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Cyclodextrin introduction to anesthesia practice: Form, function, and application

Mark Welliver CRNA, MS, ARNP
Jacksonville, Florida

Cyclodextrins, some of the select molecules exhibiting properties that are beneficial across multiple industries, are naturally occurring cyclical oligosaccharides with a lipophilic inner cavity and a hydrophilic exterior. These characteristics enable cyclodextrins to surround and bind lipophilic molecules while maintaining aqueous solubility. Agrochemistry, analytical chemistry, food, nutraceutical, and pharmaceutical industries have benefited and continue to benefit from these unique molecular properties. Though known and studied for more than 100 years, cyclodextrins have only recently been

explored for specific application to anesthesia. Numerous studies exploring cyclodextrin-improved anesthetic delivery are underway. This new class of enabling molecules will enter the anesthetic arena and will require an understanding of their form, function, and application. This knowledge will facilitate anesthesia providers' optimal use of these unique molecules and the safety and efficacy associated with them.

Key words: Anesthesia, cyclodextrins, encapsulation, host-guest assembly/inclusion complex, modified cyclodextrins/derivatives.

Objectives

At the completion of the course, the reader should be able to:

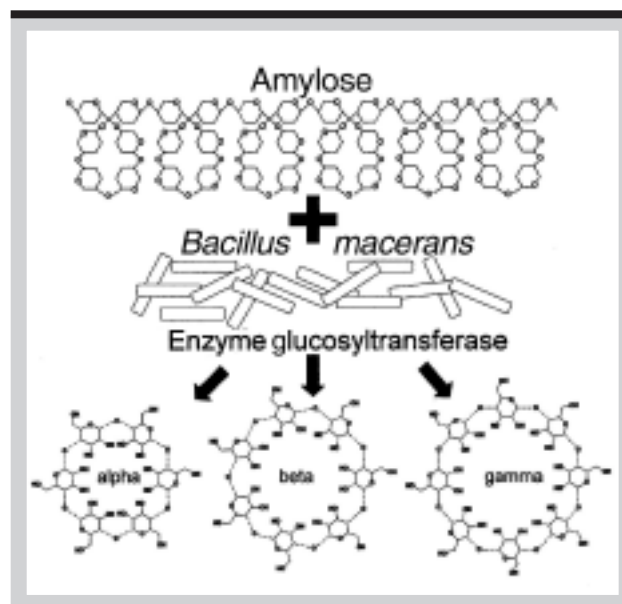
1. Understand cyclodextrin composition and chemical characteristics.
2. Describe encapsulation interactions between host and guest molecules.
3. Differentiate between natural cyclodextrins and cyclodextrin derivatives.
4. List beneficial pharmacologic properties of cyclodextrins.
5. Apply current cyclodextrin research to anesthetic pharmacology needs.

Introduction

Cyclodextrin (CD) discovery originated in the late 1800s by Villiers, and shortly thereafter Schardinger identified 3 different naturally occurring CDs.¹ He named them alpha (α), beta (β), and gamma (γ), and collectively they became known as Schardinger sugars.¹ By 1938, Freudenberg identified the glucose molecules as linked by α -(1-4) bonds in a cyclical manner creating a ring.¹ The cyclical shape of these oligosaccharides is created by enzymatic breakdown of starch

initiated by strains of *Bacillus* bacteria (Figure 1). These rings of glucose are known as the natural CDs

Figure 1. Enzymatic conversion of amylose to the natural cyclodextrins (α , β , and γ) by *Bacillus macerans* bacteria



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because they are naturally occurring in supportive environments where appropriate bacteria and starch sources exist. Research during the past 70 years has produced extensive analysis of the pharmacologic and toxicologic properties of CDs. The primary benefits of CDs are encapsulation of lipophilic molecules and promotion of water solubility.

Pharmacologic benefits

Numerous pharmacologic benefits may be derived from CD use (Table 1). The most desirable is improved solubilization of lipophilic molecules. The CDs, by molecular form and function, maintain their aqueous solubility while encapsulating lipophilic molecules. This ability to impart water solubility to hydrophobic molecules allows the elimination of toxic solvents for drug solubilization. Thus, the use of alcohol, propylene glycol, oil, and other solvents to dissolve certain drugs becomes unnecessary. The addition of hydrochloric acid or sodium bicarbonate to adjust pH in favor of drug ionization for solubilization is also unnecessary when CD encapsulation is used. Neutral pH may be maintained without altering the aqueous solubility enabled by CDs. Encapsulated drugs are protected from breakdown and interaction with other drugs. The CDs, therefore, create a protected environment around the encapsulated drug while greatly improving solubility and stability. This protection also leads to an increased shelf life of drugs. Pharmacokinetics and pharmacodynamics of drugs may be altered by CD encapsulation, allowing improvements such as controlled release of drugs and increased duration of action.² The unique improvements for drug delivery are better appreciated with an understanding of basic CD chemistry.

Form

- *Natural CDs.* The CDs occurring in nature are known as the natural cyclodextrins and are named α , β , and γ and composed of 6, 7, and 8 glucose molecules, respectively. The CDs composed of 5 or 9 glucose units have been identified but are rare and infrequently studied. The natural CDs are abundant and easily produced. As starch derivatives composed purely of glucose, the natural CDs have been deemed safe by the US Food and Drug Administration and have received status as “generally regarded as safe” for oral intake.³⁻⁵

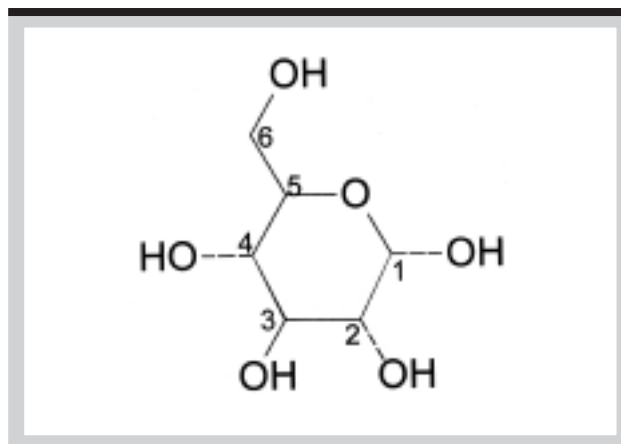
The glucose molecule (monomer) is the base unit of starch (Figure 2). Starch is composed of varying-length chains of glucose monomers called *polysaccharides*. Polysaccharides that contain 2 to 10 linked glucose monomers are further defined as *oligosaccharides*. The CDs are cyclic oligosaccharides with glucose molecules of the pyranose form linked in a circular manner.

The first and fourth carbon atoms of the glucopy-

Table 1. Cyclodextrin pharmacologic benefits

Increased aqueous solubility of water-insoluble drugs
Controlled release of drugs
Increased drug stability
Enable mixing of incompatible drugs
Prevention of drug-drug interactions
Reduction of unpleasant drug tastes and irritations
Protection from ultraviolet radiation, oxidation, and hydrolysis
Provision of a constrained medium for chemical synthesis
Emulsification of hydrocarbons, steroids, and fats
Conversion of liquid materials to dry form
Fixation of volatile compounds

Figure 2. Glucopyranose molecule with carbon atoms numbered



ranose monomers are linked by covalent α bonds (dextro orientation) (Figure 3). The enzyme glucosyl-transferase released by *Bacillus macerans* bacteria is responsible for reconfiguring the polysaccharide amylose into a circular form. Amylose is a helical polysaccharide that loops back onto itself at every sixth monomer. This proximity of overlapping glucopyranose monomers creates sites where enzymatic cleaving and reattachment of the polysaccharide chain occur, creating rings of glucose. The resulting rings, CDs, are composed of 6, 7, or 8 glucose units that geometrically resemble a truncated cone. The positioning of the glucose units is such that the sixth hydroxyl group points outward along the primary rim (narrow), and the second and third hydroxyl groups extend along the secondary rim (wide rim) (Figure 4). It is this geometric shape that creates a cavity that allows CDs to engulf smaller molecules. Encapsulation of lipophilic molecules is the primary desirable action of CDs.

Figure 3. Oligosaccharide showing α -(1-4) glycosidic linkages (bonds)

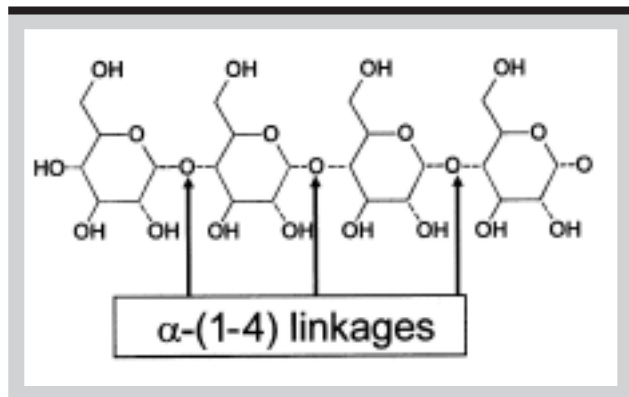
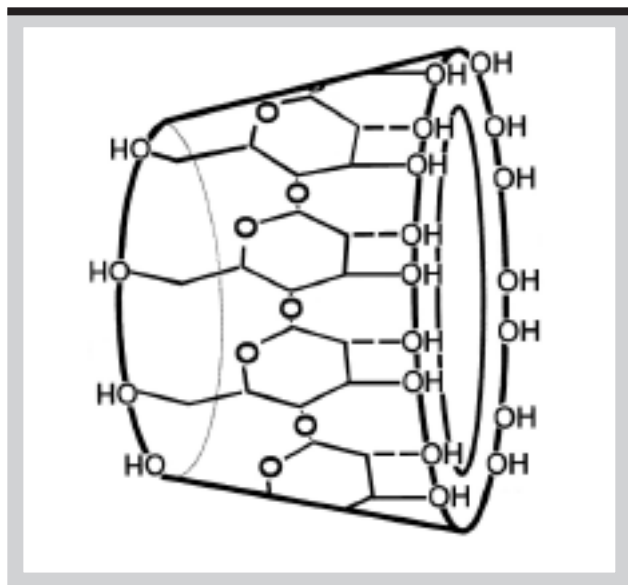


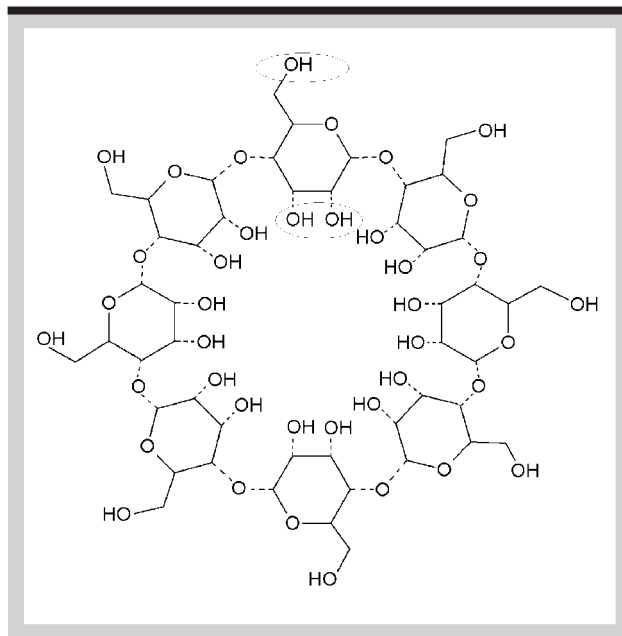
Figure 4. Truncated cone shape and glucose arrangement within a cyclodextrin



• *Modified CDs.* Modification of the natural CDs may enhance or decrease encapsulation affinities for other molecules. The ability to modify the natural CDs allows for targeted encapsulation of specific molecules while preventing encapsulation of other lipophilic molecules. Modified natural CDs are also known as *CD derivatives*. The creation of a CD that is specific to one molecule or drug has numerous beneficial applications (see Table 1). Foremost, a water-insoluble drug can be encased in a modified CD for dissolving in water and eliminate the need for irritating toxic solvents.

The available sites for modification of the natural CDs are the second, third, and sixth carbon atoms of each glucose unit that comprises the CD (Figure 5). An α CD composed of 6 glucose units will, therefore, have 18 sites for potential modification, a β CD will have 21, and a γ CD will have 24. Each site used for modification is known as a *degree of substitution*.

Figure 5. Hydroxyl modification sites on gamma cyclodextrin (circled on 1 glucose unit)



Hydroxyl group substitution by atoms or compounds on any, or each, of these carbon atoms creates a modified CD that exhibits altered characteristics from the original natural CD. Numerous atoms, ionic or anionic compounds, functional groups, or molecular structures may be added to these sites, creating a large number of possible modifications. Modifying the naturally occurring CDs allows improvement of aqueous solubility and/or improved binding to chosen molecules or drugs. Modification allows almost unlimited application to targeted molecular encapsulation.

Function

The inner cavity sizes of the α , β , and γ CDs are approximately 0.5, 0.6, and 0.8 nm, respectively. The size of the cavity dictates the size of the molecule that may be encapsulated. A larger cavity allows a larger molecule to be encapsulated; a smaller cavity limits the size of the molecule that can be encapsulated. Cavity size is the main determinant of CD encapsulation. Thus, a γ CD can encapsulate a larger molecule than can an α CD.

Close size approximation of the encapsulated molecule inside the cavity is an important factor in determining the strength of intermolecular attractions. If a molecule appropriately fits within the cavity, the binding that may occur will be determined by intermolecular thermodynamic interaction. These noncovalent thermodynamic attractions bind and hold the structures together. The glycosidic groups lining the cavity are the sites of lipophilic thermodynamic interactions with the encapsulated molecule. The structural

arrangement of the glucose units points the glycosidic linkages inward, whereas the hydroxyl groups of the second, third, and sixth carbons line the rim of the CD. Cyclodextrin encapsulation of other molecules may be a ratio of 1:1 or more.

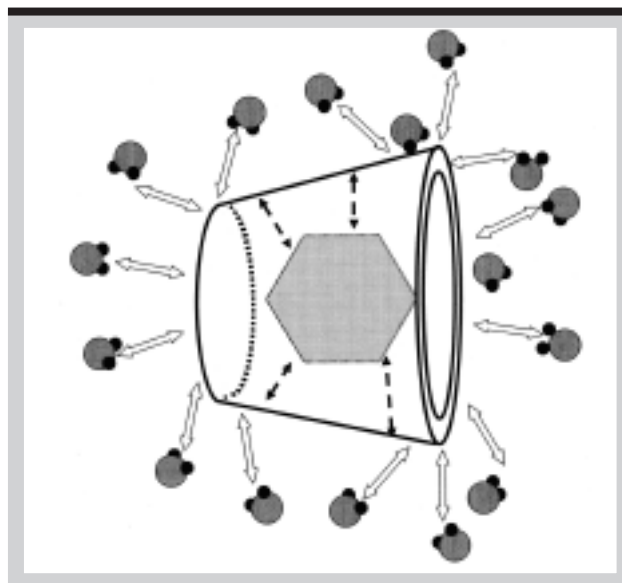
The CDs and CD inclusion complexes are water soluble. The exterior hydroxyl groups are hydrophilic and primarily responsible for CD water solubility. The negative charge of the hydroxyl groups interacts thermodynamically with the positive character of water molecules, thereby creating a very water-soluble compound (Figure 6). These intermolecular interactions that support aqueous dissolution are noncovalent, as are the interior glycosidic attractions. It is these characteristics of interior lipophilicity and exterior hydrophilicity that permit CDs to encapsulate lipid-soluble drugs, and, once encapsulated, they allow aqueous dilution. Once a molecule is encapsulated within a CD, the new structure is known as a *host-guest assembly* or an *inclusion complex*. Essentially, a new molecule is created from 2 previously separate molecules.

Inclusion complexes are often a 1:1 ratio, though more than 1 molecule may be encapsulated by a CD and more than 1 CD may bind to large molecules. Encapsulation of a drug will occur based on the CD's affinity for that drug and the concentration of the 2 that promote close association and contact time. Cyclodextrin-drug complexes are engaged in a dynamic process of binding, release, and rebinding, all within a timeframe of milliseconds. This dynamic process is expressed by the simplified formula:



The direction of this equation is dictated by the CD's affinity for the drug. A CD's ability to bind to a drug is measured by its dissociated (unbound) fractions. If a CD has a high affinity for a drug, it will have a low dissociated fraction. The CD-drug inclusion complex will be the majority form of the 3 fractions (CD, drug, CD-drug inclusion complex), and the direction of the preceding equation will be to the right. If the preceding equation's direction is to the left, the CD-drug inclusion complex is said to be *dissociated*, which reflects a low binding affinity. The degree of dissociation of an inclusion complex is expressed by its dissociation constant (K_d). The K_d formula is $[A][B]/[AB]$. The larger the K_d value, the larger the fractions of free drug and unbound CD, reflecting a low binding affinity. A low K_d reflects high binding affinity. Dissociation constants are measured in molar units. Most CD-drug inclusion complexes have moderate affinities that allow good CD-drug binding and aqueous dilution yet easily dissociate (unbind) on dilution in the bloodstream.⁶ Thus, the CD-encapsulated drug unbinds and is in free form to exert its action.

Figure 6. Cyclodextrin van der Waal interaction with water molecules promoting aqueous dissolution of encapsulated lipophilic molecule



Most CDs are considered excipients and do not exert pharmacologic properties. *Excipients* are compounds that are pharmacologically inert but are used to stabilize, solubilize, color, or in some way improve the formulation of an active compound. Enabling excipients are unique. They are inert compounds with specific beneficial properties that cannot be duplicated by other compounds.⁷ The natural CDs are excipients that may be modified to become enabling excipients. Modification may enhance a CD's application to a specific drug formulation that cannot be duplicated by another. Most CDs currently being studied to improve solubilization of hydrophobic drugs are enabling excipients. Modified CDs may be proprietary compounds, though the natural CDs are not patentable.

Clinical application

Anesthetic drug formulations using CDs have only recently been explored, and several modified CDs have shown promising study results (Table 2). Improved drug solubility, elimination of toxic diluents, enhanced pharmacokinetics and pharmacodynamics, and new drug actions all are current CD study goals. Specific agents that are being studied with CD encapsulation include propofol, etomidate, benzodiazepines, opioids, and local anesthetics. Some current studies are reviewed.

Etomidate has been successfully prepared in hydroxypropyl- β -CD and sulfobutyl ether- β -CD (SBE7- β -CD)-encapsulated aqueous forms with pharmacokinetics and pharmacodynamics similar to propylene glycol-containing formulations.^{8,9} Standard

Table 2. Modified cyclodextrins (CDs) of anesthesia-related study*

HP β CD	Hydroxypropyl- β -CD
SBE β CD	Sulfobutyl ether- β -CD
CTE γ CD	Carboxyl thioether- γ -CD

*HP indicates hydroxypropyl; SBE, sulfobutyl ether; and CTE, carboxyl thioether.

etomidate preparations contain propylene glycol concentrations as high as 35%. Propylene glycol has been found to be irritating to vessels and thrombus forming.⁹ A formulation of etomidate without toxic solvents would lessen the sequelae associated with propylene glycol. Toxic solubilizing agents and preservatives are poorly tolerated by the nasal route. Cyclodextrins have been found to be well tolerated nasally and have enhanced the absorption of drugs.^{10,11}

A nasally delivered SBE7- β -CD-encapsulated midazolam with efficacy similar to that of intravenous midazolam has been formulated by Loftenson et al.¹² Though the serum midazolam levels achieved were slightly slower and lower after nasal delivery compared with intravenously delivered midazolam, the efficacy and ease of delivery suggest this formulation may have application in children and patients lacking intravenous access.¹³

Early studies are underway using hydroxypropyl- β -CD-opioid complexes for intrathecal and epidural delivery. Increased effect and duration were found with the hydroxypropyl- β -CD-opioid complexes of sufentanil, lofentanil, alfentanil, and morphine when delivered intrathecally.¹⁴ It was suggested that the CD acted as a slow-release reservoir, thereby preventing the opioid from reaching the systemic circulation. If these results are found to be consistent, safer intrathecal opioid delivery with less respiratory depression may be enabled. This slow-release mechanism has only been suggested by the research and is refuted by others. It has been believed that drugs are "rapidly and quantitatively" released from their CD complexes once given parenterally.⁶ Conclusive evidence of controlled release of CD encapsulated drugs has yet to be compiled. Studies have also investigated epidurally delivered CD-opioid complexes compared with uncomplexed opioids. No difference in diffusion through the spinal meninges was found, which advances the conclusion of immediate CD-opioid unbinding.¹⁵ These studies of intrathecal and epidural delivery of CD-opioid complexes draw contradictory conclusions and will likely prompt further studies.

Local anesthetics have been complexed with natural and modified CDs.¹⁶⁻¹⁹ Studies using hydroxypropyl- β -

CDs have identified a reservoir effect similar to that seen with intrathecal CD-opioid complexes. Modified β CDs particularly have been the focus for increasing the safety and efficacy of local anesthetics. Cyclodextrin encapsulation has been shown to slow the release of the local anesthetic into the systemic circulation.¹⁷ This slowed absorption rate is expected to decrease the potential side effects of local anesthetics and increase their effectiveness by holding the drug at the site of action. Several studies have concluded this increased efficacy and safety.^{16,19} Ongoing studies may improve delivery of topically, subcutaneously, intrathecally, and epidurally delivered local anesthetics.

A CD-encapsulated propofol is another desirable application of improved solubilization that is currently under study. Studies are using modified CDs as enabling excipients to promote aqueous dissolution of propofol.²⁰⁻²² The goals of a CD-encapsulated propofol are to eliminate the bacterial-supportive lipid diluent, irritation on injection, and the potential allergens, sodium metabisulfite preservative and egg products. Improvement of propofol formulations using an SBE7- β -CD have been promising. Early successes with this SBE7- β -CD marketed as the proprietary CD Captisol (CyDex, Inc, Lenexa, Kansas) has successfully solubilized propofol and achieved favorable pharmacokinetics and pharmacodynamics. Egan et al²⁰ anesthetized 32 pigs with 500 to 750 μ g/kg per minute of SBE7- β -CD-encapsulated propofol or standard lipid emulsion propofol (Diprivan, AstraZeneca, Wilmington, Delaware). The bispectral index, heart rate, mean arterial pressure, and cardiac output were measured for data analysis using several pharmacokinetic and pharmacodynamic models. No significant differences were found between the SBE7- β -CD-encapsulated propofol and the standard lipid propofol group. The authors concluded that further study is warranted and comparative evaluation of hemodynamic effects is prudent.

The SBE7- β -CD-propofol formulation has exhibited antimicrobial activity that sets it apart from lipid propofol formulations.²³ This SBE7- β -CD is a β CD modified with an average of 7 degrees of substitution, randomly attached at the 2, 3, and 6 positions of the glucoses. All substitutions are with sulfobutyl ether functional groups (CH₂)₄SO₃Na (Figure 7). Its affinity for propofol ($K_d = 3,800-4,800 M^{-1}$) is such that it encapsulates well, promoting aqueous solubility, yet releases the drug easily on in vivo delivery²⁴ (G. Mosher, email communication, October 4, 2006) (Figure 8). The CyDex website states that the product has been licensed in the United States and that licensing is available in Europe. Continued study may soon offer this water-based alternative to lipid-based propofol as a marketed product in the United States.

Figure 7. Simulated molecular structure of sulfobutyl ether- β -cyclodextrin (Captisol, CyDex, Inc, Lenexa, Kansas) showing 7 degrees of modification

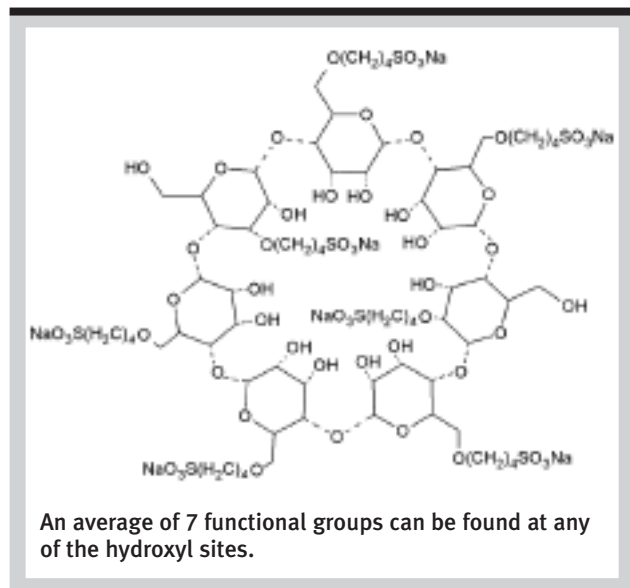
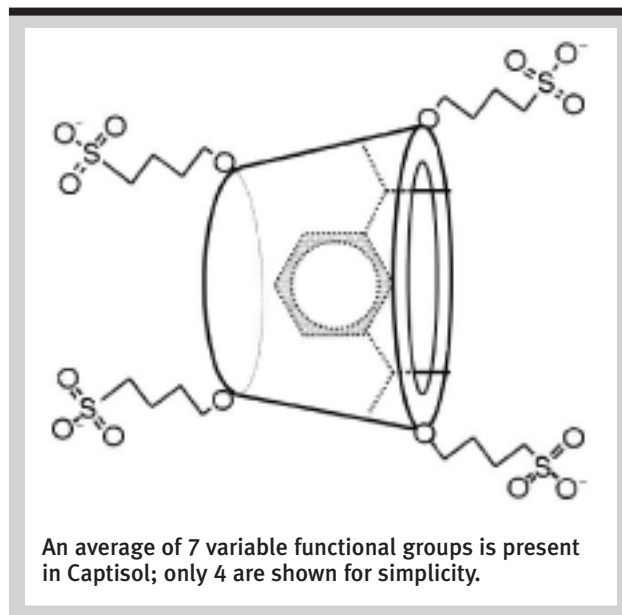


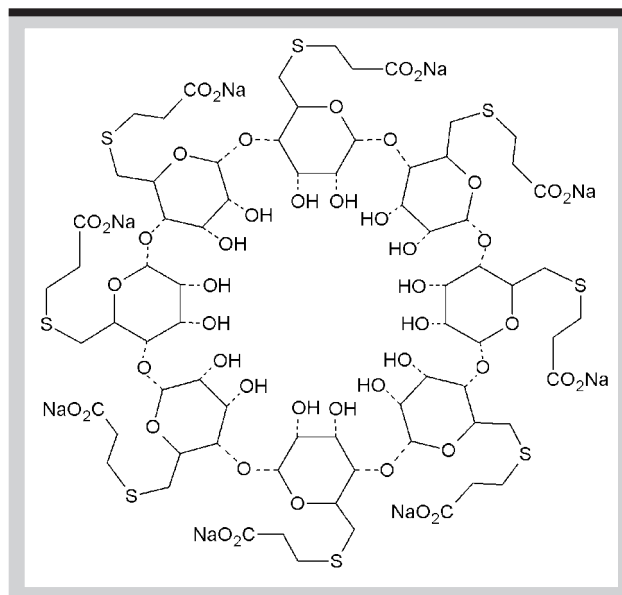
Figure 8. Simulated representation of Captisol (CyDex, Inc., Lenexa, Kansas) encapsulating a propofol molecule



The hydroxypropyl- and sulfobutyl ether-modified β CDs offer good solubilization of lipophilic drugs and are amassing significant safety and efficacy profiles. Their drug affinities have shown excellent balance between in vitro encapsulation and in vivo drug release. These specific modified CDs and others are leading the introduction of CDs into anesthesia practice.

A unique application of another modified CD focuses on encapsulation in vivo for drug effect termination rather than in vitro for drug solubilization. Sugammadex (Org 25969) is a γ CD that has been modified at the sixth carbon position to increase its affinity for aminosteroid nondepolarizing muscle relaxants (Figure 9). Eight carboxyl thioether extensions placed at each sixth carbon atom position elongate the cavity, allowing this CD to fully encapsulate an aminosteroid muscle relaxant molecule. The negatively charged extensions electrostatically bind to the rocuronium molecule, increasing the overall binding affinity (Figure 10). In addition, the negatively charged extensions contribute to the aqueous solubility imparted by the second and third hydroxyls. This modification to the base γ CD has created a host molecule that has the highest affinity for a guest molecule ever recorded ($K_d = 1.8 \times 10^7 \text{ M}^{-1}$).²⁵ Animal and clinical studies have shown fast, effective, and safe reversal of rocuronium- and vecuronium-induced neuromuscular blockade, including profound paralysis.²⁶ The in vivo encapsulation of rocuronium and vecuronium by this CD has consistently occurred in less than 3 minutes without re paralysis.²⁶⁻²⁸ The inclusion complex formed by this CD is stable, excreted intact

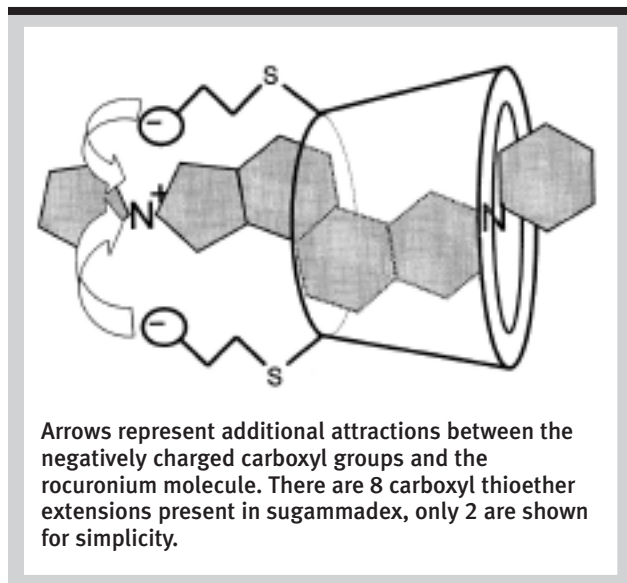
Figure 9. Modified γ cyclodextrin sugammadex showing carboxylthioether extensions at the sixth carbon positions



by the kidneys, and removable by dialysis.²⁹ The World Health Organization and the United States Adoptive Names Council have adopted the generic name sugammadex for this modified γ CD.

As shown in the preceding CD figures, modifying the natural CDs with differing functional groups promotes specific drug encapsulation. The encapsulation affinities of CDs may be modified for efficient drug binding with ease of in vivo release or increased dra-

Figure 10. Simulated representation of sugammadex encapsulating a rocuronium molecule



matically for very strong binding. The inherent properties of CDs, which include interior lipophilic attraction and exterior aqueous solubility, may be altered by modification to promote targeted drug binding and desired strength of encapsulation. As with all pharmaceutical agents, known and potential clinical interactions need to be addressed.

Clinical considerations

The CDs are considered safe drug excipients and pharmacologic agents. Current US drug formulations that use CDs include ziprasidone mesylate (Geodon, Pfizer, Inc, New York, New York), itraconazole (Sporanox, Janssen Pharmaceutica, Titusville, New Jersey), voriconazole (VFend, Pfizer, Inc), and prostaglandin E₁ (Caverject, Pfizer, Inc). Many other CD drug formulations are available throughout the world and are providing safe and effective drug delivery.

Though essentially inert, CDs may bind to endogenous lipophilic molecules, including endogenous steroids, but modification lessens this affinity while increasing the binding of the chosen molecule. Glycosidic linkages of CDs are not metabolically broken by the body, and, therefore, free glucose is not released. Parenteral CD use in healthy people or people with diabetes will not alter blood glucose levels.

The CDs are renally excreted, with the clearance mirroring the glomerular filtration rate. The CDs may also increase the excretion of water-insoluble drugs by promoting the renal clearance of the encapsulated drug. This CD-mediated increased excretion of water-insoluble drugs is illustrated well by the selective relaxant binding agent sugammadex.³⁰ Despite modifications that enhance renal clearance of CDs, β CDs

remain a concern in renally compromised patients due to potential accumulation and nephrotoxic effects.³¹⁻³³

In excessively high doses, CDs have caused erythrocyte membrane disruption in the order of $\beta > \alpha > \gamma$. There is great hemolytic variability among the modified β CDs. The sulfobutyl ether 7- and sulfobutyl ether 4- modified β CDs show little ability to hemolyze blood, whereas the sulfobutyl ether 1- β -CD and hydroxypropyl 3- and hydroxypropyl 7- β -CDs exert significant ability.³⁴ Zannou et al³⁵ found that the osmolalities of sulfobutyl ether CDs and hydroxypropyl CDs account for their hemolytic behavior. No current drug formulations contain CD quantities near the high concentration of CDs needed to cause erythrocyte damage.³⁶ Modification of the natural CDs has provided excellent binding of drugs for improved solubilization, while low to moderate doses have maximized the safety and efficacy of these agents.

Conclusion

It is apparent from recent research that the unique characteristics of CDs lend them to anesthetic drug delivery and drug extraction. Though limited applications exist, it is likely that further studies will expand the benefit derived from existing anesthetic formularies. Drug formulation using CDs to increase drug solubilization is likely to be increasingly embraced as additional safety and efficacy data are compiled. Cyclodextrin applications may also continue to expand beyond their roles as excipients and offer completely new pharmaceutical drugs. The CDs, by their unique form and function, hold great promise as safe, efficacious drug excipients and pharmacologic agents. Knowledge of this new group of molecules will become paramount as more applications become available.

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AUTHOR

Mark Welliver, CRNA, MS, ARNP, is a nurse anesthetist and clinical coordinator at University of Florida & Shands Health Science Center Jacksonville, Jacksonville, Fla, and an assistant professor in the Nurse Anesthetist Program, University of North Florida, Jacksonville, Fla.