CAVAMAX* native cyclodextrins

Pharma product overview

unique solutions for pharmaceutical formulations

CAVAMAX* cyclodextrins have the unique ability to act as molecular containers by entrapping guest molecules in their internal cavities. The resulting inclusion complexes are used in a number of applications in pharmaceutical formulations. For example, cyclodextrins increase water solubility of poorly soluble drugs to improve bioavailability, taste mask bitter actives for use in chewable and orally disintegrating tablet applications, and stabilize drug actives to inhibit light and oxidative degradation.

Ashland offers and supports a range of native cyclodextrin products, manufactured by Wacker Chemie AG, 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 native cyclodextrin products

product	cyclodextrin type	pharmacopoeial name
CAVAMAX* W6 Pharma	α-cyclodextrin	alfadex
CAVAMAX* W7 Pharma	β-cyclodextrin	betadex
CAVAMAX* W8 Pharma	γ-cyclodextrin	gamma cyclodextrin

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

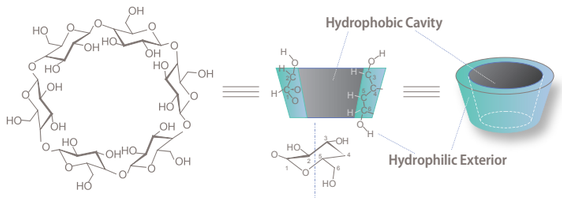
benefits

- increase bioavailability of poorly soluble drugs in oral and liquid dosage forms
- improve patient compliance through taste- and/or odor-masking of actives
- stabilize actives against light, UV radiation, temperature, oxidation and hydrolysis
- prevent drug-ingredient and drug-drug interactions
- simplify handling of volatile or liquid drug actives

bucket-shaped chemical structure derived from starch

Cyclodextrins are bucket-shaped oligosaccharides with a hydrophobic cavity and hydrophilic exterior (figure 1). As a class, cyclodextrins are composed of glucose units connected by α-1, 4 glycosidic linkages to form a series of oligosaccharide rings. In nature, the enzymatic digestion of starch by cyclodextrin glycosyltransferase (CGTase) produces a mixture of cyclodextrins comprised of 6, 7 and 8 glucose units or α, β, γ-cyclodextrin, respectively. Today, cyclodextrins are produced commercially from starch, but specific enzymes are used to selectively produce consistently pure α, β and γ-cyclodextrin, as desired.

figure 1: unique molecular structure and shape of cyclodextrins



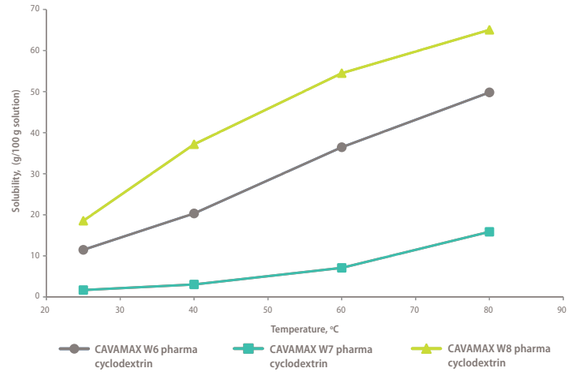
influence of cavity size on complex formation

The size of the cavity is one consideration for selecting a cyclodextrin based on molecular size of the drug active. The number of glucose units in the ring determines the internal diameter of the cavity and its volume, as the height of the cyclodextrin cavity is the same for all three native cyclodextrins (table 2). CAVAMAX* W8 Pharma γ-cyclodextrin has the largest cavity size and can accommodate larger molecules such as macrocycles and steroids. With its smaller cavity size, CAVAMAX* W6 Pharma α-cyclodextrin will typically complex smaller molecular compounds with aliphatic side chains. CAVAMAX* W7 Pharma β-cyclodextrin will complex aromatics and heterocyclic molecules.

differences in aqueous solubility

Besides molecular size, the CAVAMAX* cyclodextrins differ in water solubility. While all three materials are water soluble, the differing number of glucose units leads to slight differences in conformational structure and flexibility of the ring. These differences result in higher exposure of hydrogen bonding hydroxyl groups to the aqueous environment and higher water solubility for CAVAMAX* W8 Pharma γ-cyclodextrin (figure 2).

figure 2: CAVAMAX* W8 Pharma cyclodextrin has the highest water solubility



stable and compatible

The CAVAMAX* cyclodextrins are thermally stable (up to at least 200 °C). They are also stable in alkaline solutions (pH < 14) and in moderately acidic solutions (pH > 3). The CAVAMAX* cyclodextrins are stable in the presence of glucoamylases or γ-amylase and β-amylase, but they can be hydrolyzed by some α-amylases. CAVAMAX* W8 Pharma cyclodextrin is the most resistant to hydrolysis by α-amylases while CAVAMAX* W6 Pharma cyclodextrin is the least resistant.

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

table 2: CAVAMAX* cyclodextrins differ by cavity volume

product	cyclodextrin type	number of glucose units	cavity diameter (Å)	cavity height (Å)	cavity volume (Å3)	molecular weight
CAVAMAX* W6 Pharma	α-cyclodextrin	6	4.7–5.3	7.9	174	973
CAVAMAX* W7 Pharma	β-cyclodextrin	7	6.0–6.5	7.9	262	1135
CAVAMAX* W8 Pharma	γ-cyclodextrin	8	7.5–8.3	7.9	427	1297

good flow and highly compactable

CAVAMAX* cyclodextrins are well suited for oral solid dosage forms. The cyclodextrins have good flow characteristics (table 3) and will not have a negative impact on tablet properties, such as breaking force (figure 3) and friability.

table 3: CAVAMAX* cyclodextrins are free-flowing powders

product	flowability index	typical density (g/cm³)
CAVAMAX* W6 Pharma cyclodextrin	40	0.5–0.7
CAVAMAX* W7 Pharma cyclodextrin	40	0.5–0.7
CAVAMAX* W8 Pharma cyclodextrin	70	0.5–0.7

figure 3: pure compacts of CAVAMAX* cyclodextrins are highly compactable

suitable for use in oral pharmaceutical products

As cyclodextrins are derived from starch, they are regarded as essentially non-toxic materials. However, β-cyclodextrin can form insoluble complexes with cholesterol that disrupt the function of the kidneys; therefore, it should not be used in parenteral applications and its oral use should be limited to a daily maximum of 5 mg/kg body weight. Both α-cyclodextrin and γ-cyclodextrin are suitable for oral applications. For α-cyclodextrin and γ-cyclodextrin, the acceptable daily intakes (ADIs) are given as "non-specified" by the Joint World Health Organization and the Food & Agriculture (FAO) Expert Committee on Food Additives. A complete toxicology summary is available on request.

CAVAMAX* cyclodextrins supplied to the pharmaceutical industry are manufactured in accordance with the following quality assurance system and GMP rules: ISO 9001:2008 and 14001:2004 and 21 CFR 110.

key specifications

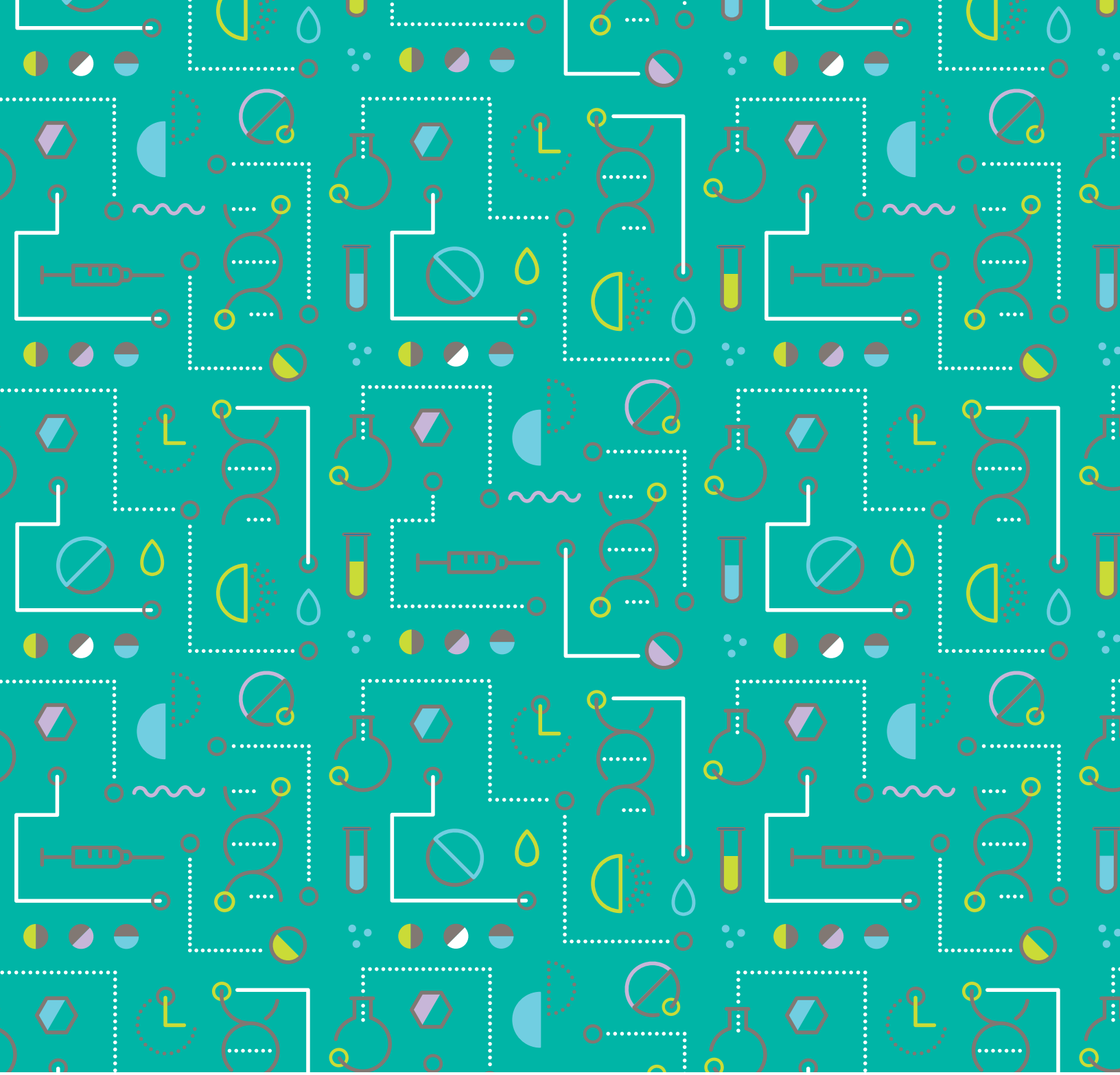
	CAVAMAX® W6 Pharma cyclodextrin	CAVAMAX® W7 Pharma cyclodextrin	CAVAMAX® W8 Pharma cyclodextrin
appearance	white crystalline powder		
% content, on dry basis	98 minimum	98–101	98 minimum
specific rotation in aqueous solution (Å) D, 20 °C	147–152	160–164	174–180
water (%)	10 maximum	14 maximum	11 maximum
micro-organisms (CFU/g)	1000 maximum	1000 maximum	1000 maximum

Full product specifications are available on request.

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 economical and available in large scale, and as formulators and regulatory agencies become more familiar with their benefits.

- One of the most common applications of 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 with enhanced drug bioavailability.
- Through encapsulation in the cyclodextrin cavity, molecules or specific functional groups that cause unpleasant tastes or odors are hidden from sensory receptors. With the growing popularity of orally disintegrating and chewable dosage forms, there is a need to mask the taste and/or odor of unpleasant drug actives.



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