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Review

Self-Assembly of Cyclodextrins and Their Complexes in Aqueous Solutions

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ABSTRACT

Cyclodextrins (CDs) are enabling pharmaceutical excipients that can be found in numerous pharmaceutical products worldwide. Because of their favorable toxicologic profiles, CDs are often used in toxicologic and phase I assessments of new drug candidates. However, at relatively high concentrations, CDs can spontaneously self-assemble to form visible microparticles in aqueous mediums and formation of such visible particles may cause product rejections. Formation of subvisible CD aggregates are also known to affect analytical results during product development. How and why these CD aggregates form is largely unknown, and factors contributing to their formation are still not elucidated. The physiochemical properties of CDs are very different from simple amphiphiles and lipophilic molecules that are known to self-assemble and form aggregates in aqueous solutions but very similar to those of linear oligosaccharides. In general, negligible amounts of aggregates are formed in pure CD solutions, but the aggregate formation is greatly enhanced on inclusion complex formation, and the extent of aggregation increases with increasing CD concentration. The diameter of the aggregates formed is frequently less than about 300 nm, but visible aggregates can also be formed under certain conditions.

With this review paper, we would like to honor our esteemed and deeply respected colleague Dr. Marcus Brewster. He was the Vice President and Scientific Fellow of the Pharmaceutical Development and Manufacturing Sciences group at Janssen Pharmaceutica R&D.

Dr. Marcus Brewster contributed to the development of several important medicines that are benefiting patients today. He was a major advocate for the use of cyclodextrins (CDs) in drug formulations, and his contributions created the foundation for the regulatory approval and marketing of 2-hydroxypropyl-β-cyclodextrin (HPβCD)–based formulations worldwide including both oral and intravenous-based dosage forms of itraconazole (Sporanox®). Thanks to his work, CDs are now routinely used in toxicologic and phase I assessments of new drug candidates.

The discovery of the self-association behavior of both CDs and certain drug–CD complexes sparked the interest of Dr. Marcus Brewster, and it quickly became one of his favorite research topics. For a number of years, we enjoyed collaborating with him on this subject. We had submitted a grant application to study self-assemble of CDs and CD complexes and its impact on CD research and applications. It took couple of years, but a few months before his death, we received a very generous grant to study “drug-CD aggregates in formulation assessment and drug delivery.” The subject of the grant originated from an observation of visible microparticles in parenteral solutions containing relative high CD concentrations. The formation of such visible and subvisible CD aggregates may cause rejections and even product withdrawal. On the other hand, these interesting constructs can also be looked at as a starting point for a new breed of drug delivery vectors. These

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structures seem to form under certain conditions but are less common in other environments.

Drug–CD constructs hold the promise of formulating difficult-to-formulate drugs as well as specifically targeting their delivery topically, orally, and parenterally. Initial studies have demonstrated that topical assessment of these systems to the skin resulted in targeted drug delivery to the hair follicles and sweat glands. In addition, work in modified $Caco_2$ cell cultures (e.g., mucus-producing systems) and other models have suggested that CD aggregates may act as mucus-penetrating delivery vectors that can rapidly translocate drugs from the intestinal lumen to the absorptive epithelium. This effect has been reported to be enhanced by nanoparticles with hydrophilic coronas that minimize protein interaction.

How and why these aggregate systems form is largely unknown, and factors contributing to their robustness are still not elucidated. The aggregation phenomena in CD solutions have been ignored for a long time by academic and industrial scientists. Only during the last decade, several research groups in the world started to focus on this problem. This article describes in more detail the observations that lead to this grant application.

Introduction

Some water-soluble solute molecules spontaneously self-assemble in aqueous solutions to form aggregates.[1] Depending on the molecular structure and solvent properties, the aggregates may take a shape of rods, discs, prolate spheroids, spheres, bilayers, vesicles, or reversible micelles.[2,3] At concentrations exceeding the critical aggregation concentration (CAC), a high degree of association may even lead to the formation of lyotropic mesomorphs, e.g., lamellar, hexagonal, cubic, and ribbon phases.[4–6] The self-assembly properties of substances can be used to develop novel pharmaceutical formulations. Different types of aggregates may be developed into drug delivery systems like micelles, nanoparticles, microspheres, liposomes, and hydrogels to overcome formulation challenges, such as poor aqueous drug solubility, drug permeation through mucus and membrane barriers, and inadequate drug stability, as well as to enhance biological properties of drugs such as to reduce or prevent their side effects.[7–10] Application of molecular self-assemble in pharmaceutical technology and other sciences will, however, require thorough understanding of the thermodynamics and kinetics involved.

Surfactants and other amphiphiles that have both hydrophilic and hydrophobic sections in their structure are known to self-assemble in aqueous solutions to form micelles with a hydrophobic core and hydrophilic outer shell. Full understanding of the micelle formation and the forces involved (e.g., van der Waals, electrostatic, and hydrophobic interactions and hydrogen and coordination bonds) is, however, still lacking.[1] Micelle formation is a thermodynamically favored process. The attraction of hydrophobic species, resulting from their avoidance of water molecules in aqueous solutions, represents the hydrophobic interaction (i.e., formation of hydrophobic bonds). This interaction is favored thermodynamically because it minimizes the contact surface between water molecules and the nonpolar group of an amphiphile with a consequent entropy increase (Fig. 1). The entropy increase (ΔS) on micellization is partly due to increased flexibility of the hydrocarbon chains (on their transfer from an aqueous environment to the hydrophobic micellar core) and partly due to release of water molecules during neutralization of the ionic charge by the counterions (in case of ionic and zwitterionic surfactants).[12] Furthermore, there is an additional enthalpic contribution (ΔH) associated with the van der Waals interactions between hydrocarbon chains and between the hydrophilic head groups and the surrounding water molecules.

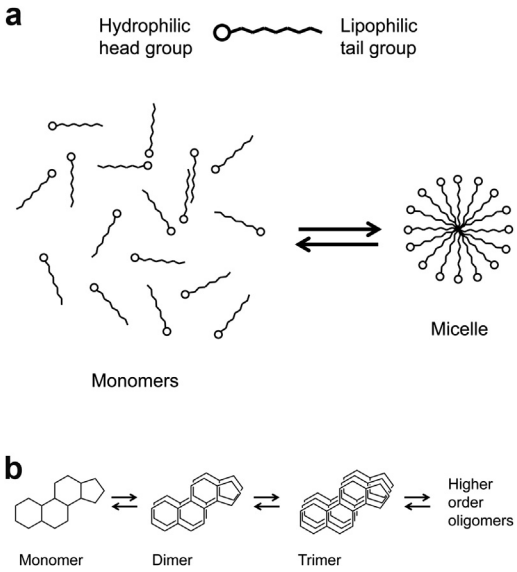

Figure 1. (a) Simple amphiphiles such as fatty acids and alcohols form micelles in aqueous solutions. The micelles have a lipophilic core and a hydrophilic surface. Formation of micelles minimizes the contact surface between water molecules and the nonpolar group of an amphiphile with a consequent decrease in free energy. (b) Hydrophobic drugs such as steroids do also self-assemble in aqueous solutions to form dimers, trimers, and higher order oligomers to reduce their contact surface with water.[11]

For many nonionic micelles, the numerical values of the enthalpic contribution to the Gibbs energy of micelle formation ($\Delta G = \Delta H - T\Delta S$) is of the order of 10 kJ per mole, whereas the entropic term ($T\Delta S$) can have a value of about 40 kJ per mole.[13] Consequently, some researchers have emphasized the significance of the entropic effect and hydrophobic interactions in the process of micelle formation.[14] Significance of the entropic components has been traced in atomistic simulations studies of the self-assemble of nonionic chromonic molecules.[15] The calculations have showed that the numerical value of the entropic term is 1.5 times higher than that of the enthalpic one. Other researchers have studied the thermodynamic properties of micellization of zwitterionic surfactants through molecular dynamic simulations and found that the aggregation process is entropy-driven and enthalpy–entropy compensated with increasing contribution of the enthalpy-driven part.[16,17] Based on an isothermal titration calorimetry study of homologous series of sulfobetaines (a form of zwitterionic surfactants), it was shown that the thermodynamics of micellization is mainly entropically driven at low temperatures but by both enthalpy and entropy at elevated temperatures. Such exchanging in dominant terms (from entropic to enthalpic) has been explained as reduction of water cohesion (or hydration ability) at elevated temperatures accompanied by consequent reduction of the hydrophobic effect.[14,18] Indeed, the free energy of aggregation involves significant changes in repulsive and attractive contributions of the various interactions between hydrocarbon chains, head groups, and solvent molecules. These interactions are equilibrium processes that occur on a microsecond timescale.

Self-assemble of solute molecules in aqueous solutions is affected by both internal and external factors. Internal factors include only native properties of the self-associated molecules, whereas the external ones depend on environmental condition of the aqueous media such as temperature and ionic strength. Influence of the molecular structure and their physicochemical properties can easily be estimated from the numerous theoretical works. Some quantitative structure–activity relationship efforts