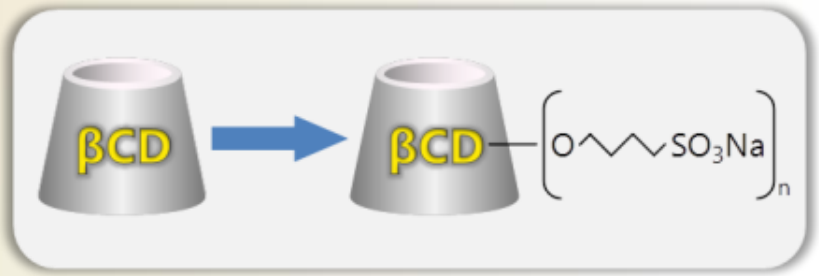
the USP compliant SBECD

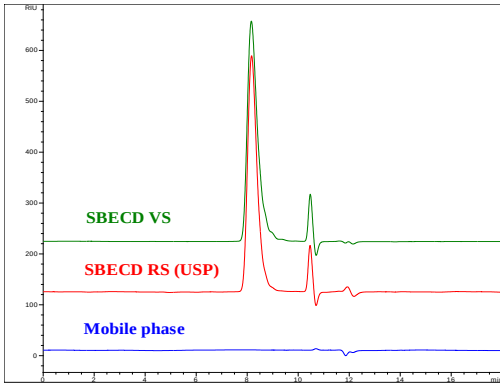
of Cyclolab Ltd

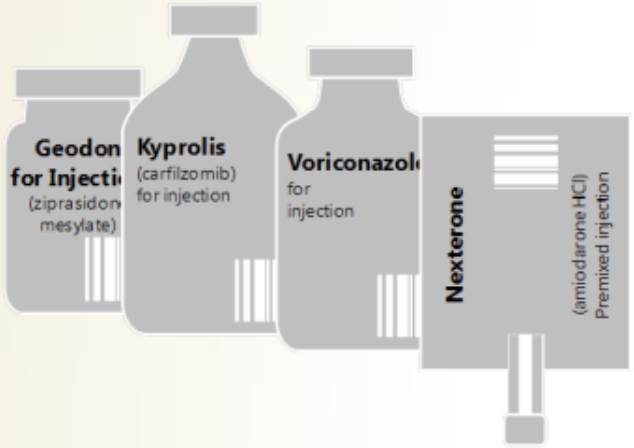
Dexolve™

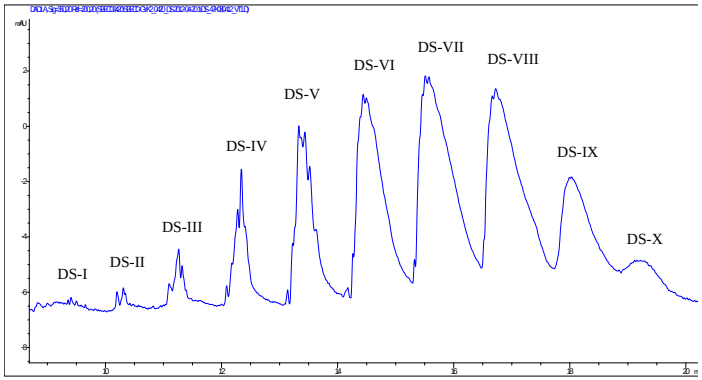
for Improved Pharmaceutical Formulations

Cyclolab Ltd is the producer of the first generic USP-conform Betadex Sulfobutyl Ether Sodium (SBECD = Dexolve™)









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E-mail: cyclolab@cyclolab.hu
Homepage: www.cyclolab.hu
VAT No.: HU 10678970

ISO 9001

FDA REGISTERED
DMF No. 21922

Drug master file of the excipient
Sulfobutyl-ether-β-cyclodextrin sodium salt
(SBECD)

EudraGMDP
OGYI/28943-2/2014

Document No.: DMF-SBECD-v02

CANADA HEALTH
DMF No. 2009-080

Dexolve™

for Improved Pharmaceutical Formulations

Why use Dexolve? Possibilities…

- Significant solubility enhancement (10 to 100,000 fold)
- Improvement of chemical stability
- Increased bioavailability, facilitated delivery
- Reduced aggregation
- Moderate irritation or reduced side-effects
- Maximized patient safety, complete renal elimination
- Enables formulation of water-insoluble APIs in all dosage forms
- Lower API doses can be achieved

Dexolve™

for Improved Pharmaceutical Formulations

There are 10 APIs on the market and at least 60 further in development in formulations containing SBECD including:

- Voriconazole
- Carfilzomib
- Amiodarone
- Ziprasidone
- Maropitant (veterinary use)
- Aripiprazole
- Posaconazole
- Carbamazepine
- Melphalan
- Delafloxacin
- Mebendazol
- Topiramate
- Omeprazole
- Clopidogrel
- Docetaxel
- Meloxicam
- Allopregnanolone

Several other nitrogen containing API bases are in various clinical phases

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for Improved Pharmaceutical Formulations

Main regulatory/QA/sales aspects:

- **Maintained DMF** for SBECD in US and Canada since 2008

- Prepared via a self-developed **proprietary, patented technology** with a process **independent from any existing patents (expires in 2031)**

- **36-month stability** data

- Successful production of over 100 subsequent USP compliant batches – **no OOS result**

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Main regulatory/QA/sales aspects:

- Dedicated production facility with a capacity of over **12000 kg/year**

  (extendable to 20-30,000 kgs/yr without investment)

- **120 kg batch size**

- Quality system compliant to **ISO 9001 and GMP** requirements (regularly audited)

No down payment, No milestone payment,
No royalty payment

Dexolve™

for Improved Pharmaceutical Formulations

Main regulatory/QA/sales aspects:

- Over 30 APIs in development using Dexolve

- **Over 60 partners in commercial and development phases using Dexolve**

- **Research grade material available at reduced price for non-clinical development**

- Flexible business model to handle partners' requests and **provide technical support** on development

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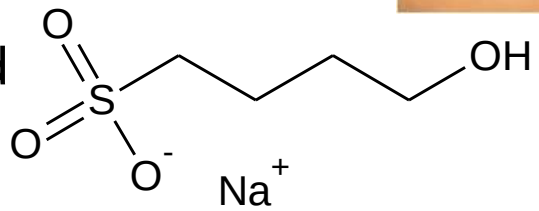
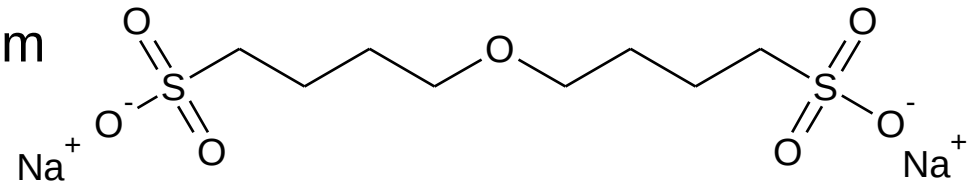
Available reference materials:

- Betadex

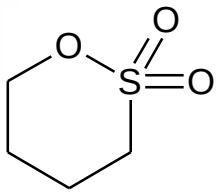
- 4-Hydroxybutane-1-sulfonic Acid



- Bis(4-sulfobutyl) Ether Disodium



- 1,4-Butane Sultone



- Betadex Sulfobutyl Ether Sodium

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ISO 9001

RELEASE SPECIFICATION (USA/CA)	Version: 08
Product: **Sulfobutyl-ether-β-cyclodextrin sodium salt (SBECD)**	Code: Rel_SBE_USP_v08
Quality: pharma grade	

Prepared by (QC)/date:	Revised by (QA)/date:	Approved by (QA)/date:
September 19,2017	September 19,2017	September 19,2017

Test	Method	Specification
Appearance #	visual (FIZ 05/06)	White or off-white powder
Identification A	IR; USP <197>, EP 2.2.24	complies with SBECD reference
Identification B (Assay method)	HPLC; USP <621>, EP 2.2.29	t_R of major peak complies with SBECD reference
Identification C	CE; USP <1053>, EP 2.2.47	Average degree of substitution: 6.2 - 6.9
Identification D	Sodium ID; USP <191>, EP 2.3.1	positive test
Assay #	HPLC; USP <621>, EP 2.2.29	95.0-105.0 % on the anhydrous basis
Heavy metals	ICP-MS, USP <232,233>	Cadmium NMT 0,2 µg/g Lead: NMT 0,5 µg/g Arsenic NMT 1,5 µg/g Mercury NMT 0,3 µg/g Chromium NMT 110 µg/g Nickel NMT 2 µg/g Molybdenum NMT 150 µg/g Vanadium NMT 1 µg/g
Limit of related substances # Beta Cyclodextrin (Betadex) Total other impurities*	HPLC; USP <621>, EP 2.2.29	NMT 0.1 % NMT 1.0 %
Limit of 1,4-Butane Sultone	GC; USP <621>, EP 2.2.28	NMT 0.5 ppm
Limit of Sodium Chloride	Limit test; USP <221>	NMT 0.2 %
Limit of 4-Hydroxybutane-1-sulfonic Acid	CE; USP <1053>, EP 2.2.47	NMT 0.09 %
Limit of Bis(4-sulfobutyl) Ether Disodium	CE; USP <1053>, EP 2.2.47	NMT 0.05 %
Bacterial Endotoxin Test #	EP-USP harmonized method	≤ 24 IU/g
Microbial Enumeration Tests #	EP-USP harmonized method	TAMC ≤ 100 cfu/g; TYMC ≤ 50 cfu/g
Test for Specified Microorganism	EP-USP harmonized method	absence of Escherichia Coli /1 g

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RELEASE SPECIFICATION (USA/CA)	Version: 08
Product: **Sulfobutyl-ether-β-cyclodextrin sodium salt (SBECD)**	Code: Rel_SBE_USP_v08
Quality: pharma grade	

Test	Method	Specification
Phosphate content*	UV-Vis Spectroscopy; USP <851>, EP 2.2.25	525-700 µg/g
Clarity of solution (30%, w/v) #	visual, see details in the USP Monograph, EP 2.2.1	the solution is clear, and essentially free from particles of foreign matter
Average Degree of Substitution [DS]	CE; USP <1053>, EP 2.2.47	6.2 – 6.9
Peak distribution	CE; USP <1053>, EP 2.2.47	Each SBECD peak (I-X) meets the limit range (peak area %) of the Monograph

SBECD sodium peaks	Limit range (% peak area)
I (DS-1)	0-0.3
II (DS-2)	0-0.9
III (DS-3)	0.5-5.0
IV (DS-4)	2.0-10.0
V (DS-5)	10.0-20.0
VI (DS-6)	15.0-25.0
VII (DS-7)	20.0-30.0
VIII (DS-8)	10.0-25.0
IX (DS-9)	2.0-12.0
X (DS-10)	0-4.0

Residual solvents: ethanol*	GC; USP <621>, EP 2.2.28	NMT 2500 ppm
pH (30%, w/v) #	USP <791>	4.0 – 6.8
Water Content #	USP <921> Method I, EP 2.5.12	NMT 10.0 %

*No requirements are given in the USP N.F. for content of residual solvents (ethanol)
#To be performed in stability study

Packaging and Storage: Preserve in well-closed containers, store at room temperature. Protect from moisture.
Labelling: indicate its use in the manufacture of injectable dosage forms.

Completely USP compliant!

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Company contacts – ASK FOR A FREE SAMPLE:

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Contact person: Tamas Sohajda, PhD

R&D Director

sohajda@cyclolab.hu **Tel: (+36) 1-347-60-72**

CYCLOLAB

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User's guide for Dexolve-7

A simple 3-step manual for successful dissolution of your drug substance

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STEP 1

Weigh in the following Dexolve-7 amounts into 20 ml vials and prepare solutions with the given volume of distilled water:

Dexolve-7*	Distilled water
3.0 g	7.0 mL
2.0 g	8.0 mL
1.0 g	9.0 mL
0.5 g	9.5 mL

**for accurate results take the water content of Dexolve-7 into consideration*

Use stirrer bar and magnetic stirrer.

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STEP 2

- After the complete dissolution of Dexolve-7, add ~50 mg or appropriate volume of your drug (candidate) to each vial. Should you be short of material, take smaller volume of the Dexolve-7 solutions and dispense reduced amount of your substance, accordingly.

- Stir the resulting suspensions for 24 hours at room temperature. If your substance is sensitive, then cool your samples and protect them from light in the meantime.

- Observe the vials. If your substance completely dissolves upon stirring, dispense additional amount of your substance. Always ensure excess of material to be dissolved.

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STEP 3

- When finished, filter the suspensions through PVDF syringe filters.

- Analyze the filtrate for your drug content.

- Establish relationship between the concentrations of Dexolve-7 and the solubilized amounts of drug substance. Compare the data with the pure aqueous solubility of your substance.

In case you need technical help to facilitate the dissolution or to improve the solubilizing potency further,

contact us!