High-throughput solubility measurements of polymer libraries in supercritical carbon dioxide†

Christopher L. Bray, Bien Tan, Colin D. Wood and Andrew I. Cooper*

A new method has been developed which allows rapid parallel solubility measurements for libraries of materials in supercritical fluids (SCFs). The technique was used to evaluate the solubility of a mixed library of 100 synthetic polymers including polyesters, polycarbonates, and vinyl polymers.

Supercritical carbon dioxide ($scCO_2$) is an inexpensive, non-toxic, and non-flammable solvent for materials synthesis and processing,[1,2] and is a potential replacement solvent for applications such as dry-cleaning, lithography, and precision cleaning.[3] One technical barrier to the use of $scCO_2$ is the limited availability of inexpensive CO_2-soluble surfactants,[4–6] ligands,[7–9] and phase transfer agents.[10] The majority of systems reported so far have been highly fluorine-substituted,[4–10] and the associated costs may prohibit industrial-scale use for many applications. In addition, fluorinated materials often have poor environmental degradability, and this could negate the environmental advantages associated with the use of $scCO_2$. The discovery of inexpensive CO_2-soluble *polymers* – as opposed to small molecules – is a particularly hard challenge:[11] CO_2 is a rather feeble solvent and, until recently, the only polymers found to have significant solubility in CO_2 under moderate conditions ($<100\ °C$, <400 bar) were amorphous fluoropolymers[12,13] and polysiloxanes.[14] Inexpensive poly(ether carbonate) (PEC) copolymers have been reported to be soluble in CO_2 under moderate conditions,[15,16] and could function as building blocks for cheap surfactants, but numerous practical difficulties remain. For example, polymer solubility does not in itself guarantee performance in the various applications of interest. Effective surfactants, in particular, tend to require asymmetric topologies such as diblock copolymers.[6] Other practical considerations are cost, biodegradability, thermal and chemical stability, and biocompatibility.

It is difficult to predict CO_2-soluble polymer structures, despite recent attempts to rationalize specific solvent–solute interactions by using *ab initio* calculations.[17] Only a few examples of CO_2-soluble polymers currently exist and, as such, there are a limited number of 'design motifs' to draw upon.[18] Moreover, it is clear that polymer solubility in CO_2 is influenced by a large number of inter-related factors[11,18] such as specific solvent–solute interactions,[15–19] backbone flexibility[15,16,18,20] topology,[18,20] and the nature of the end-groups.[20] Given the current limits of predictive understanding, the discovery of new CO_2-soluble polymers might

be accelerated using parallel or 'high-throughput' (HT) methodology. The synthetic approaches for such a strategy are already well in place; for example, a growing number of methods exist whereby one may synthesize and characterize polymer libraries.[21] By contrast, there are no examples of techniques for the rapid, parallel determination of solubility for libraries of materials in $scCO_2$ or other supercritical fluids (SCFs). The conventional method for measuring polymer solubility in SCFs is cloud point measurement,[11,15,16,20] which involves the use of a variable-volume view cell. This technique is not suitable for rapid solubility measurement and would be impractical for large libraries of materials. Previously, we developed a simple method involving a 10-well reaction vessel whereby ten solubilities could be measured in parallel using compressed fluid solvents such as liquid R134a.[22] This method was used to discover a new, inexpensive, R134a-soluble stabilizer for dispersion polymerization, but suffers from a number of limitations; for example, the pressure limit is low (50 bar) and only compressed *liquid* solvents (as opposed to SCFs) can be used with this particular equipment.[22]

In this communication, we report a new method for the rapid parallel solubility measurement of libraries of polymers or other materials in SCF solvents. The method is based on parallel gravimetric extraction.[23] In a typical experiment,‡ polymer samples (*ca.* 100 mg) are accurately weighed into borosilicate glass sample tubes and loaded into a specially-designed sample holder which will accept up to 60 tubes on this scale. This holder is then placed into a custom-built (Thar Designs) SCF extractor consisting of a vertically-mounted 500 ml extraction vessel and computer-controlled syringe pump/back pressure regulator. CO_2 is then passed through the vessel at a controlled pressure, temperature, and flow rate for a predetermined period of time. Thus, all 60 samples are subjected, in parallel, to precisely the same extraction conditions. The CO_2 is then slowly vented, the sample holder removed from the vessel, and the samples reweighed individually to determine the sample mass loss (if any) under those extraction conditions. The procedure is then repeated (typically at progressively higher CO_2 pressures) in order to build a cumulative extraction profile for the library of samples. A low molecular weight material [*e.g.* azobis(isobutyronitrile), AIBN] of known CO_2-solubility[12,13] was added as an internal standard for each run.

Fig. 1 shows extraction results for a library of 100 materials (two separate runs) at five increasing CO_2 pressures. This method is very rapid in comparison with alternative techniques: once the equipment had been installed, tested, and validated, all of the data presented in this communication were collected over the course of five days. Four classes of materials were included in this study, as colour-coded in Fig. 1: (i) a library of aliphatic polyesters (PE, blue
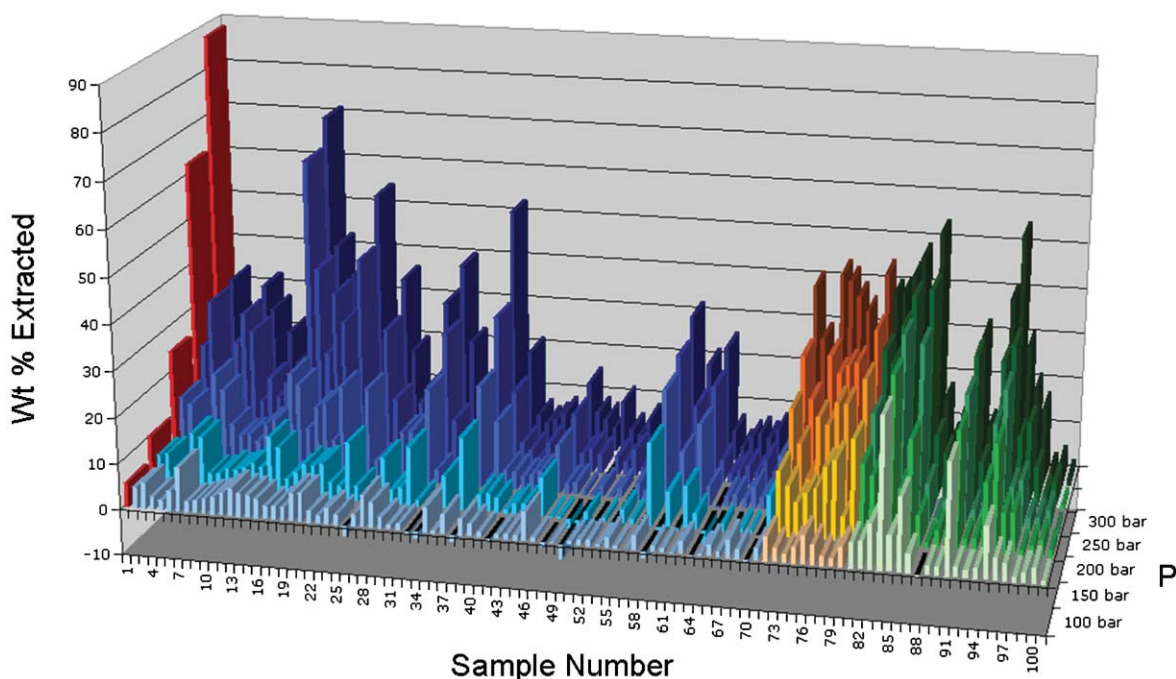
Fig. 1 Graph showing cumulative weight % extracted in CO_2 for a library of 100 polymers at five different extraction pressures (100–300 bar). Red bar = low molar mass internal standard material (AIBN); blue bars = aliphatic poly(ether ester)s (PE); yellow bars = aliphatic poly(ether carbonate)s (PEC); green bars = poly(vinyl acetate) (PVAc).

bars) synthesized by step growth polymerization; (ii) a library of aliphatic poly(ether carbonate)s (PEC, yellow bars), also synthesized by step growth polymerization; (iii) a library of poly(vinyl acetate) (PVAc, green bars) samples synthesized by free-radical chain growth polymerization in the presence of a chain transfer agent;[22] and, (iv) a CO_2-soluble low molar mass material, AIBN, as an internal standard. A number of trends emerge from these data. First, the CO_2-solubility for these materials varies over a substantial range, with some polymers (*e.g.* sample 15) exhibiting moderate solubility and others (e.g. sample 68) showing essentially no solubility over the pressure range tested. Second, for most polymers which exhibit any solubility, the solubility increases significantly and non-linearly as the pressure is ramped – that is, the materials dissolve more readily at higher pressure, and not simply as a function of CO_2 volume passed through the vessel. Third, none of the polymers shows high levels of extraction under these conditions at the lowest pressure tested (100 bar). Lastly, none of the polymers was extracted as efficiently as the low molar mass control material, AIBN (red bar).

Fig. 2 shows a plot of the total cumulative extraction percentage after the final period of extraction at 300 bar as a function of the weight-average molecular weight, M_w, for the polymers in the library. This plot also includes data for a number of commercially available polymers which are not included in Fig. 1. Fig. 2(a) shows that a clear global relationship exists between molecular weight and solubility – that is, the solubility in CO_2 drops off sharply as a function of M_w and none of the polymers tested shows significant solubility for $M_w > 20\ 000$ g mol^{-1} under these conditions. There is, however, significant variation in the total cumulative weight percentage extracted for the materials with $M_w < 20\ 000$ g mol^{-1} [Fig. 2(b)]. At a given M_w, these variations can be attributed to differences in the structure of the various

polymers in the library. For example, Fig. 2(b) shows a pronounced cluster of structurally-identical aliphatic PE samples which have much lower apparent solubilities (<10 wt%) than PEC or PVAc samples of similar molecular weights. A major difference between the PE and PEC samples is that the PEC materials incorporate a much larger number of oxygen atoms in the polymer backbone; these ether linkages contribute strongly to chain flexibility[15,16,18,20] in comparison with the exclusively methylene-linked PE samples.[23]

Both Fig. 1 and Fig. 2 show data for a diverse library of polymers which vary in both chemical structure and in molecular weight. Fig. 3 shows extraction data for a focused sub-library of PVAc samples – that is, the polymer structure is common throughout and pressure and M_w are the only variables. These data show how our new method can be used to generate a rapid 'map' of the relationship between molecular weight, pressure, and solubility for a library of closely-related materials. In general, the trends shown in Fig. 3 agree well with previous cloud point studies which show that the miscibility pressure for PVAc with CO_2 is unusually low for a hydrocarbon polymer and drops to below 400 bar for samples with low-to-moderate molecular weights (<100 repeat units).[24] It can be observed from Fig. 3(b) that the maximum weight percent extracted for these samples occurs at a molecular weight of around 2000 g mol^{-1}. The observation is reproduced in *each* of the extraction runs at the five successive extraction pressures. This apparently counter-intuitive result – that is, the low M_w oligomers are *less* soluble in CO_2 – is possibly explained by an increased contribution[20] from the hydroxyl end-groups that arise from the method of synthesis.[22]

Unlike cloud point measurements, our new parallel technique does not give an absolute measure of the miscibility pressure of the samples with CO_2. Indeed, one should be cautious about drawing
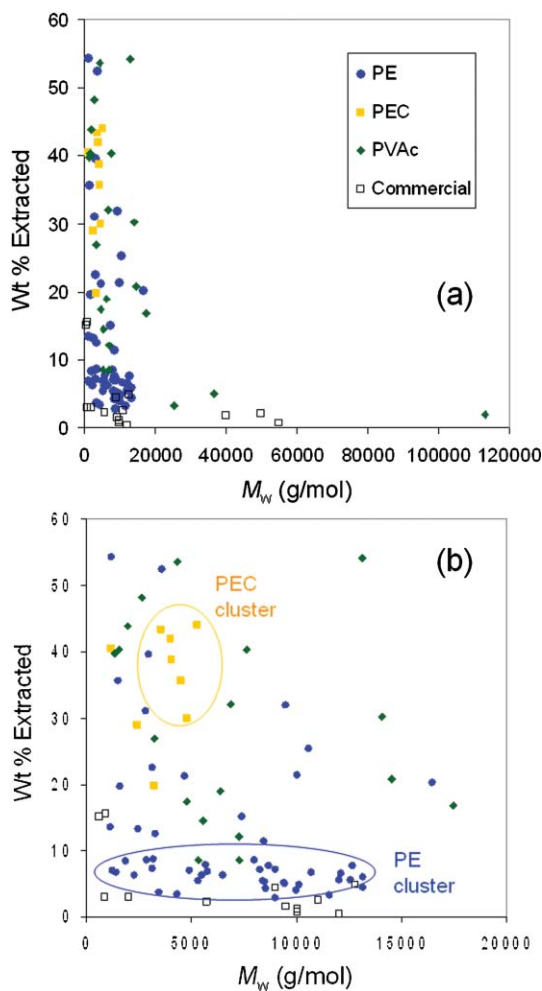
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Fig. 2 (a) Plot of total cumulative weight % extracted in CO_2 as a function of weight-average molecular weight, M_w, for a mixed library of synthetic and commercial polymers. Filled blue circles = PE; filled yellow squares = PEC; filled green diamonds = PVAc (PVAc samples vary in both M_w and in end-group structures); open squares = various commercial polymers. (b) Expansion of M_w range up to 20 000 g mol^{-1} showing 'clusters' of polymers with similar molecular structures.

Fig. 3 (a), (b) Plots of cumulative weight % extracted in CO_2 as a function of M_w for a focused sub-library of hydroxyl-terminated PVAc samples.

overly-simple correlations between the percentage material extracted and the thermodynamic 'solubility' of the samples. For example, it is possible that extraction rates for liquid samples could be higher than extraction rates for solid samples because of enhanced mass-transport, and that this could mask effects arising from the thermodynamic solubility of the materials.[25] It is also possible that a highly-soluble solute or solutes could suppress the solubility of other materials in the library, particularly in the early stages of the extraction. Nonetheless, for systems with known solubilities such as PVAc (Fig. 3), the solubility trends which we observe are broadly consistent with data from more conventional measurements.[24] Preliminary reproducibility tests suggest that our method is already reproducible enough[26] to make rapid 'high, medium, low' solubility judgments for libraries of materials at various pressures. Moreover, we believe that simple technical refinements to the method (flow-rates, venting rates, sample loading geometries) will allow us to decrease measurement variability to
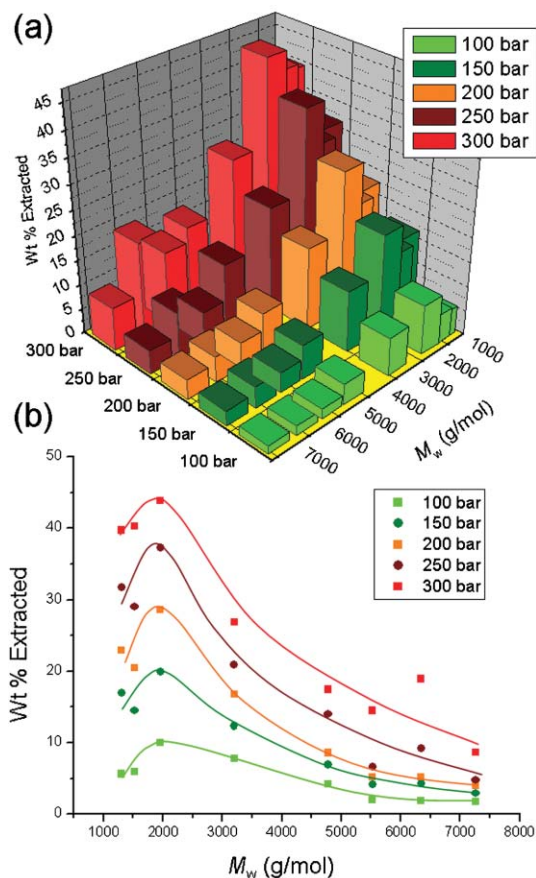
a level that will allow, for example, quantitative structure–property relationship (QSPR) approaches to be employed.

In summary, our new technique has broad potential for the rapid 'solubility mapping' for libraries of new materials in SCFs. We believe that this method is at least 50 times faster than other techniques in terms of the rate of useful information that is obtained. A powerful combined approach in the future will be to screen libraries of materials using our new HT methodology followed by further validation of CO_2 solubility for candidate materials using conventional cloud point measurements. While our preliminary experiments have involved polymer libraries, this parallel methodology is equally applicable to the discovery of novel SCF-soluble ligands, catalysts, biomolecules, fragrances, dyes, or pharmaceuticals for a wide range of materials applications.

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Notes and references

‡ The method assumes that the polymers are adequately purified – for example, by reprecipitation: any soluble low M_w oligomers or monomer residues will lead to false-positive results. Typically, polymer samples

(100 mg) were weighed into borosilicate glass sample tubes (6 mm i.d., 50 mm length). Samples were extracted in a custom-built Thar Supercritical Fluid Extractor (500 ml vessel) with a holder for up to 60 sample tubes. Samples were extracted at five pressure settings: 100, 150, 200, 250 and 300 bar for 4 h periods at a rate of 2 g min^{-1} CO_2 at 35 °C. Depressurisation was carried out at a rate of 1.7 bar min^{-1}. Given the sample weights (*ca.* 100 mg) and the volume of the system (500 ml), we believe that errors arising from the transfer of solubilized material from one sample tube to another during depressurization are relatively small, and will tend to affect all samples in an approximately equal fashion (see ESI for preliminary reproducibility data).

1 A. I. Cooper, *J. Mater. Chem.*, 2000, **10**, 207.
2 A. I. Cooper, *Adv. Mater.*, 2003, **15**, 1049.
3 J. M. DeSimone, *Science*, 2002, **297**, 799.
4 K. A. Consani and R. D. Smith, *J. Supercrit. Fluids*, 1990, **3**, 51.
5 K. P. Johnston, K. L. Harrison, M. J. Clarke, S. M. Howdle, M. P. Heitz, F. V. Bright, C. Carlier and T. W. Randolph, *Science*, 1996, **271**, 624.
6 K. P. Johnston, *Curr. Opin. Sol. Interface Sci.*, 2000, **5**, 351.
7 C. A. Bessel, G. M. Denison, J. M. DeSimone, J. DeYoung, S. Gross, C. K. Schauer and P. M. Visintin, *J. Am. Chem. Soc.*, 2003, **125**, 4980.
8 K. R. Powell, T. M. McCleskey, W. Tumas and J. M. DeSimone, *Ind. Eng. Chem. Res.*, 2001, **40**, 1301.
9 W. P. Chen, L. J. Xu, Y. L Hu, A. M. B. Osuna and J. L. Xiao, *Tetrahedron*, 2002, **58**, 3889–3899.
10 A. I. Cooper, J. D. Londono, G. Wignall, J. B. McClain, E. T. Samulski, J. S. Lin, A. Dobrynin, M. Rubinstein, A. L. C. Burke, J. M. J. Fréchet and J. M. DeSimone, *Nature*, 1997, **389**, 368–371.
11 C. F. Kirby and M. A. McHugh, *Chem. Rev.*, 1999, **99**, 565–602.
12 J. M. DeSimone, Z. Guan and C. S. Elsbernd, *Science*, 1992, **257**, 945–947.
13 J. M. DeSimone, E. E. Maury, Y. Z. Menceloglu, J. B. McClain, T. J. Romack and J. R. Combes, *Science*, 1994, **265**, 356–359.
14 K. A. Shaffer, T. A. Jones, D. A. Canelas and J. M. DeSimone, *Macromolecules*, 1996, **29**, 2704–2706.
15 T. Sarbu, T. Styranec and E. J. Beckman, *Nature*, 2000, **405**, 165–168.
16 T. Sarbu, T. J. Styranec and E. J. Beckman, *Ind. Eng. Chem. Res.*, 2000, **39**, 4678–4683.
17 P. Raveendran and S. L. Wallen, *J. Am. Chem. Soc.*, 2002, **124**, 12 590–12 599.
18 E. J. Beckman, *Chem. Commun.*, 2004, 1885–1888.
19 S. G. Kazarian, M. F. Vincent, F. V. Bright, C. L. Liotta and C. A. Eckert, *J. Am. Chem. Soc.*, 1996, **118**, 1729–1736.
20 C. Drohmann and E. J. Beckman, *J. Supercrit. Fluids*, 2002, **22**, 103–110.
21 R. Hoogenboom, M. A. R. Meier and U. S. Schubert, *Macromol. Rapid Commun.*, 2003, **24**, 16–32.
22 C. D. Wood and A. I. Cooper, *Macromolecules*, 2003, **36**, 7534–7542.
23 See Electronic Supplementary Information† for reproducibility data and photograph of equipment layout. Full technical details, equipment schematics, and synthetic procedures to be published in a future article.
24 Z. Shen, M. A. McHugh, J. Xu, J. Belardi, S. Kilic, A. Mesiano, S. Bane, C. Karnikas, E. Beckman and R. Enick, *Polymer*, 2003, **44**, 1491–1498.
25 Although this is possible, our preliminary studies show examples of solid samples (*e.g.* AIBN, certain PVAc materials) which are extracted much more efficiently than viscous liquid samples (*e.g.* some low M_w PEs) of comparable molar mass.
26 Average standard deviation in wt% extracted of 1.5–10% observed for four sets of identical samples (see ESI†). In general, the standard deviation was low for one extraction run (<3%) and increased with the number of runs due to small cumulative errors.

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