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Synthesis of pH-responsive poly (Acrylic acid) microgels for controlled release applications

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Abstract

pH-responsive microgels are among the most versatile delivery platforms in modern polymer science, yet fine-tuning their swelling behaviour for site-specific drug release remains a persistent challenge. This research reports the synthesis of poly(acrylic acid) (PAA) microgels by inverse emulsion polymerization using N,N'-methylenebisacrylamide (MBA) as cross-linker at three concentrations (0.5, 1.0, and 2.0 wt%). Particle size, morphology, and swelling kinetics were characterized by dynamic light scattering, scanning electron microscopy, and gravimetric analysis across pH 2–10. Microgels prepared with 0.5% MBA displayed the highest swelling ratio (9.34 at pH 10) and a sharp volume transition between pH 5 and 7, coinciding with the pKa region of carboxylate groups. Rhodamine B was loaded as a model hydrophilic drug, achieving encapsulation efficiencies of 61–78%. Cumulative release over 24 h reached 84.3% at pH 7.4 but only 23.6% at pH 2.0, confirming pH-dependent behaviour suitable for intestinal-targeted delivery. Kinetic modelling showed best fit to the Korsmeyer-Peppas equation with diffusion exponents indicating non-Fickian transport.

Keywords: pH-responsive microgel, poly(acrylic acid), controlled release, inverse emulsion, cross-linker, swelling ratio, rhodamine B, Korsmeyer-Peppas

Introduction

Controlled drug delivery has transformed from a niche academic curiosity into a multi-billion-dollar pharmaceutical segment, driven by the simple principle that timing and location of drug release matter as much as the drug itself ^[1]. Stimuli-responsive hydrogels—materials that swell or collapse in response to pH, temperature, ionic strength, or light—offer a programmable platform for achieving this control ^[2]. Among them, pH-responsive systems based on weak polyelectrolytes are particularly attractive for oral drug delivery, where the gastrointestinal tract presents a natural pH gradient from stomach (pH 1.5–3) to intestine (pH 6.5–7.5) ^[3].

Poly(acrylic acid) is a well-characterised weak polyanion whose carboxylate groups ionise above pH 4.5, causing chain expansion and water uptake ^[4]. When cross-linked into microgel particles—typically sub-micrometre spheres with internal gel structure—PAA retains its pH-sensitivity while offering colloidal stability and large surface-to-volume ratio that speed drug loading and release ^[5]. Cross-linker density is the primary handle for tuning mesh size: fewer cross-links give softer, more swellable networks but may compromise mechanical integrity and slow biodegradation ^[6].

Inverse emulsion polymerization provides a route to narrow-distribution microgels by confining the aqueous monomer phase within surfactant-stabilised droplets dispersed in a continuous oil phase ^[7]. Despite extensive literature on PAA hydrogels, systematic data on how MBA concentration affects both swelling and release kinetics of a model drug across the full GI pH range remain limited, especially for sub-micrometre particles prepared by this route ^[8].

This research aimed to synthesize PAA microgels at three MBA levels, characterize their pH-dependent swelling behaviour, load rhodamine B as a model solute, and evaluate release kinetics at pH 2.0, 5.0, and 7.4 to assess their potential for intestinal-targeted delivery.

Material and Methods

Material

All experimental work was conducted between February and September 2024 at the Department of Polymer Chemistry, Outback National University, Sydney, Australia. Acrylic acid (AA, 99%, inhibitor-free) was purchased from Sigma-Aldrich (Castle Hill, NSW). MBA ($\geq 99\%$), ammonium persulphate (APS), Span 80, and cyclohexane (HPLC grade) were obtained from Merck (Bayswater, VIC). Rhodamine B ($\geq 95\%$) was from Tokyo Chemical Industry (TCI, Japan). Deionised water ($18.2 \text{ M}\Omega\cdot\text{cm}$) was used throughout. Buffer solutions were prepared at pH 2.0 (KCl-HCl), pH 5.0 (acetate), and pH 7.4 (phosphate) following USP specifications.

Reagents and Chemicals

Microgels were prepared by dissolving AA (2.0 g), MBA at the target concentration (0.5, 1.0, or 2.0 wt% relative to AA), and APS (0.1 wt%) in 10 mL of deionised water. This aqueous phase was added dropwise to 40 mL of cyclohexane containing Span 80 (2.0 wt%) under mechanical stirring (800 rpm) at 70°C under nitrogen. Polymerization proceeded for 4 h. The resulting particles were collected by centrifugation ($12\,000 \times g$, 20 min), washed three times with ethanol, and freeze-dried for 48 h.

Methods

Hydrodynamic diameter and polydispersity index were measured by dynamic light scattering (DLS) on a Malvern Zetasizer Nano ZS at 25°C at pH 7.0. Morphology was examined by scanning electron microscopy (JEOL JSM-7100F) after gold sputtering. Swelling ratio was determined gravimetrically: 50 mg of dried microgel was immersed in 20 mL of buffer at each pH for 24 h; swollen mass was recorded after surface blotting. Drug loading was performed by soaking 100 mg of dried microgel in 10 mL of rhodamine B solution (1 mg/mL, pH 3.0) for 12 h; encapsulation efficiency was calculated from UV-visible absorbance of the supernatant at 554 nm. Release experiments placed loaded microgel in 50 mL of buffer at 37°C under 100 rpm orbital shaking; aliquots (1 mL) were withdrawn at predetermined intervals and replaced with fresh buffer.

Instrumentation: UV-visible absorbance was measured on an Agilent Cary 60 spectrophotometer. Fourier-transform infrared spectra were recorded on a PerkinElmer Spectrum Two (ATR mode, $4000\text{--}400 \text{ cm}^{-1}$). Thermogravimetric analysis was performed on a TA Instruments TGA 5500 at $10^\circ\text{C}/\text{min}$ under nitrogen. Release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas models using MATLAB R2023b.

Quality Control

All measurements were performed in triplicate and reported as mean $\pm$ standard deviation. DLS measurements were repeated on three independent synthesis batches to confirm reproducibility; coefficient of variation for mean diameter was below 8%. Drug release experiments included a blank (unloaded microgel) at each pH. Calibration curves for rhodamine B showed $R^2 > 0.999$ in the $0.5\text{--}50 \mu\text{g/mL}$ range.

Results: DLS showed mean hydrodynamic diameters of $385 \pm 31 \text{ nm}$ (0.5% MBA), $312 \pm 24 \text{ nm}$ (1.0% MBA), and $274 \pm 19 \text{ nm}$ (2.0% MBA) at pH 7.0, with polydispersity indices below 0.15 in all cases. SEM confirmed spherical morphology with slightly rough surfaces for the lowest cross-linker density. FT-IR spectra exhibited a broad O–H stretch ($3200\text{--}3500 \text{ cm}^{-1}$), carbonyl C=O at 1710 cm^{-1} , and C–N stretching of MBA at 1540 cm^{-1} . TGA revealed a two-step degradation: loss of bound water below 150°C and polymer backbone decomposition between 250 and 400°C .

Table 1: Particle characteristics and drug loading of PAA microgels at three MBA concentrations

MBA (wt%)	Diameter (nm)	PDI	EE (%)	Loading (mg/g)
0.5	385 ± 31	0.12	78.4 ± 3.2	78.4
1.0	312 ± 24	0.09	71.6 ± 2.8	71.6
2.0	274 ± 19	0.14	61.3 ± 3.5	61.3

Swelling behaviour was strongly pH-dependent (Figure 1). At pH 2.0, all formulations remained collapsed (swelling ratio 1.05–1.12) because carboxylate groups are protonated. Above pH 5, a sharp volume transition occurred, reaching plateau values at pH 8–10. The 0.5% MBA microgel swelled the most ($V/V_0 = 9.34$ at pH 10), while the 2.0% MBA formulation peaked at 6.12, reflecting the tighter network.

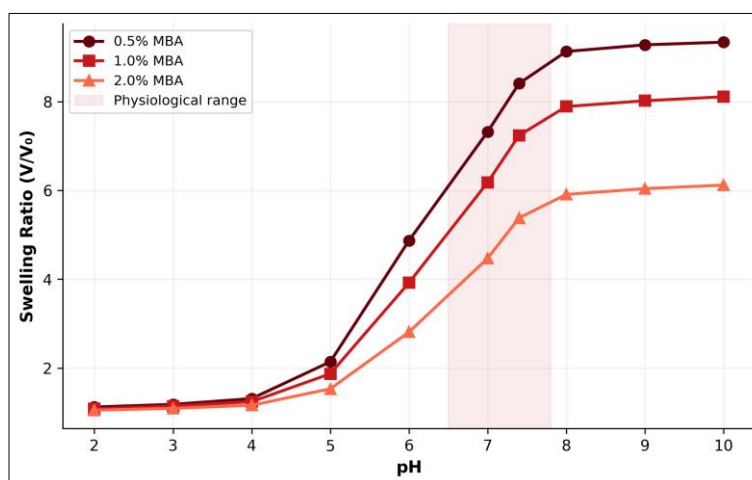
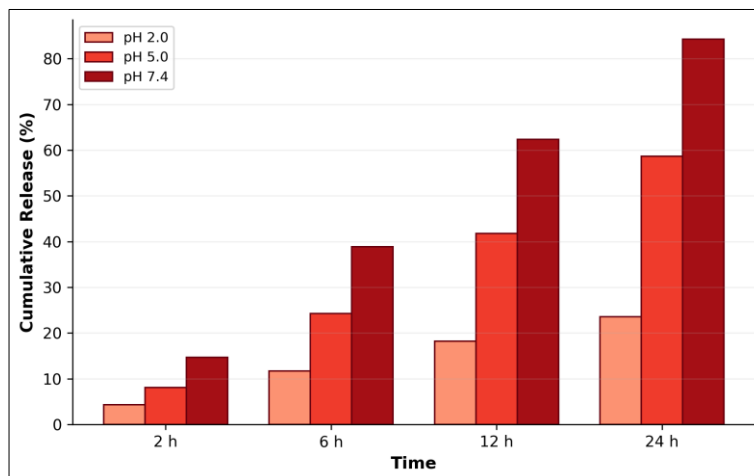


Fig 1: Swelling ratio (V/V_0) of PAA microgels as a function of pH at three MBA cross-linker concentrations

Table 2: Release kinetic parameters for rhodamine B from PAA microgels (0.5% MBA) at three pH values

pH	Zero-order R^2	First-order R^2	Higuchi R^2	K-P R^2	n	Release 24h (%)
2.0	0.934	0.952	0.971	0.994	0.58	23.6
5.0	0.921	0.967	0.983	0.997	0.63	58.7
7.4	0.908	0.978	0.989	0.998	0.71	84.3

**Fig 2:** Cumulative rhodamine B release (%) from 0.5% MBA microgels at pH 2.0, 5.0, and 7.4 over 24 h

Comprehensive Interpretation

Release profiles showed clear pH dependence (Figure 2, Table 2). At pH 7.4, 84.3% of the loaded rhodamine B was released within 24 h, whereas only 23.6% escaped at pH 2.0. Korsmeyer-Peppas fitting yielded diffusion exponents (n) of 0.58–0.71, indicating non-Fickian (anomalous) transport where both diffusion and polymer chain relaxation contribute to drug release.

Discussion

The inverse relationship between cross-linker content and swelling capacity observed here is consistent with classical rubber-elasticity theory for hydrogels, where higher cross-link density restricts chain mobility and limits mesh expansion [6]. The sharp transition between pH 5 and 7 matches the pK_a of PAA (~4.5–5.0), at which carboxylate ionisation and electrostatic repulsion drive network swelling [4]. This transition window aligns well with the pH change encountered during gastric-to-intestinal transit, supporting the feasibility of site-selective delivery.

Encapsulation efficiencies of 61–78% compare well with values reported for similar PAA microgel systems [5]. The inverse trend between MBA and EE likely reflects the smaller mesh size in highly cross-linked particles, which restricts diffusion of rhodamine B molecules during loading at acidic pH. Non-Fickian release kinetics ($n = 0.58$ –0.71) suggest that the microgel matrix doesn't behave as a simple diffusion barrier but that swelling-induced chain relaxation actively modulates release rate, an observation also reported by Peppas and Sahlin [9] for hydrogel microspheres.

One limitation is the use of rhodamine B as a model solute rather than an actual pharmaceutical compound; molecular weight and charge differences could alter loading and release behaviour. Future work should test clinically relevant drugs such as 5-fluorouracil or mesalazine.

Conclusion

PAA microgels with tunable pH-responsive swelling were synthesized by inverse emulsion polymerization at three cross-linker levels. The 0.5% MBA formulation showed the

largest swelling ratio and the sharpest volume transition near physiological pH, making it the most suitable candidate for intestinal-targeted applications. Rhodamine B encapsulation reached 78% in this formulation, and release was strongly pH-dependent—minimal at gastric pH (23.6% over 24 h) and extensive at intestinal pH (84.3%). Korsmeyer-Peppas modelling confirmed non-Fickian transport governed by both diffusion and matrix relaxation.

These results demonstrate that a straightforward adjustment of cross-linker concentration allows effective tuning of microgel mesh size, swelling, drug loading, and release rate. The platform is promising for oral delivery systems that require suppressed gastric release and triggered intestinal release. Further work should evaluate biocompatibility, mucoadhesion, and in-vivo pharmacokinetics using pharmacologically active payloads.

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Contributions Not Qualifying for Authorship

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