CAVASOL® and CAVITRON™

2-hydroxypropyl-β- and 2-hydroxypropyl-γ-cyclodextrins

unique solutions for pharmaceutical formulations

description

Ashland offers and supports a range of 2-2-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.

key features and benefits

- increase solubility and enhance 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
- offer grades with differing degrees of substitution
- provide taste masking

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.

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

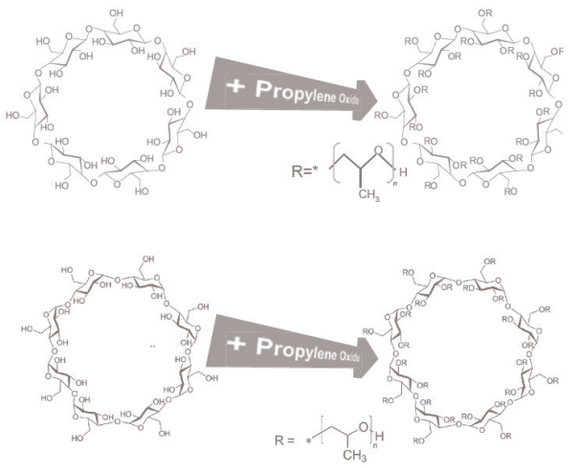
The CAVITRON™ hydroxypropyl-β-cyclodextrin grades are differentiated by degree of substitution. These grades are manufactured to meet defined bioburden and endotoxin limits if intended for use in the manufacture of parenteral preparations, while the CAVASOL* cyclodextrin grades are suitable for oral 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, the average number of hydroxypropyl groups per each cyclodextrin molecule can be controlled.

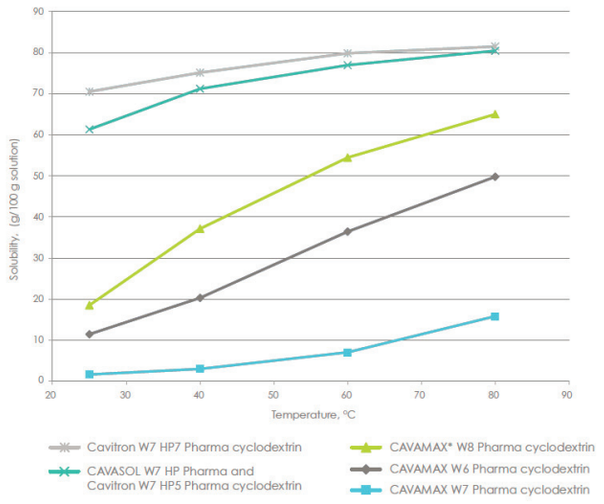
figure 1 - CAVASOL® and CAVITRON™ cyclodextrins are derived from β- or γ-cyclodextrins



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 HP pharma HPBCD.

figure 2 - hydroxypropyl-β-cyclodextrin has increased water solubility[3]



[3] The solubility of CAVASOL® W8 is greater than 60g/100g 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 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

Cyclodextrins are derived from starch and are generally regarded as nontoxic materials. 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 or 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 or 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.

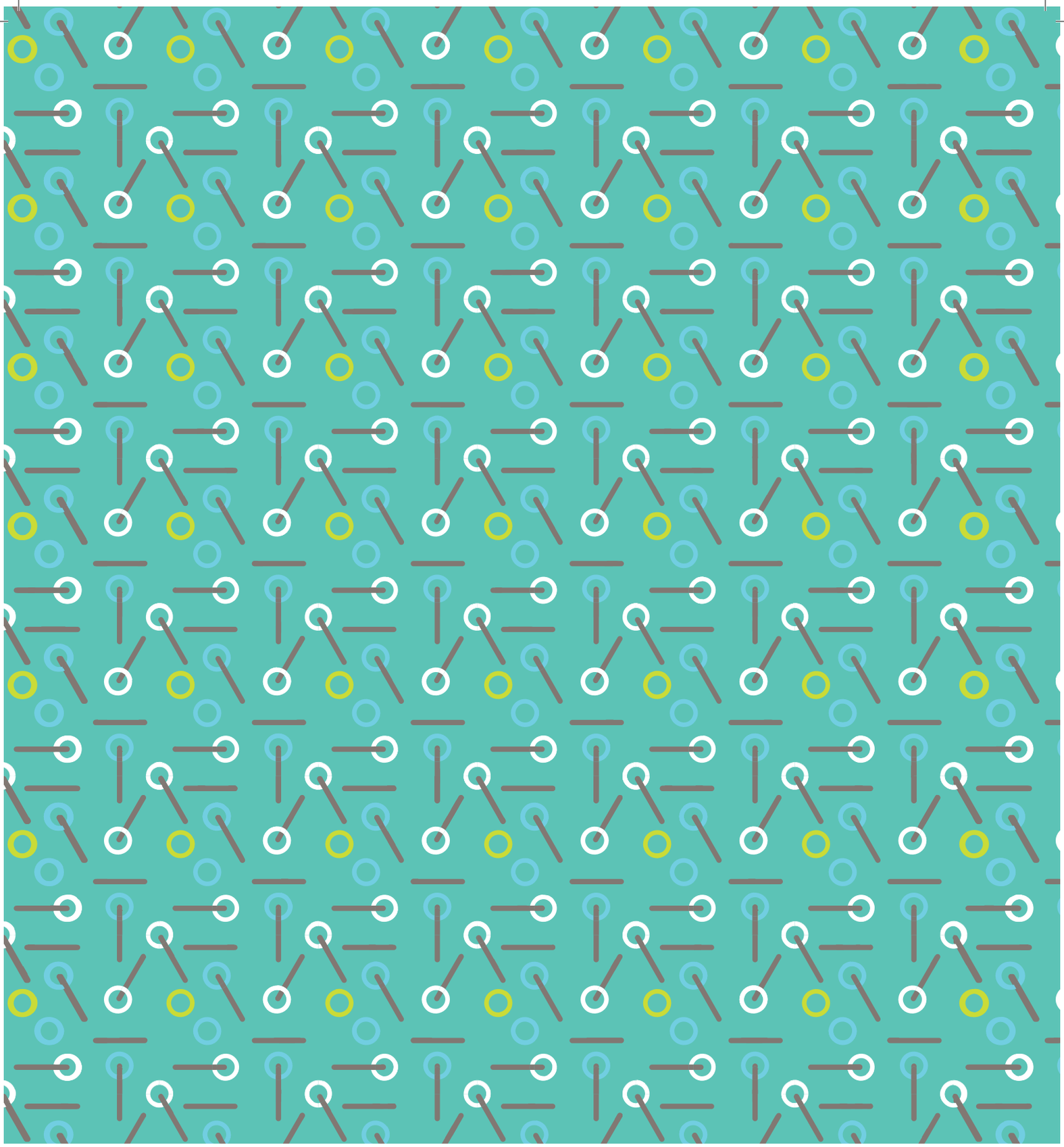
By forming a cyclodextrin inclusion complex with the active, reactions induced by radiation, heat, oxygen, water and by other chemicals can also be reduced or minimized, thus increasing the stability or the active.

[4] This application is potentially covered by patents in some countries. A patant 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 hpb
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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