



Pharmaceutical Nanotechnology

Elaborating the phase behaviour of ethylene oxide oligomers and analogues in 2H, 3H-perfluoropentane

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ABSTRACT

Pressure metered dose inhalers (pMDIs) are seen as an attractive option for the delivery of active molecules to the bloodstream via the lungs. Formulation issues are important as it is necessary to disperse the active substance into a volatile propellant. The phase behaviour of a range of common formulation agents – excipients – in 2H, 3H-perfluoropentane is reported here, focussing on the effects of simple elaboration of a central ethylene-oxide (EO) moiety. The base series of hydroxyl terminated EO fragments exhibited lower consolute solution temperature (LCST) behaviour that was strongly molecular weight-dependent. Substitution of methyl groups in place of the hydroxyl groups at the terminus of the EO fragment had a pronounced effect on the solubility of the oligomeric or polymeric material, the material becoming fully miscible with the HPPF. Substitution of methyl groups along the backbone of the hydroxyl terminated EO greatly enhanced the solubility of the materials, but the exhibited phase behaviour was still that of LCST. Longer alkyl groups at the terminus of the EO were found to promote the solubility compared to the hydroxyl terminated material, but to a relatively smaller degree compared with the methyl group. It is hoped that these simple “design rules” should facilitate the development of designer excipients tailored for a particular application.

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1. Introduction

Drug delivery *via* the lungs has long been used to treat asthma and chronic obstructive pulmonary disease. However, the large surface area of the lungs presents an efficient route to the bloodstream (Courrier, 2002), and when coupled with the much lower activity of degradatory enzymes (at least compared to the kidneys and liver) (Keller, 1999) the lungs are increasingly being seen as an attractive and viable alternative to oral or parental routes for the delivery of actives to the systemic circulation (Laube et al., 2005). This is in no small part due to the well-understood technology of pressure metered dose inhalers (pMDI) (Wilby, 2005; Pritchard, 2005).

The pMDI which contains a drug either dissolved or dispersed into a compressed propellant is an inexpensive, reliable and patient compliant form for administering the drug to the lungs. However, the switch from ozone-depleting chlorofluorocarbon (CFC) propellants to hydrofluoroalkane (HFA) propellants presents a challenge as many formulation components are reported to have a very low

solubility in these media (Byron, 1990), and accordingly, it is necessary to develop a fundamental understanding of solvation and solubility in HFA propellants (Peguin et al., 2006). HFA media find use as drug delivery systems (Riess, 2002), but this latter use is dependent on extensive formulation, usually incorporating co-solvents such as ethanol (Gupta et al., 2003).

The phase behaviour of a polymer in a solvent can exhibit a rich detail. Common characteristics include upper and lower consolute temperatures (UCST, LCST), in which the polymer undergoes a soluble/insoluble transition on passing through a well-defined temperature reflecting the balance of the enthalpic interaction term quantified by the χ parameter and the entropic interaction that favours miscibility. UCST and LCST behaviours are a result of monotonic dependencies of the χ parameter (decreasing and increasing, respectively) with temperature. “Hour glass” shaped phase diagrams arise due to an overlap of UCST and LCST behaviours (Siow et al., 1972), defined by a minimum in the χ -temperature behaviour whereas a “closed miscibility loop” (Chang and Bae, 1998; Bae et al., 1991) phase diagram is observed where the χ -temperature behaviour exhibits a maximum, often when the free energy of mixing also contains a further term relating to a specific, orientation-dependent interaction, *e.g.* hydrogen bond.

The phase behaviour has been measured for an extensive range of polymer/solvent systems and can be predicted, in the case of

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non-polar systems, by the Patterson–Flory theories of polymer solutions. However, in the case of polar polymer solutions, the phase separation phenomenon cannot be described by van der Waals forces alone (Saeki et al., 1976).

Arguably the most studied polar polymer/solvent system is poly(ethylene oxide) (PEO) in water (Saeki et al., 1976; Kjellander and Florin, 1981; Craig and Johnson, 1995; Hammouda et al., 2004); indeed, the solubility of PEO is an anathema itself since the next homologues polybutylene and polymethylene are insoluble in water (Israelachvili, 1997; Ashbaugh and Paulaitis, 2006). Short PEO chains (degree of polymerisation, $m \leq 48$) are completely miscible with water even at high temperatures; for slightly longer chains, a closed loop solubility gap is observed, yet for $m > 180$, only a LCST is found. This phase behaviour is very sensitive to molecular weight, and generally the cloud point decreases with an increase in chain length (Saeki et al., 1976; Kjellander and Florin, 1981). Various models have been proposed to account for the phase behaviour of PEO in water (Samii et al., 1991); water molecules experiencing weak van der Waals interactions with the EO groups possess higher structure compared to those in the bulk, which undergo an entropically driven disruption with increasing temperature resulting in aggregation and ultimately phase separation (Kjellander and Florin, 1981); the destruction of solubility enhancing hydrogen bonds between PEO and water (Goldstein, 1984; Hirschfelder et al., 1937) such that the solubility is then determined by the subtle balance of solvent–solvent and solute–solvent interactions; at lower temperatures the preferred gauche conformation of PEO exhibits a large dipole moment leading to a favourable interaction with the water (Karlström and Andersson, 1985), whereas at higher temperatures, non-polar isomers have higher statistical weight leading to a significant reduction in solubility.

The phase behaviour of PEO polymers in solvents other than water has received less attention. However, clouding phenomena of PEO has been reported in solvents such as formamide, *tert*-butyl acetate, super-critical carbon dioxide (sc-CO₂) and some organic solvents (Saeki et al., 1976; Silva and Loh, 1998; Spitzer et al., 2000, 2002a,b). Drohmann and Beckman (2002) report that PEG solubility in sc-CO₂ can be increased by decreasing its molecular weight or blocking the terminal hydroxyls by non-polar headgroups. The ether oxygens were found to enhance PEO solubility when compared to simple hydrocarbons, provided the oxygen was in a readily accessible position to the CO₂. As a general finding, carbonyl groups enhance the solubility of the polymer in sc-CO₂ by favourable cross-interactions, either by quadrupole (CO₂)–dipole (solute) interaction or Lewis acid/base, CO₂ being the Lewis acid (Rindfleisch et al., 1996; Kazarian et al., 1996; Meredith et al., 1996). End-group effects have also been examined extensively by Spitzer et al. (2000, 2002a,b). Despite its high water solubility, PEO can be extracted from water to organic solvent. This is due to the loss of polymer chain helicity when transferring from water to the apolar phase, resulting in an entropy increase (Bailey and Koleske, 1976). Spitzer et al. (2000, 2002a,b) showed that with increasing molecular weight, PEO favours an apolar phase. The molar mass at which PEO partitioning shifts its preference from the aqueous phase to the organic one occurred around 300–400 g mol⁻¹ for chloroform and dichloromethane. However, methylation of a sample of PEO 500 g mol⁻¹ led to a greater partitioning into apolar phase, showing that even above the 300–400 g mol⁻¹ range, the presence of glycol end-groups still contribute significantly to PEO partitioning into water. The hydrogen bond donating capability of the organic solvent was found to be crucial, so as to have strong enough interactions with the EO segments. The water displacement that resulted is associated to a high entropy increase that drives the transfer process by overcoming the loss in solvation energy.

The decrease in solubility upon heating, seen in the case of aqueous solutions of PEO, also occurs with systems of non-ionic surfactants in water, such as oligooxyethylene alkyl ethers bearing a hydrophobic alkyl tail and an EO headgroup. In such cases, the cloud point temperature occurs in the micellar phase, and depends not only on the strength of the interactions, but also on the shape and size of the micelles (Claesson et al., 1986).

Here, we report the phase behaviour of a range of common polymer and surfactant excipients in a model propellant (Rogueda, 2003), the partially fluorinated solvent 2H, 3H-perfluoropentane (HPFP), highlighting how the phase behaviour varies as a result of simple modification of the central EO moiety.

2. Materials and methods

2.1. Excipients

Poly(ethylene glycol), EO, $M_w = 200, 300, 400, 600$ and 1000 g mol^{-1} , poly(propylene glycol), PO, $M_w = 1000$ and 4000 g mol^{-1} , tetra(ethylene glycol) monododecyl ether, C₁₂EO₄ (Brij30™), deca(ethylene glycol) monododecyl ether, C₁₂EO₁₀, poly(ethylene oxide)-23-monododecyl ether, C₁₂EO₂₃ (Brij35™), poloxamers of molecular weight 1100 g mol^{-1} (EO₂PO₁₆EO₂) and 5800 g mol^{-1} (EO₂₀PO₇₀EO₂₀) and dodecane were purchased from normal sources (Sigma–Aldrich, Acros Chemicals, Apollo Scientific) and used without further purification. 2H, 3H-perfluoropentane (HPFP) (Apollo Scientific) was washed first with acidic and then basic alumina, filtered, dried and stored over molecular sieves.

2.2. Phase transition measurements

Samples were prepared by mass on a 3g scale in glass screw-top vials, sealed with polytetrafluoroethylene (PTFE) tape to prevent solvent evaporation, then wrapped into parafilm to protect against water penetration. After 48 h equilibration at room temperature, these samples were immersed in a temperature-controlled water bath and the temperature gradually raised from -20°C at a rate of 1°C every 30 min with constant agitation until the temperature reached 60°C . Hysteresis effects were negated by invoking much slower and both heating and cooling temperature ramps once an approximate phase transition temperature had been estimated. Visual phase transition temperatures were recorded.

2.3. Phase composition assessment

Temperature-induced phase separation for samples spanning a wide range of polymer concentration led to two distinct layers. The composition of these layers was assessed by a direct dry-weight method in which the layers were separated into pre-weighted vials using a flat-ended-needle syringe and the solvent removed by drying in an oven at 60°C until constant mass. Measurements were performed in triplicate and the average value presented.

2.4. Reproducibility

The phase transition measurements were performed in duplicate for each concentration. The composition of every sample was known accurately, spanning the concentration range 0.1–90 wt.% with a data frequency according to the phase transition profile. The temperature increment was typically 1 or 2°C , again dependent on the phase behavior being recorded; close to the phase boundary, smaller increments were employed.

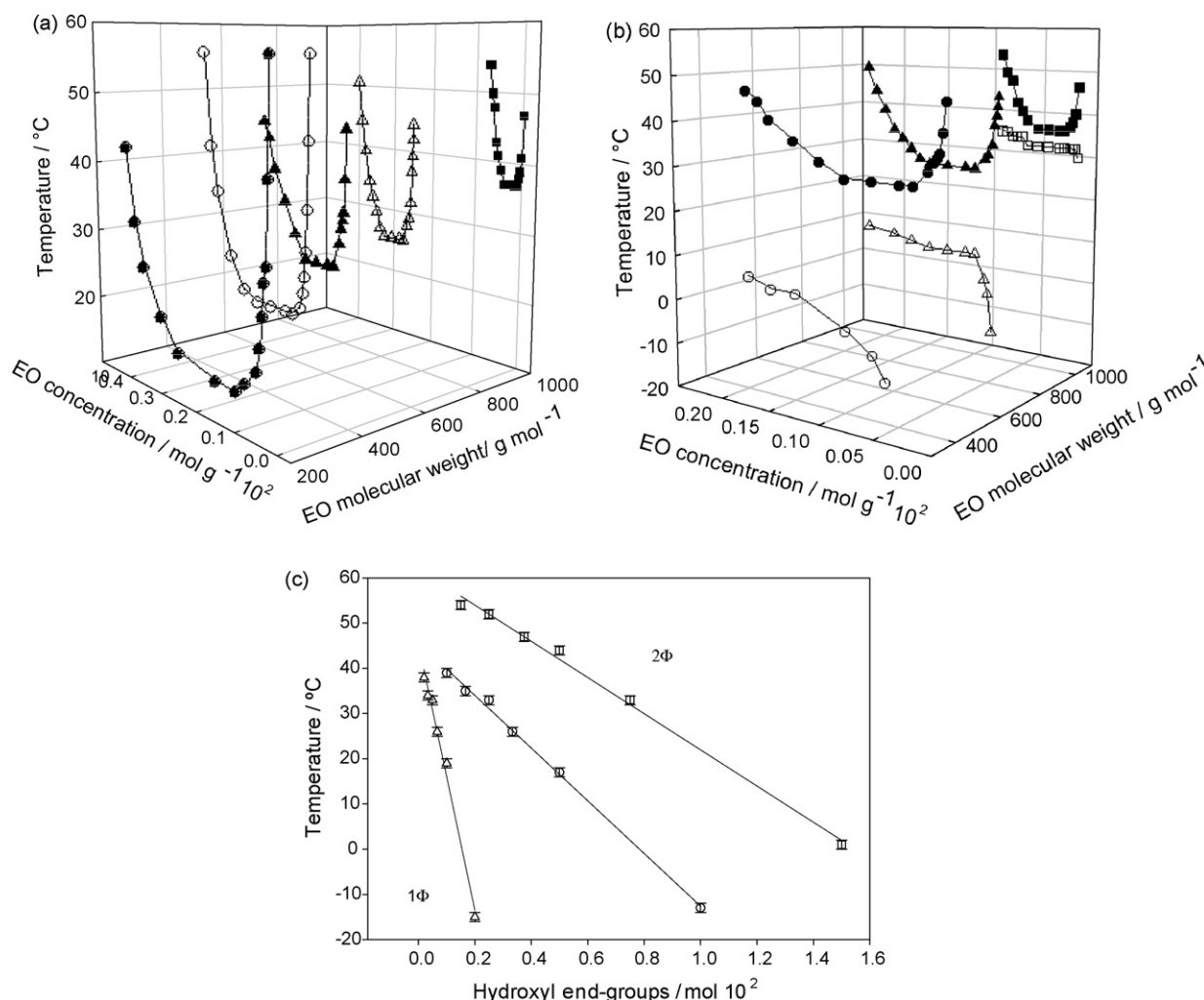


Fig. 1. (a) LCST for a series of PEG molecular weights in HPFP; EO 200 g mol⁻¹ (filled circles); EO 300 g mol⁻¹ (open circles); EO 400 g mol⁻¹ (filled triangles), EO 600 g mol⁻¹ (open triangles) and EO 1000 g mol⁻¹ (filled squares). (b) LCST (filled symbols) and melting point curves (open symbols) for a series of PEG molecular weights in HPFP; EO 400 g mol⁻¹ (circles); EO 600 g mol⁻¹ (triangles) and EO 1000 g mol⁻¹ (squares). (c) End-group analysis—cloud-point as a function of (di-)hydroxyl end-groups for a series of EO molecular weights 200, 300, 400, 600 and 1000 g mol⁻¹ at three representative concentrations, 10 wt.% (triangles); 50 wt.% (circles) and 75 wt.% (squares).

3. Results

3.1. Poly(ethylene oxide) homo-oligomers

On heating, originally clear monophasic solutions of hydroxyl end-capped EO in HPFP become opaque, and with time, separate into two clear layers. Onset of this phase separation defines the LCST. In the limited miscibility region (two phase region, 2Φ), *i.e.* $T > \text{LCST}$, samples consist of a less dense polymer-enriched (upper) phase and a more dense polymer-depleted (lower) phase. These two phases may be separated and the polymer concentration quantified by mass after evaporation of the solvent. By projecting these concentrations onto the solute concentration axis, the solubility phase diagram may be constructed.

The LCST–concentration profile is presented in Fig. 1(a) as a function of EO molecular weight. The cloud point of EO in HPFP is strongly concentration-dependent for all molecular weights, displaying a sharp increase towards both very low and very high concentrations. In water, much higher molecular weights are required before LCST behavior is observed (Saeki et al., 1976), although similar behaviour at these low molecular weights are observed in non-aqueous solvents (Spitzer et al., 2000, 2002a,b).

The molecular weight 400, 600 and 1000 g mol⁻¹ EO samples were also found to exhibit limited solubility at lower temperatures, coinciding with their melting behavior, Fig. 1(b). At low temperatures, such systems are biphasic consisting of a coexisting liquid and waxy solid. As the temperature increases through the melting point of the polymer (5–8 °C for EO 400 g mol⁻¹, 17–22 °C for EO 600 g mol⁻¹ and 35–40 °C for EO 1,000 g mol⁻¹) samples first become monophasic, before reaching the higher LCST presented in Fig. 1(a).

An increase in molecular weight drives the LCST towards higher temperatures, implying a greater solubility window but the melting curve is also a strong function of molecular weight. Low molecular weight EO s are very soluble in HPFP but over a temperature range that is not easily accessible during manufacture of formulations or storage/use of the resultant products. Higher molecular weight hydroxyl terminated EO s are largely – and for most practical purposes – insoluble in HPFP. Indeed, for molecular weights greater than 1500 g mol⁻¹, the temperature required to melt the polymer is higher than the LCST and therefore samples are always biphasic, either solid/liquid or liquid/liquid.

In stark contrast, mono-methyl (and thus mono-hydroxy-) and di-methyl end-capped EOs are fully miscible with HPFP over the

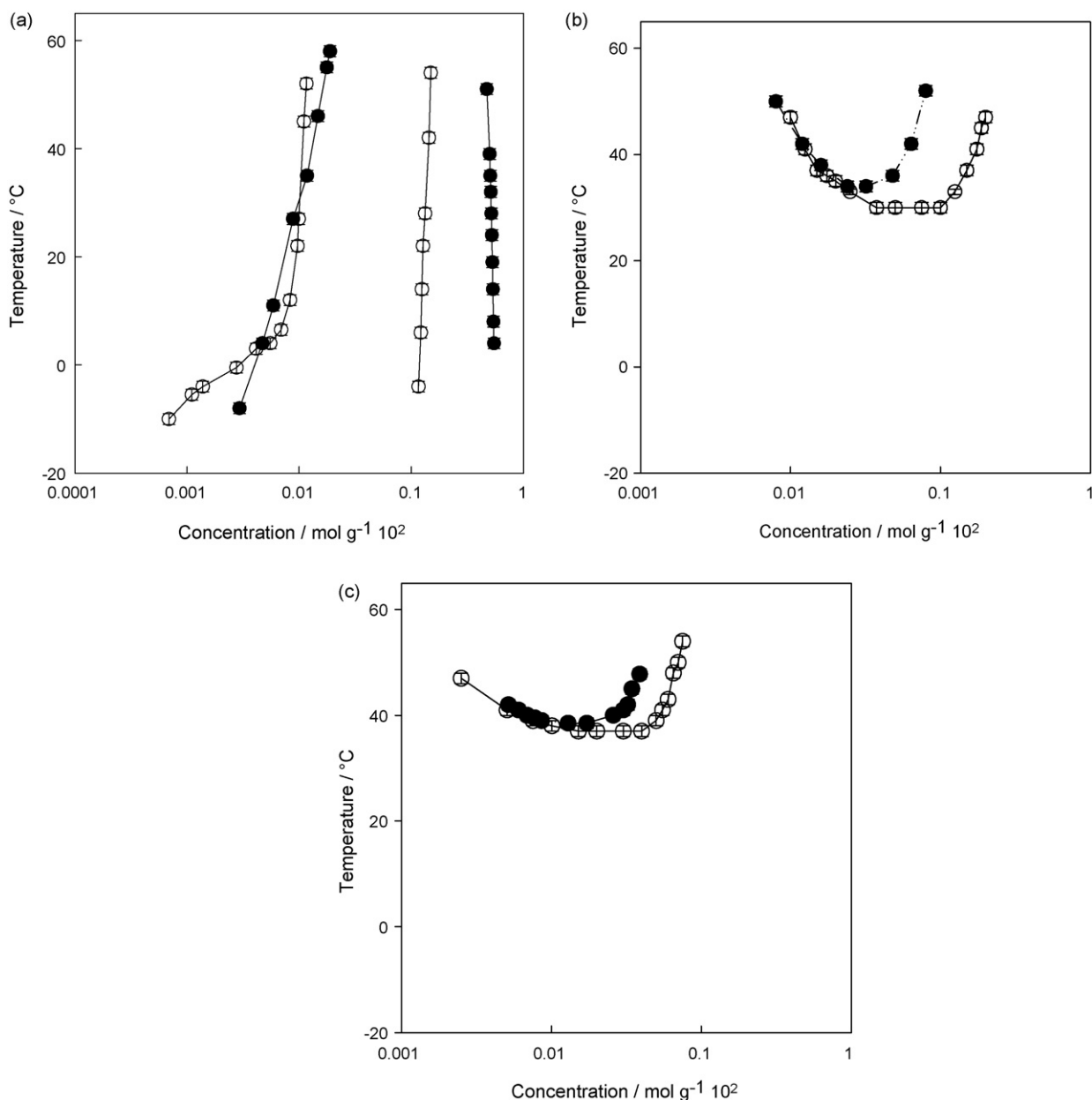


Fig. 2. (a) Phase behaviour of poly(ethylene glycol)-based surfactants in HPPF and representative comparitors in HPPF C₁₂EO₃ (filled symbols) and dodecane (open symbols). (b) Phase behaviour of poly(ethylene glycol)-based surfactants in HPPF and representative comparitors in HPPF C₁₂EO₁₀ (filled symbols) and EO 400 g mol⁻¹ (open symbols). (c) Phase behaviour of poly(ethylene glycol)-based surfactants in HPPF and representative comparitors in HPPF C₁₂EO₂₃ (filled symbols) and EO 1000 g mol⁻¹ (open symbols).

same temperature and concentration ranges, suggesting that the phase behavior is dominated by end-group/solvent interactions. By substituting HPPF for the fully fluorinated analogue perfluoropentane (PFP), the ability of these end-groups to interact with the solvent may be systemically varied and an LCST-type behavior can be induced in the previously fully miscible mono- and di-methyl end-capped EOs; concomitantly, the LCST of the di-hydroxyl end-capped EOs is driven to lower temperatures (Côte et al., 2008).

All the LCST data from the dihydroxyl ended polymers presented in Fig. 1(a) have been re-plotted in Fig. 1(c) in terms of the concentration of the end-groups. In this representation, samples at the same total polymer concentration will have an end-group concentration that is dependent on molecular weight. Accordingly, each plot on Fig. 1(c) arises due to a range of molecular weights at a fixed total concentration. However, the mono-hydroxyl data do not superimpose on the di-hydroxy data, implying that there must also

be an underlying molecular weight effect. Most importantly, an increase in the number of hydroxy end-groups for a given polymer concentration, results in a decrease in the LCST and a contraction of the solubility window.

3.2. Poly(ethylene oxide)-based surfactants

The phase behaviour of Brij30 (C₁₂EO₄), C₁₂EO₁₀ and Brij35 (C₁₂EO₂₃) surfactants was also investigated in a likewise manner; results are shown in Fig. 2(a–c). For comparison, the phase behaviours of the molecular “fragments” of the excipient, viz. dodecane and ethylene glycol are also presented. C₁₂EO₄ – having the shortest EO headgroup – shows truncated hour-glass phase behaviour, a phase behaviour that is not that dissimilar to that observed for dodecane. C₁₂EO₁₀ and C₁₂EO₂₃ on the other hand, display LCST-type behaviour, with a melting curve (not shown),

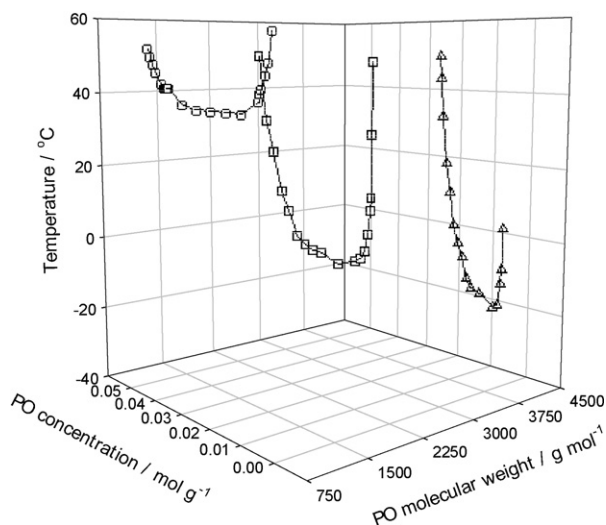


Fig. 3. Phase diagram of poly(propylene oxide) PO 1000 g mol⁻¹ (circles), 2000 g mol⁻¹ (squares) and 4000 g mol⁻¹ (triangles) in HPFP.

again not that dissimilar to the observed behaviour of the appropriate EO fragment. Clearly, the dodecane fragment dominates the behaviour of the excipient bearing the short EO chain, especially at lower concentrations, whilst the ethylene glycol fragment dominates the behaviour of the excipients bearing the longer EO chain.

3.3. Poly(propylene oxide) homo-oligomers

Low molecular weight poly(propylene oxide) polymers however, exhibit much higher solubilities and over workable temperature windows, indeed samples with molecular weight of 400 and 750 g mol⁻¹ – even with hydroxyl end-groups – are entirely miscible with HPFP over the entire range of temperature and concentration. The phase behavior in HPFP of higher molecular weight PO – Fig. 3 – does however exhibit the pronounced concentration dependence at the extremes of concentration as in the EO case, Fig. 1(b), but with one striking difference; the LCST now *decreases* with *increasing* molecular weight, the opposite to that observed for EO. Poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) copolymers

The phase behavior of two samples of poloxamer copolymers consisting of a low molecular weight copolymer EO₂PO₁₆EO₂ and a higher molecular weight copolymer EO₂₀PO₇₀EO₂₀ has also been recorded, Fig. 4. The molecular weights of the PO block in EO₂PO₁₆EO₂ and EO₂₀PO₇₀EO₂₀ are ~925 and 4050 g mol⁻¹ respectively; the striking effects of the EO blocks (and their –OH end-groups) may be observed by comparison with equivalent molecular weight homopolymer PO analogues, *viz.* 1000 and 4000 g mol⁻¹. For the lower molecular weight PO comparison, the effect of the EO block is a modest reduction (~15 °C) in the LCST over the majority of the concentration range, whereas for the larger copolymer the reduction is slightly greater (~20 °C). The phase diagram at higher concentrations of EO₂₀PO₇₀EO₂₀ has not been determined due to the solid nature of the sample.

4. Discussion

The presence of polar groups within the oligomeric or polymeric structure enhances the solubility of oxygen and nitrogen containing polymers in HPFP (Griffiths et al., 2005; James, 2005).

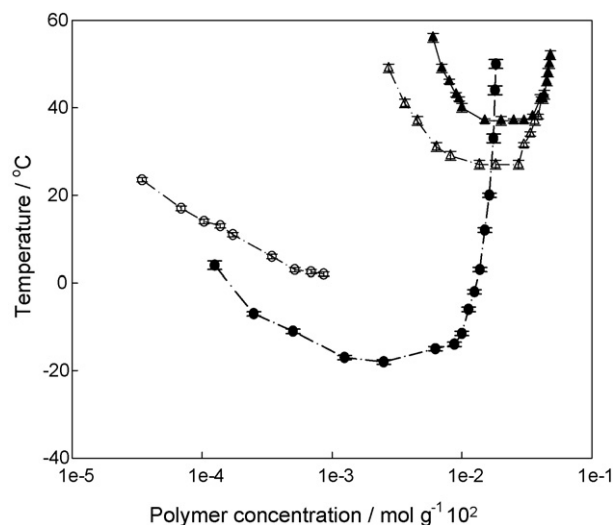


Fig. 4. Phase diagram of Pluronic copolymers EO₂PO₁₆EO₂ (open triangles), EO₂₀PO₇₀EO₂₀ (open circles), PO 1000 g mol⁻¹ (filled triangles) and PO 4000 g mol⁻¹ (filled circles) in HPFP.

The increase in solubility arises due to the presence of a specific, temperature-dependent interaction between the polar groups on the backbone of the polymer (*e.g.* the ether group of the EO moiety) and the –CH– group of the HPFP (Griffiths et al., 2005). The LCST behaviour may be rationalised by invoking an argument similar to that accounting for the aqueous behaviour, *viz.*, with increasing temperature, the EO coil adopts a less polar conformation reducing the (favourable) interactions that promotes solubility, thus leading to phase separation; a process that may be facilitated by the addition of a perfluorinated analogue (Côte et al., 2008). Accordingly, the phase behaviour is strongly dependent on the nature of the end-groups with both mono-methyl and di-methyl capped EOs exhibiting no LCST over the same wide ranges of temperature and composition over which LCST behaviour was exhibited by the di-hydroxyl EOs. Clearly, the hydroxyl groups exhibit a less favourable interaction with the solvent compared with the methyl groups, and this is manifested in terms of the molecular weight dependence of the di-hydroxyl phase behaviour—the LCST increases with increasing molecular weight as the number of unfavourable end-group/solvent contacts is reduced. The fact that there is a pronounced difference between the samples with “no” and “any” hydroxyl groups suggests that the phase separation is driven in part by a process of aggregation through the hydroxyl groups.

This model can then be simply extended to the interpretation of the phase behaviour of EO-based surfactants, tetra(ethylene glycol) monododecyl ether (C₁₂EO₄), deca(ethylene glycol) monododecyl ether (C₁₂EO₁₀) and poly(ethylene oxide)-23-monododecyl ether (C₁₂EO₂₃). For the two higher EO content materials – C₁₂EO₁₀ and C₁₂EO₂₃ – the phase behavior is only slightly different to that exhibited by the closest match EO analogues, EO 400 and EO 1000 g mol⁻¹, where in both cases the LCST–composition curve is largely unchanged in form, but merely shifted by a few degrees to slightly higher temperature values. If one considers the dodecyl group as a replacement for one of the hydroxyl groups compared to the di-hydroxyl comparator, the resultant increase in the solubility of the surfactant, is in agreement with observations of the EO homopolymers. However, these two surfactants still exhibit an LCST-type phase diagram implying that the dodecyl group does not interact as favorably with the solvent as the smaller methyl group (*i.e.* as a comparison with the mono-methyl and di-methyl EO

derivatives). Unlike the LCST-type behaviour shown by $C_{12}EO_{10}$ and $C_{12}EO_{23}$, $C_{12}EO_4$ exhibits truncated hour-glass phase behaviour, *i.e.* the shape of its phase behaviour is dominated by the dodecane moiety, especially at the lower concentration range. However, the EO groups promote the solubility of the dodecane moiety at higher concentrations, as evidenced by the wider solubility windows, implying that the presence of EO groups modify the χ -temperature behaviour to a much greater degree at higher temperatures. Clearly, methyl groups at the *terminus* of the polymer chain have a significant effect on the phase behaviour, as seen by comparisons to the hydroxyl and dodecyl terminated analogues. The effects of adding methyl groups to the EO *backbone* may be probed by comparing the phase behaviours of the EO and PO homopolymers, and ultimately, their copolymers. The most striking observations when comparing the EO and PO homopolymers are the opposite molecular weight dependencies of the LCST, and the much greater solubilities of the PO homopolymers. The decreasing LCST with increasing molecular weight for PO implies the effects of the hydroxyl end-groups are significantly weaker than in the EO case, whereas the higher solubility reflects the presence of the methyl groups. One might conclude therefore that the PO adopts a conformation in solution that maximises the exposure of the methyl groups to the HPFP whilst minimising that of the hydroxyl groups. Taking the EO and PO homopolymer behaviors together, one might hypothesize that the presence of ether oxygens promote the solubility of the polymer at lower temperatures but at higher temperatures there is a competing association process that ultimately induces the phase separation. Addition of methyl groups to the backbone weakens this tendency leading to higher the significantly higher solubility of the PO. This hypothesis also accounts for the lowering of the LCST for $EO_2PO_{16}EO_2$ copolymer compared with $EO\ 1000\ g\ mol^{-1}$, *viz.* “removal” of the CH_3 - groups. The higher molecular weight copolymer data is however, most interesting; the LCST for $EO_{20}PO_{70}EO_{20}$ is much higher than for both the simple homopolymer comparitors—in terms of the equivalent homopolymers, EO_{110} ($4800\ g\ mol^{-1}$) is insoluble in HPFP whereas PO_{110} ($5800\ g\ mol^{-1}$) is also predicted to exhibit a low solubility (*Note:* PO $4000\ g\ mol^{-1}$ is presented in Fig. 4 but the LCST decreases with increasing molecular weight thus the solubility of PO $6000\ g\ mol^{-1}$ would be even lower). Further work is on-going to establish the origin of this apparently peculiar behavior. The results reported here serve to illustrate the many interesting features of the solubility of polymers and other common excipients in fluorinated liquids.

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