Getting the best out of Cyclodextrins

CYCLOLAB Ltd.

Dexolve™

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

Dexolve™
for Improved Pharmaceutical Formulations

Geodon
for injection
(Voriconazole)
for injection
(Kyprolis
carfilzomib)
Nexterone
(Anidulafogene
HCl)
Premixed injection

SBECDD VS
SBECDD RS (USP)
Mobile phase

DS-I DS-II
DS-III
DS-IV DS-V
DS-VI DS-VII
DS-VIII DS-IX
DS-X
Dexolve™
for Improved Pharmaceutical Formulations

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

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

Document No.: DMF-SBECD-v02

DMF No. 2009-080

DMF No. F20180001741
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
There are 11 APIs on the market and at least 60 further in development in formulations containing SBECID 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
Main regulatory/QA/sales aspects:

- **Maintained DMF Type IV** for SBECO 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
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**
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
Available reference materials:

- Betadex
- 4-Hydroxybutane-1-sulfonic Acid
- Bis(4-sulfobutyl) Ether Disodium
- 1,4-Butane Sultone
- Betadex Sulfobutyl Ether Sodium
**Dexolve™**

for Improved Pharmaceutical Formulations

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**CUSTOMER SPECIFICATION**

<table>
<thead>
<tr>
<th>Product: Sulfobutyl-ether-β-cyclolesterin sodium salt (SBECD)</th>
<th>Quality: pharmaceutical USP and EP compliance</th>
</tr>
</thead>
</table>

Prepared by: [Name]

Revised by: [Name]

Approved by: [Name]

Date: [Date]

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<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Visual</td>
<td>white or off-white powder</td>
</tr>
<tr>
<td>Identification A</td>
<td>HPLC</td>
<td>SBECD reference</td>
</tr>
<tr>
<td>Identification B (Assay method)</td>
<td>HPLC</td>
<td>SBECD reference</td>
</tr>
<tr>
<td>Identification C</td>
<td>CE, USP &lt;1055&gt;</td>
<td>USP 2.2.33</td>
</tr>
<tr>
<td>Identification D</td>
<td>Sodium D, USP &lt;911&gt;, EP 2.3.1</td>
<td>positive test for sodium</td>
</tr>
<tr>
<td>Assay 1</td>
<td>HPLC, USP &lt;621&gt;</td>
<td>95.0-105.0% for SBECD base</td>
</tr>
<tr>
<td>Assay 2</td>
<td>HPLC, EP 2.3.20</td>
<td>98.0-102.0% for SBECD base</td>
</tr>
</tbody>
</table>

**重金属** (in mg/kg)

- Calcium: NMT 0.07
- Lead: NMT 0.15 mg/kg
- Arsenic: NMT 0.2 mg/kg
- Mercury: NMT 0.15 mg/kg
- Cadmium: NMT 0.1 mg/kg
- Copper: NMT 0.1 mg/kg
- Nickel: NMT 0.2 mg/kg
- Phosphorus: NMT 1.0 mg/kg

**限 度** (in mg/kg)

- 1,4-dioxane: NMT 0.2 mg/kg
- Sodium: NMT 0.2% |

**Residual solvents: ethylacetate**

- USP <621>, EP 2.3.20

**pH (1%, w/w)**

- USP <791>, EP 2.3.23

**Water Content**

- USP Method 1 <221>, EP 2.5.12

**Impurities**

- IMP A (ICD): USP <621>, EP 2.3.20
- IMP B (HBSA): USP <621>, EP 2.3.20

**Reducing impurities**

- UV, VIS, EP 2.2.19

**Microbial Enumeration Tests**

- USP <621>, EP 2.3.12

**assurance**

- USP <621>, EP 2.3.12

**assay**

- USP <621>, EP 2.3.12

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**CUSTOMER SPECIFICATION**

**Test** | **Method** | **Specification** |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Test for Specific Microorganisms</td>
<td>USP &lt;621&gt;, EP 2.3.20</td>
<td>absence of E. coli (10^-6)</td>
</tr>
<tr>
<td>Clarity of solution</td>
<td>Visual, see Section 1 of USP Monograph, EP 2.2.1</td>
<td>the solution is clear</td>
</tr>
<tr>
<td>Clarity of solution</td>
<td>Visual, EP 2.2.1</td>
<td>the solution is clear</td>
</tr>
<tr>
<td>pH (0.9%, w/w)</td>
<td>USP &lt;791&gt;</td>
<td>4.0 - 6.0</td>
</tr>
</tbody>
</table>

**Phosphate content**

- USP <935>, EP 2.2.22

**Average Degree of Substitution**

- NMR, EP 2.3.33
- CE, USP <1055>

**Average Degree of Substitution**

- USP <621>, EP 2.3.33
- USP <1055>

**Each SBECD peak (1-X) meets the limit range (peak area %) of the Monograph**

<table>
<thead>
<tr>
<th>SBECD sodium peaks</th>
<th>Limit range (peak area %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (SBECD)</td>
<td>60.0</td>
</tr>
<tr>
<td>2 (SBECD)</td>
<td>0.1</td>
</tr>
<tr>
<td>3 (SBECD)</td>
<td>0.5</td>
</tr>
<tr>
<td>4 (SBECD)</td>
<td>2.6</td>
</tr>
<tr>
<td>5 (SBECD)</td>
<td>5.0</td>
</tr>
<tr>
<td>6 (SBECD)</td>
<td>2.2</td>
</tr>
<tr>
<td>7 (SBECD)</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**Peak distribution**

- CE, USP <1055>

<table>
<thead>
<tr>
<th>Residual solvents: ethylacetate*</th>
<th>GC</th>
<th>USP &lt;621&gt;, EP 2.3.20</th>
<th>NMT 2500 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH (1%, w/w) ²</td>
<td>USP &lt;791&gt;, EP 2.3.23</td>
<td>NMT 7.5</td>
<td></td>
</tr>
<tr>
<td>Water Content ²</td>
<td>USP Method 1 &lt;221&gt;, EP 2.5.12</td>
<td>NMT 10.0%</td>
<td></td>
</tr>
</tbody>
</table>

**Impurities**

- IMP A (IC) | USP <621>, EP 2.3.20 | NMT 0.1% |
- IMP B (ROB) | USP <621> | NMT 0.1% |

**Reducing impurities**

- UV, VIS, EP 2.2.25 | NMT 0.005% |

**Microbial Enumeration Tests**

- USP <621>, EP 2.3.12 | NMT 50 Colony Forming Units |
- USP <621>, EP 2.3.12 | NMT 50 Colony Forming Units |

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* No requirements are given in USP <621>, EP 2.3.20 for assay and purity of pharmaceutical grade substances.

² To be performed in stability study.

**Packaging and Storage**

- Preserve in well-closed containers, store at room temperature. Protect from moisture. Labeling indicates its use in the manufacture of injectable dosage forms.

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Completely EP/USP NF compliant!
Company contacts – ASK FOR A FREE SAMPLE:
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Budapest, P.O. Box 435, H-1525 Hungary
Location: Illatos út 7., Budapest, H-1097- Hungary
TEL: (+36) 1-347-60-70 or -70
E-mail: info@cyclolab.hu; Homepage: http://www.cyclolab.hu

Contact person:
Tamas Sohajda, R&D Director sohajda@cyclolab.hu (+36) 30-315-70-38

Zoltán Kovács, BD specialist kovacs@cyclolab.hu (+36) 30-163-71-77
User’s guide for Dexolve

A simple 3-step manual for successful dissolution of your drug substance
Weigh in the following Dexolve amounts into 20 ml vials and prepare solutions with the given volume of distilled water:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexolve-7*</td>
<td>Distilled water</td>
</tr>
<tr>
<td>3.0 g</td>
<td>7.0 mL</td>
</tr>
<tr>
<td>2.0 g</td>
<td>8.0 mL</td>
</tr>
<tr>
<td>1.0 g</td>
<td>9.0 mL</td>
</tr>
<tr>
<td>0.5 g</td>
<td>9.5 mL</td>
</tr>
</tbody>
</table>

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

Use stirrer bar and magnetic stirrer.
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.
- 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!*