Effect of molecular weight and end-group nature on the solubility of ethylene oxide oligomers in 2H, 3H-decafluoropentane and its fully fluorinated analogue, perfluoropentane

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Abstract

Fluorinated liquids possess high chemical and physical stability, are tolerated by the human body and, therefore, show great promise in biomedical fields; however, they require extensive formulation. Phase diagrams are reported here for a series of ethylene oxide oligomeric additives in 2H,3H-perfluoropentane (HPFP), a non-chlorofluorocarbon fluorinated liquid regarded as a model propellant for pressurized metered-dose inhalers. Over a wide range of temperatures and concentrations, dihydroxyl end-capped poly(ethylene glycols) (PEGs) exhibited a lower critical solution temperature (LCST) that was strongly molecular weight dependent. In contrast, monomethyl (and thus monohydroxy) and dimethyl end-capped poly(ethylene oxides) were fully miscible with HPFP over the same temperature and concentration ranges, suggesting that the phase behaviour was dominated by end-group/solvent interactions. By systematically substituting HPFP for the fully fluorinated analogue perfluoropentane, the ability of these end-groups to interact with the solvent was perturbed and LCST-type behaviour was induced in the previously fully miscible monomethyl and dimethyl end-capped PEGs. Concomitantly, with increasing perfluoropentane content, the LCST of the dihydroxyl end-capped PEGs was driven to lower temperatures. Therefore, the phase behaviour of these systems may be controlled by 'tuning' the end-group structure of the ethylene oxide oligomers, and varying the hydrogen bonding capabilities of the fluorinated solvents.

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Introduction

Fluorinated systems are remarkably versatile, finding applications as, for example, cleaning solvents for circuitry in the electronic industry or heat-transfer medium in the refrigerant industry (Lemal 2004). Recently, they have been the focus of much attention for pharmaceutical applications, being developed as blood substitutes (Riess 2002), contrast agents for ultrasound imaging (Sanchez et al 1995; Riess 2003), liquid ventilation (Greenspan et al 2000), or pressurized metered-dose inhalers (Rogueda 2003). Indeed, fluorocarbons possess unique physical and chemical properties that make them good candidates for use in biological systems and pharmaceutics. Chemical inertness is ensured by the enhanced strength of the C-C bond in fluorocarbons, and their helical conformation shields the chain from attacks by reagents (Rigby & Bunn 1949). Their acute toxicity was found to be no greater, and was sometimes even lower, than their hydrogenated equivalents (Riess & Krafft 1998). They exhibit low surface tension, low cohesive energy density, high compressibility and high gas-solubilizing capabilities (Krafft & Riess 1998; Riess & Krafft 1999). Hydrofluorocarbons are also environmentally much less damaging than chlorofluorocarbons, but there continues to be a great need to reformulate many materials using hydrofluorocarbons (Emmen et al 1999; McCulloch 1999; Ellis 2000).

In the case of pressurized metered-dose inhaler formulations, 2H,3H-perfluoropentane (HPFP) is found to be a suitable model propellant to replace chlorofluorocarbons (Rogueda 2003). Being both hydrophobic and lipophobic, hydrofluorocarbons are generally regarded as poor solvents and the addition of additives (excipients) is often required to turn them into useful products. However, studies investigating the solution properties of even common excipients in such solvents are scarce.

The phase behaviour of ethylene oxide polymers in water has, however, received much interest because it exhibits a lower critical solution temperature (LCST) (Saeki et al 1976; Kjellander & Florin 1981; Craig 1995; Hammouda et al 2004). The solubility of poly(ethylene oxide) (PEO) in water is an anathema in itself since the next homologues polybutylene and polymethylene are insoluble in water (Israelachvili 1997; Ashbaugh & Paulaitis 2006). Short ethylene oxide chains (degree of polymerization m ≤ 48) are completely miscible in water even at high temperatures; for slightly longer chains, a closed loop solubility gap is observed, and for m > 180, only a LCST is observable. PEO solution properties in water critically depend on its molecular weight, and the clouding temperature decreases with an increase of the chain length (Saeki et al 1976; Kjellander & Florin 1981). Various arguments have been proposed to account for the solubility of PEO in water and the occurrence of LCST-type phase separation (Samii et al 1991): the structured water model was proposed by Kjellander & Florin (1981); Goldstein's approach proposed the existence of intermolecular hydrogen bonds between PEO and water, and their destruction modifies the solvent–solvent and solute–solvent interactions (Hirschfelder et al 1937; Goldstein 1984); Karlström (1985) discussed solubility and phase separation in terms of the large dipole moment residing on the preferred gauche conformation of PEO at lower temperatures, a contribution that is removed at higher temperatures since the non-polar isomers have higher statistical weight.

The phase behaviour of PEO polymers in solvents other than water has received less attention. However, the clouding phenomena of PEO has been reported in solvents such as formamide, *tert*-butyl acetate (Saeki et al 1976), carbon dioxide (Kazarian et al 1996; O'Neill et al 1998; Drohmann & Beckman 2002) and some organic solvents (da Silva & Loh 1998; Spitzer et al 2000, 2002a, b).

In this work, we focus on the behaviour of low molecular weight poly(ethylene glycols) (PEGs) in the model propellant HPFP and in mixtures with perfluoropentane (PFP). The effect of the end-group nature on the solubility of the PEGs was investigated using monomethyl and dimethyl end-capped PEG derivatives.

Materials and Methods

Materials

Dihydroxy-poly(ethylene glycol), PEG of nominal molecular weights $M_n = 200, 300, 400, 600, 1000$ and $1500 \, g \, mol^{-1}$, poly(ethylene glycol) monomethyl ether $350 \, g \, mol^{-1}$ and $500 \, g \, mol^{-1}$ and poly(ethylene glycol) dimethyl ether $250 \, g \, mol^{-1}$, were purchased from Acros Chemicals, Loughborough, UK, Fluka and Sigma-Aldrich, Gillingham, UK. All polymers were dried in a 60°C oven for 72 h before sample preparation, but otherwise used without further purification. This drying procedure had a minimal effect on the molecular weight distribution. Molecular weights were confirmed by Atmospheric Pressure Chemical Ionization (APCI) on a Waters LCT premier XE system; full molecular weight characteristics are presented in Table 1.

The nature of the end-groups for monomethyl and dimethyl end-capped PEGs were confirmed by solution ^{1}H nuclear magnetic resonance. HPFP (Apollo Scientific, Stockport, UK)

Table 1 Molecular weight characteristics of the poly(ethylene glycol) (PEG) polymers used in this study

Polymer	$M_N \, (g \, mol^{-1})$	$M_W \, (g \, mol^{-1})$	Polydispersity
PEG200	280	325	1.16
PEG300	407	430	1.05
PEG400	468	490	1.05
PEG600	630	660	1.05
PEG1000	950	985	1.04
Dimethyl end-capped PEG250	385	415	1.07
Monomethyl end-capped PEG350	430	460	1.06

was washed first with acidic and then basic alumina, filtered, dried and stored over molecular sieves; PFP was dried and stored over molecular sieves. For experiments investigating the impact of moisture on the systems, Millipore grade water was used.

Onset of phase separation

Samples were prepared by mass on a 3-g scale in glass screw-top vials, sealed with polytetrafluoroethylene tape to prevent solvent evaporation, then wrapped in parafilm to protect against water penetration. For the ternary phase diagrams, the fully miscible HPFP and PFP were first mixed in the appropriate ratio and added to polymer to yield a constant polymer concentration of 3 wt% and a range of HPFP/PFP ratios. 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 with constant agitation until the temperature reached 60°C.

For temperatures above room temperature, an approximate LCST was determined by stepping the temperature in 5°C intervals, and equilibrating the sample at each temperature for 20 min. Subsequently, the sample was allowed to cool below this temperature and a more accurate LCST was recorded, equilibrating each sample for > 1 h at 1°C intervals. For temperatures below room temperature, a similar protocol was employed but the LCST was determined principally from a controlled cooling cycle.

An iterative protocol was adopted to map out the concentration profile to span the polymer concentration range ($0.1 \, wt\% < C_{polymer} < 90 \, wt\%$), with the actual concentrations selected being determined by the shape of the phase transition profile, that is a lower frequency of data points where the curve was shallowest and higher where the profile exhibited a more pronounced concentration dependence.

Statistical analysis

The LCST measurements were performed on a minimum of two samples at each concentration, and the LCST recorded from a minimum of two heating–cooling cycles per sample. The LCST quoted is, therefore, a sample of at least six measurements. The precise composition of every sample was known, having been prepared by weight to an accuracy of ~0.5 mg polymer per 3 g solvent.

Quantification of polymer concentration in the PEG200/HPFP system

A dry-weight method was employed to quantify the polymer concentration in the two separate layers. A series of 20 wt% PEG200/HPFP samples (in triplicate) were prepared and equilibrated for 24 h in a water bath at the following temperatures: 15°C, 20°C, 25°C, 30°C, 35°C, 40°C and 45°C. All systems phase separated into two layers as expected; the upper and lower layers were separated using a plastic syringe with a flat-ended needle and transferred to pre-weighed vials. These were placed in a 60°C oven until constant mass.

Statistical analysis

These measurements were performed in triplicate at each temperature, and the determined polymer concentrations recorded to an accuracy of ~0.5 mg. Differences between individual treatments were statistically identified using the Kruskal–Wallis test (in conjunction with Dunn's post-hoc test). A probability level that was less than 0.05 denoted significance.

Preparation of PEG 200 in the HPFP/water system

Millipore water was added to aliquots of previously dried PEG200 before the sample preparation. The amounts of added water were such that: $C_{polymer} = 3$ wt% and $0 < [water] < 3000$ ppm. The pre-mixing of water with PEG200 was chosen for practical purposes because PEG200 and water are fully miscible, which is not the case for water and HPFP (the maximum solubility of water in HPFP is 390 ± 40 ppm; Rogueda 2003). The cloud point was recorded visually as previously described.

Results

Behaviour of dihydroxy-poly(ethylene glycol) 200 (PEG200) in HPFP and impact of the presence of moisture

Figure 1 presents the temperature–concentration profile of dihydroxyl end-capped PEG200 in HPFP, determined both by visual assessment and by polymer concentration quantification. On heating, clear monophasic solutions of dihydroxyl end-capped PEG200 in HPFP became cloudy and then separated over time into a less dense polymer-enriched upper phase and a more dense polymer-depleted lower phase ($\rho_{HPFP} = 1.58$ g cm³, $\rho_{PEGs} = 1.12$ g cm³), that is they demonstrated LCST-type behaviour, the critical LCST being the temperature at the minimum of the phase boundary curve (Jonsson et al 1998). 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 (Figure 1). The two methods give superimposable phase boundaries. However, the minimum of the curve was not experimentally accessible using the dry-weight method.
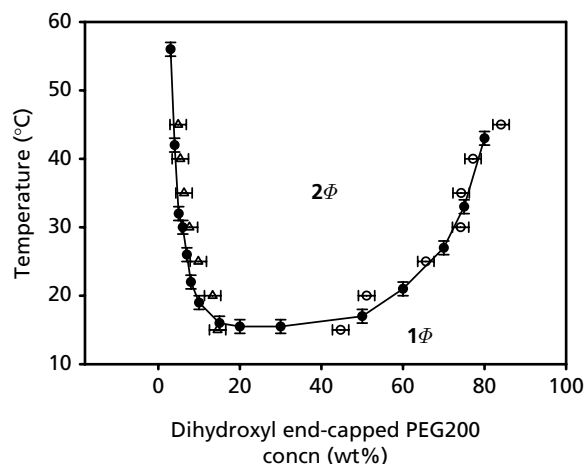

Figure 1 Temperature–polymer concentration phase diagram of dihydroxyl end-capped PEG200 in HPFP; closed symbols correspond to the visually assessed cloud point; open symbols correspond to the mass balance analysis of the upper (circles) and lower (triangle) phases.

Table 2 Clouding temperature for 3 wt% (dihydroxyl end-capped) poly(ethylene glycol)200 in 2H, 3H-perfluoropentane with water content ranging from 0 to 3000 ppm

Water (ppm)	Clouding temperature (°C)
0	47 ± 1
125	47 ± 1
250	46 ± 1
500	44 ± 1
1000	34 ± 1
2000	12 ± 1
3000	0 ± 1

The phase behaviour of PEG in HPFP was very sensitive to moisture. Table 2 presents sample data for the clouding temperature for a system comprising 3wt% dihydroxyl end-capped PEG200 and various amounts of water. As seen in Table 2, minimum amounts of water had a significant impact on the clouding temperature, driving it to lower temperatures. A shift of nearly 50°C was observed when 3000 ppm water was present, underlining the necessity of drying the polymers.

Molar mass dependence of dihydroxy-poly(ethylene glycols) solubility

Phase boundaries were visually investigated for various molecular weights of dihydroxyl end-capped poly(ethylene glycols), ranging from 300 to 1500 g mol⁻¹, and the results are presented in Figures 2 and 3.

As seen in Figure 2, LCST-type phase boundaries were observed for dihydroxyl end-capped PEGs of $300 <$ molecular weight < 1500 g mol⁻¹. The cloud-point temperature was strongly concentration and molecular weight dependent for all molecular weights, displaying a sharp increase towards
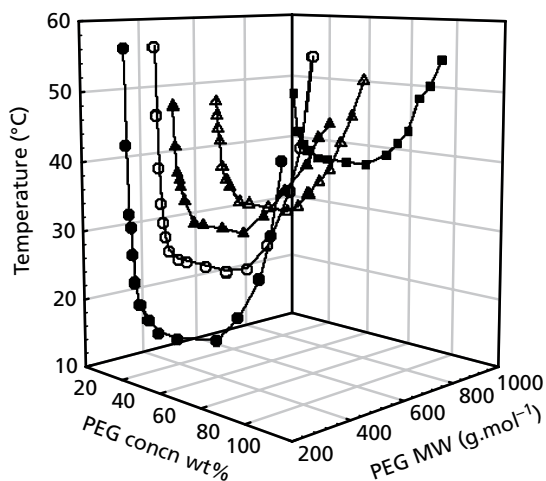
Figure 2 Temperature–polymer concentration phase diagram of dihydroxyl end-capped PEG200 (closed circles), PEG300 (open circles), PEG400 (closed triangles), PEG600 (open triangles) and PEG1000 (closed squares) in HPFP. Errors bars in the temperature axis have not been included for clarity, these estimates being slightly greater than the size of the symbol. For a more precise representation, see Figure 1.
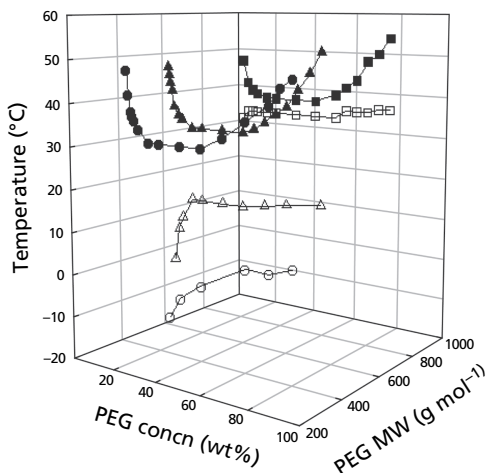

Figure 3 Superimposed cloud point (closed symbols) and melting temperature curves (open symbols) for PEG400 (circles), PEG600 (triangles) and PEG1000 (squares) in HPFP.

both very low and very high polymer concentrations. As shown on Figure 3, PEG400, PEG600 and PEG1000 were also found to exhibit a two-phase region at lower temperatures, coinciding with their melting behaviour. At low temperatures, such systems were biphasic, consisting of a coexisting waxy solid and a liquid. As the temperature increases through the melting point of the polymer (5–8°C for PEG400, 17–22°C for PEG600 and 35–40°C for PEG1000), samples first become monophasic before reaching the higher cloud-point boundary presented in Figure 2. As seen in Figure 2, an increase in molecular weight drove the LCST higher, the critical temperature being 15°C, 25°C, 30°C, 32°C and 37°C for PEG200, PEG300, PEG400, PEG600 and PEG1000, respectively, implying a greater solubility window.

However, the melting curve was also strongly molecular weight dependent and as the molecular weight was increased, these two curves coincided. For dihydroxyl end-capped PEG of MW 1500 g mol⁻¹, the two behaviours collapsed and the temperature required to melt the polymer was higher than its cloud-point phase boundary; therefore samples were always biphasic, either solid/liquid or liquid/liquid. For the lowest dihydroxyl end-capped PEG100, samples were always liquid/liquid biphasic and we hypothesize, based on molecular weight scaling, that a monophasic liquid state exists but at an experimentally inaccessible temperature range.

Considering the low molecular weights and narrow molecular weight range of the polymers investigated (~2 to ~23 ethylene oxide units), the very different solubilities and widely different phase behaviours are likely a manifestation of end-group effects rather molecular weight per se. To test this premise, the solubility of monomethyl and dimethyl end-capped PEG species of comparable molecular weights were investigated.

Effect of end-group nature on PEG solubility

In contrast to dihydroxyl end-capped PEG200, which showed a cloud-point phase separation profile, monomethyl end-capped PEG350 and dimethyl end-capped PEG250 were fully miscible with HPFP over the entire range of concentrations and temperatures investigated. The presence of hydroxyl end-groups on the polymer therefore reduced its solubility in HPFP and methylation prevented the phase separation.

Dihydroxyl, monomethyl and dimethyl end-capped PEGs in HPFP/PFP mixtures

Addition of the fully fluorinated solvent PFP to solutions of dihydroxyl end-capped PEG in HPFP resulted in a lowering of the phase separation temperature, thus reducing the solubility domain. Addition of PFP to solutions of monomethyl and dimethyl poly(ethylene glycols) in HPFP induced phase separation. Figure 4 presents the ternary diagrams for solutions of dihydroxyl end-capped PEG200, monomethyl end-capped
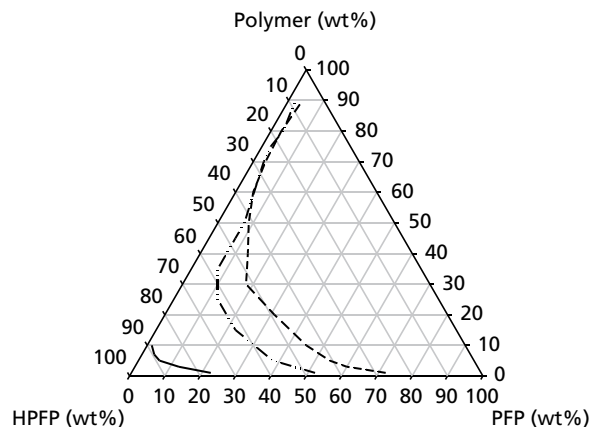

Figure 4 Ternary phase diagrams recorded at 20°C for PEG300 (solid line), monomethyl end-capped PEG350 (dashed-dotted line) and dimethyl end-capped PEG250 (dashed line).

PEG350 and dimethyl end-capped PEG250 in binary HPFP/ PFP solvents at 20°C, although temperature (20–45°C) had a negligible impact on the location of the phase boundaries. Figure 5 shows the cloud-point temperature as a function of the solvent content, at a constant polymer concentration of 3 wt%. This polymer concentration was chosen arbitrarily such that a significant change in the cloud point would be experimentally accessible.

In all cases, the presence of PFP induced phase separation, but the amount of PFP that the system could tolerate before dephasing depended on the nature of the polymer end-group. For a constant polymer concentration, the order in which higher amounts of PFP can be incorporated into a polymer/HPFP system before phase separation occurs was dimethyl > monomethyl > hydroxy end-capped PEG. For the monomethyl and dimethyl end-capped PEG, this effect was more prominent in the region diluted in polymer, and from 50 wt% polymer onwards, the two curves overlapped. This clearly demonstrates the importance of the end-group nature on the behaviour of such small polymers. As seen previously, further fully fluorinated solvent can be incorporated while keeping a monophasic sample as the methylation of the end-group was increased. However, as seen in Figure 5, the slopes of the cloud-point curves became steeper as the level of methylation of the end-group was increased. Although the amount of PFP that can be incorporated before phase separation occurred increased with the end-group methylation, the PFP range within which the cloud-point drop was observed is much narrower.

The three polymers investigated here were not commercially available in an identical molecular weight and it must therefore be questioned whether the slight variation in molecular weight could be responsible for the observed PFP uptake. To differentiate end-group and molecular weight effects, the same measurements were performed using dimethyl end-capped PEG 500, and its phase boundary was found to lie between monomethyl end-capped PEG350 and dimethyl end-capped PEG250. Therefore, dimethyl end-capped PEG500 would tolerate the presence of smaller amounts of

PFP than its lower molecular weight equivalent, but still higher than the monomethyl end-capped PEG of lower molecular weight. The results observed were therefore not a molecular weight artefact but could be confidently attributed to an end-group effect.

Discussion

Regions of high solubility were found to exist for dihydroxyl end-capped PEG polymers with molecular weight of between 300 and 1000 g mol^{-1} in HPFP, albeit under limiting temperatures. Strictly speaking, given the low degrees of polymerization (~4 to ~23), these polymers should be referred to as oligomers. Polymers are generally regarded as having very limited solubility in hydrofluoroalkanes. Indeed, it was found in this study that once the molecular weight exceeded 1000 g mol^{-1}, ethylene oxide polymers were insoluble in HPFP. However, in the lower extreme, the dimer of ethylene glycol was also found to be insoluble in HPFP. There was therefore a narrow molecular weight window for which these oligomers exhibit regions of high solubility. A LCST was observed for these systems and phase separation occurred as the temperature was increased, with LCST increasing with molecular weight. LCST-type behaviour and closed-loop phase diagrams for ethylene oxide polymers in water were reported by Saeki et al (1976), but for higher molecular weights than studied here, typically from 2180 to 1 020 000 g mol^{-1}. The LCST was found to decrease with increasing degree of polymerization of the polymer and lay mostly at temperatures above the boiling point of water. They also observed the occurrence of both upper critical solution temperature and LCST in the organic solvent *tert*-butyl acetate for molecular weights ranging from 8000 to 21 200 g mol^{-1}. LCST behaviour is usually observed for systems whose mixing is exothermic, implying strong and enthalpically favoured solute–solvent interactions. Such interactions could arise from strong hydrogen bonds between the hydrogen atoms in the solvent and lone electron pairs on PEG oxygen atoms.

The LCST was found to be highly molar mass dependent for hydroxyl end-capped PEGs in the HPFP system. Contrary to data reported in water and organic solvents, the LCST increased with increasing molecular weight, an effect that is proposed to be due to the hydroxyl end-groups, whose presence reduced the solubility. As the molecular weight was increased, the end-group effect becomes 'diluted' and therefore less important. The temperature required to destabilize the system was increased, but at the same time the melting point was also increased, narrowing the width of the solubility temperature window. This was especially pertinent for PEG1500, for which the melting and cloud-point curves overlap, leading to immiscibility over the entire range of concentration and temperature investigated. The presence of minimum amounts of water was found to dramatically decrease the cloud point of the systems. Dihydroxyl end-capped PEG200 was driven out of the HPFP solution by small quantities of water. The PEG–water interaction is stronger than the PEG–HPFP one, and once in the presence of moisture PEG tends to partition out of the fluorinated liquid to form an upper polymer-rich aqueous solution. It is not excluded that
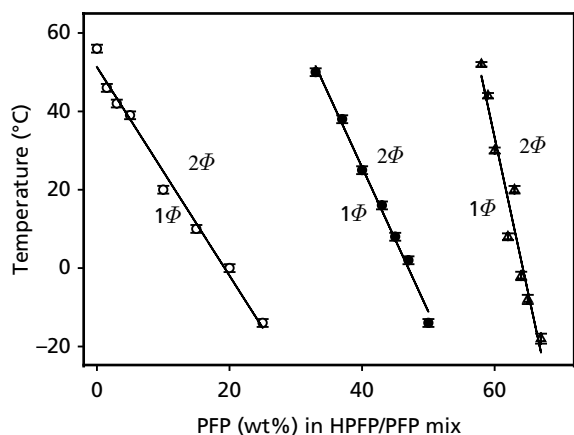

Figure 5 Cloud-point temperatures of PEG300 (open circles), monomethyl end-capped PEG350 (closed circles) and dimethyl end-capped PEG250 (open triangles) in the HPFP/PFP binary solvent mixtures as a function of the amount of PFP present.

some HPFP molecules may be driven by PEG into this new phase, but most HPFP was found to remain free of polymer in the lower phase.

Evidence for the end-group effect may be seen with the monomethylation and dimethylation of the hydroxyl end-groups with which full miscibility was observed in HPFP, for oligomers of very similar molecular weights. It is proposed that the solute–solute attractions via the terminal hydroxyl groups are reduced or fully blocked, and the hydrogen bond driven solute–solvent attraction between the ether oxygen and the partially fluorinated solvent hydrogen remains, favouring the dissolution of monomethyl and dimethyl end-capped PEGs in HPFP. The presence of oxygen in the polymer was found to be a prerequisite to achieve solubility (James 2006), but the presence of alcohol groups at the end of the chain does not enhance this characteristic, whereas their methylation favours it. One may envisage a situation where moderate polarity along the polymer backbone (CH_2CH_2-O-) will promote a favourable interaction with the polar solvent, CHFCHF, yet a terminal polar group on the polymer may offer a route to a stronger inter-polymer interaction. The molecular weight dependence of solubility, and thus the end-group effect, has already been reported by Spitzer et al (2002a, b) for the partition of dihydroxyl end-capped PEGs between water and organic solvents. A critical molecular weight above which the end-group contribution is removed occurred around $2000\,\mathrm{g\,mol}^{-1}$. However, for molecular weights as low as 300–$400\,\mathrm{g\,mol}^{-1}$, PEG was found to start favouring its partition into the organic phase. LCST for PEGs was also observed in super-critical CO_2 by Drohmann & Beckman (2002), who report that PEG solubility 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 with simple hydrocarbons, provided the oxygen was in a readily accessible position to CO_2. As a general finding, carbonyl groups enhance the solubility of the polymer in CO_2 by favourable cross-interactions, either by quadrupole (CO_2)–dipole (solute) interaction or Lewis acid/base, CO_2 being the Lewis acid (Kazarian et al 1996; Meredith et al 1996; Rind-fleisch et al 1996), a conclusion that resonates with those made here.

Monomethyl and dimethyl end-capped PEGs were found to present a cloud-point behaviour only when the partially fluorinated fluoroalkane HPFP is gradually replaced by the fully fluorinated PFP. PFP is fully miscible with HPFP, but has no solvation capability towards the ethylene oxide oligomers considered here. Indeed, the lack of any hydrogen-bond-donating capability of PFP was found to be crucial, so as to have sufficiently strong inter-actions with the ethylene oxide segments. Moreover, the addition of increasing amounts of PFP resulted in a sharp decrease of the cloud point. Although the amount of PFP that can be incorporated before phase separation occurred increased with the end-group methylation, the range of PFP amount within which the cloud-point drop was observed is much narrower as methlylation was increased. Such early precipitation of the polymer observed upon the addition a non-co-solvent is a method already used in pol-ymer fractionation (da Silva & Loh 1998; Spitzer et al 2002b). This mixed solvents study clearly shows that hydrogen bonding between the solvent and the solute, in competition with the end-group interactions, is the driving force behind the solubility of PEG oligomers in these fluorinated liquids of interest.

Conclusion

The solubility of ethylene oxide materials in model propel-lant HPFP is complex. Regions of very high solubility exist, contrary to the myth that such polymeric materials are largely insoluble in partially fluorinated media. It is hypothesized that a specific, temperature-dependent inter-action between the ether group of the ethylene oxide moiety and the -CHF group of the HPFP dominates the observed phase behaviour, along with a competing end-group effect that becomes less important as the molecular weight is increased. By suitably modifying the ethylene oxide end-groups and by tuning the hydrogen bonding capabilities of the solvents, some control of the phase behaviour may be achieved. It is hoped that this study will encourage theoretical activity on these fascinating and important systems to drive future developments in pharmaceutical applications.

References

Ashbaugh, H. S., Paulaitis, M. E. (2006) Monomer hydrophobicity as a mechanism for the LCST behavior of poly(ethylene oxide) in water. *Ind. Eng. Chem. Res*. **45**: 5531–5537

Craig, D. Q. M. (1995) A review of thermal methods used for the analysis of the crystal form, solution thermodynamics and glass transition behaviour of polyethylene glycols. *Thermochim. Acta* **248**: 189–203

da Silva, L. H. M., Loh, W. (1998) Polymer induced multiphase generation in water/organic solvent mixtures. Strategies towards the design of triphasic and tetraphasic liquid systems. *Chem. Commun*.: 787–788

Drohmann, C., Beckman, E. J. (2002) Phase behaviour of polymers containing ether groups in carbon dioxide. *J. Supercrit. Fluids* **22**: 103–110

Ellis, B. (2000) Environmental issues in electronics manufacturing: a review. *Circuit World* **26**: 17–21

Emmen, H. H., Hoogendijk, E. M. G., Klopping-Ketelaars, W. A. A., Muijser, H., Duistermaat, E., Ravensberg, J. C., Alexander, D. J., Borkhataria, D., Rusch, G. M., Schmit, B. (1999) Human safety and pharmacokinetics of the CFC alternative propellants HFC 134a (1,1,1,2-tetrafluoroethane) and HFC 227 (1,1,1,2,3,3, 3-heptafluoropropane) following whole-body exposure. *Regul. Toxicol. Pharmacol*. **32**: 22–35

Goldstein, R. E. (1984) On the theory of lower critical solution points in hydrogen-bonded mixtures. *J. Chem. Phys*. **80**: 5340–5341

Greenspan, J. S., Wolfson, M. R., Shaffer, T. H. (2000) Liquid ventilation. *Semin. Perinatol*. **24**: 396–405

Hammouda, B., Ho, D. L., Kline, S. (2004) Insight into clustering in poly(ethylene oxide) solutions. *Macromolecules* **37**: 6932–6937

Hirschfelder, J., Stevenson, D., Eyring, H. (1937) A theory of liquid structure. *J. Chem. Phys*. **5**: 896–912

Israelachvili, J. (1997) The different faces of poly(ethylene glycol). *Proc. Natl. Acad. Sci.* USA **94**: 8378–8379

James, R. (2006) *Phase behaviour of polymers in fluorinated media.* MSc Thesis, Cardiff University, UK

Jonsson, B., Lindman, B., Holmberg, K., Kronberg, B. (1998) *Surfactants and polymers in aqueous solution*. Wiley, Chichester, UK

Karlström, G. (1985) A new model for upper and lower critical solution temperature in poly(ethylene oxide) solutions. *J. Phys. Chem.* **89**: 4962–4964

Kazarian, S. G., Vincent, M. F., Bright, F. V., Liotta, C. L., Eckert, C. A. (1996) Specific intermolecular interaction of carbon dioxide with polymers. *J. Am. Chem. Soc.* **118**: 1729–1736

Kjellander, R., Florin, E. (1981) Water structure and changes in thermal stability of the system poly(ethylene oxide)-water. *J. Chem. Soc., Faraday Trans. 1*, **77**: 2053–2077

Krafft, M. P., Riess, J. G. (1998) Highly fluorinated amphiphiles and colloidal systems, and their applications in the biomedical field. A contribution. *Biochimie* **80**: 489–514

Lemal, D. M. (2004) Perspective on fluorocarbon chemistry. *J. Org. Chem.* **69**: 1–11

McCulloch, A. (1999) CFC and halon replacements in the environment. *J. Fluorine Chem.* **100**: 163–173

Meredith, J. C., Johnston, K. P., Seminario, J. M., Kazarian, S. G., Eckert, C. A. (1996) Quantitative equilibrium constants between CO_2 and Lewis bases from FTIR spectroscopy. *J. Phys. Chem.* **100**: 10 837–10 848

O'Neill, M. L., Cao, Q., Fang, M., Johnston, K. P., Wilkinson, S. P., Smith, C. D., Kersshner, J. L., Jureller, S. H. (1998) Solubility of homopolymers and copolymers in carbon dioxide. *Ind. Eng. Chem. Res.* **37**: 3067–3079

Riess, J. G. (2002) Blood substitutes and other potential biomedical applications of fluorinated colloids. *J. Fluorine Chem.* **114**: 119–126

Riess, J. G. (2003) Fluorocarbon-based injectable gaseous microbubbles for diagnosis and therapy. *Curr. Opin. Colloid Interface Sci.* **8**: 259–266

Riess, J. G., Krafft, M. P. (1998) Fluorinated materials for in vivo oxygen transport (blood substitutes), diagnosis and drug delivery. *Biomaterials* **19**: 1529–1539

Riess, J. G., Krafft, M. P. (1999) Fluorocarbons and fluorosurfactants for in vivo oxygen transport (blood substitutes), imaging and drug delivery. *Mater. Res. Soc. Bull.* **24**: 42–48

Rigby, A. H., Bunn, C. W. (1949) A room-temperature transition in polytetrafluoroethylene. *Nature* **164**: 583–585

Rindfleisch, F., DiNoia, T. P., McHugh, M. A. (1996) Solubility of polymersin supercritical CO_2. *J. Phys. Chem.* **100**: 15 581–15 587

Rogueda, P. G. A. (2003) HPFP, a model propellant for pMDI's. *Drug Dev. Ind. Pharm.* **29**: 39–49

Saeki, S., Kuwahara, N., Nakata, M., Kaneko, M. (1976) Upper and lower critical solution temperatures in poly(ethylene glycol) solutions. *Polymer* **17**: 685–689

Samii, A. A., Karlstrom, G., Lindman, B. (1991) Phase behavior of poly(ethylene oxide)-poly(propylene oxide) block copolymers in nonaqueous solutions. *Langmuir* **7**: 1067–1071

Sanchez, V., Greiner, J., Riess, J. G. (1995) Highly concentrated 1,2-bis(perfluoroalkyl)iodoethene emulsions for use as contrast agents for diagnosis. *J. Fluorine Chem.* **73**: 259–264

Spitzer, M., da Silva, L. H. M., Loh, W. (2000) Liquid biphase systems formed in ternary mixtures of two organic solvents and ethylene oxide oligomers or polymers. *J. Braz. Chem. Soc.* **11**: 375–380

Spitzer, M., Sabadini, E., Loh, W. (2002a) Entropically driven partitioning of ethylene oxide oligomers and polymers in aqueous/organic biphasic systems. *J. Phys. Chem. B* **106**: 12448–12452

Spitzer, M., Sabadini, E., Loh, W. (2002b) Poly(ethylene glycol) or poly(ethylene oxide)? Magnitude of end-group contribution to the partitioning of ethylene oxide oligomers and polymers between water and organic phases. *J. Braz. Chem. Soc.* **13**: 7–9