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Partitioning and phase equilibria of PEGylated excipients in fluorinated liquids

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ABSTRACT

Mixtures of common polymeric excipients and hydrofluoroalkane (HFA) liquids show rich and complex phase behaviour. Phase diagrams and phase compositions are reported for poly(ethylene glycol)s with varying levels of end-group methylation in mixed solvent systems consisting of the model propellant 2H,3H-perfluoropentane (HPFP) and the fully fluorinated analogue perfluoropentane (PFP). Studies have been performed as a function of molecular weight as well as end group chemistry (monomethyl, MM; dimethyl, DM; and dihydroxyl, DH), and for binary polymer mixtures in HPFP/PFP solvent systems. The solvent composition required to induce phase separation by addition of the non-hydrogen bonding PFP is strongly dependent on end-group concentrations. It shows a linear increase with increasing methylation, whilst remaining insensitive to OH group concentration in dihydroxylated PEG systems. For single polymer systems it is observed that strong partitioning of the polymer is observed, and changes in polymer concentration occurring across the phase diagram are a result of changing solvent partitioning between upper and lower phases. These solvent effects are dependent on the composition (wt% PFP) in the solvent mixture. The linear dependence of solvent composition required to induce phase separation at fixed polymer concentration on end group concentrations can be used to predict the phase behaviour for mixtures of monomethylated PEG with either dimethyl or dihydroxyl PEGs, whereas mixtures of dihydroxyl with dimethyl end-capped PEGs show a deviation from linear behaviour with dominance of the dihydroxyl end groups, which is reflected in the obtained phase diagrams. This study hence progresses understanding of factors that influence solubility of PEG-type polymers in HFAs and will facilitate the identification of predictive methodologies for formulation.

1. Introduction

Inhalation drug delivery provides an effective route for the targeted delivery of therapeutic molecules, traditionally for localised treatment of respiratory conditions, but increasingly for delivery via the lungs to the systemic circulation (Courrier et al., 2002; Chokshi et al., 2009). Pressurised metered dose inhalers are a critical part of this drug delivery process, and since the phasing out of chlorofluorocarbon propellants (CFCs) these rely on the use of volatile hydrofluoroalkane (HFA) liquids as propellant and solvent. Due to the differing solvent properties between CFCs and HFAs, FDA-approved formulations rarely work in HFA propellants and reformulation from CFCs represents a significant challenge. Co-solvents are sometimes incorporated to overcome surfactant solubility problems, although these may generate adverse effects resulting in a decrease in overall stability (Wu et al., 2008). A number of groups have reported their investigations into reformulating pMDIs. Courrier et al. discussed the two main types of pMDI formulation: (i) solution-based, whereby active ingredients are dissolved in the propellant; (ii) dispersion-based, where active ingredients are suspended in the propellant system (Wu et al., 2008). Ashayer et al. (2004) used atomic force microscopy (AFM) to investigate interparticle forces in pMDI formulations, showing that the cohesive forces that exist between particles result in dispersions being inherently unstable. Various approaches based on the formation of emulsion and microemulsion systems have also been proposed to provide a favourable environment for formulation of polar solutes (Chokshi et al., 2009). Low molecular weight surfactants and polymers are often required for dispersion formulation and ethylene oxide oligomers and polymers are commonly used as excipients for this purpose. The molecular weight and end group functionality of the polymer (poly(ethylene glycol), denoted PEG), the nature of the solvent, polymer concentration and temperature all contribute to the chemical interactions and physical characteristics which dictate phase behaviour. Studies of PEGs in non-aqueous systems are somewhat rare compared to the comprehensive literature in aqueous systems, but the work of Spitzer et al. (2000, 2002a,b) reports the effects of PEG and PEO partitioning between water and organic solvent phases, as a function of both molar mass of PEO and PEG materials and the magnitude of end-group contribution. This group

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have further reported their findings from thermodynamic investigations of these systems, having observed entropically driven partitioning effects in addition to the effects of end-groups and molecular weight (Spitzer et al., 2002a).

Previous work from the Cardiff group reported a combination of small-angle neutron scattering (SANS) and pulsed-gradient spin-echo (PGSE) NMR measurements, in conjunction with solubility studies to investigate the interactions that allow for PEG solubility in fluorinated liquids, including studies of related polymers and adsorption studies (Cote et al., 2008a,b; Paul et al., 2005a,b). In contrast to several earlier studies of PEG solubility in organic (Park and Kim, 1997; Staikos and Donods, 1986) solvents, phase separation of PEG at elevated temperatures was shown to follow lower critical solution temperature (LCST) type behaviour (analogous to aqueous solutions), suggesting temperature-dependent intermolecular forces akin to hydrogen bonding governing polymer solubility. Computer modelling of PEG in 2H,3H-perfluoropentane (HPFP) further showed a contribution from a specific interaction between the solvent hydrogen atom (highly acidic due to electron withdrawing effects of adjacent fluorine atoms) and lone pairs on the PEG oxygen atoms (Paul et al., 2005a). Cote et al. (2008b) found that with increasing molecular weight, an increase in the temperature required to destabilize the system was observed, in addition to an increased melting point which consequently narrows the solubility temperature window. The presence of hydrogen atoms in the solvent plays an important role in the phase behaviour, demonstrated by studies partially replacing HPFP with the fully fluorinated analogue perfluoropentane (PFP), which reduced the observed cloud points (Paul et al., 2005a; Cote et al., 2008b).

Cote et al. also described effects of end-group chemistry on the phase behaviour of comparable molecular weight poly(ethylene glycols) in the model propellant 2H,3H-perfluoropentane (HPFP) and the fully fluorinated analogue (PFP). Mono- and dimethylation of dihydroxyl end groups resulted in complete miscibility of similar molecular weight PEGs, attributable to enhanced solute–solvent hydrogen bonding interactions due to increased electronegativity on the terminal ether oxygen, coupled with decreased solute–solute interactions. Again, in mixed solvent systems, the addition of an increasing proportion of non-hydrogen bonding solvent resulted in a sharp decrease of the cloud-point. Increasing methylation caused an increase in the single phase region of the ternary phase diagram at 20 °C and an enhanced tolerance to addition of PFP (Cote et al., 2008b).

Research on these systems is driven by the need to achieve key predictive and prescriptive tools and techniques to describe the behaviour of excipients in these fluorinated solvents. Recently there has been increased effort to understand the molecular solvation effects in HFA solvents. Here, we investigate the temperature and molecular weight effects on the ternary phase behaviour of oligomeric PEGs with varying end-group functionality in HPFP/PFP, in order to further elucidate the influence of the contributing factors to the observed phase behaviour. In the two phase region of the phase diagram the total polymer and solvent distribution between two phases have been determined by dry weights analysis. In addition, we have been able to obtain the solvent and polymer partitioning using an NMR method. This represents the first comprehensive *quantitative* analysis of the partitioning behaviour in PEG/mixed HFA systems.

2. Experimental

2.1. Materials

Dihydroxyl end-capped poly(ethylene glycol) with average molecular weight 300 g mol^{-1} (DH PEG 300), 400 g mol^{-1} (DH PEG 400) and 600 g mol^{-1} (DH PEG 600), poly(ethylene glycol) dimethyl ether with average molecular weight 250 g mol^{-1} (DM PEG 250) and 500 g mol^{-1} (DM PEG 500) and poly(ethylene glycol) monomethyl ether with average molecular weight 350 g mol^{-1} (MM PEG 350) and 550 g mol^{-1} (MM PEG 550) were all obtained from Fluka, Sigma–Aldrich. Hence the general notation throughout the paper is X PEG Y, where X is a two letter notation for the end group character: dihydroxyl- (DH), dimethyl- (DM) or monomethyl (MM), and Y denotes polymer molecular weight. Polymers were dried for 72 h at 60 °C and stored in a dessicator prior to use. Mass spectroscopy was used to confirm the average molecular weights and molecular weight distributions. 2H,3H-Perfluoropentane (HPFP) and perfluoropentane (PFP) (Apollo Scientific) were filtered, dried and stored over molecular sieves.

2.2. Visual determination of phase separation

Samples for phase determination were prepared by mass on a 3 g scale in glass screw-top vials. Samples were shaken and immersed in a temperature-controlled water bath at 20 °C for 24 h before visually recording the sample appearance. For temperature dependence studies samples were equilibrated for 24 h at each temperature. To check for hysteresis effects the temperature was ramped up at 10 °C intervals (20 °C, 30 °C, 40 °C) and down at the intervening 10 °C intervals (35 °C, 25 °C, 15 °C).

2.3. Determination of total polymer content by dry-weight analysis

A dry-weights method was employed to characterize the polymer concentration in each separating layer. Triplicate samples were prepared in the two phase region, and the upper and lower layers carefully separated into pre-weighed vials using a flat-ended needle. These were dried to constant mass at 60 °C.

2.4. Determination of solvent and polymer distribution by NMR

2.4.1. Calibration

A 5 wt% solution of $CHCl_3$ in $CDCl_3$ was prepared by mass. A series of HPFP/PFP mixtures were prepared on 1 g scale at 0–100 wt% HPFP (in 10 wt% increments). These solutions were diluted in the $CHCl_3$/$CDCl_3$ solvent mixture (0.1 g in 0.9 g) to give a fixed total fluorinated solvent concentration (10 wt%). 1D NMR spectra were recorded on a JEOL 360 MHz NMR machine and processed using X-Win NMR. The relative integral for HPFP to $CHCl_3$ peaks were calculated as an average of five runs, and used to construct a calibration plot of HPFP concentration *vs.* relative integral. Calibration plots were prepared in the same manner for the polymers at concentrations ranging from 0 wt% to 10 wt%.

2.4.2. Determination of sample composition

Upper and lower phases were separated using a flat ended needle. 0.1 g samples of the relevant phase were dissolved in a pre-prepared solution of $CHCl_3$ in $CDCl_3$ (10 wt% $CHCl_3$) to give a 10 wt% concentration of the transferred phase. The concentrations (wt%) of HPFP and PEG were calculated from the relevant calibration plots, and corrected for sample dilution to give the concentration in the original sample.

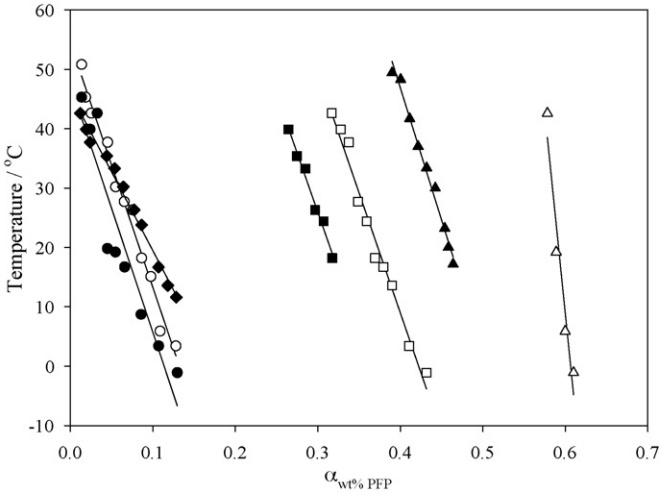

Fig. 1. Pseudo-binary phase diagram at 5 wt% polymer for various PEGs in HPFP/PFP mixtures. Samples are single phase to the left of the phase boundary. Dihydroxyl end-capped PEGs: 300 g mol^{-1} (closed circles), 400 g mol^{-1} (open diamonds), 600 g mol^{-1} (open circles); monomethyl end-capped PEGs: 350 g mol^{-1} (closed squares), 550 g mol^{-1} (open squares); dimethyl end-capped PEGs: 250 g mol^{-1} (closed triangles), 500 g mol^{-1} (open triangles). Lines are best-fit to the data.

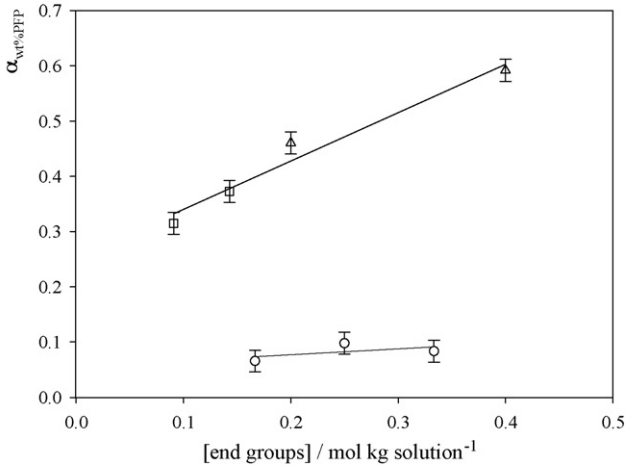

Fig. 2. Effect of polymer structure on solvent composition at the phase boundary for a fixed polymer concentration of 5 wt%. α_{PFP} = wt% PFP in solvent. Data is represented as a function of CH_3 and OH end groups for dihydroxyl end-capped PEGs (open circles), monomethyl end-capped PEGs (open squares), dimethyl end-capped PEGs (open triangles). Lines are a guide to the eye. Data are single phase to the left of the phase boundary.

3. Results and discussion

3.1. Phase boundaries

3.1.1. Binary phase diagrams

The pseudo-binary phase diagram for dihydroxyl, monomethyl and dimethyl end-capped PEGs in HPFP/PFP mixtures has been determined in terms of solvent composition $\alpha_{wt\%PFP}$ at fixed polymer concentration of 5 wt% as a function of temperature and polymer molecular weight. Data are shown in Fig. 1 where $\alpha_{wt\%PFP}$ is the mass fraction of PFP in the solvent mixture. At temperatures above the phase boundary all samples separated into two clear phases. Below the phase boundary all the dihydroxyl PEG and both the lower molecular weight monomethylated (MM PEG 350) and dimethylated PEG (DM PEG 250) systems existed as clear single phase solutions. For the higher molecular weight mono- and dimethyl-end-capped PEGs the samples cross the solid/liquid phase boundary, separating at temperatures below 3.4 °C into a solid with an accompanying lower liquid phase.

It can be seen from Fig. 1 that the dihydroxyl end-capped PEGs showed no strong molecular weight dependence on solvent composition, with the solubility of DH PEG 300, DH PEG 400 and DH PEG 600 similarly intolerant to addition of PFP to the HPFP solvent. As observed previously, increasing the degree of end group methylation of the polymer shifts the phase diagram to increasingly higher PFP content, with the phase boundary for dimethyl end-capped polymers at higher PFP mass fractions than the monomethylated PEGs. Here, as the degree of methylation increases, the phase boundary also becomes more sensitive to molecular weight, with a significant decrease in $\alpha_{wt\%PFP}$ content at the phase boundary for the higher molecular weight polymers, an effect most pronounced for the dimethyl-end-capped PEGs.

Fig. 2 shows $\alpha_{wt\%PFP}$ at 20 °C as a function of end group concentrations (*i.e.* taking into account the differences in polymer molecular weight). The limiting solvent composition appears to be dependent on the concentration of methyl ether end-groups, with a significant enhancement in the amount of PFP tolerated before phase separation occurs. This suggests that the molecular weight dependence observed in Fig. 1 (decreasing PFP content with increasing molecular weight) can be attributed to the indirect effect of diluting the favourable methyl end-group contributions, rather than being a direct consequence of the increasing polymer chain length. Also of note is the lack of molecular weight dependence of $\alpha_{wt\%PFP}$ for the dihydroxyl end-capped PEGs.

3.1.2. Ternary phase diagrams

The full ternary phase diagrams for the individual polymers were determined at 20 °C, and are shown in Fig. 3 (data for DH PEG 300, MM PEG 350 and DM PEG 250 is as published previously) (Cote et al., 2008b). Consistent with the data at fixed concentration, the region occupied by the single phase region is enhanced by increasing methylation of the polymer end groups. The differences are most pronounced below a polymer concentration of less than 50 wt% (*i.e.* the solvent rich region of the phase diagram), with a clear dominance of end-group effect observed. There is less dif-

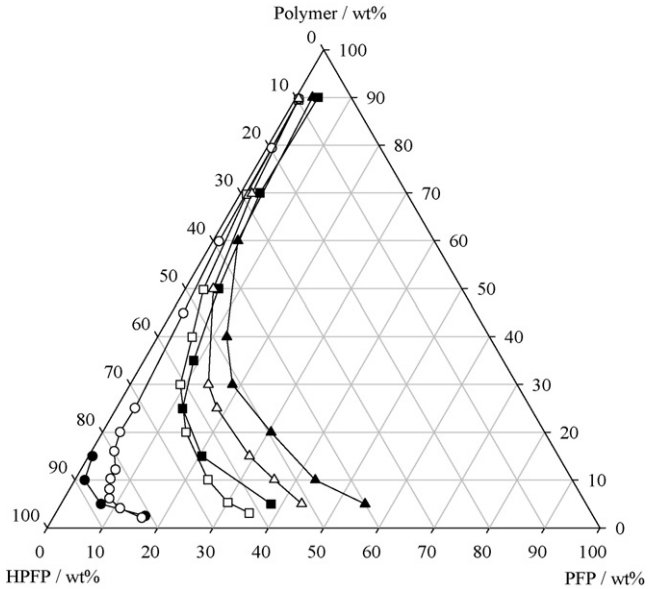

Fig. 3. Effect of polymer molecular weight on phase behaviour in HPFP/PFP at 20 °C. Dihydroxyl end-capped PEGs: 300 g mol^{-1} (closed circles), 600 g mol^{-1} (open circles), monomethyl end-capped PEGs: 350 g mol^{-1} (closed squares), 550 g mol^{-1} (open squares), dimethyl end-capped PEGs: 250 g mol^{-1} (closed triangles), 500 g mol^{-1} (open triangles). Lines are a guide to the eye.

Table 1
Polymer concentrations from dry weight analysis of upper (U) and lower (L) phases.

Initial sample composition (wt%)				Polymer concentration (wt%)					
Polymer	HPFP	PFP	Phase	DH PEG 300 (±≤0.4)[a]	MM PEG 350 (±≤1.3)[a]	DM PEG 250 (±≤1.7)[a]	DH PEG 600 (±≤0.6)[a]	MM PEG 550 (±≤1.2)[a]	DM PEG 500 (±≤0.7)[a]
40	10	50	U	95.9	86.5	74.9	95.5	89.2	85.0
			L	0.0	0.0	0.0	0.0	0.0	0.0
40	20	40	U	93.0	74.1	62.5	92.6	82.2	73.0
			L	0.0	0.0	0.0	0.0	0.0	0.1
40	30	30	U	88.4	66.2	55.6	87.6	71.7	63.4
			L	0.1	0.0	0.2	0.1	0.0	0.3
40	40	20	U	82.8	53.5	45.7	80.0	60.0	50.5
			L	0.2	0.1	0.4	0.2	0.3	0.7

[a] Errors reported are the largest standard deviation between triplicate samples.

ference between the higher molecular weight polymers, consistent with the smaller change in end-group concentration at equivalent polymer concentration.

At high polymer concentrations molecular weight effects dominate, with all the lower molecular weight polymers tending towards the same boundary, and the higher molecular weight polymers tending towards one with slightly lower PFP content.

As predicted by the relatively steep slopes of the data in Fig. 1 (and previous data (Cote et al., 2008b)), phase boundaries in the ternary system were found to be largely insensitive to temperature, with only the dihydroxyl PEG showing any statistically significant variation at low polymer concentrations (data not shown). This is in marked contrast to binary systems of PEGs in HPFP which show a strong temperature dependence (Cote et al., 2008b; Paul et al., 2005a) of the phase behaviour. A similar observation was made by Spitzer et al. (2000) who compares biphasic systems formed by PEG in methanol, chloroform or dichloromethane (which exhibit upper critical solution temperature (UCST) behaviour and for which significant temperature effects were observed), with the ternary systems, for which the influence of temperature was greatly reduced.

3.2. Phase separation

3.2.1. Polymer distribution

Studying samples at fixed polymer concentration allowed the effect of solvent composition on polymer partitioning to be studied. A dry weights analysis of samples in the two phase region was used to determine the total polymer partitioning between the two phases. Results are given in Table 1. In all cases there is strong partitioning of the polymer into the less dense (upper) phase, consistent with a cloud-point type phase separation. Polymer concentration in this layer is highest for the dihydroxyl PEGs (DH > MM > DM). There is a slight decrease in DH PEG concentrations on increasing molecular weight at comparable starting solvent composition, with the reverse trend observed for both mono- and di-methyl end capped polymers, which exhibit higher polymer concentrations for the higher molecular weight samples. The difference in molecular weight dependence of the phase behaviour is indicative of different dominating solubility/insolubility mechanisms for the two classes of polymer. For the dihydroxyl polymers there is less exclusion of the solvent as the ratio of OH to (OCH_2CH_2) groups decreases (increasing molecular weight) suggesting, *i.e.* weaker solute–solute interactions. For the methylated polymers the decrease in CH_3:OCH_2CH_2 ratio on increasing molecular weight enhances exclusion of solvent from the upper phase (higher polymer concentration), consistent with a decrease in solute–solvent interactions as OCH_3 group concentration decreases.

3.2.2. Effect of solvent composition

As can be seen from Table 1, no polymer is detected in the lower phase for any polymer at 10 wt% HPFP. As HPFP content increases, polymer concentration in the lower phase remains very low (<1 wt%), whilst the polymer-rich upper phases are diluted. Dimethyl end-capped PEGs are most sensitive to changing solvent composition and sensitivity decreases DM > MM > DH. For the low MW polymers the actual amount of polymer in the upper phase remains approximately constant with 98–99% of the polymer present located in the upper phase, regardless of starting solvent composition. Hence the decrease in polymer concentration can be attributed to changes in solvent partitioning, leading to associated changes in relative phase heights (increasing volume of upper phase) observed.

3.2.3. Solvent distribution

Whilst the dry weights analysis gives the total solvent content of each phase, the NMR technique allows the distribution of HPFP to be determined independently of the PFP content. The mass balance calculated from the NMR results and was within a reasonable error of ±5 wt%. Table 2 shows that for all polymers,

Table 2
HPFP concentrations from NMR of upper (U) and lower (L) phases for PEG/HPFP/PFP samples at 20 °C.

Initial sample composition (wt%)				HPFP concentration (wt%)					
Polymer	HPFP	PFP	Phase	DH PEG 300	MM PEG 350	DM PEG 250	DH PEG 600	MM PEG 550	DM PEG 500
40	10	50	U	0.00 (±0.49)	0.21 (±1.36)	9.7 (±1.0)	0.38 (±1.07)	3.5 (±0.7)	5.3 (±0.7)
			L	17.4 (±1.0)	13.4 (±0.8)	8.8 (±1.5)	19.9 (±1.0)	17.1 (±0.9)	11.9 (±1.6)
40	20	40	U	0.05 (±1.40)	8.5 (±1.5)	21.4 (±1.1)	4.6 (±1.8)	9.7 (±0.1)	17.8 (±1.1)
			L	32.9 (±2.8)	28.8 (±1.9)	16.4 (±0.9)	33.2 (±1.6)	29.9 (±0.5)	19.9 (±5.0)
40	30	30	U	1.9 (±1.6)	22.3 (±1.7)	32.3 (±0.3)	8.9 (±2.1)	25.1 (±1.2)	31.0 (±0.7)
			L	43.5 (±3.0)	40.6 (±1.7)	20.8 (±1.1)	50.3 (±3.9)	39.7 (±0.6)	26.4 (±1.2)
40	40	20	U	4.4 (±1.0)	30.7 (±1.7)	37.4 (±4.1)	16.5 (±0.3)	37.0 (±0.3)	40.3 (±0.5)
			L	61.2 (±2.1)	52.5 (±2.7)	29.2 (±0.3)	64.8 (±0.6)	53.8 (±0.8)	36.6 (±0.1)

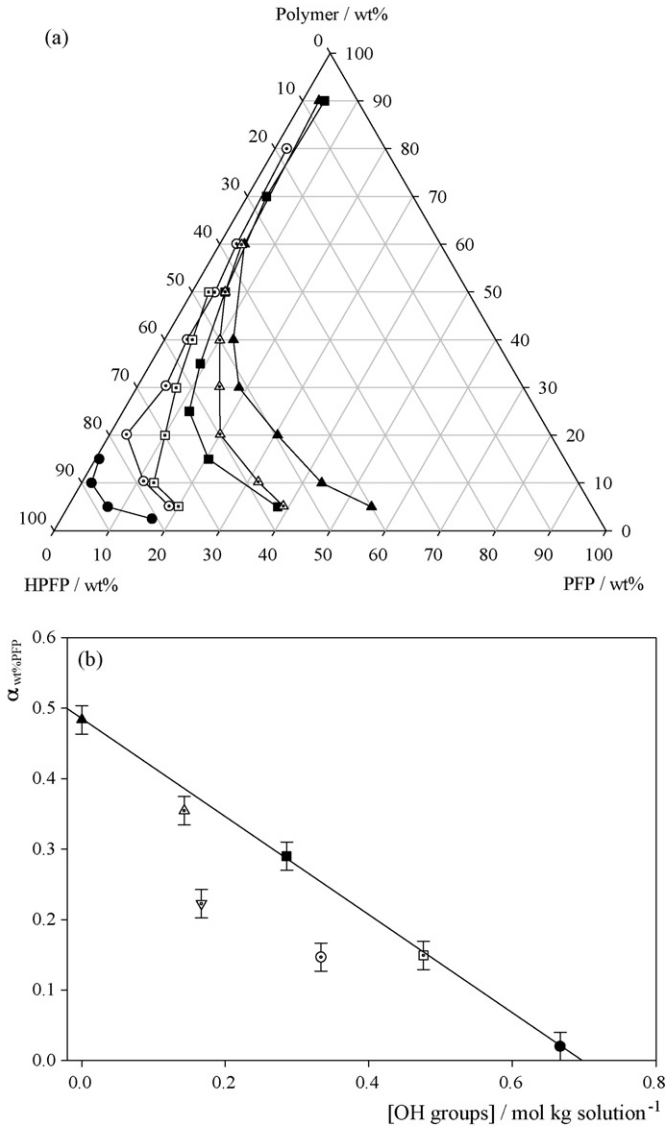

Fig. 4. (a) Ternary phase diagram for low molecular weight series PEG-based polymers in HPFP/PFP: DH (closed circles); MM (closed squares); DM (closed triangles); 50/50 DH/DM (open dotted circles); 50/50 DH/MM (open dotted squares); 50/50 MM/DM (open dotted triangles). (b) Relationship between solvent composition and OH group concentration at 10 wt% total polymer. Polymer mixtures and symbols as in (a) plus 25/75 DH/MM (open dotted inverted triangles).

as the proportion of HPFP in the original sample increases, the HPFP concentration in both upper and lower phases increases, with a concomitant decrease in HPFP partitioning. Since the distribution of polymer remains largely unchanged, this indicates that solvent–solvent interactions must contribute significantly as HPFP content influences PFP partitioning between the two phases.

3.3. Mixed polymer systems

To further investigate end group effects, phase behaviour measurements were also carried out using mixtures of the low molecular weight PEGs, the results of which are shown in Fig. 4a, with an end group analysis plot in (b) for data at 10 wt% polymer content.

All the mixtures of polymers exhibit phase boundaries intermediate to those of the individual constituent polymers; phase separation does not simply occur at the PFP content prescribed for the least soluble polymer, nor does phase separation occur at a weighted average of the two boundaries. For mixtures of DH PEG 300 and DM PEG 250 the phase boundary lies in closer proximity to that of the dihydroxyl PEG 300 system. This finding is echoed by the 25/75 DH PEG 300/DM PEG 250 sample which also lies closer to the dihydroxyl PEG boundary, despite the lower DH PEG 300 content. This indicates an overriding effect of the OH groups causing phase separation which cannot be compensated for by the enhanced solubilising effect of the methyl end-groups.

For a 50/50 mixture of MM PEG 350 with DM PEG 250 the phase boundary again sits between those for the two individual polymers, but closer to that for the MM PEG 350. This observation is in keeping with that of the first 50/50 system studied; whereby the presence of a hydroxyl group at one end of the monomethyl PEG chain allows for greater control by the monomethyl PEG. This effect is certainly lower than that observed for the 50/50 DH PEG 300/DM PEG 250 system owing to a lower number of the hydroxyl end-groups. What is more interesting is the closer relationship to that of the 25/75 DH PEG 300/DM PEG 250 phase boundary. There are nominally an equal number of both hydroxyl and methyl end-groups in each system, yet the phase boundaries clearly differ. The phase boundary for 50/50 MM PEG 350/DH PEG 300 is surprisingly similar to that for 50/50 DH PEG 300/DM PEG 250; given the increased OH group content one might have predicted a phase boundary closer to the DH PEG 300 only system than that observed. On calculating the end-group concentrations differences between the two types of mixed system (those with and without common end groups) becomes clear. Mixtures of MM PEG 350 with either DH PEG 300 or DM PEG 250 demonstrate a linear dependence on the end-group composition, giving predictive control over the solvent composition required to induce phase separation. In contrast, mixtures of DH and DM PEG show a deviation from this linear relationship. It is clearly important to consider the full range of interactions occurring in these mixed systems. Where previous groups have reported the effects of end-groups in competition with those of molecular weight (Spitzer et al., 2002b; Cote et al., 2008b), the observations of this study allow one to envisage a situation in which significant competition occurs between different end-groups present in mixed PEG systems.

4. Conclusions

The phase behaviour of poly(ethylene glycol) based polymers with dihydroxyl, monomethyl and dimethyl end groups has been evaluated for different molecular weight series in mixed HPFP/PFP solvent mixtures. The amount of fully fluorinated solvent that can be incorporated before phase separation occurs increases in a linear fashion with methyl group concentration, regardless of whether the methyl group is attached to a dimethyl of monomethylated polymer. Dry weights analysis gave the polymer concentrations in each phase, indicating significant exclusion of solvent from the polymer-rich upper phase that was particularly pronounced for dihydroxyl end-capped PEGs. Increasing methylation increases the amount of solvent present in the upper phase, and also changes the sensitivity of the phase compositions to the solvent composition, with dimethyl-end-capped PEGs showing the largest changes in polymer concentration (DM > MM > DH). NMR measurements with an internal $CHCl_3$ standard allowed the solvent partitioning to be identified, and solvent partitioning was shown to be dependent on both the initial solvent composition and polymer end-group chemistry.

For mixed polymer systems where both polymers contain at one identical end-group (*i.e.* any binary mixture except dimethyl with dihydroxyl end-capped PEGs) it is possible to predict the solvent composition required for phase separation based on those obtained for the pure polymers, scaling to the total OH group (or CH_3 group) concentration in the system. For mixtures of dihydroxyl

with dimethyl end-capped PEGs a deviation from linear behaviour is observed with dominance of the dihydroxyl end groups, which is reflected in the obtained phase diagrams.

These results suggest a change in emphasis between a dominance of solute-solute interactions driving phase separation and exclusion of solvent for the dihydroxyl polymers, to enhanced solute–solvent interaction promoting solubility for methyl terminated polymers. Ongoing spectroscopic studies are investigating the precise nature of these interactions.

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