Synthesis and Characterization of Poly{*N*-[3-(dimethylamino) propyl] methacrylamide-*co*-itaconic acid} Hydrogels for Drug Delivery

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ABSTRACT: A novel pH-sensitive hydrogel system composed of itaconic acid (IA) and *N*-[3-(dimethylamino) propyl] methacrylamide was designed. This system was prepared by aqueous copolymerization with *N*,*N*-methylene bisacrylamide as a chemical crosslinker. The chemical structure of the hydrogels was characterized by Fourier transform infrared (FTIR) spectroscopy. The microstructure and morphology of the hydrogels were evaluated by X-ray diffraction (XRD) and scanning electron microscopy (SEM). The SEM study of hydrogels on higher magnification revealed a highly porous morphology with uniformly arranged pores ranging from 40 to 200 μm in size. XRD analysis revealed the amorphous nature of the hydrogels, and it was found that an increase in the IA content in the monomer feed greatly reduced the crystallinity of the hydrogels. Swelling experiments were carried out in buffer solutions at different pH values (1.2–10) at 37°C ± 1°C to investigate their pH-dependent swelling behavior and dimensional stability. An increase in the acid part (IA) increased the swelling ratio of the hydrogels. Temperature-sensitive swelling of the hydrogels was investigated at 20–70°C in simulated intestinal fluid. The hydrogels swelled at higher temperatures and shrank at lower temperatures. 5-Aminosalicylic acid (5-ASA) was selected as a model drug, and release experiments were carried out under simulated intestinal and gastric conditions. 5-ASA release from the poly *N*-[3-(dimethylamino) propyl] methacrylamide-co-itaconic acid-80 (PDMAPMAIA-80) hydrogel was found to follow non-Fickian diffusion mechanism under gastric conditions, and a super case II transport mechanism was found under intestinal conditions. J Appl Polym Sci 119: 3199–3206, 2011

Key words: biocompatibility; bioengineering; biological applications of polymers; biomaterials; copolymerization

INTRODUCTION

The past few years have witnessed enormous advances in the field of biomaterials, especially in polymer-based controlled drug-delivery systems (CTDDSs). CTDDSs provide an alternative approach for regulating the bioavailability of therapeutic agents. In CTDDSs, an active therapeutic agent is incorporated into a polymeric network structure in such a way that the drug is released from the material in a predefined manner.[1,2] Among controlled release drug-delivery systems, hydrogels have been of considerable interest because of their unique, tuneable, time-dependent swelling behavior. In fact, hydrogels are a unique class of biomaterials that are used in drug delivery and other biomedical applications.[3–8] The biocompatibility of these materials makes them fascinating as drug carriers.

The colon is vulnerable to numerous pathological conditions, such as ulcerative colitis, Crohn's disease, constipation, colon cancer, carcinomas, and infections.[9] Ulcerative colitis and Crohn's disease are commonly known as *inflammatory bowel disease*. This inflammatory process leads to the development of ulcerations, which result in diarrhea, abdominal pain, and fecal blood loss. Recommended treatments include the administration of anti-inflammatory drugs and chemotherapy drugs, which must be released in colon.[10,11] From a biomedical perspective, it is also useful to have dosage forms that are able to specifically release drugs, such as peptides and proteins, vermifunges, and diagnostic agents, in the colon because of the capacity of this part of the gastrointestinal tract to absorb these drugs. To achieve optimum pharmacological action of these drugs, it is necessary to release the drug after it reaches the upper part of the colon. Several devices have already been proposed for colon-targeted drug-delivery systems, which include the formation of a prodrug, multicoating time-dependent delivery systems, coating with pH-sensitive polymers, pressure-dependent systems, and biodegradable polymers.[12–16]

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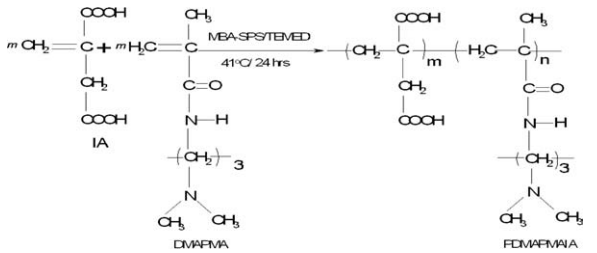

Scheme 1 Synthesis of the PDMAPMAIA hydrogels crosslinked with MBA.

Recently, Das and Ray[17,18] reported the synthesis and characterization of acrylic acid and *N*-[3-(dimethylamino) propyl] methacrylamide (DMAPMA) based pH-sensitive hydrogels for different biomedical applications. In our study, pH-sensitive copolymer hydrogels were synthesized by the aqueous free-radical copolymerization of DMAPMA and itaconic acid (IA) crosslinked with *N,N*-methylene bisacrylamide (MBA). Although poly{*N*-[3-(dimethylamino) propyl] methacrylamide} (PDMAPMA) is believed to be thermoresponsive in nature,[19] the pH-sensitive behavior and mechanical properties of this polymer is not sufficient for use in drug-delivery formulations.[20] Hence, it was copolymerized with IA, which is obtained from renewable resources (algae, molasses, hydrolyzed starch, etc.), to provide a pH-sensitive nature to the hydrogels.[21,22] It is known that IA has two ionizable groups with different pK_a values (pK_{a1} = 3.85 and pK_{a2} = 5.44).[23] This is the additional benefit of IA for use in pH-sensitive hydrogel formulations in contrast with other acrylic polymers (acrylic acid, methacrylic acid).

The as-synthesized hydrogels were characterized by Fourier transform infrared (FTIR) spectroscopy, X-ray diffraction (XRD), thermogravimetric analysis (TGA), and scanning electron microscopy (SEM). 5-Aminosalicylic acid (5-ASA), a model drug that is widely used in the treatment of colon diseases such as inflammatory bowel disease, was loaded in the hydrogels. The *in vitro* drug-release experiments were carried out in simulated intestinal fluid (SIF) and simulated gastric fluid (SGF). The swelling profile of the hydrogels was investigated in different pH buffer solutions (pH 1.2–10) and at temperatures ranging from 20 to 70°C.

EXPERIMENTAL

Materials

DMAPMA (Aldrich, USA), IA (Loba chemie, Mumbai, India), as received, were the monomers used in the study. MBA (SRL, India) as a crosslinking agent, sodium persulfate (SPS; Qualigens) as an initiator, and *N,N,N,N*-tetramethyleneethylenediamine (TEMED; SRL) as an accelerator were used in all of the polymerizations. 5-ASA was supplied by Spectrochem (India). Double-distilled water was used for all of the copolymerizations and in the preparation of the buffer solution.

Synthesis of the hydrogels

The copolymer hydrogels were prepared by the free-radical aqueous copolymerization of DMAPMA and IA with MBA, SPS, and TEMED as the crosslinker, initiator, and accelerator, respectively. The reactions were carried out in two steps, which are shown in Scheme 1.

In the first step, predetermined amounts of DMAPMA and IA were placed in a 100-mL, three-necked flask equipped with a nitrogen inlet system and stirred continuously with a magnetic stirrer for 15 min at 27 ± 1°C. A predetermined amount of distilled water was added to the flask, and stirring was continued for another 15 min. Nitrogen gas was continuously purged inside the reaction mixture followed by addition of MBA (2 mol %) and an aqueous solution of SPS (0.5 mol %). After 5 min, TEMED (3 mol %) was added to the reaction mixture under continuous stirring. Further, the reaction mixtures were transferred to glass test tubes to accomplish the second step of the reaction. Nitrogen gas was purged in the individual test tubes for 10 min each; after that, the test tubes were sealed properly and placed in a thermostated water bath at 41 ± 1°C. The reaction was carried out for 24 h, and after the completion of the reaction, transparent hydrogels were obtained. The hydrogels were cut into small discs and immersed in distilled water for 3 days to remove the unreacted monomers. The water was changed daily. The discs were dried at room temperature to xerogels. The hydrogels as synthesized were designated as PDMAPMAIA-50, PDMAPMAIA-60, PDMAPMAIA-70, and PDMAPMAIA-80. The feed composition of the poly{*N*-[3-(dimethylamino) propyl] methacrylamide-*co*-itaconic acid} (PDMAPMAIA) hydrogels and other synthesis parameters are enlisted in Table I.

The homopolymers of DMAPMA and IA [PDMAPMA and poly(itaconic acid) (PIA)] were also synthesized under the same reaction conditions used for the copolymer hydrogels. PDMAPMA and

TABLE I
Composition of the PDMAPMAIA Hydrogels[a]

Sample ID	IA (mol %)	DMAPMA (mol %)	Water (mol %)[b]
PDMAPMAIA-50	50	50	200
PDMAPMAIA-60	60	40	250
PDMAPMAIA-70	70	30	300
PDMAPMAIA-80	80	20	350

[a] The concentrations of MBA, SPS, and TEMED in the feed were 2, 0.5, and 3 mol %, respectively.
[b] Molar percentage to total monomer content.

PIA were obtained by separate precipitation in an excess of 2-butanone and isopropyl alcohol, respectively.

Characterization

FTIR spectroscopy

The infrared spectra of the homopolymers and PDMAPMAIA hydrogels were performed with a PerkinElmer Spectrum One infrared spectrophotometer, USA (attenuated total reflection–FTIR). Samples were placed separately on a ZnSe crystal, and the spectra were collected in the wave-number range 500–4000 cm^{-1} at a fixed resolution of 4 cm^{-1}.

SEM

A Stereoscan 360 scanning electron microscope (Cambridge Scientific Industries) was used to investigate the morphology of the PDMAPMAIA hydrogels after swelling in SIF. All of the samples were freeze-dried at −80°C and kept *in vacuo* until the silver sputtering treatment.

XRD analysis

XRD patterns of the homopolymers and copolymer hydrogels were obtained with a Phillips X-Pert diffractometer (USA) with Cu-Kα1 radiation at 40 kV and 25 mA. The analysis was performed at a 2θ angle between 10 and 80° and with a scan rate of 4.2°/min.

TGA

Thermal analysis of the homopolymers and copolymer hydrogels was carried out with PerkinElmer TGA7 at a heating rate of 20°C/min with nitrogen flushed at 100 mL/min.

Swelling experiment

The swelling of the hydrogel was investigated by immersion of 1-cm^3 samples of known weights into buffer solutions at pH 1.2, 4, 6, 7.4, and 10 in dependence of time at 37°C ± 1°C. The ionic strength of the buffer solutions was adjusted with 1*M* potassium chloride salt. The temperature-sensitive swelling of the hydrogels was measured at 20–70°C in a pH 7.4 buffer (SIF) solution. At predetermined time intervals, the swollen hydrogels were removed, excess water was blotted from the surface with a paper towel, and the sample was weighed. We calculated the swelling ratio (SR) from eq. (1), correlating the weight of the swollen hydrogel (W_s) to the weight of the dried hydrogel (W_d). The swelling experiments were repeated three times to check the reproducibility:

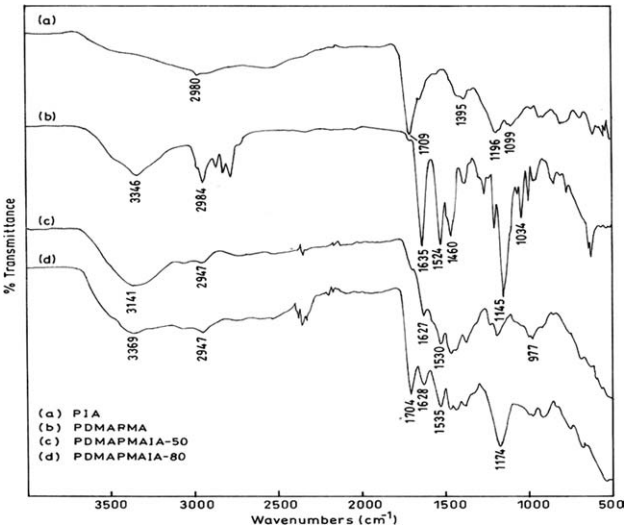

Figure 1 FTIR spectra of the homopolymers (PDMAPMA and PIA) and copolymer hydrogels (PDMAPMAIA-50 and PDMAPMAIA-80).

$$Q_s = W_s - W_d/W_d \quad (1)$$

where Q_s is the swelling ratio of the hydrogel.

Drug loading

5-ASA was dissolved separately in SGF and SIF buffer solutions to produce a 10 m*M* solution. The dried hydrogel was soaked in the respective drug (5-ASA) solutions for 3 days. Then, the drug-loaded hydrogel was dried *in vacuo* at 25°C. To determine the actual drug entrapped in the hydrogel, the sample was suspended in 50 mL of distilled water for 24 h. After 24 h, the solution was filtered, and the absorbance of the solution was measured spectrophotometrically at 211 nm. The entrapment efficiency (*E*; %) of the hydrogel was calculated by the following equation:[24]

$$E(\%) = 100\ (M_1 - M_2)/M_1 \quad (2)$$

where M_1 is the amount of 5-ASA initially loaded in the hydrogel sample and M_2 is the amount of drug present in the distilled water solution.

In vitro release study

We carried out the *in vitro* drug-release test by placing the drug (5-ASA)-loaded hydrogel (1 cm^3) separately in 25 mL of SIF (i.e., phosphate buffer solution of pH 7.4) and SGF (i.e., hydrochloric acid buffer solution of pH 1.2) and leaving it to shake (100 rpm) in an incubator at 37°C ± 1°C. At different time intervals, 2 mL of solution was withdrawn and replaced by 2 mL of fresh buffer solution. The amount of 5-ASA released was determined

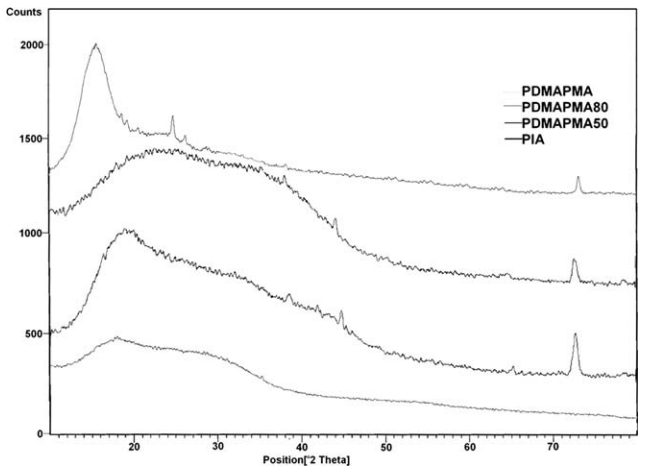

Figure 2 XRD of the homopolymers (PDMAPMA and PIA) and copolymer hydrogels (PDMAPMAIA-50 and PDMAPMAIA-80).

spectrophotometrically by an ultraviolet–visible spectrophotometer at 211 nm.

RESULTS AND DISCUSSION

FTIR–attenuated total reflection spectroscopy

Figure 1(a,b) shows the FTIR spectra of the respective homopolymers (PIA and PDMAPMA). The FTIR spectra of PIA showed an intense peak at 1709 cm^{-1} due to the stretching vibration peak of the carbonyl carboxyl group (—C=O) and a peak at 2980 cm^{-1} due to the —CH stretching vibration peak. The IR spectrum of PDMAPMA showed intense peaks at 3346, 1635, and 1524 cm^{-1} corresponding to N—H stretching and the amide I and amide II peaks, respectively. Chemical interaction between DMAPMA and IA was evident from the IR spectra of the PDMAPMAIA-50 and PDMAPMAIA-80 hydrogels [Fig. 1(c,d)]. We was observed that the intense peak at 1709 cm^{-1} was reduced to a weaker shoulder (1695 cm^{-1}) in the PDMAPMAIA-50 hydrogel. It showed amide I and amide II peaks at 1631 and 1529 cm^{-1}, respectively. On the other hand, the PDMAPMAIA-80 hydrogel showed absorption peaks at 1707, 1626, and 1529 cm^{-1}, which were due to the carboxyl stretching, amide I, and amide II absorption bands, respectively. The lowering of the carboxyl stretching peak of PIA in the case of the prepared PDMAPMAIA hydrogels indicated strong intermolecular interactions or hydrogen bonding between the DMAPMA and IA units.[25] This confirmed the formation of the PDMAPMAIA-based copolymer hydrogels.

XRD study

XRD analysis of the homopolymers (PDMAPMA and PIA) and hydrogels (PDMAPMAIA-50 and PDMAPMAIA-80) was carried out at 2θ angles of 10–80° (Fig. 2). The X-ray diffractogram of the PDMAPMA homopolymer showed an intense peak at 2θ = 18.07°, and weak diffraction peaks were observed at 2θ = 31.98 and 72.66°. This showed the semicrystalline nature of the PDMAPMA homopolymer. However, the XRD pattern of PIA showed a completely amorphous nature because it showed a single broad diffused peak at 2θ = 22.46°, whereas the XRD diffractogram of PDMAPMAIA-50 showed a broad peak at 2θ = 18.68°, and another peak was observed at 2θ = 72.62°. On the other hand, PDMAPMAIA-80 showed a single weak peak at 2θ = 72.65°. The result shows that the PDMAPMA peak (2θ = 18.07°) gradually became broader in the case of the copolymer hydrogels. This confirmed that increasing the IA amount in the monomer ratio in the copolymer hydrogels led to an increase in the amorphous nature of the prepared hydrogels. IA significantly destroyed closer packing or long-range order between the crystals; this eventually led to a decrease in the crystallinity of the PDMAPMAIA hydrogels.

TGA

TGA of the respective homopolymers (PDMAPMA and PIA) and copolymer hydrogels (PDMAPMAIA-50 and PDMAPMAIA-80) was carried out at scan rate of 20°C/min. The thermogram [Fig. 3(d)] of PDMAPMA showed a two-step thermal degradation process. The first weight loss was observed at 80–90°C; this was assigned to the elimination of bound water or moisture in the PDMAPMA homopolymer. The PDMAPMA started to thermally degrade at 300°C; this was due to the scission of the PDMAPMA chain. The rate of weight loss increased with increasing temperature from 300 to 480°C,

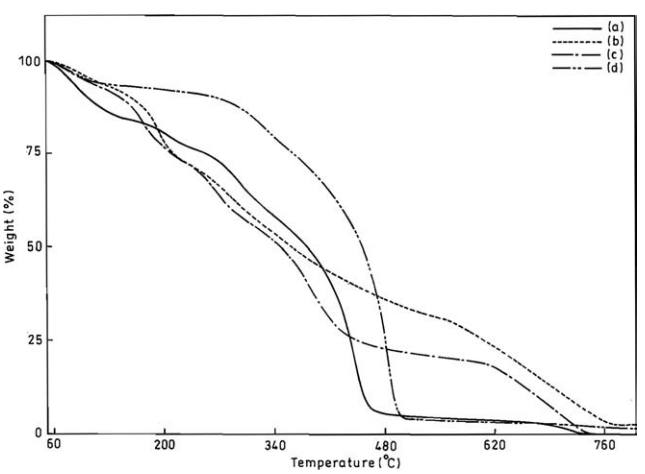

Figure 3 TGA thermograms of the homopolymers (PIA and PDMAPMA) and copolymer hydrogels (PDMAPMAIA-50 and PDMAPMAIA-80).

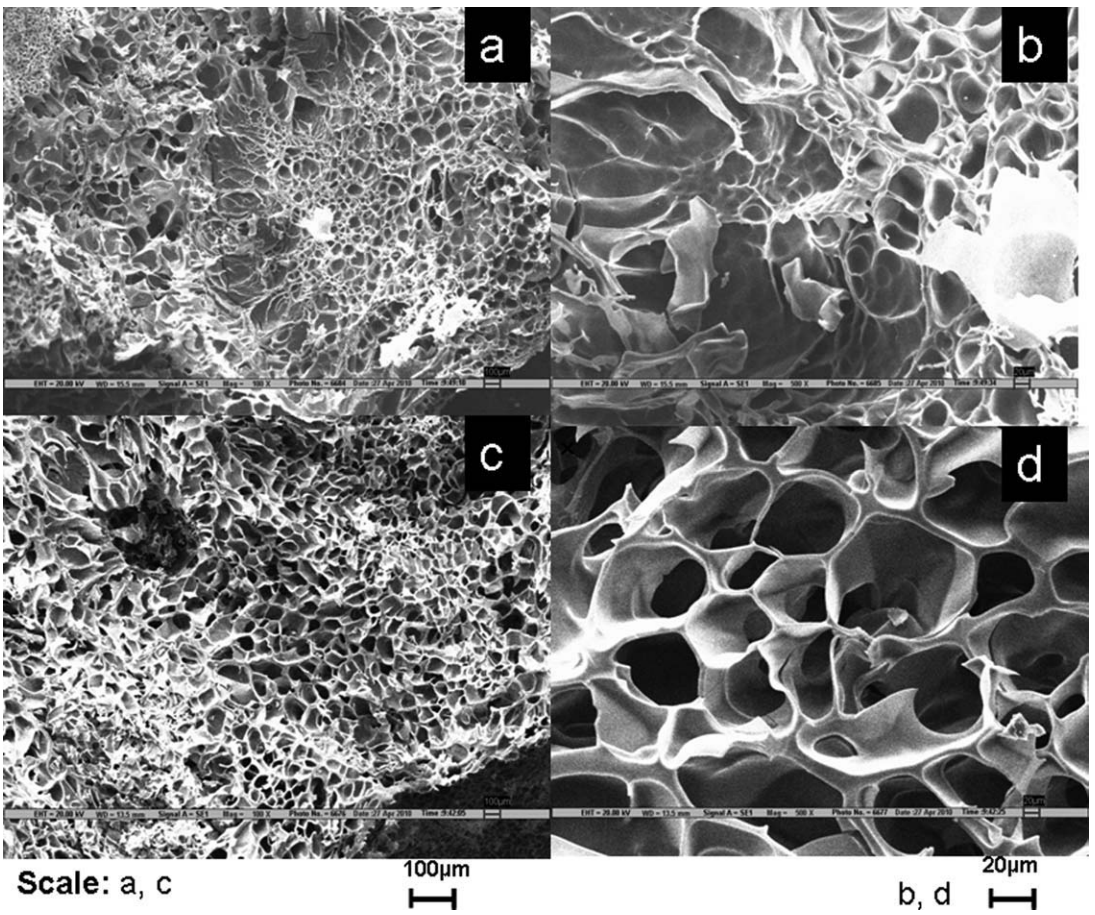

Figure 4 SEM micrographs of the PDMAPMAIA hydrogels (PDMAPMAIA-50 and PDMAPMAIA-80) after swelling in SIF.

and the maximum degradation temperature was observed at 460°C on the basis of the differential thermogravimetry curve. The final decomposition temperature for PDMAPMA was at 470°C. The thermogram of the PIA homopolymer [Fig. 3(b)] showed a four-step thermal degradation process. The first weight loss step was observed from 90 to 100°C; this was related to the elimination of solvent from the sample. The second degradation was observed at 190–200°C and was attributed to the anhydride ring formation in the PIA homopolymer chain. The third degradation step, visible at 270–280°C, might have been connected to possible decarboxylation and carbonization processes.[25,26] The final decomposition temperature of PIA was around 770°C.

The thermogram of the PDMAPMAIA-50 hydrogel also showed [Fig. 3(a)] a four-step degradation processes. The first step, due to the evaporation of solvent in the sample, was observed at 100–110°C. The second and third degradation steps commenced at 200 and 300°C, respectively. The maximum degradation temperature from the differential thermogravimetry curve was observed at 450°C. The thermogram revealed that between 410 and 480°C, PDMAPMAIA-50 rapidly lost 60–80% of its original weight. In this case, beyond 480°C, the weight loss was practically negligible. The thermogram of the PDMAPMAIA-80 hydrogel [Fig. 3(c)] showed an initial weight loss at 90–100°C, which was attributed to bound moisture in the copolymer sample. The copolymer hydrogel started to degrade at 190–200°C, and a faster rate of weight loss was observed between 150 and 330°C. The second, third, and fourth consecutive weight loss steps were observed at 240, 300, and 460°C, respectively. Interestingly, the PDMAPMAIA-80 hydrogel remained thermally stable up to 870°C, but the PDMAPMAIA-50 almost completely degraded at 480°C; this showed that PDMAPMAIA-80 was more thermally stable than the preceding PDMAPMAIA-50 and the homopolymer samples (PDMAPMA and PIA). This might have been accomplished by the more pronounced intermolecular interaction or hydrogen bonding between the carboxylic groups of IA and the amide group of DMAPMA, which needed more energy to break them;[25] eventually, it led to the enhancement of the thermal stability of the PDMAPMAIA-80 hydrogel.

SEM analysis

The morphology of the freeze-dried PDMAPMAIA hydrogels after swelling in SIF (pH 7.4) was

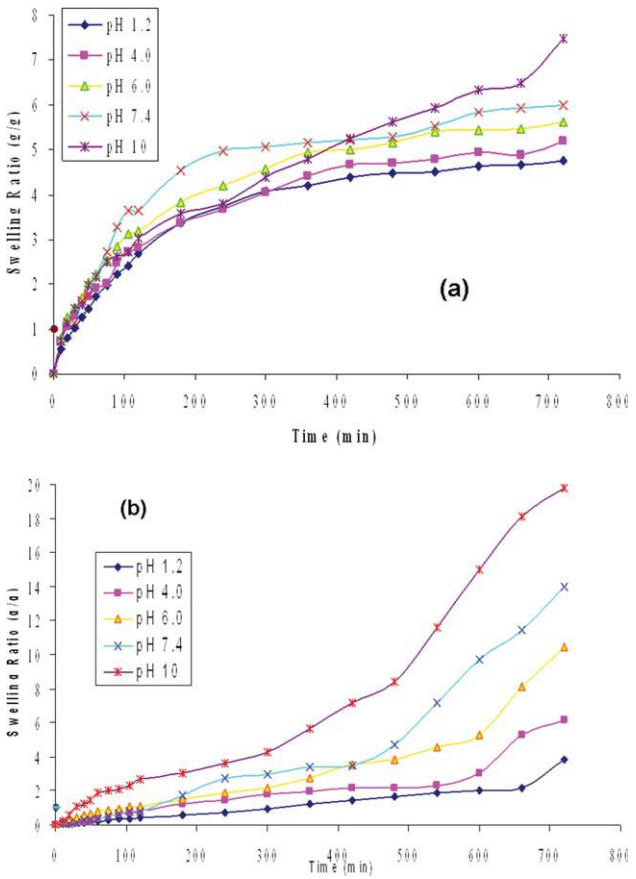

Figure 5 pH-sensitive swelling of the copolymer hydrogels in buffered solutions of various pH values at 37°C ± 1°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

investigated by SEM. It was evident from the morphology of the PDMAPMAIA-80 hydrogel [Fig. 4(c,d)] that at lower magnification (100×), it showed a highly porous architecture with uniformly arranged pores on the surface. Further magnification (500×) revealed that the hydrogels were composed of large, open, and interconnected pores with average pore sizes ranging from 40 to 200 μm. This confirmed the highly macroporous nature of the PDMAPMAIA-80 hydrogels. The SEM morphology of PDMAPMAIA-50 [Fig. 4(a,b)] revealed that few pores were visible on the surface compared to PDMAPMAIA-80. A probable reason for the larger pores inside the PDMAPMAIA-80 hydrogel network was the greater amount of IA residues, which contributed to the enlargement of the pore size by increasing the network hydrophilicity and by electrostatic repulsion of COO^- groups in IA.[27,28] The PDMAPMAIA-80 hydrogels were more dimensionally stable than the PDMAPMAIA-50 hydrogels. The swelling behavior of the hydrogels directly affected the morphology of the resulting hydrogels. The PDMAPMAIA-80 hydrogel afforded a higher ratio of IA; this led to higher swelling and the macroporous nature of the hydrogels. This seemed to indicate a higher accessibility of water to amorphous regions of the hydrogels.

pH-sensitive swelling of the hydrogels

To construct a successful drug-delivery system, it is important to determine the swelling profile of the prepared hydrogels because this process has a direct impact on drug release/delivery. Figure 5(a,b) shows the swelling behavior of the PDMAPMAIA-50 and PDMAPMAIA-80 hydrogels in different pH buffer solutions (pH 1.2–10). The data revealed the pH-sensitive nature of the PDMAPMAIA hydrogels. The PDMAPMAIA-50 hydrogel showed a maximum SR (7.48) at pH 10.0 and a minimum SR (4.74) at pH 1.2. The maximum swelling of the hydrogel at the higher pH value was due to the fact that IA had two different dissociation constant (pK_a) values (3.88 and 5.44). This led to a higher SR in the hydrogels under simulated intestinal conditions compared to simulated gastric conditions. DMAPMA is nonionic in nature and does not have any group that could be ionized in aqueous solution. With the incorporation of more hydrophilic IA parts in the hydrogel chain, the pH of the solution became the most important factor governing the swelling kinetics of the prepared hydrogels. The result suggests that under acidic conditions, the carboxylic groups of IA were protonated, and hydrogen bonding was found to exist between the COOH group of IA and the amide group of DMAPMA; this led to a decrease in the water uptake of the hydrogel.[29] This was also confirmed by the FTIR spectra of the PDMAPMAIA hydrogels. At higher pH values, the amount of ionic groups in the polymeric network increased. This led to an expansion of the hydrogel network at higher pH values due to greater electrostatic repulsion between the ionic groups (COO^-) of IA.[30] A similar trend was observed for the PDMAPMAIA-80 hydrogel [Fig. 5(b)], where SR increased with increasing pH of the surrounding medium. The maximum SR (19.76) was observed in PDMAPMAIA-80 at pH 10 as compared to the 7.48 SR value for the PDMAPMAIA-50 hydrogel. This was augmented to a higher IA ratio in PDMAPMAIA-80, which led to a higher swelling of the hydrogel. Interestingly, initially, a very slow rate of swelling was observed in the PDMAPMAIA-80 hydrogel compared to the PDMAPMAIA-50 hydrogel. This suggested that the PDMAPMAIA-80 hydrogel could be tried in sustained release formulations.

Temperature-sensitive swelling of the hydrogels

The temperature-sensitive behavior of hydrogels makes them attractive materials for the development

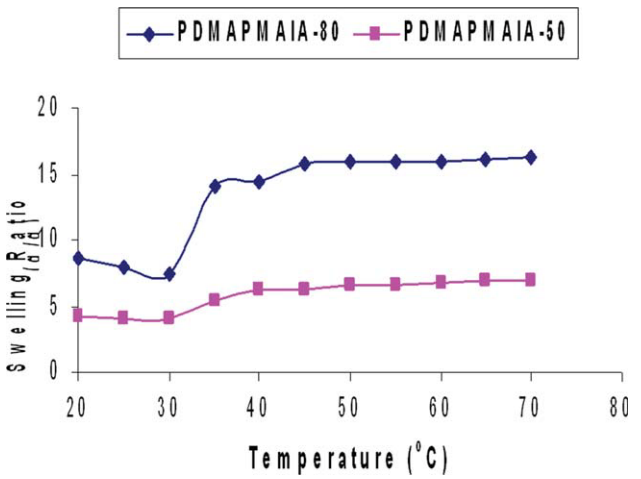

Figure 6 Temperature-dependent swelling of the PDMAPMAIA-50 and PDMAPMAIA-80 hydrogels at 20–70°C in SIF. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

of therapeutic devices for biomedical applications. Hence, the temperature-sensitive nature of the PDMAPMAIA hydrogels was investigated at 20–70°C under simulated intestinal conditions (Fig. 6). As shown in Figure 6, both hydrogels showed phase-transition behavior in the range 30–40°C. The data showed that SR of both hydrogels decreased slightly between 20 and 30°C, but between 30 and 40°C, a drastic increases in SR was observed (at the phase-transition temperature range); SR finally leveled off after 50°C. The phase-transition behavior was more efficient in case of the PDMAPMAIA-80 hydrogel compared to the PDMAPMAIA-50 hydrogel. Similar results were suggested by Caykara et al.[31] during their studies on poly *N*-[3-(dimethylamino) propyl] methacrylamide-*co*-N,N-methylene bisacrylamide [poly(DMAPMA-*co*-MBAAm)] hydrogels. They suggested that these hydrogels exhibited a positive temperature coefficient, which swelled at higher temperatures and shrank at lower temperatures.

Release study of 5-ASA through the hydrogel

The drug *E* was found to be about 80% in the hydrogel sample. The *in vitro* study of 5-ASA release was performed for PDMAPMAIA-80 at pH 7.4 and 1.2 (Fig. 7). Because PDMAPMAIA-80 showed a higher SR than PDMAPMAIA-50, it was selected for the 5-ASA release studies. In this case, the percentage cumulative drug release was plotted against time. The figure clearly shows the pH-dependent release behavior of the hydrogel. It is evident from the figure that only about 10% of total 5-ASA was released in the initial 2 h of the release study in pH 7.4 buffer; this indicated the sustained release of 5-ASA through the hydrogel. After 12 h of release study, a total of about 65% of 5-ASA was released in SIF (pH 7.4) as compared to about 10% in SGF (pH 1.2). This showed that the PDMAPMAIA-80 hydrogel could release the drug (5-ASA) more efficiently at colonic pH rather than at the pH in the upper part of the gastrointestinal tract. The higher 5-ASA release of PDMAPMAIA-80 hydrogel at pH 7.4 was correlated with the morphological studies of the hydrogels. The PDMAPMAIA-80 hydrogel was highly macroporous in nature, which could have led to a greater uptake of solute or water inside the hydrogel network; this resulted in a higher release of antibiotic (5-ASA) from the hydrogel.

Drug-release kinetics

The drug-release kinetics (*F*) from different matrices were determined by the Ritger–Peppas equation:[32]

$$F = M_t/M_\infty = kt^n \quad (3)$$

where k is a constant representing the apparent release rate (%/min) that takes into account structural and geometrical characteristics of the release device and n is the diffusion exponent. The value of n is useful for the determination of the drug-release mechanism from different matrices. In case of nonswelling matrices, the drug release is generally expressed by Fickian diffusion, for which $n = 0.5$. In case of swelling matrices, the drug release is due to a combination of swelling and erosion. They follow non-Fickian release behavior, for which n ranges from 0.5 to 1. For most erodible matrices, drug release follows zero-order kinetics, for which $n = 1$. Occasionally, a value of $n > 1$ has been observed, which has been regarded as super case II kinetics.[33–35]

The value of n was calculated by linear regression of log (M_t/M_∞) versus log t, t is the time of the

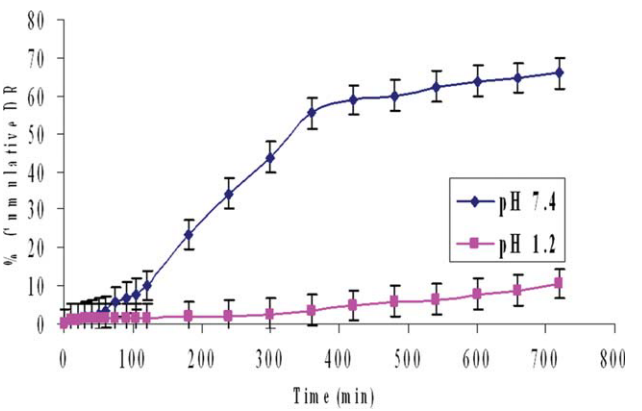

Figure 7 Percentage cumulative release of 5-ASA through the PDMAPMAIA-80 hydrogel in the SIF and SGF solutions. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE II
Analysis of the Release Data from the PDMAPMAIA-80 Hydrogel

pH medium	n	k (min^{-n})	R^2
1.2	0.5497	4.16	0.9437
7.4	1.182	7.47	0.9639

fractional release, and is listed in Table II. The results indicate that the release of 5-ASA through the PDMAPMAIA-80 hydrogel at pH 1.2 presented an n value of 0.54, which was indicative of non-Fickian or anomalous behavior. On the other hand, the release of the drug at pH 7.4 presented an n value of 1.182, which indicated a super case II transport mechanism. This type of mechanism can be attributed to increase in plasticization at the relaxing boundary (gel layer).[32]

CONCLUSIONS

Novel PDMAPMAIA hydrogels were prepared by the aqueous copolymerization of DMAPMA and IA by chemical crosslinking with MBA. Swelling studies on the hydrogels confirmed that swelling was highly dependent on the hydrogel composition and on the external environmental conditions (pH and temperature of the buffer). The 5-ASA loading ($\sim$ 80%) was quite high in the hydrogels, and higher drug release was observed in simulated intestinal conditions than in simulated gastric conditions. The kinetic data treatment showed that the hydrogel (PDMAPMAIA-80) followed a non-Fickian/super case II transport mechanism for drug release. The results suggests that these hydrogel matrices could be tried for the controlled delivery of 5-ASA to the colon.

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