HPMC CLOUD POINT: EXPLORING HYDROXYPROPYLMETHYL CELLULOSE BEHAVIOR IN PHARMACEUTICAL FORMULATIONS

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INTRODUCTION

Hydroxypropylmethyl cellulose (HPMC) is widely used in pharmaceutical applications as a sustained release agent (Viriden, Wittgren et al. 2011), tablet coating, nanoparticulate stabilisers and nucleation inhibitor (Ghosh, Bose et al. 2011). In these applications its gelation behaviour is key to its performance and therefore needs to be understood within each system. Aqueous solutions of HPMC display two characteristic temperatures: a thermal gelation temperature (TGT) and a lower critical solution temperature (LCST). The gelation behaviour of HPMC is influenced by the HPMC degree of substitution, formulation additives (such as salts, surfactants, drug molecules) and temperature (Zhang, Wang et al. 2015).

HPMC begins to precipitate out of solution at the LCST due to the loss of water of hydration at increased temperatures (Viridén, Wittgren et al. 2011). This phase separation into a polymer rich and polymer depleted phase, caused by association of hydrophobic groups leading to aggregation, allows for the cloud point to be determined as the polymer rich phase is capable of scattering light. Though there seems to be no direct relationship between TGT and cloud point, it seems that both properties are affected by electrolytes in the same manner i.e. if an electrolyte increases the TGT, it will also increase the cloud point (Mitchell, Ford et al. 1990).

The objective of this paper is to demonstrate the ability of cloud point measurements to identify the impact of formulation additives on the behaviour of HPMC within formulations during dissolution. The additives investigated include; a surfactant, docusate sodium (DOSS) and a model drug carbamazepine. The goal of this work is to use cloud point measurements to understand formulation interactions with HPMC which will increase understanding of variability in formulation behaviour during dissolution.

MATERIALS AND METHODS

The HPMC grade investigated was HPMC substitution type 2910, label viscosity 3 cp. In comparison a 2nd HPMC derivative was also investigated, HPMCAS Grade AS-MG viscosity type 3 cp. HPMCAS is a cellulose polymer which does not exhibit a cloud point. The goal of the study was to investigate both polymers in aqueous systems with and without docusate sodium and carbamazepine to assess the additive effect on cloud point behaviour.

Aqueous polymeric solutions were prepared by adding HPMC to an aqueous solution of additive while stirring with a magnetic stirrer at 500 rpm. The solutions were made up to the required volume with ice cold deionised water and left mixing for 20 minutes. The solution was degassed by a sonicator for one hour and then moved to a refrigerator to hydrate overnight.

A Chirascan circular dichroism spectrometer performed cloud point assays. Percentage transmission was examined at 800nm over a range of 25 – 91 ˚C at a rate of 1.0˚C/min. Sample was present in a 0.5mm quartz cuvette. An air background calibration was carried out prior to testing each day.

RESULTS

To ensure the accuracy of the produced results a centre point (6% HPMC, 0.5% DOSS) was ran in triplicate over 3 separate days. The average CP was calculated to be 73.25 ± 0.725 ˚C. The low standard deviation indicates the Chirascan instrument is capable of generating reproducible CP measurements.

There is a clear trend evident that as the concentration of DOSS increases the the CP increases. This we attribute to the increased energy needed to overcome the solubilisation of the hydrophobic groups of the HPMC by the surfactant (Figure 1). When ionic surfactants and non-ionic polymers are mixed, two competing phenomena take place: 1) Self aggregation of surfactant molecules to form micelles or 2) interaction of individual surfactant molecules with monomer units of the polymer chain (Acevedo, Takhistov et al. 2014). The free surfactant molecules bind to the hydrophobic parts of the polymer through adsorption until a state of saturation is reached. The priority binding of the surfactant produces polar outshells, increasing the energy barrier for the crosslinking of the HPMC chains to occur, by hindering the free access to HPMC chains. The thermal energy requirements for dismantling this shell and for the aggregation of the polymer is determined by the chemical structure and electrostatic interaction between the surfactant and HPMC (Joshi 2011).

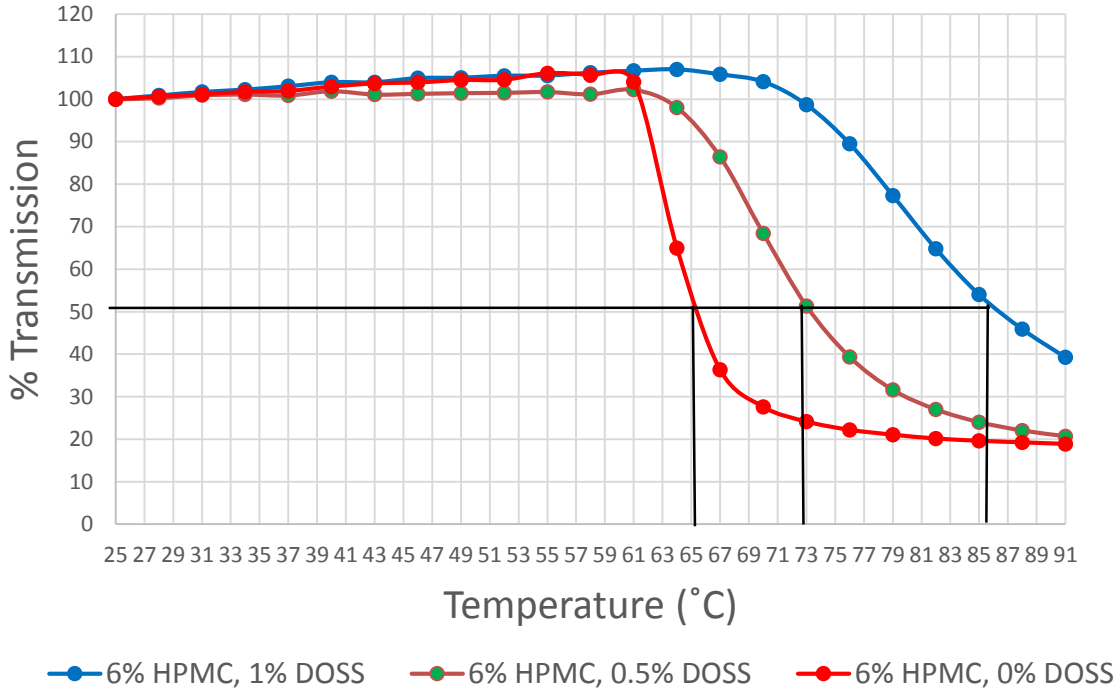

FIGURE 1: THE EFFECT OF VARYING CONCENTRATION OF DOSS ON HPMC CLOUD POINT (CLOUD POINT WAS REACHED WHEN HE OVERALL % TRANSMITTANCE OF LIGHT REACHES 50% OF THAT COMPARED TO THE SAME SAMPLE AT 25˚C (SILVA, PINTO ET AL. 2008).

Additional results will be presented looking at the effect of carbamazepine level on HPMC cloud point. Also the corresponding behaviour of HPMCAS polymer will be presented. Studies to date have not detected a cloud point for aqueous solutions of HPMCAS alone. To show the relevance of these cloud point studies, dissolution studies was be present from a range of these formulation compositions.

CONCLUSIONS

Formulation additives such as docusate sodium were shown to positively influence the cloud point of HPMC. Future work will explore how this alteration of the polymer self-assembly behaviour and cloud point can inform the HPMC-formulation behaviour during dissolution studies.

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