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The influence of substituted phenols on the sol:gel transition of hydroxypropyl methylcellulose (HPMC) aqueous solutions

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ABSTRACT

The influence of the physicochemical parameters of substituted aromatic molecules on the phase transition from sol to gel of hydroxypropyl methylcellulose (HPMC) has been investigated using a homologous series of substituted phenols. Using a turbimetric methodology, concentration dependent suppression of phase transition temperature of HPMC was observed for phenol and its derivatives, including methyl-, nitro- and chloro-substituted molecules. Although no strong direct relationship between single molecular physicochemical properties of the phenolic compounds (such as pK_a, Log P and other molecular descriptors) and Δ_{CPT} was found for the compounds tested, a successful prediction of behaviour could be obtained by using a combination of parameters. This suggested that the interaction mechanism between HPMC and the substituted aromatic moiety is a complex summation of the different molecular physicochemical properties. Identification of these potentially deleterious chemical moieties may be of value in a pharmaceutical context when considering preformulation of drug structures containing them. An incompatibility between drug and polymer may be indicative of deleterious effects resulting from formulation with hydrophilic matrix dosage forms containing cellulose ethers such as HPMC.

1. Introduction

One of the critical concerns of the pharmaceutical industry is the development of safe and effective delivery systems for drugs. One aspect of modern drug delivery is an increased interest in and application of controlled or extended-release technologies to improve patient compliance and therapeutic effectiveness of drug molecules (Ford, 1999; Li, Martini, Ford, & Roberts, 2005). A popular methodology for achieving extended release is the embedding of a pharmaceutical active in a matrix containing a hydrophilic polymer carrier material. This is generally a polysaccharide or synthetic polymer which swells in contact with aqueous fluids and prevents tablet disintegration by forming a 'gel-like' barrier to water ingress and drug release (Alderman, 1984; Ford, 1999; Melia, 1991). The cellulose ethers, including methylcellulose (MC) and hydroxypropyl methylcellulose (HPMC) are: (i) non-toxic in nature, (ii) easily compressed and (iii) capable of accommodating high levels of drug loading (Li et al., 2005). These, along with advantages such as a broad capacity to tailor desired drug-release profiles and the production of a matrix that is essentially pH-independent and compatible with conventional production techniques have resulted in cellulose ethers becoming one of the most exploited hydrophilic carrier materials in extended release technology (Alderman, 1984; Li et al., 2005; Melia, 1991).

However, the performance of HPMC as an extended release carrier material can be affected by incompatibilities with (i) drugs, (ii) electrolytes and (iii) other small molecules (e.g. Bajwa, Hoebler, Sammon, Timmins, & Melia, 2006; Khan, Anjum, Koya, & Kabir, 2013; Li et al., 2005; Liu, Joshi, Lam, & Tam, 2008; Mitchell et al., 1990; Pillay & Fassihi, 2001; Richardson et al., 2006). These disruptions to HPMC solubility and gelation characteristics can manifest as failure of pseudo gel layer formation and consequently immediate drug release. Although these potential disruptions may be significant in the formulation design for new chemical entities (NCE) or the re-formulation of pre-existing drugs for the purposes of patent extension, little work has been carried out to identify the key structural elements of the small molecules responsible for adverse interactions with HPMC and impact on the intended performance.

In the literature, there have been a small number of studies that have considered the drug molecule in its entirety and its

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propensity to modify cellulose ether solution properties. A study by Rajabi-Siahboomi, Davies, and Melia (1994) identified a reduction in cloud point temperature (CPT) and thermal gelation point (TGP) of Methocel E4M and K4M HPMC solutions containing diclofenac sodium. Hino and Ford (2001a) have studied binary mixtures of tablets containing nicotinamide and HPMC in solution and subsequently explored interactions between the two in solution (Hino & Ford, 2001b). They found that nicotinamide increased both the gelation temperature and cloud point of HPMC solutions although a precise mechanism of this "salting-in" phenomenon was not offered.

The process of polymer "salting out" describes how electrolytes and other solubles (including drugs) compete with the polymer for water of hydration, the efficiency of which can vary between electrolytes, affected by type, valency and charge (Marcus, 2009; Zhang & Cremer, 2006). This can influence diverse polymer properties including solution viscosity, dispersability and drug release (Alderman, 1984; Mitchell et al., 1990; Pygall, Kujawinski, Timmins, & Melia, 2009; Touitou & Donbrow, 1982; Williams, Ward, Hardy, & Melia, 2009). There have been a number of studies that have investigated the interaction of inorganic salts with HPMC (Joshi, 2011; Liu, Joshi, & Lam, 2008) Incompatibilities have been reported between other cellulose ethers and small aromatic molecules. The British Pharmacopoeia monograph for methylcellulose lists incompatibilities with chlorocresol, hydroxybenzoates and phenol (BP, 2009). Touitou and Donbrow (1982) found that salicylic and *p*-hydroxybenzoic acid reduce the gelation temperature of methylcellulose solutions. Critically in the context of this study, Ford (1999) has stated that a molecule's ability to reduce the CPT of HPMC aqueous solution may be predictive of its ability to form a functional gel layer.

The aim of this study was to assess the effect of various substitutions of the phenol molecule on the interaction with HPMC in aqueous solution. The critical study rationale was that these small aromatic molecular species are present in many drug molecular structures as key active moieties (e.g. non-steroidal anti-inflammatory drugs, bronchodilators, anti-Parkinsonian drugs). By assessing their influence on a critical HPMC solution property, it is anticipated that some insight into the molecular structures responsible for interactions between drugs and HPMC will be elucidated and a possible molecular mechanism for predicting incompatibility will be achieved. Highlighting and understanding the molecular structures responsible for cellulose ether incompatibilities would be of significant value for solid dosage form formulation scientists working in both academia and industry.

2. Materials and methods

2.1. Materials

Hydroxypropyl methylcellulose (HPMC) (Methocel USP 2910 grade CR Premium, batch number OD1601232, 9.3% hydroxypropyl and 29.5% methoxy substituted) was a gift from Colorcon Ltd. (Orpington, Kent, UK). Water was Maxima HPLC grade (USF Elga, Buckinghamshire, UK) with a minimum conductance of 18 MΩ cm. The substituted phenolic compounds used in this study were all obtained from Lancaster Chemical Co., UK and used as received.

3. Experimental

3.1. Preparation of solutions for turbidimetry

HPMC solutions were manufactured using an adaptation of the hot dispersion method described by the Dow Chemical Company (Dow Company Literature). One-third of the required volume of water was heated to 80–90 °C and placed in a beaker. The HPMC powder was added, with the solution mixed for 10 min on maximum speed using a high velocity laboratory emulsifier (Silverson Machines Ltd., Watersham, Chesham, Buckinghamshire, UK). The remainder of the water was added at room temperature, and mixing continued for a further 5 min or until a good dispersion was obtained. The solution, once cooled, was held between 2 and 8 °C for 24 h prior to use, to allow complete hydration of the polymer and dissipation of air bubbles.

3.2. Turbidimetric determination of phase transition temperature

The cloud point temperature (CPT) of the HPMC solutions was determined in triplicate using a temperature-ramped (1 °C/min), white light turbidimeter (C. Washington, Nottingham, UK) and 10 mm path-length cells. Cloud point temperature was defined as the temperature at which light transmission was reduced by 50% (Sarkar, 1979). The gradient of the fitted linear regression line (Δ_{CPT}) of cloud point temperature against the drug concentration was used to compare the relative influence of each aromatic molecule on the CPT.

The linear relationship applied followed the empirical equation:

$$CPT_M = \Delta_{CPT} M + CPT_o \quad (1\text{-}1)$$

where CPT_M is the cloud point temperature at concentration M, Δ_{CPT} is the gradient, M is the concentration of additive (mM) and CPT_o is the CPT in the absence of additive.

The temperature at which HPMC aqueous solutions become turbid is associated with the thermo-reversible sol:gel phase transition. This can be a sensitive indicator of the molecular hydration of the HPMC molecule and its propensity to be 'salted out'. Reversibility was confirmed by heating and cooling the solutions of interest prior to experimentation. It has been established that cloud point values do not coincide exactly with the sol–gel transition temperature determined rheologically (Ford, 1999) but are a useful surrogate measure. Touitou and Donbrow (1982) applied a similar equation when investigating the effect of additives on gelation of MC solutions using a cloud point methodology.

3.3. Molecular modelling

Molecular modelling was performed for un-ionised phenolic molecules using the Spartan PCPro modelling programme (Wavefunction Inc.). The geometry of the molecules was determined in vacuo, using quantum mechanics, the lowest energy geometries being determined using *ab-initio* Hartree Fock 6-31G* level calculations and partial atomic charges fitted to the atoms from calculations of the electrostatic potential surface (EPS). Bond lengths, total molecular energy and dipole moment were determined for each molecule. In addition, standard Hansch-type descriptors (σ_{para} and π) were also obtained for each of the molecules (Hansch & Leo, 1979). For each molecule, σ_{para} values were assigned in relation to para substituents, whereas π parameters were summed for all substituents within the phenol molecule.

The potential correlation of Δ_{CPT} values obtained from turbidity studies was tested against these molecular parameters individually, and with combinations of the parameters to identify possible relationships, using ordinary least squares (OLS) methods.

4. Results and discussion

4.1. Effect of phenols on cloud point temperature

Phenol was selected as the basic chemical moiety for this study as it is a soluble, aromatic compound and it has a recorded

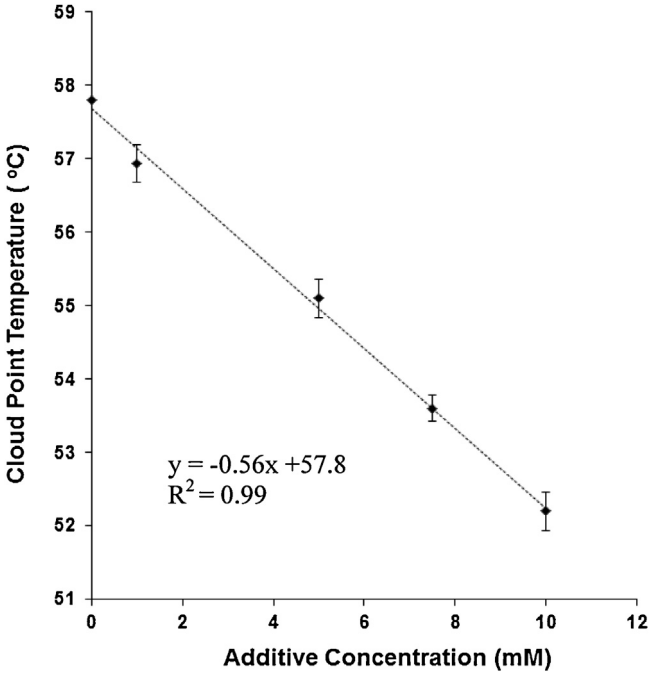
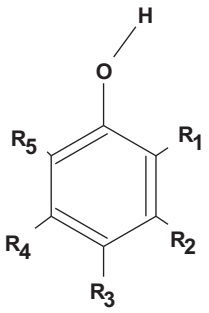


Fig. 1. The influence of phenol concentration on the cloud point temperature of 1% HPMC aqueous solutions. Cloud point temperature measured by turbidity. Mean ($n = 3$) ± SD. The gradient of the line was taken as the Δ_{CPT}.



Name	R_1	R_2	R_3	R_4	R_5	Dipole moment	π	σ_{para}
Phenol	H	H	H	H	H	1.45	0	0
2- chlorophenol	Cl	H	H	H	H	1.27	0.71	0
4- chlorophenol	H	H	Cl	H	H	2.46	0.71	0.23
2,4-dichlorophenol	Cl	H	Cl	H	H	0.99	1.42	0.23
2,6-dichlorophenol	Cl	H	H	H	Cl	2.43	1.42	0
2-nitrophenol	NO_2	H	H	H	H	3.98	-0.28	0
3-nitrophenol	H	NO_2	H	H	H	3.74	-0.28	0
4-nitrophenol	H	H	NO_2	H	H	1.71	0.56	0
2-cresol	CH_3	H	H	H	H	1.46	0.56	-0.17
3-cresol	H	CH_3	H	H	H	5.43	-0.28	0.78
4-cresol	H	H	CH_3	H	H	1.74	0.56	0

Fig. 2. The structures and properties of the various phenolic compounds considered in this investigation.

incompatibility with the cellulose ether, methylcellulose (Martindale, 2002). In addition and more critically, it is the common basic chemical moiety found in a large number of diverse drug structures including: (i) the bronchodilators (e.g. salbutamol, terbutaline, and ephedrine), (ii) anti-Parkinson drugs (e.g. carbidopa, levodopa and dopamine) and (iii) opioid analgesics (e.g. morphine). Thus its influence on HPMC sol:gel transition temperature may provide an indication of a potential interaction between these more complex chemical drug structures and HPMC in aqueous solutions.

Fig. 1 shows the effect of phenol concentration on the HPMC aqueous solution CPT. As with previous research from the group (Richardson et al., 2006), an attempt to quantify the influence of phenol on HPMC solution cloud point temperature has been made through a determination of the slope of cloud point temperature reduction as a function of additive concentration. The Δ_{CPT} of phenol was calculated to be −0.56 °C/mM with an r^2 of 0.99. This negative value indicated that phenol had a tendency to lower the CPT and hence 'salt out' HPMC as a function of increasing concentration. This 'salting-out' tendency was greater than that seen with common salts (e.g. NaCl) known to "salt-out" HPMC (Bajwa et al., 2006). For comparison, the CPT modifying parameter of sodium chloride (NaCl) was measured as −0.018 °C/mM (r^2 0.99) using the same experimental methodology. This value was thirty times less potent than the value obtained for phenol.

Originally, it was proposed that electrolytes depress CPT of cellulose ether solutions owing to their greater affinity for water compared to the polymer. In addition, the order of potency at reducing the CPT of the cellulose ether follows that of Hofmeister lyotropic series. Touitou and Donbrow (1982) proposed that the mechanism by which these small molecules reduce the phase transition is by removing water from the hydration sheath surrounding the hydrophobic groups of the polymer and hence lowering the temperature by which hydrophobic interactions of the gel state become favourable.

These results suggest that phenol has either a greater affinity for water than the most common salts previously investigated in other work (e.g. Liu, Joshi, & Lam, 2008; Mitchell et al., 1990) or that phenol alters CPT by another mechanism. This alternative mechanism may involve direct interaction of phenol with methoxy groups on HPMC.

Some recent advances in the understanding of the Hofmeister series and how it relates to the interactions between ions and macromolecules have suggested that ions do not affect bulk water but are more likely to be directly interacting with the macromolecule (Zhang & Cremer, 2006). This is based on the experimental observations that (i) anions have no effect on hydrogen bonding network outside their direct vicinity, determined spectroscopically (Omta, Kropman, Woutersen, & Bakker, 2003), (ii) no thermodynamic changes in bulk water surrounding species were observed using pressure perturbation calorimetry (Batchelor, Olteanu, Tripathy, & Pielak, 2004) and (iii) physical behaviour in Langmuir monolayers is disrupted by direct penetration of ions rather than changes to bulk water (Gurau et al., 2003). In the BP monograph for methylcellulose, reference is made to incompatibilities of methylcellulose with chlorocresol, hydroxybenzoates and phenol, although no mechanism of action was discussed (BP, 2009). Sarkar and Greminger (1983) alluded to the ability of methylcellulose to form complexes with hydroxyl benzoates although no experimental evidence or mechanism of complexation was offered.

The scope of the investigation was subsequently widened to consider the effect of various substituted phenolic compounds on HPMC phase transition temperature. The structures of the various substituted phenols investigated in this work are detailed in Fig. 2.

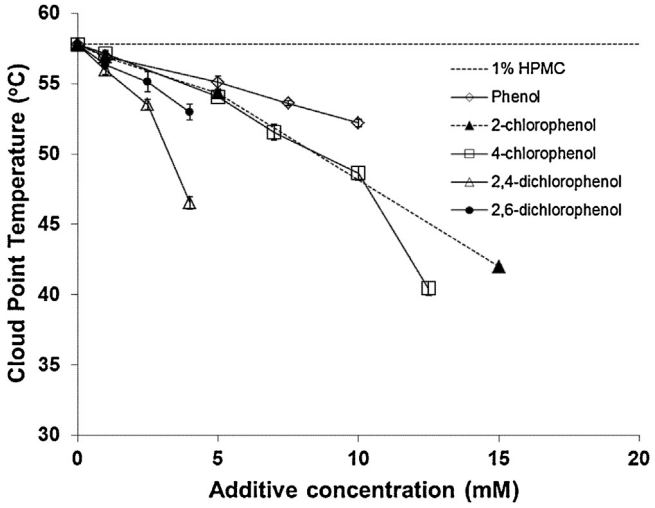


Fig. 3. The influence of chloro-substituted phenols on the cloud point temperature of 1% HPMC aqueous solutions. Cloud point temperature measured by turbidity. Mean (n = 3) ± SD.

4.2. Effect of chloro-substituted phenolic compounds on cloud point modifying parameter

These investigations with chloro-substituted phenols were performed to ascertain the effect of electron withdrawing substituents on the aromatic ring on the Δ_{CPT} of HPMC. Fig. 3 shows the effect of chloro-substituted phenols on CPT. Monochloro-substituted phenols had a more potent effect on CPT than phenol and the position of the chloro-substitution was unimportant. Dichlorophenols were more potent than monochlorophenols and the position of the chloro-substitutions was important.

Table 1 shows the Δ_{CPT}, pK_a and Log P values for the additives and it can be seen that the Δ_{CPT} of the molecules did not form a simple rank order with pK_a or Log P (linear relationships had r^2 values of 0.24 and 0.74, respectively) suggesting that the relationship between molecular properties and potency is a complex interplay between the physicochemical variables.

4.3. Effect of nitro- and methyl-substitution on HPMC cloud point temperature

Table 2 shows the pK_a, Log P and Δ_{CPT} values for nitro-substituted phenols. Nitro-substituents are, like chloro-groups, electron withdrawing and it can be seen that, with the exception of 2-nitrophenol, nitro-substituted phenols have lower Δ_{CPT} values than unsubstituted phenol. Table 2 also shows the pK_a, Log P and Δ_{CPT} of methyl-substituted phenols (commonly known as cresols). The addition of an electron donating methyl-group reduced the Δ_{CPT} to below that of phenol suggesting that the Δ_{CPT} of phenols is affected by changes in the electron withdrawing effect on the aromatic ring. Consequently, these changes impact the way the phenolic compounds are able to interact with HPMC in aqueous solution.

Table 1
pK_a, Log P and cloud point modifying parameters of 1% HPMC solutions for chloro-substituted phenols. Cloud point temperature measured by turbidity. Mean (n = 3) ± SD.

	Δ_{CPT} (°C/mM)	r^2	pK_a	Log P
Phenol	−0.56	0.99	9.89	1.46
2-Chlorophenol	−1.02	0.98	8.11	2.15
4-Chlorophenol	−1.12	0.99	9.20	2.39
2,4-Dichlorophenol	−2.48	0.92	7.80	3.06
2,6-Dichlorophenol	−1.20	0.99	6.80	2.75

Table 2
pK_a, Log P and HPMC aqueous solution cloud point modifying parameters for substituted phenols. Cloud point temperature measured by turbidity. Mean (n = 3) ± 1 SD.

	Δ_{CPT} (°C/mM)	r^2	pK_a	Log P
2-Nitrophenol	−0.27	0.64	7.23	1.79
3-Nitrophenol	−0.73	0.97	8.82	2.00
4-Nitrophenol	−0.62	0.99	7.15	1.91
2-Cresol	−0.43	0.73	10.20	1.95
3-Cresol	−0.38	0.99	10.10	1.94
4-Cresol	−0.51	0.12	10.17	1.94

2-Nitrophenol has a less negative Δ_{CPT} on HPMC aqueous solutions than phenol, indicating a reduced tendency to suppress the HPMC CPT. It is possible that the exclusive intra-molecular hydrogen bond formation of 2-nitrophenol between the hydroxyl proton and the nitro-group oxygen reduces its interaction with HPMC. This is suggestive of a critical role for the hydroxyl group of phenol in the interaction and subsequent incompatibility mechanism with HPMC.

4.4. Identification of simple physico-chemical properties important in the suppression of HPMC cloud point temperature (CPT)

From a pharmaceutical formulation science perspective, it would be desirable to identify relationships between molecular parameters and Δ_{CPT} in order to predict chemical structures that would be unsuitable for formulation with HPMC early in the process of formulation development. This would save costly development time on drugs that contain active moieties that are incompatible with HPMC and direct scientists to more appropriate controlled release technology opportunities such as osmotic tablets or controlled release multi-particulates.

Fig. 4 shows the relationship between pK_a and Δ_{CPT} for the un-ionised phenol molecules investigated. 2-Nitrophenol was not included in the relationship shown in the chart. However, even excluding this compound for the reasons described above, the relationship between CPT modifying parameter and pK_a was weak (r^2 = 0.3492).

The relationship between Log P and Δ_{CPT} of the phenolic compounds included in this investigation is shown in Fig. 5. As the Log P of the phenol molecule increased, Δ_{CPT} became more negative, indicative of the phenol's capacity to reduce CPT. The Log P of 2-nitrophenol is related to the existence and not the position of the nitro-substitution and is not affected by the intra-molecular hydration bonding. The r^2 value of the plot is 0.803, leading the inference that there was a reasonable relationship between Log P and Δ_{CPT}.

4.5. Identifying molecular properties important for the HPMC cloud point temperature modifying parameter of phenols

Fig. 6 shows the relationship between measured Δ_{CPT} values for un-ionised phenol molecules and the predicted Δ_{CPT} values determined using a combination of molecular properties. A stepwise process was followed to generate this plot. The molecular parameters used to produce a predictive model for Δ_{CPT} were: (i) the dipole moment of the molecule, (ii) the electronic substituent parameter σ (para), (ii) the lipophilicity substituent parameter (π) and (iv) the Log P value. The fit (r^2) of the model versus the experimental data was 0.954, which suggested that the relationship between prediction and measurement was good.

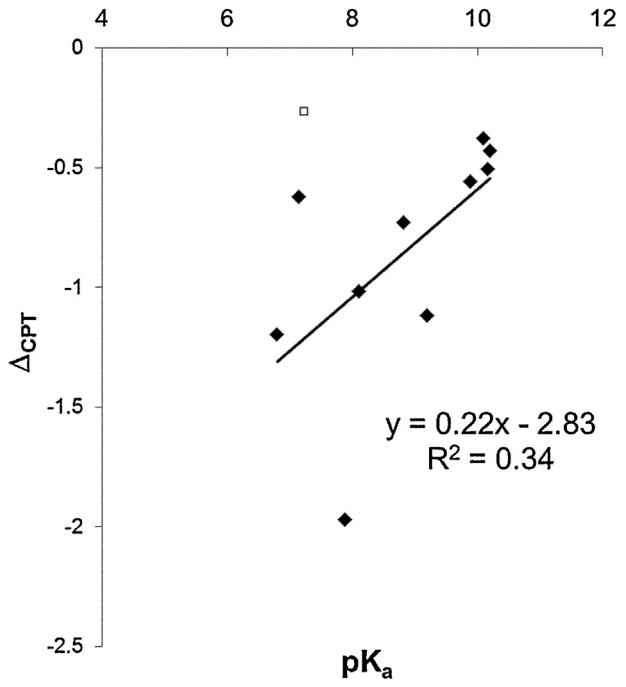


Fig. 4. Relationship between the pK_a of phenolic additives and their influence on HPMC cloud point temperature modifying parameter. □ represents 2-chlorophenol and was not included in the relationship.
pK_a values were taken from Solomons and Fryhle (2000).

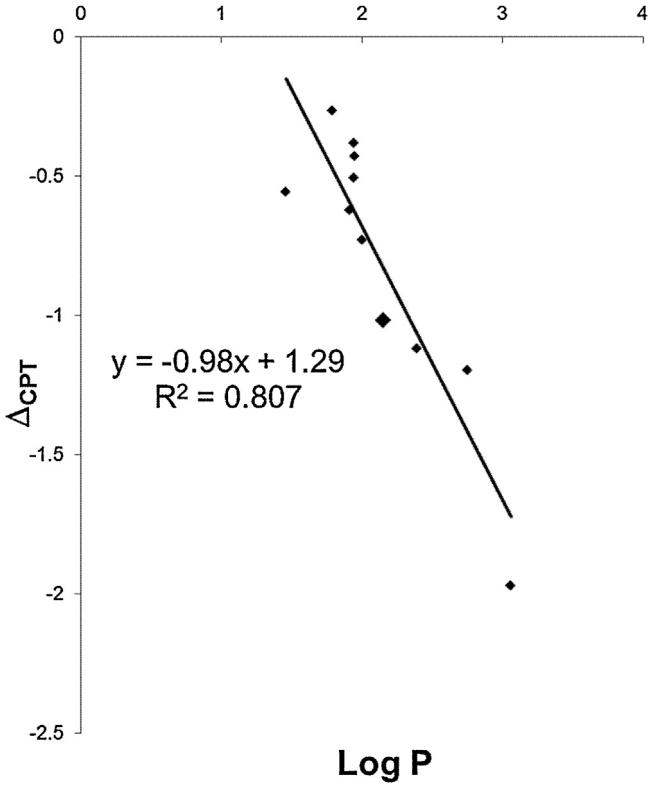


Fig. 5. Relationship between the Log *P* of phenolic additives and their influence on the HPMC cloud point temperature modifying parameter.
Log *P* values taken from Solomons and Fryhle (2000).

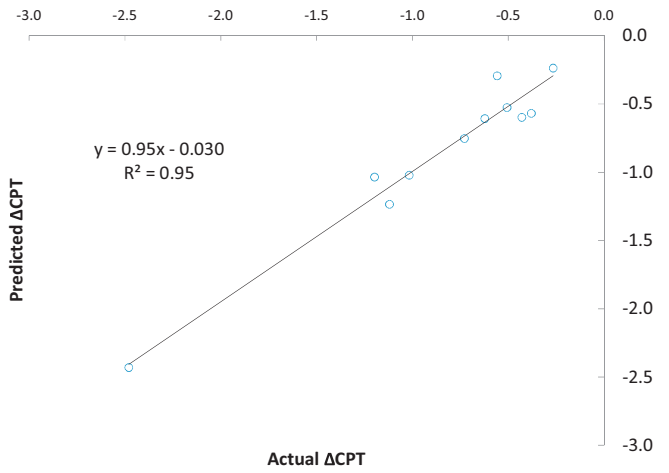


Fig. 6. Relationship between Δ cloud point temperature (CPT) of un-ionised phenols and molecular parameters determined by molecular modelling and the experimentally determined Δ_{CPT}. Molecular parameters obtained using Spartan PCPro modelling programme, included dipole moment, electron withdrawing activity (δ) and Log *P*.

The equation for predicting Δ_{CPT} is shown below:

$$\Delta_{CPT}(\text{predict}) = 2.045 + (0.395 \times \text{dipole}) - (0.900 \times \sigma_{para}) + (1.018 \times \pi) - (1.995 \times \log P)$$

These results suggest that the mechanism by which these substituted phenolic molecules interact with HPMC in aqueous solution was a complex combination of a number of molecular properties representing both electrostatic and lipophilic properties. This would explain the poor relationships identified between Δ_{CPT} and Log *P* and pK_a alone as demonstrated in Figs. 4 and 5.

4.6. The interaction of HPMC with substituted phenolic compounds in aqueous solutions

Several small aromatic molecules that cause a reduction in the CPT of 1% HPMC (E4 M) solutions have been identified. It is perhaps not surprising that phenols were found to be incompatible with HPMC as there are several reports of incompatability between methylcellulose and several phenolic molecules in the literature (BP, 2009; Martindale, 2002). Other non-ionic, water-soluble polymers have also been reported to have incompatibility with phenolic compounds. Kirci and Guner (2001) investigated solutions of PVP, a water soluble synthetic polymer that also exhibits a cloud point, in the presence of various phenolic cosolutes. The order of potency for cloud point temperature reduction followed the order: phloroglucinol > resorcinol > hydroxyquinone > catechol > phenol. The reduction in cloud point temperature by the phenols was attributed to several effects. It was proposed that phenol molecules change the structure of water, as well as interacting directly with PVP via a hydrogen bonding mechanism and finally that phenolic additives change or disrupt the hydration sheath of PVP, resulting in a lower cloud point for the HPMC solution. It is possible that the interaction between phenols and cellulose ethers follows a similar mechanism. Phenols may form hydrogen bonds with the hydroxyl groups of HPMC and displace water of hydration. The **statistics** of this interaction are unfavourable since water molecules considerably outnumber the phenol molecules in solution by several orders of magnitude. In support of Kirci and Guner hypothesis, ionisation of the hydroxyl group, reducing the ability of the group to form hydrogen bond, caused a considerable reduction in activity. Ionisation of the hydroxyl group may also alter the hydrophobic character of the molecule and the effect of ionisation on hydrogen bonding cannot

be assumed to be the only cause of the reduction in CPT lowering activity.

4.7. The relationship between physicochemical parameters of phenolic compounds and HPMC CPT

There was no significant relationship between pK_a of phenols and CPT modifying activity. Although pK_a is not a direct measure of hydrogen bonding ability, some parallel may be drawn from it as a surrogate measure. As the electro-negativity of the aromatic ring is increased by electro-negative substitution, the pK_a is reduced. The acidity of phenols is related to the electrical charge distribution on the aromatic ring causing the hydroxyl oxygen to be more positive. It is possible that increasing the electro-negativity of the aromatic ring increases this effect and enhances the group's ability to accept hydrogen bonds. As no relationship was found between pK_a and Δ_{CPT}, it may be assumed that hydrogen bonding between the polymer and phenol cannot the only factor responsible for the incompatibility and would not be relevant in the biorelevant pH range of 5–7.

A plot of Δ_{CPT} against Log P (associated with the hydrophobic character) of the phenols produced a relationship with a correlation coefficient of 0.803. This indicated that the hydrophobic character of the molecule was more important for the incompatibility with aqueous solutions of HPMC but does not provide a complete explanation. It is possible that by adsorbing onto hydrophobic regions of the polymer, such as the trimethyl-substituted sugars, the additives decrease polymer solubility with a consequent drop in CPT. Touitou and Donbrow (1982) have suggested that planar aromatic ions may adsorb onto the polymer backbone, carrying associated water of hydration. This increased the degree of polymer hydration leading to higher CPT values. These results may suggest that aromatic additives adsorbing onto the polymer backbone can reduce the CPT by increasing the hydrophobic character of the polymer.

Adding additional parameters increases the predictive ability of the model and also points to the importance of charge and hydrophobicity. Incorporating the molecular dipole (determined from molecular modelling) together with the molecular substituent σ_{para} indicates the importance of consideration of the charge distribution in the molecule. However, the model also requires consideration of the hydrophobic nature of the molecules through the parameters π and Log P.

The combined relationship identified gave an r^2 of 0.95 and was a better relationship than that found for pK_a and Log P alone (r^2 values of 0.35 and 0.80, respectively). Further work is required to test the model identified in this investigation before it can be used as a predictive tool for the suitability of drug molecules to be formulated in hydrophilic matrices containing HPMC as the drug-release rate controlling polymer. From a pharmaceutical science perspective, active compounds containing these chemical functionalities should be screened diligently before entering a costly formulation development programme since they are likely to possess an incompatibility with HPMC, particularly when present in aqueous fluids (either the in vitro dissolution test or in vivo).

5. Conclusions

The influence of the physicochemical parameters of several aromatic molecules on the phase transition from sol to gel of hydroxypropyl methylcellulose has been investigated with respect to a series of substituted phenols. No strong direct correlation between single physicochemical properties of phenolic compounds such as pK_a or Log P was found for the compounds tested. However, a combination of molecular parameters (some obtained from molecular modelling) successfully predicted the behaviour of a number of substituted aromatic compounds. This predictive capacity and identification of moieties that have a deleterious impact on HPMC gelation behaviour may be of value when considering the potential deleterious effects of drug molecules containing these active moieties, including (i) non-steroidal anti-inflammatory drugs and (ii) bronchodilators.

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