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Solution interactions of diclofenac sodium and meclofenamic acid sodium with hydroxypropyl methylcellulose (HPMC)

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ABSTRACT

Many pharmaceutical agents require formulation in order to facilitate their efficacious delivery. However, the interaction between the active species and the formulation additives has the potential to significantly influence the pharmocokinetics of the active. In this study, the solution interactions between hydroxypropyl methylcellulose (HPMC) with two non-steroidal anti-inflammatories – the sodium salts of diclofenac and meclofenamate – were investigated using tensiometric, rheological, NMR, neutron scattering and turbidimetric techniques. The two drugs behaved very differently—meclofenamate addition to HPMC solutions led to substantial increases in viscosity, a depression of the gel point and a marked reduction in the self-diffusion coefficient of the drug, whereas diclofenac did not induce these changes. Collectively, these observations are evidence of meclofenamate forming self-assembled aggregates on the HPMC, a phenomenon not observed with diclofenac Na. Any process that leads to aggregation on a nonionic polymer will not be strongly favoured when the aggregating species is charged. Thus, it is hypothesised that the distinction between the two drugs arises as a consequence of the tautomerism present in meclofenamate that builds electron density on the carbonyl group that is further stabilised by hydrogen bonding to the HPMC. This mechanism is absent in the diclofenac case and thus no interaction is observed. These studies propose for the first time a molecular basis for the observed often-unexpected, concentration-dependant changes in HPMC solution properties when co-formulated with different NSAIDs, and underline the importance of characterising such fundamental interactions that have the potential to influence drug release in solid HPMC-based dosage forms.

1. Introduction

Cellulose ethers such as hydroxypropyl methylcellulose (HPMC or hypromellose) are widely used in the pharmaceutical applications as viscosity modifiers (Zhao et al., 2009), film-formers (Fahs et al., 2010) and in extended release applications (Alderman, 1984; Melia 1991; Li et al., 2005). Reports of interactions between drugs and HPMC are relatively uncommon, but isolated studies have suggested these may influence drug and polymer functionality. For example, HPMC drug interactions have been implicated in changing the kinetics of drug crystal formation (Tian et al., 2009), the performance of drugs during spray drying (Kondo et al., 2009), the properties of drug nanoparticles (Sepassi et al., 2007) and the kinetics of drug release from HPMC matrices. (e.g. Mitchell et al., 1993; Velasco and Walker, 1999; Ford et al., 1987; Hino and Ford, 2001). There is substantially more literature describing the interaction of cellulose ethers with electrolytes and surfactants, and drug molecules may of course possess both characteristics. It is well known that simple ions can depress or raise the sol:gel transition temperature of alkyl and alkylhydroxyalkyl cellulose ethers, in a rank order potency that follows a Hofmeister-like series. The mechanism is considered to involve the re-orientation of water molecules around regions of hydrophobic substitution, and the formation of an insoluble three-dimensional polymer gel network through hydrophobic interactions (Sarkar 1979; Haque and Morris, 1993). More recent advances in our understanding of Hofmeister effects has suggested that ions can directly interact with the hydration sheath of macromolecules (Zhang and Cremer, 2006) and this can be applied to the many historical studies of 'salting-in' and 'salting-out' of HPMC by electrolyte solutions (Touitou and Donbrow, 1982; Mitchell et al., 1990; Kajiyama et al., 2008; Liu et al., 2008).

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Surfactant–polymer interactions have been studied extensively in cosmetic, oil recovery, food and pharmaceutical applications (Goddard, 2002; Taylor et al., 2007; Claro et al., 2008; Onesippe and Lagerge, 2008). The interaction between SDS and HPMC for example, has been described in detail by Nilsson (1995) who proposed that SDS adsorbs in a co-operative manner as molecular clusters, forming small micelles which act to solubilise the hydrophobic regions of the HPMC polymer chain. Using highly substituted, hydrophobic HPMCs, Kulicke et al. (1998) demonstrated SDS-dependent increases in solution viscosity accompanied by a rheological change to dilatant flow. In the case of the most hydrophobic HPMC, there was a fifteen-fold viscosity increase around the critical micelle concentration.

Richardson and co-workers (2006) have shown how more complex ionic species (a range of L-amino acids) can influence HPMC gelation temperatures, and how this is related to their molecular structure. Hydrophilic or multivalent amino acids lowered the temperature of the solution phase transition, whereas aromatic and hydrophobic amino acids elevated this temperature. The effect was critically related to amino acid hydrophobicity and they proposed that these effects reflected the ability of the amino acid to act as an amphiphile. The overall effect of an individual amino acid was a balance between the ionised moieties of the amino acid, which destabilise the polymer hydration sheath in a manner analogous to electrolytes, and the hydrophobic moieties, which would solubilise methoxyl-dominated regions of the polymer in a manner similar to surfactants.

Many drugs are amphiphilic, but to date there have been few in-depth studies of their interaction with non-ionic cellulose ethers. Several reports show (or suggest that) individual drugs can change the physiochemical properties of non-ionic cellulose ethers in solutions, gels and matrices, but few studies provide evidence to support the underlying mechanisms (Rades and Mueller-Goymann, 1998; Ridell et al., 1999; Taboada et al., 2001; Attwood, 1995; Schreier et al., 2000). Touitou and Donbrow (1982) used viscosity–temperature relationships to show how potassium phenoxypenicillin and chlorpheniramine maleate raised the phase transition temperature of methylcellulose, and showed how these drugs also stabilised the gel layer in hydrophilic matrices. Hino and Ford (2001) reported 'salting in' of HPMC solutions by nicotinamide, and proposed a hydrogen-bonded drug:polymer association. Mitchell and co-workers (Mitchell et al., 1990) report that propranolol hydrochloride and promethazine hydrochloride increase the solution phase transition temperature of HPMC. It is noteworthy that both drugs are surface active and promethazine forms micelles at concentrations greater than 0.5% (w/v) (Attwood, 1995). They suggested these drugs are adsorbed onto the polymer molecule, carrying with them water which raised the molecular hydration of the polymer. Katzhendler et al. (1998, 2000) used differential scanning calorimetry to show how naproxen sodium increased the fraction of bound water in HPMC 2208 solutions from 1.5 water hydration layers to 2.2 and postulated changes in water ordering as a result of naproxen sodium adsorption onto the polymer backbone. McCrystal et al., 1999a,b) investigated the effect of propranolol hydrochloride and diclofenac Na on the distribution of water within HPMC gels and showed how the molar bound water per polymer repeating unit increased in the presence of diclofenac Na, but not with propranolol hydrochloride. They suggested this was evidence that diclofenac Na 'salted-out' the polymer, and reduced its aqueous solubility.

The most in-depth investigation of the interaction between an amphiphilic drug and cellulose ethers was perhaps that of Ridell et al. (1999) who studied the aqueous interactions between ibuprofen sodium, HPMC and ethyl hydroxyethylcellulose (EHEC). Using a range of experimental techniques, they demonstrated the presence of mixed micelles of ibuprofen with HPMC or EHEC. They explained that drug adsorption was non-cooperative at ibuprofen sodium concentrations below the CMC but cooperative above the CMC. The increase in polymer sol:gel transition temperature above the CMC was explained in terms of ibuprofen solubilisation of polymer hydrophobic regions increasing the molecular hydration of the polymer chain (Ridell et al., 1999).

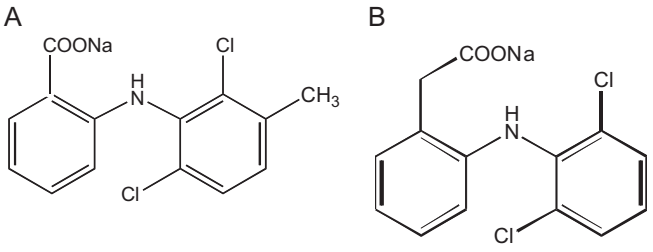

Fig. 1. Structural formulae of (A) meclofenamate Na and (B) diclofenac Na.

The present study investigates the solution interactions of HPMC with two other non-steroidal anti-inflammatory drugs, diclofenac Na and meclofenamate Na, which are structurally related. Each drug possesses a lipophilic aromatic moiety, an anionic polar head group (–COONa) and a secondary amine (Fig. 1). In aqueous solutions at pH 7, the carboxylic acid group will be deprotonated (negative) and the amine group protonated (positive). The isoelectric point for both species is around 4. However, in the case of the meclofenamate, the amine and acid groups are conjugated, and the lone pair of electrons on the nitrogen may be donated into the aromatic system and into the carbonyl, building up the electron density on that group. In essence, diclofenac is an amino acid but meclofenamate is an amide. Using a range of techniques we probe for evidence of a direct molecular interaction and investigate the physical consequences of their interaction on polymer solution properties.

2. Materials and methods

2.1. Materials

Hydroxypropyl methylcellulose (HPMC) (Methocel E4M CR Premium USP 2910) was a kind gift from Colorcon (Colorcon Ltd., Dartford, UK). Manufacturer's data showed this to be a typical USP type 2910 HPMC, with 9.3% hydroxylpropyl and 29.5% methoxyl substitution, and a nominal viscosity of 4000 cps for a 1% (w/w) solution at 20 °C. Diclofenac Na was obtained from MP Biomedicals (Eschwege, Germany) and meclofenamate Na was obtained from the Cayman Chemical Company (Ann Arbour, Michigan, USA). Both drugs were of analytical grade and used without further purification. Deuterium oxide (Fluorochem, Glossop, UK) was used for the preparation of solutions in the pulsed-gradient spin-echo NMR (PGSE-NMR) and small-angle neutron scattering (SANS) experiments. Other solutions were prepared using Maxima HPLC grade water 18.2 MΩ cm (USF Elga, Buckinghamshire, UK).

2.2. Methods

2.2.1. Preparation of HPMC and drug solutions

HPMC and drug solutions were prepared by adding HPMC powder to a weight of water sufficient to prepare one-tenth of the final weight of solution and agitating vigorously until the powder had visually dispersed. These stock solutions were then stored for 24 h at 2–8 °C. Solutions containing HPMC and drugs were prepared by mixing stock solutions by weight. Solutions for PGSE-NMR and SANS were prepared from stock polymer solutions prepared in D_2O to which dry drug had been added. The samples were sealed, turned end-over-end until dissolution, and then left 12 h to equilibrate. Samples were pipetted into 5 mm NMR tubes (0.600 g aliquot) or

into 2 mm path length circular Hellma SANS cells (0.7 g aliquot) for measurement.

2.2.2. Solution density measurements

To provide parameters needed for surface tension measurements, the density of drug solutions containing 0.1% (w/w) HPMC was measured at 20 ± 0.1 °C in a DMA 5000 oscillating U-tube Density Meter (Anton Paar, Graz, Austria).

2.2.3. Surface tension measurements

The equilibrium surface tension of HPMC drug solutions was measured using the pendant drop tensiometer PAT1 (Sinterface, Berlin, Germany). All measurements were conducted at 20 ± 1 °C. Sample solutions were prepared in triplicate and 10 measurements were obtained for each sample with relative standard deviations (n = 10) of less than 0.05%.

2.2.4. Determination of the phase transition temperatures of HPMC solutions

The sol:gel phase transition temperature of 1% (w/w) HPMC solutions, in the presence and absence of dissolved drugs, were determined by cloud point measurements in a white light turbidimeter (Cloud Point Apparatus, Medical Physics, QMC, Nottingham) using 10 mm quartz cuvettes (Optiglass, Essex) and a heating rate of 1 °C min^{-1}. The phase transition was calculated as the temperature at which light transmission was reduced by 50% (Sarkar, 1979; Sarkar and Walker, 1995).

2.2.5. Pulsed-gradient spin-echo NMR

The molecular interaction between drugs and HPMC was studied by pulsed-gradient spin-echo NMR (PGSE-NMR). A stimulated echo sequence was used to measure the self-diffusion of drugs in the presence and absence of 0.1% (w/w) HPMC in a Bruker AMX360 high-resolution NMR spectrometer, using a method described previously in which a constant current gradient amplifier (Bruker, Spectrospin) delivered pairs of read and write gradients matched to better than 10 ppm (Davies and Griffiths, 2003). The gradients are ramped to the maximum value and down again, over a time σ typically of 250 μs. This, in conjunction with three pre-pulses before every scan, minimized distortions resulting from coil heating and eddy currents.

The self-diffusion coefficient, D_s, was extracted by fitting the measured peak integral, $A(G, \delta)$ as a function of field gradient duration δ, ramp time σ, intensity G, and separation Δ to Eq. (1):

$$A(d, G, D) = A_0 \exp\left[-g^2G^2\left(\frac{30D(d+s)^2 - (10d^3 + 30sd^2 + 35s^2d + 14s^3)}{30}\right)\right] D_s \quad (1)$$

where γ is the magnetogyric ratio of the nucleus under observation, in this case protons and the A_0 term was determined by the number of protons in the sample. All experiments were conducted at 20 ± 1 °C.

2.2.6. Small-angle neutron scattering (SANS)

Small-angle neutron scattering (SANS) measurements were performed on 60 mM drug solutions in the presence and absence of 0.1% (w/w) HPMC using a fixed-geometry, time-of-flight LOQ diffractometer (ISIS Spallation Neutron Source, Oxfordshire, UK). By using neutron wavelengths spanning 2.2–10 Å, a $Q = 4\pi \sin(\theta/2)/\lambda$ range of approximately 0.008–0.25 Å^{-1} (25 Hz) is accessible with a fixed sample-detector distance of 4.1 m. The samples were contained in 2 mm path length, UV-spectrophotometer grade, quartz cuvettes (Hellma, Essex, UK) and mounted in aluminium holders on top of an enclosed, computer-controlled, sample changer. Sample volumes were approximately 0.8 cm^3. Temperature control (20 ± 0.5 °C) was achieved through the use of a thermostatted circulating bath which pumped fluid through the base of the sample chamber. Under these conditions, a temperature stability of better than ±0.5 °C can be achieved. Experimental measuring times were approximately 40 min.

All scattering data were (a) normalized for the sample transmission, (b) background corrected using a quartz cell filled with D_2O (this also removes the inherent instrumental background arising from vacuum windows, etc.), and (c) corrected for the linearity and efficiency of the detector response using the instrument-specific software package. The data were put onto an absolute scale by reference to the scattering from a partially deuterated polystyrene blend.

2.2.7. Continuous shear viscosity measurements

Continuous shear viscosity measurements were undertaken using a Physica MCR 301 rheometer (Anton Paar, Germany) equipped with a stainless steel 2°/50 mm cone and plate geometry. The sample was mounted on a Peltier temperature controlled plate (20 ± 0.1 °C), the cone was lowered and excess sample removed from the circumference of the rotating measurement cone. A thin layer of low viscosity silicone oil was placed on the peripheral surface to minimise sample water loss. Data were acquired at shear rates between 0.01 and 100 s^{-1} on an incremental log scale, using sufficiently long data acquisition times to obtain equilibrium values. Measurements were performed in triplicate.

3. Results

3.1. Solution studies of HPMC interactions with meclofenamate Na and diclofenac Na

3.1.1. Surface tensiometry

Fig. 2 shows how both drugs exhibited surface activity in solution in the absence of polymer. This is common to many other non-steroidal anti-inflammatory agents (Fini et al., 1995). In the case of meclofenamate Na, a critical concentration was observed at ~45 mM, and the solution developed a "bluish" visual appearance, implying the formation of nanometre-sized aggregates. Diclofenac Na solutions did not exhibit a critical concentration, but this is probably a consequence of the limited solubility of the sodium salt. It has been reported that a more soluble organic salt is required to achieve critical concentrations of diclofenac (Fini et al., 1995). The surface tension of a 0.1% (w/w) HPMC solution (~50 nM/m) corresponded with the literature values (Pérez et al., 2008) and Fig. 2 shows how the presence of this polymer modified the surface behaviour of the two drugs in solution. In the case of diclofenac Na, the curve is similar in shape to a weakly interacting polymer:surfactant mixture (Taylor et al., 2007). In the case of meclofenamate Na, there is little change in surface tension with drug concentration. These results should be interpreted with caution. It has been noted that surface tension measurements of strongly interacting species often produce confusing results, and the complex behaviour of two surface active species at an interface means that the nature of the interaction cannot be interpreted from tensiometry alone (Taylor et al., 2007).

3.1.2. The effect of drugs on sol:gel phase transition temperature

Fig. 3 shows the effect of each drug on the phase transition temperature of 1% (w/w) HPMC solutions. The approximate maximum solubility at 20 °C was 60 mM for both drugs. HPMC solutions in the absence of drug exhibited a phase transition at ~57 °C. This is a typical value for this grade of USP2910 HPMC. The addition of diclofenac Na resulted in a progressive decrease in the transition temperature and a reduction of 9 °C at 60 mM. This behaviour is typical of ions that suppress HPMC solubility through Hofmeister effects (Richardson et al., 2006; Pygall et al., 2009; Williams

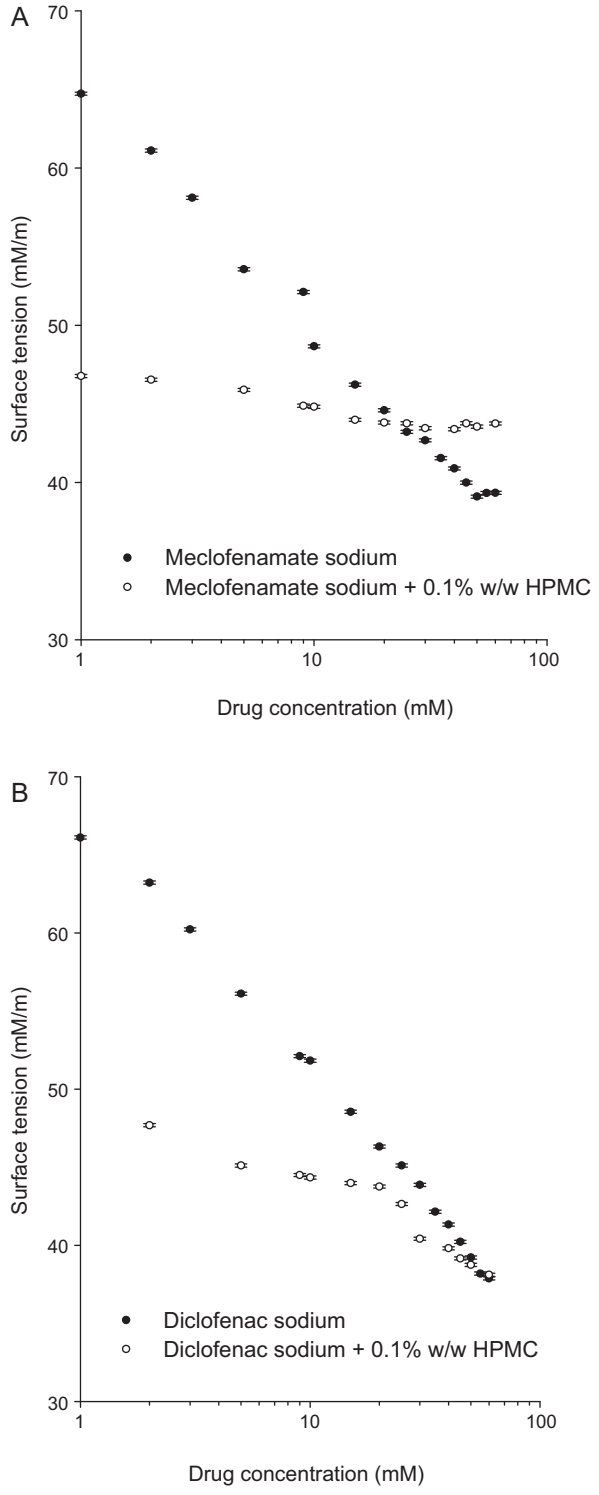

Fig. 2. Surface tension as a function of drug concentration in the presence and absence of HPMC. (A) meclofenamate Na and (B) diclofenac Na. 0.1% (w/w) HPMC. Surface tension measurements at 20 °C using the pendant drop method. Mean ± SD ($n = 5$).

et al., 2009). A low drug concentration meclofenamate Na was a more potent than diclofenac Na in reducing the phase transition temperature. A reduction of ~24 °C was observed at 40 mM, but thereafter further increases in drug concentration reversed this trend, resulting in progressively higher transition temperatures.

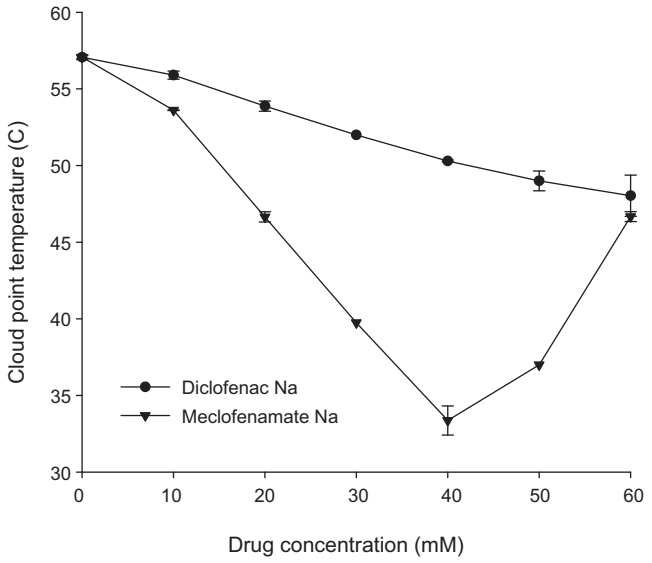

Fig. 3. The effect of meclofenamate Na and diclofenac Na on the cloud point temperature of 1% HPMC solutions. Cloud point temperature (CPT) measured turbimetrically as a 50% reduction light transmission (Sarkar 1979). Mean $n = 4 \pm 1$SD.

3.1.3. Pulsed-gradient spin-echo- (PGSE) NMR investigations

Pulsed-field gradient spin-echo nuclear magnetic resonance (PGSE-NMR) was used to compare the self-diffusion coefficient of each drug in the presence and absence of 0.1% (w/w) HPMC. PGSE-NMR has been used previously to investigate surfactant–polymer interactions as a means of determining association between the two species (Davies and Griffiths, 2003). Polymers have far lower self-diffusion values than low molecular weight species such as drugs, and changes in the drug self-diffusion behaviour can therefore be indicative of a drug–polymer interaction. Fig. 4A and B shows self-diffusion coefficient values (D_s) for diclofenac Na and meclofenamate Na in the presence and absence of 0.1% (w/w) HPMC, as a function of increasing drug concentration. In the presence of HPMC, there was a pronounced reduction in the diffusion coefficient of meclofenamate Na, which may be a consequence of hydrogen bonding between the drug and polymer stabilized the conjugated system of the meclofenamate tautomer.

This reduction in self-diffusivity is characteristic of an association between drug and polymer and the results show there was increasing drug:polymer association with increasing drug concentration. The decrease in (average) D_s arises as the fraction of aggregated material increased with total concentration. In the case of diclofenac Na, there was no reduction in self-diffusivity, suggesting little association between drug and polymer over the concentration range studied. This provides further evidence that the drug molecules were molecularly dispersed, and that over the concentration region studied this drug showed little tendency to aggregation.

3.1.4. Small-angle neutron scattering (SANS)

SANS analysis of 60 mM drug solutions at 20 (±0.2)°C in the presence and absence of 1% polymer is presented in Fig. 5. Additionally, the SANS data for the HPMC alone are shown. The scattering from meclofenamate Na solutions (Fig. 5A) was weak but is perhaps discernible, consistent with the apparent blue tinge of these samples. The weak signal suggested that aggregates were present, but their concentration was low. Diclofenac Na solutions showed no measurable scattering (Fig. 5B) which suggested an absence of any self-associated structures. The scattering of HPMC solutions was weak and unaffected by the presence of 60 mM diclofenac Na, indicating that no measurable change in polymer conformation had

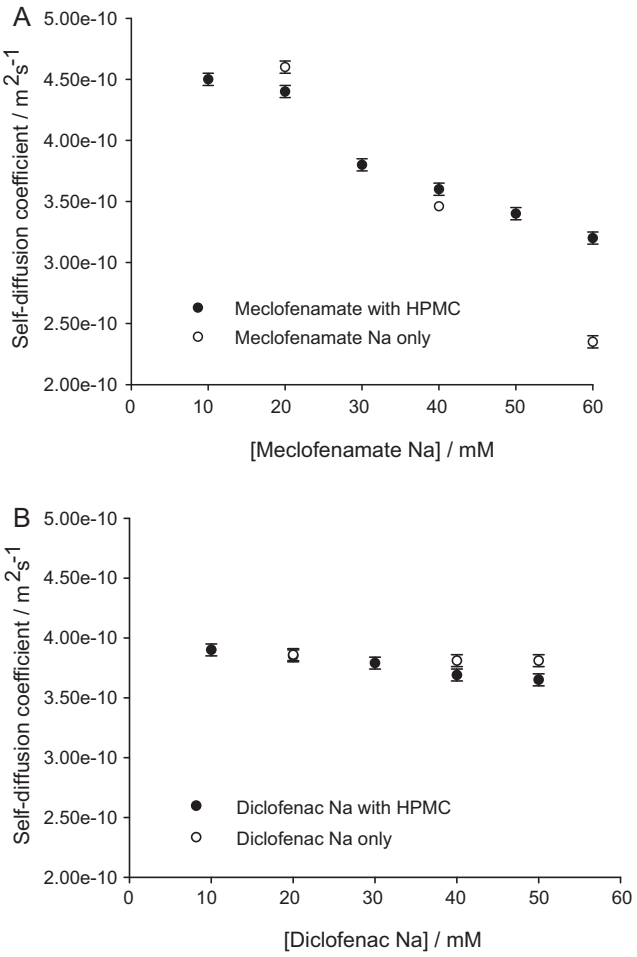

Fig. 4. Self-diffusion coefficient as a function of drug concentration in the presence and absence of 0.1% (w/w) HPMCsolution at 20 °C. (A) Meclofenamate Na and (B) diclofenac Na. Measurements made at 20 °C.

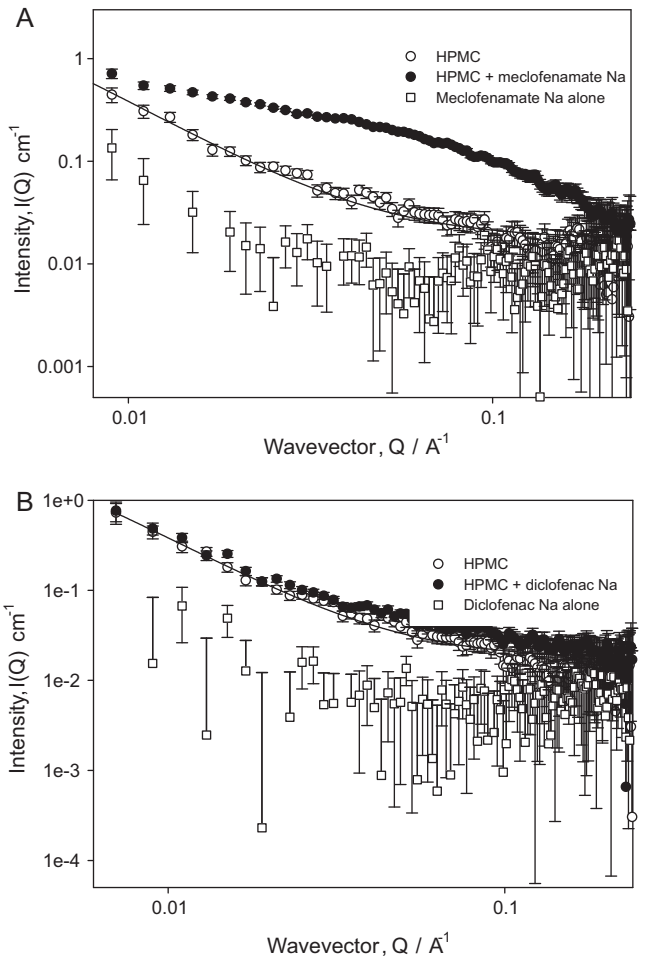

Fig. 5. The influence of 1% (w/w) HPMC on the SANS scattering curves of (A) 60 mM meclofenamate Na and (B) 60 mM diclofenac Na solutions. Measurements made at 20 °C. Data fitted as per Lindell and Cabane (1998).

occurred. However, addition of 60 mM meclofenamate Na to HPMC resulted in a sizeable increase in intensity over and above the intensity of the polymer alone. There was some evidence of a structure peak located at approximately 0.04 Å^{-1} in the meclofenamate Na-containing polymer solutions (Fig. 5A). This evidence of structure peak was absent in the diclofenac Na samples.

The HPMC scattering data can be analysed in terms of a semi-dilute polymer solution equation as originally proposed by Lindell and Cabane (1998):

$$I(Q) = I_0(1 + Q^2x^2)^{-1} \quad (2)$$

where $I(Q)$ is the scattering intensity as a function of Q the scattering vector, and x is the correlation distance of the mesh of macromolecules. The yielded fits are depicted in both Fig. 5A and B, with correlation length 425 (±25) Å. This distance remained unaltered in the presence of diclofenac Na (not shown for clarity). In the case of meclofenamate Na the data could not be adequately defined by this model as the functional form is now characteristic of polymer-bound aggregates. Overall this data supported the hypothesis of association between meclofenamate Na and HPMC, as determined by the surface tension and PGSE-NMR studies.

3.1.5. Continuous shear viscosity

Fig. 6 shows viscosity profiles for 1% (w/w) HPMC solutions at 20 °C, as a function of shear rate (0.01–100 s^{-1}) at drug concentrations up to 60 mM. HPMC solutions in the absence of drug exhibited a Newtonian plateau at low shear rates, and a tendency to shear-thin at high shear rates. The addition of 10 and 20 mM meclofenamate Na had little influence on these solution properties, but at higher drug concentrations there were substantial increases in solution viscosity (Fig. 6A). The addition of 40 mM meclofenamate Na resulted in a one order of magnitude increase in viscosity, and 50 mM and 60 mM in a two-order magnitude increase at low shear rates. These solutions showed considerable shear thinning at higher shear rates. There is a 'feature' in the data for 30 mM meclofenamate Na at around 20 1/s. This might indicate that above this shear rate, the association between polymer and drug is weakened and shear-induced mixing has occurred giving data analogous to lower drug loadings. At 40 mM the drug–polymer system appeared stable with a transition occurring between 40 and 60 mM drug concentration. We propose that the drug associates with the polymer between these two concentrations, leading to macromolecular coiling and resulting in an enhanced viscosity. The presence of diclofenac Na in a 1% (w/w) HPMC solution, however, hardly affected the viscosity behaviour (Fig. 6B) and the only discernable change in the viscosity profile was a reduction in shear thinning at high shear rates.

The enhanced solution viscosities at meclofenamate Na concentrations of 30 mM and above suggests drug-mediated intermolecular association between the polymer chains, with the formation of a weak network or other supramolecular structure which breaks down at high shear rates.

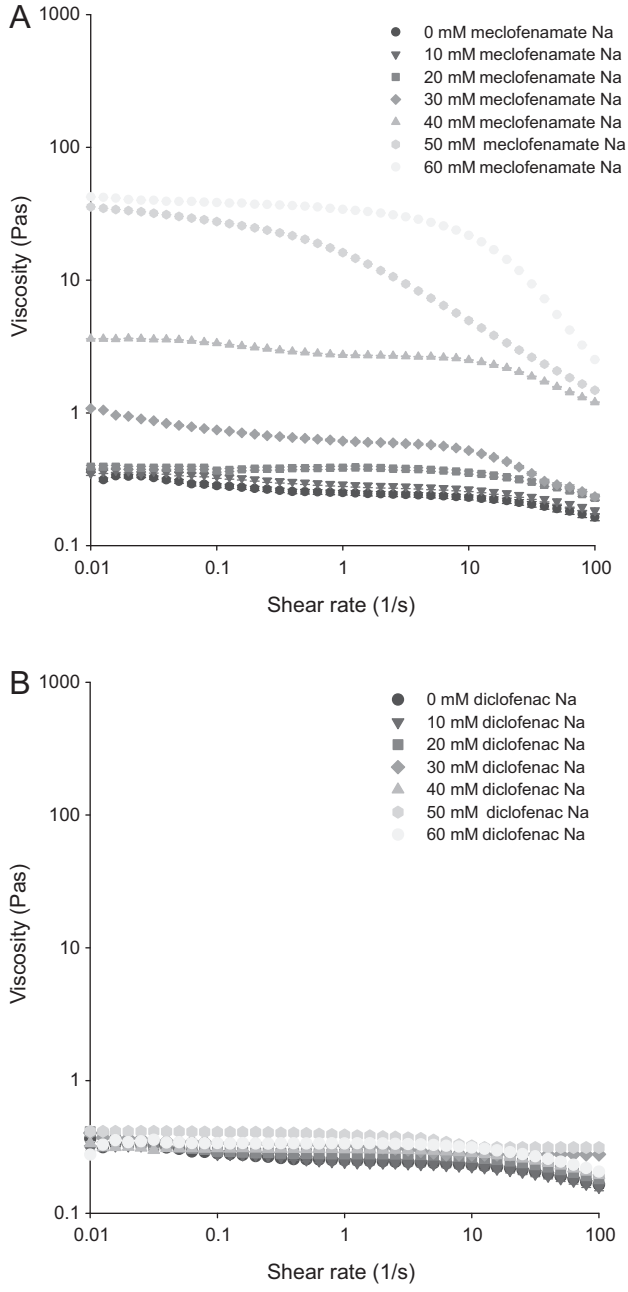

Fig. 6. The continuous shear viscosity of 1% HPMC solutions with respect to drug concentration (A) meclofenamate Na and (B) diclofenac Na. Measurements at 20 ± 0.1 °C Geometry2°/50 mm cone and plate.

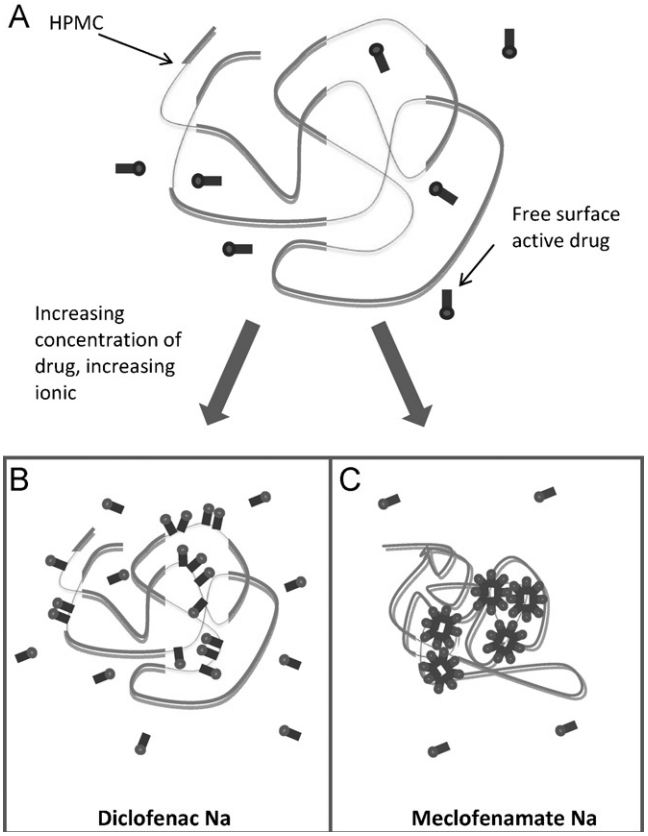

Fig. 7. Proposed schematic of HPMC interaction with meclofenamate Na diclofenac Na in solution.

4. Discussion

4.1. The evidence for drug–polymer interactions

The current work provides considerable evidence for a molecular interaction between HPMC and meclofenamate Na, but not with diclofenac Na. The PGSE-NMR and SANS experiments provide evidence for a direct molecular association between meclofenamate Na and HPMC. The reversal and subsequent concentration-dependent increase in HPMC sol:gel transition temperature at drug concentrations above 40 mM, suggests that drug association is improving the molecular hydration of the polymer. The significant rheological changes in this drug concentration range show the formation of a weak supramolecular network through strengthened interactions between polymer chains. This evidence allows postulation of a cooperative interaction between drug and polymer, as seen with surfactants. In contrast, diclofenac Na does not undergo detectable association with HPMC despite close gross structural similarities between these two drug molecules. At the concentrations investigated the tensiometry experiments indicate that meclofenamate Na self-associates in solution, whereas diclofenac Na does not, implying that micelle formation may be a prerequisite of the changes observed. This mechanism may be related to the capability of meclofenamate Na to exist in tautomeric forms, which results in the wider distribution of electrons across the amine and into the carboxylic acid functionality. Each drug possesses a lipophilic aromatic moiety, an anionic polar head group (–COONa) and a secondary amine. In aqueous solutions at pH 7, the carboxylic acid group will be depronated (negative) and the amine group protonated (positive). The isoelectric point for both species is around 4. However, in the case of the meclofenamate, the amine and acid groups are conjugated, and the lone pair of electrons on the nitrogen may be donated into the aromatic system, generating an enolate, building up the electron density on the carbonyl oxygen. This in turn would facilitate hydrogen bonding with the polymer structure and effectively allow a concentration of associated drug on the polymer structure and changing its solution properties.

4.2. Proposed mechanism of interaction

Fig. 7 depicts a hypothetical scheme describing how diclofenac Na and meclofenamate Na molecules might interact with HPMC, based on the differences in the chemical structure and the observed experimental phenomena. At low drug concentrations, diclofenac Na and meclofenamate Na are free in solution and there is limited interaction between the hydrated polymer and the drugs as evidenced by PGSE-NMR diffusion, tensiometry and cloud point data.

The predominant effect is the 'salting-out' propensity of the free drug molecule, as seen by the decrease in the sol:gel transition temperatures. This is likely to be a water-restructuring 'Hofmeister' effect, resulting from the presence in solution of ionic species. Current understanding suggests this leads to polymer dehydration and increased hydrophobic interactions between polymer chains. HPMC solution properties such as solubility and viscosity are largely unaltered at these drug concentrations (<10 mM). However, as the concentration of drug increases one of two scenarios unfold. In the case of meclofenamate Na, the diffusivity and tensiometry data shows that the drug begins to associate with the polymer conferring poly(electrolyte) properties upon the polymer. This competes with and reverses the 'salting-out' behaviour of the free drug molecule as evidenced by the cloud point measurements and we observe an inflexion in the sol:gel phase transition temperature curve from "salting out" behaviour to "salting in". In addition, rheological measurements clearly show that the solution viscosity is increased as a result of coil expansion and there is evidence of increased connectivity between polymer chains due to (i) adsorbed drug molecules or (ii) the introduction of "cross-links" arising from adsorbed aggregates. This may be driven by the existence of meclofenamate Na as a tautomer. The electron density on the nitrogen in the chemical structure is donated into the carboxylic acid which facilitates hydrogen bonding to the polymer structure. In the case of diclofenac Na, the drug is unable to associate in sufficient molar quantities to afford changes to the polymer solution properties as outlined above to the inability to form tautomeric structures.

4.3. Pharmaceutical consequences of drug–HPMC interactions

The potential pharmaceutical consequences of these interactions are considerable. The increased intermolecular association of HPMC observed in the presence of amphiphilic drugs such as meclofenamate Na, would result in unexpected and concentration-dependent viscosity changes in liquid formulations that incorporate HPMC as a viscosity-increasing additive. The change in flow properties could markedly affect the ability to pour liquid medicines, and would affect the spreading and shear-dependency of topically applied semi-solid dosage forms such as gels. If these molecular associations progressively change with time or with temperature, then unexpected effects might be seen in accelerated stability tests. The removal of polymer from solution by phase separation, the salting-out effects of drugs such as diclofenac Na, might lead to unpredictable reductions in solution viscosity, and for example, loss of suspending ability. By their physicochemical nature, we can expect both types of drug:polymer interaction to be sensitive to the presence of other additives in the formulation, particularly the presence of ionic species such as dissolved salts, and this could cause problems in formulation design. Low viscosity HPMCs are widely used in film-forming applications, such as tablet film coatings, and these drug interactions might influence the mechanical properties of the coat, and will almost certainly affect the spreading and thermal response of the coating solution during the coating process. In the case of hydrophilic matrix extended release dosage forms, where the establishment of an adequate surface gel diffusion barrier is a critical stage in achieving extended release (Melia, 1991; Li et al., 2005), these drug:HPMC interactions drug may influence the polymer viscosity and gel strength of the gel layer, and change its mechanical and diffusion barrier properties, altering the drug release kinetics.

However, in some pharmaceutical systems, the interactions between surface active drugs and polymers have been noted as being potentially useful for example in achieving efficient control of drug release from aqueous dispersions (Paulsson and Edsman, 2001; Jimenez-Kairuz et al., 2002) or in chemically cross-linked hydrogels (Gonzalez-Rodriguez et al., 2002; Rodriguez et al., 2003a). In these systems, polymer association with complementary additives might rapidly strengthen or induce connections between polymeric chains and may be a useful way of obtaining considerable increases in the viscosity of dispersions.

5. Conclusions

The effect of the sodium salts of diclofenac Na and meclofenamate Na on the solution properties of HPMC was investigated. Tensiometry demonstrated surface activity and. PGSE-NMR experiments, SANS and rheological studies provided evidence for a direct association of HPMC with meclofenamate Na and a change in solution properties which could have significant effects on pharmaceutical systems. This effect was absent in the diclofenac Na and HPMC system, which we attribute to the inability of this drug to exist in tautomeric forms.

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