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Synthesis of poly(glycolide) in supercritical carbon dioxide in the presence of a hydrocarbon stabiliser†

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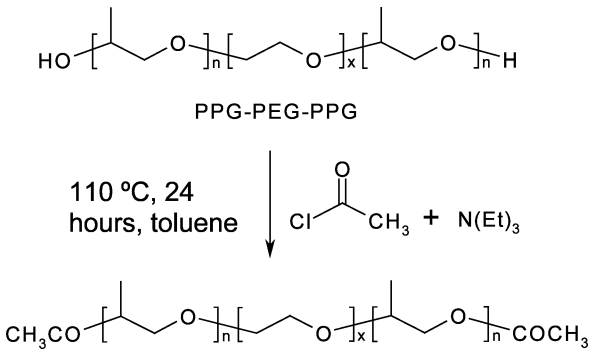
The first example of a hydrocarbon based stabiliser for ring opening polymerisation in $scCO_2$ is reported, allowing the preparation of solvent free poly(glycolide) microparticles in a clean, one step process.

Supercritical carbon dioxide ($scCO_2$) has attracted much attention in recent years as a replacement for traditional organic solvents.[1] The key advantages with the use of $scCO_2$ are the ease of recovery of product and the elimination of potentially toxic solvent residues.[2] There has been a great deal of focus upon free radical polymerisation in $scCO_2$ and it has been demonstrated that an effective stabiliser is required for synthesis of high molecular weight polymers of well defined morphology, *i.e.* as latexes or microparticles.[3] Such stabilisers have so far largely contained fluorinated[4] or siloxane[5] functionalities, these being examples of the few classes of polymer to provide sufficient CO_2-philicity. Recent work by Beckman[6,7] has focused attention on the possibility of $scCO_2$ soluble hydrocarbon polymers, *i.e.* those containing only carbon, hydrogen and oxygen. Beckman proposed that copolymers of ethers and carbonates have the most promising $scCO_2$ solubility. Such polymers are attractive because they should be relatively inexpensive and environmentally benign compared to fluorinated or siloxane based materials. To date however, only one example exists of a hydrocarbon stabiliser being successfully used in $scCO_2$, during the synthesis of poly(carbonate) *via* a condensation route.[8] In contrast to the body of work conducted on free radical polymerisation in $scCO_2$, comparatively little has been reported concerning ring opening polymerisation (ROP).[9–11] The precipitation polymerisation of ε-caprolactone has been reported,[12] whilst the synthesis of poly(D,L-lactide)-*ran*-(glycolide) in the presence of a fluorinated stabiliser, poly(fluorooctylacrylate), was described but with no reported morphological control.[13] More recently, we reported the development of a fluorinated triblock stabiliser that was effective for ROP in $scCO_2$, leading to high yields of resorbable microparticles of poly(L-lactide) (PLLA) in a one step process.[14] This was the first example of an effective stabiliser leading to morphological control over ROP in $scCO_2$. Poly(glycolide) (PGA) is a related aliphatic polyester that is very important in the biomedical and drug delivery industries.[15] It is normally synthesised in bulk, leading to intractable solid materials. In fact, PGA is widely regarded as extremely difficult to process owing to a high melting point and the general insolubility of PGA in most organic solvents. Only hexafluoroisopropanol (HFIP) has sufficient solvating ability to allow further processing of the bulk-derived material. Here we report the discovery of a hydrocarbon stabiliser that allows the polymerisation of glycolide in $scCO_2$ leading to easily processed resorbable microparticles of PGA. The stabiliser is based upon poly(propylene glycol)-poly(ethylene glycol)-poly(propylene glycol) (PPG-PEG-PPG), a commercially available block copolymer (M_n = 2700, Aldrich). Copolymers of this type have a long history of use in biomaterial studies, and are known to have low toxicity.[16] We hypothesised that the PEG section would anchor to the growing PGA particles, whilst the PPG sections would provide the necessary CO_2-philicity.[7] Initial studies of the commercially available triblock copolymer were unsuccessful. The material did not show sufficient solubility, and the hydroxyl terminal functionalities were found to initiate the ROP reaction. Thus, these functionalities were end-capped with acetyl chloride before use to improve $scCO_2$ solubility[7] and prevent this undesirable side reaction (Scheme 1). Full experimental details for this step can be found in ESI.†

Polymerisation studies were conducted in a 60 ml stainless steel autoclave equipped with a magnetically driven overhead stirrer at 80 °C for 24 hours at 3500 psi (24 MPa, 249 bar). Tin(II) ethyl hexanoate ($Sn(Oct)_2$) was used as catalyst and butanol as initiator. After 24 hours, the autoclave was cooled to room temperature and vented slowly over a half hour period. The molecular weight characteristics and yields (determined gravimetrically) of the PGA obtained can be found in Table 1. In the absence of stabiliser, PGA is obtained as a hard block-like material that must be chipped out of the reactor vessel. This morphology is very similar to that obtained by conventional bulk polymerisation at this temperature. By contrast, the same procedure performed in the presence of 10% w/w of the end capped PPG-PEG-PPG stabiliser leads to the formation of a fine, free flowing powder, obtained directly from the autoclave



Scheme 1 End capping PPG-PEG-PPG.

Table 1 PGA synthesised in $scCO_2$

Sample[a]	% Stabiliser[b]	Stirring rate (rpm)	M_n[c]	PDI[c]	Yield[d] (%)	Morphology[e]	$D_{3,2}$[f]/ μm
1	0	300	4170	2.2	> 80	Aggregated	—
2	10	300	4800	2.3	92	Fine powder	5.6
3	10	50	4080	2.2	94	Fine powder	6.6
4	10	0	4150	2.9	> 80	Aggregated	—
5	5	50	4850	2.3	92	Fine powder	20
6	2.5	300	4280	2.4	> 80	Aggregated	—

[a] PGA synthesised at 80 °C, 4 g monomer loading, 0.11 ml $Sn(Oct)_2$, 0.06 ml butanol (M/I = 50) for 24 h. [b] Amount of stabiliser added as % with respect to the mass of monomer (4 g). [c] GPC recorded in HFIP at 40 °C, using 2 × PL HFIP Gel columns and an RI detector against PMMA standards (Polymer Laboratories Ltd.). [d] Mass of product obtained from the autoclave. [e] Appearance of product directly from the autoclave. [f] Salter mean average diameter ($D_{3,2}$) of particles obtained on a Malvern Mastersizer S laser diffractometer, using isopropyl alcohol as a dispersant.

† Electronic Supplementary Information (ESI) available: Full experimental section and scheme of PGA synthesis. See http://www.rsc.org/suppdata/cc/b3/b313358c/

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after venting of the $scCO_2$ (sample 2, Table 1). SEM analysis reveals that the powder consists of irregularly shaped microparticles of PGA (Fig. 1). Experiments in a view cell demonstrate that both glycolide monomer and PGA are insoluble in $scCO_2$ (at 3500 psi, 80 °C). Thus, the polymerisation must proceed *via* a suspension mechanism, which involves the direct conversion of monomer droplets in the continuous phase to polymer. Irregularly shaped microparticles are formed in powder suspension polymerisations,[17] *i.e.* one in which the polymer is not softened by its monomer, as is the case for PGA. The stabiliser remains effective down to 5 wt% loadings, and attempts to further reduce the loading lead only to aggregated solids, implying that there is insufficient stabiliser coverage on the PGA particles to prevent aggregation. Table 1 also shows that the presence or absence of a stabiliser does not significantly affect the final molecular weight, which is good additional evidence that the end capping of hydroxyl functionalities was successful, as hydroxyl groups act as initiators for ROP.

In suspension polymerisation, the morphology of the particles is known to be sensitive to the rate of sirring during the reaction.[17] Stirring is required to disperse the monomer droplets throughout the continuous phase, and we have confirmed that in the absence of stirring, no particles are formed (entry 4, Table 1). At higher stirring speeds, smaller particles are formed as the monomer is dispersed into smaller droplets. Fig. 2 shows the particle size distribution of entries 2, 3 and 5 from Table 1. It can be seen that at 300 rpm with 10 wt% stabiliser the bulk of the particles formed are smaller than those formed at 50 rpm (5.6 μm compared to 6.6 μm, Salter mean diameter). All samples show a small amount of particulate material less than 1 μm in size, which is apparently insensitive to stirring. This is indicative of a small amount of emulsion polymerisation taking place in the vessel in addition to suspension polymerisation. This is a common occurence in suspension polymerisations conducted with high stabiliser concentrations.[17] The particle size distributions given in Fig. 2 show an inverse relationship between particle size and stabiliser concentration, as is commonly observed in suspension polymerisation. Lowering both the stabiliser concentration and the stirring rate leads to significantly larger particulate material (entry 5, Table 1).

In summary, inexpensive non-toxic hydrocarbon stabilisers based on easily modified commercially available materials have been developed for ROP in $scCO_2$. It has been shown that these stabilisers are effective for the production of highly processable fine, free flowing PGA powder. This is a significant breakthrough, as previous stabilisers effective for ROP in $scCO_2$ were based on fluorinated materials, which may be inappropriate for biomedical applications. Future publications will describe the effect of stabiliser architecture on particle size.

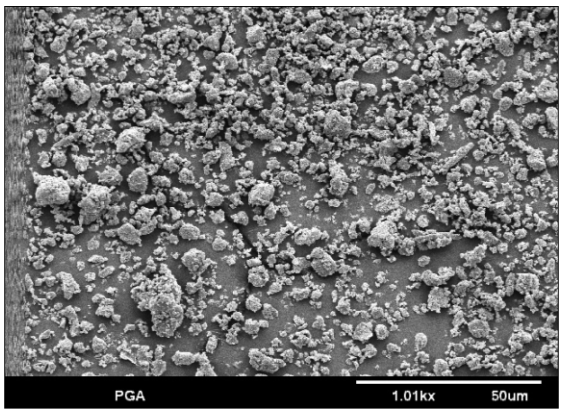

Fig. 1 SEM image of PGA synthesised in $scCO_2$, 10% w/w stabiliser, 300 rpm stirring. Microparticles around 10 μm in size can be seen.

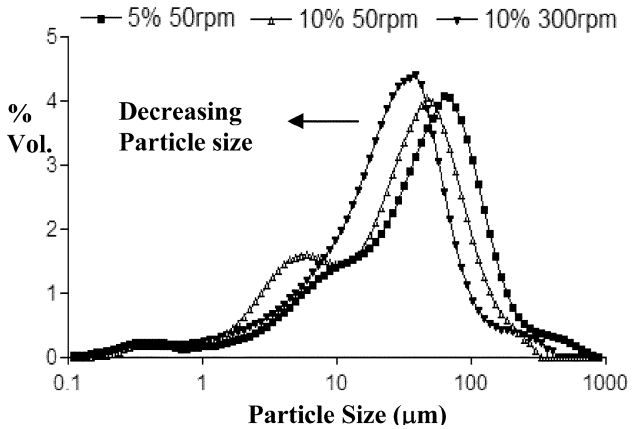

Fig. 2 Particle size distributions of particles obtained with (▼) 10% stabiliser, 300 rpm stirring, (△) 10% stabiliser, 50 rpm stirring, (■) 5% stabiliser, 50 rpm stirring. It can be seen that particle size is inversely proportional to stabiliser concentration and stirring rate.

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