Polymer Bulletin 57, 11–20 (2006)
DOI 10.1007/s00289-006-0533-3

Polymer Bulletin

# Synthesis and Properties of Lightly Crosslinked Poly((meth)acrylic acid) Microparticles Prepared by Free Radical Precipitation Polymerization

**J. Brock Thomas[1], Courtney M. Creecy[2], James W. McGinity[3], and Nicholas A. Peppas[1,2,3] (✉)**

(1) Department of Chemical Engineering, Texas Materials Institute, Center for Nano and Molecular Science and Technology
(2) Department of Biomedical Engineering
(3) Division of Pharmaceutics
The University of Texas at Austin, 1 University Station, C0400, Austin, TX 78712-1062, USA

email: peppas@che.utexas.edu; Fax: +1 512 471 8227

Received: 2 December 2005 / Revised version: 7 February 2006 / Accepted: 9 February 2006
Published online: 21 February 2006 – 

**Summary**

Microparticles composed of (meth)acrylic acid, potassium (meth)acrylate, and trifunctional pentaerythritol were prepared using a thermally initiated free radical precipitation polymerization in ethyl acetate. The particle synthesis method was investigated, and the structure and morphology of the microparticles was evaluated using Fourier transform infrared spectroscopy and scanning electron microscopy. Results indicate that the physicochemical properties of the microparticles are dependent on the crosslinking ratio and type of carboxylic acid monomer employed in the polymerizations. The glass transition temperature behavior is significantly affected by the monomer type and the amount of crosslinking agent employed. The swelling dynamics of the microparticles are also pH, monomer, and crosslinking ratio dependent.

**Keywords:**

Poly((meth)acrylic acid) microparticles, pH responsive hydrogels, bioadhesion, drug delivery

## Introduction

Poly(carboxylic acid)-containing materials have been investigated for a diverse range of applications such as coatings [1,2], superabsorbents [3-5], adhesives [6,7], and drug delivery carriers [8-18]. Through the combination of the later two concepts, drug delivery systems (DDS) employing poly(carboxylic acid)-containing hydrogels have the ability to contribute to the development of an adhesive bond between the drug carrier and the absorption site of the drug molecule, acting as bioadhesive drug delivery systems [19-24]. The prolonged residence time of a drug at the site of

administration, whether it is the gastrointestinal or respiratory tract, ocular cavity, or skin, could enhance the overall effectiveness of the drug leading to a higher bioavailability. Hydrogels possess the ability to swell upon contact with aqueous solutions due to the hydrophilic nature of the polymers and the presence of either physical or chemical crosslinks. Upon the introduction of ionizable carboxylic acids as pendent groups, the hydrogel network is capable of being triggered by an environmental stimulus such as pH [25-27].

By utilizing the pH shift that occurs as an oral DDS is transported from the acidic environment of the stomach to the near-neutral duodenum and small intestine, both drug release and adhesion can be triggered [28]. Micro- and nano-sized devices and systems [29,30] are desirable for their use in oral drug delivery due to their ability to be formulated into conventional dosage forms and the ease of administration of particle suspensions. For the development of conventional dosage forms such as tablets and capsules, the rate controlling polymer must possess a high degree of compressibility and be in a particulate state that can be easily formulated with the active pharmaceutical ingredient (API). The synthesis of highly compressible microparticles is desirable to provide a polymeric material that is effectively utilized in these DDS. The integration of these biomaterials into a DDS that utilizes the polymer as a carrier is also facilitated by the synthesis of microparticles.

The aim of this work was to synthesize terpolymer microparticles prepared from pendant carboxylic acid monomers, pendant potassium carboxylate monomers, and a trifunctional pentaerythritol and characterize the polymer's physicochemical properties as a function of monomer and crosslinking agent composition.

## Materials and Methods

*Materials*. Methacrylic acid (MAA, inhibited with 250 ppm hydroquinone), anhydrous potassium carbonate ($K_2CO_3$), and ethyl acetate (EtAc) were obtained from Fisher Scientific and used as received. Acrylic acid (AA, inhibited with 200 ppm hydroquinone) was obtained from Sigma Aldrich (Milwaukee, WI) and was used as received. Allyl pentaerythritol (APE), pentaerythritol triacrylate (PETA), and di(4-tert-butylcyclohexyl) peroxydicarbonate (BCHPC) were kindly supplied by Perstorp Polyols (Toledo, OH), Sartomer (Exton, PA), and Degussa Initiators (Elyria, OH), respectively. All other chemicals were of reagent grade and used as received.

*Synthesis.* In a typical thermally initiated free radical precipitation polymerization, (M)AA, $K_2CO_3$, and deionized distilled water ($ddH_2O$) were combined and mixed to form a homogeneous mixture, allowing the escape of the neutralization by-product carbon dioxide. The crosslinking agent, APE or PETA, was dissolved in ethyl acetate. The monomer mixture and crosslinking agent were added to a four-necked round bottom flask equipped with an overheard stirrer, nitrogen purge, and condenser containing the polymerization solvent EtAc. Following a 20 minute purge with nitrogen, the initiator BCHPC dissolved in the polymerization solvent was added to the vessel and further purged for an additional 10 minutes.

The molecular structures of the monomer, crosslinking agent, and thermal initiator are shown in Figure 1. The vessel was placed in a thermostatic bath at 50°C where precipitation was evident in a matter of minutes. The reaction was allowed to proceed

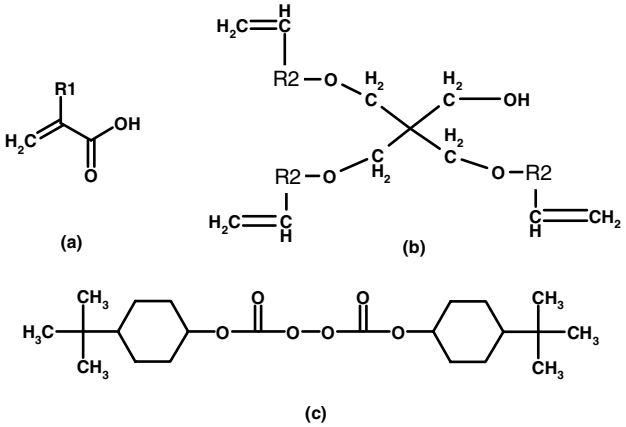



Figure 1. Molecular structures of (a) the carboxylic acid monomer (R1 = H for AA or R1 = $CH_3$ for MAA), (b) the tri-functional pentaerythritol (R2 = CH for APE or R2 = COH for PETA), and (c) the thermal initiator BCHPC.

for 16 hours to ensure a high percentage of monomer conversion. Following the polymerization, the particle slurry was centrifuged and washed with fresh ethyl acetate and dried using a rotary evaporator at elevated temperature and reduced pressure (90°C/40 mmHg). Table 1 lists the various polymeric microparticles prepared.

Table 1. Feed composition for the precipitation polymerizations of the P(M)AA microparticles.

| monomer/crosslinking agent | AA/APE | MAA/PETA |
|---|---|---|
| wt % initiator (based on monomers) | 0.5 | 0.5 |
| wt % monomer in EtAc | 10.0 | 10.0 |
| mol % crosslinking agent | 0, 0.2, 0.43, 0.75, 1.46, 3.00 | 0, 0.43, 0.75, 1.46, 3.00 |
| mol % of acid monomer neutralized | 3.1 | 3.1 |
| vol % $H_2O$ in EtAc | 0.27 | 0.27 |

*Characterization.* Microparticle suspensions were prepared using ethyl acetate, and the particle size distribution was determined with a laser light diffraction particle analyzer (Malvern Mastersizer-S, Malvern Instruments Ltd., Worcestershire, UK). The measurement was repeated three times. A scanning electron microscope (SEM, Hitachi Model S-4500, Hitachi Ltd., Tokyo, Japan) was used to obtain SEM photographs. The vacuum-dried polymer microparticles were mounted on an aluminum stage using double-sided carbon conductive tape and coated with gold for 45 seconds with a sputter-coater (Pelco Model 3, Pelco Int., Redding, CA) in an argon atmosphere.

Pellets containing 1 mg of sample and 150 mg of KBr were prepared on a Carver laboratory press using a 67 kN compression force. Infrared spectra of the microparticles were obtained in the wavenumber range of 400-4000 $cm^{-1}$ on a Fourier transform infrared spectrophotometer (FT-IR, Thermo Mattson Infinity, Thermo

Electron Corp., Waltham, MA) in transmission mode equipped with a KBr beamsplitter and DTGS detector. Each spectrum is an average of 64 scans at a resolution of 1 $cm^{-1}$.

The thermal properties of the microparticles were characterized using a differential scanning calorimeter (DSC, MDSC 2920, TA Instruments, New Castle, DE). Approximately 10-15 mg samples were analyzed at a sample rate of 10°C/min over the range of 80°C to 160°C for poly(acrylic acid) and 80°C to 300°C for poly(methacrylic acid) using a heat/cool/heat method to erase the thermal history.

The equilibrium weight swelling ratio of the polymeric hydrogel microparticles was determined by carefully weighing 50 mg of dried particles and combining them with 35 mL of $NaHCO_3$ solution (1.5 g / 100 mL). The suspension was agitated for 60 min and then centrifuged for 60 min at 2000 rpm, carefully discarding the supernatant. The pellet was resuspended in an additional 35 mL of $NaHCO_3$ solution and agitated for 60 min. The suspension was centrifuged at 2000 rpm for 60 min, carefully removing the supernatant, and the weight of the gelled mass was determined. This procedure was also carried out in a 0.1 N HCl solution.

Potentiometric titrations were carried out on aqueous solutions of the microparticles. Approximately 400 mg of polymer were slowly added to 400 mL of deionized distilled water. During the polymer addition, the solution was agitated using a three-blade marine style propeller at 1000 rpm. The particles were allowed to agitate and hydrate for 15 minutes before recording the initial pH of the suspension. After a reduction in the agitation speed, titration was performed using a 1 N NaOH hydroxide solution. The pH was allowed to equilibrate before any further addition was made.

## Results and Discussion

*Particle Size and Morphology*

All monomers, crosslinking agent, and initiator are soluble in the ethyl acetate polymerization solvent. Upon heating the reaction mixture to the polymerization temperature, oligomers begin to form as outlined in Figure 2. As these oligomers grow into polymers, the polymers become insoluble in the solvent. At this point, precipitation is evident and particle formation occurs. Microparticle formation occurs through the continuation of agglomeration of these primary particles. Polymerization of copolymers of PMAA and PAA and the crosslinked terpolymers result in no significant differences in their particle size.

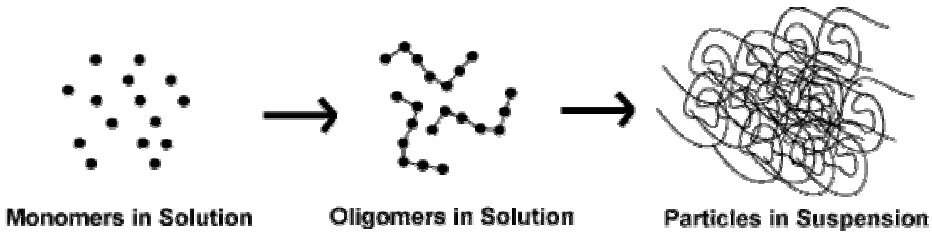
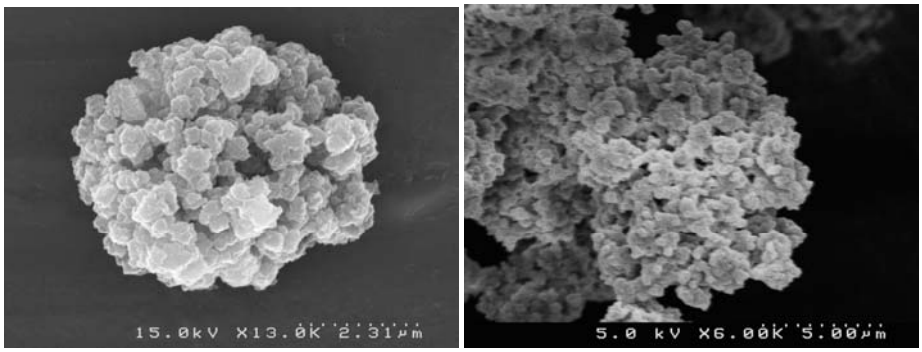



Figure 2. Precipitation polymerization of (meth)acrylic acid in ethyl acetate.

As determined using laser light diffraction, the particle size of both copolymers and terpolymers as suspensions in EtAc results in a D(v, 0.5) of approximately 15 μm and D(v, 0.9) of approximately 30 μm. Particles composed of MAA show significantly different primary particle morphology as can be seen in Figure 3. This is due to the additional polymer growth that occurs at the primary particle's surface as opposed to negligible growth upon the PAA surface. Through polymer bridging and crosslinking that occurs within the primary particles of both monomers, the resulting microparticles are physically and chemically inseparable. However, for the copolymers, polymer dissolution is achieved upon polymer neutralization indicating the absence of crosslinking.




(a) (b)

Figure 3. Morphology of (a) crosslinked PMAA and (b) crosslinked PAA microparticles as determined using SEM.

*FT-IR Spectroscopy of Poly(carboxylic acid) Microparticles*

Figure 4 shows the IR spectra for both crosslinked PMAA and crosslinked PAA microparticles recorded at ambient temperature in the dried state. Both structures exhibit the characteristic C=O stretching, with the acrylic acid carbonyl stretching occurring at 1710 $cm^{-1}$ and methacrylic acid at about 1715 $cm^{-1}$. The potassium carboylate in both materials is represented by the shift in the carbonyl stretching to approximately 1560 $cm^{-1}$. The stretching of C=O coupled with the bending of O-H is responsible for the peaks occurring in the region between 1180 and 1270 for both crosslinked PMAA and crosslinked PAA [31,32]. The symmetric bending of the $CH_3$ planar deformation occurs at 1391 $cm^{-1}$ for crosslinked PMAA. The $CH_2$ deformation bending gives a band about 1456 $cm^{-1}$ for both structures with $CH_3$ deformation asymmetric bending at about 1488 $cm^{-1}$. O-H bonded groups give rise to vibration bands at about 2620 $cm^{-1}$ for both materials. $CH_2$ stretching exhibits bands at about 2948 $cm^{-1}$, while the spectrum of crosslinked PMAA exhibits the asymmetric vibration of the $CH_3$ group at 2997 $cm^{-1}$. The broad region from 3100 to 3500 shows the O-H stretching (3100 $cm^{-1}$) for both structures along with the free O-H groups at approximately 3440 $cm^{-1}$ for crosslinked PMAA.

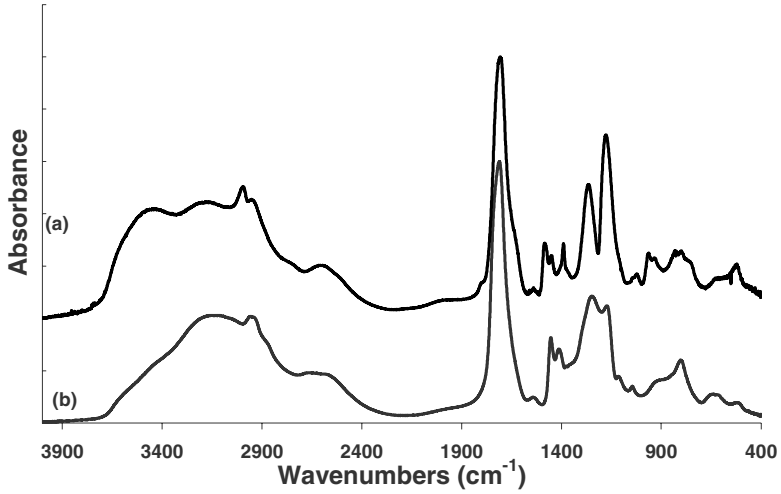



Figure 4. FT-IR spectrum of (a) crosslinked PMAA and (b) crosslinked PAA.

*Differential Scanning Calorimetry*

The glass transition temperature, $T_g$, of potassium acrylate is approximately 194°C, and due to its presence in the uncrosslinked PAA copolymer, the $T_g$ is expected to be higher than the reported value of 105°C for PAA [32]. As the pentaerythritol crosslinking agent was incorporated into the networks, the $T_g$ passed through a transition regime indicating heterogeneous crosslinking or branching that occurred, thus limiting the mobility of the polymer network as shown in Figure 5 (b). As the crosslinking agent was increased to 0.43 mol %, a significant increase in the glass transition indicated homogenous crosslinking which was verified by the polymer microparticles' insolubility in aqueous solutions as compared to the 0.2 mol % crosslinked PAA and the linear copolymer. As the level of crosslinking was increased, the mobility of the polymer chains was decreased which is evident by the higher glass transitions.

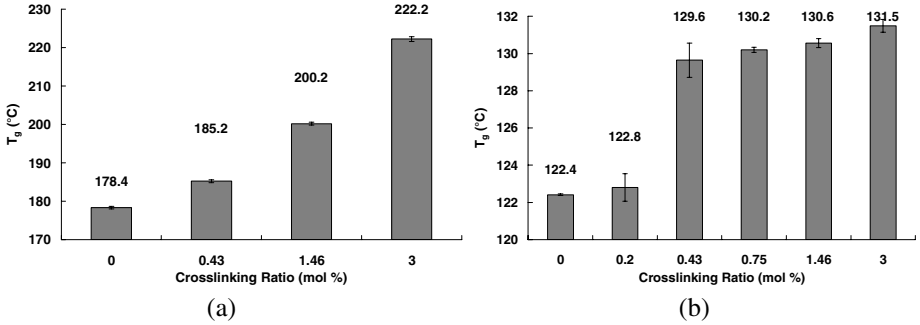



Figure 5. Glass transitions of (a) crosslinked PMAA microparticles and (b) crosslinked PAA microparticles as a function of mol % crosslinking. Each bar represents the mean ± SD (n=3).

Upon heating of the PMAA copolymer and terpolymers to 300°C, a large endotherm is observed indicating dehydration and anhydride formation [31]. The glass transition observed after this initial heating and cooling step is shown in Figure 5 (a). The PMAA copolymer exhibits a higher $T_g$ than the PAA due to both the mobility inhibition of the methyl group and the anhydride formation. As the mobility is hindered by the presence of crosslinks, the $T_g$ increases with more significance than the crosslinking effects of PAA. This is due to the synergistic effects of both crosslinking and anhydride formation and their effects on the mobility of the chains in the network.

*Physicochemical Properties of Poly(carboxylic acid) Microparticles*

The equilibrium weight swelling ratio, q, was calculated using equation 1, where $W_s$ and $W_d$ are the weight of the microparticles in the swollen and dry state, respectively.

$$q = W_s / W_d \qquad (\mathbf{1})$$

The crosslinked PAA samples show a significantly higher equilibrium swelling ratio in the carbonate buffer than polymers containing MAA at similar crosslinking ratios as can be seen in Figure 6.

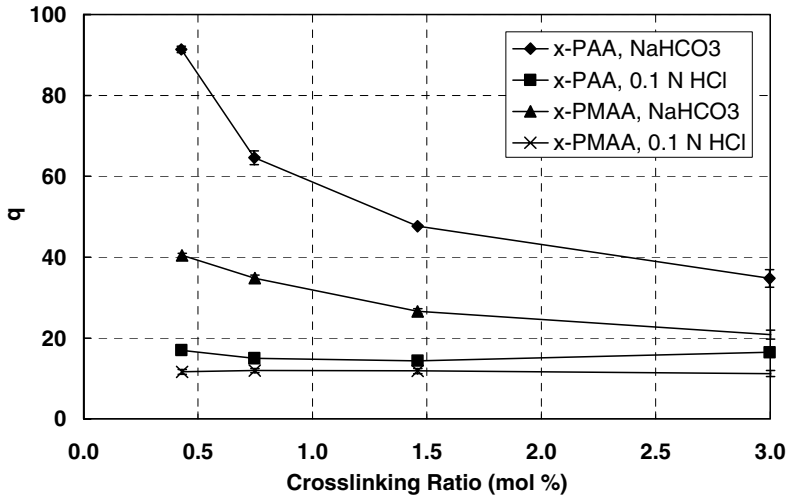



Figure 6. pH responsive equilibrium swelling behavior of crosslinked microparticles as a function of crosslinking ratio. Each point represents the mean ± SD (n=4).

This is due to the more hydrophilic acrylic acid. The presence of the methyl group in methacrylic acid imparts more hydrophobicity to the hydrogel structure, limiting the amount of solution uptake. The swelling of the carboxylic acid microparticles is heavily dependent on the crosslinking ratio, with the heavier crosslinked particles exhibiting a significantly lower swelling ratio. The pH dependent swelling of these polymers is evident by the effects of the acidic medium on the equilibrium swelling ratio. Both crosslinked PAA and crosslinked PMAA exhibit a significantly lower

swelling ratio in 0.1 N HCl than in the carbonate buffer due to protonation of the carboxylic acid groups and the lack of ionization. Due to the ability of crosslinked PMAA to form stronger inter- and intra- polymer complexation at a pH below its $pK_a$, the swelling ratio of these polymers was lower than crosslinked PAA. Ionization of the acidic groups caused the polymer chains to repel one another, expanding the hydrogel network.

The number of carboxyl groups, $n_{COOH}$, present in the microparticles was calculated according to equation 2, where V is the volume of NaOH consumed at the endpoint of the titration, N is the normality of the NaOH solution, and $m_{particles}$ is the weight in mg of microparticles.

$$n_{COOH} = (45.02 \bullet V_{NaOH} \bullet N_{NaOH}) / m_{particles} \quad (\mathbf{2})$$

The degree of neutralization, $\alpha_n$, was calculated according to equation 3 where $C_{Base}$, $C_{H+}$, $C_{OH-}$, and $C_{COOH}$ are the molarities of base, hydrogen ions, hydroxide ions, and microparticle contributed carboxylic acid in the titration solution [33].

$$\alpha_n = (C_{Base} + C_{H^+} - C_{OH^-}) / C_{COOH} \quad (\mathbf{3})$$

The molarity of microparticle contributed carboxylic acid was determined from $n_{COOH}$ according to equation 4.

$$C_{COOH} = \left(n_{COOH} \bullet m_{particles}\right) / \left(45.02 \bullet V_{total\ solution}\right) \quad (\mathbf{4})$$

The apparent dissociation constant, $pK_{app}$, was obtained from the degree of dissociation and pH according to equation 4. The value of the $pK_{app}$, which corresponds to $\alpha_d = ½$, was determined from the titration curve.

$$pK_{app} = pH + \log[(1 - \alpha_n)/\alpha_n] \quad (\mathbf{5})$$

Crosslinked PAA microparticles exhibit a $pK_{app}$ of 6.9 with the particles containing approximately 0.55 carboxyl groups. Crosslinked PMAA microparticles exhibit a $pK_{app}$ of 7.4 and contain approximately 0.44 COOH groups. The difference in $pK_{app}$ is derived from the slight difference in the $pK_a$ of the acidic monomers. The lower number of carboxyl groups as compared to the theoretical maximum is due to the presence of the potassium carboxylates. Also, due to the methyl group, the crosslinked MAA particles possess a lower amount of carboxyl groups.

## Conclusions

Microparticles composed of (meth)acrylic acid were successfully prepared using a thermally initiated free radical precipitation polymerization in ethyl acetate. Particle size was shown to be dependent on the degree of crosslinking and amount of monomer. Slight morphological differences were observed due to differing polymer growth at the surface of the primary particle. Structural differences were observed and interpreted using FT-IR with only slight differences being observed due to the presence of the methyl group. The glass transition behavior of the materials was

significantly different with MAA-based materials exhibiting a much higher $T_g$. The $T_g$ was also heavily dependent on the amount of crosslinking present in the network. Crosslinked PAA exhibited a higher swelling ratio than crosslinked PMAA with both polymers exhibiting pH dependent swelling.

The microparticles have the potential to be employed as pH responsive drug delivery carriers. Due to the presence of carboxylic acid groups, these materials can be formulated into mucoadhesive drug delivery systems capable of forming hydrogen bonds with the mucins present in mucus lining the oral cavity. The particles produced have the necessary physical characteristics that enable them to be formulated into conventional drug delivery dosage forms such as tablets and capsules, enabling their development into a pH responsive DDS.

*Acknowledgements.* This work was supported by an NIH grant EB-000246 and the Welch Foundation. This research was performed while on appointment as a U.S. Department of Homeland Security (DHS) Fellow (to JBT) under the DHS Scholarship and Fellowship Program, a program administered by the Oak Ridge Institute for Science and Education (ORISE) for DHS through an interagency agreement with the U.S Department of Energy (DOE). ORISE is managed by Oak Ridge Associated Universities under DOE contract number DE-AC05-06OR23100.

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