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Hollow microspheres and aqueous phase behavior of pH-responsive poly(methyl methacrylate-*co*-methacrylic acid) copolymers with a blocky comonomer distribution

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ABSTRACT

Copolymers of methyl methacrylate (MMA) and methacrylic acid (MAA) were prepared by partial hydrolysis of PMMA in bad solvent. These copolymers evidently have a blocky comonomer distribution –strands of predominantly MMA or MAA across the polymer– and show sharp transitions in aqueous solution upon pH change. Additionally, their hollow microcapsules show an exceptional and prolonged stability at acidic conditions (pH 2) and pH-triggered release at physiological conditions.

1. Introduction

Polymers containing ionizable groups, such as carboxylic acid and amines, are the focus of intensive research, since their pH-dictated ionization can be utilized for the development of systems with reversible pH-controlled water solubility [1–7]. These polymers are typically water-soluble when charged, and become water-insoluble when neutral. Beyond the basic research focused on their phase behavior, these materials also find application, *e.g.*, in the form of hollow microspheres, in fields such as controlled release of drugs [7], protection of sensitive species in acidic environments [8], and microreactors [9].

Acrylic and methacrylic acid copolymers, including commercial materials [10,11], are particularly relevant for biomedical use because, beyond their biocompatible characteristics, they are neutral at low pH and become negatively charged at higher pH ($pKa^{COOH} \approx 4$). However their proliferation in drug delivery applications has been hampered by challenges in designing polymers with sharp transition tailored at a predefined pH, while maintaining high stability when in their water-insoluble state [10,11]. Both these requirements necessitate a well-defined copolymer microstructure that contains long sequences of single type monomers –chargeable-only or hydrophobic-only strands– currently only common in block-copolymers [1–3]. Their much easier preparation by free radical copolymerization [5,10,11] suffers, in most cases, from poor control over the comonomer distribution (*cf.* statistical monomer insertion) and over the copolymer composition (*cf.* compositional drift during the reaction results in a very wide distribution of copolymer compositions). Both these factors broaden the copolymer transition [12] and severely impact the ability to control the structure of the collapsed state and the pH-onset of the phase separation [13].

Here we report on an approach to prepare copolymers of methyl-methacrylate (MMA) and methacrylic-acid (MAA), by partial hydrolysis of PMMA in a bad solvent. These copolymers evidently have a blocky microstructure, with strands composed predominantly of MMA or MAA, and show sharp transitions in aqueous solutions upon pH variation, consistent with a hydrophobically-stabilized collapsed state. We further demonstrated their use in preparing hollow microcapsules, which showed an exceptional and prolonged stability in acidic environments (pH 2), and readily release at physiological conditions (pH 7).

2. Experimental

2.1. Copolymer preparation and characterization

All reagents were purchased from Sigma-Aldrich in *purum* grade and used with no further purification; all water is deionized (>10 MΩ cm). The copolymer preparation was carried out by alkaline hydrolysis [14] of a commercial poly(methyl methacrylate) (PMMA, Mw = 350,000 g/mol, Mw/Mn ≈ 4.5, Sigma-Aldrich), which yields well-controlled conversion of methyl methacrylate (MMA) to methacrylic acid (MAA). In brief, for each copolymer, 10 g of PMMA were hydrolyzed in a mixture of 1 eq NaOH and 1 eq deionized water in 80 g of isopropyl alcohol at 85 °C (a rather bad solvent). The degree of hydrolysis, *cf.* the copolymer acid content, was controlled by varying the reaction time (12 to 72 h). The hydrolyzed product was

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dissolved in a large excess of water, and the copolymer was precipitated by HCl, filtered, and dried at 50 °C (vacuum, 24–48 h). The MAA content of each copolymer was determined by potentiometric titration of a 0.2 wt.% solution in 0.05 M standardized NaOH, by recording the pH while slowly adding 0.05M HCl. In addition, the copolymer composition was independently confirmed by ^{1}H NMR. Turbidity (cloud point) measurements followed the pH of a copolymer solution (0.03 wt.% to 2 wt.%, in 0.125 M aqueous NaOH) as acetic acid was added, while recording the transmitted intensity of a laser ($\lambda = 650$ nm, 2 mW) with a digital photodetector. As the pH decreases, the solution remains optically clear (transmittance $\equiv I_{\text{transmitted}}/I_{\text{incident}} = 1$) and upon phase-separation (demixing) it changes abruptly to almost 0; the cloud point (binodal pH) is set *ad hoc* at 0.8 transmittance.

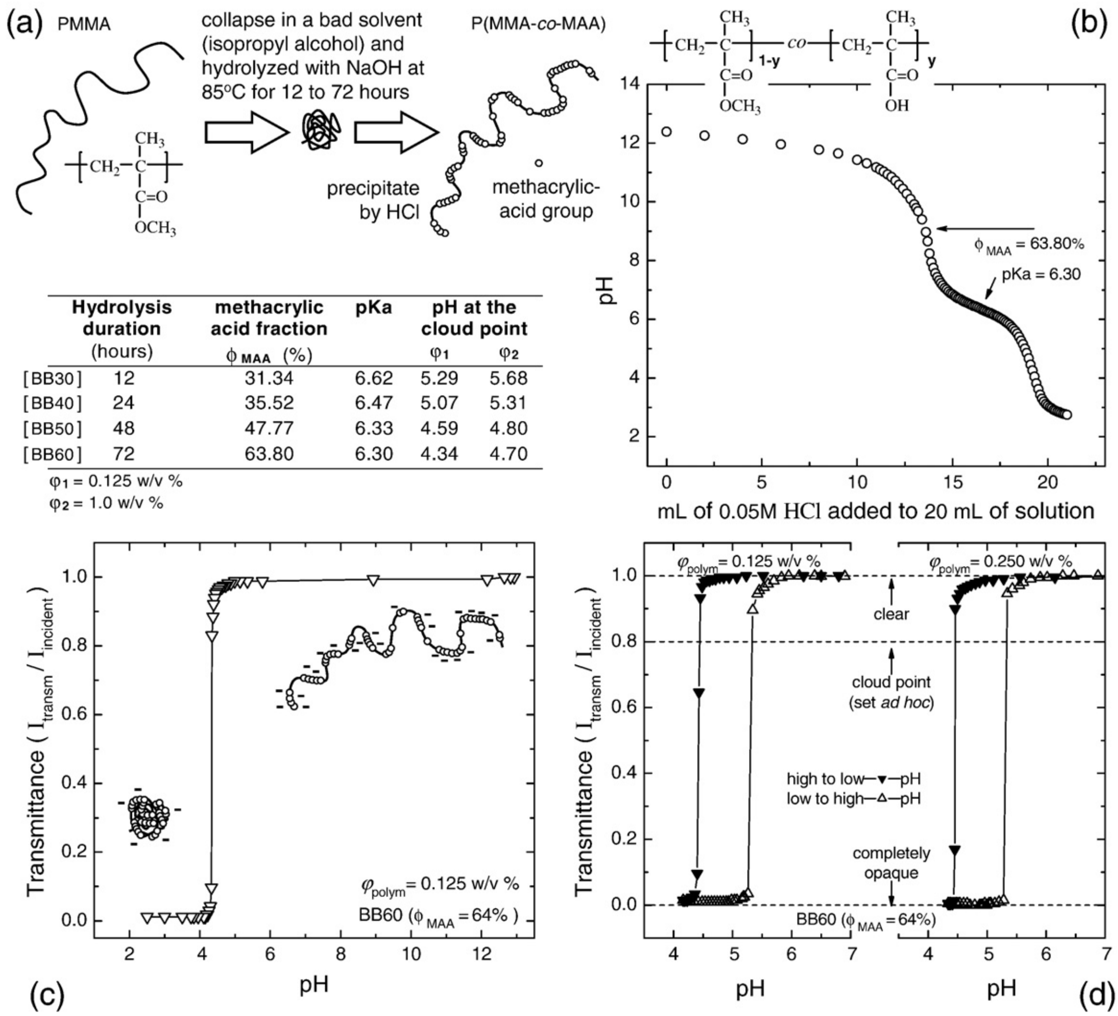
2.2. Microcapsule preparation and characterization

An oil-in-oil encapsulation method [15,16] was used to form copolymer microcapsules containing an organic solution of a water-soluble dye (0.1 wt.% methylene-blue, MB, in 95/5 methanol/benzyl-alcohol). Specifically, a predefined mass of copolymer (0.5, 0.7 and 1.0 g) was dissolved in 10 g of the MB solution and was slowly emulsified in 53 g of a second oil phase (paraffin oil containing 1 wt.% emulsifier, sorbitan trioleate) under constant stirring (*ca.* 150 rpm), at room temperature, until all methanol evaporated (*ca.* 24 h). The microcapsules were retrieved, washed with n-hexane, and dried under vacuum at room temperature. The microcapsules were characterized in saline suspension by optical microscopy, and dry by environmental scanning electron microscopy (ESEM, FEI Quanta 200), also after freezing with liquid Nitrogen and fracturing. Release studies were performed from 30 mg of microcapsules dispersed in 100 mL of two release media with different pH (phosphate buffered saline solution, PBS, pH 7.4; and aqueous HCl solution at pH 2.3). Small amounts of the release medium were withdrawn as a function of time, and the concentration of released encapsulant was measured by UV–vis absorbance (following the intensity of the 664 nm peak of MB).

3. Results

3.1. Aqueous phase behavior and pH-response of the copolymers

The partial hydrolysis of PMMA resulted in methyl methacrylate/methacrylic acid copolymers, poly(MMA-*co*-MAA), with the same molecular weight and varied methacrylic acid content (ϕ_{MAA}-controlled by the duration of hydrolysis; Fig. 1). Since the hydrolysis was carried out in a bad solvent the copolymer microstructure is expected to be segmented [12], *i.e.*, rather blocky with long strands composed predominantly or exclusively by chargeable (MAA) or by hydrophobic (MMA) groups. The results for four copolymers are shown in Fig. 1. The MAA-fraction in the copolymer was determined by titration (Fig. 1b) from the first equivalence point around pH 9, and was varied between 31.34 ± 0.01 mol.% and 63.80 ± 0.01 mol.%, for 12 to 72 h of hydrolysis (ϕ_{MAA} was also confirmed by ^{1}H NMR, *e.g.*, at 61 ± 1 mol.% MAA for BB60, in



	Hydrolysis duration (hours)	methacrylic acid fraction ϕ_{MAA} (%)	pKa	pH at the cloud point φ_1	pH at the cloud point φ_2
[BB30]	12	31.34	6.62	5.29	5.68
[BB40]	24	35.52	6.47	5.07	5.31
[BB50]	48	47.77	6.33	4.59	4.80
[BB60]	72	63.80	6.30	4.34	4.70

$\varphi_1 = 0.125$ w/v %
$\varphi_2 = 1.0$ w/v %

Fig. 1. Aqueous phase behavior and characteristics of the copolymers. (a) A schematic of the PMMA hydrolysis and details of the P(MMA-*co*-MAA) copolymers as a function of hydrolysis duration. (b) Potentiometric titration of 20 mL of 0.2 wt.% BB60 solution; the MAA content can be determined from first equivalence point (at about pH 9) and increases with more prolonged hydrolysis. (c) pH-induced phase separation of an aqueous solution of the BB60 (64%-MAA) copolymer at 25 °C, including a schematic of the corresponding copolymer charge and conformations. (d) Hysteresis of the phase separation transition upon reducing (higher-to-lower) or increasing the pH.