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An environmentally-friendly process to prepare well-defined cross-linked particles of poly(2-hydroxyethyl methacrylate) (PHEMA) was investigated. The dispersion polymerisation of 2-hydroxyethyl methacrylate (HEMA) with a cross-linker ethylene glycol dimethacrylate (EGDMA) was performed in supercritical carbon dioxide (scCO₂). Stabilisers based only on vinyl acetate (VAc) and vinyl pivalate (VPi) random copolymers P(VAc-stat-VPi) were employed thus avoiding the use of silicone or fluorine based stabilisers which are normally required in scCO₂. The effect of molecular weight and composition of the P(VAc-stat-VPi) stabilisers on the size and shape of the produced microparticles was investigated. A copolymer stabiliser with 56:44 (VAc:VPi) molar composition ($M_n = 12.8 \text{ kg mol}^{-1}$) was found to be the most efficient, resulting in well-defined spherical cross-linked PHEMA particles with a diameter of 1.2 μm . This particular stabiliser was found to provide good steric stabilisation for a range of cross-linker ratios and the addition of a co-monomer such as *N*-vinylpyrrolidone (NVP) allowed tuning of the properties of the microparticulate products. Finally, the stabiliser plays a second very important role. Partial hydrolysis of the ester groups of the stabiliser located on the surface of the microparticles leads to a hydrophilic surface with alcohol moieties and hence facilitates dispersion of the microparticles into water leading to valuable microgels.

Introduction

Green chemistry is defined as the design of products and processes that eliminate the use and/or the generation of hazardous substances.¹ Green chemistry is described by 12 principles and across the world research groups and companies are trying to design synthetic methods that utilise these principles; for example to replace volatile organic conventional solvents.² In that framework, supercritical carbon dioxide (scCO₂) is an excellent candidate with accessible critical temperature (31.1 °C) and pressure (73.8 bar), gas-like diffusivity and liquid-like densities. Moreover, scCO₂ is a naturally highly abundant, non-toxic, non-flammable solvent which makes it a good candidate for VOC replacement. Most importantly, scCO₂ can be removed by simple depressurisation, this can also help significantly in removing unreacted monomer and hence eliminating post-reaction purification processes.³ The use of scCO₂ as a solvent has witnessed tremendous

growth⁴ in many areas; from commercialized extractions in the food industry⁵ to intricate pharmaceutical formulations for drug delivery⁶ or as a solvent or non-solvent to produce polymer particles with controlled size and shape.⁷ One of the most versatile routes to polymer particles is heterogeneous free-radical polymerisation.⁸ Most common monomers are soluble in scCO₂, but their corresponding high molecular weight polymers are usually insoluble making scCO₂ an ideal candidate for dispersion polymerisation.⁸

A key factor for the successful dispersion polymerization and control of the particle size is the selection of a relevant stabiliser. Stabilisers can either adsorb or chemically graft onto the growing polymer microparticles limiting growth and preventing aggregation by steric stabilisation.⁹ Efficient stabilisers for dispersion polymerization in scCO₂ require macromolecules exhibiting a "CO₂-philic" part to ensure solubility in scCO₂ and provide steric stabilisation to prevent particle aggregation.¹⁰ Up till now only fluorinated and silicone based polymers have shown sufficient scCO₂ solubility. However, these are expensive and this might limit large scale application.¹¹ Consequently, an area of interest has been the synthesis of alternative hydrocarbon based stabilisers. Kazarian et al. have shown that polymers containing electron donating functional groups such as carbonyls, interact with CO₂ molecules via Lewis acid-base type interactions.¹² Sarbu et al. proposed that a CO₂-philic block could be based on a combination of a monomer (A) which gives flexibility and free

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volume to the polymer chain and enhances the entropy of mixing, and a co-monomer (B) containing a Lewis base group, such as a carbonyl group, to facilitate interaction with CO₂. Poly(ether carbonate)s (PEC)s were reported to be scCO₂ soluble at reasonable temperatures and pressures.¹³ Similarly, Tan et al. reported the facile synthesis of scCO₂ soluble poly(ether carbonate)s and poly(ether ester)s by step-growth polymerisation.¹⁴ In addition they showed that block copolymers composed of poly(ethylene glycol) (PEG) and oligo(vinyl acetate) (OVAc), PEG-*b*-OVAc diblock and OVAc-*b*-PEG-*b*-OVAc triblock copolymers could be efficient emulsifiers for water in scCO₂. These diblock and triblock copolymers were able to emulsify significant levels of water in CO₂ and polymerisation in this medium resulted in highly porous poly(acrylamide) (PAM) networks.¹⁵ The porosities of the PAM networks were found to be higher than those of networks synthesized with a perfluoropolyether (PFPE) showing that OVAc-based block copolymers might advantageously replace fluorinated materials in scCO₂.^{15,16} Poly(vinyl acetate-*alt*-dibutyl maleate) P(VAc-*alt*-DBM) copolymers also showed good CO₂ solubility.¹⁷ Cloud point measurements demonstrated that random copolymers of vinyl acetate and vinyl butyrate P(VAc-*stat*-VBU), 50:50 molar composition, have a higher solubility than PVAc and PVBU homopolymers. These materials were then exploited to perform the first successful dispersion polymerisations in scCO₂ using hydrocarbon based stabilisers.¹⁸ The dispersion polymerisation of *N*-vinylpyrrolidone (NVP) led to monodisperse poly(*N*-vinylpyrrolidone) (PNVP) microparticles.¹⁸ This work was then extended by using stabilisers from copolymers of vinyl pivalate (VPi) and vinyl acetate (VAc) (P(VAc-*stat*-VPi)). Again, micron sized spherical PNVP particles were produced successfully.¹⁹ Park et al. extended this study to the synthesis of copolymers based on VAc, vinyl butyrate (VBU) and vinyl octanoate (VOC). Their cloud point data indicate that the solubility of the P(VAc-*stat*-VBU) stabiliser increased with increasing VBU content in the copolymer, which also lead to better stabilisation of PNVP particles, while in the case of P(VAc-*stat*-VOC) stabilisers the opposite behaviour was observed.²⁰ Girard et al. reported the synthesis of poly(*N,N*-dimethyl acrylamide)-*b*-poly(vinyl acetate) (PDMA-*b*-PVAc) diblock copolymers and showed that their solubility in scCO₂ decreased at higher PDMA content.³ Cross-linked PHEMA²¹ microparticles have shown utility as drug carriers, in dental, ophthalmic and tissue engineering applications.²² A key challenge is to find routes to their synthesis that are clean, but do not require perfluorinated or silicone based stabilisers. Moreover, the materials produced should be easily dispersible in water. Hence, in this paper we focus on the dispersion polymerisation of 2-hydroxyethyl methacrylate (HEMA) in the presence of ethylene glycol dimethacrylate (EGDMA) as a cross-linker using P(VAc-*stat*-VPi) copolymer stabilisers to obtain microparticulate PHEMA networks directly from scCO₂. Block copolymer architectures have been shown to be less soluble than comparable statistical copolymer stabilisers.²³ This was attributed to the segregated arrangement of the VAc and VPi components. To ensure a high enough solubility it was essential that the block copolymers had a lower

overall molecular weight. This led to spherical microparticles, albeit with larger particle size diameter and broader particle size distributions than those obtained from the statistical copolymers of the same chain length.

After successful synthesis of microparticles, P(VAc-*stat*-VPi) stabiliser must be present on the microparticle surface. One idea that we intend to explore is to determine whether hydrolysis could provide a facile route to surface bound hydrophilic vinyl alcohol units to allow dispersion of the microparticles into water.

Experimental

Materials

All chemicals were used as received unless otherwise noted. 2,2'-Azobis(2-methylpropionitrile) (AIBN, 98%), ethylene glycol dimethacrylate (EGDMA, 98%), 2-hydroxyethyl methacrylate (HEMA, ≥99%), potassium ethyl xanthogenate (96%) and vinyl pivalate (VPi, 99%, stabilised with 5-30 ppm hydroquinone) were purchased from Sigma Aldrich. Dichloromethane (DCM, AnalaR NORMAPUR® ACS, Reag. Ph. Eur. analytical reagent), ethanol (EtOH, ≥99.9%), and methanol (MeOH) were purchased from VWR. *N*-Vinylpyrrolidone (NVP, 98%, Merck Millipore), and 2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70) were purchased from Wako Chemicals. Vinyl acetate (VAc, 99%, stabilised with 8-12 ppm hydroquinone) was purchased from Alfa Aesar. Carbon dioxide (CO₂, 99.99%) was purchased from BOC, UK.

Methods

Synthesis of *O*-ethyl-*S*-(1-methoxycarbonyl) ethyl dithiocarbonate

Methyl bromoacetate (16 g, 104.6 mmol) was dissolved in methanol (75 mL) in a 250 mL round bottom flask with a stirring bar and in an ice bath. Potassium ethyl xanthogenate (19.515 g, 121.7 mmol) was dissolved in ethanol (100 mL) in a beaker for 30 minutes and added dropwise to the flask using an addition funnel. The mixture was stirred at room temperature for 24 hours and filtered to remove KBr salts. The filtrate was concentrated under reduced pressure, dissolved in dichloromethane (50 mL) and washed with water (3x15 mL). The organic phase was dried with magnesium sulfate and dried under vacuum to yield a yellow liquid. Yield = 79%. ¹H-NMR (CDCl₃): δ = 4.5 ppm (q, 2 H), 3.8 ppm (s, 2H), 3.6 ppm (s, 3H), 1.3 ppm (t, 3H).

Synthesis of P(VAc-*stat*-VPi) copolymers Typical copolymer synthesis in bulk: vinyl acetate (17.99 g, 209 mmol), vinyl pivalate (2.97 g, 23.23 mmol), *O*-ethyl-*S*-(1-methoxycarbonyl) ethyl dithiocarbonate (0.684 g, 3.6 mmol) and AIBN (0.06 g, 0.36 mmol) (RAFT:AIBN molar ratio = 10:1) were placed in a sealed round bottom flask with a stirring bar and degassed with argon for 30 minutes in an ice bath. The mixture was stirred at 60 °C for 5 hours to a conversion of around 60% as determined by NMR. The polymer product was precipitated in a mixture of ice cold methanol:water (4:1 v:v) and dried under vacuum for 24

hours to remove both the solvent and unreacted monomer. ^1H -NMR (CDCl_3) is shown in Figure 1.

Dispersion polymerisation in scCO_2

Dispersion polymerisations were performed in a 60 mL high pressure autoclave. A typical one-pot procedure was followed for the free radical dispersion polymerisation of HEMA and/or copolymerisation with NVP in scCO_2 unless otherwise noted. The autoclave body was charged with 6 mL of monomer ($10\% \text{ } v_{\text{monomer}}/v_{\text{CO}_2}$), 0.1368 g of V-70 ($1\% \text{ } w_{\text{V-70}}/w_{\text{monomer}}$), 60 μL of EGDMA ($1\% \text{ } v_{\text{cross-linker}}/v_{\text{monomer}}$), and 0.6 g of stabiliser ($10\% \text{ } w_{\text{stabiliser}}/v_{\text{monomer}}$). Initially the autoclave was filled with 800 psi with CO_2 (55 bar), then stirring was started at 200 rpm. The cell was heated up to 35 $^\circ\text{C}$. When the final temperature was reached and stabilised for a few minutes, the cell was pressurised progressively to 3500 psi (240 bar) or the desired final pressure. The reaction was left stirring overnight at 35 $^\circ\text{C}$ and 3500 psi. To stop the reaction the heating jacket was disconnected, and the autoclave was allowed to cool down to room temperature and depressurised very slowly by the outlet tap into the fume hood. Stirring was left on at all times until a low pressure (700–600 psi) was reached. The autoclave was opened once atmospheric pressure was reached (14–18 psi). Polymer products were then collected for analysis.

Hydrolysis of the stabiliser and stabilised particles

Two conditions have been tested to hydrolyse the P(VAc-*stat*-VPi) copolymer into PVOH based on previously reported conditions for PVAc homopolymer (condition 1) and for VPi homopolymer (condition 2) by Bernard et al.²⁴ The following procedures were applied first on the stabiliser only and then on the PHEMA stabilised particles.

Condition 1 “PVAc conditions”: 100 mg of statistical copolymer was dissolved (or 100 mg of particles were suspended) in 10 mL of methanol and a solution of 200 mg of KOH in 10 mL methanol was added. The mixture was stirred for 24 hours at room temperature then dialysed against methanol for 24 hours with Spectropore (cut-off 3.5kDa) dialysis membranes from Spectrum. The solvent was removed under reduced pressure (particles were freeze-dried in order to eliminate the small amount of residual solvent).

Condition 2 “VPi conditions”: 90 mg of statistical copolymer was dissolved (or 90 mg of particles were suspended) in 1 mL ethanol and a 1 mL solution of NaOH (1 wt% in methanol) was added on the mixture. The mixture was stirred for 24 hours at 60 $^\circ\text{C}$ then dialysed against methanol for 24 hours. The solvent was removed under reduced pressure (particles were freeze-dried in order to eliminate the small amount of residual solvent).

Characterisation

Cloud point measurements of the stabilisers in scCO_2 / monomer mixture

The solubility of the statistical copolymers in scCO_2 indicates their potential to be used as stabiliser for dispersion

polymerisation in this solvent/medium. Cloud point measurements were recorded for a range of copolymers of different compositions and molecular weights. The cloud point in scCO_2 can be defined as the pressure at which the polymer starts to precipitate out from the solution at a fixed temperature.¹⁴ The cloud points of synthesised statistical copolymers were determined in the CO_2 /monomer mixture by using a high pressure variable volume view cell.²⁵ For a typical cloud point measurement 3 g (15 wt% monomer/ CO_2) of HEMA, 150 mg of stabiliser (5 wt% stabiliser/HEMA) and 20 g of CO_2 were used. The stabiliser was dissolved in a given amount of HEMA and injected into the view cell. CO_2 was then transferred to the view cell by using a small stainless-steel CO_2 sample cylinder, the weight of which was recorded before and after addition to calculate the exact amount of CO_2 introduced in the cell. The cell was heated up to the desired temperature and allowed to stabilise. Thereafter, the hydraulic piston was slowly moved forward to increase the pressure in the cell until a single phase was observed through the sapphire window. At this pressure, the light placed at the end of the view cell was visible. The piston was moved back again slowly to decrease the pressure in a controlled manner to observe the pressure at which the solution was no longer a single phase. A cloudy mixture was observed due to precipitation of the polymer from the solution. Measurements were repeated in triplicate. Cloud points were taken at 35, 45, 55, 65 and 75 $^\circ\text{C}$. The cloud points are reported as an average value of the three repetitions.¹⁹

The glass transition temperatures (T_g s) of the collected particles were analysed by using a Triton Technology TT DMA using powder pockets which allow analysis of samples in powder form. The analysis pocket was filled with the particles as collected from the high-pressure reactor. Dynamic mechanical analysis (DMA) was performed in single cantilever bending mode with a temperature ramp from room temperature to 120 $^\circ\text{C}$ or 150 $^\circ\text{C}$ at a heating rate of 5 $^\circ\text{C min}^{-1}$.

^1H -NMR was used to determine the structure, composition, conversion and molecular weights of the polymers. Analyses were performed on a Bruker AV3400 spectrometer equipped with a 400 MHz magnet, using deuterated chloroform (CDCl_3) as solvent. End group analysis was performed using relaxation times of 1 second and after recording 256 scans. All data were processed using the MestreNova software.

Size exclusion chromatography (SEC) was performed using an Agilent 1260 Infinity system equipped with two polystyrene columns of 8x300 mm and a Wyatt OptilabREX refractive index detector. THF was used as eluent at 0.5 mL min^{-1} flow rate. PMMA standards were used for calibration.

The morphology of the obtained polymer particles was analysed by scanning electron microscopy (SEM) using a JEOL 6490LV SEM and JEOL JSM 840-A in secondary electron image (SEI) mode under high vacuum (HV). Samples were prepared on aluminium stubs supplied by Agar. Two-sided carbon discs were placed on the aluminium stub and sufficient amounts of samples were spread on the discs. Average diameter of the particles (D_n) is determined from a conventional SEM images by measuring of randomly selected individual particles with the aid

of software (VistaMetrix, V.1.33.0). Approximately 25-30 particles were counted per image and several images of the same sample were analysed to get statistical measurement. Coefficient of variance (C_v) is calculated according to the following equation: $C_v = (\sigma/D_n) \cdot 100$. Hydrodynamic diameters of polymer particles in diluted solutions were recorded using DelsaNano C by Beckman Coulter. The size distribution of the diluted water dispersions was estimated by photon correlation spectroscopy (PCS) using a particle-size analyser at 25 °C. The intensity of the scattered light was detected at an angle of 165° to the incident beam.

Results and discussions

Synthesis of the stabilisers *via* RAFT polymerisation

Stabilisers composed of VAc and VPi of different composition and molecular weight were synthesized *via* RAFT/MADIX polymerisation (Figure 1) because of its ease of implementation and good control over the polymerisation of vinyl ester monomers.^{26,27}

Conversions around 60% were achieved after 5 hours in all cases. Reactions were typically stopped at 60% conversion to optimize the control of chain growth. The macromolecular characteristics of the obtained copolymers were determined by ¹H-NMR and SEC after purification and all results are summarized in Table 1. A representative ¹H-NMR spectrum is

shown in Figure S1 as an example. The VAc:VPi ratio was calculated by comparison of the integrations of the resonances b (VPi, 9H from ^tBu), c and d [5VAc (3H from CH₃ + 2H from CH₂) + 2VPi (2H from CH₂)] (Figure 1). Molecular weight was calculated assuming 100% of the chains were initiated with the reinitiating fragment of the initial RAFT agent and using the integral of the resonance for the corresponding methoxy end group (f in Figure 1) as a reference. The degree of polymerisation was then obtained considering the integration of the signal h (Figure 1). The data provided in Table 1 show that P(VAc-*stat*-VPi) with M_n between 4.6 and 22 kg mol⁻¹ and VAc:VPi molar ratio ranging between 9:91 to 75:25 were successfully obtained with rather low dispersities (<1.5). There is a good agreement between theoretical M_n values (estimated taking into account the conversion) and those calculated by NMR from the integration of the chain end protons (Table 1).

Figure 1: Chemical structure of the P(VAc-*stat*-VPi) stabilizers employed and protons used to determine the composition and the molecular weight by ¹H NMR. See Figure S1 for complete ¹H NMR assignments.

Table 1 Macromolecular characteristics of the synthesized stabilisers and the size and size distribution of the PHEMA particles obtained using those stabilisers in dispersion polymerisation in scCO₂.

Entry	Composition ([VAc:VPi], ¹ H-NMR)	M_n (stabiliser) (kg mol ⁻¹ , theo)	M_n (stabiliser) (kg mol ⁻¹ , ¹ H-NMR)	M_n (stabiliser) (kg mol ⁻¹ , SEC)	$\bar{D}$ (SEC)	Particle Size (μ m, SEM) ^a	C_v (%) ^b
1	9:91	5.0	4.6	4.5	1.22	3.7	11.2
2	12:88	6.0	7.5	7.4	1.42	2.3	8.3
3	17:83	12.0	9.8	10.6	1.49	4.4	9.6
4	23:77	11.0	9.8	11.9	1.42	Porous	
5	29:71	9.3	10.6	9.0	1.20	Aggregate	
6	36:64	8.8	7.8	10.0	1.02	1.2*	10.8
7	36:64	8.0	9.9	11.5	1.08	2.1	11.6
8	42:58	8.5	10.3	10.0	1.20	Aggregate	
9	44:56	12.8	10.7	12.0	1.08	2.3	10.5
10	47:53	7.8	6.6	8.2	1.13	Irregular shaped	
11	50:50	14.0	12.0	13.8	1.47	1.9	9.0
12	49:51	17.0	14.5	21.8	1.50	Aggregate	
13	50:50	25.0	22.0	29.4	1.42	0.9*	12.5
14	56:44	8.4	8.6	10.0	1.05	2.2	7.5
15	56:44	9.8	12.8	14.0	1.07	1.3	13.2
16	75:25	12.0	9.5	13.5	1.38	Porous	

a: The average size of the particles determined from individual SEM images (D_n), b: $C_v = (\sigma/D_n) \cdot 100$ where σ indicates the standard deviation. *: In these samples a particle size is reported for individual particles but also significant aggregation was observed. For entry 3 the RAFT ends could not be determined.

Table 2 Cloud points of two representative copolymers in HEMA/CO₂ (Entries 1 and 2) or NVP/CO₂ (Entry 3).

Entry	Copolymer				Cloud Points [T (°C) vs. P(bar)]				
	[VAc: VPi] (¹ H-NMR)	M_n total (kg mol ⁻¹ , ¹ H-NMR)	$\bar{D}$ (SEC)	T_g (°C, DSC)	35 °C	45 °C	55 °C	65 °C	75 °C
1	47:53	7.8	1.13	51.5	174	207	237	263	286
2	57:43	9.3	1.02	48.3	175	217	250	278	305
3	44:56	9.4	1.50	47.4	154*				

*Data was taken from the reference 19.

Cloud point measurements

The cloud point in scCO_2 is defined as the pressure where the polymer starts to precipitate out from the medium at a given temperature and is measured at the point where the LED lights in the system are no longer visible. Therefore, by measuring cloud points one is able to estimate the reaction conditions for the copolymer to be used efficiently as a stabiliser in dispersion polymerisation in scCO_2 . The cloud points of the two synthesized P(VAc-stat-VPI) copolymers shown in Table 2 were measured in the dispersing medium (scCO_2) containing the HEMA monomer which mimics the initial phase of dispersion polymerisation. Moreover, in this mixture the monomer also behaves as a co-solvent enhancing the solubility of the copolymers in scCO_2 . Photographic images (Figure 2) were taken at discrete phase changes during cloud point measurements, which represent the different stages of a cloud point experiment (Figure 2).

A clear trend is observed; an increase in temperature (35 °C to 75 °C) led to higher cloud point pressures for both samples. This behaviour is strongly related to the lower CO_2 density at higher temperatures, which necessitates an increase in the pressure in order to have the same solvent strength. Nevertheless, the copolymers show similar cloud points at 35 °C (175 bar) to the conditions under which our dispersion polymerisations in scCO_2 will operate.

Figure 2: Illustrative pictures of the cloud point measurements for the typical P(VAc-co-VPI) stabiliser. 1: Initial mixture of HEMA (3 g), stabiliser (150 mg) and carbon dioxide (20 g) at initial pressure (around 50 bar) and room temperature; 2: The view cell is heated to the desired temperature (i.e. 35 °C) and pressure is increased until there is complete dissolution of the copolymer in the monomer and carbon dioxide mixture; 3: Keeping the temperature constant the rear sapphire piston is withdrawn to lower the pressure (and density) and the copolymer starts to precipitate out from the mixture forming the cloud and obscuring the LED back-lights.

In addition, the cloud point of a stabiliser with roughly similar molecular characteristics ($\text{VAc:VPI} = 44:56/M_n = 9.4 \text{ kg mol}^{-1}/\bar{D} = 1.5/T_g = 47.4 \text{ °C}$) was measured in scCO_2 in the presence of a different monomer, NVP (Table 2-Entry 3). The cloud point data at 35 °C show very similar values to the HEMA system, i.e. 154 bar (2236 psi) thus indicating that perhaps the syntheses with

HEMA may proceed just as effectively as those previously demonstrated for NVP.¹⁹

In light of these measurements, it would be expected that in terms of copolymer composition when the VPI content increases the solubility in CO_2 increases. And all the synthesized stabilisers should be soluble for HEMA dispersion polymerisations carried out 35 °C and 240 bar.

Dispersion polymerisation of HEMA in scCO_2

Dispersion polymerisation of HEMA was performed in scCO_2 as described above. Cross-linked PHEMA particles have been widely investigated for biomedical applications especially for sustained release. The cross-linking degree defines the swelling of the networks thus affect the release behaviour of the entrapped molecules within the network. Synthesis conditions and feed ratios for producing cross-linked PHEMA particles have been selected on the basis of cloud point measurements along with our previous work using fluorinated stabilisers,⁹ i.e. 35 °C and 240 bar which are above the critical conditions for CO_2 .

In the course of the dispersion polymerisations in scCO_2 we observed an increase of the final pressure of around 14 bar (200 psi). This phenomenon was also reported by other researchers for polymerisation of styrene (Sty)²⁸, methyl methacrylate (MMA)²⁹ and HEMA³⁰ in scCO_2 and is attributed to the thermodynamics of mixing leading to expulsion of both CO_2 and monomer from the polymer phase.

After overnight polymerisation at 35 °C and 240 bar the heating was turned off and the autoclave was left to cool to room temperature and remaining CO_2 was slowly vented. After complete depressurisation, the polymer was collected from within the autoclave as either a free-flowing powder or as a brittle disc from the bottom of the reactor (See supporting info-S2). Further inspection by SEM of polymer obtained in two of the experiments (Figure 3) showed that only aggregated polymer products are formed by coalescence of well-defined spherical particles. Similarly, large aggregates of polystyrene particles have been observed before by Canelas et al. using poly(styrene)-*block*-poly(dimethylsiloxane) (PS-*b*-PDMS) block copolymers as stabiliser.²⁸ They explained the formation of polystyrene aggregates by the collapsing of PDMS chains as solubility in CO_2 decreased during venting process.

Figure 3: Representative SEM images of the solid disc polymer product obtained by dispersion polymerisation in scCO_2 ; (Table 1: Entry 14) i. 100X magnification ii. 1000X magnification; (Table 1: Entry 15) iii. 100X magnification iv. 1000X magnification.

Effect of stabiliser composition and molecular weight

i. Composition

A series of P(VAc-*stat*-VPi) copolymers having roughly similar molecular weights ($\sim 10 \text{ kg mol}^{-1}$ according to NMR) with different compositions (Table 1, entries 3/4/5/7/8/9/11/15/16) were tested to find the most suitable VAc:VPi ratio for stabilising PHEMA particles in scCO_2 . The initial feed ratios were kept constant for all the reactants; HEMA (monomer, 10% v/v_{CO_2}), EGDMA (cross-linker, 1% $\text{v/v}_{\text{monomer}}$), stabiliser (10% $\text{w/v}_{\text{monomer}}$) and low temperature initiator (V-70, 1% $\text{w/v}_{\text{monomer}}$). After overnight polymerisation, for all copolymer stabilisers, high HEMA conversions were achieved typically $>90\%$ in each case. However, depending on the molecular characteristics of the stabilisers, different polymer product morphologies were observed by SEM (Figure 4). The stabilisers and the characteristics of the corresponding particles are listed in Table 1.

Figure 4: SEM images of the particles obtained after dispersion polymerization of HEMA (10% v/v_{CO_2}) and EGDMA (cross-linker, 1% $\text{v/v}_{\text{monomer}}$) with stabiliser (10% $\text{w/v}_{\text{monomer}}$) of different compositions (see entries of Table 1) and initiator (V-70, 1% $\text{w/v}_{\text{monomer}}$).

The copolymer composition was shown to have a major impact on particle stabilisation, morphology and size. It was observed that the best defined and smallest particles were obtained when the copolymer compositions (VAc:VPi) were close to 50:50 (especially 56:44, Entry 15). Increased VAc content in the copolymers resulted in better stabilisation of the PHEMA cross-linked particles (Entry 5 to Entry 15) affording diameters around 2 microns. This behaviour of the P(VAc-*stat*-VPi) copolymer was in line with already reported observations for the dispersion polymerisation of NVP in scCO_2 .¹⁹

There appears to be a morphology change of the PHEMA product for stabiliser compositions that were clearly rich in one of the co-monomers (23:77 and 75:25 VAc/VPi ratio). These copolymers led to formation of porous PHEMA monoliths instead of particles (Figure 4, Entry 4 and 16). For these extreme compositions the copolymers were not able to stabilize the growing PHEMA particles, and the breakdown of steric stabilisation leads to a porous PHEMA network.

It is worth mentioning that anchoring to the particles *via* RAFT end-groups cannot be considered since xanthates are indeed known to show no reactivity towards methacrylic radicals.¹⁸ Therefore, the origin of stabilisation appears to be mainly by adsorption of the stabiliser on the particle surface which imparts long-range repulsion.

ii. Molecular weight

P(VAc-*stat*-VPi) stabilisers with different molecular weight were tested for their effect on particle formation, morphology and size. Surprisingly, quite well-defined particles are formed for stabilisers with very low VAc content and low molecular weights (Table 1 - Entry 1/2/3). This is attributed to the higher solubility of these lower molecular weight stabilisers. However, the particles produced do remain quite large in diameter (Table 1 - Entry 1/2/3). The best-defined and smallest particles are produced with a composition of 56/44 (Figure 4 and Table 1: Entry 14/15). In general, the composition appears to be the dominant parameter for efficient stabilisation of the particles. At this composition (56/44) an increase of molecular weight from 8.6 kg mol^{-1} to 12.8 kg mol^{-1} shows a significant and controllable decrease of the particle size from $2.2 \mu\text{m}$ to $1.3 \mu\text{m}$, although the size distribution was slightly broadened.

In previous work we produced PHEMA nanoparticles in scCO_2 aided by a perfluorinated diblock stabiliser composed of polyethylene oxide (PEO) and poly(heptadecafluorodecyl acrylate) (PFDA) (PEO-*b*-PFDA). The particles were obtained with diameter as small as 200 nm .⁹ Others have shown that dispersion polymerisation in scCO_2 using a silicone based stabiliser can yield controlled particle sizes from 300 nm to $7 \mu\text{m}$ for PMMA.³¹ Although the particles obtained in this work are of

a larger size (micrometres) they are still very well defined and of practical interest. In conclusion, the most efficient stabiliser was found to be the copolymer with 56:44 composition and 12.8 kg mol^{-1} (Figure 4 and Table 1, Entry 15) and was therefore selected for further investigation.

Effect of cross-linker content

It has been reported that mechanical properties such as stiffness and surface hardness of bulk or particle hydrogel networks can be tuned by tailoring the composition of the network by incorporating co-monomers or varying cross-linking density.^{32,33} Thus, dispersion polymerisation of HEMA was carried out with three different initial concentrations of EGDMA whilst keeping the other parameters constant (*i.e.* stabiliser composition, ratio). The effects of initial cross-linking content on the particle size and morphology were demonstrated by SEM images (Figure 5). Surprisingly we found that in our control experiments with no added EGDMA the PHEMA particles were found to be slightly cross-linked as evidenced by the particles swelling but not dissolving in DMF, a good solvent for PHEMA. We believe this can be explained by small levels of EGDMA that are present as an impurity in the monomer.³⁴ A clear trend (Figure 5) is seen as the cross-linker initial concentration increases (0 to 3 wt%); more uniform and discrete particles were formed. The likely reason for the apparently better stabilisation is that the particle surfaces have become rigid because of the action of the cross-linker and this helps in preventing coalescence of the particles when they collide in the dispersion process or after depressurisation.³⁵ In addition to better stabilisation, the particle size also decreased from 1.3 to $1.22 \mu\text{m}$ as EGDMA cross-linker concentration was increased from 1 wt% to 3 wt%.

Figure 5: Effect of cross-linker concentration on particle morphology. A: 0% EGDMA, B: 1% EGDMA, C: 3% EGDMA added (v/v_{monomer}). The feed ratios for stabiliser (10% w/v_{monomer}) and initiator (1% w/v_{monomer}) were kept constant as well as the reaction conditions (35°C and 240 bar). Stabiliser characteristics are listed in Table 1 Entry 15.

Dynamic mechanical analysis (DMA) was conducted in order to see the effect of the cross-linking density on the particle properties. DMA plots (Figure 6) indicate two distinctive peaks.

The first peak at around 50 °C in the DMA curves is ascribed to the stabiliser present on the particle surface, a conclusion drawn from comparison with DSC analyses of the stabiliser alone which gives a peak at around 50 °C (Table 1). The second peak (80 °C – 140 °C) is clearly assigned to the PHEMA network (Figure 6) based on literature data³⁶ and this peak increases with cross-linking density. A clear trend is seen, with high concentration of cross-linker leading to higher T_g s and indicating that higher cross-linking density was achieved in the resultant networks (Table S3 - Entry 3).

Figure 6: Dynamic mechanical analysis of the PHEMA particles obtained with various cross-linker concentrations as well as copolymerisation of HEMA with NVP using 1% cross-linker.

Copolymerisation with NVP

As mentioned earlier, another approach to vary the properties of the PHEMA particles is to introduce a co-monomer. To test this approach, copolymerisation of HEMA with NVP has been performed using 50% v/v_{HEMA} initial feed ratio in the presence of 1 wt% EGDMA crosslinker. The incorporation of NVP as co-monomer was evidenced using ATR-IR (Figure S4). Successful copolymerisation of HEMA with NVP was confirmed by the appearance of the characteristic peak of a carbonyl group (C=O) assigned to the NVP moieties at 1650 cm⁻¹. In addition, as shown by the SEM image (Figure 7), the copolymerisation of HEMA with NVP results in largely spherical particles (1.8 µm) with a very small amount of aggregation, essentially very similar to those obtained for PHEMA (1.3 µm) with the same stabiliser.

Figure 7: Copolymerisation with 50% v/v NVP with respect to HEMA. Stabiliser: 10% w/v_{monomer} (VAc:VPi 56/44, 12.8 kg mol⁻¹, Table 1 - Entry 15); cross-linker EGDMA: 1% v/v_{monomer}; initiator V-70: 1% w/v_{monomer}; 35 °C and 240 bar.

While the implication of the xanthate chain end was previously ruled out in the case of HEMA polymerization, the addition of NVP as a comonomer requires to reconsider this assumption. Indeed, previous studies have investigated the effect of the xanthate end groups in dispersion polymerisations in scCO₂. Poly(vinylalkylate) stabilisers bearing xanthate end groups were found to easily and reproducibly form micron-sized PNVP particles.^{18,19} Lee et al. demonstrated that the RAFT mechanism was essential for that stabiliser P(VAc-co-VBu) to anchor onto the PNVP growing particles in scCO₂. This was proven by an experiment in which the xanthate end-group was converted to a thiol. Even though the thiol terminated copolymer had roughly similar solubility (similar cloud points) in scCO₂ compared to xanthate bearing copolymer it was found to be ineffective for stabilisation of PVP particles in dispersion polymerisation.

Therefore, we hypothesised that the observed stabilisation of the particles in the presence of NVP might be slightly different from that obtained with HEMA alone as the presence of the xanthate chain end of the stabiliser will not be neutral. The literature offers a bunch of reactivity ratios for NVP/HEMA copolymerization systems^{37,38} that, although different, are all pointing to a faster incorporation of HEMA in the chains compared to NVP. Although HEMA terminated growing radicals will not add to the xanthate moiety of the stabilizer as mentioned above, PNVP oligoradicals can add onto the xanthate chain end, and release P(VAc-stat-VPi) macroradicals to form block copolymers that will be involved in particle stabilization.

The introduction of NVP units in the PHEMA network also impacts the properties of the particles (Figure 6). DMA measurements demonstrate that the T_g of the network containing NVP is shifted from 101 °C to 113 °C as would be expected from the higher T_g of PNVP.

All of these data clearly show that we have developed a robust and fluorine-free dispersion process in scCO₂ that allows production of well-defined hydrophilic networks of PHEMA and P(HEMA-co-NVP) with adjustable T_g in both cases and variable cross-link density; both of which could be used to potentially modulate their swelling in water.

Hydrolysis of the stabilizer towards hydrogel microparticles

Finally, the dispersion process results in particles that have stabiliser located at the surface; in this case P(VAc-stat-VPi), which is hydrophobic and does not allow the cross-linked particles to be dispersed in aqueous systems. To make these materials dispersible in water, we began to look closely at the possibility of hydrolysing the stabiliser attached to the particle surface. Poly(vinyl esters) (PVAc and PVPi) are used commercially to obtain water soluble systems by conversion through hydrolysis to introduce some level of poly(vinyl alcohol) (PVOH). Therefore, we hypothesized that subjecting the synthesized particles to hydrolysis would convert the surface located P(VAc-stat-VPi) to PVOH which would enable us to redisperse the particles in water.

However, the challenge is to check that this can occur successfully on the microparticle surfaces. Two different

hydrolysis procedures were initially tested on the stabiliser itself and were analysed by FTIR-ATR (Figure S5). The results clearly demonstrate that hydrolysis occurs since broad OH peaks have clearly appeared at around 3500 cm^{-1} . As expected, the carbonyl peak at around 1700 cm^{-1} decreases, but it does not completely disappear.

Most importantly, when applied to our crosslinked particles, this very simple hydrolysis system must provide sufficient hydrolysis of the surface located stabiliser molecules to allow the microparticles to become dispersible in water. This would represent a significant improvement upon the previously published fluorinated systems⁹ that are hydrophobic and required a photochemical cleavage process.

Having established the two sets of hydrolysis parameters, we repeated these experiments on PHEMA particles prepared with the selected P(VAc-*stat*-VPi) stabiliser in presence of 1% or 3% of cross-linker. Hydrolysed particles were isolated from the hydrolysis process by removing the solvent under reduced pressure and subsequent freeze-drying. Particle morphologies were further inspected by SEM and compared to the non-treated particles. SEM images (Figure 8 - left) clearly show that hydrolysis was non-destructive for the PHEMA particle morphology, especially for the 3% cross-linker content. The hydrolysed particles were redispersed in water at a

concentration of 5 mg mL^{-1} and treated for 2 minutes using a horn sonicator at high amplitude and frequency. The solution behaviour (Figure 8 -right) clearly demonstrates that hydrolysis enables dispersion in water. Before hydrolysis, most of the particles settle to the bottom of the vial (Figure 8 - Vials 1 and 4) whereas after hydrolysis a much larger portion of the particles are clearly dispersed in water (Figure 8 – Vials 2, 3, 5 and 6) and the dispersion remain stable for a significant period of time (ca. 45 minutes). This shows clearly the increased hydrophilicity of the microparticle surfaces through hydrolysis of the ester groups of the stabiliser. Having established these hydrolysis parameters we repeated the same experiment for PHEMA cross-linked particles that had been prepared in the presence of the PEO-*b*-PFDA diblock copolymer stabiliser.⁹ Here, the hydrolysis procedure had a minimal effect (Figure S6) with just a very slight improvement in the dispersion of the particles in aqueous media, and the resettling of the PEO-*b*-PFDA stabilised particles was found to be rapid. The fact that there was any improvement at all is somewhat surprising but could perhaps be a result of some modest hydrolysis of PFDA polymer at or near the particle surface.

Nevertheless, the hydrolysis procedure very strongly enhances the redispersibility of the particles synthesised in the presence of the P(VAc-*stat*-VPi) stabiliser.

Figure 8: Left: SEM images for PHEMA particles obtained with either 1% (Samples 1 to 3) or 3% cross-linker (samples 4 to 6), before and after hydrolysis. Right: pictures of the same particles re-dispersed in water, clearly showing that only the hydrolysed samples (2,3 & 5,6) are dispersed. The others (1,4) are clumped on the bottom of the vial.

Swelling of the homo/copolymer networks in water

Since PHEMA is highly hydrophilic, the swelling of the networks after hydrolysis can be gauged by DLS. The size of the particles was measured by DLS directly after suspension in water. DLS measurements were done in triplicates and the values are reported as an average in Table 3. The obtained values were compared to the size measured in the dry state from SEM micrographs. It is clear that all the particles exhibit a significant

size increase in water compared to the dry state confirming their capability to swell rapidly.

Table 3 Particle size for the homo- and copolymer networks determined by SEM and DLS

Entry	Monomer(s)	Cross-linker (%v)	SEM size (Dry, μm)	DLS size (μm)	
				Peak 1	Peak 2
1	HEMA	1	1.3	0.35	3.7
2	HEMA	3	1.2	3.0	
3	HEMA+NVP	1	1.8	4.8	

In the case of lightly cross-linked (1%) PHEMA, a bimodal distribution is observed with two peaks (at around 350 nm and 3.7 μm). This bimodal distribution suggests that not all the particles were evenly cross-linked leading to size differences throughout the sample. By contrast a monomodal distribution was observed for PHEMA particles with higher cross-linker content (3%). In this case, particle size increases from $\sim 1\ \mu\text{m}$ in the dry state to $\sim 3\ \mu\text{m}$ in water. As anticipated, the more highly cross-linked particles are more constrained and hence swell less. The P(HEMA-co-NVP) particles showed a rapid swelling from $\sim 2\ \mu\text{m}$ to $\sim 5\ \mu\text{m}$. This higher swelling capacity is likely due to increased hydrophilicity of the network owing to the presence of lactam groups of NVP units.³²

Thus, DMA and DLS analyses demonstrate that the mechanical and swelling properties of the polymer networks can be altered either by copolymerisation or by varying the cross-linking density. More importantly, the swelling behaviour of the homo/copolymer networks in the aqueous suspensions provides a clean route to PHEMA microgels that is highly versatile and can be adjusted by varying various parameters to obtain particles with tailored properties.

Conclusions

PHEMA particles were successfully obtained in scCO_2 using a fluorine-free copolymer composed of VAc and VPi as the stabiliser system. After studying various stabilisers of different molecular weight and composition, the optimised stabiliser was based upon P(VAc-stat-VPi) with a molecular weight of 12.8 kg mol^{-1} and a molar composition of 56:44. Indeed, this stabiliser is the most efficient for the dispersion copolymerisation of HEMA and EGDMA in scCO_2 , leading to well-defined particles of ca. 1.2 μm (for 3% EGDMA). The stabiliser was sufficiently robust to be applied to HEMA copolymerisations with various amounts of cross-linker and addition of other monomers, e.g. NVP allowing control of the physico-mechanical properties of the obtained particles. The glass transition temperatures (T_g) of the networks could also be modified by varying the degree of cross-linking or by introducing a comonomer (*i.e.* NVP). In addition, the P(VAc-stat-VPi) stabiliser located on the surface of the particles could be hydrolysed to PVOH to facilitate the redispersion of the particles in water leading to hydrogels of a few micron-size.

This facile and green route to PHEMA based microgels opens a pathway to a wide range of formulations for biomedical applications and could be used to encapsulate solvent and temperature sensitive bioactive ingredients, such as protein/peptide-based drugs.

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