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Effect of amphiphilic drugs on the cloud point of hydroxypropylmethyl cellulose: Modulation with salt excipients

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ABSTRACT

In this paper we have reported the effect of two amphiphilic drugs, i.e., amitriptyline hydrochloride (AMT) and promethazine hydrochloride (PMT), on the cloud point (T_{CP}) of hydroxypropylmethyl cellulose (HPMC) in the absence and presence of electrolytes. T_{CP} of HPMC increased on increasing the [drug] and both drugs behaved almost in a same manner. In the presence of a small amount of NaCl (0.01 mol kg^{-1}) T_{CP} of the drug–polymer system showed a slight increase with a similar pattern as observed in its absence. The pattern of TCP change was different in the presence of high concentrations of NaCl (0.1 and 0.2 mol kg^{-1}) which displayed a minimum in [drug] vs. TCP plots while the steepness and appearance of minimum depend upon the electrolyte concentration. The effect of other monovalent salts (NaBr, KCl, KBr) was also seen and it was noted that bromide and sodium ions were found to be more effective as compared to chloride and potassium ions, respectively, for affecting the T_{CP} of HPMC. The energetics of the cloud point have been calculated and discussed.

1. Introduction

Derivatives of various biopolymers (cellulose, starch, etc.) play important roles in food, pharmaceutical and cosmetics industries where careful addition of these can be used to regulate the rheology of the system [1,2]. For illustration, owing to its prominent viscoelastic and structure-forming properties, the cellulose ether hydroxypropylmethyl cellulose (HPMC; Scheme 1) is employed as a flow developer, tablet binder, tablet disintegrant, wet granulation binder, and also as a suspending and thickening agent [3,4].

Aqueous solutions of some polymers, such as cellulose derivatives and poly ethylene glycols, have a tendency of reversible phase separation at higher temperatures which is termed as cloud point (T_{CP}) or lower critical solution temperature (LCST) [5–13]. The LCST implies that the effective solute–solute interactions have noteworthy temperature dependencies and alterations from repulsive to attractive interactions with increasing temperature. The T_{CP} phenomenon of cellulose ethers is believed to be due to the decrease in the dipolar character of the C – O bond as a result of either increase in temperature and/or making the solvating environment less polar [5–13].

Clouding of polymers is strongly dependent on the cosolutes. Electrolytes may either increase or decrease the cloud point (salting in or salting out, respectively) which generally depends on the Hofmeister series [11]. Surfactants play important roles in polymer chemistry due to their amphiphilic nature [14,15]. The hydrophobic interaction together with hydrophilic or polar interaction (electrostatic in the case of polymers and surfactants of opposite charges) imparts the polymer–surfactant complex somewhat new properties [14–16]. Many types of drugs such as tricyclic antidepressants, phenothiazines and non-steroidal anti-inflammatory drugs display an amphiphilic character and form micelles or micelle like aggregates above a critical concentration [17–22].

In recent years there is a huge development in the field of drug delivery which includes the targeted delivery, sustained release and stimuli responsive drug release formulations [23–25]. Sometimes, it is desired to target the therapeutic agents according to the physiological conditions of the particular organ. Since electrolytes have a tremendous role in the biological processes, we have designed our study which is based on the phase separation of the polymer affected by amphiphilic drugs in the presence of electrolytes (NaCl, NaBr, KCl, KBr) which are often used as excipients in various drug formulations [26–28]. The results may be helpful to modulate the delivery systems which contain the cellulose derivatives. The targeted as well as sustained release can be achieved by taking the desired amount of drug in combination with the appropriate quantity of the electrolyte.

In this study, the effect of two model amphiphilic drugs amitriptyline hydrochloride (AMT, 3-(10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene-5-ylidene)-*N*,*N*-dimethylpropan-1-amine hydrochloride) and promethazine hydrochloride (PMT, (*RS*)-*N*,*N*-dimethyl-1-(10H-phenothiazin-10-yl)propan-2-amine hydrochloride) on the phase separation of cellulose ether HPMC was seen in pure aqueous medium and in the presence of various salts.

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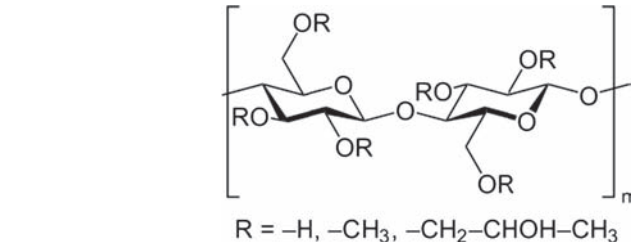
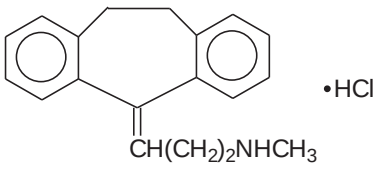
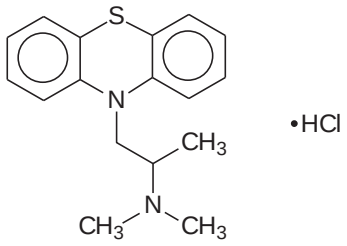


Hydroxypropylmethyl cellulose



Amitriptyline hydrochloride



Promethazine hydrochlorid

Scheme 1. Structures of HPMC, AMT and PMT.

2. Materials and methods

HPMC (hydroxypropoxyl content ~9%, molecular weight = 10,000, Sigma, USA), AMT (99.0%, Sigma, USA), and PMT (>99%, Sigma, USA) were used as received.

Freshly prepared stock solutions of the polymer were used to obtain samples for T_{CP} measurements (containing HPMC with or without drugs). The double-distilled water with the specific conductance of 1–2 μS was used throughout. Since we have studied the T_{CP} of HPMC, use of buffer solution was avoided due to the possible phase separation of amphiphilic drugs in the presence of buffer. T_{CP}s were obtained by placing Pyrex glass tubes (containing the sample solutions) into a temperature controlled bath, the temperature of which was ramped at the rate of 0.1 K/min near the T_{CP} and onset of clouding was noted by visual inspection. However, the temperature was oscillated slowly through the T_{CP} until reproducible (±0.1 K) [10,11].

3. Results and discussions

3.1. Effect of amphiphilic drugs on cloud point of HPMC

Both AMT and PMT are amphiphilic drugs, however, these are structurally slightly different (Scheme 1). When the solution of pure HPMC (1×10^{-3} mol kg^{-1}) is heated, phase separation occurs at about 333 K; which means that below this temperature HPMC molecules are surrounded by a network of water molecules and, at higher temperature, entropy destroys the network and phase separation occurs due to the weak van der Waals' attraction between the polymer chains [29].

Figs. 1 and 2 describe the effect of AMT and PMT on the cloud point of HPMC (1×10^{-3} mol kg^{-1}) in the presence and absence of various amounts of NaCl. In the absence of electrolyte, an increase in T_{CP} is observed as the concentration of drug increases. A change in the T_{CP} attributed to the mixed micelle formation between the amphiphilic drug and HPMC. Any change in T_{CP} of a polymer/water system on the addition of the additive such as surfactant or salt can be ascribed to the variation of the hydrophobic/hydrophilic balance in the system and, as a result, modification of the interaction [30,31]. The interaction of polymers with amphiphilic substances starts with the binding of surfactant and polymers and the resulting complex could be considered as a polyelectrolyte. As the concentration of drug increases a monotonic increase in T_{CP} indicates increased solubility of the polymer. This effect can be attributed to the binding of drug to the HPMC thereby imposing a repulsive interaction between different polymer chains [31–33]. When more amount of drug is added the increase in the effective charge density (due to the drug–polymer binding) may lead to an increase in the repulsive electrostatic forces. Amphiphiles play an important role in polymer chemistry due to their unique amphiphilic feature [14,15]. For example, the hydrophobic portion of amphiphile interacts with hydrophobic polymers or rather with hydrophobic groups of water soluble polymers and the formed complex has somewhat new properties due to the presence of the hydrophilic portion of amphiphile. The distinct increase of T_{CP} with higher concentration of amphiphile is a usual sign of a polymer's strong binding with amphiphile.

NaCl has an interesting effect on the T_{CP} of the drug–HPMC system (Figs. 1 and 2). In the presence of low amount of NaCl the T_{CP} increment follows the same pattern as compared to the one in which only drug was present, though, a slight increase in the value of T_{CP} was observed

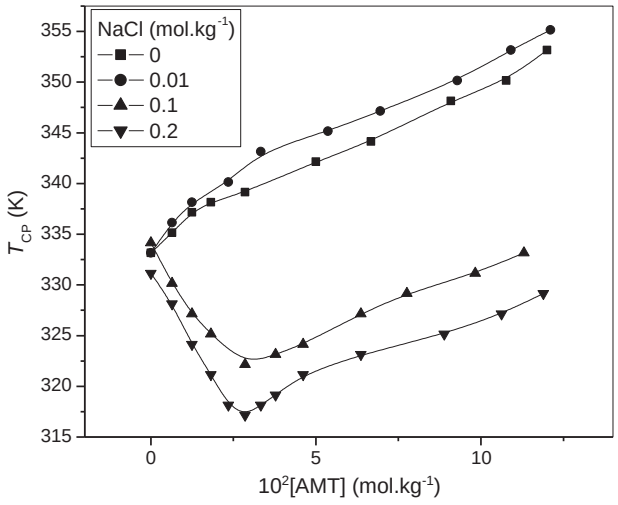


Fig. 1. Effect of various concentrations of NaCl on the T_{CP} of the AMT–HPMC system.