9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for hydroxyethylmethyl cellulose.

<table>
<thead>
<tr>
<th>Test</th>
<th>PhEur 6.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
</tr>
<tr>
<td>Characters</td>
<td>+</td>
</tr>
<tr>
<td>Appearance of solution</td>
<td>+</td>
</tr>
<tr>
<td>pH</td>
<td>5.5–8.0</td>
</tr>
<tr>
<td>Apparent viscosity</td>
<td>75–140% of value stated on label</td>
</tr>
<tr>
<td>Chlorides</td>
<td>≤ 0.5%</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>≤ 20 ppm</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>≤ 10.0%</td>
</tr>
<tr>
<td>Sulfated ash</td>
<td>≤ 1.0%</td>
</tr>
</tbody>
</table>

10 Typical Properties

Acidity/alkalinity  pH = 5.5–8.0 (2% w/v aqueous solution)
Moisture content    ≤ 10%
Solubility  Hydroxyethylmethyl cellulose is practically insoluble in hot water (above 60°C), acetone, ethanol (95%), ether, and toluene. It dissolves in cold water to form a colloidal solution.
Viscosity (dynamic)  8.5–11.5 mPa s (8.5–11.5 cP) for Culminal MHEC 8000 2% w/v aqueous solution at 20°C.

11 Stability and Storage Conditions

Hydroxyethylmethyl cellulose is hygroscopic and should therefore be stored under dry conditions away from heat.

12 Incompatibilities

—

13 Method of Manufacture

—

14 Safety

Hydroxyethylmethyl cellulose is used as an excipient in various oral and topical pharmaceutical preparations, and is generally regarded as an essentially nontoxic and nonirritant material.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. Eye protection and gloves are recommended.

16 Regulatory Status

GRAS listed. Included in nonparenteral medicines licensed in Europe (oral suspensions, tablets, and topical preparations).

17 Related Substances

Ethylcellulose; hydroxyethyl cellulose; hypromellose; methylcellulose.

18 Comments

—

19 Specific References


20 General References


21 Author

PJ Sheskey.

22 Date of Revision

10 January 2009.

Hydroxypropyl Betadex

1 Nonproprietary Names

BP: Hydroxypropylbetadex
PhEur: Hydroxypropylbetadex
USP-NF: Hydroxypropyl Betadex

2 Synonyms

Cavasol W7; 2-hydroxypropyl-β-cyclodextrin; 2-hydroxypropyl cyclomaltoheptaose; hidroksipropilbetadeksas; hydroxipropilbetadex; hidroksipropilbetadeks; hydroxypropilbetadeks; hydroxypropilbetadexum; Kleptose HPB.

3 Chemical Name and CAS Registry Number

β-Cyclodextrin, 2-hydroxypropyl ether [94035-02-6] and [128446-35-5]

4 Empirical Formula and Molecular Weight

C_{42}H_{70}O_{35}(C_{3}H_{6}O)_{x}(where x = 7 molar substitution)

The molecular weight depends on the degree of substitution. The molecular weight of unsubstituted β-cyclodextrin is 1134.98.

5 Structural Formula

Hydroxypropyl betadex is a partially substituted ether of β-cyclodextrin. USP32–NF27 requires that the molar substitution is
between 0.4 and 1.5 hydroxypropyl groups per anhydroglucose unit.

\[ R = \text{H or CH}_3\text{CH}((\text{CH}_3))\text{OH} \]

### 6 Functional Category
Complexing agent; dissolution enhancer; release-modifying agent; sequestering agent; solubilizing agent; stabilizing agent; tonicity agent.

### 7 Applications in Pharmaceutical Formulation or Technology
Hydroxypropyl betadex has been widely investigated in pharmaceutics and has principally been used as a solubilizer for hydrophobic molecules in oral liquids, \(^{(1,2)}\) oral solids, \(^{(3)}\) parenterals, \(^{(4,5)}\) pressurized metered dose inhalers, \(^{(6)}\) dry powder inhalers, \(^{(7)}\) and topical formulations. \(^{(8)}\) It has also been shown to act as a stabilizer during processing \(^{(9)}\) and storage of formulations. \(^{(10)}\)

Hydroxypropyl betadex inclusion complexes have been reported to show mechanical properties distinct from the pure materials. \(^{(11)}\) The reported advantage of hydroxypropyl betadex over unsubstituted \(\beta\)-cyclodextrin is its greater water solubility. \(^{(3)}\)

See also Section 18.

### 8 Description
Hydroxypropyl betadex occurs as a white or almost white, amorphous or crystalline powder.

### 9 Pharmacopeial Specifications
See Table I.

### 10 Typical Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>PhEur 6.3</th>
<th>USP32–NF27</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acidity/alkalinity</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(pH) of a 20 g/L solution at 20°C for Cavasol W7 HP Pharma</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Density (bulk)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\sim 0.4\text{ g/cm}^3) for Cavasol W7 HP; (0.2–0.3\text{ g/cm}^3) for Cavasol W7 HP Pharma.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ignition temperature</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(420°C) for Cavasol W7 HP; (&gt;400°C) for Cavasol W7 HP Pharma.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Melting point</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(278°C; 120–160°C) for Cavasol W7 HP</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Specific rotation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\lbrack\alpha\rbrack_D^25 = +140°) to (+145°)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 11 Stability and Storage Conditions
Store in well-closed containers.

### 12 Incompatibilities
—

### 13 Method of Manufacture
Hydroxypropyl betadex is prepared by the treatment of an alkaline solution of \(\beta\)-cyclodextrin with propylene oxide. The substitution pattern can be influenced by varying the pH. Formation of O-6 and O-2 substituted products is favored by high and low alkali concentration, respectively. The mixture of products produced may be refined by preparative chromatography. \(^{(12)}\)

### 14 Safety
The pharmaceutical toxicology of hydroxypropyl betadex has been reviewed, \(^{(13)}\) and in general, the material was found to be of low toxicity. It has been suggested that hydroxypropyl betadex may have a synergistic toxic effect with, for example, carcinogens, by increasing their solubility and thus bioavailability. \(^{(14)}\)

### 15 Handling Precautions
Observe normal precautions appropriate to the circumstances and quantity of the material handled.

### 16 Regulatory Status
Included in oral and parenteral medicinal products. Included in an injectable preparation licensed in the UK for intramuscular or intravenous administration.

### 17 Related Substances
Cyclodextrins; 3-hydroxypropyl-\(\beta\)-cyclodextrin; sulfobutylether \(\beta\)-cyclodextrin

### 18 Synonyms
2-HP-\(\beta\)-CD.

### Appearance
White crystalline powder.

### Solubility
Freely soluble in water and propylene glycol. Soluble in ethanol, methanol, dimethyl sulfoxide and dimethylformamide. 2300 g/L water solubility at 24°C for Cavasol W7 HP; 2300 g/L water solubility at 25°C for Cavasol W7 HP Pharma.

### Water content
Typically <3.0%.

### Table I: Pharmacopeial specifications for hydroxypropyl betadex.

<table>
<thead>
<tr>
<th>Test</th>
<th>PhEur 6.3</th>
<th>USP32–NF27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Characters</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Clarity of solution</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Appearance of solution</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Microbial limits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aerobic microbial count</td>
<td>(&lt;10^3\text{ cfu/g})</td>
<td>(&lt;1000\text{ cfu/g})</td>
</tr>
<tr>
<td>Yeasts and molds</td>
<td>(&lt;10^2\text{ cfu/g})</td>
<td>(&lt;100\text{ cfu/g})</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>(&lt;20\text{ ppm})</td>
<td>(&lt;20\text{ µg/g})</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>(&lt;10.0%)</td>
<td>(&lt;10.0%)</td>
</tr>
<tr>
<td>Conductivity</td>
<td>(&lt;200\text{ µS cm}^{-1})</td>
<td>(&lt;200\text{ µS cm}^{-1})</td>
</tr>
<tr>
<td>Related substances</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sterility</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Bacterial endotoxins</td>
<td>(&lt;10\text{ IU/g}) (^{(a)})</td>
<td>+</td>
</tr>
<tr>
<td>Molar substitution</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Propylene oxide</td>
<td>-</td>
<td>(&lt;0.0001%)</td>
</tr>
</tbody>
</table>

\(^{(a)}\) If intended for parenteral use.
use in parenteral formulations. The degree of substitution of hydroxypropyl groups can vary.

18 Comments
Hydroxypropyl betadex has been investigated as an absorption (permeation) enhancer in oral\(^{(15)}\), transdermal\(^{(16)}\), and nasal\(^{(17)}\) systems. It was found to be effective in increasing penetration in some studies, although the mechanism of action may be compound specific.

19 Specific References

20 General References

21 Author
W Cook.

22 Date of Revision
27 February 2009.

Hydroxypropyl Cellulose

1 Nonproprietary Names
BP: Hydroxypropylcellulose
JP: Hydroxypropylcellulose
PhEur: Hydroxypropylcellulose
USP-NF: Hydroxypropyl Cellulose

2 Synonyms
Cellulose, hydroxypropyl ether; E463; hydroxypropylcellulose; hypromellose; Klucel; Nisso HPC; oxypropylated cellulose.

3 Chemical Name and CAS Registry Number
Cellulose, 2-hydroxypropyl ether [9004-64-2]

4 Empirical Formula and Molecular Weight
The PhEur 6.0 and USP32–NF27 describe hydroxypropyl cellulose as a partially substituted poly(hydroxypropyl) ether of cellulose. It may contain not more than 0.6% of silica or another suitable anticaking agent. Hydroxypropyl cellulose is commercially available in a number of different grades that have various solution viscosities. Molecular weight has a range of 50,000–1,250,000; see also Section 10.

5 Structural Formula

R is H or \([\text{CH}_2\text{CH(CH}_3\text{)O}]_m\text{H}\) where \(m\) is a common integral number of cellulose derivatives.

Hydroxypropyl cellulose is an ether of cellulose where some of the hydroxyl groups of the cellulose have been hydroxypropylated forming –OCH\(_2\)CH(OH)CH\(_3\) groups. The average number of