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Thermodynamics of aggregate formation between a non-ionic polymer and ionic surfactants: An isothermal titration calorimetric study

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ABSTRACT

This report examines the energetics of aggregate formation between hydroxypropyl methylcellulose (HPMC) and model ionic surfactants including sodium dodecyl sulfate (SDS) at pharmaceutically relevant concentrations using the isothermal titration calorimetry (ITC) technique and a novel treatment of calorimetric data that accounts for the various species formed. The influence of molecular weight of HPMC, temperature and ionic strength of solution on the aggregate formation process was explored. The interaction between SDS and HPMC was determined to be an endothermic process and initiated at a critical aggregation concentration (CAC). The SDS-HPMC interactions were observed to be cooperative in nature and dependent on temperature and ionic strength of the solution. Molecular weight of HPMC significantly shifted the interaction parameters between HPMC and SDS such that at the highest molecular weight (HPMC K–100 M; >240 kDa), although the general shape of the titration curve (enthalpogram) was observed to remain similar, the critical concentration parameters (CAC, polymer saturation concentration (C_{sat}) and critical micelle concentration (CMC)) were significantly altered and shifted to lower concentrations of SDS. Ionic strength was also observed to influence the critical concentration parameters for the SDS-HPMC aggregation and decreased to lower SDS concentrations with increasing ionic strength for both anionic and cationic surfactant-HPMC systems. From these data, other thermodynamic parameters of aggregation such as ΔH°_{agg}, ΔG°_{agg}, H°_{agg}, ΔS°_{agg}, and ΔC_p were calculated and utilized to postulate the hydrophobic nature of SDS-HPMC aggregate formation. The type of ionic surfactant head group (anionic vs. cationic i.e., dodecyltrimethylammonium bromide (DTAB)) was found to influence the strength of HPMC-surfactant interactions wherein a distinct CAC signifying the strength of HPMC-DTAB interactions was not observed. The interpretation of the microcalorimetric data at different temperatures and ionic strengths while varying properties of polymer and surfactant was a very effective tool in investigating the nature and energetics of HPMC and ionic surfactant interactions.

1. Introduction

Nanoparticle drug delivery systems (NDDS) are one of the several possible routes for bioavailability enhancement of poorly soluble drugs through enhanced dissolution rate, solubility, or both (Lipinski, 2000). However, NDDS often encounter varying degrees of thermodynamic instability leading to nanoparticle aggregation (Lipinski, 2000; Merisko-Liversidge and Liversidge, 2011). This instability is attributed to the extensive surface area that is generated by either of the two distinct approaches used to produce NDDS: (Lipinski, 2000) top down method where larger particles are broken down into nanoparticles through attrition, and (Merisko-Liversidge and Liversidge, 2011) bottoms up method where new nanosized particles are created. The higher surface area is accompanied by a large positive free energy and without any effort to dampen the surface energy, the system prefers to move to an equilibrium state of the lowest free energy via aggregation of the smaller particles into larger particles (Murdande et al., 2015; Elsayed et al., 2014; Van Eerdenbrugh et al., 2008).

Nanosized particles generated by these approaches are typically physically stabilized by steric or ionic surface modification (Van Eerdenbrugh et al., 2009). Some recent reports have investigated the role of surface modifiers for providing physical stability to nanoparticles of various sizes and shapes (Van Eerdenbrugh et al., 2008). It has been observed that certain excipients such as surfactants and polymers are effective (i.e.,

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steric or ionic surface modification) in producing physically stable NDDS by adsorption of free polymer, surfactant and polymer-surfactant aggregates on the surface of NDDS, potentially decreasing the surface energy of these particles (Merisko-Liversidge and Liversidge, 2011; Dizaj et al., 2015). Towards understanding the adsorption behavior of these polymer and surfactants, their concentration dependent interaction and speciation behavior needs to be explored. In general there are typically three critical concentration dependent behaviors reported for polymer-surfactant interactions (Goddard, 1986). The first critical concentration dependent behavior is when the surfactant concentration exceeds a critical concentration where the surfactant begins to interact with the polymer, which is defined as a critical aggregation concentration (CAC) (Goddard, 1986). The second is the polymer saturation concentration (C_{sat}) when the surfactant molecules completely saturate the polymer chains and additional binding of the surfactant molecules cannot occur. This binding however, was observed by Persson et al. (Persson et al., 1994) to depend on the concentration of the polymer being studied and may be altered as a result of properties of the polymer such as concentration, molecular weight and polymer structure. The third concentration behavior is known as the critical micelle concentration (CMC) that results in the formation of surfactant micelles either after the saturation of the polymer in polymer-surfactant mixtures or pure surfactant micelles in the absence of a polymer (Evertsson and Nilsson, 1997). Goddard et. al. (Goddard, 1986) has provided a good review of these critical concentration parameters along with a surface tension/concentration plot of SDS in the presence of polyvinylpyrrolidone (PVP) at various concentrations; the various breakpoints (CAC, C_{sat} and CMC) are shown with schematic assignments to direct the eye.

Although there has been a good effort in the literature on understanding the interaction behavior of polymers and surfactant however, there is still a need to understand what parameters govern the energetics of the aggregation process of pharmaceutically relevant polymers such as PVP, HPMC and PEG as well as surfactants such as SDS and polysorbates at the concentrations typically used in formulation development. Moreover, some of the significant gaps identified from the review of these studies are: (Lipinski, 2000) the higher concentrations of HPMC typically utilized (Murdande et al., 2015; Van Eerdenbrugh et al., 2009; Lestari et al., 2015) in formulation of NDDS (0.25-1%w/w) have not been evaluated, (Merisko-Liversidge and Liversidge, 2011) the influence of molecular weight of polymer (HPMC) that could help provide insight into the number of binding site constraints for HPMC, (Murdande et al., 2015) the effect of ionic strengths of solution and surfactant properties (i.e., head group, chain length) on the interaction between surfactants with HPMC has also not been investigated to the best of our knowledge, and (Elsayed et al., 2014) finally in our opinion the treatment of calorimetric data conducted while studying such polymer/surfactant systems (Singh and Nilsson, 1999) do not properly account for the enthalpies of dilution associated with the formation of various species (i.e., surfactant monomers, HPMC-surfactant aggregates, micelles) during the course of the titration experiment and needs to be treated more critically in order to allow for more accurate interpretation. This critical treatment of data will be discussed in detail in the methods section of this chapter. As discussed earlier since the effect of molecular weight, surfactant properties and ionic strength on the nature and strength of the HPMC-surfactant interactions remain unanswered, there is an additional need to understand which of these parameters govern the energetics of the aggregation process of pharmaceutically relevant polymers at the concentrations typically used in drug product development and will be explored systematically in this work. Furthermore, at present there is very little molecular-level understanding that relates the interactions of surfactant and polymer in the bulk state to the adsorption of these excipients on solid surface that may ultimately lead to the final stability of NDDS. A lack of this mechanistic understanding and its relationship to the drug-excipient interactions in the bulk and the surface is a significant gap. This gap in the mechanistic understanding contributes to a complete lack in manipulation and control strategy for optimizing these excipients to maximize stability of NDDS. The development of this understanding can help in an a priori selection of type and level of pharmaceutical excipients to maximize the long term stability of NDDS with minimal experimentation. In order to develop this understanding, it would be critical to first develop an in-depth understanding of the concentration dependent speciation and energetics of the interactions between pharmaceutically relevant polymers and surfactants as well as how the excipient and solution properties influence the polymer-surfactant aggregate formation. The goal of this study was to determine the energetics of aggregate formation between a model non-ionic polymer, hydroxypropyl methylcellulose (HPMC), and model ionic surfactants, sodium dodecyl sulfate (SDS), hexadecyltrimethylammonium bromide (CTAB), and dodecyltrimethylammonium bromide DTAB. The influence of ionic strength, molecular weight of HPMC, and type of ionic surfactant head group on the aggregate formation process was explored using an isothermal titration calorimetry (ITC) method.

ITC technique has gained momentum over the last couple of decades to investigate the thermodynamics of micellization where researchers have determined critical micelle concentration (CMC) parameters, enthalpy, Gibbs free energy and entropy of micelle formation. In recent years, the use of ITC for understanding polymer-surfactant interactions has grown particularly due to the increased sensitivity of the technique which has been utilized to quantitatively study the aggregation process between polymers and surfactants including polyethylene glycol (PEG)/SDS (Olofsson and Wang, 1994), ethyl hydroxyethyl cellulose (EHEC)/HPMC/SDS (Torn et al., 1999), polyethylene oxide (PEO)/SDS (Wang et al., 1998; Wang and Olofsson, 1998; Dai and Tam, 2001; da Silva et al., 2004; Dai and Tam, 2006), and polyvinylpyrrolidone (PVP)/sodium dodecylbenzenesulphonate (SDBS) (Singh and Nilsson, 1999; Olofsson and Wang, 1994; Dai and Tam, 2001; da Silva et al., 2004; Torn et al., 1999; Torn et al., 2003) systems. A number of good reviews are available for more detailed description and application of ITC (Olofsson and Wang, 1994; Blandamer et al., 2003; Blandamer et al., 1998a). The ITC method was utilized to conduct a full thermodynamic characterization of the aggregation parameters between HPMC and the model ionic surfactants since it provides quantitative information on the critical concentration parameters (i.e., CAC, C_{sat} and CMC) and energetics of the aggregation process (Dai and Tam, 2001). The critical thermodynamic parameters derived from ITC enthalpograms are known to contain information about rearrangement of polymers, micelle/aggregate formation and their disassociation, however, the interpretation of enthalpograms is still not very well developed area and hence there is significant scope for further understanding (Wang and Olofsson, 1998). The fundamental information can be obtained on how molecular properties of HPMC and ionic surfactants influence these parameters that may provide further insights into the molecular interactions driving the process. The learning from this study would be applied to future studies in characterizing the nature of HPMC-ionic surfactant aggregates and their adsorption onto the surface of nanoparticles.

2. Materials and methods

2.1. Materials

Sodium dodecyl sulfate (>98%) was obtained from Sigma-Aldrich (St. Louis, MO). The SDS thus obtained was further purified