CYCLOLAB

The Cyclodextrin Company

Getting the best out of Cyclodextrins

CYCLOLAB Ltd.

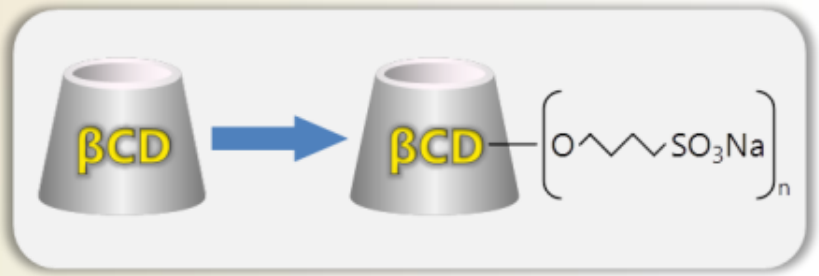
Dexolve™

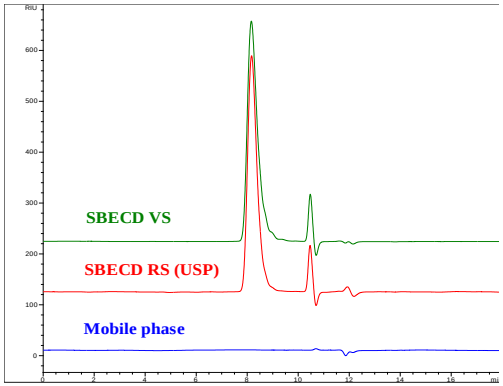
the USP and EP compliant SBECD of Cyclolab Ltd

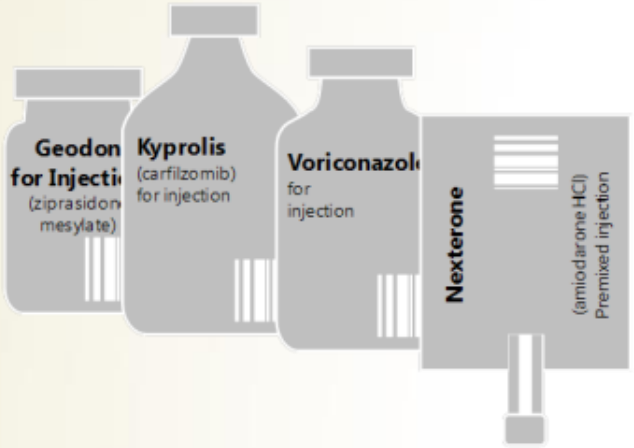
Dexolve™

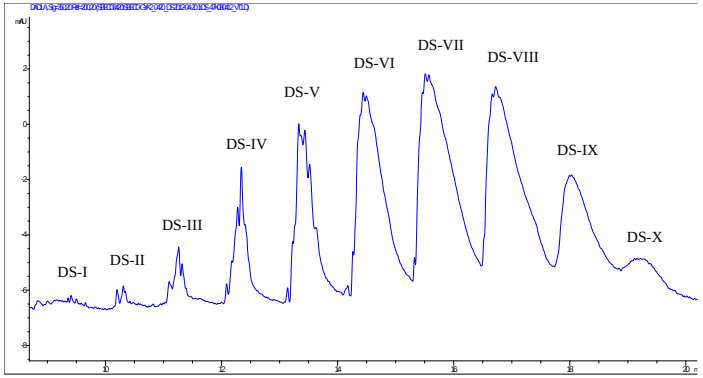
for Improved Pharmaceutical Formulations

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









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CYCLOLAB
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ISO 9001

FDA REGISTERED

DMF No. 21922

GMP

OGYÉI/57792-7/2018

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

Document No.: DMF-SBECD-v02

CFDA China Food and Drug Administration

DMF No. F20180001741

CANADA HEALTH

DMF No. 2009-080

EudraGMDP

OGYÉI/30391-2/2018

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

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for Improved Pharmaceutical Formulations

There are 11 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
- Brexanolone
- Mebendazol
- Topiramate
- Omeprazole
- Clopidogrel
- Docetaxel
- Meloxicam
- Allopregnanolone
- Iohexol

Several other nitrogen containing API bases are in various clinical phases

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Main regulatory/QA/sales aspects:

- **Maintained DMF Type IV** for SBECD in US and Canada since 2008, in China since 2019

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

- **36-month stability** data (48-month from July, 2019)

- Successful production of over 150 subsequent USP compliant batches – **no OOS result in the production**

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for Improved Pharmaceutical Formulations

Main regulatory/QA/sales aspects:

- Dedicated production facility with a capacity of over **15000 kg/year** (extendable to 20-30,000 kgs/yr without investment)

- **110-125 kg batch size**

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

No down payment, No milestone payment, No royalty payment

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for Improved Pharmaceutical Formulations

Main regulatory/QA/sales aspects:

- Over 60 APIs in development using Dexolve

- **Over 100 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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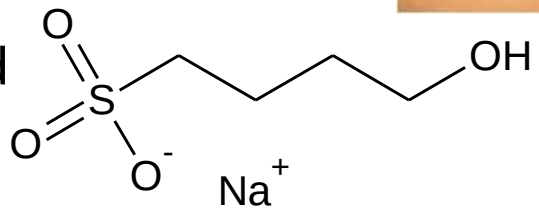
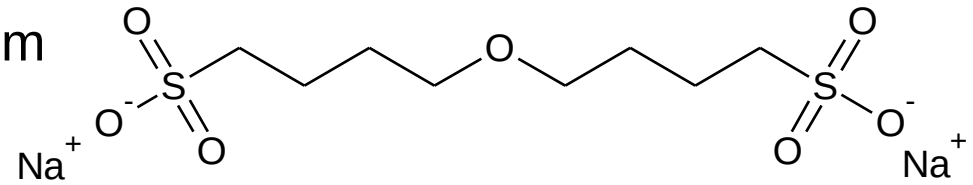
Available reference materials:

- Betadex

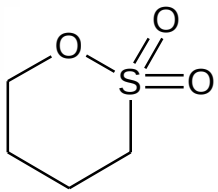
- 4-Hydroxybutane-1-sulfonic Acid



- Bis(4-sulfobutyl) Ether Disodium



- 1,4-Butane Sultone



- Betadex Sulfobutyl Ether Sodium

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ISO 9001

CUSTOMER SPECIFICATION	
Product: **Sulfobutyl-ether-β-cyclodextrin sodium salt (SBECD)** Quality: pharma grade USP and EP compliance	Version: 02 Code: Rel_SBE_USP_EP_v02

Prepared by (QC)/date:	Revised by (QC)/date:	Approved by (QA)/date:
21 February 2019	February 21, 2019	21 February 2019

Test	Method	Specification
Appearance* #	visual	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> NMR USP <761> EP 2.2.33	Meets the requirement of average degree of substitution
Identification D	Sodium ID; USP <191>, EP 2.3.1	positive test for sodium
Assay #	HPLC; USP <621>	95.0-105.0 % on the anhydrous basis
Assay #	HPLC; EP 2.2.29	98.0-102.0 % 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 Cromium NMT 110 µg/g Nickel NMT 2 µg/g Molybdenum NMT 150 µg/g Vanadium NMT 1 µg/g
Limit of Beta Cyclodextrin (Betadex) #	HPLC; USP <621>	NMT 0.1 % on the anhydrous basis
Limit of 1,4-Butane Sultone	GC USP <621>	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>	NMT 0.09 %
Limit of Bis(4-sulfobutyl) Ether Disodium	CE; USP <1053>	NMT 0.05 %
Bacterial Endotoxin Test #	USP <85>, EP 2.6.12	≤ 24 IU/g
Microbial Enumeration Tests #	USP <61>, EP 2.6.12	TAMC ≤ 100 cfu/g; TYMC ≤ 50 cfu/g

* No requirements are given in USP 35-NF 30 for appearance and limits of cyclodextrin related substances
# To be performed in stability study

CUSTOMER SPECIFICATION	
Product: **Sulfobutyl-ether-β-cyclodextrin sodium salt (SBECD)** Quality: pharma grade USP and EP compliance	Version: 02 Code: Rel_SBE_USP_EP_v02

Test	Method	Specification
Test for Specified Microorganism	USP <62>, EP 2.6.13	absence of Escherichia Coli /1 g absence of Salmonella /10 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
Clarity of solution (15%, w/v) #	visual, EP 2.2.1	the solution is clear and colorless
pH (30%, w/v) #	USP <791>	4.0 – 6.8
Phosphate content	UV-VIS USP <857>, EP 2.2.25	525-700 µg/g
Average Degree of Substitution [DS]	NMR; EP 2.2.33	5.9 – 6.6
Average Degree of Substitution [DS]	CE; USP <1053>	6.2 – 6.9
Peak distribution	CE; USP <1053>	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 (13%, w/v) #	USP <791>, EP 2.2.3	5.0-7.5
Water Content #	USP Method I <921>, EP 2.5.12	NMT 10.0 %
Impurites IMP A (BCD) IMP C (HOBSA) IMP D (DIBSA)	HPLC EP 2.2.29	 NMT 0.1% NMT 0.1% NMT 0.05%
Limit of 1,4-Butane Sultone (IMP B)	GC, EP 2.2.28	NMT 0.5 ppm
Reducing sugar	UV VIS; EP 2.2.25	NMT 0.05%

* No requirements are given in USP 35-NF 30 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 EP/USP NF compliant!

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Company contacts – ASK FOR A FREE SAMPLE:

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CYCLOLAB

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User's guide for Dexolve

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

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STEP 1

Weigh in the following Dexolve 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 into consideration*

Use stirrer bar and magnetic stirrer.

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STEP 2

- After the complete dissolution of Dexolve, 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 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 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!