CO_2-in-Water Emulsion-Templated Poly(vinyl alcohol) Hydrogels Using Poly(vinyl acetate)-Based Surfactants

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ABSTRACT: We present here a methodology to produce highly porous cross-linked hydrogel materials by templating concentrated CO_2-in-water (C/W) emulsions. Poly(vinyl alcohol) (PVA), blended PVA/PEG, and naturally derived chitosan materials were produced via this route. The technique can be carried out at moderate temperatures and pressures (25 °C, <120 bar) using inexpensive hydrocarbon surfactants such as PVAc-based block copolymers which are composed of biodegradable blocks. This methodology opens up a new solvent-free route for the preparation of porous biopolymers, hydrogels, and composites, including materials which cannot readily be produced by foaming.

Introduction

Polymeric hydrogels have been studied for applications in a variety of fields such as in chemical engineering, pharmaceuticals, food, and agriculture.[1,2] Hydrogels can change their volume and shape reversibly as a result of external physicochemical factors such as temperature, solvent composition, pH, and ionic concentration.[3−5] These large volume or shape changes, which can be induced by supplying thermal, chemical, or electrical stimuli, offer a range of possibilities for advanced functional polymers. Hydrogels are appealing as scaffold materials because they are structurally similar to the extracellular matrix of many tissues, may often be processed under relatively mild conditions, and may be delivered in a minimally invasive manner. A variety of synthetic and naturally derived materials have been used to form hydrogels for tissue engineering scaffolds.

Poly(vinyl alcohol) (PVA) hydrogels have been proposed as promising biomaterials to replace diseased or damaged articular cartilage. PVA has been widely explored for use in space filling and drug delivery applications. It can be physically cross-linked by repeated freeze-thawing cycles of aqueous polymer solutions[6] or chemically cross-linked with glutaraldehyde[7] or acid chlorides[8] to form hydrogels. It can also be blended with other water-soluble polymers and again cross-linked either physically or chemically.[9−11]

It is not easy to control the pore size and porosity in such materials, partly as a result of the solid−liquid interface which exists between the matrix polymer and porogen (usually water). Current challenges in this field include the provision of appropriate preparation methods for controlled macroporous structures. Emulsion-templating techniques are versatile for the preparation of well-defined porous organic polymers,[12−15] inorganic materials,[16−20] and inorganic−organic composites.[21] In general, these techniques involves forming a high internal phase emulsion (HIPE) (>74.05% v/v internal phase) and locking in the structure of the continuous phase, usually by reaction induced phase separation (e.g., free-radical polymerization, sol−gel chemistry). Subsequent removal of the internal phase (i.e., the emulsion droplets) gives rise to a porous replica of the emulsion. In principle, templated oil-in-water (O/W) emulsions provide a direct synthetic route to a variety of porous hydrophilic polymers for applications such as separation media, catalyst supports, biological tissue scaffolds, and controlled release devices. However, a significant disadvantage is that concentrated O/W emulsion techniques are very solvent intensive. Usually, large amounts of oil or organic solvent are required for the internal phase (>80% v/v) which brings about the disadvantage of high levels of organic waste. Moreover, this solvent may be hard to remove completely and residues are often left in the structure. Organic solvent residues may be problematic, particularly for applications such as biomaterials.

As a possible solution to this problem, high internal phase CO_2-in-water (C/W) emulsions have been considered in order to produce emulsion-templated materials without using any organic solvents.[22] Supercritical carbon dioxide ($scCO_2$) has been promoted recently as a sustainable solvent because it is nontoxic, non-flammable, and naturally abundant.[23−25] In particular, $scCO_2$ has been shown to be a versatile solvent for polymer synthesis and processing.[23−28] Carbon dioxide has been exploited quite widely for the preparation of porous materials.[26−28] For example, $scCO_2$ has been used for the production of microcellular polymer foams,[29,30] biodegradable composite materials,[31] macroporous polyacrylates,[32−35] and fluorinated microcellular materials.[36]

We recently developed a new approach to the synthesis of porous materials which involves the polymerization of high internal phase CO_2-in-water emulsions (C/W HIPEs). This technique has wide appeal because it allows the synthesis of materials with well-defined porous structures without the use of any volatile organic solvents, just water and CO_2. Surfactants such as perfluoropolyether ammonium carboxylate provide stability to the emulsion, enabling low-density materials (~0.1 g/cm^3) with large pore volumes (~6 cm^3/g) to be produced from water-soluble vinyl monomer systems such as acrylamide and hydroxyethyl acrylate.[37,38] Less expensive hydrocarbon surfactants were also evaluated for the stabilization of these systems and these proved successful albeit less so than the fluorinated surfactants. The macropore structure observed in these materials is directly templated from the concentrated C/W emulsion, giving cell densities of 0.5×10^8 to 5×10^8 cells/cm^3 and pore volumes of up to 6 cm^3/g. However, there are four key

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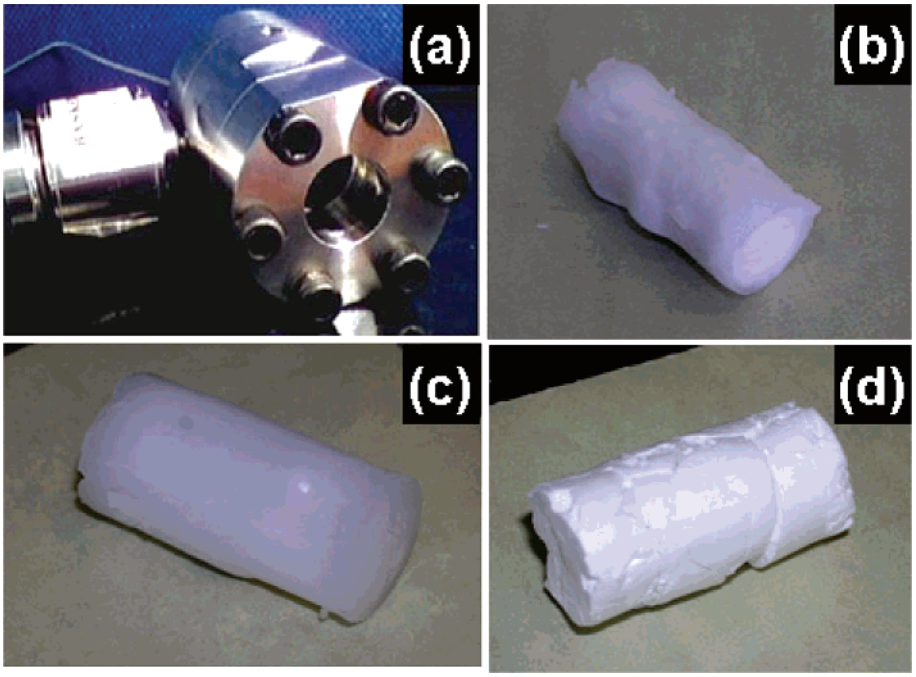
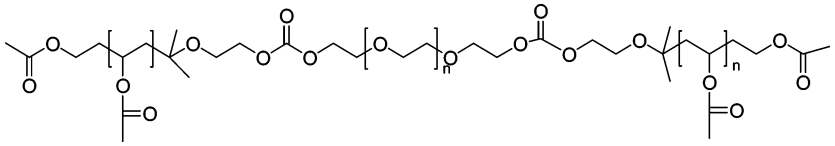


Figure 1. Photographs of a PVA hydrogel (sample **1**) formed by gelation of a C/W emulsion using a biodegradable hydrocarbon (PVAc-*b*-PEG-*b*-PVAc) surfactant. The resulting solidified gel conforms closely to the interior of the reaction vessel: (a) high-pressure reactor used in this experiment, (b) sample obtained after venting CO_2 (with a small degree of shrinkage), (c) sample recovered several seconds after placing the sample in water, and (d) freeze-dried sample (no significant shrinkage was observed upon drying the water phase).

Scheme 1. Poly(vinyl acetate)-*b*-poly(ethylene glycol)-*b*-poly(vinyl acetate) (PVAc−PEG−PVAc) Biodegradable Hydrocarbon Surfactants



limitations associated with our previous approaches,[37,38] particularly with respect to the potential for synthesizing biomaterials. First, the method involves a fluorinated surfactant (perfluoropolyether ammonium carboxylate) which is expensive and non-biodegradable. Second, acrylamide is toxic, and PAM materials are not in general biocompatible. Third, the method involves high pressures (>300 bar), which contribute to energy consumption and increase the capital equipment costs. Finally, the polymerizations were initiated by thermal methods (50−60 °C); in general, elevated temperatures would not be desirable for the incorporation of thermally sensitive biological species such as proteins or enzymes.[31]

In this study, we have extended our C/W HIPE methodology from radical polymerization with acrylic monomers to gelation of the aqueous phase using PVA, blended PVA-PEG mixtures, and chitosan in order to produce potential biomaterials. We have also developed emulsions with enhanced stabilities to produce materials with significantly increased levels of porosity by using poly(vinyl acetate)-based surfactants, as reported in our preliminary communication.[39] We also present a solution to each of the problems outlined above and show that it is possible to

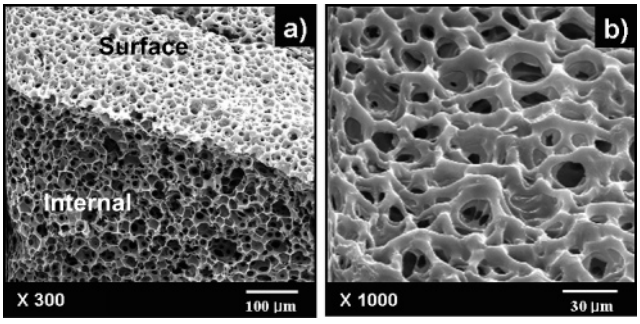


Figure 2. Electron micrographs of open-cell porous PVA hydrogel (sample **1**) produced from C/W emulsions in the presence of PVAc-based surfactant. Key: (a) micrograph showing internal and surface pore structures; (b) micrograph showing surface morphology with higher magnification.

Table 1. Preparation of C/W Emulsion-Templated Hydrogels Using a PVAc-*b*-PEG-*b*-PVAc Biodegradable Hydrocarbon Surfactant[a]

sample	solid content[b] (% w/v)	vol fraction CO_2 (%)	V_{pore} (cm^3/g)[c]	av pore size (μm)[d]	bulk density (g/cm^3)[d]
1	10	74	14.9	6.1	0.054
2	14	74	12.7	5.8	0.055
3	18	74	8.0	3.7	0.098
4	10	79	19.1	9.2	0.033
5	15	79	13.5	6.3	0.059
6	18	79	10.9	3.1	0.080
7[e]	15	79	14.6	5.4	0.043
8[f]	15	79	17.0	12.3	0.043
9[g]	0.4	60	*i*	*i*	*i*
10[h]	0.6	60	*i*	*i*	*i*

[a] Reaction conditions: PVA (80% hydrolyzed, M_w = 10 kg/mol), glutaraldehyde (20% w/w based on PVA: 50% w/v solution in H_2O), PVAc−PEG-PVAc surfactant (2% w/v, based on aqueous phase: M_w: 2000−2000-2000 g/mol), HCl (catalyst: 2 N, 0.1 mL), 25 °C, 100−120 bar, 12 h, Reactor volume = 10 cm^3. [b] Solid contents = PVA/aqueous phase. [c] Total intrusion volume, as measured by mercury intrusion porosimetry over the pore size range 7 nm-100 μm. [d] Measured by mercury intrusion porosimetry. [e] PVA/PEG = 75/25 w/w (poly(ethylene glycol), M_w = 400 g/mol). [f] PVA/PEG = 50/50 w/w. [g] 1% w/v chitosan in acetic acid solution. [h] 1.5% w/v chitosan in acetic acid solution. [i] Not determined.

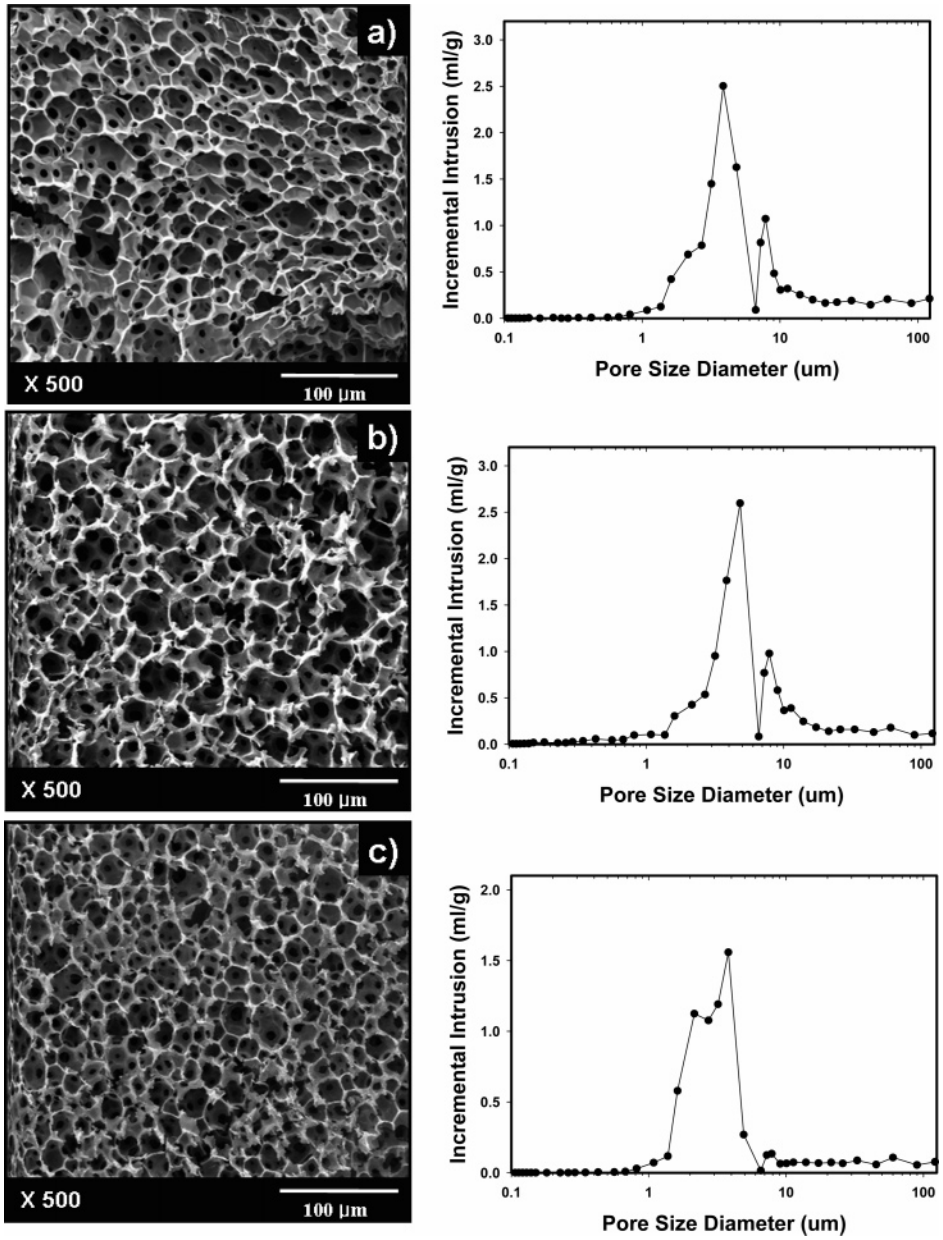


Figure 3. Variation in sample morphology for C/W emulsion-templated PVA hydrogels prepared using varying solid contents of PVA at a CO_2 phase volume fraction of 74% v/v, as characterized by electron microscopy (left), and mercury intrusion porosimetry (right): (a) sample **1**, using 10% w/v PVA, (b) sample **2**, 14% w/v PVA, and (c) sample **3**, 18% w/v PVA, based on the aqueous phase.

prepare C/W emulsion-templated materials by the gelation at low temperatures and pressures (25 °C, < 120 bar) using inexpensive and potentially biodegradable hydrocarbon surfactants.

Results and Discussion

PVA-Based Materials. Many conventional hydrocarbon surfactants used in O/W systems exhibit low solubilities in CO_2 and are incapable of forming either W/C or C/W emulsions.[40] By contrast, surfactants with poly(vinyl acetate) tails are quite soluble because the weak dispersion forces for these tails are well matched to those of CO_2. We have shown that poly(vinyl acetate)-*b*-poly(ethylene glycol)-*b*-poly(vinyl acetate) (PVAc-*b*-PEG-*b*-PVAc) surfactants (Scheme 1) can form both W/C and C/W macroemulsions and that these emulsions can exhibit kinetic stability.[39,41]

Our preliminary studies suggested[39] that these concentrated C/W emulsions were considerably more stable at lower tem-

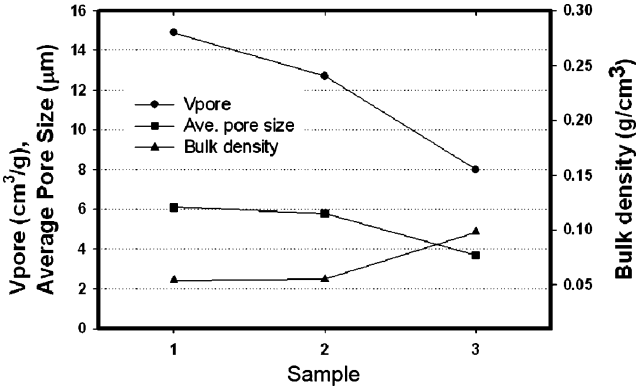


Figure 4. Effect of PVA solid contents (sample **1**, using 10% w/v PVA, sample **2**, 14% w/v PVA, and sample **3**, 18% w/v PVA, based on aqueous phase) on the intrusion volume, the average pore size, and the bulk density. A decrease in pore volume and average pore size was observed while the bulk density decreased.

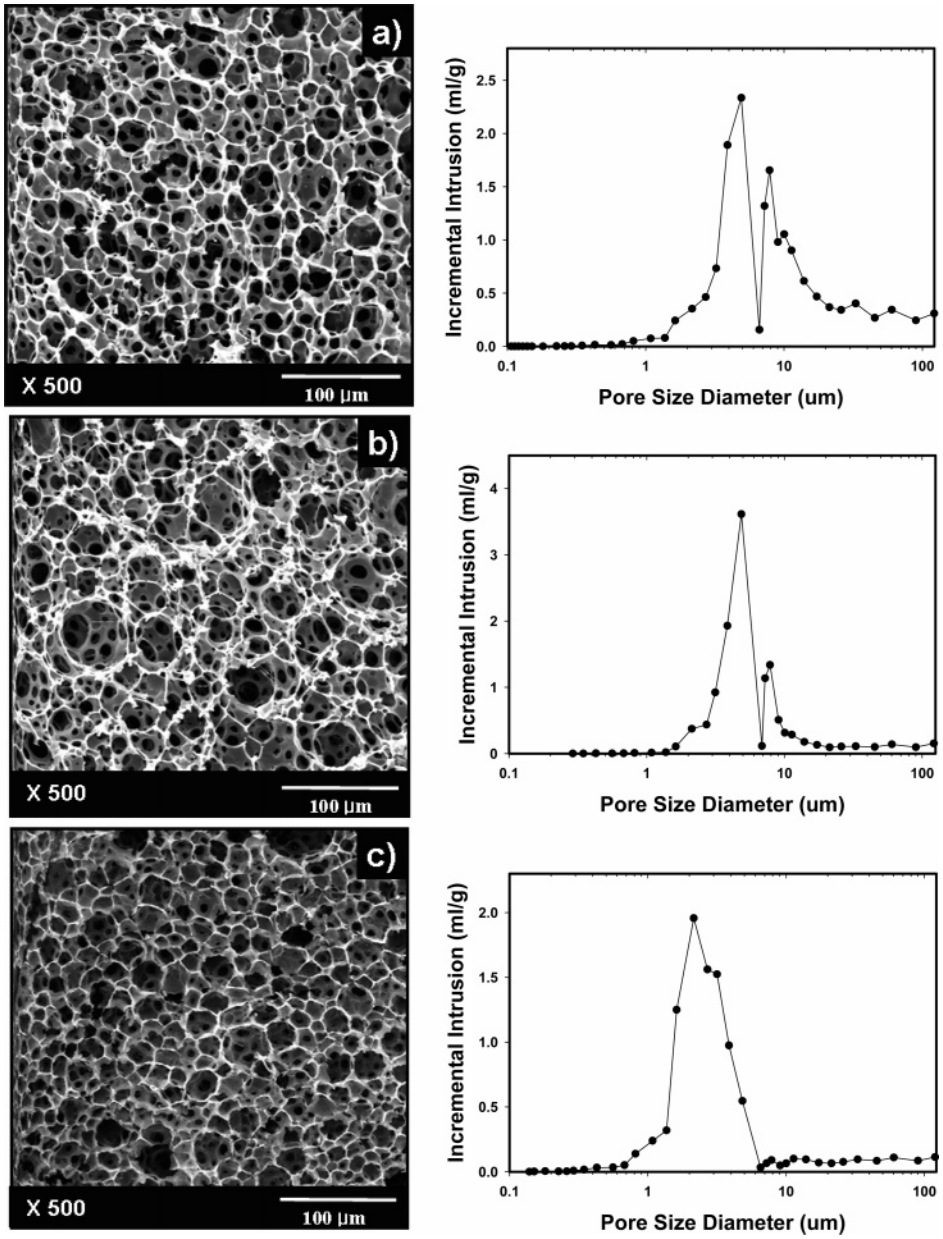


Figure 5. C/W emulsion-templated PVA hydrogels obtained by using varying solid contents of PVA and increasing CO_2 volume fraction from 74% to 79%, as characterized by electron microscopy (left) and mercury intrusion porosimetry (right): (a) sample **4**, 10% w/v PVA, (b) sample **5**, 15% w/v PVA, and (c) sample **6**, 18% w/v PVA, based on aqueous phase.

peratures when a PVAc-*b*-PEG-*b*-PVAc block copolymer was used. Until now our studies have involved mostly acrylamide as the monomer. Cross-linked polyacrylamide has been used in applications such as enzyme immobilization[42] but is less useful, for example, in the production of biocomposites. We have therefore investigated the preparation of other biocompatible cross-linked PVA hydrogels via this route. We chose to use a PVAc-*b*-PEG-*b*-PVAc surfactant with same composition (M_w = 2000−2000−2000 g/mol) as reported previously since this molecule exhibits solubility in water and has a propensity to form stable C/W emulsions.[39,41]

First, we prepared a C/W emulsion by using an aqueous solution of PVA (temperature = 25 °C, CO_2 pressure = 100 bar, volume fraction of CO_2 = 74−79%, glutaraldehyde = 20% w/w based on PVA, surfactant concentration = 2% w/v based on aqueous phase). Milky-white C/W emulsions were formed which filled the entire reaction vessel. Depending on the precise conditions, the emulsions could be stable for more than several hours after stirring was ceased. These results suggested that this system was suitable for PVA emulsion-templating. A catalyst, HCl (2 N, 0.1 mL), was then injected rapidly into the vessel by flushing a reservoir under higher pressure (120 bar) into the main reactor (at 100 bar). It was thus possible to perform the reactions using liquid CO_2 at relatively low reaction pressures and temperatures (25 °C, 120 bar). The remarkable stability of these emulsions was further demonstrated by gelation of the aqueous continuous phase to give porous, cross-linked emulsion-templated PVA hydrogels. The solidified gel occupied 100% of the reactor volume. After reaction, a dry sample was obtained (by air drying) with a small degree of physical shrinkage (Figure 1b). When the sample was placed in water, its original shape was recovered completely in a few seconds (Figure 1c). The material conformed closely to the interior of the reaction vessel. When an equivalent sample was dried in a freeze dryer (Figure 1d), no significant shrinkage was observed as shown previously

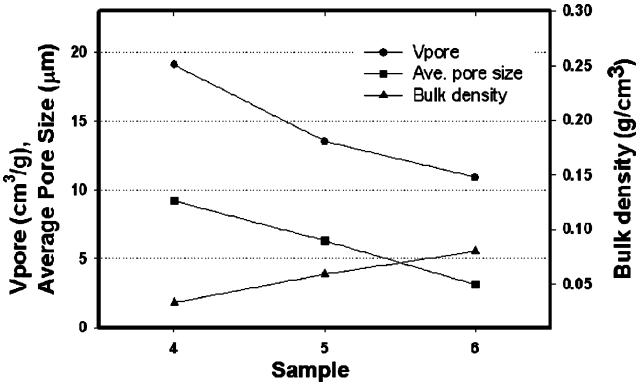


Figure 6. Effect of PVA solid contents (sample **4**, using 10% w/v PVA, sample **5**, 15% w/v PVA, sample **6**, 18% w/v PVA) on the intrusion volume, the average pore size, and the bulk density. The total pore volume in these materials showed a maximum of 19.1 cm^3/g (sample **4**), showing a much larger average pore size than the samples obtained at CO_2 volume fraction of 74%.

for polyacrylamide materials produced via C/W templating routes.[41]

In the presence of these PVAc-based surfactants the C/W emulsions were sufficiently stable for templating to occur and for open-cell porous materials to be produced, as shown in Figure 2. It was observed that the internal structure was uniformly porous and consisted of a skeletal replica of the original C/W HIPE. The pore structure was highly interconnected and there were open pores on the surface that were connected to the interior (Figure 2a). The diameter of the macropores was found to be in the range 3−15 μm.

We next investigated the effect of both the PVA concentration and the CO_2 volume fraction on the porous properties of the emulsion-templated PVA hydrogels. First, a series of emulsion-templated, cross-linked PVA hydrogels was prepared over range of PVA solid contents (10−18% w/v based on the aqueous phase) at a constant CO_2 volume fraction of 74% v/v. Open-cell porous polymers were formed with pore volumes in the range 8.0−14.9 cm^3/g and average pore sizes in the range 3.7−6.1 μm (Table 1, samples **1**−**3**). The average pore size as measured by mercury intrusion porosimetry agreed qualitatively with the size of the pore "windows" observed by SEM in the cell walls between the templated CO_2 emulsion droplets (Figure 3). Other variables such as concentration of surfactant, CO_2 pressure, stirring speed, and temperature were kept constant. In most cases, uniform, white C/W emulsions were observed that filled the entire reaction vessel and were sufficiently stable to form emulsion-templated polymers which conformed to the internal dimensions of the reaction vessel. At lower PVA solid contents (<10% w/v), however, a C/W emulsion was not formed due to the propensity to form W/C emulsions rather than C/W emulsions. Figure 3 shows a series of electron micrographs and mercury intrusion porosimetry plots for PVA hydrogel materials prepared at increasing PVA solid content. Although the morphology of the porous structure did not vary dramatically, a slight decrease in the average pore size was observed (from 6.1 to 3.7 μm as measured by mercury porosimetry). The effect of PVA solid content on the intrusion pore volume, the average pore size, and the bulk density is summarized in Figure 4. The total pore volume in these materials showed a maximum of 14.9 cm^3/g at a PVA content of 10% w/v. A decrease in pore volume and average pore size was observed when the PVA content was raised from 10% to 18% w/v; this is to be expected in general when the solid content in the emulsion is increased. The corresponding bulk densities showed an increasing trend.

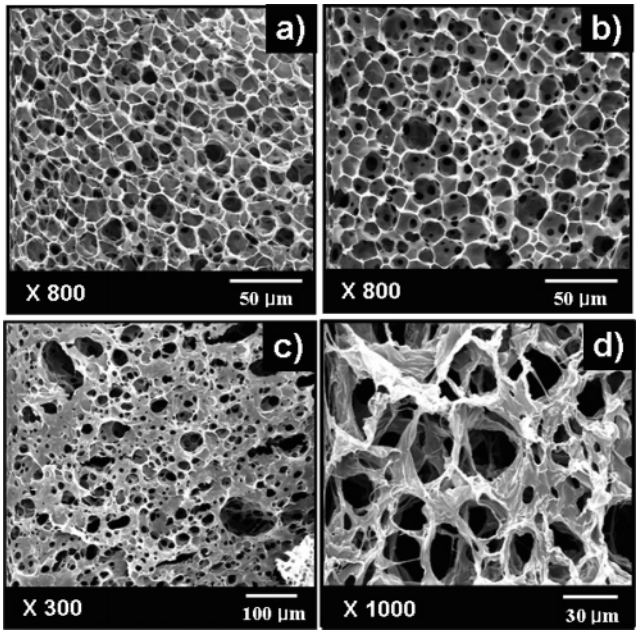


Figure 7. Blended PVA/PEG hydrogels and naturally derived chitosan with porous, open-cells prepared by C/W emulsions with poly(vinyl acetate) based surfactant: (a) sample **7**, PVA/PEG = 75/25% w/w, (b) sample **8**, PVA/PEG = 50/50% w/w, (c) sample **9**, chitosan obtained by using 0.4% w/v solid content, and (d) sample **10**, chitosan obtained by using 0.6% w/v solid content.

In an attempt to increase the level of porosity in the samples, the volume fraction of the CO_2 internal phase was increased from 74% to 79% (Table 1, samples **4**−**6**). Even under such concentrated conditions, it was possible to form C/W emulsions that filled the entire reaction vessel, although stable C/W emulsions were not formed under these conditions at CO_2 phase volume fractions of 80% or greater. Gelation behavior of these C/W HIPEs led to materials with an even more open, porous structure, and with total pore volumes as high as 19.1 cm^3/g. Samples **4**−**6** exhibited much larger average pore sizes than the samples obtained at a CO_2 phase volume fraction of 74% and the same PVA solid contents (see Figure 5a−c). The reason may be that the concentration of surfactant was kept constant relative to the external aqueous phase while the volume fraction of the internal CO_2 phase was increased, as previously reported for PFPE surfactants.[37,38] At this higher CO_2-to-water phase ratio, it was found that the intrusion pore volume (10.9−19.1 cm^3/g) and average pore size (3.1−9.2 μm) decreased with increasing PVA solid content (see Figure 6). Likewise, the bulk density of these samples increased with the PVA solid content. Samples **4**−**6** were derived from high internal phase emulsions (>74.05% v/v)—as such, the internal phase volume exceeded the close-packed sphere limit. This causes the emulsion droplets to deform into polyhedra and creates a more open structure in the templated material (Figure 5).[13,14] The C/W emulsion droplets were not monodisperse, as evident from the distribution of pore sizes observed in the electron micrographs (see Figures 3 and 5).

PVA—PEG-Based Materials. Substitution of PVA with other water-soluble polymers and naturally derived chitosan polymers also led to porous, open-cell materials by C/W emulsions using PVAc-based surfactants. We first investigated the gelation of C/W emulsions comprised of blended PVA/PEG mixtures, which can be cross-linked chemically (Table 1) (samples **7** and **8**). All systems were found to form stable, milky-white C/W HIPEs (CO_2:H_2O = 79:21 v/v). In each case, a blended PVA /PEG hydrogel (PVA/PEG = 75/25 and 50/50%

w/w) was prepared at constant solid content of 15% w/v. Under these conditions, it was possible to produce porous blended PVA/PEG materials with emulsion-templated pore structures that replicated the original C/W emulsion (Figure 7a,b). Samples **7** and **8** had pore volumes of 14.6 and 17.0 cm^3/g, respectively, and a bulk density of 0.043 g/cm^3. The equivalent materials prepared by using only PVA (sample **5**) had slightly lower pore volume (13.5 cm^3/g) and a higher bulk density (0.059 g/cm^3). The exact pore volume depended on the PEG concentration in the system, either because of changes in the overall surface tension and/or changes in viscosity which resulted from the composition of the aqueous phase.

Chitosan-Based Materials. We also investigated the preparation of emulsion-templated chitosan materials by using C/W emulsions. In general, chitosan has been studied for a variety of tissue engineering applications because it is degradable by enzymes in humans. It is soluble in dilute acids which protonate the free amino groups.[43−45] Once dissolved, chitosan can be gelled by increasing the pH[43−45] or by extruding the solution into a nonsolvent.[43−45] Chitosan derivatives and blends have also been gelled via glutaraldehyde cross-linking.[46,47] First, we prepared two kinds of chitosan solution at 1.0 and 1.5% w/v in dilute acetic acid which were then gelled through the same route in C/W emulsions as described above (temperature = 25 °C, CO_2 pressure = 120 bar, volume fraction of CO_2 = 60%, glutaraldehyde = 20% w/w based on chitosan, surfactant concentration = 2% w/v based on aqueous phase). In both cases, stable white C/W emulsions were observed that filled the entire reaction vessel when PVAc-*b*-PEG-*b*-PVAc was used as the surfactant. Under these conditions, open-cell porous chitosan materials were formed, but these materials showed much greater shrinkage upon venting of the CO_2 (and removal of the water) than the PVA or PVA/PEG samples. This may be because the chitosan was used at too low a solid content (sample **9** = 0.4% w/v; sample **10** = 0.6% w/v) for reasons of viscosity reduction (i.e., it was not possible to mix the phases at much higher concentrations). Nonetheless, these emulsion-templated chitosans were also found to have highly porous structures (Figure 7c,d), albeit subject to distortion and shrinkage during drying.

Conclusions

In summary, a number of limitations were apparent in our initial C/W emulsion templating approach; namely that the PFPE surfactant was expensive and nondegradable, reaction pressures were high (250−290 bar), and reaction temperatures were elevated (50−60 °C).[38] In this study, we have extended our methodology to produce highly porous cross-linked PVA materials, blended PVA/PEG, and naturally derived chitosan by the gelation of C/W HIPEs. Moreover, we have shown that this technique can be carried out at much lower temperatures and pressures (25 °C, < 120 bar) using inexpensive, biodegradable hydrocarbon surfactants such as PVAc-based block copolymers. Our methodology opens up a new solvent-free route for the preparation of porous biopolymers, hydrogels, and composites, including materials which cannot readily be produced by foaming. We plan to use this knowledge in future studies to develop highly porous materials, and to achieve fine control over porous structure by tuning the CO_2 density for a number of applications, particularly those in which organic solvent residues pose a problem.

Experimental Section

Materials. Poly(vinyl alcohol) (PVA, M_w = 10 000 g/mol, 80% hydrolyzed, Aldrich), glutaraldehyde (50% w/v solution in water, Aldrich), polyethylene glycol (PEG, M_w = 400 g/mol, Aldrich), chitosan (from crab shells, Aldrich) were all used as received. HCl (2 N solution) as a catalyst was used for gelation experiments.

Preparation. The poly(vinyl acetate)-based surfactants (PVAc-*b*-PEG-*b*-PVAc triblock copolymer, M_w = 2000−2000−2000 g/mol) were synthesized by described previously.[41] High-pressure reactions were carried out in a stainless steel reactor (10 cm^3), equipped with a sapphire window for observation of phase behavior. In a typical preparation, the reactor was charged with an aqueous solution of PVA (see Table 1), PVAc-*b*-PEG-*b*-PVAc triblock copolymer as surfactant (2% w/v based on the aqueous phase) before purging with a slow flow of CO_2 for 15 min. The reactor was then pressurized with liquid CO_2 (25 °C, 100 bar) and stirring (poly(tetrafluoroethylene), PTFE, stir bar) was commenced, whereupon a white, milky C/W emulsion was formed. Stirring was continued for 10 min, and HCl catalyst (2 N solution, 0.1 mL) was injected after the reactor window was fully covered by the white C/W emulsion. The reactor to the same reaction temperature and pressure overnight (25 °C, 120 bar, 12 h). The CO_2 was then vented and the templated polymers were removed from the reactor. Residual water was removed from the samples by freeze drying for 24 h or by air-drying at room temperature. The materials were not washed to remove, for example, any catalyst residues although aqueous washing prior to freeze-drying might be important for applications such as cell growth where such residues may cause problems.

Characterization. For analysis, the continuous polymer samples were fractured into millimeter-sized pieces with a scalpel. Pore size distributions were recorded by mercury intrusion porosimetry using a Micromeritics Autopore IV 9500 porosimeter. Samples were subjected to a pressure cycle starting at approximately 0.5 psia, increasing to 60000 psia in predefined steps to give pore size/pore volume information. The samples fractured into small pieces, and polymer morphologies were investigated with a Hitachi S-2460N SEM. Samples were mounted on aluminum studs using adhesive graphite tape and sputter coated with approximately 10 nm of gold before analysis.

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