Industrial Applications of Cyclodextrins

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I. Production of Complexes

Complexes are easily formed. The most commonly used methods are the coprecipitation, slurry, paste, and dry mixing methods. They are all similar, with each method using successively less water.

Water is important in the formation of complexes. In addition to being a driving force for the hydrophobic interaction of the guest with the cavity of the cyclodextrin, water is a medium for dissolution of both the cyclodextrin and the guest. Complexation is a molecular phenomenon where one molecule of guest and one molecule of cyclodextrin come into contact with each other to associate and form a complex.

In some cases, water is required to maintain the integrity of the complex. Water is present in the crystals of the complex. The water can form a bridge between the hydroxyl groups of adjacent molecules of cyclodextrin to form a cage to assist in trapping the guest in the complex.[1]

A. Coprecipitation Method

The coprecipitation method is the most widely used method in the laboratory. A solution of cyclodextrin is made, and the guest compound is added to the solution while stirring. Conditions are selected so that the solubility of the complex is exceeded and the complex can then be collected as a precipitate by filtration or centrifugation. For β-cyclodextrin, the least soluble of the cyclodextrins, the solution is heated to about 60 °C to dissolve the β-cyclodextrin before adding the guest. The solution of cyclodextrin is allowed to cool to ambient temperature as it is stirred with the guest to form the complex. The collected complex can be dried.

This method is essentially a laboratory method. It is performed with readily available equipment, a beaker, stirrer, and heat source. It has the advantage that one can easily see the complex forming and see that the guest has been included in the complex by the disappearance of the guest. Because of the large amount of water used, this method is not frequently used for large-scale formation of complexes because of the size of tanks required and wastewater disposal considerations. This method is used to prove feasibility of complexation of a particular guest, to obtain small quantities of complex to test functioning of the complex in applications, and to characterize the complex to determine the properties of the complex to be able to scale-up complexation using other methods.

B. Slurry Method

The cyclodextrin need not be completely dissolved to form complexes. For the slurry method, cyclodextrin is suspended in water up to a 40−45% w/w concentration. The guest can have an effect upon the viscosity of the slurry, and concentrations are adjusted to allow mixing of the cyclodextrin and guest.

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As the cyclodextrin which is in solution forms complexes and the complex precipitates, more of the cyclodextrin dissolves to form more complex. Heating can be used if desired and is compatible with the guest. The amount of time needed to complete the complexation is dependent upon the particular guest and the vigorousness of the stirring. The mixing time needed is determined by experimentation and comparison of the characteristics of the resulting complex with the characteristics of the complex made using the coprecipitation method. The complex is generally collected by filtration and dried if a dry complex is required.

C. Paste Method

The paste method uses a minimum amount of water, 20−30% w/w, about the same amount of water as is found in the filter cake from a complex made by the coprecipitation method. The cyclodextrin, water, and guest are added to a mixing device and mixed. Because of the high viscosity, this method is usually not performed in the laboratory. Various mixers, such as an extruder, σ blade mixer, or other kneading type of mixer, can be used. The mixing time varies with the guest to be complexed, amount of water, and mixing device used. A mixing device providing high shear generally completes the complexation in a shorter amount of time than a low-shear mixer. Mixing time is determined experimentally by comparing the properties and performance of the complex formed with those of the complex made using the coprecipitation method. In most cases, a mixing time of about 30 min is sufficient, depending upon the mixer selected and the guest. The complex is then dried without any further treatment.

In some cases, this method can be done in two steps, a mixing step followed by a holding step to allow completion of the complexation reaction. In the literature, this is referred to as the heat and seal method.[2] The guest and cyclodextrin are mixed with a minimum amount of water. The mixture is placed in a container or is left in the mixer if it can be closed and sealed. The mixture is then held while heating to complete the complexation reaction. Temperature, time, the amount of water, and the particular guest control the rate at which the complexation reaction is completed.

D. Dry Mixing Method

The dry mixing method involves mixing the cyclodextrin with the guest with no added water. This is generally not an efficient method of making complexes since mixing times can range from hours to days. There are some exceptions, such as lemon oil, where complexation is completed in a few minutes. In these cases, the guest might also be serving as a solvent for the cyclodextrin.

E. Drying of Complexes

When drying complexes, it is desirable to remove the water as quickly as possible, especially when a volatile guest has been complexed. In the presence of water, even with the small amounts of water present in the filter cake or paste, there is an equilibrium between the insoluble complex and soluble complex. The small amount of complex will dissociate, resulting in some free guest. With volatile guests, this will result in some evaporative loss of the guest so that the time for drying and reduction of the amount of water supporting solubilization of the guest should be as short as possible. Any of several types of dryer, such as a tray dryer, spray dryer, fluid bed dryer, or vacuum-dryer, can be used. Dryers with heated surfaces can have some local hot spots. In addition to the usual problems of charring and coating of these surfaces, the heat can also cause dissociation of the complex. Use of hot air ovens avoids these surface concerns. The circulating air also helps to remove water vapor more quickly than diffusion. A dryer that physically mixes the complex is also preferred. Dissolution and decomplexation of the complex can occur while the hot complex remains stationary while the water slowly moves from the interior of the mass of complex to the surface to be removed. Constant turning of the complex provides a more rapid means of removing water to keep the complex intact.

Properties of the complex also effect the choice of dryer to be used. Soluble complexes are most frequently dried using a spray dryer. Some complexes will partially melt or solubilize when exposed to heat. A glass or very hard complex requiring milling can result from drying soluble complexes unless the water is removed rapidly. Use of a vacuum-dryer and lower temperatures, such as freeze-drying, generally results in a dry powdery complex.

Drying temperatures in ovens are generally around 100 °C, the boiling temperature of water. Some adjustment of the temperature might be needed for volatile guests. If the boiling temperature of the guest is exceeded, the guest will evaporate. For a volatile guest, a drying temperature from 3 to 5 °C below the boiling temperature of the guest is usually optimal. If the temperature is too low, volatile guest will also be lost due to the free guest resulting from the equilibrium established by the complex with the water present.

There is no single method or process for making complexes. A process must be developed for each guest to be complexed with the cyclodextrin. Selection of equipment is frequently based upon use of existing available equipment, and the process is then developed around use of that equipment. Factors such as temperature, amount of water, mixing time, and drying conditions must be established for the equipment and each guest and cyclodextrin used to optimize the process.[3]

II. Analysis of Complexes

A variety of techniques are used to analyze complexes. Only NMR proves that a complex is formed. A shift in peaks can be observed for both the cyclodextrin and the guest. As the environment around the hydrogen atoms in the cavity changes with association with the guest, a shift in the peaks for the cyclodextrin can be observed. Similarly, shifts

can be observed for peaks corresponding to the atoms of the guest which penetrate into the cavity of the cyclodextrin.

Most users of complexes do not have access to a NMR and use other means to characterize the complex. While these methods do not prove that a complex has been formed, evidence can be obtained that is consistent with a complex having been formed.

Extraction of the guest from the complex is frequently used to determine the load and the homogeneity of the complex. A small quantity of complex is placed into a container with some water and a water-immiscible solvent and heated and mixed thoroughly. The heat destabilizes the complex. The cyclodextrin becomes solubilized in the water, and the guest is extracted into the organic phase. The guest in the organic phase is assayed using the chromatographic or spectrophotometric procedures normally used for the assay of the guest.

Differential scanning calorimetry (DSC) or thermogravimetric analysis (TGA) can also be used. For analysis by these techniques, the guest must have a melting or boiling temperature below about 300 °C, the temperature at which the cyclodextrins decompose. Using DSC, no energy absorption is observed at the melting temperature of the guest when the guest is complexed. Since the guest is surrounded by the cyclodextrin and not interacting with other guest molecules, there is no crystalline guest structure to absorb energy. With both techniques, an increase in the boiling temperature is observed. Interaction of the guest with the cyclodextrin provides a higher energy barrier to overcome for volatilization so that an increase in boiling temperature of about 10 °C is observed. An estimation of the amount of noncomplexed guest can be obtained from DSC, especially if large amounts of guest are not complexed.

Fourier transform infrared spectroscopy (FTIR) and Raman spectroscopy have also been used for analyses of complexes. Upon complexation of the guest, shifts or changes in the spectrum occur. There are interferences in the spectra from the cyclodextrin, and some of the changes are very subtle, requiring careful interpretation of the spectrum.

Several other techniques have also been used to characterize complexes, such as optical rotary dispersion, circular dichroism, mass spectroscopy, fluorescence, and X-ray crystallography. Selection of some these specialized techniques frequently depends on equipment available and properties of the guest which make the particular technique most sensitive or reliable for the particular complex.

Some functional assays can also be used. For labile guests, accelerated stability tests can be done to determine if decomposition of the guest is prevented or is within the expected range for a complex. Since most guests complexed by cyclodextrins are hydrophobic, their interaction with water is altered so that tests measuring wetability, dissolution rate, or even rate of release of guest from some complexes can be used.

III. Applications of Cyclodextrins

Cyclodextrins are used to obtain certain benefits that result from complexation with the cyclodextrins. These include alteration of the solubility of the guest compound, stabilization against the effects of light, heat, and oxidation, masking of unwanted physiological effects, reduction of volatility, and others. In some applications, more than one benefit is obtained by complexation with cyclodextrins. These are discussed below with examples of uses for the complexes. Table 1 lists selected products containing cyclodextrins.

A. Control of Solubility

The solubility of a guest compound can be changed upon complexation with a cyclodextrin either to increase or to decrease the solubility. When a guest compound is complexed by a cyclodextrin, the guest in the cavity of the cyclodextrin is essentially surrounded by the molecule of cyclodextrin. The hydrophobic groups of the guest that would be in contact with the solvent in the free state interact with the atoms of the cavity of the cyclodextrin instead. The outer surface of the cyclodextrin interacts with the solvent. As a result, this outer surface of the cyclodextrin contributes to the solubility of the complex and not the portion of the guest interacting with the cavity of the cyclodextrin. In many cases the contribution of the outer surface to the solubility of the complex is not sufficient to obtain the desired solubility properties. Modification of the hydroxyl groups of the outer surface of the cyclodextrin can alter the solubility properties markedly. Substitution with a neutral group, such as a hydroxypropyl group, or an ionic group, such as a carboxymethyl, tertiary amine, or quaternary amine group, increases the solubility of the modified cyclodextrin to 60% or greater in water. Modification with aliphatic groups, such as hexyl groups, or nearly complete substitution with smaller groups, such as acetyl groups, results in decreased, nondetectable solubility in water and increased solubility in organic solvents. The guest will have some effect on the solubility since a portion of the guest will be exposed at the open ends of the molecule of cyclodextrin.

Hespiridin is found in the juice of some oranges and imparts an undesirable cloudiness to the juice of canned orange slices. Adding β-cyclodextrin to the juice resulted in solubilization of the hesperidin and a clear syrup.[4] In addition to solubilizing the hespiridin, the bitter flavor of the hesperidin was masked. Triterpenes, such as oleanolic acid, ursolic acid, or gederogenin, are insoluble in water. Using cyclodextrin, a solubility of 400 μg/mL and greater was achieved.[5] The minimum inhibitory concentration for *Streptococcus mutans* was decreased from 80 to 5 μg/mL because of the greater bioavailability of the solubilized triterpene. While the solubility of many compounds is not sufficiently increased using unmodified cyclodextrins, derivatives can be used to increase the solubility to higher concentrations than can be achieved with the unmodified cyclodextrins. Sporanox Liquid is a clear solution containing 10 mg/

Table 1. Selected Applications of Cyclodextrins

	Food	
cinnamon-flavored apples	stabilize flavor	Hungary
flavored tea	stabilize flavor	Hungary
peppermint-flavored chewing gum	flavor delivery	Hungary
mustard oil steak sauce	improve solubility	Japan
acetic acid	convert to a powder	Japan
cinnamon-flavored chewing gum	flavor delivery	Japan
aloe-containing beverage	mask bitterness	Japan
lemon and grapefruit candies	flavor delivery	Japan
mint and green tea mints	flavor delivery	Japan
vitamin B fruit juice beverage	mask vitamin odor	Japan
water purifier	absorb odor	Japan
lemon-flavored sugar	flavor stabilization	Hungary
processed cheese	cholesterol removal	Belgium
	Pharmaceutical	
itraconazole	increased solubility	U.S., U.K.
piroxicam	reduce irritation	Europe
PGE_1	increased stability	Germany, Italy, Japan
PGE_2	solubility, stability	Japan
garlic oil	mask odor	Germany
hydrocortisone	increased solubility	
	Cosmetics and Personal Care Items	
artificial tanning lotion	stability, mask odor	U.S.
powdered hair bleach	stability	U.K., Belgium, U.S.
perfume	prolonged release	Japan
cold cream	solubility	U.S.
skin cleanser	tocopherol carrier	Italy
	Miscellaneous	
laundry drier sheet	fragrance control	U.S.
chromatography column	separations	U.S.

mL of an antifungal agent, itraconazole, which is insoluble in water.[6] Itraconizole can be solubilized using cosolvents, but the itraconazole precipitates in the stomach and is unavailable for adsorption. Use of hydroxypropyl β-cyclodextrin prevents precipitation in the stomach, allowing use in an oral dosage formulation. A 30-fold increase in the solubility was reported for tolnaftate with hydroxypropyl β-cyclodextrin and an increased dissolution rate.[7] Solubility of miconazole was increased by an order of magnitude with 80−90% of the drug being released within 2 min and the minimum inhibitory concentration was one-tenth that of the free drug.[8] The solubility characteristics imparted by complexation with cyclodextrins are stable. Glibornuride was complexed with β-cyclodextrin and stored for 1 year. After the 1-year storage period, the dissolution characteristics and bioavailability remained unchanged.[9]

Peptides can also complex with cyclodextrins. Phenylalanine, tyrosine, and tryptophane units of the peptide complex well with cyclodextrins. Ovine growth hormone has a molecular weight of 20 000 and is insoluble in water except at high pH, such as 11.5, which is not suitable for pharmacological use. Complexed with hydroxypropyl β-cyclodextrin, ovine growth hormone is solubilized at pH 7.5−8.5.[10]

Branched β-cyclodextrin has also been used to solubilize drugs.[11] Testosterone and progesterone are about 10 times more soluble using the branched β-cyclodextrin than using α-, β-, or γ-cyclodextrin. Hydrocortisone is solubilized only by a factor or 4 or 5 greater than α-, β-, or γ-cyclodextrin with the branched β-cyclodextrin.

Urushiols are oils produced by plants such as poison ivy, poison oak, and poison sumac. When these oils contact the skin, they cause a rash and itching. Washing the exposed area can cause spreading of the oils and increased irritation. The urushiols complex with cyclodextrin so that they can be removed from the skin without spreading the oil over the surface of the skin.[12] Hydroxypropyl β-cyclodextrin and γ-cyclodextrin are particularly effective. Urushiol was removed from the surface of a glass slide placed in a solution of γ-cyclodextrin in 1 h, with half of the oil being removed in 12 min. Urushiol was applied to the skin and covered with a pad saturated with a 10% solution of γ-cyclodextrin. Only a slight rash resulted after the treatment, while both a rash and itching developed when no γ-cyclodextrin was used. Large lipids, such as ear wax, can also be solubilized.[13] After 10 min of exposure to a solution of γ-cyclodextrin, the ear wax was disintegrated, resulting in a cloudy solution. Using other preparations for removal of ear wax, removal was not completed in 10 min and the treatment solutions remained clear, indicating no disruption of the mass of wax.

Drugs for nasal delivery are generally administered as a water-based liquid or as a powder. Drugs administered intranasally have a tendency to flow down into the throat soon after administration or become mixed with nasal secretions and excreted through the nostrils. Powders of small particle size enter the trachea, while large particles settle in the nonvillous anterior part of the nasal cavity. These losses make frequent administration of the drug necessary. Loteprednol was complexed with α-cyclodextrin and administered intranasally.[14] The rate of elimination of the complexed drug was much slower, one-twentieth as fast as that of the uncom-

plexed drug. The area under the curve (AUC) was 10 times greater for the complexed drug, and the C_{max} was 2-fold higher for the complexed drug than for the uncomplexed drug.

Flufenamic acid is a nonsteroidal anti-inflammatory drug (NSAID). The use of NSAIDs is limited because of their gastrointestinal side effects. Flufenamic acid is soluble in water, and an insoluble triacetyl β-cyclodextrin derivative was used to complex the drug to slow the release of the drug.[15] Release of the flufenamic acid from the complex consisted of a faster and a slower rate, with the faster rate due to uncomplexed drug in the complex preparation. The complexed drug did not have an immediate sharp increase in the plasma concentration, as did the uncomplexed flufenamic acid, but had a sustained plasma plateau lasting 6−8 h. Desirable plasma concentrations were achieved from the complex without reaching high plasma levels which have adverse side effects.

A flavor complex was incorporated into some chewing gum and compared with chewing gum made without cyclodextrin.[16] A coating composition was also made to contain the complex or free flavor. The cyclodextrin complex and coated free flavor released the flavor at about the same rate when the gum was chewed. The release of the flavor was extended using the combination of complex and coating matrix. After 5 min, the combination of cyclodextrin and coating matrix had about twice as much flavor as the coated flavor or complexed flavor without the coating. Some flavor was still present in the gum made with the coated complex, while all of the other gums had no flavor. A complex of 3−1 methoxypropane-1,2-diol was used in chewing gum.[17] The gum with the complex had a higher flavor impact and greater sensation of coolness than the gum with uncomplexed methoxypropanediol. The texture of the gum containing the complex was also desirably firmer.

The α-hydroxy acid glycolic acid is used as an emollient and to induce superficial peeling of the skin. Glycolic acid is irritating to the skin. Complexed with cyclodextrin, glycolic acid was found to be nonirritating due to the lower concentration of glycolic acid in the free form.[18] Due to the equilibrium between the free and complexed states, there was a prolonged release or availability of the glycolic acid with increases in the efficacy of exfoliating action and cellular removal.

Cyclodextrins can effect the denaturation and renaturation of proteins. Carbonic anhydrase was denatured using guanidine hydrochloride.[19] Aggregation of the enzyme was decreased using α-cyclodextrin. The optical density was about 0.2 without cyclodextrin and about 0.03 in the presence of cyclodextrin, demonstrating a decrease in aggregation. Cyclodextrins are able to complex the hydrophobic amino acids of proteins to solubilize them. The enzyme could be renatured to restore enzymatic activity. In the presence of α-cyclodextrin, 90% of the original activity was recovered. Using β- or γ-cyclodextrin 70 or 80% of the activity was recovered. In the absence of cyclodextrins, only 35% of the original activity was recovered. Similar studies were performed using MM-creatine kinase.[20] Hydroxypropyl β-cyclodextrin was used. The cyclodextrin did not protect the enzyme against aggregation, but 85% of the activity was recovered after denaturation compared to only about 10% of the activity of the enzyme when the cyclodextrin was not used.

Cyclodextrins have been used for dying fabrics. Using cyclodextrins, more dye went on to the fabric, reducing the amount of dye remaining in the wastewater.[21] The solubility of the dye in water was increased, and no other auxiliaries were needed to solubilize the dye. Preformed complexes performed better than adding the dye and cyclodextrin to the dying solution, and the complexes dissolved rapidly. Hydrophobic tosyl derivatives of β-cyclodextrin have also been used.[22] Using these derivatives, about a 3-fold increase in the binding of fluorescent dye to polyester fiber was observed.

Solubility enhancement by cyclodextrins has also been tested for soil remediation to remove organic pollutants. Surfactants can be used, but sorption, retardation, and pore exclusion reduce their effectiveness. Hydroxypropyl β-cyclodextrin showed no sorption to the soil, retardation, or pore exclusion.[23] The retardation factor was reduced 70-fold for pyrene, 50-fold for trichlorobiphenyl, and 40-fold for phenanthrene using hydroxypropyl β-cyclodextrin to remove these compounds from soil. Another soluble derivative, carboxymethyl β-cyclodextrin, was also evaluated.[24] The solubilities of trichlorobenzene, anthracene, and biphenyl were increased. Because of the anionic groups on the derivative, salts could be removed simultaneously with the organic pollutants. Calcium ions, which occur abundantly in soil, cause precipitation of sodium dodecyl sulfate at a concentration of 2000 mg/L, but no precipitation was observed at concentrations as high as 10 000 mg/L with carboxymethyl β-cyclodextrin. Cadmium ions were selectively complexed by the derivative, and the effect of salts on complexation of anthracene was negligible. There was some decrease in the binding of the cadmium in the presence of calcium salts. Above pH 5.0, the pK_a for the carboxyl groups, there were no pH effects on the binding of the salts. A mixture of polyaromatic hydrocarbons was added to soil, and extractions of these using hexane, randomly methylated β-cyclodextrin, hydroxypropyl β-cyclodextrin, or soluble polymers of β- or γ-cyclodextrin were compared.[25] Randomly methylated β-cyclodextrin and heptane were equally effective for removal of anthracene. The β-cyclodextrin polymer was more effective than heptane, removing 84% vs 74% of the anthracene from the soil. The derivatives removed 61−95% of the pyrene vs only 53% removal by heptane. Perlene, however, was removed more effectively by heptane, 79% vs only 10−32% by the derivatives. Use of cyclodextrins can also increase the efficiency of biodegradation of hydrocarbons.[26] In addition to increasing the solubility of the hydrocarbons, toxicity is decreased, resulting in an increase in microbial and plant root growth.

Viscosity of water-based paints during their manufacture can be controlled using cyclodextrins.[27] Thickeners are added to paints to impart desired viscosity

properties. By complexing with the thickener during the manufacture of the paint, the viscosity is reduced, making mixing easier. Viscosity is restored upon addition of paint components which displace the thickener from the cavity of the cyclodextrin to give the paint its desired viscosity properties. Other benefits obtained from the use of cyclodextrin include reduced foaming, especially for roller application of the paint, and reduced color development problems caused by surfactants used in some formulations to control viscosity.

B. Process Aids

Cyclodextrins can also be used as process aids, where the benefits of the control of solubility of the guest are used, but the cyclodextrin is removed and not present in the final product. The most widely used example of the use of cyclodextrins is that of removal of cholesterol from animal products such as eggs, dairy products, and animal fats such as lard and tallow.[28−31] Cyclodextrins added to the material from which the cholesterol is to be removed and mixed. In the cases of lard and tallow, the cyclodextrin is added as an aqueous solution and is mixed at a temperature high enough to melt the fat but not so high to destabilize the complex. While the cyclodextrin is mixed with the material containing cholesterol, the cyclodextrin forms complexes with the cholesterol which are insoluble in the water or the fat. The complex is removed from the treated material by filtration or centrifugation. Only very small amounts of cyclodextrin remain in the product due to the low solubility of the cyclodextrin−cholesterol complex. The treated material typically has 80% of the cholesterol removed.

The cyclodextrin−cholesterol complex can be suspended in water and heated. The heat destabilizes the complex, causing the cyclodextrin to be solubilized in the water and the cholesterol to float to the surface of the water. The cholesterol is collected and can be sold for other uses, and the cyclodextrin can be used again for cholesterol removal. Depending upon the material to be treated, the cyclodextrin can be cleaned up by filtration, ion exchange, charcoal treatment, or other process to make it sufficiently pure for further use.

Free fatty acids lead to undesirable properties and degradation of frying properties of the fat during frying, causing excessive smoke formation, foaming or boiling, excessive browning before cooking is completed, and deposition of an oily residue on the surface. Free fatty acids can also be removed from fats using cyclodextrins, improving the frying properties of the fat.[32]

Fruit and vegetable juices can also be treated with cyclodextrins to remove polyphenolic compounds which cause enzymatic browning.[33] Polyphenol oxidase, an enzyme which is present in the juice, converts the colorless polyphenols to colored compounds. By removing the polyphenols from the juice, there is no substrate on which the enzyme can act, and as a result, no color forms. Juices from grapes, apples, pears, and celery were treated with a polymer of β-cyclodextrin, and no browning occurred. The polymer is insoluble in water and is easily removed by filtration or centrifugation and functions analogously to an ion-exchange resin, removing organic compounds instead of ions. No analyses were done to determine if other components were removed. β-Cyclodextrin can also be added to the juice to prevent browning, but the cyclodextrin remains in the juice. The complex is sufficiently soluble so that it does not form a precipitate that can be removed. The polyphenol complexed in the cavity of the cyclodextrin is unavailable to the enzyme because it is surrounded by the cyclodextrin. Citrus juice has also been treated with β-cyclodextrin polymer to remove the bitter components naringen and limonen.[34] Chemical and organoleptic analyses showed that none of the nutrients or flavor components were removed from the juice.

Bioconversions of organic compounds are frequently done in the presence of a surfactant or solvent to increase the solubility in water of the compound to be acted upon. The surfactants or solvent also have an effect upon the organisms performing the bioconversion and can be used only in limited quantities. Podophyllotoxin can be solubilized by methylated β-cyclodextrin.[35] A 6-fold increase in the bioconversion rate was found compared to bioconversion without the cyclodextrin.

C. Stabilization

Cyclodextrins can be used to stabilize compounds. The cavity of the cyclodextrin is a finite space. Once that this space has been occupied by a molecule of guest, other molecules are excluded from occupying the space at the same time. This prevents interaction and reaction with other molecules. Although the ends of the cavity are open, some steric hindrance is provided to prevent the approach other molecules at the exposed portion of the molecule. Association with the cavity or hydroxyl groups surrounding the cavity can also stabilize the guest in less reactive forms of the guest molecule.

Penicillin G is stabilized in aqueous solution in chloroacetate buffer with hydroxypropyl β-cyclodextrin.[36] The rate of degradation is about 9 times slower for the complex as compared to uncomplexed drug. The activation energy for the degradation reaction was the same for both the complexed and free drug, but a reduction of the entropy of activation was found, suggesting that steric hindrance made the approach of the catalytic proton more difficult.

Thymopentin is a peptide which blocks the stimulation of smooth muscle contractions induced by (+)-anatoxin-a, which is produced by blue green algae. Thymopentin is unstable in aqueous solution and cannot be stored in a ready to use form. Complexed in aqueous solution with hydroxypropyl β-cyclodextrin, activity was retained over 14 months of storage at 25 °C. In the absence of the cyclodextrin, all of the activity was lost within 1 week.[37]

Erythropoeten is a glycoprotein hormone which induces an increase in red cell mass. Complexed with hydroxypropyl β-cyclodextrin, 100% of the activity was maintained for 10 days compared to only 50% of the activity in the absence of cyclodextrin.[38] After

20 days, the complexed erythropoeten retained 62% of its activity compared to only 24% in the absence of cyclodextrin. Bioavailability of the erythropoeten was the same for the complex as for the uncomplexed hormone.

Nicardipine is sensitive to light and decomposes if exposed to light. By complexing nicardipine with cyclodextrins, the rate of photodegradation can be reduced.[39] Nicardipine was complexed with cyclodextrins and exposed to UV irradiation. Photodegradation was slowed by a factor of 10 with methylated β-cyclodextrin, 8 with hydroxypropyl β-cyclodextrin, 6.5 with α-cyclodextrin, and 5 with γ-cyclodextrin.

Unsaturated fats, such as fish oils and vegetable oils, contain unsaturated fatty acids which are easily oxidized, resulting in unpleasant taste and odor. Complexation with cyclodextrins protects them from oxidation.[40] Complexation also converts them from oils into solids containing 18% and greater oil in the complex.

Peroxy acids are used as bleaching agents and disinfectants for home, industry, and medical equipment. Storage and thermal stability are concerns in using these materials. Complexation with cyclodextrins improves storage and thermal stability.[41] Odor is also reduced for the complexed peroxy acids, and the complex is stable without using diluants. Tablets can be made for use, and increased solubility of the peroxy acids is achieved as a complex. Explosive compounds can also be stabilized with cyclodextrins.[42]

Hair dye preparations were made and evaluated immediately after making them and after storing them for 6 months.[43] The quality of the hair, as measured by flexibility and ease of combing, was rated as superior for the formulations made with complexes of cyclodextrin immediately after making the formulation and after 6 months of storage. No difference was found for the characteristics related to color for the freshly prepared formulations made with or without cyclodextrins. After 6 months of storage, the preparations made with the complexed dye were judged by panelists to have a deeper and richer color and to have more resistance to being washed out of the hair by shampoo and to bleaching by the sun.

D. Masking of Effects of the Guest

When a guest is included in a molecule of cyclodextrin, it is isolated and prevented from coming into contact with surfaces of the body where it could cause unwanted side effects such as irritation or an off flavor. Release of the guest from the complex is slow. As a result, the amount of free guest is lower than if the free guest alone is used so that the amount of guest to elicit a physiological response is reduced, resulting in masking or decrease in intensity of the unwanted effect of the guest.

Pilocarpine was administered as a prodrug, *O*,*O*′-dipropionyl(1,4-xylenylene)bispilocarpine acid diester with hydroxypropyl β-cyclodextrin.[44] The amount of irritation decreased as the amount of cyclodextrin was increased. At a concentration of 15%, the irritation was reduced to the same level as that with the commercial formulation and the occular delivery was substantially improved.

A complex of diclofenac was compared to a commercial preparation, Voltaren.[45] Lysis of red blood cells was used to evaluate cellular lysis. Fifty percent of the red blood cells were lysed by 10.77 mM pure diclofenac, 61.88 mM hydroxypropyl β-cyclodextrin, and 40.67 mM hydroxypropyl β-cyclodextrin−diclofenac complex. The amount of complex needed to lyse the red blood cells of the complex was 4 times higher than for diclofenac alone. Voltaren lysed 22.7% of the cells at a 0.1% concentration, while at the same concentration, pure diclofenac or the complex did not lyse the cells. A surfactant is used in the Voltaren, which is not needed when using the cyclodextrin. At pH 7.4, the complex had a lower permeability, but at pH 6.0−6.5, it had a higher permeability. Lag time was also reduced. At pH 7.4, the lag time for the complex was 63 min while the lag time for Voltaren was 75 min. At lower pHs the lag time for the complex was 31 min at pH 6.5 and 35 min at pH 6.0. The results indicated the suitability of the hydroxypropyl β-cyclodextrin to optimize the ophthalmic application of the drug for improved transcorneal permeability and in vivo tolerance based upon the hemolysis studies.

The off taste from can coatings can be reduced or eliminated using cyclodextrins in the coating.[46] Aldehydes and ketones containing 6−18 carbons are implicated in producing tastes similar to that of stale beer. Coatings were made with and without cyclodextrin and extracted with methylene chloride. More aldehydes, in both amount and kind, were extracted from the coatings which did not contain cyclodextrins, demonstrating the ability of cyclodextrins to keep the undesirable flavor constituents out of the contents of the coated can.

The irritating or toxic effects of insecticides can be reduced or eliminated by complexing the insecticide with cyclodextrins. Azinphos-methyl forms an odorless complex with β-cyclodextrin.[47] No systemic toxic effects were observed when the insecticide was administered dermally at a dose of 4000 mg/kg in the complex, while the free insecticide shows toxicity when administered dermally at 17.84 mg/kg. Complexation resulted also in a 3.8-fold increase in solubility, and the insecticidal activity was comparable to that of the commercial formulation.

E. Reduction of Volatility

Compounds can be complexed with cyclodextrins to reduce their volatility. Interaction of the guest with the cyclodextrin produces a higher energy barrier to be over come to volatilize. Menthol, for example, can be complexed with β-cyclodextrin to form an odorless complex. The complex can be dried at 100 °C, and the amount of menthol in the complex is very close to the expected theoretical amount of menthol in the complex. Free menthol subjected to the same drying conditions will be completely volatilized.

The release of fragrance from laundry dryer sheets can be controlled by complexing the fragrance with cyclodextrins.[48] During the drying process the cy-

clodextrin−fragrance complex is transferred from the dryer sheet to the fabric. Because of the moisture present during the drying process, some of the fragrance is released, but most of it is transferred to the fabric. When the fabric is remoistened by perspiration or other moisture, fragrance is released from the complex to give an impression of freshness. The fragrance is composed of many components, some more volatile than others. Some of the more highly volatile components are easily lost, but complexed with cyclodextrin; these are retained so that the character of the fragrance is not changed.

Solutions containing cyclodextrins can be sprayed on surfaces from which odor emanates, such as counter tops, clothing, or other fabric.[49] A perfume can also be encapsulated in the cyclodextrin and be replaced by the equilibrium mechanism or by displacement by odiferous compounds to assist in masking of the odor by the release of the perfume. The solution can dry on the treated surface, and upon rewetting, more odor can be absorbed and more perfume can be released.

A dry cyclodextrin powder can be used in products such as menstrual products, diapers, tissues, paper towels, etc.[50] A small particle size of less than 12 μm works best. As particle size becomes smaller, the surface area increases with respect to the volume, resulting in more rapid dissolution rates. Because of the rapid dissolution rate, only small amounts of water are needed for dissolution and dispersion of the molecules of cyclodextrin, making them effective scavengers of unwanted and unpleasant odors. Perfumes can also be complexed in the cyclodextrin to be released upon dissolution of the complex and displacement by odiferous compounds.

Cyclodextrins can be used in hair care preparations to reduce volatility of odiferous mercaptans. Cationic polymers and cyclodextrins act synergistically to reduce odor form permanent wave solutions.[51] α-, β-, or γ-Cyclodextrin and polymers such as cellulosics and quaternized vinylpyrolidine polymers can be used. When polymer alone was used, only 40% of the panelists judged the results as good. More (40−60%) of the panelists judged results obtained with cyclodextrin alone as good, and 80% of the panelists judged the preparation using both cyclodextrin and polymer as good. In some other formulations, cyclodextrins were used with a series of cyclic mercaptan compounds having electron attractive groups.[52] In the presence of cyclodextrins, the formulations had no substantial odor and no odor was generated or less odor was generated when the formulation was used. The odor was selectively captured without decreasing the reducing effect or power.

Cyclodextrins can also be used to prevent odor in skin tanning preparations.[53] Dihydroxyacetone or imidazoles are used to develop tanning. Physical and chemical degradation occurs over time as the product is stored, resulting in unpleasant odors and loss of stability and tanning efficiency. As a result of reaction of the active ingredients with components of the skin, an odor develops after application of the tanning formulation to the skin. When cyclodextrin is included in the formulation, storage stability is achieved, the odiferous compounds generated upon application to the skin are complexed, and odor is not released.

Another form of masking is the prevention of chemical reactions. Silane resins are made using a 1,5-cyclooctadieneplatinum catalyst. Once the catalyst is added, the reaction proceeds. The catalyst was complexed with β-cyclodextrin.[54,55] Complexation of the catalyst with cyclodextrin resulted in a one-part heat-curable silicone with a shelf life exceeding 7 months since complexation prevented immediate catalysis and reaction. No gelation occurred at ambient temperature. The catalyst was released by heating to 150 °C, and curing was achieved in 30 min. Use of cyclodextrins offered the advantage over other encapsulation systems because of the smaller particle size of the cyclodextrin complex. Use of cyclodextrin also prevented the formation of metal crystallites which were present when the cyclodextrin was not used. β-Cyclodextrin also has an accelerating effect on platinum-catalyzed reactions with styrene and triethoxysilane.[56] At 50 °C, the reaction is 45% complete in 30 min but is 100% complete under the same conditions if cyclodextrin is present.

F. Directing of Chemical Reactions

When a guest is complexed with a cyclodextrin, a portion of the guest is inside of the cyclodextrin and not available to come into contact with other molecules because of the finite space in the cavity. Portions of the guest which project out of the cavity are available for reaction with other molecules. Because of the hydroxyl groups or other groups which might be substituted onto the hydroxyl groups, some steric hindrance can occur to prevent reactions from occurring readily. Interaction of the side groups on the guest molecule with the hydroxyl groups of the cyclodextrin or other groups substituted on the hydroxyl groups can also have an effect on the reactivity of the guest molecule. Depending upon the group on the guest molecule, this can result in catalysis of the reaction or prevention of chemical reactions.

Many reactions result in a mixture of reaction products. Irradiation of benzyl phenyl sulfone in benzene and methanol gave a mixture of products: biphenyl, diphenylmethane, dibenzyl, benzenesulfonic acid, and *o*-methyldiphenyl sulfone.[57] Irradiation of a complex of benzyl phenyl sulfone in water gave mostly benzenesulfonic acid. When a solid complex of benzene phenyl sulfone was irradiated, only *o*-methyldiphenyl sulfone was formed. In water there is an equilibrium between the free and complexed states so that the relative amounts of components in a mixture would be dependent upon the relative amount of time the guest spends complexed or in the free state. In the solid complex, the guest would remain in the cavity of the cyclodextrin so that the reaction would be directed to formation of only one product.

2,6-Naphthalenedicarboxylic acid is synthesized from naphthalene in a four-step process.[58] It is an intermediate for high-performance polymers and liquid crystals to obtain better mechanical properties, thermostability, and gas barrier properties for the

polymer. Using β-cyclodextrin as a catalyst, it can be synthesized in one step. α- and γ-cyclodextrins do not function as well. With the β-cyclodextrin, a 65 mol % yield was obtained with a 79% selectivity.

A one-pot synthesis of α-hydroxy acids was performed using triethylbenzylammonium chloride β-cyclodextrin in the presence of sodium hydroxide and chloroform.[59] Yields ranged from 81 to 89% in the presence of the cyclodextrin derivative and only 28−41% in the absence of the derivative.

Polymerization of *p*-styrenesulfonate was accelerated using γ-cyclodextrin.[60] Radical polymerization was initiated using γ-irradiation. After 30 min of conversion, 87% conversion was found with γ-cyclodextrin and only 19% with no cyclodextrin. After 2 h, 82% conversion was obtained with no cyclodextrin, demonstrating an acceleration of the reaction with cyclodextrin. Higher molecular weight polymers were also obtained using the cyclodextrin. After 30 min with cyclodextrin a M_n of 5.3×10^4 was obtained compared to 4.2×10^4 in the absence of cyclodextrin.

Cyclodextrins can also be used for phase-transfer catalysis. Organic compounds that are insoluble in water can be complexed by the cyclodextrin to make them soluble in water where the reaction occurs. Without making the organic compound soluble in water, the reaction is limited to the interface between the organic and aqueous phases, limiting the rate of the reaction.

The oxidation of various olefins in the presence of per(2,6-di-*O*-methyl)-β-cyclodextrin was studied in a solvent-free two-phase system.[61] The efficiency of the mass transfer was dependent upon the substituent groups on the olefin. Oxidation of the terminal olefins was the most efficient. Internal double bonds were in the cavity of the cyclodextrin and were not available for oxidation. In the absence of cyclodextrin or in the presence of acyclic oligosaccharides, there was no catalytic effect.

A catalytic derivative was made for the decolorization of colorants used for printing.[62] To recycle paper, the inks have to be extracted from the paper. A radiation transorber is substituted onto the cyclodextrin. In the presence of ultraviolet light, the transorber absorbs the ultraviolet light and reacts with the colorant in the cavity of the cyclodextrin, making it colorless. The paper can then be recycled directly without the usual deinking process and repulping.

G. Control of Fluorescence and Light Absorption

Some compounds when included in the cavity of a cyclodextrin exhibit an increase or decrease in the intensity of fluorescence or light absorption. This is of obvious benefit in areas of analytical chemistry to increase the sensitivity of assays or to block the effects of interfering compounds. An optical brightener was complexed with a methylated cyclodextrin for use in a photographic application.[63] The increased fluorescent intensity made the white areas of the photograph whiter. Additional benefits of decreased migration and heat stability were also obtained.

H. Compatibility of Cyclodextrins with Other Materials

Cyclodextrins can be incorporated structurally into materials to obtain benefits or to alter the properties of the cyclodextrin complex. Incorporation of cyclodextrins into films and other matrices is an emerging technology for cyclodextrins.

Cyclodextrins can be used in plastic films. β-Cyclodextrin was added at a level of 5% to a poly(vinyl chloride) polymer.[64] Leaching of components used in forming the polymer or formed from side reactions into materials into which they come into contact is a concern. A 44.9% reduction in the leaching of bis(2-ethylhexyl)phthalate into the methanol−water extraction solution was observed compared to the polymer film which did not contain cyclodextrin. Cyclodextrins have also been used to increase the biodegradation of polymers.[65] β-Cyclodextrin was added at a level of 5% to a polyurethane polymer. After being buried in soil for 3 weeks, the polymer containing the cyclodextrin showed a loss of weight while the polymer made without the cyclodextrin showed a negligible loss of weight. The weight loss was confirmed by scanning electron microscopy. The polymer made with cyclodextrin was porous, while the control polymer showed no porosity. The β-cyclodextrin was also blended into the polymer more easily than other materials because of the lower molecular weight of the β-cyclodextrin. Incorporated into polymer films such as packaging films, cyclodextrins can be used to complex organic compounds present in the air to prevent them from contaminating the product.[66] As a result of being encapsulated by the cyclodextrin derivative in the film, the organic compounds do not permeate the film to reach the wrapped product.

Cyclodextrins can also be attached covalently to surfaces to complex with organic molecules. Cyclodextrins were attached to the oxide surface of a chemical microsensor and used to detect aromatic, polyaromatic, halogenated, and oxygen-containing organic molecules.[67] Fast responses were obtained with gaseous organic compounds. By heating the microsensor to 60 °C, the complexed molecules were released and the microsensor could be reused.

Release characteristics of guest compounds from complexes can be modified by encapsulation of the complex in various matrices. When complexes are exposed to water, dissolution and release of guest occurs. A wax coating can be placed over a complex to protect it from the effects of water.[48] In applications, such as the use of fragrance complexes in laundry dryer sheets, the dryer sheet comes into contact with the clothing when it is wet enough to release fragrance from the complex. The complex is encased in a wax which does not melt until certain temperature conditions are met. While there is still some water in the clothing being dried, some of the fragrance is release as the wax melts, exposing the complex, but a sufficient amount of fragrance remains to obtain the intended effect.

A combination of a water-soluble cyclodextrin derivative and methacrylic matrix was used to control the release of fragrance for a room freshener.[68]

The cyclodextrins derivatives were used to solubilize the fragrance in water to obtain release. Due to the high aqueous solubility of the complex, fragrance was released over only a short time period. By incorporating the fragrance into a carboxymethylcellulose matrix, fragrance was released over an 8-h period. Using β-cyclodextrin, the time over which the fragrance was released was increased to 20 h and with hydroxypropyl β-cyclodextrin to 12 h. Although the time period over which the fragrance was released with hydroxypropyl β-cyclodextrin was shorter than that for β-cyclodextrin, more fragrance was released due to the greater solubility of hydroxypropyl β-cyclodextrin in water.

Liposomes can also be used with complexes of cyclodextrins. Nifedipine causes a phase transition as detected by differential scanning calorimetry when incorporated into liposomes.[69] When the nifedipine was complexed with hydroxypropyl β-cyclodextrin, only a slight change was found. The rate of release was dependent upon the method used to prepare the liposome and could be either increased or decreased. Entrapment of drug complexes in liposomes depends on the lipid composition of the liposome, and release is dependent upon both the lipid composition and the drug complexed.[70]

This review has presented selected information, mainly published within the last 5 years. More extensive reviews have been published in the form of books, and the reader is referred to these major publications for more information.[71−73]

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