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Effect of DMSO on micellization, gelation and drug release profile of Poloxamer 407

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ABSTRACT

The application of many recently developed or approved drugs and pharmaceuticals is seriously hampered by their low solubility in aqueous media. Hence, numerous promising pharmaceutical delivery systems (including novel "smart" systems based on poloxamer gels, which have highly advantageous thermo-reversible characteristics and low toxicity) cannot solubilize required doses of various drugs without additives such as co-solvents or salts. Therefore, we have studied the effects of dimethyl sulphoxide (DMSO) – a commonly used co-solvent during drug development stages – on the micellization, gelation and dissolution properties of aqueous poloxamer solutions. Differential scanning calorimetry and tube inversion experiments clearly showed that DMSO induces reductions in the critical micellization and gelation temperatures of poloxamer systems. In addition, high resolution solid state ^{1}H Magic Angle Spinning Nuclear Magnetic Resonance (MAS NMR) analyses provided indications of the specific chemical groups in the poloxamer affected by DMSO, and the molecular mechanism involved. The presence of DMSO accelerated dissolution of the pure gel in water and the release of a hydrophobic drug (flufenamic acid) from poloxamer gel, while it reduced the release of a hydrophilic drug (metoprolol tartrate).

1. Introduction

Poloxamer 407 (P407), also known as Pluronic® F127, belongs to a family of more than 30 ABA block copolymers, in all of which a hydrophobic poly-propyleneoxide (PPO) block is sandwiched between two hydrophilic poly-ethyleneoxide (PEO) blocks. The general structural formula of a poloxamer is $E_xP_yE_x$, where x and y denote the number of ethylene and propylene oxide monomers per block, respectively (Fig. 1). In general, poloxamers behave like non-ionic surfactants due to the ampiphilic nature of their block units. In concentrated aqueous solutions, these polymers form thermo-reversible gels, which makes them ideal for smart drug delivery systems (Schmolka, 1994). Poloxamers have been shown to be biocompatible and of low toxicity (Singh-Joy and McLain, 2008), hence they have been extensively studied for many potential drug and gene delivery applications (Kabanov and Alakhov, 2002; Kabanov et al., 2002; Dumortier et al., 2006).

These polymers form various, specific structures – ranging from micellar to gel-like features – in certain solvents, in which their behavior is concentration and temperature dependent. Micelle formation occurs when the concentration and temperature rise above the critical micellization concentration (CMC) and critical micellization temperature (CMT) (Schmolka, 1977; Alexandridis and Hatton, 1995; Bohorquez et al., 1999). Further increases above the critical gelation concentration (CGC) and critical gelation temperature (CGT) lead to physical entanglement of the micellar structures and packing into gel-like states (Yu et al., 1992; Cabana et al., 1997).

One of the most widely used poloxamers is P407, which has been approved for use as a formulation adjuvant in oral solutions, ophthalmic solutions, periodontal gels and topical emulsions (FDA Database, 2009). P407 gels have also been evaluated for ocular delivery of pilocarpine (Desai and Blanchard, 1998), periodontal delivery of local anaesthetics (Scherlund et al., 2000) and the delivery of proteins and peptides (Liu et al., 2007). A comprehensive review of applications of P407 gels in pharmaceutical formulation has been published (Escobar-Chavez et al., 2006). For all these applications specific additional substances have to be added to the formulations to provide sufficient drug solubility, isotonicity and an appropriate pH. However, additional factors (which include co-solvents, salts and various other species) can have pronounced effects on the micellization and gelation behavior of the P407 matrix (Armstrong et al., 1996; Pandit et al., 2000; Matthew et al., 2002; Rhee et al., 2006; Bonacucina et al., 2007; Talasaz et al., 2008). The effects of various alcohols on P407 have been studied (Kwon et al., 2001), but the effects of dimethyl sulphoxide (DMSO)

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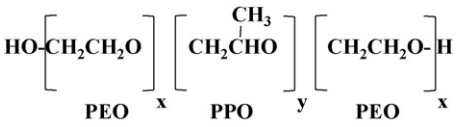

Fig. 1. Chemical structure of the P407 poloxamer, which contains between 95 and 105 monomeric ethyleneoxide (x) subunits and 54 to 60 propyleneoxide (y) subunits.

on the physico-chemical and drug release properties of P407 have not been studied in detail previously (to our knowledge). DMSO is an aprotic, polar solvent and is highly suitable for screening organic and inorganic compounds in preclinical research. Indeed, it is sometimes called "universal solvent". It has a unique capability for crossing biological membranes (Szmant, 1975) and it also enhances the topical penetration of drugs (Williams and Barry, 2004). DMSO has been approved as solubilizing solvent in subcutaneously implanted osmotically driven pumps (FDA Database, 2009; Strickley, 2004). In recent years, drugs of a new generation have entered the preclinical research phase, many of which are very hydrophobic and pH sensitive, hence their solubility in aqueous poloxamer systems is severely limited. Generally, limited amounts of compounds are available in early drug development stages, and detailed solubility studies are often not possible for each compound prior to animal testing. In this context DMSO appears to be highly promising, as an adjuvant in poloxamer gels, for subcutaneous, ocular, vaginal, rectal and transdermal administration during preclinical animal testing of potential drug candidates.

Therefore, the main aim of this study was to elucidate the impact of the co-solvent DMSO on the basic physico-chemical properties of thermo-reversible P407 gel and its controlled drug release features. For this purpose, first the micellization and gelation behavior of the gel was characterized by differential scanning calorimetry (DSC), ^{1}H MAS NMR and tube inversion methods. This was followed by determination of the release characteristics of the hydrophilic drug metoprolol tartrate (an antihypertensive agent) and the hydrophobic drug flufenamic acid (an anti-inflammatory) from the DMSO/P407 gel system.

2. Materials and methods

2.1. Materials

P407 (Pluronic F127, culture-tested, manufactured by BASF, USA) with an average molecular weight of 12,600 Da and flufenamic acid were purchased from Sigma (Sweden), DMSO (99.5%) from Fluka, D_2O (99.9%) from Aldrich (USA), DMSO-d_6 (99.8%) from Euriso-top, while metoprolol tartrate was a gift from Astra Zeneca (Sweden). All water used in the experiments was deionized and further purified by a Milli-Q system (MilliQ USA).

2.2. Sample preparation

Poloxamer solutions were prepared according to the "cold method" first described by Schmolka (Irving, 1972). Briefly, a weighed amount of P407 was added to water or an aqueous DMSO solution that had been equilibrated at 4–8 °C in a refrigerator before use. The poloxamer solution was kept for a further 24–36 h in an ice bath/refrigerator until a clear solution was obtained. For micellization studies, 1 mM (1.26%) P407 solutions were prepared by diluting the stock solution with defined amounts of DMSO, DMSO-d_6, water or D_2O. For studying the impact of DMSO on the gelation temperature and dissolution or release profiles, P407 solutions were prepared on w/w basis.

2.3. Differential scanning calorimetry

Calorimetric experiments were carried out using a Microcal VP-DSC microcalorimeter (MicroCal USA) equipped with VP Viewer software. For analyses of all samples the reference cell was filled with pure water, the pressure was adjusted to 15 psi and thermograms were obtained using heating and cooling cycles between 2 and 65 °C at temperature scan rates of 90, 60, 30, 15 or 5 °C/h, depending on the concentration of the test solution, except for precise determinations of the gelation temperature of highly concentrated solutions (when a rate of 0.5 °C/h was applied across a much narrower temperature interval). The pre/post-scan equilibration time was set to 5 min. All the data were analyzed using Microcal Origin.

2.4. ^{1}H MAS NMR spectroscopy

^{1}H MAS NMR experiments were performed using a CMX 100 instrument (Varian, USA) operating at 100.13 MHz at different temperatures. The samples used were 1 mM Poloxamer 407 (1.26%, w/v) in D_2O in the presence of DMSO at 0, 0.14, 0.33, 0.5, 1, 2, and 3 M. The sample spinning rate was kept at ca. 1700–1800 Hz and all NMR acquisitions started after sample equilibration for at least 10 min at the required temperature (±0.5 °C). The acquired data were processed using Spinsight software (Varian, USA). The water peak at 294 K was used as an external reference (4.796 ppm) for the chemical shift determinations of the NMR peaks in all samples. The intensity of detected peaks was integrated with the methylene peak set to 100%.

2.5. Gelation temperature

The gelation temperatures of the examined formulations of P407 were determined by the "Visual Tube Inversion Method", with slight modifications as previously described (Yu et al., 1992; Kwon et al., 2001). Briefly, two glass vials of 13 mm diameter, one containing 1 g of sample and the other 1 ml of water, were placed in a water bath. The temperature was slowly increased and the temperature at which the solution in the former stopped flowing on tilting was noted as the gelation temperature (t_1). Similarly, the temperature of the water bath was lowered and the temperature, at which the gel started flowing, was noted (t_2). The thermo-couple of a digital thermometer (Fluke USA) was placed in the water tube. The mean ± S.D. of t_1 and t_2 is reported as the critical gelation temperature.

2.6. Gel dissolution

Dissolution profiles of the P407-based gels in aqueous environments were determined by the gravimetric method (Zhang et al., 2002). For this purpose a pre-weighed glass vial of 13 mm diameter containing 0.6 g of the gel was equilibrated at 37 °C and 0.3 ml of water previously equilibrated at 37 °C was layered over it. After pre-determined time intervals the liquid medium was removed, the vial was re-weighed and the weight of dissolved gel was calculated from the difference in weight of the vial. Whole process was carried out in an incubation room maintained at 37 °C.

2.7. In vitro drug release

A membrane-less dissolution model was applied to study the effect of DMSO on the release profile of metoprolol tartrate and flufenamic acid, as reported elsewhere (Zhang et al., 2002). Flufenamic acid, dissolved in 50 μL of 1 M NaOH, and metoprolol tartrate were diluted with water to prepare standard solutions and drug-loaded gels. The drug-loaded gels were treated as described in Section 2.6 above, and the concentration of drug in the released

medium, collected at pre-determined time intervals, was then determined by measuring the absorbance of the medium using a Cary 5000 UV–vis spectrophotometer (Varian), and applying the associated software to process the acquired data. In the metoprolol tartrate experiment the absorbance at 274 nm was measured and the values were converted to amounts of the drug released using a calibration curve (Abs = 0.00427 × conc − 0.00343; R^2 = 0.99966) based on determinations of standard solutions over the range 5–150 μg/ml. Similarly, for flufenamic acid, a linear calibration curve obtained from measuring the absorbance of standard solutions with concentrations of 0.5–25 μg/ml at 288 nm (Abs = 0.05124 × conc + 0.0035; R^2 = 0.99929) was used to determine its concentration in the release medium. In all cases, water was used as blank, all samples were diluted to 2 ml before analysis and further diluted if the concentrations of the analyte were beyond the linear range.

3. Results and discussion

3.1. Differential scanning calorimetry

To determine the micellization behavior of aqueous poloxamer systems, DSC profiles were acquired. Illustrative thermograms, showing endothermic peaks indicative of micellization, for 1 mM (1.26%) and 22% P407 aqueous solutions, are displayed in Fig. 2a. The pronounced endothermic peak is caused by dehydration of the PPO building block in the P407 molecules, which leads to micelle formation of the PEO–PPO–PEO copolymers (Alexandridis et al., 1994; Alexandridis and Holzwarth, 1997). The DSC profile obtained for 22% (w/w) solutions shows three major changes, relative to those for dilute 1.26% solutions: the critical micellization temperature is reduced, the peak height (the intensity of micellization) is increased, and a second small peak indicating the transition from a micellar to a gel-like system can be observed at higher temperature. In general, the micellization process is endothermic and it can be characterized by (i) the onset temperature (T_{onset}); (ii) the area under the peak, which reflects the enthalpy change (Deng et al., 1992); (iii) the peak temperature (T_{peak}); and (iv) the endset temperature (T_{endset}) (Trong et al., 2008). T_{onset} is the temperature at which micelles start to form and T_{endset} is the temperature at which the micellization process is completed (Alexandridis and Hatton, 1995). Here, the T_{peak} is always referred to as the CMT. Additional experiments with P407 at varying concentrations in aqueous media revealed a clear relationship between its concentration and the observed CMT. Fig. 2b shows the effect of P407 concentration on its CMT in H_2O and H_2O–DMSO mixtures where DMSO is 5% (w/w). When the concentration of P407 is increased from 0.1% to 30% the CMT decreases from ca. 31 °C to below 8 °C, while the peak intensity and peak area increase dramatically. The temperature range of this process, as defined by the temperature interval from T_{onset} to T_{endset}, is around 14–16 °C. This concentration dependent decrease in CMT is in agreement with previous studies (Alexandridis et al., 1994; Scherlund et al., 2000). The transition of highly concentrated samples at elevated temperatures to the gel-state can also be discerned, as a small endothermic peak at the high temperature shoulder of the micellization peak. The presence of 5% DMSO resulted in reductions of 1.5–3.5 °C in the CMT of P407, relative to those of aqueous solutions with the same concentrations of P407.

In a second series of experiments, the effect of the presence of varying amounts of DMSO on the phase behavior of aqueous P407 systems was investigated. Resulting thermograms of aqueous, 1 mM (1.26%) P407 solutions containing increasing concentrations of DMSO (0–3 M) are shown in Fig. 3a. DMSO clearly has pronounced effects on T_{onset}, CMT and T_{endset}. Most pronounced are the changes in CMT, as illustrated in Fig. 3b (as a function of DMSO

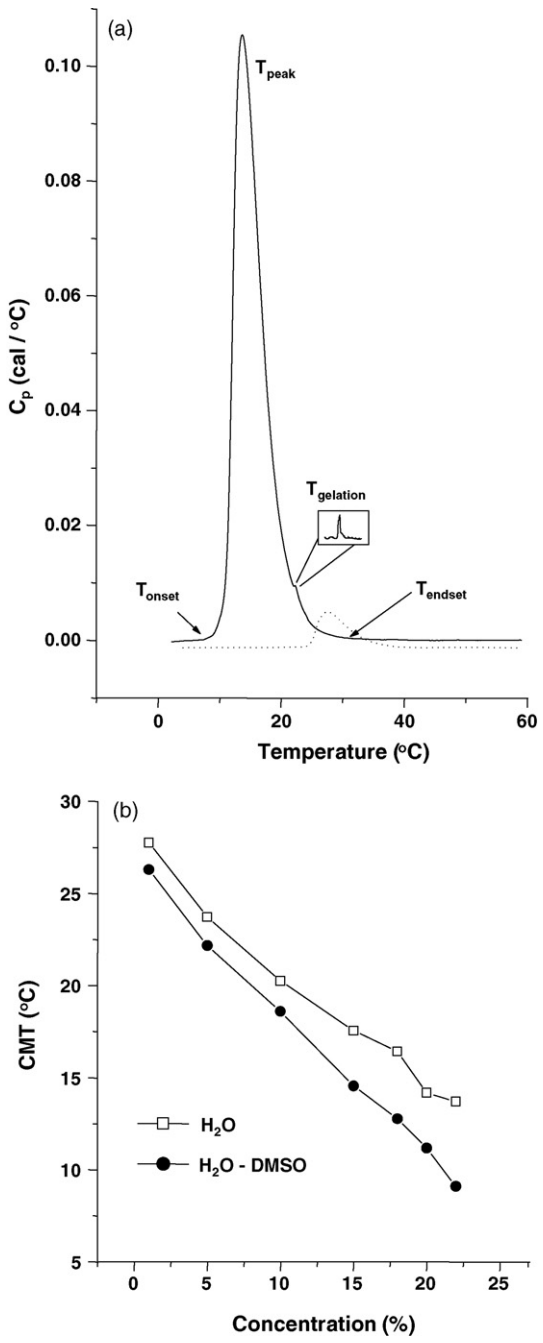

Fig. 2. Results of differential scanning calorimetry analyses of poloxamer (P407) aqueous solutions, showing the effects of P407 concentration and the presence of DMSO. (a) Representative thermograms of aqueous solution containing P407 at 22% (solid line) and 1.26% (dotted line). T_{onset}, T_{peak} and T_{endset} define the micellization process. *Inset*: The small endothermic peak indicates onset of the gelation process. (b) Critical micellization temperature (CMT) as a function of P407 concentration in pure H_2O (□) and aqueous solution containing 5% DMSO (●).

concentration) for 1 mM P407 solutions. Clearly, the micellization process starts to occur at lower temperatures as the concentration of DMSO increases, however the area under the endothermic peak is reduced. The results show that increasing the DMSO concentration reduces the CMT, as observed for increasing concentrations of poloxamer. However, in marked contrast to increasing the poloxamer concentration, an increase in the concentration of DMSO reduces the intensity of micellization (manifested in a reduction in the area under the endothermic peak). These effects might be due to DMSO's ability to disrupt water structures (Cowie and Toporowski,

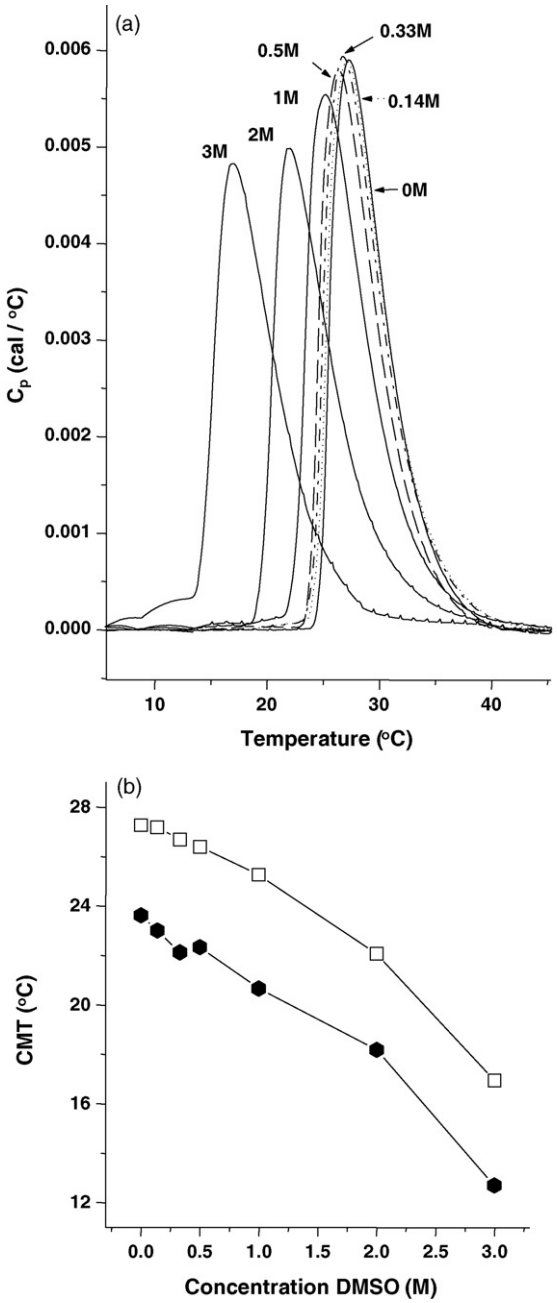

Fig. 3. Effect of DMSO concentration on the micellization behavior of 1 mM P407 aqueous solution. (a) Differential scanning calorimetry curves as a function of the DMSO concentration. (b) Effect of DMSO concentration on the T_{onset} (●) and T_{peak} (□) of the micellization transition.

1961), and thus modulate the water shells around the PPO groups of the poloxamer.

Both PEO and PPO blocks of poloxamer display good water solubility below their respective CMC and CMT, most likely due to the formation of hydrogen bridges between water and the oxygen of the monomeric unit (CH_2CH_2O and $CH_2C(CH_3)HO$). However, following increases in concentration or temperature, the solubility of PPO blocks is reduced due to a decrease in polarity (Alexandridis and Hatton, 1995). Similar reductions in the CMT have been observed, when the effect of salts on the association behavior of poloxamers was investigated with fluorescence intensity and FTIR analyses (Su et al., 2002; Su et al., 2003). The cited authors concluded that NaCl-induced changes in the charge distribution and polarity of the solution can cause shrinkage of the hydrophobic PPO block, and at temperatures below CMT the addition of salts decreases the polarity and proportion of hydrated methyl groups. We hypothesize that the association of H_2O–DMSO complexes, in dilute DMSO solutions, may disrupt water–water channels around the P407, thus reducing the solvation of the PPO group, and hence the CMT.

3.2. ^1H MAS NMR

To obtain insights at a molecular level into the behavior of the various molecular segments of the polymer during the temperature-induced phase transitions, ^1H MAS NMR spectra were acquired, at a range of temperatures, of solutions with varied concentrations of poloxamer in D_2O. A typical ^1H MAS NMR spectrum of a 1 mM (1.26%) P407 solution in D_2O at 294 K (below the CMT) is presented in Fig. 4a, which shows the following features. The methylene group of the PEO segment generates a sharp NMR resonance at the chemical shift value of 3.7 ppm, a doublet peak appears at 1.1 ppm that can be assigned to the methyl groups of the PPO segment (Wanka et al., 1994) and the proton signals of the CH2–CH units of PPO give rise to a broad set of resonance lines between 3.1 and 3.6 ppm. The sharp peak at 4.7 ppm is the HOD signal. The splitting (of 5.6 Hz) in the methyl peak at temperatures below the CMT is due to J-coupling between the methyl protons and the adjacent methylene protons. Spectra of 0.1, 5 and 20% P407 (w/w) solutions in D_2O were also collected. The methyl proton resonances remain unchanged at all concentrations below the CMT. However, when the temperature is raised above the solutions' respective CMT, the NMR lineshapes broaden and the splitting of the peak disappears (Fig. 4b), typically for motional processes occurring at the low kHz timescale.

To test the hypothesis that H_2O–DMSO complexes have more pronounced effects on the hydrophobicity of the PPO group of P407 than pure water, the effect of DMSO on the mobility of the methyl group of the PPO group was also studied by NMR. For this purpose, 1 mM P407 solutions in D_2O with DMSO concentrations up to 3 M were used. The signals arising from methyl protons of PPO block of P407 in pure D_2O and D_2O–DMSO mixture (0.5 M DMSO) for various temperatures between 294 K and 314 K are shown in Fig. 4b. There are similar trends in the observed changes in lineshape and splitting of the methyl protons in both types of samples. A doublet methyl peak can be seen at low temperature, which broadens upon temperature increase. To check the effect of increasing the P407/D_2O mole ratio in DMSO solutions, spectra of aqueous solutions with the same mole ratios but no DMSO were also obtained. The NMR signals arising from methyl protons in D_2O and D_2O–DMSO at 294 K with increasing DMSO concentration are shown in Fig. 4c. It is apparent that at 294 K the presence of DMSO at 0.14 or 0.5 M has no significant effect on the lineshape of the methyl protons, but peak broadening occurs in the presence of 1 M and 2 M DMSO. In addition, there was a splitting (J-coupling) in the methyl peak of the PPO block in the low DMSO concentration samples. The presence of high concentrations of DMSO resulted in a broadened methyl peak at room temperature, similar to the broadening observed when the polymer concentration was increased. Clearly, the increased hydrophobicity of the PPO group observed in D_2O–DMSO mixtures is due to the DMSO, and not to increases in the P407/D_2O mole ratio.

As mentioned above, several studies have indicated that at low concentration DMSO can interfere with water structures, due to conformational changes since it forms stronger bonds with water than water–water hydrogen bonds (Cowie and Toporowski, 1961; Qian et al., 1995; Catalan et al., 2001; Lu et al., 2009). Further, addition of small amounts of DMSO induces an increase in the chemical shift of the H_2O protons, indicative of an increase in the polarization of water (Mizuno et al., 2000). We also observed a slight increase in the chemical shift value for water in the presence of DMSO at 294 K.

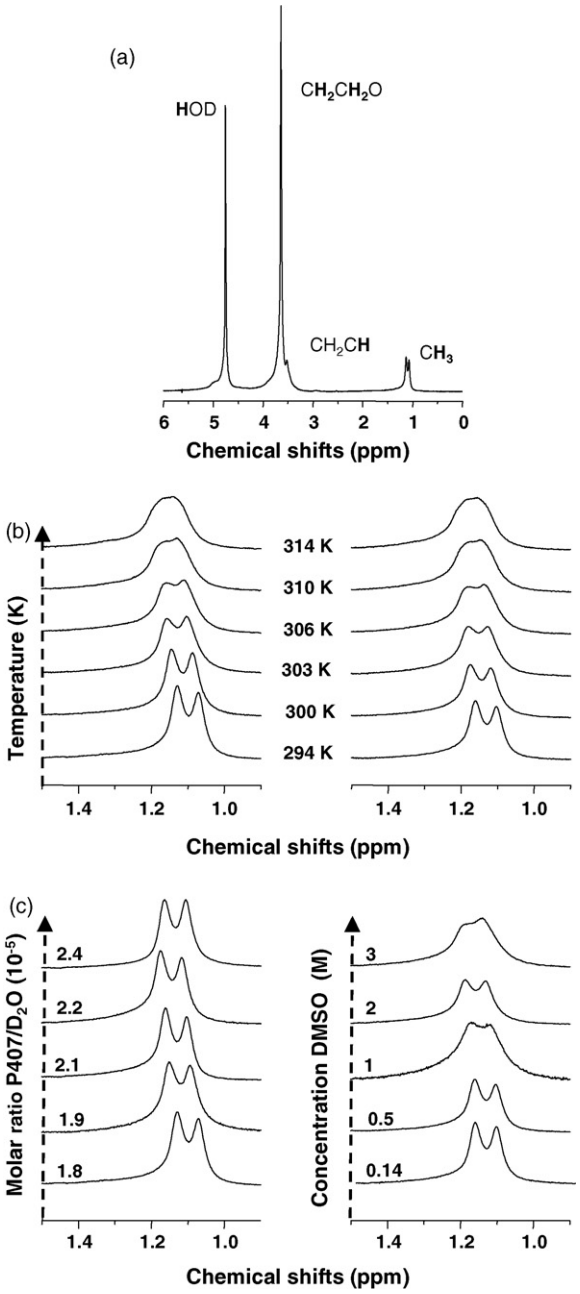

Fig. 4. ^{1}H MAS NMR spectra of aqueous P407 solutions as functions of temperature and DMSO concentration. (a) Representative NMR spectrum of 1 mM P407 solution at 294 K. NMR peak assignment of the various chemical groups, as indicated. (b) Temperature-dependent methyl proton NMR lineshapes for aqueous solution in the absence of DMSO (left panel) and with 0.5 M DMSO (right panel). (c) Methyl proton NMR lineshapes at 294 K for solutions with various DMSO concentrations (right panel) and corresponding DMSO-free aqueous solutions, with identical P407/D_2O ratios (left panel).

The associated increase in the polarity of the aqueous solution may explain the hydrophobicity of the PPO block at lower temperatures, and hence the accompanying reduction in the CMT.

3.3. Gelation temperature

The gelation of poloxamer solution is a reversible process, i.e. gels revert to free-flowing solutions when the temperature drops below the CGT. Many drug delivery approaches have exploited this property by loading and administering drugs in poloxamer systems in the liquid state, following which gel formation and the slow release of drug molecules from the gel matrix occur at body temperature. Hence, it is important to ascertain the gelation temperature to develop optimum formulations.

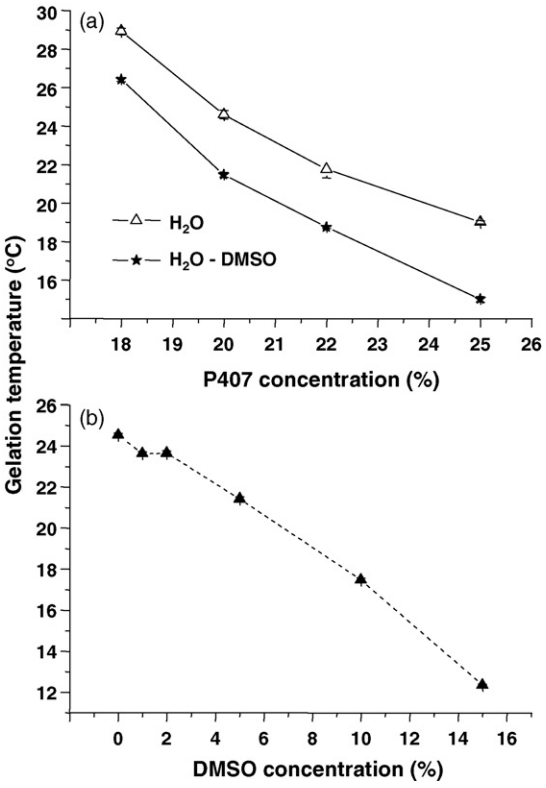

Fig. 5. Changes in the gelation temperature of aqueous P407 solutions as functions of poloxamer and DMSO concentration. (a) Effect of P407 concentration in DMSO-free solution (Δ), and in aqueous solution containing 5% DMSO (*). (b) Effect of DMSO concentration on the gelation temperature of 20% aqueous P407 solution. (Data shown are means ± S.D. of gelation and melting temperatures of the poloxamer gels obtained from 3 determinations.)

Unfortunately, the DSC studies could not provide precise information about the gelation behavior of the studied poloxamer solutions, except at very high concentrations. As shown in Fig. 2a, only a small endothermic peak was visible in the right shoulder of the micellization peak in thermograms obtained for 22% solutions, which form a gel at elevated temperature. Therefore, concentrated solutions were equilibrated and scanned solely in the vicinity of this peak. The resulting thermograms showed a clear endothermic transition (see arrow in Fig. 2a), in the form of a small endothermic peak, which was not present in thermograms of poloxamer at low concentrations. It has been proposed that the observed small endothermic peak is due to ordering of micelles into crystalline structures, in accordance with previous indications, obtained from SANS analysis, indicating that the micelles form a BCC cubic structure (Mortensen and Talmon, 1995; Cabana et al., 1997; Jiang et al., 2008). However, we could not obtain reproducible trend in gelation temperature while studying effect of DMSO by DSC, so simple tube inversion method was applied.

The CGTs of different poloxamer solutions, obtained from tube inversion experiments, are shown in Fig. 5. As can be seen in Fig. 5a, increasing the concentration of poloxamer in aqueous solutions reduces the gelation temperature, and it is further lowered in the presence of 5% DMSO. No gelation at all was observed in samples with poloxamer concentrations lower than 15%, which excluded the possibility of DMSO-induced gelation in non-gel forming poloxamer solution. The effect of increasing concentrations of DMSO on the CGT of 20% P407 aqueous solutions is visualized in Fig. 5b. The impact of DMSO on the gelation behavior of poloxamer solutions is

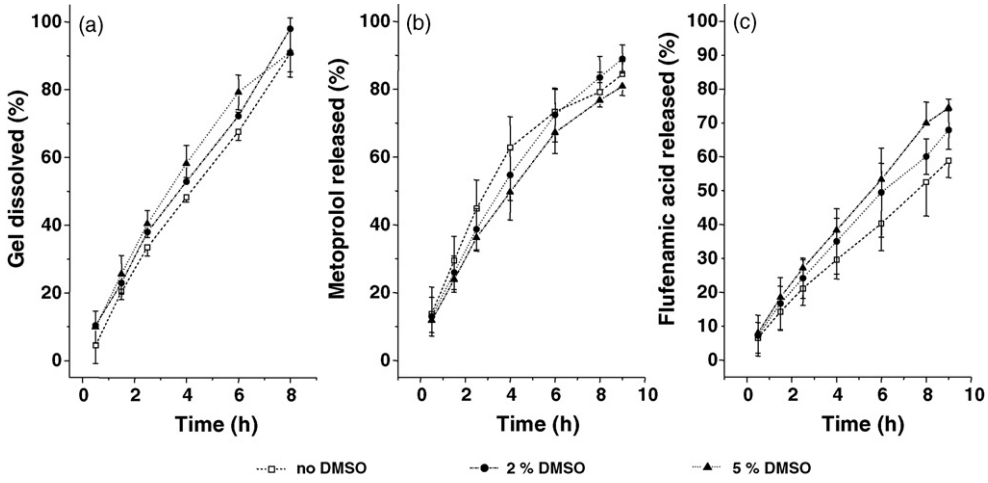

Fig. 6. Effects of DMSO on the dissolution and drug release profile of 20% P407 gel at 37 °C in water. (a) Dissolution profile of 20% P407 gel in the presence of 0 (□), 2 (●) and 5% (▲) DMSO. (b) Effect of 0 (□), 2 (●) and 5% (▲) DMSO on release of the hydrophilic drug, metoprolol tartrate. (c) Release curves of the hydrophobic drug flufenamic acid in the presence of 0% (□), 2% (●) and 5% (▲) DMSO ($n = 3$, mean ± S.D.).

consistent with the results of previous studies, in which salts such as sodium and calcium chloride have been found to decrease the gelation temperature (Gilbert et al., 1987; Malmsten and Lindman, 1992). It is apparent from the gelation experiment that the presence of more than 5% DMSO in 20% poloxamer P407 aqueous solutions can lead to the formation of a gel phase below room temperature. Since P407 has pronounced hyperlipidimic effects after parenteral administration (Blonder et al., 1999), and thus low concentrations should be used, DMSO may be useful for ensuring *in situ* gelation in such applications while acting as co-solvent. However, higher concentrations of DMSO may be added to formulations for external applications such as burn and transdermal patches.

3.4. Dissolution and release profiles of poloxamer gels

The release of any drug from a poloxamer gel depends on the environment. The release is controlled by dissolution of the gel if it is placed in an aqueous environment (as in ophthalmic, rectal, vaginal or parenteral administration), while diffusion is the main mechanism if the gel is confined by a membrane, as in transdermal applications (Gilbert et al., 1986; Moore et al., 2000; Ricci et al., 2005). Here, the previously described membrane-less dissolution release method (Zhang et al., 2002; Liu et al., 2009) was applied to determine the effect of DMSO (2 and 5%) on the release of two model drugs.

Gravimetrically determined dissolution profiles of 20% P407 gel in water and water–DMSO mixtures at 37 °C are shown in Fig. 6a. The dissolution of the gel is accelerated in the presence of DMSO (2 and 5%). The accelerated dissolution induced by DMSO may be due to the formation of more compact micelles and less entanglement of the PEO block, as is the case with NaCl, which reduces the gel strength. Gels containing 0.1% metoprolol, a hydrophilic drug, have slightly higher dissolution curves, while those containing 0.02% of the hydrophobic drug flufenamic acid have slightly lower dissolution curves. However, the presence of DMSO in drug-loaded gels reduces these effects (data not shown).

Release profiles of metoprolol tartrate and flufenamic acid in presence of DMSO (0, 2 and 5%) are shown in Fig. 6b and c, respectively. As in the dissolution trials, the release rate of metoprolol tartrate is slightly decreased, while that of flufenamic acid is slightly accelerated in the presence of DMSO. From the data it is apparent that low concentrations of DMSO (5%) have no pronounced effect on the dissolution and release of either drug from P407 gel.

4. Conclusion

DMSO, at low concentrations, influences the micellization and gelation of poloxamer in aqueous solutions in a concentration-dependent way and reduces the temperature at which both micelles and gels are formed. The effect of DMSO on the micellization of poloxamer is similar to that of salts, such as NaCl, that lower the CMT by breaking ordered water channels around the poloxamer molecule, leading to increased hydrophobicity and micellization. The presence of DMSO at low concentration has minor effects on the dissolution and release profile of poloxamer gel. DMSO can be safely used as a co-solvent at low concentrations (≤5%) for the controlled delivery of hydrophobic drugs, without compromising the thermo-reversibility of poloxamer gel.

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