

CAVAMAX® AND CAVASOL® CYCLODEXTRINS – THE INNOVATOR'S MOLECULE

DISCOVER AN ALL-AROUND TALENT AND SOURCE OF INSPIRATION





Cyclodextrins were first documented in 1891 by Villiers, but it wasn't until nearly 100 years later that commercial production of these molecules began. In 1990, following many years of research, WACKER started producing them biotechnically. While many interesting applications have surfaced since that time, there is still a great deal of commercial potential to exploit, which makes cyclodextrins truly an innovator's molecule.

Cyclodextrins offer unique opportunities in many industries, including the following:

- Food
- Dietary supplements
- Consumer care
- Pharma
- Agrochemical solutions
- Textiles
- Paints & coatings
- Remediation
- Polymers

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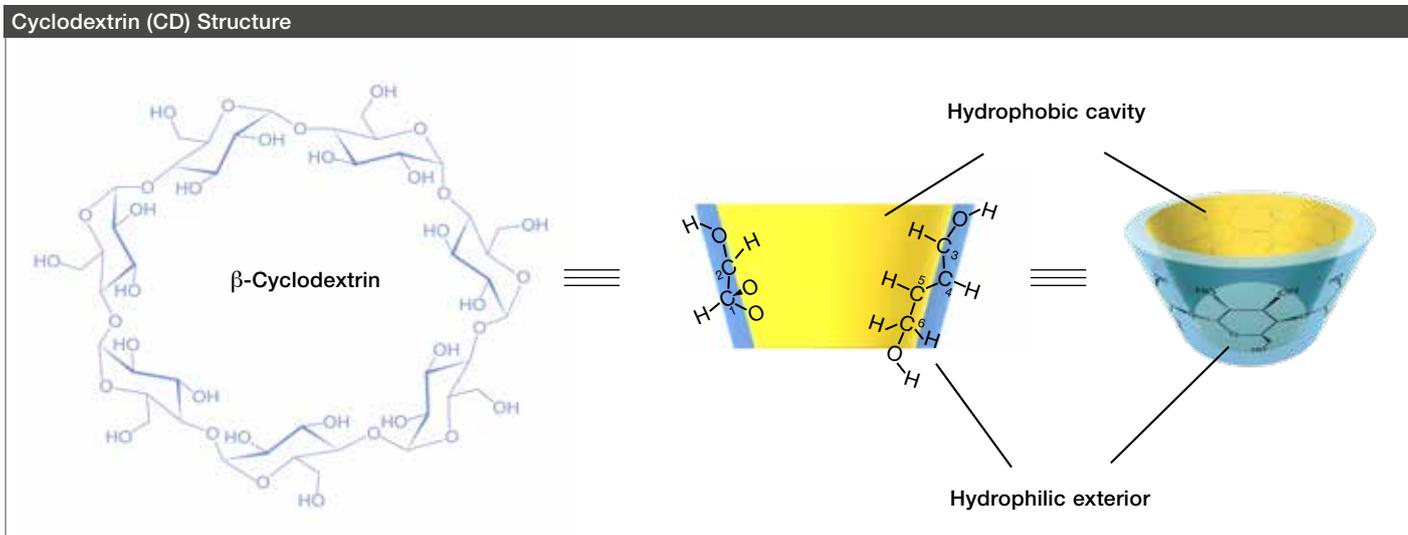
Excellent Opportunities for First Movers

In many industries, product life cycles are getting shorter, requiring continuous innovations and product improvements. In many cases, the use of cyclodextrins leads to surprising and efficient ways of bringing innovations to life.

Talk to the Experts!

WACKER is one of the most research-intensive companies in the chemical world, with a long history of developing new approaches for and with customers. Regarding cyclodextrins, WACKER has application development laboratories on three continents and is the only company in the world able to produce all three types of natural or parent cyclodextrins, as well as the broadest range of chemically modified derivatives. This background makes WACKER BIOSOLUTIONS the perfect partner to help you implement innovations in your industry. Just talk to us – we're open to your ideas!

HOW CYCLODEXTRINS WORK THEIR MAGIC

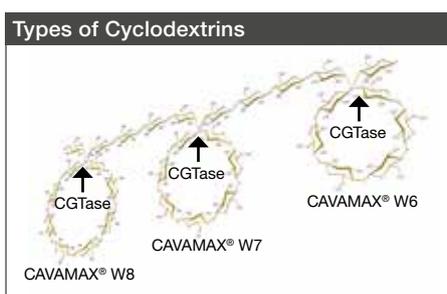


Chemically speaking, cyclodextrins are sugars. To innovative minds they are the key to a world of opportunities.

Natural Source

Cyclodextrins (CDs) are a naturally occurring group of cyclic oligosaccharides, consisting of 6 or more 1-4 linked α -anhydroglucose moieties. Produced biotechnically from starch via an enzymatic reaction, there are three commercially interesting natural or parent cyclodextrins. According to the number of glucose units, these are described as α -cyclodextrin (6 units), β -cyclodextrin (7 units) and γ -cyclodextrin (8 units). Their inner diameters vary depending on whether they contain 6, 7 or 8 sugar molecules.

WACKER is the only company worldwide offering all three parent cyclodextrins, which are marketed under the trademark CAVAMAX[®]. WACKER also manufactures and offers chemically modified cyclodextrin derivatives, which are marketed under the trademark CAVASOL[®].



A Unique Structure

Cyclodextrins resemble a hollow truncated cone or bucket, and it is this three-dimensional structure that makes them so interesting.

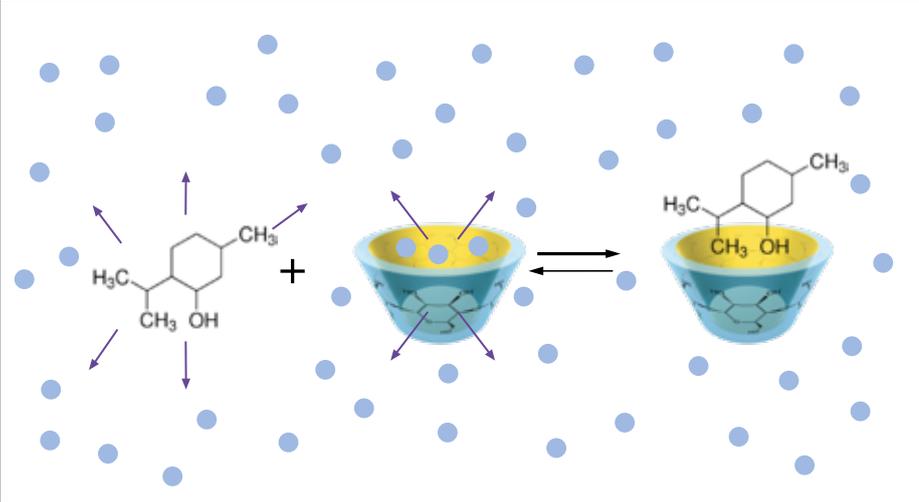
The secondary hydroxyl groups on C2 and C3 of the glucose units are directed towards the wider top opening, whereas the primary hydroxyl groups on C6 are located around the narrower bottom opening, making the outside hydrophilic. The associated C-H groups and the ring of glycosidic oxygen bonds are directed inside the cavity, which produces its hydrophobic character.

Cyclodextrin Derivatives

Chemical modification or derivatization of parent cyclodextrins has been known for many years and was initially performed to increase the water solubility of the poorly water-soluble β -cyclodextrin. Today, the industrially significant derivatives are all produced with a statistical average number of substituents, and are characterized by either the degree of substitution (DS = number of modified hydroxyl groups/number of glucose units) or the average molar substitution (MS = number of substituents per anhydroglucose). Chemically, the main derivatives can be classified as either ethers or esters, and can be produced by either chemical or enzymatic modification of a parent cyclodextrin. This derivatization affects only the outer hydroxyl groups, and consequently does not usually affect the inner hydrophobic cavity. The main benefit of derivatization is a significant increase in the water solubility of the cyclodextrin.

This increase in water solubility enables cyclodextrins to solubilize poorly soluble or hydrophobic guest molecules without the use of solvents or surfactants. WACKER markets its cyclodextrin derivatives under the CAVASOL[®] trademark.

Cyclodextrin Inclusion Complex Formation



Molecular Encapsulation

The hydrophobic cavity in cyclodextrins is able to incorporate other guest molecules. This process of molecular encapsulation is controlled by chemical equilibria in water and produces a cyclodextrin inclusion complex, also commonly referred to as an adduct or a clathrate.

Benefits of Cyclodextrin Inclusion Complexes

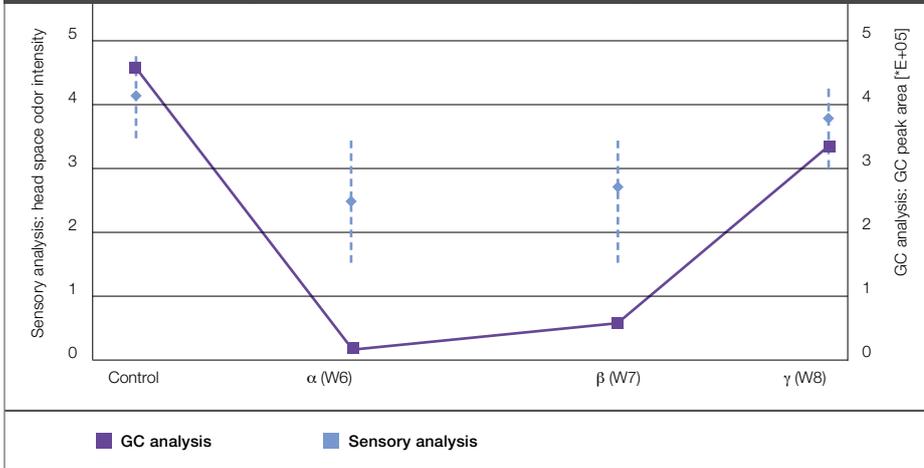
<p>Increased bioavailability</p> <p>Emulsifying effect</p> <ul style="list-style-type: none"> • Emulsion stabilization • Compatibilization <p>Masking</p> <ul style="list-style-type: none"> • Unpleasant odor • Bad taste 	<p>Controlled release</p> <p>Solubilization</p> <ul style="list-style-type: none"> • Enhancement of solubility in water • No organic solvents • No change in rheological properties <p>Stabilization against</p> <ul style="list-style-type: none"> • Light, UV radiation • Heat and cold • Oxidation
<p>Reduction of volatility</p> <ul style="list-style-type: none"> • Flavors • Gases 	<p>Selective extraction</p> <ul style="list-style-type: none"> • Cleaning effect • Absorption

Cyclodextrins and the Advantages of Molecular Encapsulation

The modification of the guest with this molecular cage leads to the various applications of cyclodextrins. Complexes with CAVAMAX® cyclodextrins stabilize substances against heat, oxidation, UV light and enzymatic degradation. They mask odors or tastes, stabilizing oils, and much more. These complexes are compressible, water dispersible and easily formulated, and their particle size can be adjusted by grinding.

MASKING TASTES AND ODORS

Figure 1: CAVAMAX® Cyclodextrins Reduce the Odor Intensity of Garlic Powder

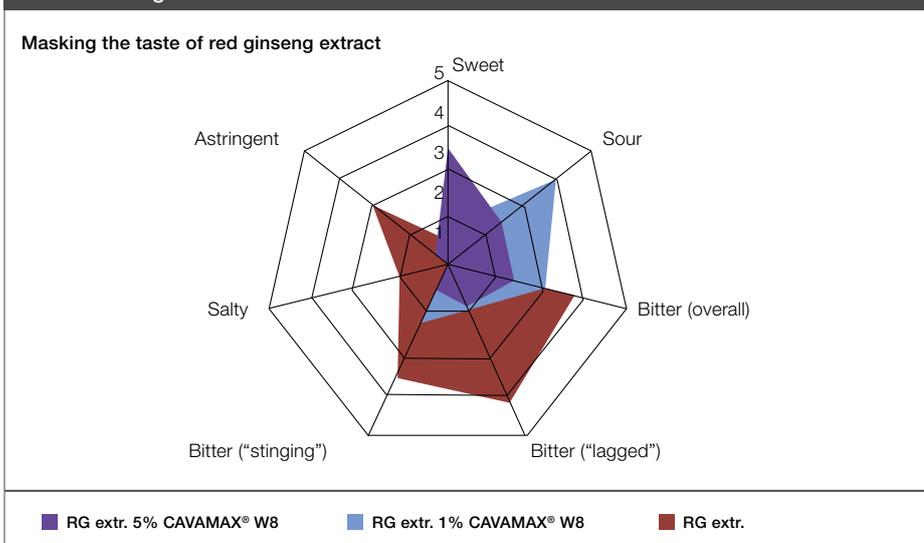


Odor and Taste Control

Inclusion complex formation of organoleptic or volatile compounds modifies the sensory properties of the guest molecule. If the guest has a strong odor or taste, then this will be reduced or even eliminated. It is even possible to make inclusion complexes of gases. As illustrated in figure 1, a randomized panel was asked to evaluate the reduction in odor intensity of a test compound with different cyclodextrins. CAVAMAX® W6 and CAVAMAX® W7 both reduced the odor intensity of the guest molecule.

The same effects can be seen with the taste of plant extracts. As shown in figure 2, CAVAMAX® W8 significantly reduced the bitter taste of some plant extracts.

Figure 2: CAVAMAX® W8 Gammadextrin Effectively Masks the Unpleasant Taste of Red Ginseng



Unpleasant odors and flavors such as bitterness can be masked efficiently, improving the overall flavor profile and the sensory perception of foods.

01 = not detectable, 02 = faintly detectable, 03 = detectable, 04 = pronounced, 05 = unpleasant

DERIVATIVES: THE SOLVENT-FREE SOLUTION

Figure 3: Table of Water Solubility of CDs and Derivatives

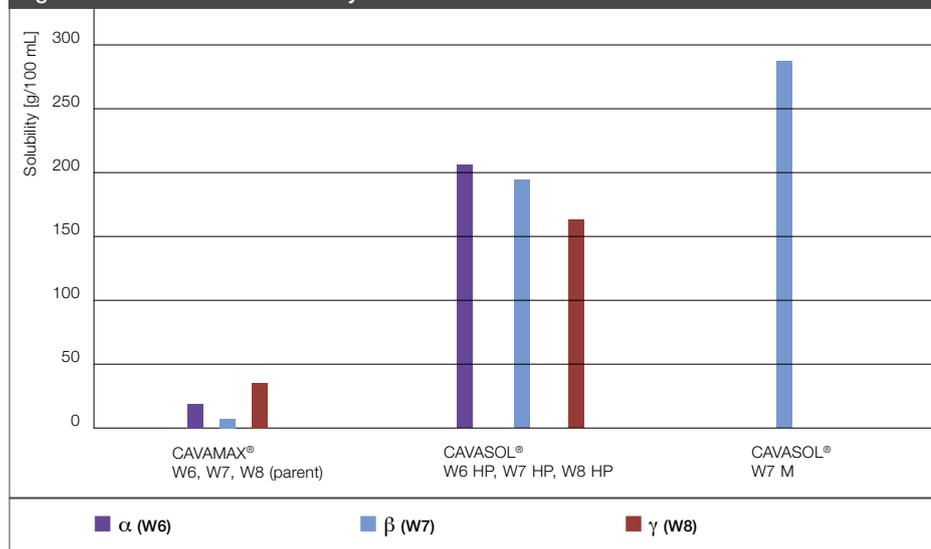
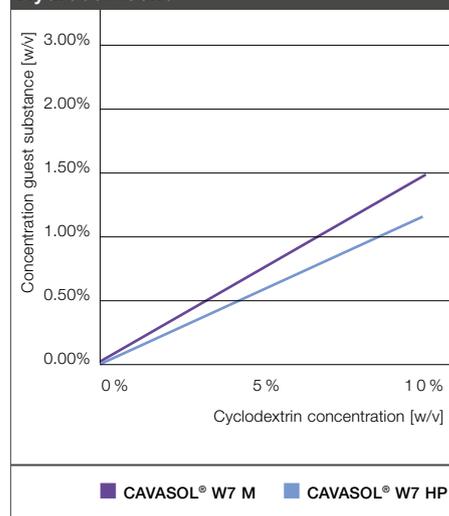


Figure 4: Improved Water Solubility of Hydrocortisone



Increasing Bioavailability

The hollow bucket shape of CAVAMAX® cyclodextrins enables them to form inclusion complexes with certain compounds. WACKER cyclodextrin complexes are ready-to-use products with substantially increased bioavailability, dispersibility and stability of the encapsulated molecules. Two prominent examples are CAVACURMIN® and CAVAQ10®, which include the lipophilic molecules of curcumin and coenzyme Q10, respectively. Usually the bioavailability of these functional ingredients is poor, but it is enhanced

considerably by complexation with gamma-cyclodextrin CAVAMAX® W8. This also significantly improves dispersibility, paving the way for innovative routes of administration.

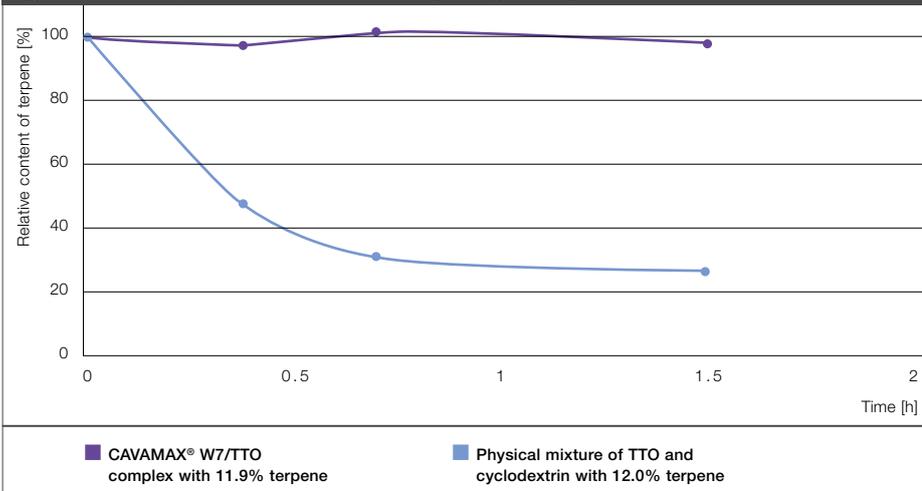
Solubility

When a poorly soluble, apolar, hydrophobic guest molecule forms an inclusion complex in water with a cyclodextrin, the properties of the cyclodextrin modify those of the guest. This generally leads to an increase in the apparent water solubility of the guest, an effect that is strongest

when the cyclodextrin used is a highly water-soluble derivative, i. e., CAVASOL® W7 M (figure 3). As can be seen in figure 4, the concentration of the guest molecule increases linearly with the concentration of the cyclodextrin derivative. Increased solubility of guest molecules opens the door to numerous applications. In addition to the advantages of having a higher concentration of the guest in solution, for example, we can also consider non-detergent cleaning, phase-transfer catalysis, separation and improved extraction processes.

THE POWER UNIT FOR PRODUCT PERFORMANCE

Figure 5: Stability of Tea Tree Oil at 45 °C (Sunlight Test)



Stabilization

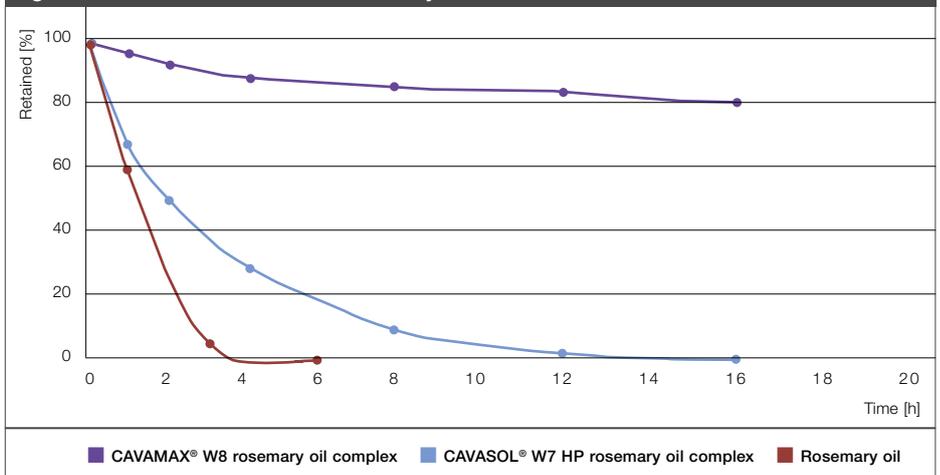
Inclusion complex formation between a poorly stable guest molecule and a cyclodextrin improves the stability of the guest due to protection by the rigid cyclodextrin molecule. Many examples of stabilization are known, such as reduced oxygen uptake of essential oils, vitamins or omega 3 or 6 oils, and improved light or UV stability of vitamins and other compounds. Figure 5 demonstrates that cyclodextrin complexes protect the unsaturated bonds of the compounds in tea tree oil from damage by UV radiation in simulated sunlight (UV-A & UV-B) at elevated temperatures. The cyclodextrin complex of tea tree oil loses no tea tree oil after 2 hours of irradiation at 45 °C. A physical mixture of tea tree oil and cyclodextrin loses 50% of the tea tree oil content after 30 minutes, and is 70% degraded after 1 hour.

Controlled Release

Inclusion complex formation of guest molecules with cyclodextrins in water is an equilibrium-controlled process. This equilibrium process can be manipulated to provide controlled release of the guest from the cyclodextrin over a significant period of time. At 40 °C in water, 75% of

the guest evaporates in 2 hours. Under the same conditions, the inclusion complex with CAVASOL® cyclodextrins takes 6 hours to evaporate, while 80% of the guest is still present after 16 hours with CAVAMAX® cyclodextrins (see figure 6).

Figure 6: Controlled Release of Rosemary Oil in Water at 40 °C



A SAFE PRODUCT FROM A SECURE SOURCE. WHAT ELSE DO YOU NEED?



Natural cyclodextrins and their chemically modified variants are safe to use.

A Reliable and Secure Source

WACKER has been working in biotechnology since the mid-1980s, and the first commercial products from our research activities were cyclodextrins.

Today, WACKER is the only company in the world able to produce all three types of parent cyclodextrin commercially, along with their chemically modified variants and derivatives.

WACKER developed the enzymes and the production process, and owns the corresponding intellectual property rights. A manufacturing plant using WACKER's enzyme technology was built in Eddyville (Iowa, USA), and has been producing cyclodextrins since March 1999.

The reasons why this site was chosen include a plentiful supply of the raw material cornstarch and the fact that there is an economic outlet for the residual starch left over from the process.

Research and development is not the whole story. As a responsible manufacturer of chemical products, WACKER has generated and published significant data on the toxicology and environmental impact of cyclodextrins, and registered its products on the world's major markets. This means our customers can feel safe and secure in using CAVAMAX® and CAVASOL® cyclodextrins in their own products and processes.

WACKER Offers a Broad Product Portfolio of Cyclodextrins and Derivatives							
Product	Physical Form	Registration			Product Grades		
		REACH	TSCA	EPA	Food	Pharma	Technical
CAVAMAX® W6	Solid – powder	●	●	●	●	●	
CAVASOL® W6 HP TL	Liquid – solution (50%)	●	●	●			●
CAVAMAX® W7	Solid – powder	●	●	●	●	●	
CAVASOL® W7 HP	Solid – powder	●	●	●		●	●
CAVASOL® W7 HP TL	Liquid – solution (40%)	●	●	●			●
CAVASOL® W7 M	Solid – powder	●	●	●		●	●
CAVASOL® W7 M TL	Liquid – solution (50%)	●	●	●			●
CAVAMAX® W8	Solid – powder	●	●	●	●	●	
CAVASOL® W8 HP*	Solid – powder					●	

* Pharmaceutical grade only; technical grade unavailable ● Full registration

Remarks

CAVAMAX®: WACKER's trade name for natural cyclodextrins,
 CAVASOL®: WACKER's trade name for cyclodextrin derivatives,
 W6 = α-cyclodextrin, W7 = β-cyclodextrin, W8 = γ-cyclodextrin,
 HP = hydroxypropyl, M = methylated, TL = technical solution



YOUR PARTNER: EXPERIENCED IN INNOVATION

Introducing a new technology is sometimes a tough call. Not so with **CAVAMAX[®]**, **CAVASOL[®]** and **WACKER**. Here you have innovative yet natural and uncomplicated products. And a partner with powerful expertise and considerable production capacity.

A Partner to Trust

As the world's most important cyclodextrin producer, WACKER BIOSOLUTIONS offers unique expertise in this field. You profit from over 20 years of product know-how and a strong and experienced R&D team that has held numerous presentations at conferences over the years.

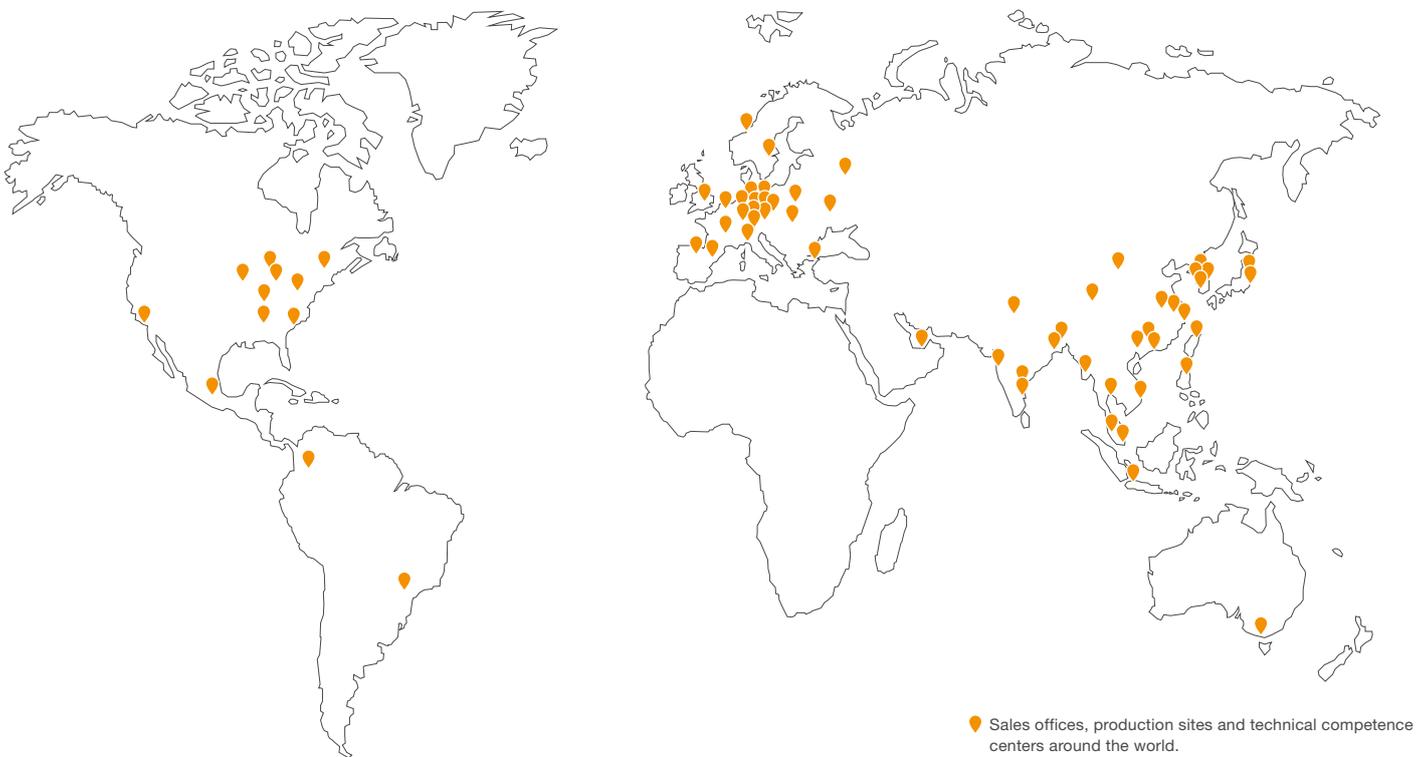
With application development laboratories located in Adrian (Michigan, USA) and Burghausen (Germany), our application chemists are ideally positioned to help you develop innovative solutions for your industry's problems and serve your key markets.

WACKER has several application patents for cyclodextrins.

Green and Safe Production

Cyclodextrins are natural, starch-derived oligosaccharides. Since production starts with a renewable raw material source, the process has a low impact on the environment and is therefore truly green. Obviously, as a key global chemical player, WACKER can produce for its customers on an industrial scale.

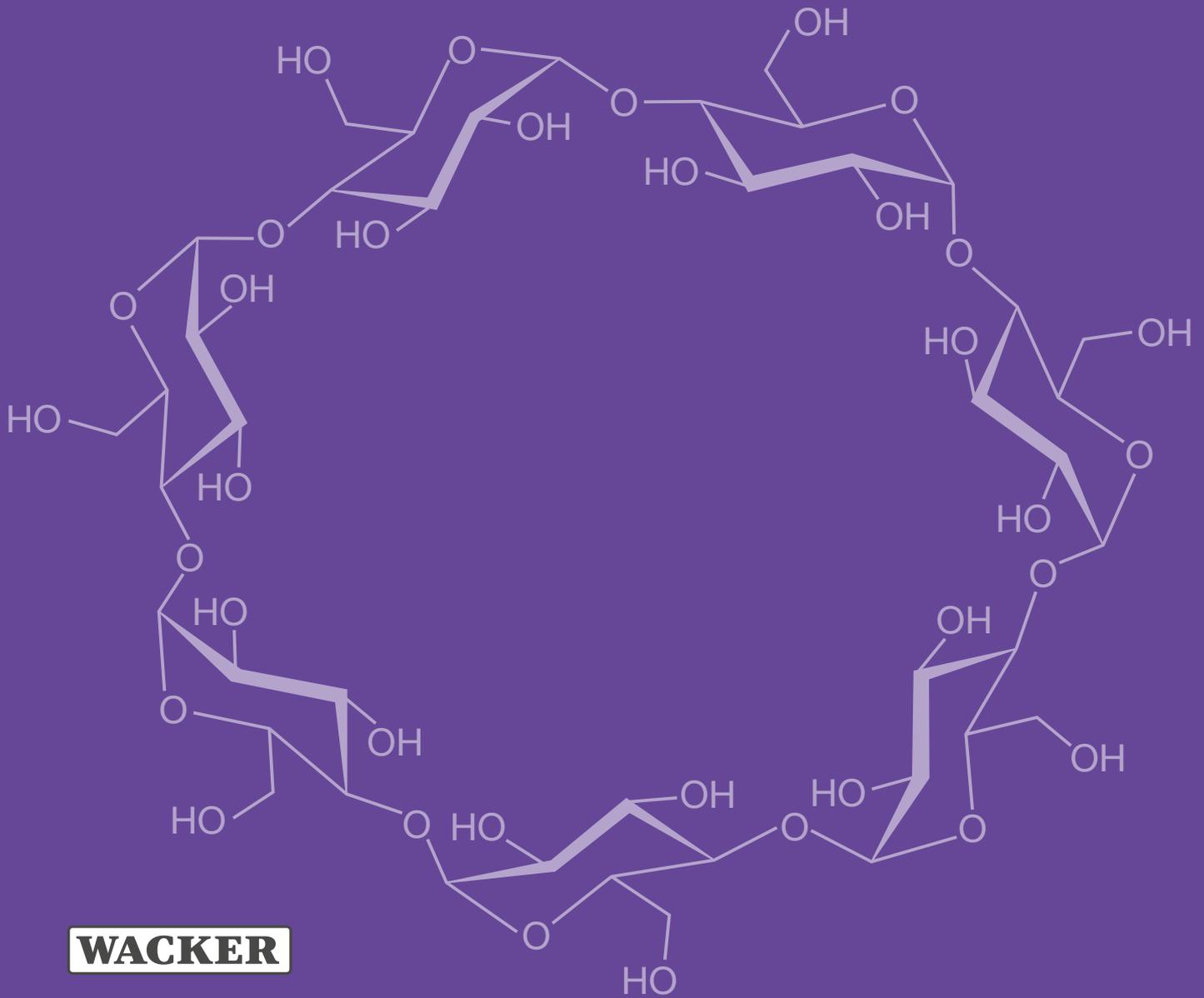
EXPERTISE AND SERVICE NETWORK ON FIVE CONTINENTS



WACKER is one of the world's leading and most research-intensive chemical companies, with total sales of €4.98 billion. Products range from silicones, binders and polymer additives for diverse industrial sectors to bioengineered pharmaceutical actives and hyperpure silicon for semiconductor and solar applications. As a technology leader focusing on sustainability, WACKER promotes products and ideas that offer a high value-added potential to ensure that current and future generations enjoy a better quality of life, based on energy efficiency and protection of the climate and environment.

Spanning the globe with 4 business divisions, we offer our customers highly-specialized products and comprehensive service via 24 production sites, 22 technical competence centers, 13 WACKER ACADEMY training centers and 50 sales offices in Europe, North and South America, and Asia – including a presence in China. With a workforce of some 14,500, we see ourselves as a reliable innovation partner that develops trailblazing solutions for, and in collaboration with, our customers. We also help them boost their own success. Our technical competence centers employ local specialists, who assist

customers worldwide in the development of products tailored to regional demands, supporting them during every stage of their complex production processes, if required. WACKER e-solutions are online services provided via our customer portal and as integrated process solutions. Our customers and business partners thus benefit from comprehensive information and reliable service to enable projects and orders to be handled fast, reliably and highly efficiently. Visit us anywhere, anytime around the world at: www.wacker.com



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