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Cyclodextrin

For years, chemistry teachers have taught that “like dissolves like” commonly referring to the example of oil and vinegar in salad dressing. Dissolving a nonpolar molecule in a polar solvent? Impossible. What these teachers taught as “impossible” was being used to create products that we use in our everyday lives as emulsifiers, deodorizers, and flavor-masking molecules. Cyclodextrin is a family of molecules composed of a cyclic ring of sugar molecules with chemical and structural properties that have allowed chemists to achieve what chemistry teachers have taught was impossible. It has created a new perspective to chemistry with seemingly limitless possibilities and endless applications.

![Structure of cyclodextrin](Figure 1. Structure of cyclodextrin)

Cyclodextrin is a family of molecules that have the fundamental structure of 6, 7, or 8 D-glucopyranosyl residues, referred to as α, β, and γ cyclodextrin respectively. Structurally, the D-glucopyranosyl residues of cyclodextrins hydrogen bond to give a 3-dimensional shape of a bottomless bowl. Cyclodextrin is an amphipathic molecule with a hydrophobic cavity lined with ether-like oxygens and a hydrophilic exterior lined with hydroxyl groups. Thus, the nonpolar hydrophobic cavity of cyclodextrin will interact with the nonpolar or hydrophobic molecule, while the hydrophilic exterior will interact with the polar solvent, allowing the cyclodextrin and its attached molecule to dissolve. Essentially, cyclodextrins allow nonpolar hydrophobic molecules to dissolve into polar solvents.

The household product industry has been using this unique property of cyclodextrins for decades. One of the most popular products containing cyclodextrin is Febreze, an odor-eliminating spray manufactured by Procter and Gamble. According to US Patent: US5714137 A, “the composition[of Febreze] comprises from about 0.1% to about 5%, by weight of the composition, of solubilized, water-soluble, uncomplexed cyclodextrin…” The solubilized cyclodextrin will interact with the odor-causing molecule.

![3-dimensional view of cyclodextrin](Figure 2. 3-dimensional view of cyclodextrin)
on fabrics and prevent them from binding to receptors in the consumer’s nose. Thus, the molecule is not eliminated, but prevented from being detected by humans. While, cyclodextrins can be used to trap odor-causing molecules, they can also be designed to release odor or scents. Scientists can load a pleasant scent molecule onto cyclodextrin, which can release a burst of scent at high temperatures. Dryer sheets like Bounce, manufactured by Procter and Gamble, utilize cyclodextrins to release the scent that many consumers associate with fresh laundry. “In the dryer, water molecules evaporating from wet clothes help release the perfume molecules from the cyclodextrin carriers, according to Günter Wich, corporate R&D director of biotechnology at Wacker Chemie AG, the company that produces cyclodextrins for P&G.” Many household products that we use everyday, utilize the unique properties of cyclodextrin.

Beyond household products, cyclodextrins are also heavily used in food production. In the household product industry, cyclodextrins were used to mask or release odors. Similarly, in the food industry, cyclodextrins are used to mask or stabilize flavors. Cyclodextrins can be added to foods in order to remove an unpleasant taste. Additionally, they can add vitamins, colorants, bactericides, and unsaturated fats to provide healthier foods. Used particularly in microwaveable entrees, snacks, and desserts, the humid air and heat from the microwave releases the flavors before consumption. Additionally, cyclodextrins can be used to stabilize water in oils, creating emulsions that are used in mayonnaise and salad dressing. The use of cyclodextrins in food has additional positive health benefits. Due to the high levels of cholesterol in consumers, many food manufacturers have resorted to using the cholesterol binding capabilities of cyclodextrin to remove cholesterol from food. One example is margarine, in which cyclodextrin is added to the food, allowed to bind to cholesterol, and then removed as a cyclodextrin-cholesterol complex, lowering the cholesterol content. The properties of cyclodextrins are used heavily in the food industry and are eaten by many consumers on a daily basis.

In the pharmaceutical industry, as drug pipelines are becoming increasingly difficult to formulate, approximately 90% of drugs can be characterized as being poorly soluble. Cyclodextrin can be dissolved into a solvent, and allow solvation of the drug. Once the drug has entered the body, competition with other fats that have a higher affinity for cyclodextrin allows the release of the drug. Overall, the addition of cyclodextrin to drug products increases the bioavailability in oral products. Furthermore, the ability to dissolve drugs into a solution vastly increases the drug’s flexibility for formulation. In one case, the drug can be dissolved into ethanol and spray-dried onto other components of a pill, allowing even dispersion of the drug and increasing the flowability of the tableting blend. Cyclodextrins greatly improve the bioavailability of drugs and flexibility of drug formulation.

In 2013, the FDA granted approval for the NIH clinical trials for the use of cyclodextrin as a treatment for Niemanns-Pick Type-C, a disorder in which cholesterol builds up in the tissues and organs leading to neurodegenerative disorders. A recent rodent study showed that the injection of cyclodextrin directly into the central nervous system prevented the build-up of cholesterol, thus preventing neurodegeneration. The
unique properties of cyclodextrin to bind cholesterol can be used as a treatment for disease.

Cyclodextrins have helped chemists maximize their creativity in making the impossible possible. They have been used in a variety of industries, such that they are unavoidable. However, are cyclodextrins safe for human use and consumption? The use of cyclodextrin as an ingredient in food and drug products is generally recognized as safe (GRAS) by the FDA. However, there are limitations place on the amount of cyclodextrin that can be used in food. For β-cyclodextrin, the maximum percent composition is 2% and estimated that its intake level would be 1.44 mg/kg of body weight/day, which does not present a safety concern for the FDA.

Cyclodextrins are natural products that are formed from the bacterial digestion of cellulose. Thus, they can be found in rotting starches, because of digestion by bacterial enzymes. Bacterial digestion of starches produce α, β, and γ cyclodextrin, which are considered natural products as they are a results of natural processes. However, these natural cyclodextrins, can be modified with specific functional groups in order to provide additional solubility or higher affinity for a molecule.

What makes all of these properties of cyclodextrin possible? Cyclodextrins possess loosely bound, easily replaceable water molecules on the hydrophobic interior of the molecule. Binding of a nonpolar hydrophobic molecule to the interior of the protein is entropically and enthalpically favorable because these loosely bound water molecules are returned to the bulk phase of the polar solvent. Thus, there is an increase in entropy that makes binding of a molecule to cyclodextrin favorable.

Natural cyclodextrins have a diameter ranging from 0.56 - 0.88nm, with α being the smallest, followed by β then γ. Their solubilites range from 18.4 – 249.2 g/kg of water, with β being the least soluble and γ being the most soluble. Of the natural cyclodextrins, β is the most commonly occurring, therefore the cheapest, followed by α then γ. While, the most common cyclodextrins are natural products, cyclodextrins can be synthesized by the addition of glucopyranosyl residues to increase the diameter of the molecule. However, larger rings decrease the stiffness of the rings, causing them to twist and reduce binding capacity.

![Figure 3. Comparison of natural cyclodextrins](image-url)
In addition to the vast amount of progress cyclodextrins have achieved, the outlook for cyclodextrin research and use is promising. The number of cyclodextrin related publishings have been increasing. Intensive research is taking place in order to research further enzymatic and chemical modification of cyclodextrins. Cyclodextrins contain 18-24 hydroxyl groups that can be modified, making the possibilities endless. For example, the interior hydroxyl groups can be substituted for long fatty-acid chains, which can act as detergents. Furthermore, research on cyclodextrin derivatives is in high demand as there is yet to be an ideal cyclodextrin that can overcome most solubility, stability, and toxicology problems. Thus, on the search for the ideal cyclodextrin, researchers have created hetero-dimers and homo-dimers of cyclodextrins (figure 5.) that have an increased stability.

![Figure 4. Comparison of the properties of natural cyclodextrins](image)

<table>
<thead>
<tr>
<th>Cyclodextrin</th>
<th>Mass</th>
<th>Outer diameter, (nm)</th>
<th>Cavity diameter (nm)</th>
<th>Cavity volume, (mL/g)</th>
<th>Solubility, g/kg H₂O [915]</th>
<th>Hydrate H₂O [915]</th>
</tr>
</thead>
<tbody>
<tr>
<td>α, (glucose)₆</td>
<td>972</td>
<td>1.52</td>
<td>0.45</td>
<td>0.53</td>
<td>0.10</td>
<td>129.5</td>
</tr>
<tr>
<td>β, (glucose)₇</td>
<td>1134</td>
<td>1.66</td>
<td>0.60</td>
<td>0.65</td>
<td>0.14</td>
<td>18.4</td>
</tr>
<tr>
<td>γ, (glucose)₈</td>
<td>1296</td>
<td>1.77</td>
<td>0.75</td>
<td>0.85</td>
<td>0.20</td>
<td>249.2</td>
</tr>
</tbody>
</table>

In addition to the increased research interest in cyclodextrins, there is also increasing interest in their applications. The number of cyclodextrin related patents has been increasing. For example, patent CA 2526928 C, patents an idea for a chewing
gum that will remove stains from teeth and other dental material through the use of cyclodextrins. Similarly, patent CN103260656 A, patents the idea of using cyclodextrins in personal hygiene product, such as diapers and tampons, in order to absorb foul odors. While cyclodextrin use has already been vastly recognized by the food, household product, and pharmaceutical industries, their use is expected to spread to fields such as, environmental protection, biotechnology, and textile industries.

Cyclodextrins and their unique properties have unleashed a new perspective of chemistry that many had not considered. It has sparked a creativity that has changed consumer products, food, and pharmaceutics. Most importantly, it has allowed chemists to go beyond the over-generalized teachings of basic chemistry. It has allowed scientists to think outside of the box and rethink what was considered impossible regarding both the fundamentals of chemistry and its applications. Furthermore, it forces us to rethink what we have considered impossible.

Works Cited


