CAVASOL* and Cavitron™

2-hydroxypropyl-β- and 2-hydroxypropyl-γ-cyclodextrins Product Overview

Unique solutions for pharmaceutical formulations

Ashland offers and supports a range of 2-hydroxypropyl-β-cyclodextrin (HPBCD) and 2-hydroxypropyl-γ-cyclodextrin (HPGCD) products. These 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.

CAVASOL and Cavitron 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 the water solubility of poorly soluble drugs, leading to improved bioavailability and taste-masking abilities.

Table 1 – Ashland offers a range of HPBCD and HPGCD products

Product	Typical Degree of Substitution	Approximate Molecular Weight	Bacterial Endotoxin
CAVASOL W7 HP Pharma cyclodextrin	4.1-5.1	~1410	Not tested
CAVASOL W8 HP Pharma cyclodextrin	4.0-5.6	~1540	Not tested
Cavitron W7 HP5 Pharma cyclodextrin	4.1-5.1	~1410	10 IU/g max
Cavitron W7 HP7 Pharma cyclodextrin	6.0-8.0	~1520	10 IU/g max

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

Benefits

– Increase solubility and bioavailability in oral, parenteral, ophthalmic and liquid-dosage forms

– Provide low bioburden and endotoxin grades that meet defined limits for use in parenteral and ophthalmic dosage forms[1]

– Offer grades with differing degrees of substitution

– Provide taste masking

[1]Ashland does not represent that these product grades, as provided by Ashland, are sterile or meet parental requirements. It is the purchaser's responsibility to determine the suitability of each component of its own manufactured product for that product's intended use or uses.

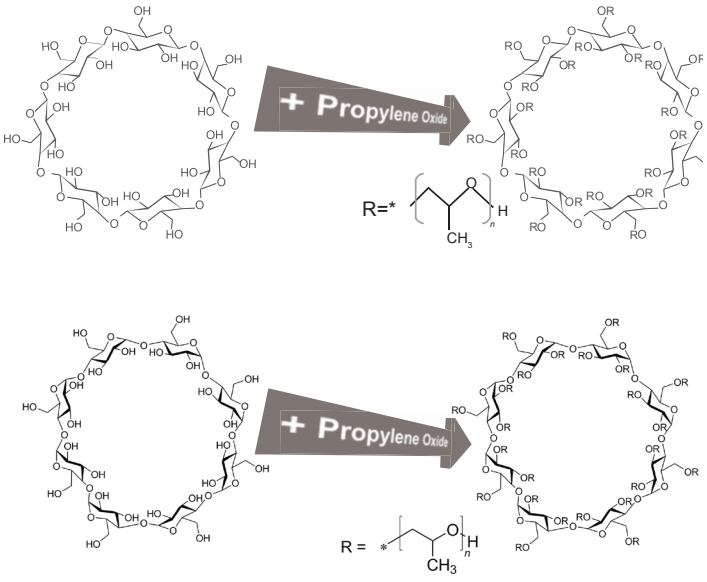
The Cavitron™ hydroxypropyl-β-cyclodextrin grades are differentiated by degree of substitution. These grades are manufactured to meet defined bioburden and endotoxin limits if intended for use in the manufacture of parenteral preparations, while the CAVASOL* cyclodextrin grades are suitable for oral applications. [2]

[2] Ashland does not represent that these product grades, as provided by Ashland, are sterile or meet parental requirements. It is the purchaser's responsibility to determine the suitability of each component of its own manufactured product for that product's intended use or uses.

Cyclodextrin derivatives

HPBCDs and HPGCD are produced by reacting β- or γ-cyclodextrins with propylene oxide. The original bucket structure and cavity volume of the cyclodextrin remains intact. The propylene oxide reacts randomly with the hydroxyl groups of the 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.

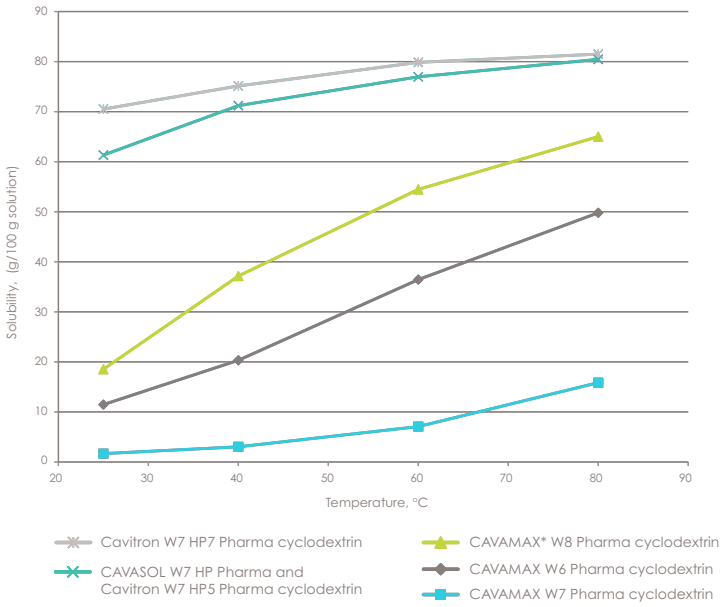
Figure 1 – CAVASOL and Cavitron cyclodextrins are derived from β- or γ-cyclodextrins



Increase in aqueous solubility

The hydroxyl groups and hydroxypropyl groups located on the exterior of the HPBCD or HPGCD 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.

Figure 2 – Hydroxypropyl-β-cyclodextrin has increased water solubility[3]



[3] The solubility of CAVASOL* W8 is greater than 60 g/100 g from 20°C to 80°C.

Stable and compatible

CAVASOL and Cavitron HPBCDs and HPGCD are stable in bases and weak organic acids, but they are hydrolyzed by strong acids. The rate of hydrolysis depends on the concentration of acid and temperature.

The CAVASOL and Cavitron cyclodextrins are also stable in the presence of glucoamylases or γ-amylase and β-amylase. The ability of amylases to hydrolyze CAVASOL and Cavitron 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 cyclodextrin derivative is to hydrolysis.

CAVASOL and Cavitron cyclodextrins are 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).

Table 2 – Osmolality of aqueous Cavitron™ cyclodextrin solutions at 25°C

Product	Conc g/100 mL	mOsm/kg
Cavitron W7 HP5 Pharma cyclodextrin	10	91
	20	221
Cavitron W7 HP7 Pharma cyclodextrin	10	87
	20	240

Safety and Regulatory

Cyclodextrin is derived from starch and generally regarded as essentially nontoxic materials. HPBCD does not exhibit the nephrotoxicity associated with β-cyclodextrin. A complete toxicology summary is available on request.

CAVASOL* and Cavitron HPBCDs conform to current NF and Ph. Eur. monographs for hydroxypropylbetadex.

A Drug Master File (DMF) for CAVASOL W7 HP Pharma cyclodextrin is currently maintained with the United States Food & Drug Administration.

CAVASOL and Cavitron cyclodextrins supplied to the pharmaceutical industry are manufactured in accordance with cGMP, USP<1078> and the *Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients, 2017*–as published under the auspices of the International Pharmaceutical Excipient Council.

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.

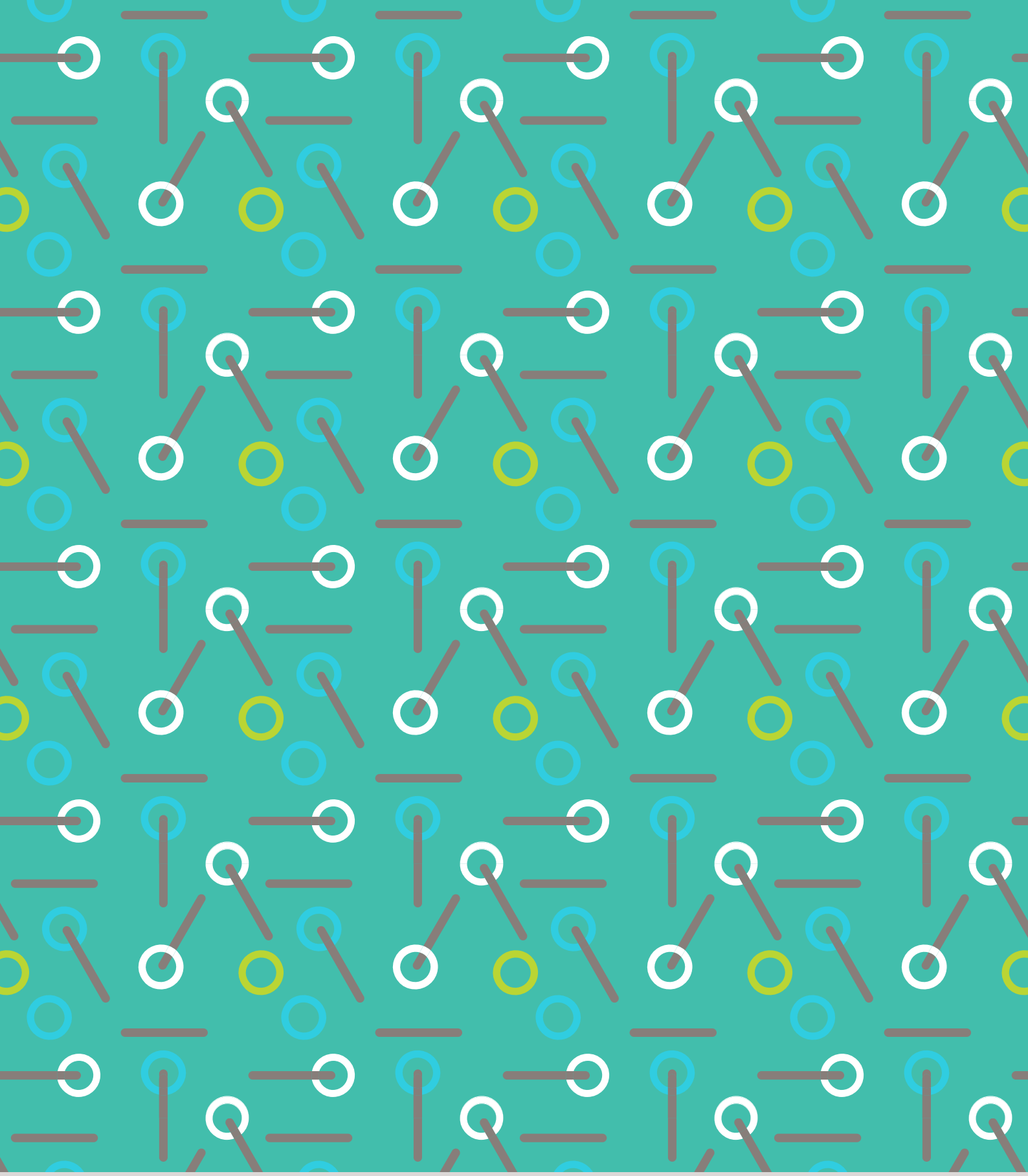
The primary application for HPBCDs and HPGCD is to form inclusion complexes with poorly soluble drug actives.[4] The resulting drug-cyclodextrin complex hides most of the hydrophobic functionality of the drug active in the interior cavity of the cyclodextrin while the hydrophilic hydroxyl groups on its 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.

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

Key Specifications

	CAVASOL W7 HP Pharma HPB	Cavitron W7 HP5 Pharma HPB	Cavitron W7 HP7 Pharma HPB	CAVASOL W8 HP Pharma HPG
Appearance of solution	Clear, colorless			
Molar substitution (per anhydro glucose unit)	0.59 - 0.73	0.59 - 0.73	0.86 - 1.14	0.50 - 0.70
% β-cyclodextrin	1 Maximum	1 Maximum	1 Maximum	—
% Loss on drying	10 Maximum	10 Maximum	10 Maximum	—
Bacterial endotoxin (IU/g)	Not tested	10 Maximum	10 Maximum	Not tested

Full product specifications are available on request.



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