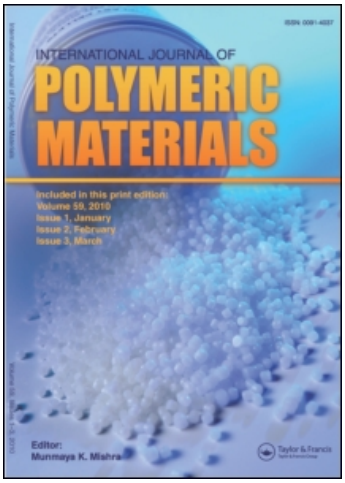

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Surfactant-Modified Poly(acrylamide-*co*-acrylamido propane sulphonic acid) Hydrogels

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Surfactant-Modified Poly(acrylamide-*co*-acrylamido propane sulphonic acid) Hydrogels

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Recent advances in drug delivery have been directed towards the design of a number of intelligent systems for the treatment of various diseases. In this regard, we developed novel surfactant-modified hydrogels which are synthesized from acrylamide (AM) and acrylamido propane sulphonic acid (AMPS), in the presence of a surfactant (Latemul PD-104) using ammonium persulfate/N,N,N′,N′–tetramethylethylene diamine (APS)/(TMEDA) as an initiating system and N,N′-methylenebisacrlyamide (MBA) as a crosslinker. The hydrogel formation was confirmed by Fourier transform infrared spectroscopy (FTIR) and scanning electron microscopy (SEM). The variation in the hydrogel networks formation employing different levels of synthetic parameters was verified by swelling studies. Influences of salt, biological fluids, and buffer solutions on the developed systems were also investigated. It was found that, compared to PAM hydrogel, all the surfactant-modified hydrogels were responsive towards salt concentration and pH. A robust drug release behavior was observed from surfactant-modified hydrogel systems.

Keywords: crosslinker, drug release, hydrogels, surfactant, swelling kinetics

INTRODUCTION

The modification of hydrogels has been extensively investigated over the past few decades due to their combined superior properties that

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alter their unique mechanical and physicochemical properties [1,2]. Typically, hydrogel networks can be described as highly swollen hydrophilic polymers that do not dissolve in water because of their three-dimensional crosslink structures [3]. Recently a number of structurally varied hydrogel networks have been proposed for their distinctive properties (higher swelling capacity, hydrophilicity, and biocompatibility) which enhance their practical utility in medical, pharmaceutical and environmental applications [4–11]. Apart from crosslinked hydrogel networks, strategies have been explored recently to design a number of novel gel family networks including macroporous and microporous, comb type, and double crosslinked networks that allow us to tailor the gel macromolecular architecture at a molecular level to achieve specific physicochemical properties for the desired functions [6,7,10,11].

For drug delivery applications, hydro-, micro- and nanogels constructed from hydrophobic and hydrophilic portions (for example, poly(*N*-isopropylacrylamide) PNIPAM gels) focused attention on loading both hydrophilic and hydrophobic drugs and allow us to control the release behavior by external stimuli such as temperature, pH, ionic strength, electric and magnetic field, pressure, light intensity, solvent composition, and so on [11–13]. In addition, various biodegradable polymeric nanoparticles and gel macromolecules have been developed and approved for cancer, ulcer, inflammatory and other conventional disease treatments [14–16]. Recently, bottom-up approaches have been developed to obtain nano-ordered structures at the molecular level in materials such as polymeric nanocapsules, physical nanogels, pluronic polymers, and core-shell polymers by self-assembly mechanisms of molecules, in which hydrophobic and hydrophilic segments are spontaneously associated to form nanostructures [16–20]. However, the effective function of these systems as drug delivery carriers strictly depends on their stability, or static structure.

A specific influence of anionic, cationic and nonionic surfactant molecules on the hydrogel characteristics was clearly observed [21–25]. For example, Kokufuta et al. [26] showed that ionic surfactants such as sodium dodecylsulfate (SDS) and dodecyltirmethylammonium chloride (DTAC) affected the swelling of a nonionic PNIPAM hydrogel. Volume transition temperature increased remarkably with increased SDS or DTAC concentration. This phenomenon was explained as due to the adherence of surfactant molecules to the nonionic PNIPAM hydrogel, through hydrophobic interactions, that converted it into an ionic hydrogel. Such interactions also depend on the physicochemical properties of the hydrogel as well as the

surfactant, and they increase with increasing hydrophobic chain length [27]. Mashelkar et al. [28] investigated the swelling behavior of hydrophobically modified PNIPAM hydrogels in aqueous solution of SDS. The swelling ratios and the volume phase transition temperatures were found to be remarkably enhanced, which can be interpreted on the basis of electrostatic repulsion between SDS functional groups and PNIPAM functional polymer chains. The change in the volume phase transition temperature was found to be strongly influenced by the addition of small amounts of ionic surfactants and the nature of the hydrophobic group.

From the above literature survey it is clear that the surfactant molecules have great influence on the hydrogel properties, and these surfactant molecules may enable us to improve the drug-loading and release characteristics of drugs. Therefore, we are interested in designing novel surfactant-modified poly(acrylamide-*co*-acrylamido propane sulfonic acid) poly(AM-*co*-AMPS) hydrogel. This study also includes optimizing various reaction parameters to obtain higher swelling characteristics of the hydrogels, as well as to evaluate their drug delivery application, using a model drug (ranitidine).

MATERIALS AND METHODS

Materials

Acrylamide (AM), ammonium persulfate (APS) and *N,N′*-methylenebisacrylamide (MBA) were supplied by S.D. Fine Chemicals Ltd. (Bombay, India). 2-acrylamido-2-methyl propane sulfonic acid (AMPS) was purchased from Merck (Bombay, India). *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) was purchased from Aldrich Chemical Company Inc. (Milwaukee, WI, USA) and the surfactant (Latemul PD-104, [poly(propylene oxide) PPO and poly(ethylene oxide) PEO]) was a kind gift from Polymer Materials & Additives Chemical Company, Kao Corporation (Tokyo, Japan). All the chemicals were used as received. Double-distilled water was used for all the copolymerization reactions as well as for the swelling studies.

Solutions

Monomer, Crosslinker, and Initiator Stock Solutions

MBA (1 g/100 ml distilled water), APS (5 g/100 ml distilled water) and TMEDA (1 g/100 ml distilled water) were prepared for gel preparations.

pH Solution Preparation

To prepare different pH solutions, buffer solution A (12.3 g of anhydrous boric acid (0.20 M) and 10.51 g of citric acid (0.05 M) in 1000 ml distilled water), and buffer solution B (38.01 g of trisodium phosphate in 1000 ml distilled water) were utilized. To prepare a specific buffer solution, buffer solutions A and B were mixed in different volumes based on Shugar and Dean [29].

Physiological Fluids Preparation

To investigate the water uptake phenomena of hydrogels in biological media, different simulated biological fluids were prepared in 100 ml of distilled water. The solutions prepared were: saline water: 0.9 g NaCl/100 ml; synthetic urine: (0.8 g NaCl + 0.10 g $MgSO_4$ + 2.0 g urea + 0.06 g $CaCl_2$)/100 ml; urea: 5 g/100 ml; and d-glucose: 5 g/100 ml.

Preparation of Surfactant/Poly(AM-*co*-AMPS) Hydrogels

Surfactant-modified poly(acrylamide-*co*-acrylamido propane sulphonic acid) hydrogels were prepared at room temperature by solution redox copolymerization using AM, AMPS, latemul PD-104 reactive surfactant, in the presence of a crosslinker (MBA) and an APS/TMEDA initiating system. In a typical series of reactions, 1 g of AM, 0.3 g of AMPS and different amounts of surfactant (0.1–1.0 g) were dissolved in 2 ml distilled water in a 100 ml beaker. To this solution, 1 ml of MBA (1 g/100 ml), 1 ml of APS (5 g/100 ml) and 1 ml of TMEDA (1 g/100 ml) solutions were added sequentially by stirring at 100 rpm on a magnetic stir plate. The polymerization was initiated instantaneously and the gels were formed within 30 min in all the cases, but to get complete hard networks throughout the hydrogels, we continued the reaction for about 8 h. The gels were purified by placing them in a 1 l beaker containing 500 ml DI water (refilled fresh water every 8 h for a week) to extract unreacted monomers, crosslinker, surfactant, initiator and activators from the gels. Finally, the gels were dried and cut into small pieces for further studies.

In a similar way, the polymerization reactions were carried out by varying the reaction parameters such as concentration of AMPS, MBA, APS and TMEDA. Table 1 provides detailed information of various ingredients used to synthesize hydrogels, and the hydrogel codes.

TABLE 1 Composition of Monomers, Surfactant, Crosslinker, Initiators Used to Synthesize PAM, Surfactant-Modified Hydrogels

Hydrogel code	Latemul PD-104 (mg)	AMPS (mM)	MBA (mM)	APS (mM)	TMEDA (mM)
Latemul PD-104 variation					
PAM	NIL mg	1.2	0.648	2.18	0.86
PAM-S1	100 mg	1.2	0.648	2.18	0.86
PAM-S2	200 mg	1.2	0.648	2.18	0.86
PAM-S3	300 mg	1.2	0.648	2.18	0.86
PAM-S4	500 mg	1.2	0.648	2.18	0.86
PAM-S5	800 mg	1.2	0.648	2.18	0.86
AMPS variation					
PAM-S3-AMPS1	0.3 gram	0.48	0.648	2.18	0.86
PAM-S3-AMPS2	0.3 gram	0.723	0.648	2.18	0.86
PAM-S3-AMPS3	0.3 gram	0.965	0.648	2.18	0.86
PAM-S3-AMPS4	0.3 gram	1.2	0.648	2.18	0.86
PAM-S3-AMPS5	0.3 gram	1.44	0.648	2.18	0.86
PAM-S3-AMPS6	0.3 gram	2.41	0.648	2.18	0.86
MBA variation					
PAM-S3-MBA1	0.3 gram	1.2	0.13	2.18	0.86
PAM-S3-MBA2	0.3 gram	1.2	0.19	2.18	0.86
PAM-S3-MBA3	0.3 gram	1.2	0.32	2.18	0.86
PAM-S3-MBA4	0.3 gram	1.2	0.45	2.18	0.86
PAM-S3-MBA5	0.3 gram	1.2	0.77	2.18	0.86
PAM-S3-MBA6	0.3 gram	1.2	0.97	2.18	0.86
PAM-S3-MBA7	0.3 gram	1.2	1.29	2.18	0.86
APS variation					
PAM-S3-APS1	0.3 gram	1.2	0.648	0.438	0.86
PAM-S3-APS2	0.3 gram	1.2	0.648	0.657	0.86
PAM-S3-APS3	0.3 gram	1.2	0.648	1.09	0.86
PAM-S3-APS4	0.3 gram	1.2	0.648	1.53	0.86
PAM-S3-APS5	0.3 gram	1.2	0.648	2.63	0.86
PAM-S3-APS6	0.3 gram	1.2	0.648	3.28	0.86
PAM-S3-APS7	0.3 gram	1.2	0.648	4.38	0.86
TMEDA variation					
PAM-S3-TMEDA1	0.3 gram	1.2	0.648	2.18	0.172
PAM-S3-TMEDA2	0.3 gram	1.2	0.648	2.18	0.258
PAM-S3-TMEDA3	0.3 gram	1.2	0.648	2.18	0.43
PAM-S3-TMEDA4	0.3 gram	1.2	0.648	2.18	0.60
PAM-S3-TMEDA5	0.3 gram	1.2	0.648	2.18	1.03
PAM-S3-TMEDA6	0.3 gram	1.2	0.648	2.18	1.29

Characterization of Hydrogels

FTIR Analysis

The dried hydrogel (crushed powder) samples were ground with KBr to make pellets. The FTIR spectra were taken on a Thermo Nicolet Nexus 670 spectrophotometer (Washington, USA).

SEM Analysis

To image the surface characteristics and the morphological variations in hydrogels, the samples were coated with a thin layer of palladium gold alloy, and were observed using a JEOL JSM 840A (Tokyo, Japan) scanning electron microscope (SEM).

Swelling Study

The conventional gravimetric method was employed to determine the swelling ratio (S) of hydrogels [30]. In the swelling studies, about 20–30 mg of hydrogel were placed in 100 ml distilled water/swelling medium. The weight of swollen gels was determined at different time intervals and the swelling experiment was continued to a constant weight. At the end, the excess water was removed superficially by filter paper and the gels were then weighed accurately. By using the swelling experimental weights of hydrogels, the swelling ratio of hydrogels was calculated using the following equation:

$$\text{Swelling (S)} = [(W_s - W_d)/(W_d)],$$

where W_d and W_s denote the weight of dry gel and swollen gel, respectively.

Mechanism of Water Diffusion [30–32]

Based on the relative rate of diffusion of water into the polymer matrix and the rate of polymer chain relaxation, the swelling of polymers has been classified into three types of diffusion mechanisms. These mechanisms are Case I or Fickian diffusion, Case II diffusion, and non-Fickian diffusion or anomalous diffusion.

In the case of hydrogels, the dynamics of the water sorption process were investigated by monitoring the change in the amounts of water imbibed (uptake) by the hydrogel at various intervals. In the present *diffusion* study, only the initial swelling results (up to 60%) were utilized. Water uptake or swelling of hydrogel is described by the following equation:

$$F = W_s - W_d/W_d = kt^n,$$

where F, W_s and W_d denote the fraction swelling ratio at time t, the weight of the swollen hydrogel at time t, and the weight of the dried hydrogel at time $t = 0$, respectively; k is a swelling constant related

to the structure of the network; and n is the swelling exponent, which indicates the water transport mechanism. Normal Fickian diffusion is characterized by $n = 0.5$ (controlled diffusion) while Case II diffusion is indicated by $n = 1.0$. When the n value is in between 0.5 and 1.0 it represents a mixture of Fickian and Case II diffusions which is termed as non-Fickian or anomalous diffusion. In anomalous diffusion, diffusion and relaxation are said to be isochronal effective. Therefore, the swelling exponent is a direct measure to relative transportation of water molecules into hydrogels. To determine the swelling exponent (n) by using the above equation up to 60% of the swelling ratio values, ln F versus ln t graphs were plotted to obtain straight lines. The swelling exponent was calculated from the slope of the lines of ln F–ln t plots.

Drug Loading into the Hydrogel

Ranitidine hydrochloride (RH) (gift sample from Aurobindo Pharmaceutical Limited, Hyderabad, India) is a hydrophilic drug (anti-ulcer drug) used to treat ulcers and gastroesophageal reflux disease (GERD) [33]. It was used to load into hydrogels. To load the drug, RH (10 mg/25 ml phosphate buffer solution PBS, pH 7.4) drug solution was employed.

The loading of RH into hydrogels was conducted by swelling equilibrium method. Typically, 50 mg of hydrogel sample were allowed to swell in drug solution for 24 h. Then, the hydrogel was taken out from the drug solution and washed with 20 ml of water (3 times) to remove an excess of drug present on the surface of hydrogel. Finally, the hydrogel was dried at room temperature for 48 h to obtain the release device. Drug encapsulation efficiency was calculated by using the remaining amount of the drug solution after hydrogel loading was done. After removing the hydrogel from the drug solution, the remaining solution was analyzed by Elico SL164 UV spectrophotometer (The Science House, Hyderabad, India) at λ_{max} 315 nm. The encapsulation efficiency was calculated using the equation:

$$\% \text{ Encapsulation efficiency} = \left(\frac{\% \text{ Drug loading}}{\% \text{ Theoretical loading}} \right) \times 100$$

In Vitro Drug Release

In vitro drug release from the drug-loaded hydrogel formulations was investigated in PBS. These hydrogels were suspended in 5 ml PBS and transferred into dialysis tube (8 kD MWCO, 12 mm flat width, Spectrum Lab, Houston, TX). The sample within the dialysis bag

was taken in a conical flask containing 50 ml of PBS as the dissolution medium placed on rotary shaker (REMI Instruments Limited, Vasai, India) at 100 rpm at 37°C. The amount of drug released from hydrogels to medium was determined by withdrawing 1 ml aliquots of the solution at selected specific time intervals. The volume withdrawn was immediately replaced with an equal volume of prewarmed PBS solution at 37°C. The drug-released samples were analyzed by using Elico SL164UV spectrophotometer (The Science House, Hyderabad, India) at λ_{max} 315 nm.

RESULTS AND DISCUSSION

During the last few decades a number of investigations were conducted either by the interaction of surfactants with different hydrogel networks or by modification of hydrogels with surfactants. A recent study by Noguchi et al. [34] revealed an approach for fast temperature-responsive hydrogel networks with surfactant-grafted PNIPAM hydrogels that is highly superior to the conventional graft/comb-type gels. In contrast to the above methods we followed a facile approach for the development of a surfactant-modified hydrogel by crosslinking terpolymer of AM, AMPS with latemul PD-104 in the presence of a crosslinker and initiating pair. A few similar polymerizations followed to produce hydrogels without surfactants [30–32]. In the current strategy, the existence of surfactant molecules in the hydrogel networks promoted the creation of hydrogel networks that facilitated a rapid shrinkage of the networks. As a result, the imbibed/entrapped/loaded drug molecules' diffusion or eliminations occurs rapidly.

Preparation of Hydrogels

Poly(acrylamide) (PAM), latemul PD-104 modified PAM hydrogels (PAM-S1 to PAM-S5), and latemul PD-104 modified poly(AM-*co*-AMPS) hydrogels (PAM-S3-AMPS1 to PAM-S3-AMPS6; PAM-S3-MBA1 to PAM-S3-MBA7; PAM-S3-APS1 to PAM-S3-APS7; and PAM-S3-TMEDA1 to PAM-S3-TMEDA7) were prepared by redox-initiated free-radical crosslinking polymerization of aqueous mixtures of AM/AMPS/latemul PD-104 monomers, MBA cross-linker, and APS/TMEDA initiators for 30 min (Table 1). Typically, most of the AM or PNIPAM-based hydrogels and surfactant/AM/PNIPAM hydrogels formed rapidly by the free radical crosslinking copolymerizations within 30-min cure time following the usual redox initiating mechanism [30–32]. The redox initiation is an efficient technique to produce gels with low soluble contents.

SEM of Hydrogels

PAM hydrogel showed a plain surface morphology throughout the gel (Figure 1a) but the addition of surfactant to the polymerization caused a change in their morphologies (Figure 1b–e). Previously, Mohan et al. observed dominant morphological changes by altering the amount and type of surfactant with the interaction of hydrogel networks [35]. In the current study, it was demonstrated that the increase of surfactant content (latemul PD-104) modifies their morphologies to a large extent. From Figure 1 we learn that surfactant molecules are morphologically homogeneously distributed in the gels (transparent gels) at lower concentration (up to 300 mg latemul PD-104) whereas those formed with surfactant at higher concentration (above 500 mg) are heterogeneous and opaque. The reason for forming a heterogeneous system with higher surfactant is due to phase separation or insolubility of surfactant molecules during the polymerization. According to the current data, 300 mg surfactant is optimal to obtain a perfect porous structure of the hydrogels, and thus we used this amount to prepare a number of combinations of hydrogel systems (Table 1).

FTIR Spectra of Hydrogels

A representative FTIR spectrum of surfactant hydrogel is illustrated in Figure 2. All the surfactant hydrogels synthesized in this study exhibited similar peaks, as those presented in Figure 2, that correspond to AM, AMPS, MBA and latemul PD-104 polymeric repeating units. A clear and broad peak was observed between 3500 and 3000 cm^{-1} that can be attributed to the N-H stretching of poly(AM/AMPS/MBA) repeat units. Further, two prominent peaks appeared at 1643 and 1608 cm^{-1} due to band I and band II peaks of amide groups of poly(AM/AMPS/MBA) repeat units. The presence of additional peaks at 1082 and 1032 cm^{-1} is assigned to C-O-C peaks of latemul PD-104 surfactant molecule [poly(propylene oxide) PPO and poly(ethylene oxide) PEO]. A typical peak at 1411 cm^{-1} corresponds to C-H bending vibrations of repeating units. Therefore, from the above data we confirm the presence of all monomeric units in the hydrogel network systems.

Influence of Reaction Parameters on Hydrogel Characteristics

It is well-known that the synthesis of hydrogels by crosslinking polymerization involves the utilization of a number of components, including

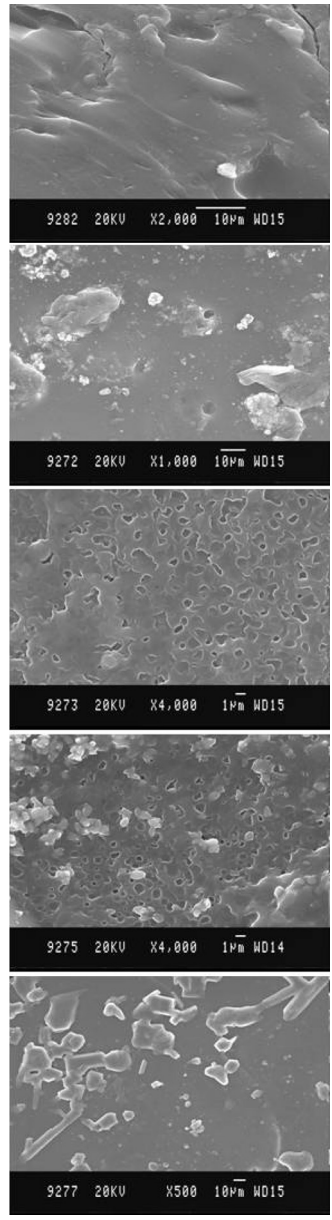


FIGURE 1 Scanning electron microscope images of (top to bottom) PAM hydrogel, PAM-S1, PAM-S3, PAM-S4, and PAM-S5 hydrogels.

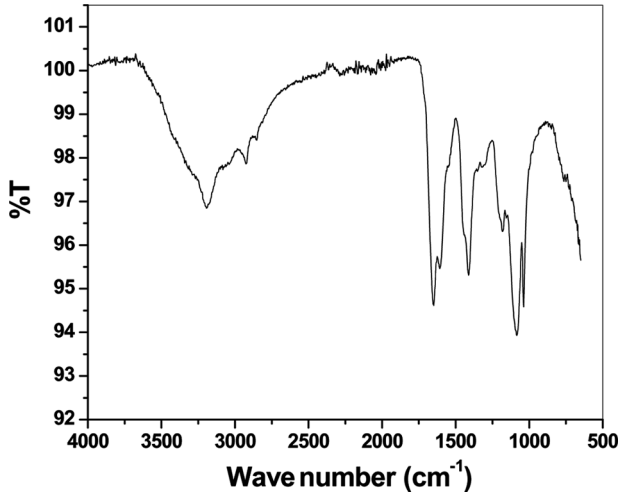


FIGURE 2 FTIR spectrum of surfactant-modified hydrogel (PAM-S3-MBA6).

different monomers, crosslinkers, and an initiator/activator. The components' concentrations not only affect the reaction kinetics but also the characteristics of the final hydrogel networks. Therefore, we have studied all the components' influence on the resulting hydrogel swelling characteristic which is the most important property of our gel system.

Swelling of Hydrogels

To find out the influence of the surfactant (latemul PD-104) concentration (100–800 mg) on poly(latemul PD-104)/poly(acrylamide) hydrogel swelling behavior, the concentrations of various components are fixed at AM (1 g), AMPS (1.2 mM), MBA (0.648 mM), and APS/TMEDA (2.18 mM/0.86 mM). It was found that there are no significant changes in the swelling behavior with different concentrations of latemul PD-104 (Figure 3a). The PAM hydrogel has showed an absorbance of 55.75 g/g. The addition of different concentrations of surfactant molecules has led to blocking of the available free spaces between the PAM hydrogels by surfactant polymers. This restricts the penetration of water molecules into the gel networks by decreasing the swelling capacity of gels. Therefore for all the surfactant-containing crosslinked hydrogels, the swelling capacity (53.93–42.84 g/g) is lower than PAM hydrogel. PAM-S3 showed a reasonable swelling capacity which is close to PAM hydrogel.

To know the effect of AMPS (0.48–2.4 mM) on the preparation of the hydrogel, the reaction system was fixed at a concentration of AM (1 g),

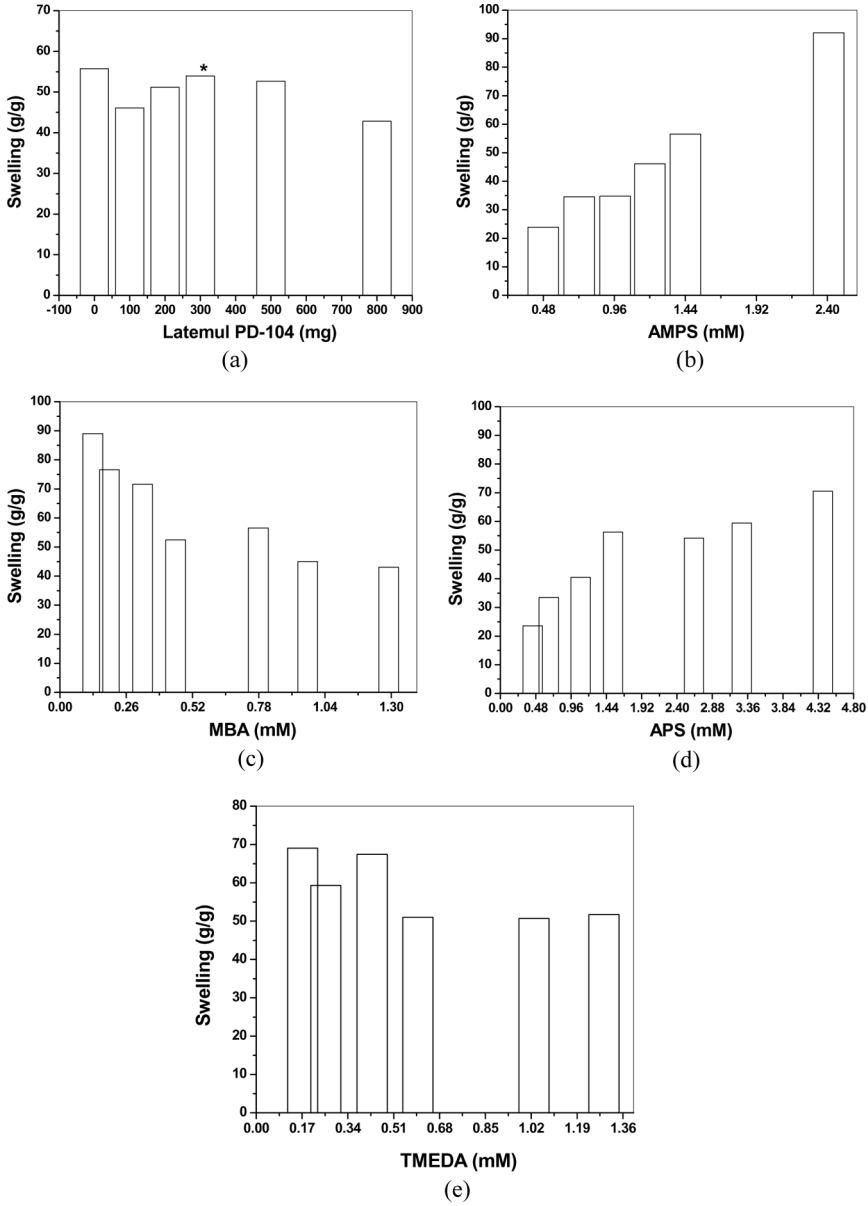


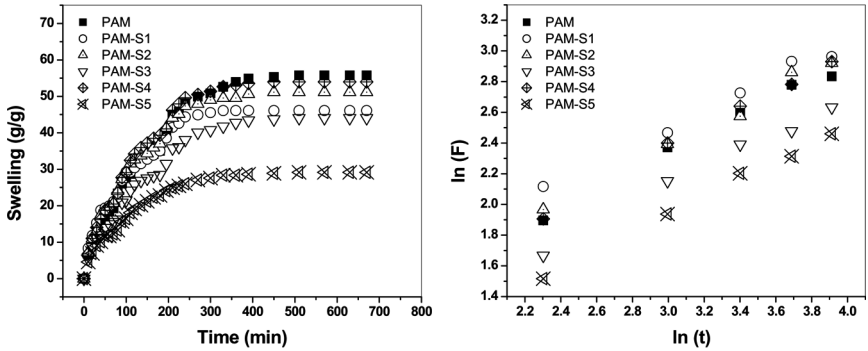
FIGURE 3 Swelling behavior of various surfactant-modified hydrogels in water; (a) surfactant, (b) AMPS, (c) crosslinker, (d) initiator, and (e) activator variations in hydrogel synthesis.

latemul PD-104 (0.3 g), MBA (0.648 mM), APS/TMEDA (2.18 mM/0.86 mM). A continuous increase in the swelling of hydrogels from 23.90 to 96.51 g/g with increase of AMPS from 0.48 to 2.4 mM (Figure 3b) was observed. This behavior implies lower crosslink density as well as an increase in hydrophilic nature to the hydrogel networks with the addition of AMPS. A similar pattern of swelling behavior was noticed for hydrogels constructed with AMPS polymeric chains [36,37]. However, we have employed 0.96 mM AMPS for our further studies because we don't want to use higher amounts of AMPS to make hydrogels, and at the same time we need to maintain optimal latemul PD-104 with the PAM networks in our formulations.

Crosslinker concentration is another major component which decides the swelling characteristic of any hydrogel. In our case, with increase of MBA concentration from 0.13 to 1.29 mM, the swelling capacity decreases of the resulting hydrogels at a fixed concentration of AM (1 g), surfactant (0.3 g), AMPS (1.2 mM), and APS/TMEDA (2.18 mM/0.86 mM) (Figure 3c). It is very clear that higher crosslinker content makes the gel network denser and lowers swelling capacity thereby restricting the penetration of the water molecules into the hydrogel networks. It is widely accepted by all hydrogel scientists that higher MBA (mostly all crosslinkers) concentrations always reduce the hydrogel network mesh size and ultimatly lower swelling properties [30–37]. The swelling capacity decreased from 89.0 to 43.04 g/g with the increase of MBA from 0.13 to 1.29 mM (Figure 3c). Similar to AMPS variation, the increase of APS concentration from 0.43 to 4.38 mM in the reaction leads to an improved swelling (23.59 to 70.51 g/g) for hydrogels (Figure 3d). This is due to the formation of larger amounts of free radicals during the reaction with an increase of APS concentration that results in less crosslinked gel networks (lower density crosslinked networks), which ultimately increases the swelling behavior. In contrast, an increase of TMEDA concentration (0.17 to 1.7 mM) in hydrogel synthesis leads to a continuous fall in the swelling capacity of hydrogels (70.05 to 40.26 g/g) (Figure 3e).

Mechanism of Water Diffusion into Hydrogels

Figure 4a demonstrates the swelling behavior of PAM hydrogels modified with different amounts of surfactants, i.e., PAM and PAM-S1 to PAM-S6 hydrogels, at different time intervals. In all of these crosslinked hydrogels, it can be seen that swelling (S) increases with time until a certain point, where it becomes constant. At a stage where there is no change in the weight of the gel with time, the swelling ratio of the hydrogel may be called "equilibrium swelling ratio or equilibrium swelling" (Seq). However, to evaluate the type of diffusion for



(a) (b)

FIGURE 4 (a) Influence of surfactant amount on swelling behavior of hydrogels and (b) $\ln(F)$ vs. $\ln(t)$ graph to determine the influence of different surfactant amounts in hydrogels on water diffusion constant value.

the hydrogels, graphs were plotted of $\ln F$ versus $\ln t$ to yield straight lines (Figure 4b). The n values were obtained from the slope of the straight lines. The diffusion constant (n) values were found between 0.64 and 0.54 for these PAM and PAM-S1 to PAM-S6 hydrogels, indicating the diffusion of water into these gels is of non-Fickian type. In a similar way, the diffusion constant (n) values of all other poly(surfactant)/poly(AM-*co*-AMPS) hydrogels were found between 0.68 and 0.90 (PAM-S3-AMPS1 to PAM-S3-AMPS6); 0.97 and 0.72 (PAM-S3-MBA1 to PAM-S3-MBA7); 0.38 to 0.76 (PAM-S3-APS1 to PAM-S3-APS7); and 0.63 to 0.79 (PAM-S3-TMEDA1 to PAM-S3-TMEDA6). All imply that the diffusion of water into these gels is of non-Fickian type.

Effect of Salts, Biological and pH Solutions on the Swelling Behavior

In the present investigation the effect of different concentrations of NaCl solution on the swelling behavior of PAM and surfactant/poly(AM-*co*-AMPS) hydrogels was studied. Figure 5a, illustrates the swelling ratio of hydrogels as a function of different concentrations of saline solutions. This study indicates that the swelling ratio of hydrogels decreased in sodium chloride solution as the ionic concentration increased. This is caused by the repulsive forces of counter ions on the polymeric chains shielded by the bound ionic charges. Therefore the osmotic pressure differences between the gel networks and the external solutions decreased with an increase in the ionic strength

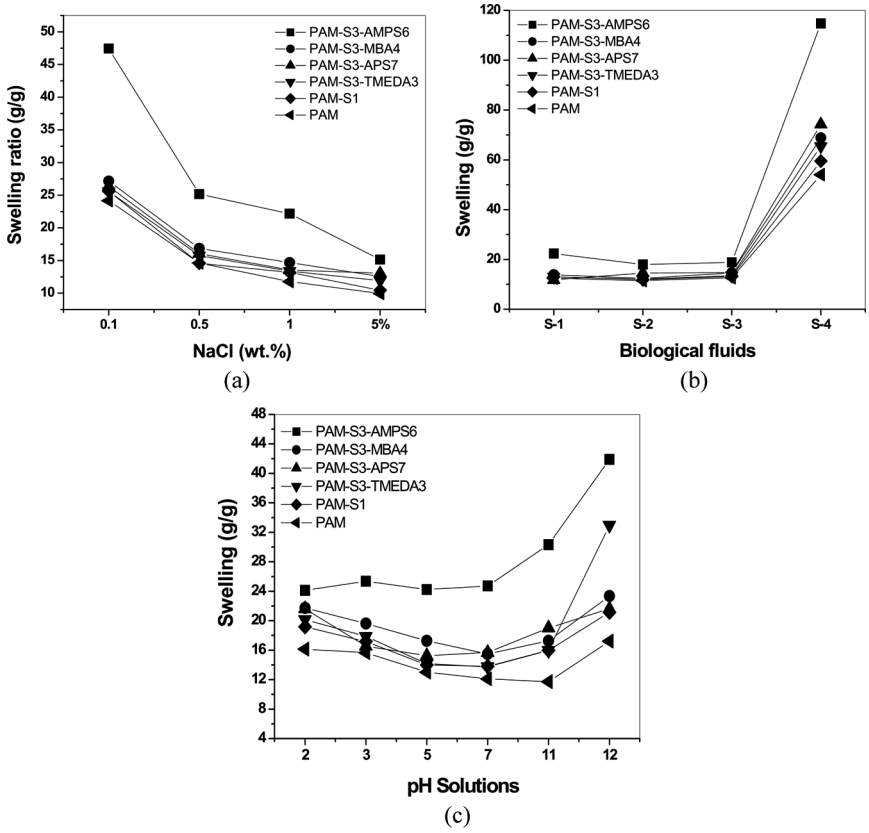


FIGURE 5 Swelling profiles of different hydrogels in (a) different concentrations of $NaCl_2$ solution; (b) different biological solutions, S1: saline (0.9 g Nacl/100 ml), S2: synthetic urine (0.8 g NaCl + 0.1 g $MaSO_4$ + 2 g Urea + 0.06 g $NaCl_2$/100 ml), S3: 5 g KI/100 ml, S4: 5 g Urea + 5 g D-glucose/100 ml; and (c) different buffer solutions.

of the saline concentration. The lowest swelling ratio is observed in PAM hydrogel, whereas PAM-S3-AMPS6 hydrogel has exhibited the highest swelling. This is attributed to their original swelling capacities (Figure 3). For the remaining hydrogel samples the swelling is between PAM and PAM-S3-AMPS6 hydrogel.

To find out the influence of simulated biological fluids on the swelling phenomena of hydrogels, four different biological fluids were employed and the results are presented in Figure 5b. The results indicate that the swelling ratio is lower in all biological fluids when compared to water as the swelling medium. This can be explained

due to the presence of various ionic species in different concentrations in the swelling medium. It was further observed that out of the four simulated biological fluids, the D-glucose solution had the highest swelling ratio, whereas the potassium iodide solution had a very low swelling ratio. A higher swelling ratio was obtained for the hydrogel in D-glucose solution with in a short period because of the formation of hydrogen bonds between copolymeric chains of the hydrogel and the D-glucose unit. The order of swelling behavior of hydrogels in different biological fluids is as follow: $S_4 > S_1 > S_3 > S_2$. Similar to swelling behavior of hydrogels in different NaCl solutions, here the PAM-S-AMPS6 hydrogel has showed the highest swelling and PAM hydrogel exhibited the lowest swelling.

The importance of pH-sensitive hydrogels has been found from their number of applications in the biomedical field. The aim of the present work is also to prove that these hydrogels have a significant effect of pH (2–11) on their swelling behavior (Figure 5c). In more acidic medium the number of sulphonic acid groups of AMPS are in unionized form without any repulsive forces between the chains. In the alkaline medium the sulphonic acid groups are ionized, thereby promoting the repulsive forces between the anionic groups of the chains. This leads to an increase in the space between the chains, thereby enhancing the swelling capacity. However, this trend was observed only in PAM-S3-AMPS6 hydrogel due to the presence of a large number of AMPS groups employed for making this gel. The remaining hydrogel samples showed a downward trend with increase of pH from 2 to 11, and the swelling order follows: PAM-S3-MBA4 > APS7 > PAM-S3-TMEDA3 > PAM-S1 > PAM hydrogels. But the variation in the swelling is not large between these samples. In addition to our previous reports, many hydrogel systems comprised with hydrophilic polymeric chains are considerably influenced by pH and salts [38–40].

Drug Delivery Evaluation

It is well-recognized that hydrogels have been employed for the controlled release of therapeutics for a long time. These are suitable for a wide number of drug molecule delivery and, moreover, the release characteristics from the guided hydrogel networks can be easily tailored. In this work, with the current novel formulations, we have simply tested for drug loading and for rapid release.

To investigate the loading efficiency of ranitidine hydrochloride (RH) into hydrogels, PAM, PAM-S3-AMPS1, PAM-S3-AMPS7, PAM-S3-MBA1 and PAM-S3-MBA7 samples were selected. The loading efficiency of RH was found to be highest in PAMS3-AMPS7 (77.95%) and

PAM-S3-MBA7 (77.90%) than PAM-S3-AMPS1 (63.95%) and PAM-S3-MBA1 (65.37%). This can be explained on the basis of crosslink density of hydrogels, i.e., lower crosslink density increase the uptake of drug loading. It also depends on the amount of AMPS present in the hydrogel system. Overall, the drug loading efficiency depends on the swelling behavior of hydrogels which provides the path for the drug to enter inside the hydrogel networks (Figure 6a). Further, the loading efficiency is higher in our formulations than in conventional hydrogel formulations, i.e., ~16 mg in 100 mg of hydrogel. It is also proved that drug clusters are present on the surface of the hydrogels. The SEM image shows that due to drug addition to PAM-S3-AMPS7 formulation, the excess bound drug can be seen as clumps on the surface of the gel (Figure 6b). The plain PAM hydrogel loading is also very similar to surfactant-modified hydrogel (63.3%) but its release is

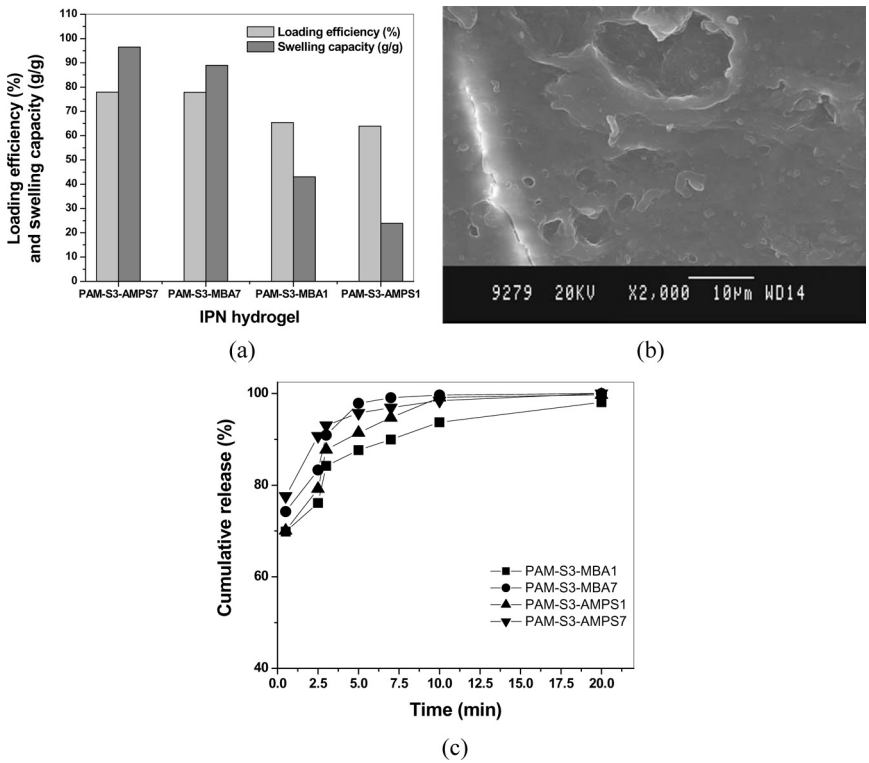


FIGURE 6 (a) Drug loading efficiency of surfactant-modified hydrogels, (b) SEM of PAM-S3, AMPS7, and (c) drug-release profiles from different surfactant hydrogels.

somewhat poorer than the surfactant-modified hydrogels, i.e., 80–85% release was observed for this gel in 20 h (data not shown).

Interestingly, all the formulations have exhibited a huge amount of drug release (~70 to 77.5%) within 30 min, due to the surfactant effect which squeezed out the drug molecules from the hydrogel networks (Figure 6c). In contrast, sterculia gum-g-methacrylic acid hydrogel and HPMC matrices exhibited a release of RH of about 65–80% for 6–8 h [41,42]. Another delivery system, namely chitosan/cellulose acetate microspheres, also suggests <55% release from their matrices after 60 h [43]. Though these formulations show variation in their drug-loading capacities, 100% release was observed in 20 h. We could not figure out the reason for the difference in their drug-release variations.

CONCLUSIONS

We have designed novel surfactant-modified hydrogel systems that can be employed to deliver hydrophilic drugs. A systematic evaluation was performed for different compositions of hydrogels through their swelling behavior. The morphological and chemical structures of the systems were confirmed using SEM and FTIR analyses. It was demonstrated that the hydrogels had excellent pH sensitivity and had little influence on the swelling behavior over the range of concentration of NaCl aqueous solution. We further propose that the surfactant hydrogels can also be useful for hydrophobic drug delivery.

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