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Gelation of microsphere dispersions using a thermally-responsive graft polymer

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ABSTRACT

Dispersions of microspheres (MSs) that form self-supporting particle gels are fundamentally interesting from the viewpoints of gel formation and mechanical properties. Here, we investigate model mixed MS/thermally responsive polymer dispersions that exist as particle gels at 37 °C. The MS comprised poly(caprolactone) (PCL) and was prepared by solvent evaporation. The thermally responsive polymer contained a cationic backbone and poly(2-(2-methoxyethoxy)ethyl methacrylate) side chains and is abbreviated as PMA. Mixed PCL/PMA dispersions formed weak gels due to depletion at 20 °C. At higher temperatures they formed stronger gels due to a combination of bridging of PCL MS by PMA and reinforcement by a PMA network. A key parameter controlling the mechanical properties of the reinforced MS particle gels was the volume fraction of PMA with respect to total polymer present (Φ_{PMA}). Self-healing behaviour was observed for the gels using dynamic rheology and this depended on Φ_{PMA}. The MS particle gel mechanical properties were conceptually described in terms of isostress and isostrain blending laws. At Φ_{PMA} less than or greater than 0.057 the gels were dominated by the PCL or PMA networks, respectively. The latter value is suggested to be analogous to a phase inversion point.

1. Introduction

Particle gels are space-filling networks comprising inter-connected polymer particles [1–4]. They have attracted considerable academic interest because they are believed to form by the same type of thermodynamic phase instability that applies to solid–gas equilibrium. The gel formation is termed arrested phase separation [3]. The elasticity of a particle gel is determined by the number density of elastically effective particle chains and the inter-particle bond strength. We have previously investigated particle gels for potential application as injectable scaffolds [4–6]. Biocompatible injectable gel forming dispersions can be readily prepared [4,5]. They have usually comprised a mixed dispersion of microspheres (MSs) and thermoresponsive polymer. The use of MS particles followed earlier work where emulsion droplets were used [7]. The fundamental aspects of gel formation and elasticity of thermally responsive particle gels have received little attention. Here, we investigate poly(caprolactone) (PCL) MS dispersions containing added thermally responsive polymer. The latter consisted of a positively charged backbone and poly(2-(2-methoxyethoxy) ethyl methacrylate) side chains (PMe_2OMA) and is abbreviated as PMA. PMA triggered formation of MS particle gels. Here, we investigate the roles of each network (PCL–PCL and PMA–PMA) in determining the mechanical properties of the mixed gel. We examine whether the elasticities of the mixed gels could be conceptually described in terms of the isostrain and/or isostress blending law models proposed by Morris [8]. The models provided in that seminal study envisaged hard filler particles dispersed within a soft matrix (isostress) and soft filler particles dispersed within a hard matrix (isostrain). Here, we vary the proportions of the MS and thermoresponsive polymer to move between composition regions where each model should apply.

Thermoresponsive polymers, particles and gels have attracted considerable interest [9–15]. PMA is shown in Scheme 1a and contains PMe_2OMA side-chains (shown in black). The latter belong to the thermally responsive polymers developed by Lutz and Hoth [11] and provides PMA with thermoresponsive properties. PMA differs in composition, charge and architecture to previous thermally responsive polymers that have been used to prepare biodegradable dispersions that form gels when heated [4–6]. Our previous work showed that PMA existed as unimolecular micelles at room temperature [16] in dilute solutions. As part of the present study, we show here for the first time that concentrated PMA solutions form physical gels when heated (Scheme 1a).

Polymers that form gels when heated to 37 °C have received considerable attention for potential biomaterials applications and have been the subject of a number of reviews [17–20]. By forming a space-filling gel they can occupy the whole space of a defect or injury in the body. Furthermore, they can be delivered using a minimally-invasive injection. However, gels that form through

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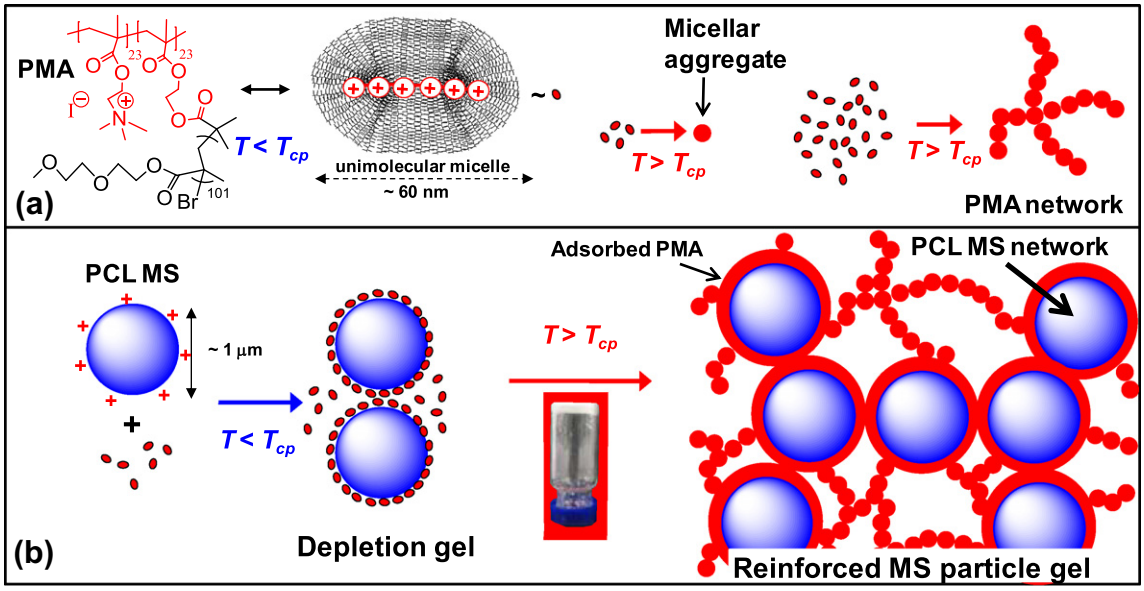

Scheme 1. Thermally-triggered bridging gel formation of PCL/PMA particle gels. (a) PMA exists as unimolecular micelles at low temperature and forms micellar aggregates at temperatures greater than the cloud point temperature (T_{cp}). At higher concentrations physical gels form. (b) Mixed PCL/PMA dispersions formed weak depletion gels at temperatures less than T_{cp}. At temperatures greater than T_{cp} reinforced MS particle gels form.

thermally-triggered physical gel formation tend to have low to moderate elasticities. Their potential regenerative medicine applications are principally for non-load-bearing soft tissue repair. Injectable gels have improved prospects for delivery if they can be loaded with high concentrations of actives. We have investigated mixtures of thermally responsive polymers and biodegradable particles [4,21] for use as injectable scaffolds. Inclusion of biodegradable particles offers potential advantages in the form of higher active loadings than conventional polymer gels as well as built-in porosity, due to space-filling aggregate structures which tend to form when thermally-triggered gelation occurs. The principles governing gel formation and mechanical properties need to be fully understood in order to maximise the potential of injectable gel forming MS dispersions for biomaterial use. Here, we focus on the fundamental aspects of a model system.

The approach used in this study is depicted in Scheme 1. PCL MS particles were prepared using solvent evaporation in the presence of cetyltrimethylammonium bromide (CTAB) and this gave cationic microspheres (Scheme 1b). CTAB would not be suitable for application as a biomaterial because it is well known to be cytotoxic. The present system was a model gel forming mixture. PCL MS particles have also been prepared using PVA in our laboratories and the dispersions can also form gels when mixed with PMA. Those systems are not considered here. PMA existed as unimolecular micelles at [16] 20 °C and underwent micellar aggregation and gelation when heated [16] (Depicted in Scheme 1a). It will be shown that PCL/PMA dispersions formed depletion gels at temperatures less than the cloud point temperature (T_{cp}) due to non-adsorbed PMA (Scheme 1b). At temperatures greater than T_{cp} we envisage mixed PMA/PCL particle gels containing two networks (PCL–PCL and PMA–PMA). We aimed to identify the factors governing the elasticity of each of the networks and, hence, their contributions to the elasticity of PCL/PMA gels. Here, we invoke the isostress and isostrain blending law models [8] to provide useful frameworks for describing the mechanical properties of these reinforced MS particle gels. The results of this study should be generally applicable to gel-forming mixtures of colloid particles and polymers, especially those that involve temperature-responsive gelation.

2. Experimental section

2.1. Reagents

Polycaprolactone (PCL, Aldrich, M_n of about 10,000 g/mol) and CTAB (⩾99%) were purchased from Sigma Aldrich. CH_2Cl_2 (99%, Fisher Scientific) was analytical reagent grade. Water was Milli-Q grade quality.

2.2. Thermally responsive cationic polymer synthesis

The method used to synthesise PMA is depicted in Scheme S1 and was described fully earlier [16]. This involved use of a polycationic macroinitiator established by Chen et al. [22]. PMA was prepared using ATRP [16]. The polycationic backbone for PMA contained 46 units and the side chains contained 101 MeO_2MA units (Scheme 1a). The number-average molecular weight for PMA determined in previous work was 450,600 g/mol. PMA was cationic and adsorbed strongly to negatively charged surfaces and the polar phase used for GPC analysis. Because this prevented use of GPC the polydispersity for PMA was not able to be determined [16].

2.3. PCL dispersion preparation

PCL dispersions were prepared using solvent evaporation. PCL (1.5 g) was dissolved in CH_2Cl_2 (100 mL). The CH_2Cl_2 solution was then fed into a beaker of aqueous 1 wt.% CTAB solution (200 mL) with a feeding rate of 2.5 mL/min whilst high shear mixing using a Silverson LR4 high speed mixer. Throughout this process the beaker was cooled to 0 °C. The final product was stirred overnight at room temperature to remove CH_2Cl_2. The PCL dispersion was then centrifuged and the supernatant removed and replaced with water and the particles redispersed. These steps were repeated once more. The PCL dispersion was filtered using pre-CTAB washed filter paper (11 μm pore size). Finally, freeze-drying was used to obtain the PCL MS particles as a redispersable