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Materials processing in supercritical carbon dioxide: surfactants, polymers and biomaterials†

Helen M. Woods,[a] Marta M. C. G. Silva,[a,b] Cécile Nouvel,[a] Kevin M. Shakesheff[b] and Steven M. Howdle*[a]

[a]*School of Chemistry, University of Nottingham, University Park, Nottingham, UK NG7 2RD. E-mail: steve.howdle@nottingham.ac.uk*
[b]*School of Pharmaceutical Sciences, University of Nottingham, University Park, Nottingham, UK NG7 2RD. E-mail: steve.howdle@nottingham.ac.uk*

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Supercritical carbon dioxide ($scCO_2$) is a unique solvent with a wide range of interesting properties. This review focuses upon recent advances in the use of $scCO_2$ in materials synthesis and materials processing. In particular, we consider the advances made in three major areas. First the design and application of new surfactants for use in $scCO_2$, which enable the production of metal nanoparticles, porous polymers and polymers of high molecular weight with excellent morphology. Second the development of new polymer processing and polymer blend technologies in $scCO_2$, which enable the synthesis of some very complex polymer composites and blends. Finally, the application of $scCO_2$ in the preparation of novel biomedical materials, for example biodegradable polymer particles and scaffolds. The examples described here highlight that $scCO_2$ allows facile synthesis and processing of materials, leading to new products with properties that would otherwise be very difficult to achieve.

Introduction

Supercritical fluids (SCFs) are unique solvents with tuneable properties that have been exploited widely in extraction,

† Electronic supplementary information (ESI) available: video clips relating to work carried out in the Howdle research group. See http://www.rsc.org/suppdata/jm/b3/b315262f/

Helen Woods

Helen Woods obtained an MSc Chemistry degree from the University of Nottingham in 2001. She completed her final year project on the phase behaviour of binary mixtures in supercritical carbon dioxide ($scCO_2$) at the New University of Lisbon. She started her PhD in the Clean Technology Group at the beginning of 2002, working under the supervision of Prof. Steve Howdle. Her research is based on the design of novel surfactants for free radical polymerisations in $scCO_2$.

Marta Silva

Marta Silva graduated in Applied Chemistry in Biotechnology in 2001 at the New University of Lisbon. She began her PhD in January 2002 working in both the Clean Technology (S. M. Howdle) and Tissue Engineering Groups (K. M. Shakesheff) as part of a Foresight LINK project. Her research involves the production of porous biomaterials in $scCO_2$ for tissue regeneration.

Cécile Nouvel

Cecile Nouvel obtained her PhD in 2002 at LCPM (INPL-NANCY, France). Her work focused on the controlled synthesis of amphiphilic copolymers, polylactide-grafted dextran, and their ability to perform as biodegradable surfactants. In 2002, she joined Steve Howdle's Group as a postdoctoral research fellow. Her project involved the synthesis of new stabilisers in the dispersion polymerisation of methyl methacrylate in $scCO_2$. Since October 2003, she has been a lecturer at ENSIC (INPL, NANCY).

Kevin Shakesheff

Kevin Shakesheff is Professor of Tissue Engineering and Drug Delivery at the School of Pharmaceutical Sciences, The University of Nottingham. He became interested in tissue engineering during his time as a NATO Postdoctoral Fellow at MIT in the mid-1990s. His research focuses on the role of 3D culture environment on the behaviour of cells and the engineering of polymers to create biomimetic environments for tissue regeneration.

Steven Howdle

Steve Howdle was born in Rotherham, South Yorkshire in 1964 and his main interests are family and football. He obtained a first degree in Chemistry from Manchester in 1986 and his PhD on "Spectroscopy in Liquefied Noble Gases" from Nottingham in 1989. Steve's academic interests focus on the utilisation of $scCO_2$ for polymer synthesis, polymer processing and preparation of novel polymeric materials for tissue engineering and drug delivery. A more detailed description and some movies of supercritical fluids can be viewed at http://www.nottingham.ac.uk/~pczctg/index.htm

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synthesis and materials processing. $scCO_2$ is by far the most widely used fluid largely because it is freely available, inexpensive and chemically inert. Much of the focus on $scCO_2$ has been upon its use as an environmentally acceptable replacement solvent for a wide range of potentially toxic organic solvents that are currently in use. Legislation around the globe is indeed beginning to clamp down on solvent emissions and solvent residues. However, the key driver to research in SCFs, and in particular $scCO_2$, is the ability to carry out chemical or materials processing that is not possible in conventional solvents. The key properties of SCFs and $scCO_2$ have been widely reviewed elsewhere[1] but the main important features are the exploitation of liquid like density and gas like viscosity, and rapid and clean product separation. Several important reviews were published in 1999/2000 covering polymer synthesis,[2] polymer processing,[3–6] and the development of surfactants and stabilisers in $scCO_2$.[7,8] This review describes the very wide range of developments since 2000 in three key areas; surfactants, polymers and biomaterials.[9]

Surfactants

Surfactants are being designed to overcome the limitations associated with using CO_2 as a solvent. Generally the aim is to allow solubilisation or dispersion of molecules that are incompatible with this medium, *e.g.* water or macromolecules. Applications include the formation of polymer particles, water-in-$scCO_2$ emulsions, and the synthesis of metal nanoparticles. In all these cases, the surfactant sterically stabilises the dispersion of solid particles or water droplets in the $scCO_2$ phase. Surfactants for use in CO_2 are amphiphilic molecules containing both a CO_2-phobic and a CO_2-philic portion. The CO_2-phobic portion displays poor solubility in CO_2 and therefore prefers to reside away from the continuous phase; the CO_2-philic tail has good solubility in CO_2 and extends out into the bulk solvent. (Fig. 1a).

To achieve this, the CO_2-phobic part of the surfactant must have a high affinity for the compound being dispersed. This portion is thus hydrophilic in the case of water-in-CO_2 emulsions, or has some affinity for the polymer particles being formed in polymer synthesis. We will first examine surfactant design for the stabilisation of water-in-CO_2 emulsions and their applications, then we will present the surfactants that have been used to synthesise polymer particles in CO_2.

Emulsions

First we consider the use of surfactants to form water-in-$scCO_2$ (W/C) emulsions and in some rare cases $scCO_2$-in-water emulsions (C/W). In a typical CO_2/water/surfactant mixture, water partitions into the core of the surfactant micelles leading to the formation of a microemulsion or macroemulsion depending on the stabilising ability of the surfactant used. Macroemulsions are composed of kinetically stable large droplets within the size 0.1 to a few μm. They are normally formed in the presence of vigorous agitation and collapse in the absence of this. However, microemulsions are thermodynamically stable and optically clear as they are composed of nanodroplets (within the range 2–5 nm).

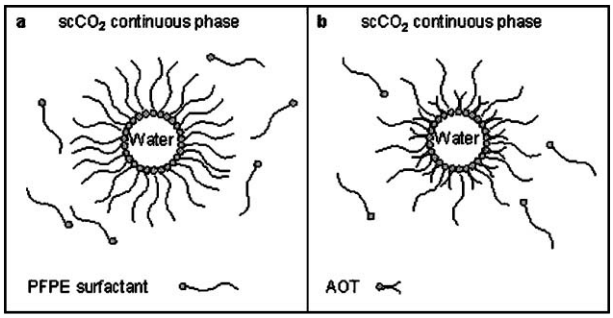

Fig. 1 Water in CO_2 micelles (**a**) stabilised by a perfluoropolyether (PFPE) surfactant and (**b**) stabilised by AOT with the assistance of PFPE as a co-surfactant. The PFPE is unable to form a microemulsion phase with large water cores by itself. It partitions into the interface region of AOT micelles and the fluorinated tails reduce inter-droplet attractive interactions.

As the polarizability per unit volume is relatively low for $scCO_2$ compared to organic solvents, it is difficult to overcome the strong attractive van der Waals interactions between water droplets and to obtain a stable W/C macroemulsion or microemulsion.[10,11] Therefore relatively few materials have been found as effective surfactants. The surfactants used in conventional water-in oil emulsions, for example sodium bis-ethylhexyl sulfoccinate (AOT) (**1** — Fig. 2), do not work alone in CO_2[12] but can be used in association with other cosurfactants[13] (Fig. 1b). Incorporation of fluorinated or silicone units in the CO_2-philic portion of a surfactant encourages good solubility in dense CO_2. Recent molecular simulations[14] of the surfactant $(C_7F_{15})_2CHSO_4^-\ Na^+$ have shown that the CO_2-philic groups actually provide a protective layer around the water droplets leading to weaker van der Waals interactions at the droplet interface, thus preventing destabilisation of the emulsion.

Surfactants for macro or microemulsions. A key driver in the development of surfactants for $scCO_2$ is the possibility of new materials synthesis strategies. As in conventional solvents, effective surfactants for use in $scCO_2$ are either low molecular weight or polymeric in nature. Several detailed reviews have already been published[7,8,15,16] and the reader is referred to these for a fundamental understanding of the challenges and difficulties in identifying and preparing surfactants for use in $scCO_2$. Here we discuss the most recent research in the area and emphasize the importance of surfactants in developing clean reactions and new materials. First we will deal with surfactants with a molecular weight of less than 600 g mol^{-1} these are **low molecular weight surfactants**. Most of these are anionic. The assembly of anionic surfactants in CO_2 has been investigated using $(C_7F_{15})_2CHSO_4^-\ Na^+$ as a model. A two step mechanism is followed: the anionic head groups and Na^+ counterions are first hydrated followed by aggregation of the surfactant molecules.[17] The time scale of aggregation was found to be much faster in CO_2 compared to aqueous systems due to the electrostatic nature of the system and the faster diffusion of surfactant molecules in CO_2. Erkey and Liu[18] and Eastoe and Steytler[19] have shown that analogues of AOT incorporating a fluorinated tail (**2** — Fig. 2) are highly effective as surfactants in $scCO_2$. When studying a series of these molecules[19] ("di-HCFt", "di-CFt" and "di-CFtH", **2a**–**2b**–**2c** — Fig. 2), the end group was found to have a crucial effect on surfactant ability with H-terminated compounds displaying significantly weaker surfactancy than F-terminated materials. In addition, the "di-CF4H" ($n = 2$, X = F, $m = 4$), "di-CF4" ($n = 1$, X = F, $m = 4$) and "di-CF6" ($n = 1$, X = F, $m = 6$) were the most effective, indicating a strong chemical specificity that is consistent with an optimum surfactant chain length for W/C formation. A close correlation was found between the aqueous phase surface tension at the critical micelle concentration of the surfactant solution, and performance in stabilising W/C microemulsions. The lower the surface tension, the better the surfactant ability. This correlation might in future be used as a guide for designing highly efficient surfactants without the need for time-consuming phase stability measurements in $scCO_2$.[19] Other fluorinated dichain surfactants with phosphate rather than sulfate head groups ("di-HCFt-P" or "di-CFtH-P", **3a**–**3b** — Fig. 2) have very effectively formed W/C microemulsions.[20,21] According to Eastoe and Steytler[20] the surfactant

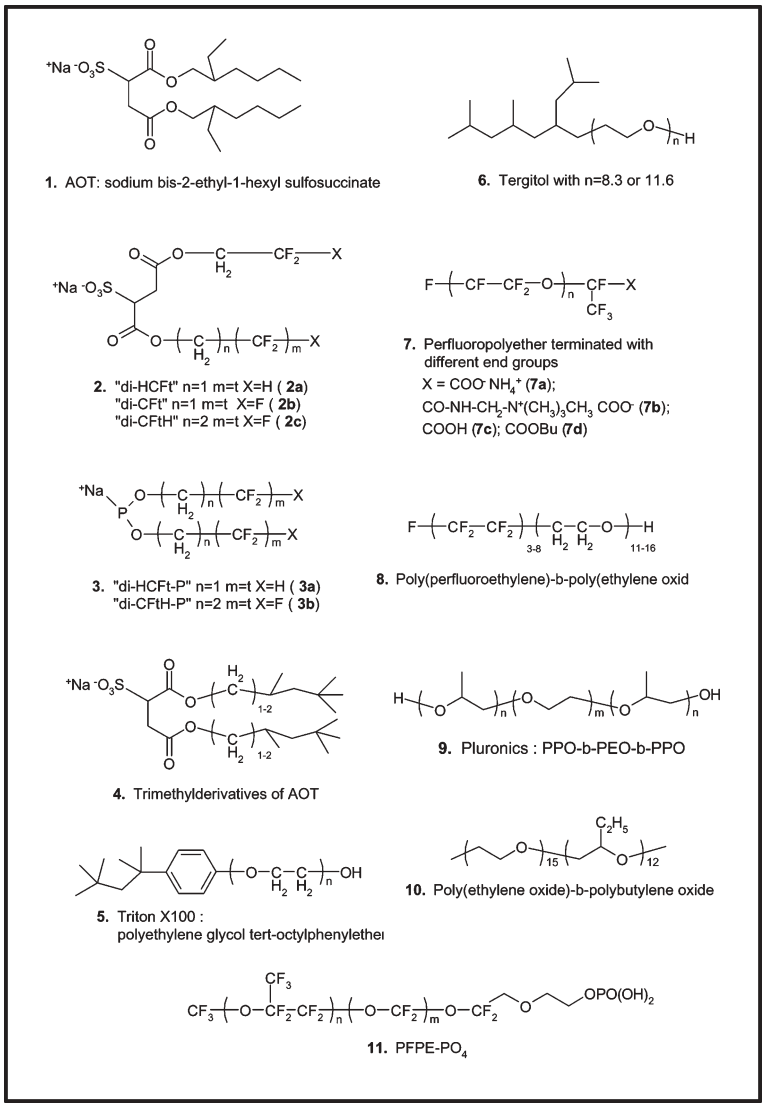

Fig. 2 Structures of the different surfactants used for $scCO_2$ emulsions.

"di-HCF6-P" (**3a** — Fig. 2, $n = 1$, X = H, $m = 6$) was effective at stabilising W/C microemulsions at pressures considerably lower than the sulfate based surfactant di-HCF6 (**2a** — Fig. 2).

The high cost of fluorinated stabilisers and their potential toxicity are major barriers facing the implementation of $scCO_2$ micro- or macroemulsions in industrial applications. Researchers are now focusing on the development of effective hydrocarbon surfactants. Although AOT is ineffective as a surfactant when used alone, the addition of methylated groups (**4** — Fig. 2) at the end of the hydrocarbon tail considerably increases its solubility in $scCO_2$ allowing the formation of W/C emulsions as demonstrated by small angle neutron scattering (SANS).[22] The ability of these methylated analogues of AOT to form stable dilute emulsions and macroemulsions (50 nm–4 μm) has been demonstrated, but stable microemulsions were not formed.[23] This limitation comes from the inability of CO_2 to fully solvate the surfactant tails, which is required to deter inter-droplet interactions. The commercially available, non-ionic surfactant Triton X100 (**5** — Fig. 2), which has a trimethyl group at one end, did not show good solubility in CO_2 and demonstrated no surfactant ability. However, these molecules did form aggregates in dense CO_2 by aggregation of their ethylene oxide (EO) chains and were successfully used in reactions to extract metal ions.[12] A new class of non-ionic amphiphiles with very short and bulky CO_2-philic trisiloxane head groups $[(CH_3)_3SiO)_2Si(CH_3)(CH_2)_3\text{-}EO_n]$ have been shown to be very surface active at CO_2/air interfaces. They were found to stabilise concentrated and dilute emulsions of water in $scCO_2$.[24] Similar results were obtained for a trifunctional hydrocarbon surfactant incorporating EO and propylene oxide (PO) groups.[25,26] The low molecular weight (below 600 g mol^{-1}) of these compounds and the presence of branched methyl groups cause them to have relatively high solubility in CO_2 and they are able to form W/C microemulsions but with only a low water uptake (with water-to-surfactant mole ratios, $W_o \sim 8$). Further research has demonstrated that incorporation of a short highly branched hydrocarbon block (Tergitol, **6** — Fig. 2), leads to stable W/C microemulsions with nanodroplet radii in the range 1.6–3 nm.[10] Sugar pentaacetates have also been found to have a high degree of solubility in CO_2, in part due to favourable specific polar interactions, and these may well make interesting candidates for the design of 'low-cost' surfactant tails.[27,28]

High molecular weight surfactants (>600 g mol^{-1}) are also referred to as polymeric surfactants and may consist of a CO_2-philic tail, which is usually fluorinated and an ionic CO_2-phobic head group. Ionic derivatives of perfluoropolyethers (PFPE, **7** — Fig. 2) have been studied in detail. Johnston and co-workers[29] reported the formation of stable reverse micelles in $scCO_2$ by Fourier Transform Infra-Red spectroscopy (FTIR) and many other studies have since been aimed at better understanding these systems. Recently, FTIR spectroscopic measurements revealed that the chain length of a PFPE

surfactant strongly affects its ability to form W/C microemulsions.[30] Among the surfactants investigated, a PFPE tail with an average molecular weight of 2500 g mol^{-1} led to W/C microemulsions with the highest water content.[30] The surfactant head group was found to have a significant effect. Non-ionic carboxylic acids (**7c** — Fig. 2) did not form micelles in dense CO_2 but cationic species (**7b** — Fig. 2) led to the formation of W/C emulsions with $W_o \sim 28$ and droplet radii in the range 1.6–3.6 nm.[31] Da Rocha and Johnston measured the interfacial tension at the water/CO_2 interface and determined that the surface area per molecule of surfactant was considerably larger than the surface area per molecule of surfactant at a water/oil interface.[32] This is a result of the much smaller interfacial tension at the water/CO_2 interface as well as the increased penetration of small CO_2 molecules into the extended tails of the surfactant molecules. A thick, structured monolayer is formed around the water droplets, comparable to the assembly of analogous hydrocarbon surfactants at water/oil interfaces.[33]

Interest in C/W emulsions and microemulsions has been stimulated recently. Here, water-soluble surfactants with a CO_2-philic portion are required. Lee *et al.* reported the use of ammonium carboxylate PFPE (PFPE-K) in the first formation of C/W microemulsions.[34] CO_2 is completely miscible with the low molecular weight ($\sim$600 g mol^{-1}) PFPE-based surfactants and aqueous PFPE micelles were found to swell substantially with addition of CO_2 (up to 8 CO_2 molecules per molecule of surfactant). Others have demonstrated that block copolymers containing blocks with very dissimilar solubility in $scCO_2$ can also be used as non-ionic surfactants. The self-assembly of such surfactants has already been reported extensively.[7,8,16] Some of these block copolymers can also stabilise concentrated C/W macroemulsions. For example, a very stable microemulsion system was reported by da Rocha *et al.*[35] where the surfactant used was a diblock copolymer with 3 to 8 units of perfluoroethylene as the CO_2-philic tail and 10 to 15 units of EO as the hydrophilic portion (**8** — Fig. 2).

The key to commercialisation of surfactant based technologies will be to eliminate the reliance upon expensive fluorinated and siloxane based materials and to find viable, hydrocarbon based CO_2-philes.[36–38] Recent investigations have revealed that pluronic materials (for example poly(PO)-*b*-poly(EO)-*b*-poly(PO) triblock copolymers, **9** — Fig. 2) have high activity at water/CO_2 interfaces.[39] Poly(PO) has improved CO_2-philicity compared to poly(EO) because of the methyl groups along its backbone. An investigation into the block copolymer poly(EO)-*b*-poly(butylene oxide) (**10** — Fig. 2), revealed this material to preferentially stabilise C/W microemulsions.[35] The ultimate design for effective block co-polymer stabilisers still remains a challenge.

Applications. The poor solubility of many polar compounds in $scCO_2$ limits their reactivity and W/C microemulsions have been reported as serving as effective reaction vessels or nanoreactors for inorganic,[40] organic,[41] and enzymatic reactions.[42]

Nanoparticles can be synthesised within the core of microemulsion droplets. The use of CO_2 provides many advantages: high diffusivity, acceleration of reaction rates, tuneable solvent strength through manipulation of the fluid density and easy separation of product particles. The first example of a stable suspension of metal nanoparticles was reported by Wai and co-workers.[13] Microemulsions containing $AgNO_3$ were stabilised by a mixture of AOT (**1** — Fig. 2) and PFPE-PO_4 (PFPE-PO_4, **11** — Fig. 2), acting as surfactant and co-surfactant, respectively (**1b** — Fig. 1). On addition of a reducing agent to the microemulsion system, silver particles were formed inside the emulsion droplets and particle dimensions were controlled by the size of the water cores.[15,43] The metal nanoparticles formed in this way can be used as *in situ* catalysts for chemical reactions in the fluid phase, for example the hydrogenation of olefins.[44] When used alone, PFPE-PO_4 is not able to stabilise microemulsions with large water cores and must be combined as a co-surfactant with AOT for successful stabilisation to be achieved[13] (**1b** — Fig. 1). However, in the case of an anionic PFPE, like PFPE-K (**7a** — Fig. 2), it is sufficiently active to stabilise microemulsions alone (**1a** — Fig. 1). Johnston and Korgel have prepared CdS semiconductor particles using PFPE-K.[45] An aqueous solution of Na_2S was injected inside a reactor containing a W/C microemulsion with $Cd(NO_3)$ dissolved in the emulsion droplet cores. The same stabiliser material was used in the formation and stabilisation of silver nanoparticles by the reduction of an aqueous $AgNO_3$ solution dispersed in reverse micelles in CO_2.[43] Particles synthesised by this technique were recovered by rapid expansion (RESS) or by deposition through depressurisation. However, agglomeration of small nanoparticles (5–15 nm) was observed during the recovery procedure.[13,46] Very recently it has been shown that agglomeration can be prevented by redispersing the metal nanoparticles (silver, palladium or silver/palladium) in an aqueous solution of the PFPE surfactant.[47] An alternative method for synthesising nanoparticles is to mix two microemulsions containing different metal ions in their micelle water cores. As a result of rapid exchange of the microemulsion content, new nanomaterials can be obtained such as the semiconductors CdS and ZnS[48] or silver halide compounds.[49]

Such advances in the formation of nanoparticles using W/C microemulsions as nanoreactors has opened up several opportunities for new research. Yu *et al.* have investigated the synthesis of palladium nanoparticles within a porous solid silica structure with the aid of surface-tethered fluorinated surfactants.[50] They suggest that tiny solid supported surfactant assemblies can act as nanoreactors, analogous to the micelle nanoreactors of microemulsions, allowing the synthesis of well-dispersed nanoparticles inside the porous structure.

Some work by Tsang and co-workers investigated the use of W/C emulsions for the oxidation of toluene to benzoic acid.[51] Emulsion drops containing the catalytic species for the reaction (Co^{2+} and Br^{+}) were stabilised by a fluorous surfactant in an $scCO_2$/toluene/O_2 continuous phase. The use of $scCO_2$ was found to allow easy separation and purification of the product, and high catalytic activity with selectivity and with no loss of solvent by oxidation. The nature of the fluorinated surfactant and its affect on the rate of micellar oxidation catalysis has since been investigated for this system.[52]

Cooper and co-workers have developed a new method for the production of well-defined porous polymers by templating C/W emulsions.[53,54] In this work, an emulsion of CO_2 in a solution of monomer (acrylamide) and cross-linking agent was prepared using a low molecular weight PFPE ammonium carboxylate surfactant (**7a** — Fig. 2, $M_w \sim 570$ g mol^{-1}). The temperature was then increased to allow polymerisation of the monomer solution. The resulting gel was found to template the emulsified CO_2 drops forming a porous structure. SEM micrographs of the dried product revealed that the templated pores were isolated and exclusively closed-cell in nature. Interestingly, poly(vinyl alcohol) (PVA) was found to improve the stability of the C/W emulsion leading to materials with improved pore volume, although the specific action of the PVA is not yet fully understood. This method is particularly useful because no organic solvents are used in either the synthesis or purification steps and no solvent residues are left in the materials. Very recently, this work has been extended by investigating the factors affecting C/W emulsion stability;[53] the viscosity of the aqueous continuous phase, the molecular weight of the PVA used and the nature of the surfactant. Also reported were various inexpensive hydrocarbon surfactants that have been shown to generate C/W emulsions with sufficient stability to form templated structures.

Polymer synthesis

A second important area of work often requiring the use of a surfactant (in this case also known as a stabiliser) is the synthesis of polymers in $scCO_2$. This area has already been extensively reviewed[2,3,7,8,16] and many active surfactants have been developed. In this type of process, the surfactant stabilises monomer droplets, or solid polymer particles formed during the polymerisation. A stabiliser consists of a CO_2-phobic portion, usually a hydrocarbon polymer that anchors inside or onto the surface of the growing polymer particles, and a CO_2-philic segment that extends into the CO_2 continuous phase preventing particle aggregation by steric stabilisation.

In both emulsion and suspension polymerisations, the monomer and polymer are insoluble in the continuous phase. Thus, suspension and emulsion polymerisations are relatively rare in $scCO_2$ since most monomers are highly soluble, although a few examples have been reported recently.[55–58] In emulsion polymerisation, the monomer and initiator are segregated, the monomer is insoluble in CO_2 and forms droplets, but the initiator is preferentially dissolved. The polymer formed is insoluble in CO_2 and must be stabilised as precipitated particles. Reverse emulsion polymerisations of water-soluble monomers can be performed in $scCO_2$, as reviewed elsewhere.[2,3] It is also possible to polymerise oil-soluble monomers like lactide or glycolide by the emulsion polymerisation technique. Hile and Pishko reported the first synthesis of poly(D,L-lactide-co-glycolide) ($P_{DL}LGA$) by emulsion polymerisation in $scCO_2$ using poly(perfluorooctyl acrylate) (PFOA) as the stabiliser (**12** — Fig. 3).[57] However, emulsion polymerisation typically leads to small, uniform particles and in this study there is no mention of the product morphology. The surfactant (PFOA) consists of a CO_2-phobic hydrocarbon backbone with a series of fluorinated graft side chains and has been developed and used extensively by others for dispersion polymerisation (*vide infra*).

In suspension polymerisation, the polymer and initiator are

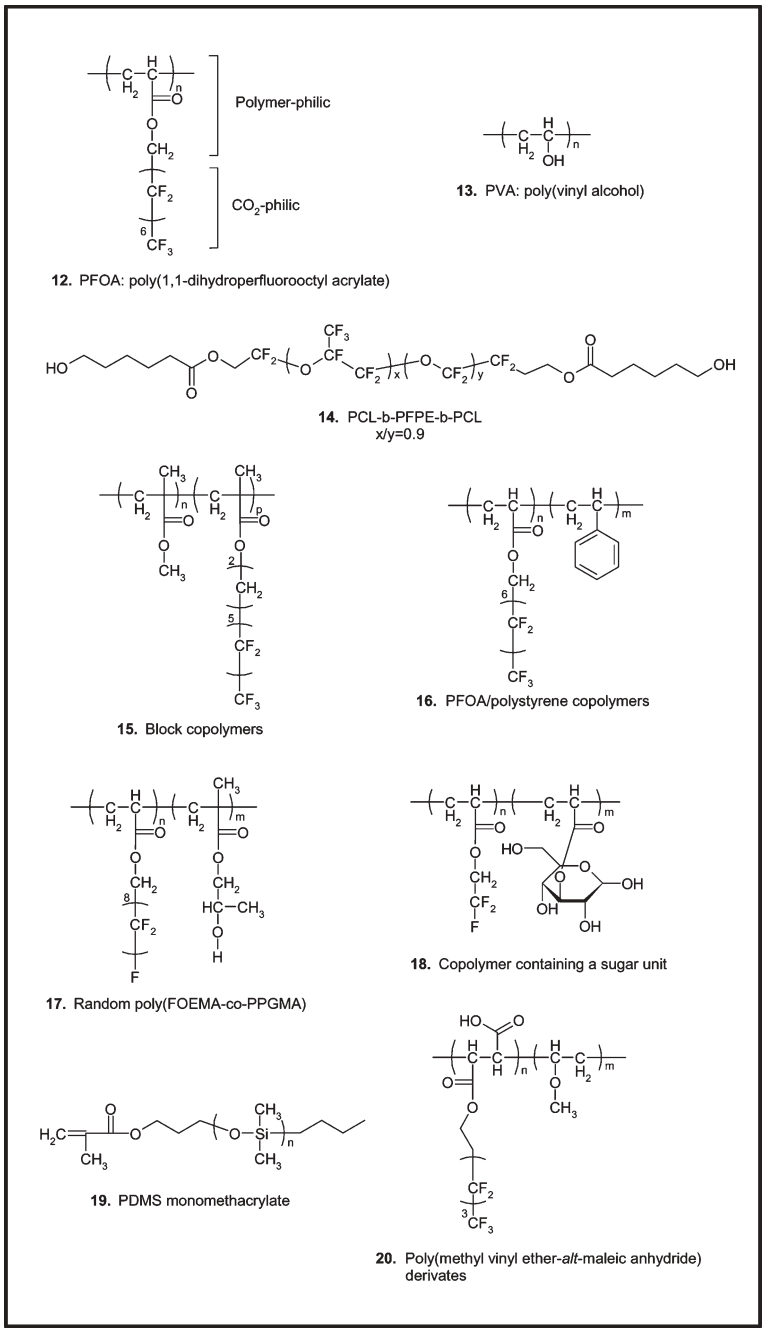

Fig. 3 Structures of the stabilisers used for polymerisations in $scCO_2$.

both soluble in the dispersed monomer droplets. Cooper *et al.* reported the free radical polymerisation of trimethylpropane trimethacrylate in a $scCO_2/H_2O$ continuous phase in the presence of PVA (**13** — Fig. 3) as the stabiliser.[58] The particle size is large (diameter $\sim$ 50 μm), and because of the unique porogen effect of CO_2, very highly controlled macroporous polymer beads were obtained. The average pore size and surface area in the beads can be tuned over a wide range by varying the CO_2 density. More recently, Bratton *et al.*[56] have carried out the suspension polymerisation of L-lactide in $scCO_2$ using a well-defined triblock copolymer as the surfactant (**14** — Fig. 3). The central block of the stabiliser is a PFPE which acts as the CO_2-philic portion; the two outer arms are short chains of poly(ε-caprolactone) (PCL) and act as the CO_2-phobic segments. These PCL chains anchor to the growing polylactide particles *via* transesterification and thus provide colloidal stability. This stabiliser can be used at loadings as low as 5 wt% and fine particles are produced (5–10 μm in size). As with conventional suspension polymerisation, the stirring rate has a crucial effect on the morphology of the powder. This is the first time that ring opening polymerisation has been performed in $scCO_2$ to yield polymer particles with a very fine morphology.

In dispersion polymerisation, the monomer and initiator are both soluble in the continuous phase. Once the polymer chains reach a critical molecular weight, they precipitate out of solution and this impacts dramatically upon the quality of polymer obtained. The key to making high molecular weight polymer is to use a surfactant, which ensures that the growing polymer chains remain dispersed in solution. This also leads to the formation of discrete polymer particles. The concentration and nature of the stabilising molecule significantly affects the molecular weight and morphology of the polymer product. Most reports so far concern the polymerisation of methylmethacylate (MMA) in $scCO_2$.[59–63] Many of the successful surfactants developed for the stabilisation of poly(methyl methacrylate) (PMMA) in $scCO_2$ have been fluorinated block copolymers[63] (**15** — Fig. 3) or grafted polymers (**20** — Fig. 3)[59] Variables such as chain length, block ratio, graft length and graft number density have been shown to have a dramatic effect on the outcome of the polymerisation. Recently, hydroxyethyl methacrylate[64] and glycidyl methacrylate[65] have been polymerised successfully in $scCO_2$ using a PFOA-*b*-PS block copolymer (**16** — Fig. 3) as the stabiliser. It has been suggested that random copolymers could also be effective as stabilisers. DeSimone and co-workers[66] investigated the dispersion polymerisation of styrene using poly(styrene-*co*-FOA) random copolymers (**16** — Fig. 3) as stabilisers. Olesik and Ding[67] stabilised PMMA dispersions with copolymers combining a CO_2-philic portion, perfluorooctylethylene methacrylate (FOEMA) or FOA, and a CO_2-phobic portion such as poly(propylene glycol)methacrylate (PPGMA) (**17** — Fig. 3). These copolymer stabilisers had large polydispersities and their specific structural order was also undetermined. However, controlled particles of PMMA were produced and the particle diameter of the polymer product was found to be dependent on the copolymer composition and on the amount of stabiliser used. Random fluorinated copolymers have also been investigated as surfactants[38] for the dispersion polymerisation of polar monomers such as 2-hydroxylethyl methacrylate. Sugar unit grafts act as the CO_2-phobic portion of the stabilisers while FOA units ensure good solubility in $scCO_2$ (**18** — Fig. 3). Interestingly, peracetylated sugar derivatives have recently been reported to have high solubility in CO_2 by both Beckman[28] and Wallen.[27] This has triggered research into the design of surfactants incorporating monosaccharides and cyclodextrin derivatives as the CO_2-philic portions.

Siloxane-based stabilisers are less-expensive alternatives to fluorinated materials and demonstrate reasonable solubility in CO_2. Block copolymers incorporating siloxanes have been used successfully as stabilisers for dispersion polymerisation in $scCO_2$.[68] An alternative approach is to use a macromonomer which has a reactive end-group that can graft into the growing polymer particles. Recent studies have investigated the commercially available methacrylate terminated poly(dimethyl siloxane) (PDMS-MMA) macromonomer (molar mass $\sim$10 kD, **19** — Fig. 3).[69–72] Additionally, a low molecular weight PDMS-MMA polymer (molar mass $\sim$ 2 kD) is effective at stabilising dispersion polymerisations of MMA in $scCO_2$ at concentrations as low as 0.2 wt%.[69] Such macromonomers stabilise dispersion polymerisations of glycidyl methacrylate,[73] or copolymerisation of MMA with hydrophilic monomers such as *N*,*N*-dimethylacrylamide[70] or 2-(dimethylamino) ethyl methacrylate.[74]

The majority of stabilisers reported in the literature contain a hydrocarbon backbone from which hydrogen atoms may be abstracted during free radical polymerisation. This can lead to the stabiliser covalently bonding to the polymer product. When the CO_2-phobic (or polymer-philic) portion of the stabiliser is large, the stabiliser can also become physically entrapped within the polymer product by entanglement. If the stabiliser has a reactive end group, it is likely to be chemically bonded to the polymer product. In all these cases, the final polymer is not completely pure and is contaminated with surfactant material. A commercially available PFPE that stabilises dispersions of PMMA in $scCO_2$ by a mechanism that avoids contamination of the final product has been reported.[59,75–78] This stabiliser anchors to the growing polymer particles by a very simple and reversible hydrogen bonding interaction. The stabiliser contains a PFPE tail providing CO_2-philicity and a carboxylic acid or ester head group that interacts with the PMMA particles (**7c** and **7d** — Fig. 2). FTIR spectroscopic measurements reveal that there is a hydrogen bonding interaction between the ester group of MMA and the carboxylic acid head group of the PFPE stabiliser. The main advantage is that this is a reversible interaction, which appears to prevent incorporation of the surfactant into the PMMA backbone. Very recently, the same behaviour has been observed for an ester[78] terminated PFPE material. These stabilisers are remarkably active. The carboxylic acid terminated material works effectively down to 0.1 wt% with respect to the monomer leading to PMMA product with high molecular weight and good morphology (Fig. 4). Similar behaviour was observed for a range of fluorinated graft stabilisers, synthesised by modification of a commercially available hydrocarbon polymer (**20** — Fig. 3).[59,77] In this case, the reversible interaction occurs between the acid side chain groups of the surfactant and the ester groups of the MMA repeat units. This type of interaction again seems to ensure that the stabiliser material does not contaminate the final polymer product. This method provides a clean synthetic route to high purity polymer products, which may be suited for use in medical applications.

To conclude, the commercialisation of polymerisation processes in CO_2 is rare. Only the surfactantless process for fluoropolymer syntheses[79] has so far been reported. This may well be attributable to the lack of cheap, recyclable surfactants for use in $scCO_2$. Thus, an important target is to develop low cost, non-fluorinated surfactants with good solubility in CO_2. Recently, some progress has been made. A modified hydrocarbon based upon a Pluronic stabiliser has been utilised for the ROP synthesis of the biomedically important poly(glycolide).[55] Thus, $scCO_2$ could replace hexafluoroisopropanol — the only other solvent appropriate for synthesis and processing of this material. Additionally, spherical polycarbonate nanoparticles were formed in CO_2 from a condensation polymerisation, again using a Pluronic triblock copolymer (**9** — Fig. 2).[80] These preliminary studies open a new route to the future design of cheaper surfactant materials.

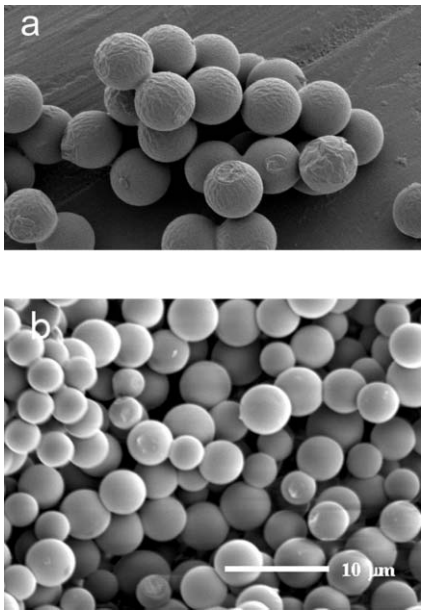

Fig. 4 Scanning electron microscopy (SEM) images of PMMA particles prepared using (**a**) Krytox 175FSL as the stabiliser (1 wt% wrt MMA)[76] and (**b**) 2 wt% of stabiliser based upon poly(methyl vinyl ether-*alt*-maleic anhydride).[59] Copyright 2000/2001 The American Chemical Society.

Other applications of surfactants

There is increasing interest in the development of inexpensive surfactants for a wide range of industrial processes. Examples include commercially available surfactants (Triton X100, **5** — Fig. 2), which have been utilised for microenscapsulation of aqueous polymer latex particles in $scCO_2$. The surfactant provides colloidal stability of the particles, which facilitates impregnation of additives into the aqueous polymer phase.[81] The same material has also shown some utility for replacing fluorinated surfactants for metal ion extraction[82] and selective separation based upon pressure induced pH switches.[83] Further developments include the preparation of classical water-in-oil (W/O) emulsions with conventional solvents (*e.g.* dichloromethane or heptane) and then the utilization of $scCO_2$ as an anti-solvent to yield micro- or nanoparticles.[84] This method has been applied to make magnetically responsive particles for medical applications.[85] Here, a W/O emulsion was prepared by suspension of a degradable polymer (*e.g.* $P_{DL}LGA$) and magnetic nanoparticles in dichloromethane using a fatty acid surfactant. This W/O emulsion was subsequently exposed to $scCO_2$. Silica nanoparticles have also been obtained by precipitation of a W/O emulsion using CO_2 both as an antisolvent and as a reactant.[86] A W/O microemulsion of an aqueous sodium silicate solution in isooctane or n-heptane was injected into $scCO_2$. The CO_2 rapidly removed the organic solvent and condensed the sodium silicate reverse micelles by reacting with them to form silica nanoparticles and sodium carbonate, which was later removed by filtration. Finally, surfactants are being used commercially for textile dry cleaning in liquid CO_2. This has been developed by ICI (Uniqema), the Linde gas group and a range of dry cleaning equipment manufacturers.[87] This liquid CO_2 cleaning process is called Washpoint and makes it possible for commercial dry cleaning operators to clean garments effectively without the use of chlorinated solvents at low temperature.

Polymers: blends and impregnation

The ability of $scCO_2$ to swell and plasticise a wide range of polymeric materials has proved invaluable in the development of many polymer-processing techniques, including polymer blending and impregnation. CO_2 interacts with polymer sites, such as electron donating functional groups (*e.g.* carbonyls), acting as a molecular lubricant and depressing the glass transition temperature (T_g) of the polymer, this is referred to as plasticisation.[88,89] This enhances polymer chain mobility and thus facilitates polymer processing.[6] Over the past decade, it has been shown that $scCO_2$ can accelerate the absorption of organic penetrants and organometallic compounds into a polymer substrate leading to the synthesis and development of a variety of new materials.[3–6,90]

Immiscible blends

One area of interest is the synthesis of immiscible polymer-polymer blends and interpenetrating networks (IPNs). This work was pioneered by McCarthy and Watkins who investigated the free radical polymerisation of styrene in a range of polymer hosts including, poly(chlorotrifluoroethylene), low density polyethylene and poly(4-methyl-1-pentene).[91] In this study, styrene monomer and the chosen free radical initiator (AIBN or *tert*-butyl perbenzoate) were impregnated into the polymer substrate by soaking the substrate in an $scCO_2$/styrene/initiator solution. The final polymerisation process was then conducted at raised temperature in either the presence of $scCO_2$ or after venting the CO_2 solution. Significant incorporation of pure polystyrene (PS) in all polymer substrates was confirmed using differential scanning calorimetry (DSC) and IR analysis. Since this work, McCarthy and others have extended this processing method to prepare several different immiscible polymer–polymer blends.[92–96]

Han and co-workers have investigated the phase behaviour of various CO_2/styrene/polymer substrate systems and the preparation of the corresponding polymer substrate/PS blends.[97–102] For example, films of blended poly(ethylene terephthalate) (PET) and PS were prepared by soaking weighed PET films in a solution of styrene monomer and AIBN in $scCO_2$.[100] The CO_2 was then released and the impregnated film heated to polymerise the styrene. The effects of soaking time, styrene concentration and CO_2 pressure on the mass uptake of styrene in the PET film were investigated. Styrene uptake was found to increase with increasing CO_2 pressure up to a maximum, beyond which further increases in pressure led to a reduction in styrene load. Similar behaviour has been observed for other blend systems[97,98] and this is likely a result of the improved solvent power of $scCO_2$ at higher pressures causing the styrene monomer to preferentially reside in the supercritical phase rather than partition into the polymer substrate. Successful blending of PET with PS was established using IR spectroscopy. Mechanical testing revealed that a PET/PS blend containing 33% PS has improved tensile strength and toughness. In some cases it was possible to extract the PS phase from the PET host by use of THF or toluene. For other blends very little PS could be removed. This suggests a degree of cross-linking in the blend, or that the PS chains significantly entangle with the PET substrate. A similar study was carried out for polypropylene (PP)/PS blends.[102] In this case, FTIR spectra revealed that the PS existed in two different states: free PS homopolymer, which can be extracted by THF, and PS entangled within the PP. DSC measurements for a blend containing $\sim$18% PS showed a glass transition corresponding to the PS phase and a melting transition corresponding to unmodified crystalline PP. This indicates that the styrene polymerisation occurs mainly within the amorphous regions of the PP substrate. This is consistent with the fact that $scCO_2$ swells amorphous polymers to a much greater extent than crystalline polymers[103,104] and is therefore likely to deliver styrene monomer to these regions more effectively. Transmission electron microscopy (TEM) was used to examine the distribution of PS from the surface of the blends to the centre. TEM

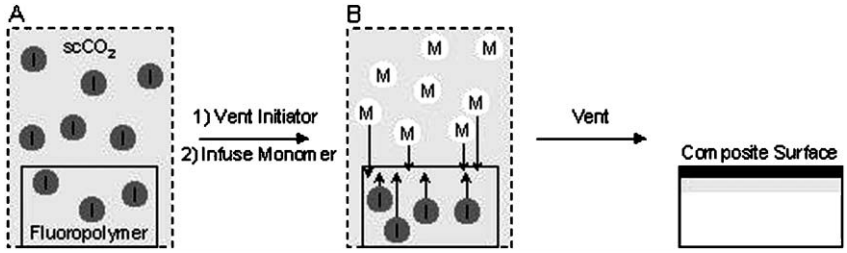

Fig. 5 (**A**) $scCO_2$ is used to impregnate initiator throughout the fluoropolymer substrate. (**B**) In a second step, $scCO_2$ carries ECA monomer into the fluoropolymer and at the same time initiator diffuses out. Polymerisation occurs where these reactants meet.

revealed that PS was dispersed homogeneously throughout the PP matrix, but that phase separation had occurred with PS domains in the nanometre size range. In mechanical testing, the Young's modulus, tensile strength and the elongation-at-break of the blends were shown to have improved significantly, with maximum improvement recorded for a sample containing ~9% PS. Recently, PP/PS IPNs have been synthesised.[101] In this case, a cross-linking agent, divinyl benzene, was added and considerable improvements in the mechanical properties of blended products were recorded.

It is possible to modify the surface of a polymer substrate by manipulating the blending conditions.[94] Kung *et al.* investigated recently the modification of a fluoropolymer surface with poly(ethyl 2-cyanoacrylate) (PECA) by anionic polymerisation in $scCO_2$.[105] The technique described previously for preparing polymer blends[91] was modified in this work to encourage the formation of a composite surface. The polymer substrate was first soaked in a solution of nucleophilic initiator (pyridine or triphenylphosphine) in $scCO_2$. The system was then vented, so as to trap the initiator within the polymer matrix. The polymer was exposed to a solution of the monomer ethyl 2-cyanoacrylate (ECA) in $scCO_2$. As the monomer absorbed into the substrate, the initiator was desorbed causing the two species to meet and react in the upper surface regions of the polymer. The aim was to form a polymer core material possessing a composite surface. However, the precise location of the PECA formed within the substrate was found to depend on the relative diffusion rates of the monomer and initiator into and out of the polymer matrix (Fig. 5). When pyridine was used as the initiator all the PECA was formed outside the substrate in the fluid phase, indicating that this initiator diffuses out of the substrate faster than the monomer diffuses in. When the initiator was triphenylphosphine, no polymerisation occurred in the fluid phase and analysis of the composite products revealed that the PECA phase had formed below the surface of the polymer. The ECA monomer therefore diffuses into the polymer matrix faster than the triphenylphosphine diffuses out. These results are likely due to the varying solubility of ECA, pyridine and triphenylphosphine in CO_2 and the interaction of the various reactants with the substrate polymer. By choosing the appropriate monomer/initiator system the location of composite formation within a substrate should be controllable.

Zhang *et al.* have reported the synthesis of PMMA/ultra high molecular weight polyethylene (UHMWPE) blends in $scCO_2$.[106] Blends of UHMWPE are typically very difficult to prepare due to the high melt viscosity of this polymer and its very low solubility in common organic solvents. Supercritical CO_2 was shown to provide an excellent medium for processing this polymer at relatively low temperatures. UHMWPE is not soluble in $scCO_2$, but is penetrated effectively. Blends were prepared in a one-pot synthesis by $scCO_2$-assisted impregnation of methyl methacrylate (MMA) monomer into a UHMWPE substrate followed by *in situ* polymerisation. Tapping mode atomic force microscopy (TMAFM) across thin sections of the resulting composites provided direct spatial mapping of the composite surfaces. The phase images were recorded (Fig. 6) for the virgin UHMWPE, $scCO_2$-treated UHMWPE and an UHMWPE/PMMA blend. Three distinct phases were identified in the blends: crystalline regions of UHMWPE, amorphous regions of UHMWPE and amorphous regions of PMMA. Clearly, treatment with $scCO_2$ alone has only a modest affect on the observed phase images. In the presence of MMA the two polymers are clearly phase separated and do not mix at the molecular level; PMMA amorphous domains were found to be 10–100 μm in size. The formation of

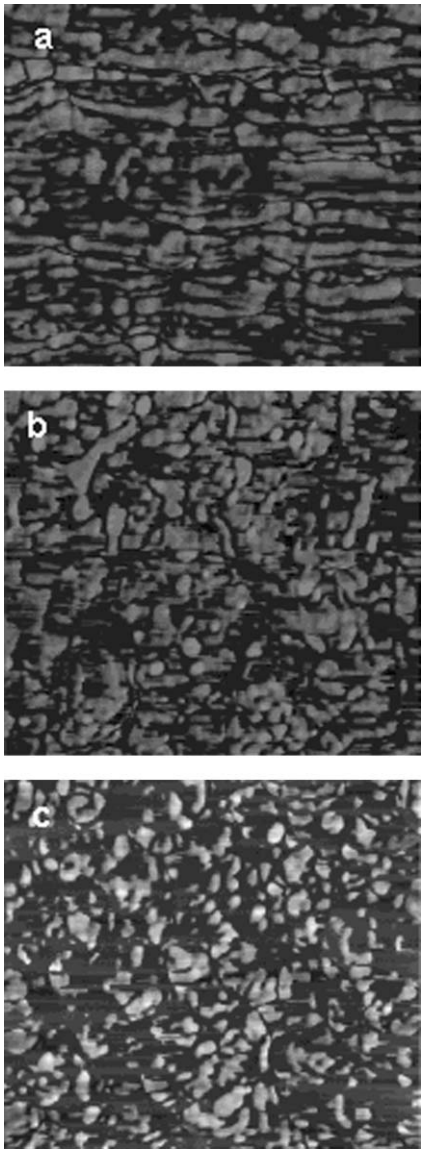

Fig. 6 TMAFM phase images of (**a**) as received UHMWPE, (**b**) $scCO_2$-treated UHMWPE — a modest effect is observed — and (**c**) a 53/47 (w/w) UHMWPE/PMMA blend. The bright regions are identified as crystalline phase and the dark regions as amorphous phase. PMMA resides only in the amorphous regions of the blend.[106]

larger regions of PMMA is restricted by the UHMWPE crystallites. Interestingly, the incorporation of PMMA caused the crystalline UHMWPE lamellar regions to break up into smaller crystallites. This is probably due to the partial melting of the crystalline UHMWPE at the processing temperature of 120 °C, allowing MMA to diffuse into the molten portions and polymerise. This work has been extended to other alkyl functionalised monomers such as ethyl methacrylate (EMA) and propyl methacrylate (PMA).[107] As the size of the side chain on the monomer increases, the loading of methacrylate in the substrate was found to decrease. This is likely due to the larger monomers diffusing more slowly through the UHMWPE matrix. FTIR spectroscopic analysis across the composite samples revealed PEMA-UHMWPE blends to be homogeneous throughout the bulk whereas PPMA-UHMWPE blends were found to have a much lower concentration of PPMA at the centre of the sample. Very recent studies have extended this methodology to the preparation of composites of nanoparticulate biodegradable polymers within the UHMWPE host.[106]

Innovative work by Lesser and co-workers has explored $scCO_2$ as a reaction/processing medium for the fabrication of fibre-reinforced composite materials.[108] The demand for these materials is increasing because of their high strength and low density. Nylon 6,6 fabric was initially placed in a mould and covered with a solution of initiator (*tert*-butyl-peroxybenzoate) and MMA or styrene monomer. The mould was then placed in a press, so as to apply a compressive force, and CO_2 added to the desired pressure. The negligible surface tension of $scCO_2$ ensured that the monomer was carried throughout the mould vessel, wetting all surfaces of the fabric. It also plasticised the Nylon fibres, impregnating initiator and monomer preferentially into amorphous regions. The system was heated to initiate polymerisation of the monomer, which occurred within the fibres as well as in the surround. The aim was to create good adhesion between the fibres and the polymer matrix without the need for chemically specific compatibilisers often required in conventional fabrication techniques. Fig. 7 shows composites prepared with and without the use of $scCO_2$. It can be seen that when $scCO_2$ is used to aid impregnation of MMA, the fibre volume increases significantly and the fibres grow to the extent that they impinge on each other. In Nylon/PS composites, the crystalline regions of the Nylon fibres seemed to template the polymerisation of PS leading to a fairly ordered structure of amorphous Nylon and PS sandwiched between crystalline Nylon lamellar regions. Composites were therefore prepared with an ordered structure not only on the macroscale of fibre reinforcement, but also on the nanoscale of crystal structure reinforcement. In principle, this methodology could lead to a dramatic increase in the range and control of composite mechanical properties in the future.

$scCO_2$ has attracted attention as a solvent for the preparation of electrically conductive composites.[109–114] Conducting polymers, including polypyrrole and polythiophene, are of interest in applications such as chemical and optical sensors,[115] light emitting diodes[116] and rechargeable batteries.[117] However, these materials are usually hard, brittle, nonfusible and insoluble in most solvents. Therefore, they are often blended with other insulating polymers so as to combine good electrical and mechanical properties. Tang and co-workers have investigated the synthesis of polypyrrole (PPy)-PS composites using $scCO_2$ (50 °C, 131.4 atm) or high-pressure liquid CO_2 (30 °C, 79.5 atm) as the processing solvent.[111,112] A PS substrate was first soaked in a solution of pyrrole monomer and CO_2. The impregnated substrate was then exposed to an oxidant ($FeCl_3$) to allow polymerisation to occur. The morphology and conductivity of the resulting products was found to strongly depend on the blending and doping conditions. Using $scCO_2$ rather than high pressure liquid CO_2 during the impregnation stage considerably improved the conductivity of

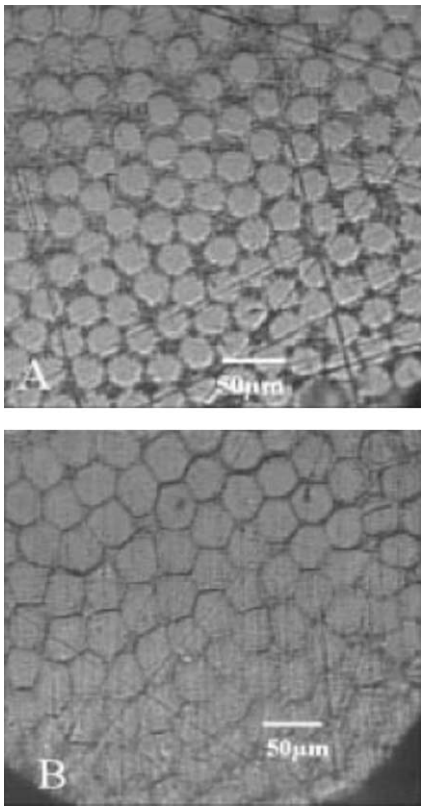

Fig. 7 Optical images of Nylon fibre/PMMA composite cross-sections (**A**) control composite prepared in the absence of $scCO_2$ and with a minimal compressive force, (**B**) composite fabricated using 14 MPa $scCO_2$ and 2.8 MPa compressive force.[108] Copyright 2003 Wiley.

the product material. The key to a successful conducting blend is good interconnectivity of the electrically conducting polymer throughout the substrate. $scCO_2$ leads to improved plasticisation (or swelling) of the PS matrix during impregnation and therefore enhances the incorporation of monomer, which encourages the formation of a conducting network. Abbett *et al.* impregnated porous, cross-linked PS with a solution of $scCO_2$ and the oxidant ferric triflate.[113] The pores of the substrate allowed rapid diffusion of the $scCO_2$/oxidant solution throughout the sample. The host polymer was then exposed to a solution of $scCO_2$ and the monomer 3-undecylbithiophene (3UBT). Oxidative polymerisation occurred *in situ* leading to the formation of a film of conducting polymer inside the porous host. The morphology and conductivity of composite products were again greatly influenced by experimental conditions such as temperature and pressure. Increasing either of these parameters led to an increase in the uptake of oxidant and monomer and therefore to an increase in the conductivity of the composite product. However, above a certain temperature twisting of the poly(3UBT) chains reduced the conjugation of the polymer and therefore lowered conductivity. Additionally, above a certain pressure, pneumatic stresses on the polymer were thought to reduce the uptake of reactants, again leading to a reduction in conductivity. Optical micrographs (Fig. 8) of P3UBT/PS blends prepared under different experimental conditions show those blends found to have highest (micrograph **A**) and lowest (micrograph **B**) electrical conductivity. It is clear that interconnected networks of conducting polymer (**A**), rather than segregated domains (**B**), are essential for the composite to have significant electrical conductivity and that interconnectivity is dependent on experimental conditions. The preparation of conductive PPy/polyurethane (PU) composite foams has also been reported.[109] Here, the PPy and the conductivity were found to be restricted to a relatively thin layer near the surface of the foam as a result of poor

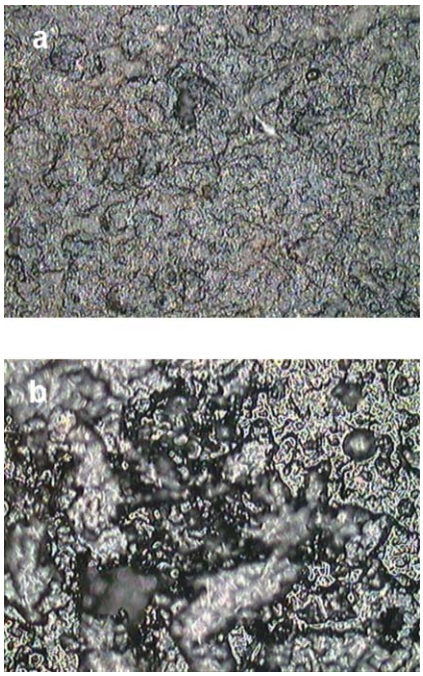

Fig. 8 Optical micrographs of composites of P3UBT/PS prepared at (**A**) 313 K and 20.7 MPa and (**B**) 413 K and 10.5 MPa.[113] Copyright 2003 The American Chemical Society.

penetration of the oxidant into the polymer matrix. This is caused by the low solubility of ferric triflate in $scCO_2$ and the inability of $scCO_2$ to effectively swell PU. In a further study, the authors improved uptake and dispersion of PPy throughout the sample by using ethanol as a co-solvent with $scCO_2$.[110]

Inorganic/organic composites

Polymeric materials incorporating nanosilicate reinforcements have been found to have interesting physical and mechanical properties.[118] Lesser and co-workers have developed a synthetic route to polymer-based composites with high concentrations of nanosilicate and a high degree of order.[119] $scCO_2$ was used as the reaction medium allowing homogeneous dispersion of monomer, initiator and subsequent polymerisation under lower viscosity. This overcomes the challenges of high viscosity usually encountered in the processing of these materials at silicate concentrations above 20 wt%. Composites were prepared by adding a known amount of organically modified layered silicate, MMA or styrene monomer and *tert*-butyl peroxybenzoate initiator into a reaction vessel. The vessel was then pressurised with CO_2 and the reactants allowed to equilibrate before temperature was increased to initiate polymerisation. In the final stage of the processing procedure a mechanical force was applied to the top of the chamber to compact the sample and induce a nematic orientation to the silicates. Products were analysed by SEM and small angle X-ray scattering (SAXS), which revealed them to have an intercalated morphology with PMMA confined to the galleries between silicate stacks leading to well ordered alternating layers of polymer and silicate. In terms of physical properties, these materials offer true polymer–ceramic hybrid properties. The nanocomposites exhibited a significantly higher storage modulus, and by inducing a nematic order to the silicates, a 220% increase in tensile modulus was achieved for the glassy polymer. Green *et al.* have prepared silicon containing organic/inorganic composites by infusing $SiCl_4$ into poly(styrene-co-allyl alcohol) (PSAA) or soluble starch (SS) using $scCO_2$ as the carrier medium.[120] The $SiCl_4$ went on to react with the alcohol groups present along the polymer backbones to form Si–O–CH_2PSAA and Si–O–SS linkages (determined by FTIR analysis) and therefore silica-crosslinked composites. It is reported that SEM images reveal the silica to be dispersed homogeneously throughout the PSAA matrix and the size of the silica particles to be in the range 50–200 nm, although no micrographs are shown. Thermal data indicate that the formation of the reinforcing inorganic network throughout the organic substrates improved the thermal stability of the polymers and solvent resistance was also enhanced. Using $scCO_2$ as an alternative processing medium eliminates the problems associated with drying in the sol–gel reactions usually used to prepare such materials.

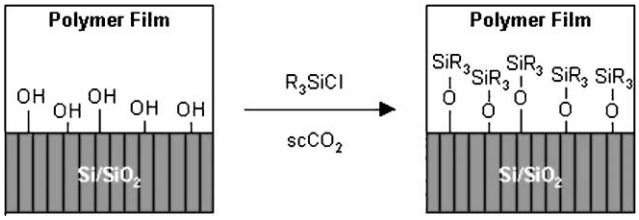

Fig. 9 Hydroxyl groups of a silicon wafer surface buried in a polymer are modified *in situ* with FDCS using $scCO_2$ as a solvent and swelling agent.

It has been shown that organic/inorganic buried interfaces can be chemically modified using $scCO_2$ as a solvent and swelling agent. Jia and McCarthy used silicon wafers coated with polymer films (PS or PMMA) to create model organic/inorganic composite systems and (tridecafluoro-1,1,2,2-tetrahydrooctyl)dimethylchlorosilane (FDCS) to covalently attach and chemically modify the buried silica surface (Fig. 9).[121] The extent of reaction at the buried interface depends on the diffusivity of the silane in the CO_2-plasticised polymer film, the accessibility of the silanol groups on the silica surface and the reaction kinetics of FDCS with the surface silanols. In the case of the SiO_2/PS interface, changing from liquid CO_2 (1100 psi, 23 °C) to $scCO_2$ (1200 psi, 35 °C) led to increased surface modification. At supercritical conditions the degree of swelling of the polymer film and the diffusion rate of the silane solution throughout the polymer matrix were considerably improved leading to enhanced modification. A complete monolayer was difficult to obtain at the buried surface because of confinement and solubility effects, although surface coverage as a high as 90% was observed. Modification at the SiO_2/PMMA interface was less effective than SiO_2/PS because the ester groups of PMMA hydrogen bond with the surface silanols limiting chain mobility at the surface and inhibiting reaction. Appropriate choice of silane reagents will lead to improved mechanical properties for such organic/inorganic composites.

Mokaya and co-workers investigated the use of $scCO_2$ and other supercritical solvents for post synthesis alumination of mesoporous silica to form mesoporous aluminosilicates.[122] These materials are of considerable research interest as solid acid catalysts and the low viscosity and high diffusivity inherent to SCFs might lead to good Al dispersion throughout the silica substrate and therefore to improved hydrothermal stability; a key requirement for the successful use of mesoporous aluminosilicates as solid acid or ion exchangers. The processing procedure involved soaking the silica substrate in a solution of $scCO_2$ and aluminium isopropoxide at elevated temperature with vigorous stirring, followed by calcination at 600 °C for several hours. From nuclear magnetic resonance (NMR) spectroscopic analysis, products were found to have at least 60% tetrahedrally coordinated Al indicating efficient transport of reactants throughout the substrate by $scCO_2$.

The unique transport properties of $scCO_2$ have also been exploited to impregnate metal precursor complexes into polymers. Watkins and McCarthy first reported the formation of metal nanoparticles with the $scCO_2$ assisted infusion of

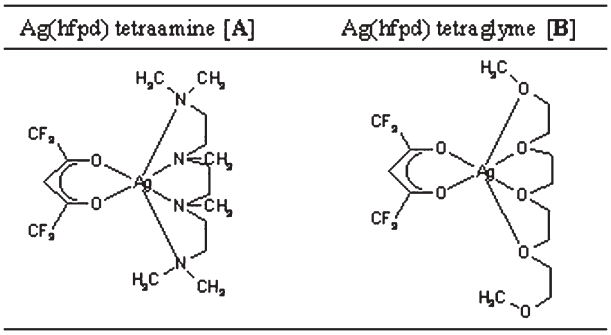

Fig. 10 Coordination precursor complexes used in the impregnation process.

$PtMe_2(COD)$ into poly(4-methylpent-1-ene) and poly(tetrafluoroethylene).[92] Composite products of this nature are interesting for a wide range of chemical and physical applications; from catalysis to microelectronics,[123] novel magnetic materials[124,125] and for specialised optical applications.[126] Recently, silver precursor complexes ($Ag(hfpd)L_1$, **A**, and $Ag(hfpd)L_2$, **B**, shown in Fig. 10) have been infused into poly(styrene-divinylbenzene) beads and silica aerogels using $scCO_2$ as the processing solvent.[127] The precursor complex was then reduced to silver metal nanoparticles using hydrogen, followed by $scCO_2$ extraction of the complex ligands. The precursor must be soluble in $scCO_2$ and must decompose to release the metal and generate soluble organic ligand residues. The ligands enhance the solubility of the precursor by shielding the metal centre so that $scCO_2$ encounters only a hydrophobic shell. By controlling the solubility of the precursor complex through ligand design, it should be possible to control the dispersion and concentration of metal particles throughout the support.

The effect of substrate material and precursor structure on the formation and size distribution of metal nanoparticles has been investigated. The precursors yielded nanoparticles of silver metal in the poly(styrene-divinylbenzene) beads and silica aerogels, and complete reduction and removal of the precursor complexes was confirmed by powder X-ray diffraction (XRD). TEM micrographs of nanocomposites revealed fine dispersions of particles within the two different matrices (Fig. 11). Complex **B** led to better incorporation of silver into the solid supports because of the higher solubility in $scCO_2$. Increasing the amount of precursor in the carrier solvent leads to better transfer of the complex into the support matrix. The same process has now been adopted to create novel catalytic materials.[128]

$scCO_2$ has also been used as a solvent for the deposition of metal films on inorganic and organic substrates[129] as well as the impregnation of polymer films with metal particles.[130,131] In 1999, Watkins *et al.* reported the deposition of platinum metal onto silicon wafers, poly(tetrafluoroethylene) (PTFE) sheets and Anopore aluminium oxide porous membranes by the reduction of a solution of $scCO_2$ and the organometallic compound $CODPtMe_2$.[129] SEM and X-ray photoelectron spectroscopy (XPS) analysis revealed continuous films, free of ligand-derived contamination. This work demonstrated the use of $scCO_2$ as a clean solvent for the reduction of organometallic compounds at low temperature to produce high purity metal. Taylor and co-workers have studied the impregnation of silver complexes into polyimide[130] and poly(etheretherketone) (PEEK)[131] films using $scCO_2$ as the carrier fluid. Optimal conditions for the production of a reflecting polyimide film were 100 °C/5000 psi/120 min for impregnation followed by 100 °C/60 min/30 standard cubic feet per hour air flow for the cure process. Thermal treatment of the impregnated film resulted in a highly reflective silver surface on all sides. PEEK films with high reflectivity have also been obtained. The size of the silver clusters and reflectivity of the surface was again found to strongly depend on the impregnation and cure conditions.

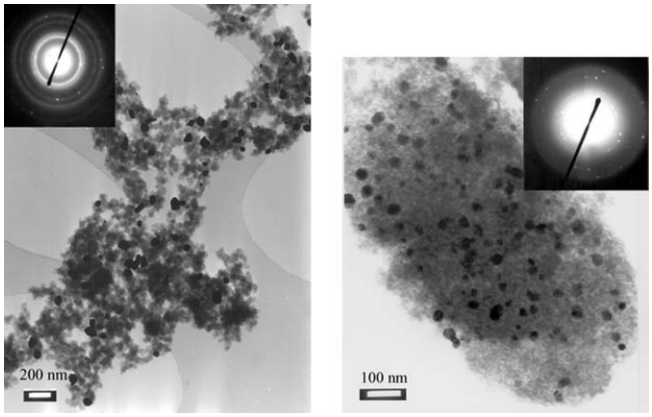

Fig. 11 TEM images of poly(styrene-divinylbenzene) (left) and silica aerogel (right) impregnated with silver nanoparticles (*via* complex **B**). Inset, ring diffraction patterns confirming the particles to be metallic silver.[127] Copyright 2002 The Royal Society of Chemistry.

Biomaterials

Organ and tissue loss or failure as a result of trauma, infection, disease or age-related degeneration is a major human health problem.[132,133] Certain organs or tissues cannot heal adequately by themselves and require treatment to restore their function. Transplantation is a standard therapy but a shortage of donor tissue means that not enough patients can receive the life-saving organ/tissue transplantations that they need. Thus, both clinical and commercial research has focussed recently on developing techniques for tissue regeneration.[134,135] Novel materials are needed to induce cell attachment, differentiation and proliferation for tissue growth *in vitro* and/or *in vivo*.

Porous, three-dimensional polymer scaffolds can be used as cell supports to provide mechanical stability and structural guidance and to allow a high density of cells to be seeded before or after transplantation into the body. These porous devices can be loaded with drugs, nutrients, hormones and growth factors to promote cell differentiation and vascularisation of the developing tissue.[136,137]

Another aspect of biomaterials involves the production of polymer particles. These particles can be used to encapsulate active factors and enable controlled delivery to well targeted locations in the body.[133,136,138–140]

Conventional techniques for preparation of polymer scaffolds or particles typically use organic solvents and high temperatures that may be harmful to adherent cells, nearby tissues or biologically active factors. Therefore, the use of supercritical fluids, in particular $scCO_2$, is seen as an attractive alternative approach for a variety of biomedical applications in the tissue-engineering field and pharmaceutical sciences in general.

Particle formation

Conventional techniques for the micronisation, co-precipitation, impregnation and encapsulation of pharmaceuticals can be problematic because the heat and mechanical stresses involved can cause thermal and chemical degradation of the drug and alter its properties.[141] Large amounts of solvent and surfactants/emulsifiers are also used which can lead to unacceptable levels of residual impurities necessitating further purification steps. $scCO_2$ technology has emerged as a promising alternative for the precipitation of particles from solution as it is environmentally benign, has tunable solvent properties and produces particles that are free from solvent residues after processing.[90] In particular, this technology provides a clean way to process thermally labile or unstable

biological compounds and produce active particles for controlled delivery in the body.

Several methods for the preparation of particles using supercritical fluids have been described (for reviews see Jung *et al.*[84] and Ye *et al.*[15]). These methods include Rapid Expansion of Supercritical Solutions (RESS), Supercritical Antisolvent precipitation (SAS) and related processes (Gas Antisolvent precipitation, GAS; Solution Enhanced Dispersion by Supercritical fluids, SEDS; Precipitation with Compressed Antisolvent, PCA; and Aerosol Solvent Extraction System, ASES) and Particles from Gas Saturated Solutions (PGSS). All of these involve the use of supercritical fluids, but in each case the role of the fluid is very different.[141,142]

In the **RESS** method, the solutes, drug and polymer, are dissolved in an SCF and expanded rapidly into a region of much lower pressure.[15,143,144] This results in a substantial drop in their solubility and subsequent co-precipitation. The precipitate forms very small molecular clusters, ion pairs or dispersed individual molecules. A very wide range of morphologies and particles sizes are possible.[145] However, the key drawback is that the solutes must first be soluble in the SCF and the lack of solubility of many compounds in $scCO_2$ is, therefore, a disadvantage.[146]

In **antisolvent techniques** *e.g.* SAS, the solid of interest is first dissolved in a suitable solvent and this solution is then rapidly introduced into $scCO_2$ through a narrow capillary tube. The conventional solvent is chosen to be miscible with the $scCO_2$ so that the fluid removes the solvent to cause precipitation of the solute as fine particles.[147–149] The technique is very broadly applicable because many conventional organic solvents are miscible, and most pharmaceutical materials are completely insoluble in $scCO_2$.[146] The technique has very wide applications, for example Gupta and Chattopadhyay *et al.*[148] have used SAS for the size reduction of fullerene particles, a new stable form of carbon which has potential uses in a variety of applications including pharmaceuticals, lubricants, composite materials, specialised coatings and interfacing membrane surfaces. Using this method, many other pharmaceutical substances, such as proteins, antibiotics and steroids, have been processed successfully into nanoparticles or encapsulated inside biodegradable polymers to form particles that can be used for drug delivery and controlled release.[85,146]

The **PGSS** method does not rely upon $scCO_2$ as a solvent or an anti-solvent. In this case the high solubility of CO_2 in some solid materials can result in a so-called gas-saturated solution/suspension in which plasticization or melting occurs at significantly lower temperatures than one might normally expect. The liquefied materials can subsequently be foamed, or expanded through a nozzle to form solid particles or droplets. The process occurs because the solubility of the compressed gases in liquids and solids is usually higher than the solubility of the liquids and solids in the compressed gas phase.[84] Examples of application of this technology include the novel preparation of powder coatings[84] and the micronization of the drug nifedipine.[150,151] The PGSS method can also be used to suspend active compounds in polymer supports or to load polymeric microspheres. Again, a key advantage of the technique is that the carrier/polymer and the active substance do not need to be soluble in the SCF, making it applicable for a very wide range of applications.[152]

Recently, Hao *et al.*[153] have developed the PGSS method to exert control on particle size and morphology by implementing a backpressure of inert gas (N_2) to slow the rate of CO_2 loss from the polymer and therefore control the solidification process. Again, neither the protein (drug) nor the polymer needs to be soluble in $scCO_2$, and no conventional solvents are used to dissolve the drug or the polymer. This contrasts with both the RESS and the antisolvent methods and in addition, the whole process is carried out at near ambient temperatures. The mixing and particle generation process simply require the polymer to be plasticised efficiently by $scCO_2$. Amorphous poly(D,L-lactide) ($P_{DL}LA$) is a good example of a polymer processable by PGSS, it liquifies effectively under conditions close to the critical point of CO_2 or even at much lower temperatures (<10 °C). Solid drug particles are incorporated into the plasticised polymer and under controlled depressurisation the mixture is sprayed into a collecting chamber, through a cone nozzle where a substantial drop in pressure induces particle formation. The drug particles are completely unaffected by the processing. Experimental conditions must be manipulated in order to control the polymer/drug particle morphology. Spraying the plasticised mixture into a collecting chamber with a controlled backpressure of N_2 is key to the final particle size and morphology. This control is clearly illustrated (Fig. 12) in the differences in morphology of sprayed product generated by spraying into atmospheric pressure or into a backpressure of N_2. Variation in the backpressure of the collecting chamber allows particle size to be controlled.[153]

Another application for particle formation is the preparation of metal particles within a wide range of solid supports leading to materials with a wide range of chemical and physical applications.[15,92,127,154] The incorporation of silver complexes into solid polymer supports has led to the formation of inorganic/organic composites. Such composites may have a particular interest in many applications for example, in fluorescent labelling for cellular imaging.[155] Silver is known to be a very good antibacterial agent because it is a non-toxic, naturally occurring, metal that can kill many harmful microorganisms.[156] One major concern in present day healthcare is the number of hospital infections resulting from surgical implants, such as urinary and central venous catheters, brain shunts and aorta grafts.[157] These catheter tubes provide an ideal environment for bacterial growth. The conventional route to prevent infection is to modify the surface of the material (polydimethylsiloxane (silicone) and polyurethane), with an antibacterial coating (antiseptic, antibiotic, *etc.*).

We recently reported an $scCO_2$ method to prepare silver nanoparticles within commercially available silicone and polyurethane polymers in a controlled and reproducible way.[158] This alternative approach seems to be a very promising

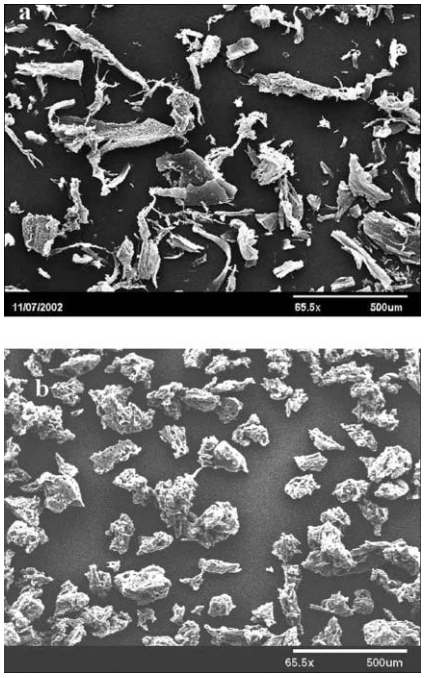

Fig. 12 SEM images; (**a**) product prepared by spraying the CO_2/$P_{DL}LA$ mixture into atmospheric pressure and (**b**) product generated with a N_2 backpressure.[153]

route to produce materials with controlled loadings and high surface area of silver. Moreover, it provides an alternative to the use of conventional antibiotics, and the inherent problems of antibiotic resistance, as a route to prevent infection in medical devices

Scaffolds

A number of fabrication techniques have been used to produce scaffolds from synthetic and naturally derived biodegradable polymers (for reviews see Chen *et al.*[132] and Hutmacher[159]). These include; poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic-*co*-glycolic acid) (PLGA), collagen and chitosan, as well as inorganic materials such as hydroxyapatite. All have been used in the tissue engineering of cartilage, bone, skin and ligament. Current techniques for preparation of scaffolds include solvent casting and particulate leaching, fibre extrusion and bonding, three dimensional printing, phase separation and emulsion freeze-drying, and gas and supercritical foaming.[89,132,159–161] In most of these techniques, solvents such as chloroform or methylene chloride are used to dissolve the polymer and high temperatures are often required. This is a drawback because of potential solvent residues that may have a deleterious effect upon the growth factors and hormones incorporated at the processing stage.

Gas-foaming techniques can use high-pressure CO_2 gas and avoid the reliance upon potentially toxic organic solvents. This novel approach was introduced in 1990[162] and subsequently by Mooney *et al.*[161] for the fabrication of porous PLA, PGA and PLGA scaffolds. The process involves the formation of polymer disks by heated compression moulding, followed by exposure of these disks to CO_2 gas in a high-pressure chamber (55 bar). After this equilibration period, the gas is rapidly released bringing the chamber to ambient pressure. Porosities of up to 93% and pore sizes of up to 100 μm can be obtained by this technique but the pores are largely unconnected, especially on the surface of the foam. A combination of this technique with particulate leaching was proposed[137,163] to improve interconnectivity as well as to reduce the temperatures required during processing. More recently, a new approach was developed using ammonium bicarbonate salt as both a gas foaming agent and a porogen. On exposure to an acidic aqueous solution or at elevated temperature the salt breaks down to evolve ammonia and CO_2 gas for foaming.[164,165]

$scCO_2$ has also been utilised by Barry *et al.*[166] to fabricate porous poly(ethylmethacrylate/tetrahydrofurfuryl methacrylate) (PEMA/THFMA) foams (Fig. 13) with controlled porosity and pore geometry and interconnectivity. This control is desirable to maximize nutrient diffusion and interstitial fluid and blood flow; to control cell adhesion, growth and function; to manipulate tissue differentiation, and to optimise scaffold mechanical function and the mechanical properties of the regenerated tissue.[167] PEMA/THFMA is a non-degradable polymer that has been proposed as a support material for cartilage repair[138] because of both the surface and bulk properties of the polymer, which promote cell attachment, cell

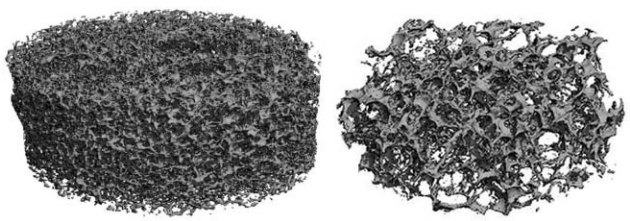

Fig. 13 Micro-Computerized Tomography (Micro-CT) image of a PEMA/THFMA scaffolds processed in $scCO_2$. These two images were obtained at different depressurisation times. The very large difference in porosity can be clearly seen.[170]

phenotype and morphology maintenance over extended periods.[168] This cross-linked polymer system is plasticised with $scCO_2$ at 100 bar for a period of 8 hours followed by controlled depressurisation.[169] Porous foams are generated with a uniform, interconnected pore structure, which seems to provide a more favourable environment for the retention of the rounded morphology of hyaline chondrocytes and also acts to prevent their spreading. Porosity, pore size, pore interconnectivity, surface chemistry and mechanical properties are structural features that make a scaffold suitable as a tissue-engineering device. These were determined through SEM, mercury porosimetry, helium pycnometry and microarchitectural and mechanical analysis.[170] Total porosity was measured to be greater than 80% with at least 60% being open porosity. This is significantly greater than the 10–30% obtained in other polymer systems.[161] Pore sizes ranged between 35 and 400 μm depending on the pressure, exposure time and depressurisation time. For fibroblasts and hepatocytes, the optimum pore size for growth has been suggested to fall in the range 20–125 μm. For skin regeneration, pore size can vary between 100–250 μm and for bone regeneration, between 200–400 μm.

The low processing temperatures and the lack of conventional solvents make $scCO_2$ an ideal route to incorporate thermal and solvent sensitive bioactive guest materials such as proteins into polymeric scaffolds.[152,169] $scCO_2$ plasticises amorphous polymers under pressure, effectively liquifying them. Under these conditions it is possible to physically mix active growth factors into the liquified polymer.[169] Upon depressurisation, the polymer is supersaturated with CO_2 and a thermodynamic instability results. The T_g begins to rise as the gas escapes from the polymer phase and nucleation of gas bubbles occurs leading to the formation of macroporous foams (Fig. 14a).[161] This leads to trapping and encapsulation of active factors and these have been shown to encourage cell growth (Fig. 14b and c).

By varying the depressurisation rate of the system using a backpressure regulator,[169] the pore size within the foams can be controlled.[171] No solvent residues remain after processing and high protein loads (up to 70 wt%) can be incorporated into the scaffolds if required. Most importantly, because they are exposed to neither high temperatures nor conventional organic solvents, the bioactives retain full activity on subsequent release from the scaffold.[133,169,172] Hile *et al.*[136] used $scCO_2$ to produce PLGA foams containing encapsulated proteins. A basic fibroblast growth factor (bFGF) mixed with bovine serum albumin (BSA) was incorporated within PLGA foams prepared using $scCO_2$ and scaffolds produced by the solvent casting-salt leaching technique. The activity of released bFGF from polymer scaffolds and foams was determined by measuring the uptake of 3H-thymidine in bFGF-stimulated fibroblast cells. Total protein release rates (including bFGF and BSA) were found to be greater from foams prepared in $scCO_2$ than scaffolds made by solvent casting-salt leaching. Initial protein release from foams processed in $scCO_2$ was approximately twice the rate observed in the salt leached scaffolds and also higher over a period of 30 days. Other studies regarding polymeric systems for growth factor delivery, report a dual incorporation and release of angiogenic factors involved in the formation of a mature vascular network.[173] Vascular endothelial growth factor (VEGF) and platelet-derived growth factor were encapsulated within porous PLGA scaffolds, processed in high-pressure CO_2,[163] and implanted in subcutaneous pockets of Lewis rats. Dual-release scaffolds led to higher blood vessel density in comparison to individual release of the factors, showing the relevance of these polymeric systems for tissue-specific delivery of active factors.[173]

The incorporation of proteins such as ribonuclease A, catalase, β-D-galactosidase, VEGF and bone morphogenetic protein-2 (BMP-2) into PLGA and PLA scaffolds has also been

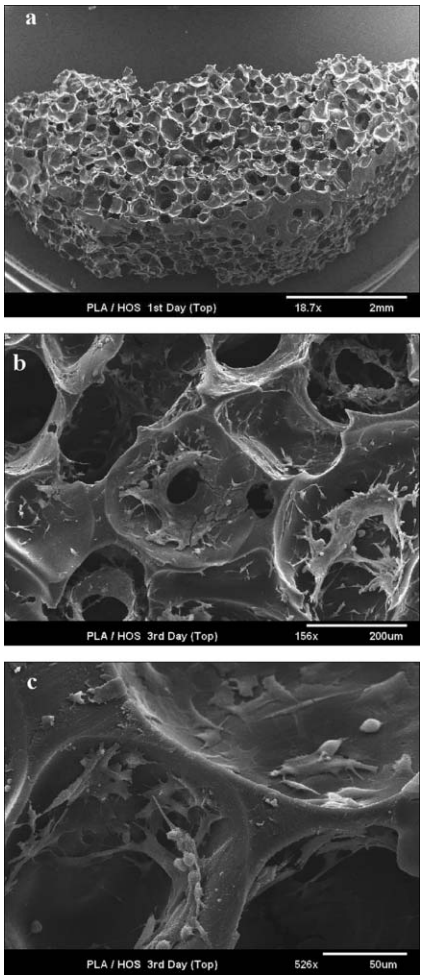

Fig. 14 SEM images: (**a**) three-dimensional porous $P_{DL}LA$ scaffold processed in $scCO_2$; (**b**) and (**c**) porous scaffold seeded with osteoblast cells.

carried out using $scCO_2$ at near ambient temperatures (35 °C) and modest pressures (200 bar) with protein activity being retained in all cases.[169,174] *In vitro* and *in vivo* studies (Oreffo and co-workers[175–178]) have demonstrated the potential of these scaffolds to engineer bone tissue for orthopaedic applications. Human bone marrow osteoprogenitor cells infected with a vector carrying the BMP-2 gene were combined with biodegradable PLGA scaffolds, produced by $scCO_2$ and implanted in nude mice. The osteoprogenitor cells successfully expressed active BMP-2 on the porous PLGA scaffold, leading to the formation of mineralised bone tissue (Fig. 15).[176] The same authors have examined effects of pleiotrophin, an osteoblast stimulating factor adsorbed into PLGA scaffolds, on primary human bone marrow stromal cell growth and differentiation *in vivo*.[179]

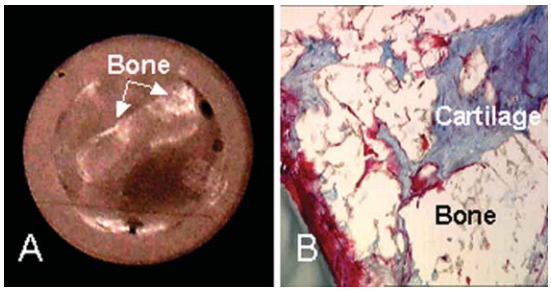

Fig. 15 Cartilage and bone formation from primary human bone marrow cells cultured in PLGA scaffolds processed in $scCO_2$. (**A**) X-Ray analysis of the new bone formation within shaped PLGA scaffolds and (**B**) Islands of cartilage and bone within the PLGA scaffolds viewed by Alcian blue staining.[176] Copyright 2002 Elsevier.

Concluding remarks

Our aim in this review was to highlight the very broad range of research that is focussed on materials processing using $scCO_2$. The many examples presented here demonstrate that $scCO_2$ is likely to have a very high impact in the next few years, leading to new science and technology that could not be achieved without a solvent, or by use of conventional solvents. It is clear that scientists and engineers are beginning to overcome the major hurdles to widespread acceptance of use of high pressure CO_2. Dry cleaning is already demonstrating commercial viability,[87] and scale-up issues have been addressed in at least two important industrial scale synthetic processes, *i.e.* fluoropolymers[79] and continuous fine chemicals,[180] and others are undoubtedly in the pipeline in the preparation of pharmaceuticals, drug delivery devices and biomaterials applications. Additionally, $scCO_2$ has much to offer in the preparation of nanomaterials and next generation nanoscale devices. Many applications require the use of surfactants and stabilisers, and currently the successful ones are almost exclusively fluorinated and siloxane based. The development of widely available hydrocarbon based materials with high $scCO_2$ solubility is underway, and as these become available, the applications of $scCO_2$ will undoubtedly grow.

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