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Influence of polymer network parameters of tragacanth gum-based pH responsive hydrogels on drug delivery

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ABSTRACT

The present article deals with design of tragacanth gum-based pH responsive hydrogel drug delivery systems. The characterization of hydrogels has been carried out by SEMs, EDAX, FTIR, ^{13}C NMR, XRD, TGA/DTA/DTG and swelling studies. The correlation between reaction conditions and structural parameters of polymer networks such as polymer volume fraction in the swollen state (ϕ), Flory–Huggins interaction parameter (χ), molecular weight of the polymer chain between two neighboring cross links ($\overline{M}_c$), crosslink density (ρ) and mesh size (ξ) has been determined. The different kinetic models such as zero order, first order, Higuchi square root law, Korsmeyer–Peppas model and Hixson–Crowell cube root model were applied and it has been observed that release profile of amoxicillin best followed the first order model for the release of drug from the polymer matrix. The swelling of the hydrogels and release of drug from the drug loaded hydrogels occurred through non-Fickian diffusion mechanism in pH 7.4 solution.

1. Introduction

Site specific drug delivery to colon is desirable for local treatment of a variety of bowel diseases and colonic bacterial infections. Amoxicillin is a broad spectrum antibiotic. It is used to treat intestinal bacterial infections (de Sousa, 2005) and required some targeted drug delivery system to deliver the drug to the colon, which would ensure the relief from side effects along with the direct delivery of drug to the colon in a controlled manner. The colon specific drug delivery system should be able to protect the entrapped drug from the physiological environment of gastrointestinal tract (GIT) during its journey to colon (Philip & Philip, 2010). Hydrogels based on polysaccharides have been considered as one of the best drug delivery system to the colon (Singh, 2007). Tragacanth gum polysaccharide has been used as laxative, emulsifier, stabilizer and thickening agent in pharmaceuticals and food products and is generally recognized as safe by the Food and Drug Administration. It is a highly branched, heterogeneous polysaccharide, which consists of two fractions named as tragacanthic acid and arabinogalactan (Anderson & Grant, 1989; Eastwood, Brydon, & Anderson, 1984; Weiping, 2000). Tragacanth gum is highly hydrophilic, non-toxic, stable over wide pH range, biocompatible, safe for oral intake and medicinally imported polysaccharide. It exhibited a considerable potency for wound healing. This is probably due to an acceleration of collagenation and proliferation phases of the wound repair (Moghbel, Hemmati, Agheli, Rashidi, & Amraee, 2005). Tragacanth gum has hydroxyl groups, which can act as active sites for grafting/crosslinking of polymer initiation reactions and forming the hydrogels (Weiping, 2000).

Hence, it could be explored for making a colon specific drug delivery system along with some pH specific polymers. Poly(acrylic acid) based hydrogels are highly pH sensitive and can be used as colon specific drug delivery devices (Jabbari & Nozari, 1999).

The properties of hydrogels that make them suitable for various biomedical applications mostly arise from their crosslinked structure, which is influenced by the concentration of backbone, monomers and crosslinker used during synthesis of hydrogels. The diffusion of drug from the gels can be controlled by tailoring the crosslinked network structure (Ende, Hariharan, & Peppas, 1995; Sannino, Demitri, & Madaghiele, 2009). In order to understand the crosslinked structure of the gel, the most common approach is to study the swelling of the hydrogels (Kim & Peppas, 2002). Once this information is known, the gel can be manipulated by varying mesh size to enable diffusion of drug in specific manner (Gander, Gurny, Doelker, & Peppas, 1989). The most important parameters used to characterize network structure are the polymer volume fraction in the swollen state (ϕ), molecular weight of the polymer chain between two neighboring cross links ($\overline{M}_c$), crosslink density (ρ), and the corresponding mesh size (ξ). Due to the random nature of the polymerization process, only average values of $\overline{M}_c$ could be determined which measures the degree of crosslinking in the networks irrespective of nature of crosslinking (i.e. physical or chemical) (Singh, McCarron, Woolfson, & Donnelly, 2009). $\overline{M}_c$ can be determined by a various methods but swelling equilibrium is

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the most popular method (Katime & Diaz de Apodaca, 2000; Lira, Martins, & de Torresi, 2009; Rao & Ha, 2009; Singhal, Tomar, & Nagpal, 2009). The drug diffusion from the drug loaded polymers is directly related to the polymer swelling (Bertz et al., 2013). The diffusion rate of the encapsulated substances could be reduce upon increasing the polymer concentration in the hydrogel preparation due to decrease in pore size and increase in network density (Brazel & Peppas, 1999; Chan & Neufeld, 2009).

In the present work attempts have been made to design the tragacanth gum and poly(acrylic acid) based polymer networks (hydrogels) meant drug delivery system for an antibiotic drug. The correlation between synthetic reaction parameters and structural parameters was determined. The different release kinetics models were applied to study the release profile of drug from polymeric network. The characterization of polymers was carried out by SEM, EDAX, FTIR, ^{13}C NMR, XRD, TGA and swelling studies.

2. Experimental

2.1. Materials and methods

Acrylic acid (AAc) was obtained from Merck Specialities Private Limited (Mumbai India), N,N′-methylenebisacrylamide (NN-MBA) and ammonium persulphate (APS) were obtained from Qualigens Fine Chemicals (Mumbai, India), tragacanth gum (TG) was obtained from Loba Chemie (Mumbai, India) and amoxicillin sodium was obtained from Ranbaxy Laboratories Limited, Hyderabad, India. All the materials were used as received.

2.2. Synthesis of polymer networks

The polymerization reaction was carried out with 6% (w/v) of tragacanth gum, definite concentration of AAc, initiator and crosslinker, taken in the aqueous reaction system. Reaction contents were stirred for 3 h at 25 °C temperature to get homogeneous reaction mixture. Then reaction system was kept in water bath at 65 °C for 2 h for reaction. The crosslinked hydrogel was then stirred in distilled water to remove the soluble fractions left after completion of reaction and then were dried in oven at 40 °C until the constant weight was obtained. The crosslinked polymers were named as of TG-*cl*-poly(AAc) hydrogels. The optimum reaction parameters for synthesis of hydrogels were evaluated by varying the [AAc] from 0.146 to 1.0120 mol/L, [NN-MBA] from 0.0130 to 0.0649 mol/L. The optimum reaction conditions were obtained as TG = 6% (w/v), [AAc] = 0.874 mol/L, NN-MBA = 0.0389 mol/L, APS = 0.0263 mol/L. These conditions were determined on the basis of swelling have the hydrogels and surface consistency maintained by these hydrogels after 24 h swelling. Network parameters for polymeric networks were determined for each variation by swelling equilibrium method. At the optimum reaction parameters, further polymers were synthesized and were used to study the effect of pH, [salt] and temperature of the swelling medium on hydrogel swelling and network parameters. These polymers were also used to study the release profile of the drug from the drug loaded hydrogel for the evaluation of drug release mechanism.

2.3. Characterization

The polymers were characterized by scanning electron micrographs (SEMs), electron dispersion X-ray analysis (EDAX), Fourier transform infrared spectroscopy (FTIR), solid state ^{13}C NMR spectroscopy, X-ray diffraction study (XRD), thermo gravimetric analysis (TGA), differential thermal analysis (DTA), differential thermogravimetry (DTG) and swelling studies. SEMs and EDAX were taken on FEI SEM Quanta 256, Model D9393 (Singapore). FTIR spectra of polymers were recorded in KBr pellets on Nicolet 5700FTIR THERMO (USA), the solid state ^{13}C NMR was carried out on BRUKER DSX-300 solid state NMR spectrometer, XRD measurements were made using PAN-analytical X'Pert Pro powder diffraction system (The Netherland), thermogravimetric analysis was carried out on EXSTAR TG/DTA 6300 thermal analyzer under air atmosphere at 10 °C/min heating rate. Swelling studies of the polymeric networks were carried in triplicate by gravimetric method (Singh, 2007).

2.4. Drug release studies

The release profile of model drug amoxicillin from the drug loaded hydrogel was determined in distilled water, pH 2.2 buffer and pH 7.4 buffer. All the studies were carried out in triplicate. Preparation of buffer solution, calibration curves, drug loading, drug release, and preparation of reagents have been discussed elsewhere (Singh, 2007). The calibration curves of amoxicillin sodium were prepared in distilled water, pH 2.2 buffer and pH 7.4 buffer solution at λ_{max} 273 nm on the UV Visible spectrophotometer (Cary 100 Bio, Varian). The loading was carried out in large number of samples and then samples of constant loading were chosen for release study. The drug release was studied in triplicate. The loading of a drug into the hydrogels was carried out by swelling equilibrium method. The hydrogels were allowed to swell in the drug solution of known concentration for 24 h at 37 °C and then were dried to obtain the release device. The release of drug from the polymer samples was measured from the calibration graphs.

Based on the relative rate of diffusion of water into polymer matrix and rate of polymer chain relaxation, swelling of the polymers and the drug release profile from the drug loaded polymers have been classified into three types of diffusion mechanisms i.e. Fickian, non-Fickian and case II diffusion mechanisms. Ritger and Peppas showed that the power law expression (Eq. (1)) could be used for the evaluation of drug release from swellable systems (Ritger & Peppas, 1987a, 1987b).

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where M_t/M_∞ is the fractional release of drug in time t, 'k' is the constant characteristic of the drug-polymer system and 'n' is the diffusion exponent characteristic of the release mechanism. M_t and M_∞ are the amount of drug released at time 't' and at equilibrium respectively.

Different parameters of release kinetics of amoxicillin from the drug loaded hydrogels were determined. The maximum amount of drug release and initial rate of drug release was calculated by using Eq. (2).

$$\frac{t}{C_t} = \alpha + \beta t \tag{2}$$

Here C_t is the amount of drug released at time t, $\beta = 1/C_{max}$ is the inverse of the maximum amount of released drug, $\alpha = 1/(C_{max})^2$ $k_{rel} = 1/r_o$ is the inverse of the initial release rate, and k_{rel} is the constant of the kinetic of release (Ekici & Saraydin, 2004).

Different kinetic models were applied (Eqs. (3)–(6)) to drug release data obtained for release of amoxicillin sodium from loaded hydrogels in different medium.

$$\frac{M_t}{M_\infty} = kt \tag{3}$$

$$\frac{M_t}{M_\infty} = 1 - \exp(-kt) \tag{4}$$

$$\frac{M_t}{M_\infty} = kt^{1/2} \tag{5}$$

$$\left(1-\frac{M_t}{M_\infty}\right)^{1/3}=1-kt \tag{6}$$

where "M_t" is the amount of drug released at time (t), "M_∞" is the maximal amount of the drug released at maximum interval and "k" is the rate constant of drug release. To find out the mechanism of drug release from hydrogels the data were treated in different mathematical models, i.e. zero order (Eq. (3)), first order (Eq. (4)), Higuchi square root law (Eq. (5)), Korsmeyer–Peppas model (Eq. (1)) and Hixson–Crowell cube root (Eq. (6)) (Sullad, Manjeshwar, & Aminabhavi, 2010).

2.5. Determination of network parameters

The release of drug from the drug loaded hydrogels is dependent on the swelling of the hydrogels which is controlled by the network density and porosity of the hydrogels. The network structure is defined by several parameters, i.e., the number of cross-links, their functionality and distribution, network defects (dangling chains and loops), and entanglements (Valentin, Carretero-Gonzalez, Mora-Barrantes, Chasse, & Saalwachter, 2008). $\overline{M}_c$ can be determined by studying swelling of polymer. In order to calculate the $\overline{M}_c$ values, the Flory–Rehner Eq. (7) in following form was used (Aithal, Aminabhavi, & Cassidy, 1990; Kulkarni, Soppimath, Aminabhavi, Dave, & Mehta, 2000).

$$\overline{M}_c=-d_P v_{m,1}\phi^{\frac{1}{3}}[\ln(1-\phi)+\phi+\chi\phi^2]^{-1} \tag{7}$$

Here $v_{m,1}$ is the molar volume of the swelling agent (18.1 cm^3/mol for water), χ is the Flory–Huggins interaction parameter and ϕ is the polymer volume fraction in the swollen state which is a measure of the amount of fluid imbibed and retained by the hydrogel. The volume fraction, ϕ of the polymer in the swollen state was calculated by using Eq. (8).

$$\phi=\left[\left(\frac{d_p}{d_s}\right)\left(\frac{w_\infty-w_o}{w_o}\right)+1\right]^{-1} \tag{8}$$

where d_p and d_s are densities of polymer and solvent (g/cm^3) respectively; w_o and w_∞ are respectively, the weight of polymer before and after 24 h swelling. Flory–Huggins interaction parameter (χ) were calculated experimentally from the temperature coefficient of volume fraction ($d\phi/dT$) (Eq. (9)) (Aithal et al., 1990; Kulkarni et al., 2000).

$$\chi=[\phi(1-\phi)^{-1}+N\ln(1-\phi)+N\phi]\left[2\phi-\phi^2N-\phi^2T^{-1}\left(\frac{d\phi}{dT}\right)^{-1}\right]^{-1} \tag{9}$$

where $N=(\phi^{2/3}/3-2/3)(\phi^{1/3}-2/3\phi)^{-1}$ and $(d\phi/dT)$ is the slope obtained by plotting the volume fraction data versus temperature (K). For this purpose swelling was determined at 300.15, 310.15 and 320.15 K in distilled water for 24 h. The swelling behavior is strongly dependent on the number of intermolecular junctions per unit volume, namely the crosslink density (Mantovani, Grassi, Colombo, & Lapasin, 2000). To further analyze the swelling behavior of these hydrogels in aqueous medium, the cross link density (ρ), was calculated from Eq. (10) (Jhaveri et al., 2009).

$$\rho=\frac{1}{\overline{v}(\overline{M}_c)}=\frac{d_p}{\overline{M}_c}, \tag{10}$$

where $\overline{v}=1/d_p$ is the specific volume of polymer.

The mean pore size (nm) of the polymeric network of the hydrogels (ξ) was estimated using Eq. (11) (Chung, Vlugt-Wensink, Hennink, & Zhang, 2005; Stenekes et al., 2000).

$$\xi=0.071\phi^{-1/3}(\overline{M}_c)^{1/2} \tag{11}$$

3. Results and discussion

The plausible mechanism for the synthesis of TG-*cl*-poly(AAc) hydrogels is given in Scheme 1. The graft copolymerization and crosslinking copolymerization of poly(AAc) onto tragacanth gum occurred by free radical polymerization mechanism which was generally considered to involve three steps: (a) initiation, which involved the generation of free radicals and thus the generation of reactive sites on substrate polymer (i.e. polysaccharide backbone tragacanth gum) through hydrogen abstraction; (b) propagation, which involved the addition of monomer to the substrate reactive sites and further propagation of that monomer thus formation of macroradicals; and (c) termination in which polymeric macroradicals may combine to give a cross-linked product. APS was used as free radical initiator and it produces sulfate anion-free radicals $(SO_4)^-$ (step i) which may react with water to produce hydroxyl radicals ($OH^\bullet$) (step ii). These radicals are capable of abstracting hydrogen atom from tragacanth gum backbone and, therefore, producing radical sites for grafting on the macromolecular backbone i.e. $TGO^\bullet$ (step iii). Like other polysaccharides, the hydrogen abstraction, in general, occurred through four possibilities (i) from the —OH groups present in the polysaccharide, (ii) from the hydrogen present in the carbon skeleton, (iii) from the hydrogen present on the C6 carbon of the backbone and (iv) abstraction of hydrogen from the —COOH groups present in the galacturonic acid chain. During initiation, the $OH^\bullet$ radical also abstracts hydrogen from the vinyl monomer, which further reacts with oxygen and generates a peroxide free radical (steps iv and v) (Bajpai & Giri, 2002; Mondal, Ubukata, & Itoyama, 2008; Singh & Sharma, 2009). During propagation, homo-polymerization of AAc to poly(AAc) and grafting of poly(AAc) onto tragacanth gum has formed the grafted TG-*g*-poly(AAc) macroradicals (steps viii–ix). In the presence of the cross-linker NN-MBA, a new macroradical forms that has four reactive sites, and these sites can be linked with the radical on the tragacanth gum, poly(AAc), and TG-*g*-poly(AAc) macroradicals (step x). This was lead to the formation of three-dimensional network, and named as TG-*cl*-poly(AAc) hydrogels.

3.1. Characterization

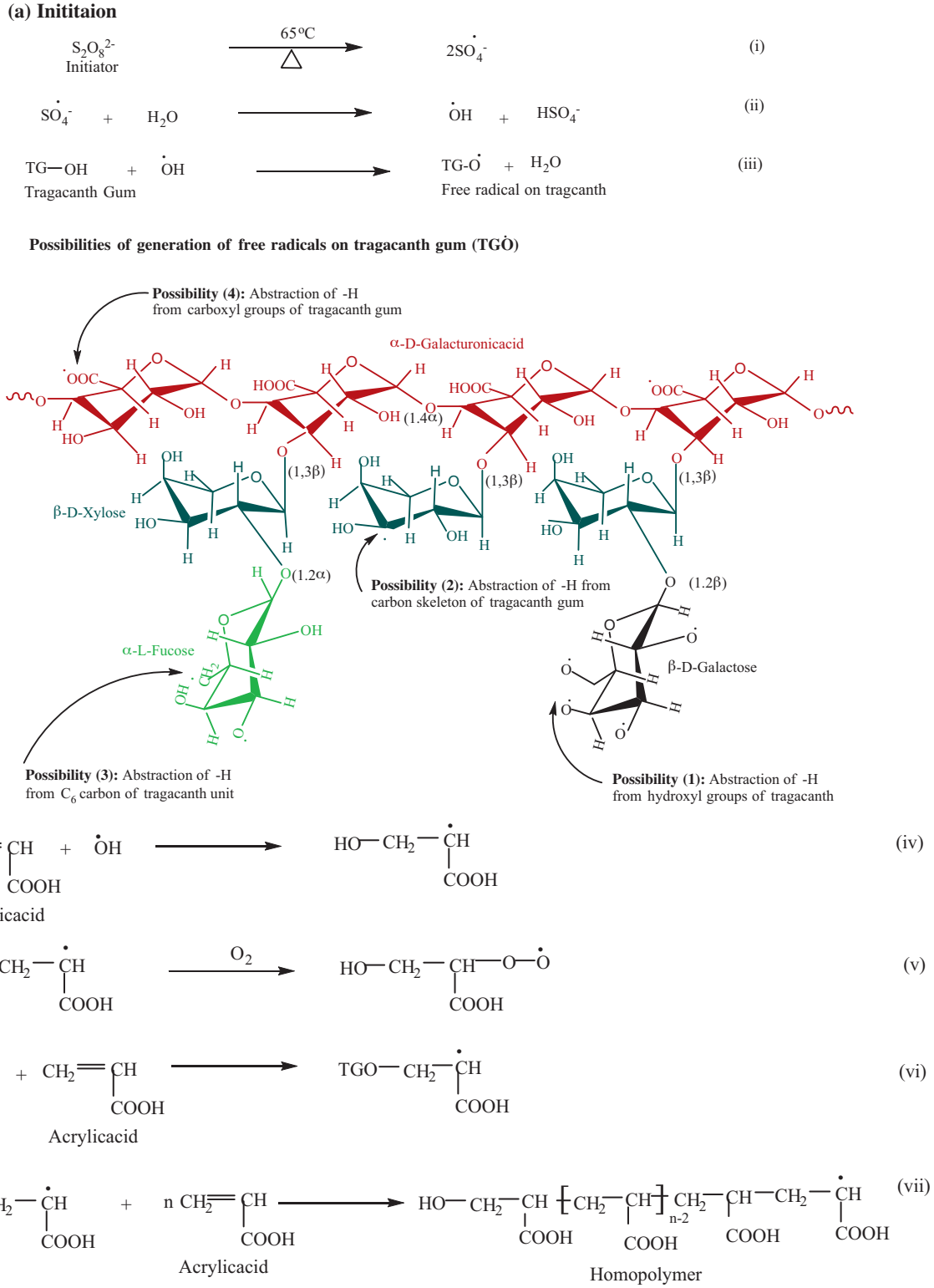
3.1.1. SEM and EDAX analysis of polymers

It is observed from the SEM images that the tragacanth gum has smooth and homogeneous morphology whereas hydrogel has shown structural heterogeneity. The some polymeric networks have been observed in the SEMs of the hydrogels. The increase in pore size has been observed in case of SEM image of hydrogels in swelled form (Fig. 1.1). These pores are the regions of water permeation and interaction sites of external stimuli with the hydrophilic groups of polymeric networks (Pourjavadi, Barzegar, & Zeidabadi, 2007). Surface morphology of swelled polymer matrix showed more stretched pattern as compared to that of dry one. The results of the energy dispersion X-ray analysis (EDAX) for elemental composition (wt %) analysis of the polymers showed that carbon, oxygen and nitrogen in tragacanth gum (62.51, 33.40 and 2.95%) and in TG-*cl*-poly(AAc) hydrogels (64.05, 28.55 and 6.32%) respectively. The increase in nitrogen indicates the crosslinking of NN-MBA crosslinker in polymer matrix.

3.1.2. FTIR spectra of polymers

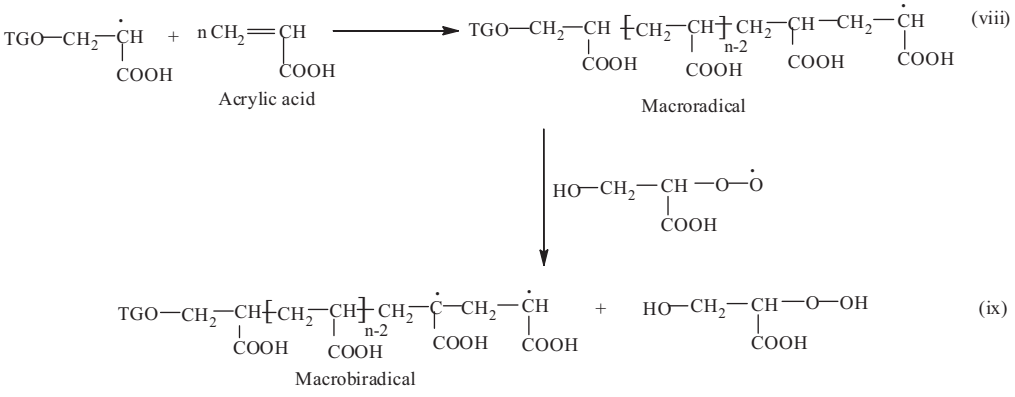
FTIR spectra of tragacanth gum and TG-*cl*-poly(AAc) hydrogels are presented in Fig. 1.2. In case of tragacanth gum, a broad band at 3408.9 cm^{-1} (due to —OH stretching vibrations), at 1300–900 cm^{-1} (due to C—O, C—C, ring structures and deformation vibrations of CH_2 groups) bands in the region 1070–1030 cm^{-1} (due to C—O and C—C stretching vibrations of pyranose rings of polysaccharide) have been observed (Gomez-Ordonez & Ruperez,

2011). The shoulder at 1150 cm^{-1} is assigned to the antisymmetric C—O—C vibrations in glycosidic groups of polysaccharides (Haxaire, Marechal, Milas, & Rinaudo, 2003). The absorption bands in the region 1727 cm^{-1} ($\nu_{C=O}$, —COOH) and 1620 cm^{-1} ($\nu_{C=O}$, $-COO^-$) may be due to carboxylic acid or carboxylate anion form of D-galacturonic acid present in tragacanth. The band around 1420 cm^{-1} is assigned, to C—OH deformation vibration with contribution of O—C—O symmetric stretching vibration of carboxylate group (Leal, Matsuhiro, Rossi, & Caruso, 2008). The absorption band at 901 cm^{-1} may be assigned to pyranose ring vibrational modes. FTIR spectrum of TG-*cl*-poly(AAc) polymer shows absorption bands at 3412.7 cm^{-1} (—OH stretching vibrations), 2927.0 and 2860.0 cm^{-1} (asymmetrical and symmetrical stretching vibrations of C—H respectively), 2363.8 cm^{-1} (overtones and combinations



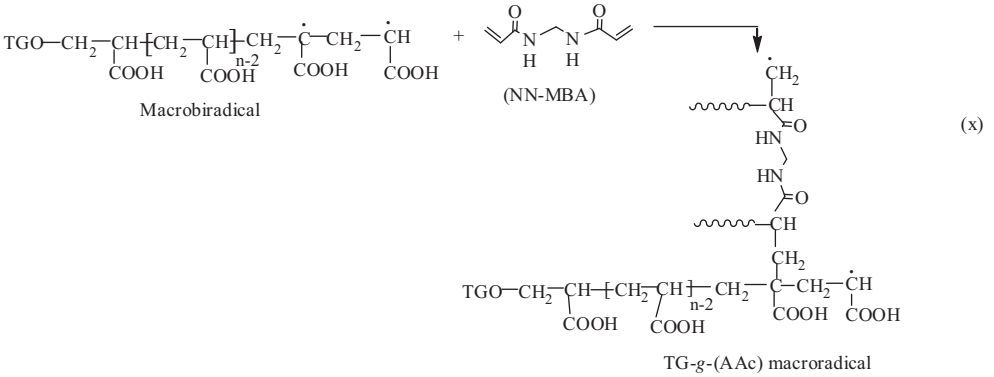
Scheme 1. The plausible proposed mechanism for the synthesis of TG-*cl*-poly(AAc) hydrogels.

(b) Propagation



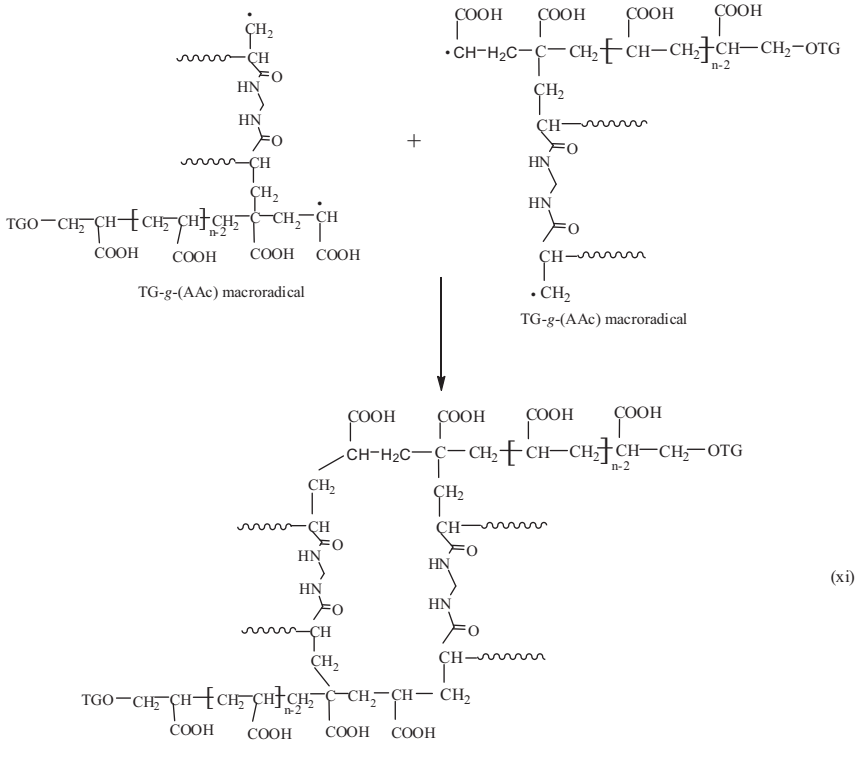
(viii)

(ix)



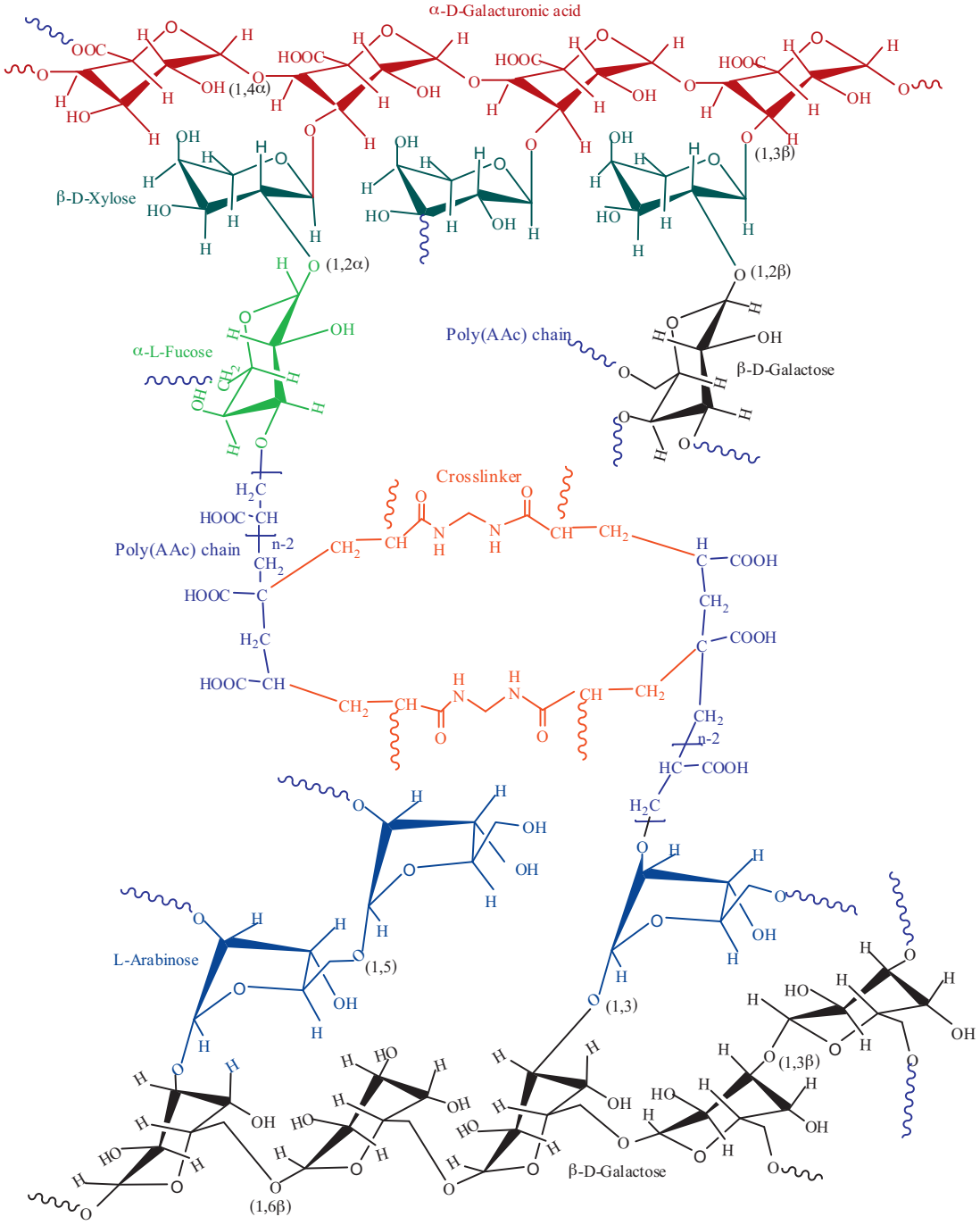
(x)

(c) Termination



(xi)

Scheme 1. (*Continued*)



Scheme 1. (*Continued*).

of —OH bending and C—O stretching vibrations), 1727.1 cm^{-1} (C=O stretching), 1454.5 cm^{-1} ($—CH_2$ bending), 1300–1200 cm^{-1} (C—O—C stretching vibration), 1075–1190 cm^{-1} (C—O stretching of —COOH) beside the bands appeared in tragacanth gum spectra. The presence of more predominant band at 1727 cm^{-1} as compared to gum and absorption band at 1543.1 cm^{-1} (COO^- asymmetric stretching), indicate the grafting of poly(AAc) on to the polysaccharide backbone (Srivastava, Mishra, Singh, Srivastava, & Kumar, 2012).

3.1.3. ^{13}C NMR spectroscopy of polymers

Solid-state ^{13}C NMR has proven to be a powerful technique for the study of cross-linked polymer spectra of polymers. The solid state ^{13}C NMR spectra of tragacanth gum and TG-*cl*-poly(AAc) hydrogel are shown in Fig. 1.3. In case of tragacanth gum peaks in region 18–22 ppm can be assigned to primary and secondary carbons ($—CH_3$, $—CH_2$) of polysaccharides. Broad peak centered at 73.1 ppm can be assigned to carbons (—C—OH) attached to hydroxyl groups and peak at 104.5 ppm may be due to anomeric carbon atom of polysaccharide. The peak at 174.9 ppm may be due to —COOH groups of galacturonic acid chain present in tragacanth gum (Tischer, Iacomini, & Gorin, 2002). In case of TG-*cl*-poly(AAc) hydrogel, peaks at 18.7 ($—CH_3$), 22.2 ($—CH_2—$), 42.4 (—CH— of polyacrylic acid), 71.09 (—C—OH), 103.9 (anomeric carbon of polysaccharide) and 178.3 ppm (—COOH groups of polyacrylic acid) were observed. Presence of peaks at the chemical shift of 42.4 and 178.3 ppm were

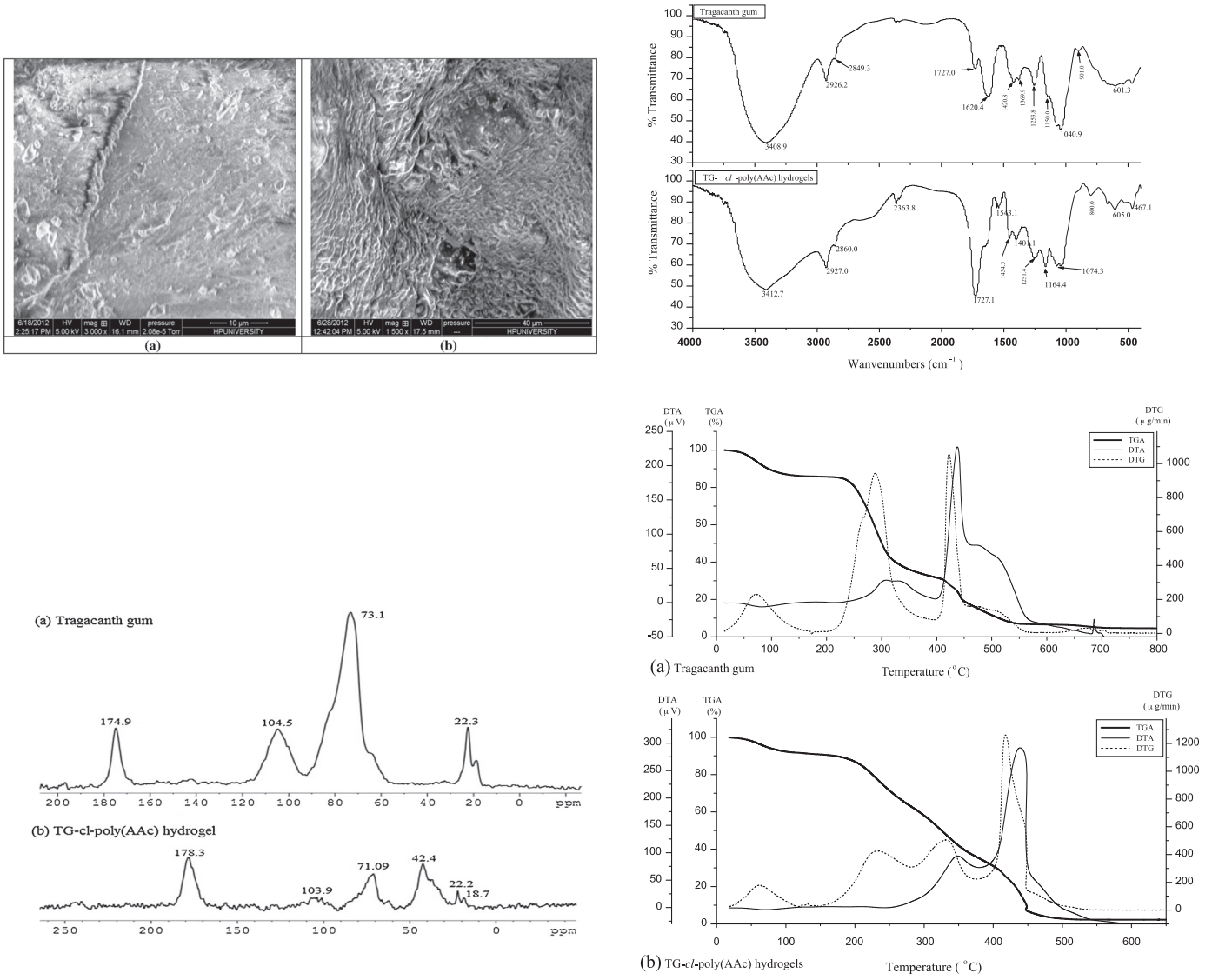


Fig. 1. 1: SEMs of (a) tragacanth gum and (b) TG-*cl*-poly(AAc) hydrogels. 2: FTIR spectra of tragacanth gum and TG-*cl*-poly(AAc) hydrogels. 3: Solid state ^{13}C NMR of (a) tragacanth gum and (b) TG-*cl*-poly(AAc) hydrogels. 4: TGA, DTA and DTG of (a) tragacanth gum and (b) TG-*cl*-poly(AAc) hydrogels.

may be due to grafting of poly(AAc) chains onto gum (Axelson & Russell, 1985; Tanodekaew et al., 2004).

3.1.4. XRD studies of polymers

In case of XRD spectra of gum, a broad peak of less intensity (characteristic amorphous peak) along with a small sharp peak at diffraction angle (2θ) of 28° (d spacing = 3.8674 Å, relative intensity = 100%) was observed which may be due to microcrystalline structure of natural polysaccharide. While in case of crosslinked TG-*cl*-poly(AAc) hydrogel a broad peak of less intensity show amorphous nature of crosslinked hydrogels. Mishra and co-workers have also reported amorphous nature of okra-*cl*-poly(AAm) crosslinked hydrogels (Mishra, Clark, & Pal, 2008). Amorphous nature of hydrogel may be due to grafting of poly(AAc) chains which restrict any long- or short-range regular pattern in polymeric samples (Biswal et al., 2007).

3.1.5. TGA, DTA and DTG of polymers

The TGA, DTA and DTG of tragacanth gum and TG-*cl*-poly(AAc) polymers are shown in Fig. 1.4. The decomposition temperature per 10% weight loss along with the initial decomposition temperature (IDT) and final decomposition temperature (FDT) is given in Table 1. In each case, weight loss due to entrapped moisture has been ignored and IDT has been taken as the temperature where the actual degradation of polymers started (Zohuriaan & Shokrolahi, 2004). In initial 10.75% and 7.7% weight loss (due to bounded water) occurred between 20 and 100 °C in tragacanth gum and TG-*cl*-poly(AAc) polymers respectively. The IDT and FDT of gum are observed at 227 °C and 706 °C (residue left = 4.79%) respectively. In two stages decomposition mechanism, first stage started at 227 °C (residue left = 85%) and second at 412 °C (residue left = 30.5%). During first stage of decomposition, about 42% weight loss occurred in between 227 to 315 °C, which may be due to the loss of hydroxyl groups of gum (Soppirnath & Aminabhavi, 2002). The thermal degradation of polysaccharides is quite complex and starts with depolymerization through random chain scission associated with degradation followed by molecular rearrangements. In general, decomposition of polysaccharides consists of four phases: desorption of physically absorbed water, removal of structural water (dehydration reactions), depolymerization and finally the formation of polynuclear aromatic hydrocarbon (Parikh & Madamwar, 2006). In case of TG-*cl*-poly(AAc) polymers, IDT and FDT are observed at 189 °C and 520 °C (residue left = 2.37%), respectively. Three stages decomposition mechanism has been observed for the decomposition of

Table 1
Thermogravimetric analysis (TGA) of tragacanth gum and TG-*cl*-poly(AAc) hydrogels.

Sample	IDT (°C)	FDT (°C)	Decomposition temp. (°C) at every 10% weight loss									
			10	20	30	40	50	60	70	80	90	100 (residue left)
Tragacanth gum	227	706	94	252	271	286	300	325	415	446	513	706 (4.79%)
TG-*cl*-poly(AAc) hydrogel	189	520	171	225	254	293	325	357	404	432	448	520 (2.37%)

crosslinked polymer networks. The first stage started at 189 °C (residue left = 88.5%), second stage (mild) started at 311 °C (residue left = 54.7%) and third stage started at 411 °C (residue left = 28.1%). About 50% of the polymer decomposition occurred at the end of second stage of decomposition. The gradual weight loss occurred in crosslinked polymer matrix whereas sudden weight loss has been observed in case of TGA of tragacanth. The lower IDT of polymer matrix may be due to the formation of anhydride with elimination of water molecule from the two neighboring carboxylic groups.

DTA curves of gum and hydrogels show endothermic peaks at 83 °C and 71.6 °C respectively, due to release of water from polymers. Additionally, presence of exothermic peaks at 308 °C and 438 °C in case of gum, and at 439 °C in case of crosslinked polymers, suggested oxidative decomposition of polymers (Jelicic, Friedrich, Jeremic, Siekmeyer, & Taubert, 2009).

DTG analysis of polymers was studied as a function of rate of weight loss (μg/min) versus temperature (°C). There are two DTG peaks after IDT of tragacanth gum and three DTG peaks in case of crosslinked polymer matrix, which indicate two and three stage thermal decomposition for gum and polymer matrix respectively. In case of gum, T_{max} for first and second stage of decomposition has been observed at 288 °C (943 μg/min) and 422 °C (1057.58 μg/min) while in case of hydrogels the T_{max} for first and third stage of decomposition found at 233.6 °C (425 μg/min) and 418 °C (1260.21 μg/min) respectively. TGA/DTA/DTG indicates that modification occurred in tragacanth gum after grafting and crosslinking reaction.

3.2. Swelling studies

3.2.1. Effect of feed [AAc] on swelling and network parameters of hydrogels

In order to study the effect of feed [AAc] on network density of the hydrogels, the hydrogels were prepared with different AAc concentration and their swelling was determined (Fig. 2.1). The results show that the swelling of the hydrogels first increased and then decreased with increase in feed [AAc] in reaction system during polymerization. This may be due to the reason that after formation of networks of optimum pore size, further increase in feed monomer concentration has increased the network density of the hydrogels which has decreased the swelling of the hydrogels (Yazdani-Pedram, Retuert, & Quijada, 2000). The decrease in swelling after attaining optimum pore size may be due to preferential homopolymerization over graft copolymerization and increase in the viscosity of reaction mixture which resists the movement of free radicals and monomer molecules. Additionally, due to more probability of chain transfer reaction to monomer molecules lesser swelling has been observed (Pourjavadi, Harzandi, & Hosseinzadeh, 2004). However, the crosslinked polymers were not formed with lower monomer concentration or those get formed, have shown degradation during swelling. It is worthy to mention here that during the synthesis of hydrogels, when the AAc concentration was varied, the all other contents, that is, amount of tragacanth gum, NN-MBA and APS were kept constant in the reaction system. The values of diffusion exponent '*n*' indicate that swelling of the polymers occurred through non-Fickian diffusion mechanism. In this mechanism, the rate of diffusion of water molecules into the polymer matrix and rate of polymer chains relaxation are comparable. The values of late time diffusion coefficients are observed higher than initial diffusion coefficients (Table 2). These results indicate that the expansion of polymer network by the water is slower at the earlier stages of the process, since the gel goes from xerogel (glass state) to hydrogel form (Tomic, Micic, Filipovic, & Suljovrujic, 2007).

Swelling results also indicate that increase in feed monomer concentration during synthesis has influenced the network parameters (Li, Wu, Wang, & Duan, 2006). The mesh size (ξ) of hydrogels first increased then decreased with increase in feed AAc concentration. However the crosslink density (ρ) first decreased and then increased with increase in feed AAc concentration. These results are corresponding to the swelling trends (Table 3).

3.2.2. Effect of feed [NN-MBA] on swelling and network parameters of hydrogels

Swelling of hydrogels decreased (from 4.083 ± 0.053 to 2.710 ± 0.085 g/g of gel) with increase in crosslinker concentration (from 0.0130 to 0.0519 mol/L) (Fig. 2.2) except in case of hydrogels prepared with 0.0649 mol/L of NN-MBA. The decrease in swelling with increasing [NN-MBA] may be due to the increase in number of crosslinks in the gel network which results in a reduction in pore size of the voids available between the network chains. This leads to a slow diffusion of water molecules into the network and restricted relaxation of network chains in the hydrogels (Hosseinzadeh, 2010). Swelling of hydrogels occurred through non-Fickian diffusion mechanism. At lower crosslinker concentration, late time diffusion coefficients are higher than initial and average diffusion coefficients and a reverse trend is obtained for higher [NN-MBA] (Table 2). This may be due to the fact that for lower [NN-MBA], degree of crosslinking is low and hence the polymer chains are relaxed to a greater extent in the later stages of swelling, thus causing a faster diffusion of water into the polymer matrix (Bajpai & Singh, 2006).

The crosslink density (ρ) of polymer networks of hydrogels increased (from 3.06120×10^{-5} to 39.18182×10^{-5}) with increase in crosslinker concentration from 0.0130 to 0.0649 mol/L. The mesh size (ξ) and molecular weight between two crosslinks ($\overline{M}_c$) regularly decreased with increase in [NN-MBA] (Table 3). Similar trend for ρ, ξ and $\overline{M}_c$ values of hydrogels with increase in crosslinker (i.e. NN-MBA) concentration have been reported in literature (Singhal et al., 2009). The χ values are more than 0.5 for most of cases for [NN-MBA] variations. Mesh size is an important factor for determining mechanical strength, degradability, and diffusivity of the releasing molecule and can be modulated by altering crosslinker ratio in the reaction mixture (Canal & Peppas, 1989). Wang and coworkers have also observed decrease in $\overline{M}_c$ value and reduction in water absorption with increase in [NN-MBA] of hydrogels (Wang & Wang, 2010). Mostly hydrogels used in biomedical applications have mesh size ranging from 5 to100 nm in their swollen state. The mesh size is a very important parameter in understanding of transport of macromolecules through the polymer network (Hariharan & Peppas, 1996). The rate of drug release depends on the water content of the swollen hydrogel, as well as on its network parameters, i.e., degree of crosslinking and mesh size (Vakkalanka & Peppas, 1996). The swelling ratio change of polymeric networks translates into a change in the mesh size of the gel, which modulates drug release. Hence the cross-linking agent due to its multiple functional

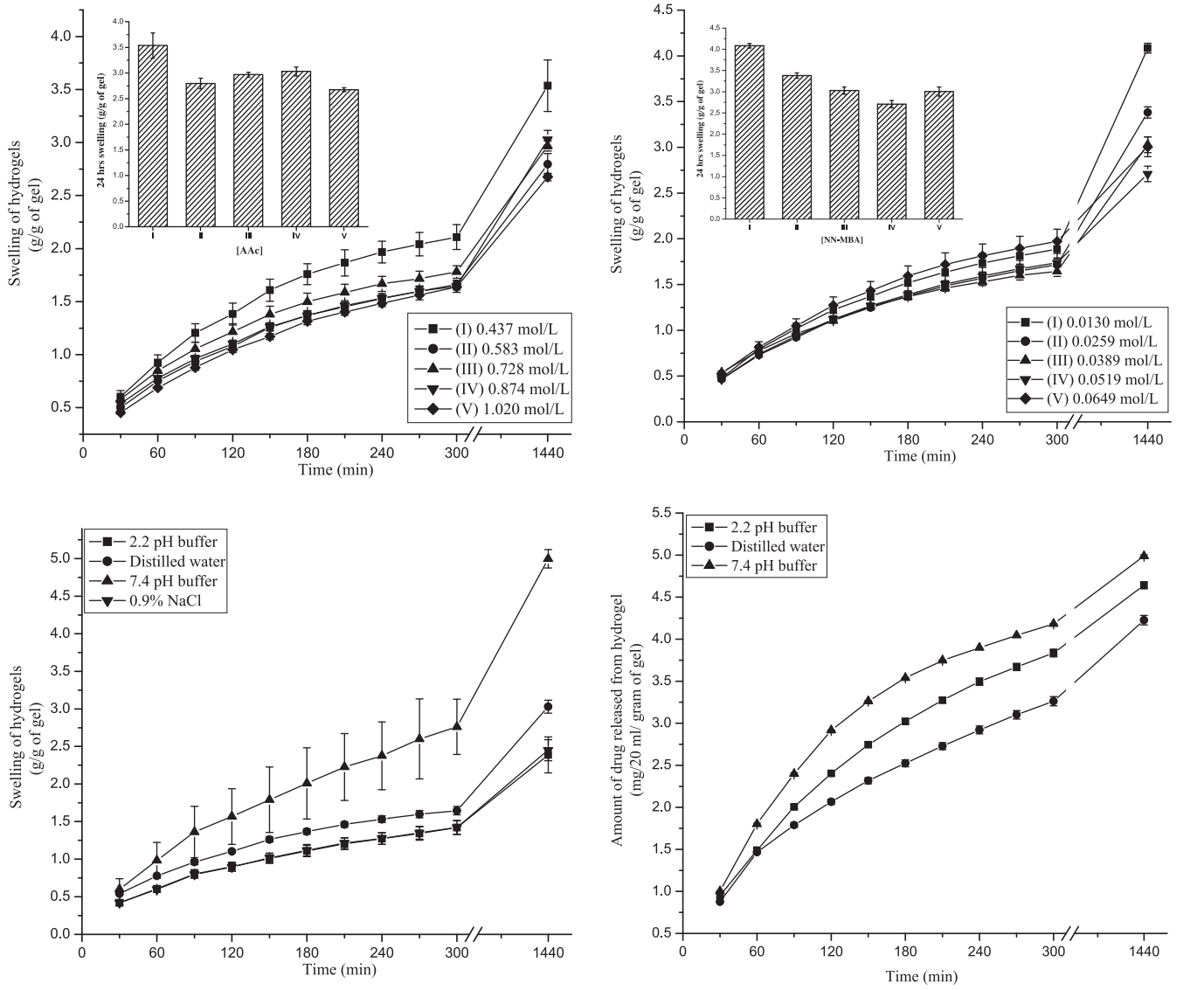


Fig. 2. 1: Effect of [AAc] on swelling kinetics of TG-*cl*-poly(AAc) hydrogels in distilled water at 37 °C. 2: Effect of [NN-MBA] on swelling kinetics of TG-*cl*-poly(AAc) hydrogels in distilled water at 37 °C. 3: Effect of pH and salt concentration of swelling medium on swelling kinetics of TG-*cl*-poly(AAc) hydrogels at 37 °C. 4: Effect of pH on release profile of amoxicillin sodium from drug loaded TG-*cl*-poly(AAc) hydrogels in different medium at 37 °C.

tendencies increases the percentage gelation of hydrogel systems and help in formation of three dimensional polymeric networks which prevent dissolution of the hydrophilic polymer chains in an aqueous environment and modify the drug release profile from drug loaded hydrogels (Malana, Zafar, & Zuhra, 2012).

3.2.3. *Effect of pH, [salt] and temperature of swelling medium on the swelling and network parameters of hydrogels*

Swelling of hydrogels increased with increase in pH of swelling medium (Fig. 2.3). This may be due to opening of the pores caused by ionic repulsion of the constituted ions formed after partial hydrolysis at higher pH (Burugapalli, Bhatia, Koul, & Choudhary, 2001; Yun, Oh, Im, Kim, & Lee, 2012). The effect of pH on network parameters of hydrogels has been studied and results are presented in Table 3. The mesh size (ξ) of hydrogel has been increased with increase in pH of swelling medium. The ξ values (15.098–22.834 nm) and $\overline{M}_c$ values (17,246.985–28,747.744 g/mol) have been increased, whereas, volume fraction (ϕ) and crosslink density (ρ) have been decreased with increase in pH of swelling medium from 2.2 to 7.4 pH. Yarimkaya and Basan (2007) have observed similar increase in $\overline{M}_c$ and ξ values and decrease crosslink density of poly(HEMA-*co*-AAc-*co*-NaAc) hydrogels on increasing the pH swelling medium from 2.0 to 8.0 at 37 °C. With increase in pH of the swelling medium, partial ionization of the polymer matrix occurred and due to ionic repulsion, pore size of the polymer networks increased and swelling of hydrogel increased. These hydrogels showing change in their structural and swelling properties in response to pH of swelling medium and hence can be used as site specific drug delivery system.

The water uptake by the hydrogels in 0.9% NaCl solution (2.45 ± 0.14 g/g of gel) has been observed less as compared to the distilled water (3.029 ± 0.086 g/g of gel) (Fig. 2.3). It may be due to the screening effect of the additional cations (Na^+) and decrease in osmotic pressure difference between the hydrogel networks and the external solution. The ξ and $\overline{M}_c$ values decreased, and ρ and ϕ values increased in saline solution as compared to distilled water (Table 3).

Swelling of hydrogel increased with increase in temperature of swelling medium. With increase in temperature of swelling medium from 27 to 47 °C, ϕ and ρ values of hydrogel decreased

Table 2
Results of diffusion exponent '*n*', gel characteristic constant '*k*' and various diffusion coefficients for the swelling kinetics of chemically crosslinked TG-*cl*-poly(AAc) hydrogels.

S. no.	Variation	Diffusion exponent '*n*'	Gel characteristic constant '*k*' $\times 10^3$	Diffusion coefficients (cm^2/min)		
				Initial $D_i \times 10^5$	Average $D_A \times 10^5$	Late time $D_L \times 10^5$
Variation of [AAc] (mol/L)						
1	0.437	0.549	27.671	8.210	8.253	8.402
2	0.583	0.524	31.187	8.594	8.865	9.082
3	0.729	0.492	38.039	8.314	9.719	9.166
4	0.874	0.492	34.218	6.596	7.137	7.455
5	1.020	0.561	25.813	9.291	8.633	9.356
Variation of [NN-MBA] (mol/L)						
6	0.0130	0.591	16.865	5.151	4.546	5.563
7	0.0259	0.568	20.853	6.428	5.540	6.803
8	0.0389	0.492	34.218	6.596	7.136	7.455
9	0.0519	0.571	25.923	8.248	7.486	8.189
10	0.0649	0.579	25.453	7.537	6.674	7.366
Swelling medium						
11	pH 2.2 buffer	0.527	29.905	5.919	5.749	6.285
12	pH 7.4 buffer	0.652	13.585	6.366	4.725	6.088
13	Distilled water	0.492	34.218	6.596	7.136	7.455
14	0.9% NaCl	0.534	28.121	7.051	6.789	7.441
Temperature						
15	27 °C	0.610	18.825	10.255	8.052	9.784
16	37 °C	0.492	34.218	6.596	7.136	7.455
17	47 °C	0.509	34.815	8.966	9.977	9.726

and corresponding ξ and $\overline{M}_c$ values of polymer network have been increased. Kulkarni et al. (2000) have also studied the effect of temperature on network structure of sodium alginate beads and observed increase in $\overline{M}_c$ values with increasing temperature. The χ values are more than 0.5 for all cases for different variation in swelling medium (Table 3). The swelling of hydrogels has been occurred through non-Fickian diffusion mechanism at different pH, [salt] and temperature of swelling medium (Table 2).

Similar swelling trends have been observed in case of swelling of polymers prepared with other polysaccharides. Further, amount of water uptake by the polymer networks varied with change in nature of polysaccharides and composition of the polymer networks. The guar gum/poly(acrylic acid) semi-interpenetrating polymer network hydrogels showed pH responsive swelling behavior and showed more swelling in pH 7.52 (~13 g/g) as compared to pH 1.44 (~3 g/g) (Li et al., 2006). However in the present study, TG-*cl*-poly(AAc) polymers showed (4.99 ± 0.12 g/g) in pH 7.4 buffer and (2.38 ± 0.24 g/g) in pH 2.2 buffer. Swelling behavior of chitosan/AAc showed more swelling in pH 7.4 (~15 g/g) as compared to pH 2 (~10 g/g) (Yazdani-Pedram et al., 2000). Dextran/AAc based hydrogels showed increase in swelling from 7 to 35 g/g of gel with increase in [AAc] from 10 to70 mol% (Chiu, Lin, & Hsu, 2002). In one study tara gum/AAc based hydrogels have showed decrease in swelling ratio (from 40 to 20 g/g) with increase in NN-MBA (from 2 to 4%) (Alla, Sen, & El-Naggar, 2012). Sodium alginate/AAc based hydrogels showed swelling ratio between (10 to 30 g/g) for polymers prepared with different ratio of sodium alginate/AAc (El-Din, Taleb and El-Naggar, 2008). kappa-Carrageenan/AAc acid based superabsorbent hydrogels have shown similar swelling trends for [AAc] variation. Swelling first increased with increase in monomer

Table 3
The network parameters of TG-*cl*-poly(AAc) hydrogels as a function of different variations.

S. no.	Parameter	Density 'd_p' (g/cm^3)	Polymer volume fraction (ϕ)	*N*	Flory–Huggins interaction parameter, χ	Molecular weight between two crosslinks, $\overline{M}_c$ (g/mol)	Crosslink density, $\rho \times 10^5$ (mol/cm^3)	Mesh size ξ (nm)
Effect of [AAc] (mol/L)								
1	0.437	1.11249 ± 0.034	0.20161	−1.22147	0.57280	44441.245	2.50328	25.526
2	0.583	1.18649 ± 0.033	0.23049	−1.17823	0.58162	21555.309	5.50440	17.001
3	0.729	1.22262 ± 0.048	0.21491	−1.20046	0.56598	14571.878	8.39027	14.309
4	0.874	1.35385 ± 0.079	0.19499	−1.23270	0.56326	28747.744	4.70941	20.760
5	1.020	1.45140 ± 0.053	0.20373	−1.21798	0.56623	26286.506	5.52146	19.563
Effect of [NN-MBA] (mol/L)								
6	0.0130	1.36565 ± 0.078	0.15121	−1.32440	0.54386	44611.555	3.06120	28.149
7	0.0259	1.33897 ± 0.055	0.17994	−1.26050	0.55782	36110.225	3.70801	23.898
8	0.0389	1.35385 ± 0.079	0.19499	−1.23270	0.56326	28747.744	4.70941	20.760
9	0.0519	1.36821 ± 0.091	0.21129	−1.20599	0.54475	8425.060	16.23976	10.942
10	0.0649	1.36143 ± 0.084	0.19537	−1.23204	0.46857	3474.647	39.18182	7.213
Swelling medium								
11	pH 2.2 buffer	1.35385 ± 0.079	0.23556	−1.17149	0.57980	17246.985	7.84978	15.098
12	pH 7.4 buffer	1.35385 ± 0.079	0.12876	−1.38784	0.51938	26372.371	5.13359	22.834
13	Distilled water	1.35385 ± 0.079	0.19499	−1.23270	0.56326	28747.744	4.70941	20.760
14	0.9% NaCl	1.35385 ± 0.079	0.23164	−1.17670	0.57794	17716.054	7.64194	15.388
Temperature								
15	27 °C	1.35385 ± 0.079	0.24284	−1.16216	0.58340	16328.021	8.29157	14.542
16	37 °C	1.35385 ± 0.079	0.19499	−1.23270	0.56326	28747.744	4.70941	20.760
17	47 °C	1.35385 ± 0.079	0.18316	−1.25428	0.55967	37190.809	3.64028	24.110

Table 4
Results of diffusion exponent '*n*', gel characteristic constant '*k*', various diffusion coefficients and release kinetic parameters for the release of amoxicillin sodium from drug loaded TG-*cl*-poly(AAc) hydrogels.

Release medium	Diffusion exponent '*n*'	Gel characteristic constant '*k*' × 10^3	Maximum amount of released drug, C_{max} (mg L^{-1})	Constant of the kinetic of release, $k_{rel} \times 10^5$ (s^{-n})	Initial release rate, $r_o \times 10^2$ (mg L^{-1} s^{-1})	Diffusion coefficients (cm^2/min)		
						Initial $D_i \times 10^5$	Average $D_A \times 10^5$	Late time $D_L \times 10^5$
pH 2.2 buffer	0.610	26.742	181.159	3.128	102.656	20.901	15.932	21.134
D.W.	0.551	34.260	139.470	5.093	99.076	15.191	13.963	16.103
pH 7.4 buffer	0.608	28.939	190.476	3.519	127.670	21.689	19.731	22.847

Table 5
Kinetic interpretation of drug release by using different models for release of amoxicillin sodium from TG-*cl*-poly(AAc) hydrogels.

Release medium	Zero order R^2, k_0 (min^{-1})	First order R^2, k_1 (min^{-1})	Higuchi R^2, k_H ($min^{-1/2}$)	Korsmeyer–Peppas R^2, k_{KP} (min^{-n})	Hixson–Crowell R^2, k_{HC} ($min^{-1/3}$)
pH 2.2 buffer	0.96015, 0.00224	0.99979, 0.0056	0.99631, 0.0535	0.99428, 0.02674	0.99622, 0.00136
Distilled water	0.9645, 0.00195	0.99728, 0.00441	0.99731, 0.04637	0.99180, 0.03426	0.99387, 0.00111
pH 7.4 buffer	0.908, 0.00221	0.99133, 0.00586	0.97383, 0.05362	0.96951, 0.02894	0.97265, 0.00139

concentration than decreased. Decrease in swelling has been observed with increase in crosslinker concentration (Pourjavadi et al., 2004). However it is pertinent to mention here that in these studies, these superabsorbent hydrogels were in powder form and due to greater surface area these hydrogel shows more swelling ratio as compared to TG-*cl*-poly(AAc) polymer matrix.

3.3. Drug release studies

The release profile of amoxicillin from the drug loaded hydrogels is shown in Fig. 2.4. The release of drug from the drug loaded hydrogels dependent on the swelling of the polymer matrix and solubility of the drug. In the present case more swelling has been observed in pH 7.4 buffer as compared to the pH 2.2 buffer. Hence release should be more in pH 7.4 as compared to the pH 2.2 buffer. However, there is not very significant difference have been observed in release of drug in pH 7.4 buffer (4987 μg/20 mL/g of gel) and pH 2.2 buffer (4641 μg/20 mL/g of gel). The observed trends may be explained on the basis of solubility of drug. It may be due the more solubility of the amoxicillin in the pH 2.2 buffer as compared to the pH 7.4 (Tsuji, Nakashima, Hamano, & Yamana, 1978). Besides providing the slow release of drug from the polymer matrix, it also protects the entrapped drug in hydrogel from acidic pH of stomach. Liu and co-workers have also reported that hydrogel based colon specific drug delivery system remained intact when traveling through the acidic environment of upper GI tract in order to protect the incorporated drugs from chemical and enzymatic degradation. They released the incorporated drugs immediately upon reaching the colon segment of the lower GI tract (Liu, Fishman, Kost, & Hicks, 2003). The use of starch/PMAAc polymer matrix for the release of amoxicillin provided a protective effect toward pepsin and hydrolytic degradation at acidic pH of stomach and is useful tool to overcome the very harsh environment of the stomach for site specific drug delivery systems (Clausen & Bernkop-Schnürch, 2001).

The mesh size and crosslinked density of hydrogels has an influence on the release of entrapped drug from loaded hydrogels. The mesh size of hydrogel was more in case of pH 7.4 buffer as compare to pH 2.2 buffer, it means crosslinked density (ρ) is more in case of acidic buffer which results in lesser release of entrapped drug in pH 2.2 buffer. In case of hydrogel based drug delivery system, it is not only swelling increases progressively with time, but also the mesh size of the hydrogel in order to molecularly accommodate the drug. The polymer structure and composition were shown to greatly influenced drug diffusion (Brazel & Peppas, 1999). It is also reported that polymethacrylate derivative based hydrogels showed slow and controlled release of loaded drug which is further depended upon polymer composition and crosslink density of polymeric networks. HEMA (0.5%) based hydrogels showed loading dependent release rate of drug (Garcia, Blanco, Martin, & Teijon, 2000; Teijon, Trigo, Garcia, & Blanco, 1997). Poly(2-hydroxyethyl methacrylate/itaconic acid/poly(ethylene glycol) dimethacrylate) hydrogels showed pH depended swelling and drug release (Dobic, Filipovic & Tomic, 2012).

The release of drug from the drug loaded polymers occurred through non-Fickian diffusion mechanism. The rate of diffusion of amoxicillin from drug loaded hydrogels was higher in later stages of drug release as compared to initial stages in all releasing medium (Table 4). It is clear from Table 4 that maximum amount of drug (C_{max}) has been released in pH 7.4 buffer solution at highest initial release rate (r_o) as compared to other release medium and showed highest constant of kinetics of drug release in case of distilled water.

The release data were plotted according to the equations of relevant models. It has been observed that drug release from hydrogels followed best by First order model with highest value of regression coefficient (R^2) in all release medium (Table 5). In case of first order kinetics the release rate constant is directly linked with initial concentration of drug and polymer nature.

4. Conclusions

It is concluded from the foregone discussion that the composition of the hydrogels and nature of the swelling medium affected the swelling and network parameters of the hydrogels. Swelling decreased and crosslink density increased, with increase in feed crosslinker concentration during crosslinking reaction. Mesh size of hydrogels decreased with increase in crosslinker concentration. However, the mesh size has been increased with increase in pH of swelling medium. Swelling of hydrogels and release of amoxicillin from the drug loaded hydrogels have been observed more in pH 7.4 buffer as compared to the pH 2.2 buffer. The swelling and release of drug occurred through non-Fickian diffusion mechanism. It has been found that drug release from hydrogels followed best by first order model. Overall, it is concluded from the forgone discussion that network parameters influenced the drug release from the polymer matrix and are directly related to the polymer swelling which is dependent on the mesh size, crosslinking and composition of the polymer networks. Further, these hydrogels can be used as site specific drug delivery system for the release of antibiotic to the colon.

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