Unique solutions for pharmaceutical formulations

Cavitron and Cavasol cyclodextrin derivatives, like the native Cavamax cyclodextrins, have the unique ability to act as molecular containers by entrapping guest molecules in their internal cavity. The resulting inclusion complexes are most commonly used to increase water solubility of poorly soluble drugs to improve bioavailability.

In addition to the Cavamax native cyclodextrins, Ashland offers and supports a range of 2-hydroxypropyl-β-cyclodextrin (HPBCD) products. The HPBCD products are manufactured by Wacker Chemie, for pharmaceutical applications around the world (Table 1). The alliance with Wacker combines Wacker’s cyclodextrin manufacturing expertise with Ashland’s technical sales and customer service capabilities to provide solutions for formulating pharmaceutical products.

Table 1
Ashland offers a range of 2-hydroxypropyl-β-cyclodextrin products

<table>
<thead>
<tr>
<th>Product</th>
<th>Typical Degree of Substitution</th>
<th>Approximate Molecular Weight</th>
<th>Bacterial Endotoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavasol W7 HP Pharma cyclodextrin</td>
<td>4.1-5.1</td>
<td>~1410</td>
<td>Not tested</td>
</tr>
<tr>
<td>Cavitron W7 HP5 Pharma cyclodextrin</td>
<td>4.1-5.1</td>
<td>~1410</td>
<td>10 IU/g max</td>
</tr>
<tr>
<td>Cavitron W7 HP7 Pharma cyclodextrin</td>
<td>6.0-8.0</td>
<td>~1520</td>
<td>10 IU/g max</td>
</tr>
</tbody>
</table>

* Registered trademark owned by Wacker Chemie AG. Ashland acts as a worldwide distributor for Wacker.

Benefits

- Increase bioavailability in oral, parenteral, ophthalmic and liquid dosage forms
- Provide low endotoxin grades for use in parenteral and ophthalmic dosage forms
- Offer grades with differing degrees of substitution
The Cavitron™ hydroxypropyl-β-cyclodextrin grades are differentiated by degree of substitution. These grades are manufactured to control endotoxin levels and are acceptable for use in parenteral and ophthalmic applications, while the Cavasol® cyclodextrin grade is suitable for oral applications.

β-cyclodextrin derivatives

Hydroxypropyl-β-cyclodextrin is produced by reacting β-cyclodextrin with propylene oxide. The original bucket structure and cavity volume of the β-cyclodextrin remains intact. The propylene oxide reacts randomly with the hydroxyl groups of the β-cyclodextrin resulting in a mixture of compounds with respect to the amount (degree) and position of substitution of hydroxyl groups. By controlling the amount of propylene oxide used, the degree of substitution or average number of hydroxypropyl groups per each cyclodextrin molecule can be controlled.

Figure 1: Cavitron and Cavasol cyclodextrins are derived from β-cyclodextrin

增加水溶性

The hydroxyl groups and hydroxypropyl groups located on the exterior of the hydroxypropyl-β-cyclodextrin provide increased aqueous solubility (Figure 2). With its higher degree of substitution, Cavitron W7 HP7 Pharma HPBCD has slightly higher water solubility than Cavitron W7 HP5 Pharma HPBCD.

Stable and compatible

Cavitron and Cavasol hydroxypropyl-β-cyclodextrins are stable in bases and weak organic acids, but are hydrolyzed by strong acids. The rate of hydrolysis depends on the concentration of acid and temperature.

The Cavitron and Cavasol cyclodextrins are also stable in the presence of glucoamylases or γ-amylase and β-amylase. The ability of amylases to hydrolyze Cavitron and Cavasol cyclodextrins is limited. The substitution provides steric hindrance resulting in less hydrolysis by the enzyme. The greater the degree of substitution or amount of substitution, the more resistant the hydroxypropyl-β-cyclodextrin is to hydrolysis.

Cavitron and Cavasol cyclodextrins are biocompatible and compatible with a wide range of ingredients commonly used in pharmaceutical applications.

Osmolality

Osmolality is important for formulating ophthalmic, nasal and injectable dosage forms. The osmolality of different concentrations of Cavitron cyclodextrins was determined using a cryoscopic osmometer (Table 2).
Applications

Cyclodextrins find use in a wide range of pharmaceutical applications. Many have been well studied and a significant amount of information exists in the technical literature. However, it is only recently that cyclodextrins have started to become commercially significant as process improvements have made them more economically available in large scale, and as formulators and regulatory agencies become more familiar with their benefits.

The primary application for hydroxypropyl-β-cyclodextrins is to form inclusion complexes with poorly soluble drug actives. The resulting drug-cyclodextrin complex hides most of the hydrophobic functionality of the drug active in the interior cavity of the cyclodextrin while the hydrophilic hydroxyl groups on its external surface remain exposed to the environment. The net effect is a water-soluble cyclodextrin drug complex. By forming a cyclodextrin inclusion complex with the active, reactions induced by radiation, heat, oxygen, water and by other chemicals can also be reduced or minimized thus increasing the stability of the active.

This application is potentially covered by patents in some countries. A patent review in the geographic markets of commercial interest is recommended.

Safety and Regulatory

Cyclodextrins are derived from starch and are generally regarded as essentially non-toxic materials. Hydroxypropyl-β-cyclodextrin does not exhibit the nephrotoxicity associated with β-cyclodextrin. A complete toxicology summary is available on request.

Cavitron and Cavasol* cyclodextrins conform to current USP/NF and Ph. Eur. pharmacopeia monographs for hydroxypropylbetadex.

A Drug Master File (DMF) for Cavitron and Cavasol cyclodextrins is currently maintained with the United States Food & Drug Administration.

Cavitron and Cavasol cyclodextrins supplied to the pharmaceutical industry are manufactured in accordance with cGMP.

Key Specifications

<table>
<thead>
<tr>
<th>Product</th>
<th>Cavasol W7 HP Pharma HPB</th>
<th>Cavitron W7 HP5 Pharma HPB</th>
<th>Cavitron W7 HP7 Pharma HPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance of solution</td>
<td>Clear, colorless</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molar substitution (per anhydro glucose unit)</td>
<td>0.59 - 0.73</td>
<td>0.59 - 0.73</td>
<td>0.86 - 1.14</td>
</tr>
<tr>
<td>% β-cyclodextrin</td>
<td>1 Maximum</td>
<td>1.5 Maximum</td>
<td>1.5 Maximum</td>
</tr>
<tr>
<td>% Loss on drying</td>
<td>10 Maximum</td>
<td>10 Maximum</td>
<td>10 Maximum</td>
</tr>
<tr>
<td>Bacterial endotoxin (IU/g)</td>
<td>Not tested</td>
<td>10 Maximum</td>
<td>10 Maximum</td>
</tr>
</tbody>
</table>

Full product specifications are available on request.

Table 2

Osmolality of aqueous Cavitron™ cyclodextrin solutions at 25ºC

<table>
<thead>
<tr>
<th>Product</th>
<th>Conc g/100 mL</th>
<th>mOsmol/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavitron W7 HP5 Pharma cyclodextrin</td>
<td>10</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>221</td>
</tr>
<tr>
<td>Cavitron W7 HP7 Pharma cyclodextrin</td>
<td>10</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>240</td>
</tr>
</tbody>
</table>
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