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Research Article

Synthesis and Characterization of Chemically Cross-Linked Acrylic Acid/Gelatin Hydrogels: Effect of pH and Composition on Swelling and Drug Release

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This present work was aimed at synthesizing pH-sensitive cross-linked AA/Gelatin hydrogels by free radical polymerization. Ammonium persulfate and ethylene glycol dimethacrylate (EGDMA) were used as initiator and as cross-linking agent, respectively. Different feed ratios of acrylic acid, gelatin, and EGDMA were used to investigate the effect of monomer, polymer, and degree of cross-linking on swelling and release pattern of the model drug. The swelling behavior of the hydrogel samples was studied in 0.05 M USP phosphate buffer solutions of various pH values pH 1.2, pH 5.5, pH 6.5, and pH 7.5. The prepared samples were evaluated for porosity and sol-gel fraction analysis. Pheniramine maleate used for allergy treatment was loaded as model drug in selected samples. The release study of the drug was investigated in 0.05 M USP phosphate buffer of varying pH values (1.2, 5.5, and 7.5) for 12 hrs. The release data was fitted to various kinetic models to study the release mechanism. Hydrogels were characterized by Fourier transformed infrared (FTIR) spectroscopy which confirmed formation of structure. Surface morphology of unloaded and loaded samples was studied by surface electron microscopy (SEM), which confirmed the distribution of model drug in the gel network.

1. Introduction

Stimuli-responsive polymers offer a drug delivery platform that can be utilized to deliver drugs at a controlled rate and in a stable and biologically active form. These polymers respond to small changes in environmental conditions, such as temperature, pH, light, ionic strength, electric or magnetic fields, or the presence of enzymes or specific ligands. Hydrogels are three-dimensional hydrophilic polymer networks that swell in water or biological fluid without dissolving due to chemical or physical cross-links [1]. These three-dimensional networks of a hydrogel are formed by either reversible bonds (physical bonds), which can be made or broken under certain environments, or covalent bonds. If the cross-links are based on physical bonds, such as hydrogen, ionic, or van der Waal's bonds, the responses of the hydrogels to external stimuli are often reversible [2]. In order to keep the spatial structure of hydrogel, the polymer chains are usually physically or chemically cross-linked [3].

Hydrogels have become excellent carriers for release of drugs and bioactive macromolecules either in their swollen equilibrium state or as dynamically swelling systems. The relatively low mechanical strength of the hydrogels can be overcome either by cross-linking, by formation of interpenetrating networks (IPNs) or by crystallization that induces crystallite formation and drastic reinforcement of their structure [4]. The swelling properties of these hydrogels have attracted the attention of researchers and technologists and have found widespread applications in drug delivery devices, separation processes, sensors, contact lens devices, and many other fields [5].

Cross-linking is responsible for the three-dimensional network structures that characterize these materials. The elasticity and swelling properties are attributed to the presence of physical or chemical cross-links within polymer chains. The cross-linking level of the hydrogels is also important because the physical states of the hydrogels alter with the changing of the cross-linking level [6].

Acrylic acid is a pH sensitive, synthetic polymer extensively used in the area of the site-specific drug delivery of the gastrointestinal tract [7]. It is one of the principal superabsorbent polymers and a typical pH-responsive polyelectrolyte. The original pH-dependent release characteristic could be modified by varying the composition of polymers. Therefore pH-responsive polymeric networks have been extensively studied [8]. The interpenetrating networks (IPNs) and copolymers containing acrylic acid have also been reported to exhibit thermoresponsive, electroresponsive, and pH-responsive behavior [9]. Poly(acrylic acid) is well recognized for its polyanionic nature and has been extensively employed in designing pH-responsive macromolecular architectures mainly used in targeted drug delivery [10]. The pKa value of poly(acrylic acid) is between 4.5 and 5.0, and PAA hydrogels swell significantly at the physiological pH of 7.4 due to ionization of the anionic carboxylic acid groups [11].

Gelatin is a protein product produced by partial hydrolysis of collagen extracted from skin, bones, cartilage, and ligaments [12]. Gelatin mainly contains the residues of 3 amino acids, glycine, proline, and 4-hydroxyproline in its structure [13]. Collagen is the major protein component of cartilage, skin, bone, and connective tissue and constitutes the major part of the extracellular matrices in animals; however, collagen has antigenicity due to its animal origin. In contrast, gelatin has relatively low antigenicity because of being denatured [14]. Gelatin is known for its biodegradability, noncarcinogenicity, and hydrophilicity [15]. Among natural polymers, preferred for their low toxicity and biocompatibility, gelatin is a good raw material candidate because of its excellent physical and chemical properties [16]. At a temperature of about 40°C, gelatin aqueous solutions are in the sol state and form physical thermoreversible gels on cooling. During gelling, the chains undergo a conformational disorder-order transition and tend to recover the collagen triple-helix structure [17].

Pheniramine maleate ($C_{16}H_{20}N_2{\cdot}C_4H_4O_4$), chemically known as N,N-dimethyl-3-phenyl-3-(2-pyridyl) propyl amine hydrogen maleate, is an antihistamine H_1 receptor antagonist used as an antihistaminic for the symptomatic relief of a hypersensitivity reaction. It is clinically used for the treatment of acute allergic attacks, all itching skin condition, nausea, vomiting, and vertigo associated with motion sickness [18]. Figure 1 represents the structure of pheniramine maleate.

The purpose of the present study was to prepare AA/Gelatin hydrogels by free radical polymerization method using EGDMA as cross-linking agent and ammonium persulfate as initiator. The prepared hydrogel samples were used to evaluate the effect of pH and composition of IPNs on dynamic and equilibrium swelling and drug release in 0.05 M USP phosphate buffer solutions of varying pH 1.2, pH 5.5, pH 6.5, and pH 7.5. Pheniramine maleate was loaded as model drug in these hydrogel samples. The release pattern of the model drug was studied in USP phosphate buffer solutions of varying pH values. Sol-gel fraction analysis, cross-linked density, porosity, and network parameters were also calculated for these hydrogels. Hydrogels were characterized by Fourier transform infrared spectroscopy (FTIR) to confirm the formation of network and to investigate the presence of specific chemical groups in the hydrogels. The surface morphology of the hydrogels was studied by scanning electron microscopy (SEM).

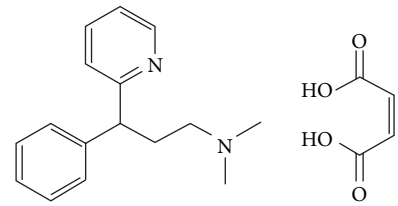


Figure 1: Structure of pheniramine maleate.

2. Experimental Procedures

2.1. Materials. For the preparation of pH sensitive hydrogels, acrylic acid (AA) (Mw ~ 72.06 g mol^{-1}) (Sigma Aldrich) was used as monomer. Gelatin type B from bovine skin (Ge) (Mw ~ 402.47 g mol^{-1}) (Merck, Germany) was used as polymer. Ethylene glycol dimethacrylate (EGDMA) (Aldrich) and ammonium persulfate were used as cross-linking agent and initiator, respectively. Potassium hydrogen phosphate, sodium chloride, sodium hydroxide, and hydrochloric acid (Merck, Germany) were used. For characterization of hydrogels by FTIR, potassium bromide (KBr) was purchased from Fisher Scientific (UK). All chemicals used were of analytical grade.

2.2. Synthesis of Interpenetrating Networks of AA/Gelatin. In the present work, different formulations of hydrogels with different feed composition were prepared by free radical copolymerization technique [7, 19]. A weighed quantity of gelatin (Ge) was added into predetermined amount of distilled water under constant stirring at room temperature. When a clear gelatin solution is formed then ammonium persulfate used at a concentration of 1 wt% of AA was dissolved in this gelatin solution. Varying amounts of ethylene glycol dimethacrylate (EGDMA) as cross-linking agent were added and dissolved in acrylic acid solution. The two solutions were mixed together thoroughly. The final volume of the solution was made up to 100 gm with distilled water. The polymerization of the prepared solution was carried out in glass tubes (Pyrex) having 16 mm internal diameter. These test tubes were deoxygenated with nitrogen gas bubbling for 15–20 minutes and then snugly fitted with lid. The capped tubes were placed in water bath. The temperature was gradually increased to avoid autoacceleration and bubble formation. The temperature scheme for solution polymerization was 45°C for 1 h, 50°C for 2 h, 55°C for 3 h, 60°C for 4 h, and

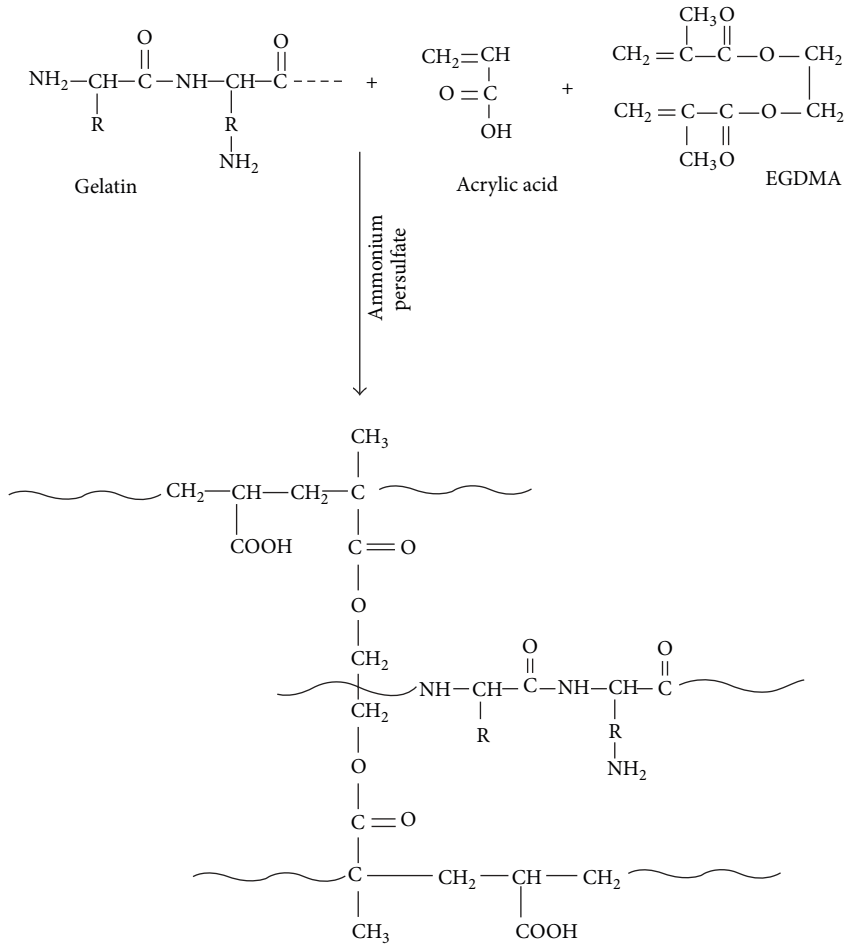


Figure 2: Presumptive structure of EGDMA cross-linked interpenetrating networks of AA/Gelatin hydrogels.

65°C for 24 h. After this period, tubes were cooled to room temperature, and cylinders of obtained gel type product were removed from the tubes and cut into discs of 6 mm size. These cylindrical discs were washed with 50% v/v ethanol water for 1-2 weeks, for complete removal of the unreacted monomers. During this period the solvent was changed daily. These gel discs were thoroughly washed until the pH of the washing was the same as that of ethanol water mixture before washing. Then disks were dried, first at room temperature and then in oven at 40–45°C until the solid reached constant mass. The hydrogels were stored in a desiccator for further use. The presumptive structure of the EGDMA cross-linked interpenetrating networks of AA/Gelatin hydrogels is shown in Figure 2. A list of different composition of AA/Gelatin hydrogels is given in Table 1.

2.3. Swelling Experiments of AA/Gelatin Hydrogels

2.3.1. Dynamic Swelling Experiment. The dynamic swelling experiments were carried out in 100 mL solution at 37°C. Dry discs were weighed and immersed in USP phosphate buffer solutions of varying pH values, that is, 1.2, 5.5, 6.5, and 7.5, with constant ionic strength. Concentration of buffering agent was 0.05 M. Samples were taken out at regular intervals for 8 h and weighed after removing the excess surface water by blotting with filter paper. After weighing, each sample was placed in the same flask. The dynamic swelling ratio of each sample was calculated by [20]

$$q = \frac{W_s}{W_0}, \tag{1}$$

where W_s indicates the weight of hydrated gels after swelling and W_0 shows the initial dry hydrogel disc at time (t).

2.3.2. Equilibrium Swelling Experiments. To carry out the equilibrium swelling experiments, samples remained in the same buffer medium and were used for equilibrium swelling studies. Swelling ratio was equilibrium when hydrogel reached a constant weight. For equilibrium swelling, the swollen gels were weighed regularly to a constant weight which takes 15–21 days.

Equilibrium swelling ratio was calculated by using [21]

$$S_{(\mathrm{Eq})} = \frac{W_h}{W_d}. \tag{2}$$

Table 1: Different composition of AA/Gelatin hydrogels.

Sample codes	AA/100 g solution	GE/100 g solution	AA : GE (wt %)	(EGDM)/100 g solution
U_1	35.00	4.00	89.74/10.26	0.70
U_2	35.00	5.00	87.50/12.50	0.70
U_3	35.00	6.00	85.37/14.63	0.70
U_4	28.00	6.00	82.35/17.65	0.70
U_5	32.00	6.00	84.21/15.79	0.70
U_6	36.00	6.00	85.71/14.29	0.70
U_7	35.00	6.00	85.37/14.63	0.65
U_8	35.00	6.00	85.37/14.63	0.75
U_9	35.00	6.00	85.37/14.63	0.85

2.3.3. Diffusion Coefficient. Release of drug from cross-linked hydrogels generally follows diffusion mechanism. To calculate the diffusion coefficient of hydrated gels, swollen hydrogels were subjected to drying at room temperature and then weighed after 15 minutes till they reached an equilibrium weight. Water diffusion coefficients of hydrogels samples were calculated by [22]

$$D = \pi \left(\frac{h \cdot \theta}{4 \cdot Q_{\text{eq}}} \right)^2, \tag{3}$$

where D represents the diffusion coefficient of the hydrogels, Q_{eq} indicates the equilibrium swelling of the gel, θ is the slope of the linear part of the swelling curves, and h refers to the initial thickness in dry state.

2.4. Interpenetrating Polymeric Networking Parameters of AA/Gelatin Hydrogels

2.4.1. Molecular Weight between Cross-Links (M_c). Flory-Rehner theory was used for calculating average molecular weight (M_c) values between interpenetrating polymeric networking of AA/Gelatin hydrogels, which represents the degree of cross-linking of hydrogel networks between two adjacent cross-links. According to this theory, M_c values increase as the swelling ratio of hydrogels increased. Molecular weight between adjacent cross-links is calculated by using [23]

$$M_c = -\frac{d_p V_s \left(V_{2,s}^{1/3} - V_{2,s}/2 \right)}{\ln\left(1 - V_{2,s}\right) + V_{2,s} + x V_{2,s}^2}. \tag{4}$$

Volume fraction of the polymer $V_{2,s}$ indicates the capacity of hydrogel to allow the diffusion of solvent into the network structure. It is calculated by the following equation:

$$V_{2,s} = \left[1 + \frac{d_p}{d_s} \left(\frac{M_a}{M_b} - 1 \right) \right]^{-1}, \tag{5}$$

where d_p and d_s are densities (g/mL) of the hydrogel and solvent, respectively, M_a and M_b are the masses (g) of the swollen and dry hydrogels, respectively, $V_{2,s}$ (mL/mol) refers to the volume fraction of the swollen hydrogel in the equilibrium state, and χ indicates the Flory-Huggins polymer solvent interaction parameters.

2.4.2. Solvent Interaction Parameters (χ). To investigate the compatibility of monomer and polymer in the AA/Gelatin hydrogels with the molecules of surrounding media, solvent interaction parameters were measured. Flory-Huggins theory was used to calculate solvent interaction parameters (χ). The following equation was used to calculate χ values given in the following [24]:

$$\chi = \frac{\ln\left(1 - V_{2,s}\right) + V_{2,s}}{V_{2,s}^2}, \tag{6}$$

where $V_{2,s}$ (mL/mol) indicates the volume fraction of the hydrated gel in the equilibrium state and χ is the Flory-Huggins polymer solvent interaction parameters.

2.4.3. Cross-Linked Density (q). Cross-linked hydrogels are characterized by cross-linked density. The following equation is used for cross-linked density [25]:

$$q = \frac{M_c}{M_r}, \tag{7}$$

where M_r is molar mass of the repeat unit and is calculated as per

$$M_r = \frac{m_{\text{AA}} M_{\text{AA}} + m_{\text{Ge}} M_{\text{Ge}} + m_{\text{EGDMA}} M_{\text{EGDMA}}}{m_{\text{AA}} + m_{\text{Ge}} + m_{\text{EGDMA}}}, \tag{8}$$

where m_{AA}, m_{Ge}, and m_{EGDMA} are the masses of the monomer (AA), polymer (Ge), and EGDMA, respectively, while M_{AA}, M_{Ge}, and M_{EGDMA} are the molar masses of AA, Ge, and EGDMA, respectively.

2.5. Sol-Gel Fraction Analysis. In order to calculate uncross-linked polymer sol-gel fraction is used. Hydrogel samples were cut into pieces with a diameter of 3-4 mm, first dried at room temperature and then in a vacuum oven at 45°C to a constant weight (W_o), and subjected to Soxhlet extraction for 4 h with deionized water as solvent at boiling temperature. Uncross-linked polymer was removed from the gel structure with this extraction. Extracted gels were dried again in a vacuum oven at 45°C to constant weight (W_i). The gel fraction

was calculated by using initial weight of dry gel (W_o) and weight of extracted dry gel (W_i) according to [26]

$$\text{Sol fraction (\%)} = \left[\frac{W_o - W_i}{W_o}\right] \times 100$$
$$\text{Gel fraction (\%)} = 100 - \text{Sol fraction}. \quad (9)$$

2.6. Porosity Measurement. For the measurement of porosity of hydrogels, which represents the fraction of the volume of pores over the total volume between 0 and 100 percent, solvent replacement method was used. Weighed dried hydrogel discs were immersed in absolute ethanol overnight and weighed after excess ethanol on the surface. The porosity (%) was calculated by [27]

$$\text{Porosity} = \frac{(M_2 - M_1)}{\rho V} \times 100, \quad (10)$$

where M_2 and M_1 are the mass of the hydrogel before and after immersion in ethanol, respectively, ρ is density of absolute ethanol, and V is the volume of the hydrogel.

2.7. Loading of Pheniramine Maleate. Selected samples which showed maximum swellings were used for loading and release study of the model drug, that is, pheniramine maleate. The drug loading into disks of weighed dried hydrogel samples was achieved by soaking them in 1% (w/v) drug solution of the pheniramine maleate up to equilibrium swelling. Drug solution of pheniramine maleate was prepared by dissolving water soluble drug in buffer solution of 7.5 pH. After achieving the equilibrium value, swelled hydrogel discs were removed from the drug solution, blotted with filter paper, first dried at room temperature, and then placed in an oven at 45°C to constant weight [20, 26].

2.8. Quantification of Drug Loading. Amount of drug loaded in discs of hydrogels was calculated by three methods. The first method known as weight method used to calculate the amount of drug loaded in hydrogel discs is represented by [22]

$$\text{Amount of drug} = W_D - W_d. \quad (11)$$

For calculating percentage of drug loading, the following equation is used:

$$\text{Drug Loading \%} = \frac{W_D - W_d}{W_d} \times 100, \quad (12)$$

where W_D is the weight of dried discs of hydrogels after immersion in drug solution and W_d is the weight of dried hydrogel discs before immersion in drug solution.

In the second method to calculate the amount of drug loaded in the hydrogels, drug entrapped in the hydrogel samples was calculated by repeatedly extracting weighed drug loaded hydrogel samples using phosphate buffer solution of pH 7.5. Each time 25 mL fresh phosphate buffer solution of pH 7.5 was used until there was no drug in the drug solution. Drug concentration was determined spectrophotometrically. Total amount of drug present in all portions was considered as amount of drug entrapped or loaded. This method is known as extraction method.

In the third method, which is known to be swelling method, weighed hydrogel discs were placed in drug solution up to equilibrium swelling. Loaded hydrogel discs were weighed again after blotting with blotting paper. Difference in weight before and after swelling is the weight of drug solution. Volume of drug solution absorbed by gel discs can be calculated by knowing the density and weight of drug solution. By knowing the volume of drug solution, amount of drug absorbed by the gel discs was also calculated.

2.9. Drug Release Study In Vitro. Drug release from cross-linked AA/Gelatin hydrogels was measured using the dissolution apparatus (Pharmatest; type PT-DT 7, Germany) and UV-Vis spectrophotometer (IRMECO, UV-Vis U2020). The weighed hydrogels disc was immersed in 500 mL dissolution medium at 37°C and dissolution medium was stirred at a rate of 100 rpm for maintaining a uniform drug concentration in the medium. 0.05 M USP phosphate buffer solutions of pH 1.2, pH 5.5, and pH 7.5 were used for dissolution medium. The determination of pheniramine maleate released was carried out at λ_{max} 265.6 with readings up to 12 hrs. With each sampling 5 mL solution was taken for UV analysis and solution was changed with fresh USP phosphate buffer solution [28, 29].

2.9.1. Analysis of Drug Release Pattern. Release of the solute from the cross-linked structure is based on the swelling of polymers and rate of diffusion. To determine the release mechanism, drug release from the cross-linked interpenetrating networks of AA/Gelatin hydrogels has been studied by zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. Equations (13), (14), (15), and (16) used for these models are given in the following.

Zero-order kinetics [30] is as follows:

$$F_t = K_o t, \quad (13)$$

where F indicates the fraction of drug release in time t and K_o is the zero-order release constant.

First-order kinetics [31] is as follows:

$$\ln(1 - F) = -K_1 t, \quad (14)$$

where F shows the fraction of drug release in time t and K_1 is the first-order release constant.

Higuchi model [22] is as follows:

$$F = K_2 t^{1/2}, \quad (15)$$

where F represents the fraction of drug release in time t and K_2 is the Higuchi constant.

Korsmeyer-Peppas model [23] is as follows:

$$\frac{M_t}{M_\infty} = K_3 t^n. \quad (16)$$

Table 2: Equilibrium swelling ratio of AA/Gelatin hydrogels.

Sample codes	Feed composition (AA/Gelatin)	Degree of cross-linking (EGDMA) % W/W	pH of the solution			
			1.2	5.5	6.5	7.5
U_1	35.00/4.00	0.70	5.48	16.43	29.62	34.58
U_2	35.00/5.00	0.70	5.26	14.82	26.81	30.95
U_3	35.00/6.00	0.70	4.76	12.88	24.01	27.94
U_4	28.00/6.00	0.70	4.22	11.51	22.75	26.18
U_5	32.00/6.00	0.70	4.68	14.66	26.66	32.63
U_6	36.00/6.00	0.70	5.66	17.27	33.56	38.28
U_7	36.00/6.00	0.65	5.52	16.83	33.00	37.21
U_8	36.00/6.00	0.75	4.64	12.64	26.43	27.59
U_9	36.00/6.00	0.85	4.014	8.48	22.75	24.61

Here M_t is the mass of water absorbed at any time (t) or penetrant time (t), M_∞ is the amount of water at equilibrium or mass uptake at equilibrium, K_3 is the kinetic constant, and n is the exponent describing the swelling mechanism.

2.10. FTIR Spectroscopy. For FTIR spectroscopy using pestle and mortar, dried discs of hydrogel samples were powdered. Potassium bromide (Merck, IR spectroscopy grade) was mixed with powdered material in 1 : 100 proportions and dried at 40°C. By applying a pressure of 65 KN (pressure gauge, Shimadzu) for 2 minutes, the mixture was compressed to a semitransparent disc of 12 mm diameter. The FTIR spectrum over the wavelength range of 4500–500 cm^{-1} was recorded using FTIR spectrometer (FT-IR 8400 S, Shimadzu) [20, 24].

2.11. Scanning Electron Microscopy (SEM). The surface morphology of AA/Gelatin hydrogels was determined using a scanning electron microscope (Hitachi, S 3000 H, Japan). Hydrogel samples were mounted on an aluminium mount and sputtered with gold palladium. An accelerating voltage of 10 KV, having working distance of 10–25 mm, is used to scan samples [19, 20].

3. Results and Discussion

3.1. Effect of pH on Swelling and on Drug Release of AA/Gelatin Hydrogels. In order to determine the swelling behavior of the hydrogels, the pH of the medium and pKa values of the acidic component of the polymer play an important role. To attain efficient swelling, the pKa of the buffer components should be above the pKa of the gel carboxylic group. At this pKa, the buffer will accept protons and ionizes the gel. The swelling capacity for the synthesized hydrogels was determined by using buffer solutions of 0.05 M USP phosphate buffer solutions of pH 1.2, pH 5.5, pH 6.5, and pH 7.5. The ionization of carboxylic groups varies with pH of the immersion medium that results in great variation in swelling behavior of hydrogel as shown in Table 2. As the pH of the medium increases above the pKa values of the acidic component of the polymer, it starts swelling due to the ionization of the carboxyl groups. These results can be correlated to Ranjha et al. [19]. At higher pH, the hydrogels swell due to the ionic repulsion of protonated carboxylic groups and collapse at low pH because of influence of unprotonated carboxylic group. The ionized COO^- groups become COOH groups as the pH of the buffer solution decreases and the resulting neutralization of ionic groups causes the hydrogels to be precipitated. Similar results were investigated by Byun et al. [32]. Maximum swelling was obtained at pH 7.5. Most of the carboxylate groups are protonated under acidic pH (pH < 3), so the main anion-anion repulsive forces are eliminated and consequently swelling values are reduced. Some of the carboxylate groups are ionized at higher pH (pH > 4) and the electrostatic repulsion between $-COO^-$ groups results in enhancement of the swelling capacity. Table 2 indicates the effect of pH on equilibrium swelling ratio of the AA/Gelatin hydrogels.

The effect of pH on drug release behavior was investigated by immersing the pheniramine maleate loaded samples in solutions of different pH values (1.2, 6.5, and 7.5). It is observed that by increasing the pH of medium the drug release increased as shown in Table 3. At higher pH (7.5) the osmotic pressure inside the gel also causes maximum drug to release as compared to lower pH (1.2). Figure 3 represents the EGDMA cross-linked AA/Gelatin hydrogels.

3.2. Effect of Acrylic Acid Concentration on Swelling and on Drug Release of AA/Gelatin Hydrogels. To investigate the effect of monomeric composition on swelling and drug release, AA/Ge hydrogels of different monomeric concentrations were prepared using EGDMA as cross-linking agent (0.70 wt% of AA). Figure 4 shows the dynamic swelling behavior of different acrylic acid concentration. The pKa value of acrylic acid is 4.28; therefore, at pH less than 4, acrylic acid chains are in the collapsed state, thus reducing the swelling ratio. However, as the pH increases above 6 and 8, acrylic acid forms carboxylate ions, which cause repulsion between the networks, resulting in rapid increase in the swelling ratio. Similar observations were made by Sullad et al. [5]. In Table 2 the samples (U_4 to U_6) show the effect of monomer concentration on equilibrium swelling ratio, keeping polymer and cross-linker concentrations constant. It is investigated that drug release and swelling of gel increased with increase of acrylic acid concentration due to availability of more carboxylic groups of acrylic acid for ionization and

Table 3: Amount of pheniramine maleate loaded and released.

Sample codes	Amount of pheniramine maleate loaded (g/g of dry gel)			Amount of pheniramine maleate released (%) (pH of the solution)		
	By swelling	By weight	By extraction	1.2	5.5	7.5
U_4	0.069	0.066	0.068	25.53	52.67	71.01
U_5	0.073	0.071	0.075	27.81	56.92	76.54
U_6	0.077	0.075	0.079	29.73	62.45	80.55
U_7	0.081	0.079	0.082	30.37	67.76	82.83
U_8	0.078	0.075	0.071	22.28	54.29	74.45
U_9	0.071	0.069	0.066	20.09	50.62	69.59

Figure 3: EGDMA cross-linked AA/Gelatin hydrogels.

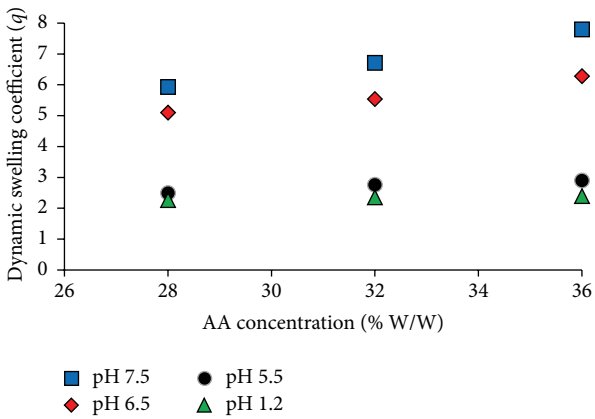


Figure 4: Dynamic swelling coefficient of AA/Gelatin hydrogels with different concentration of acrylic acid (28, 32, and 36 g) using EGDMA as cross-linking agent (0.7%) of acrylic acid in 0.05 M USP phosphate buffer solutions of different pH values at 37°C.

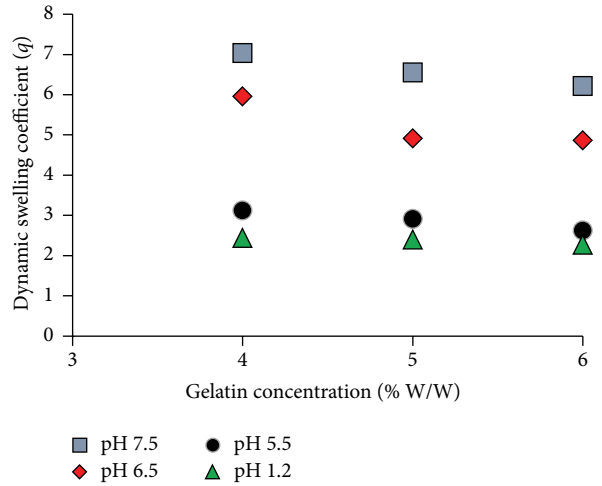


Figure 5: Dynamic swelling coefficient of AA/Gelatin hydrogels with different concentration of gelatin (4.0, 5.0, and 6.0 gm) using EGDMA as cross-linking agent (0.7%) of acrylic acid in 0.05 M USP phosphate buffer solutions of different pH values at 37°C.

electrostatic repulsion along the chain takes place that causes an expansion of the originally coiled molecules.

In order to investigate the effect of acrylic acid concentration on release of the drug, release study was carried out at pH 1.2, pH 5.5, and pH 7.5 for 12 hrs. The effects of acrylic acid concentration on release of drug from hydrogels have been shown in Figure 7. In phosphate buffer at pH 7.5, the amount of drug released from hydrogels was significantly higher than at pH 1.2 and pH 5.5. The swelling of AA/Ge hydrogels increased when the pH of the medium changed from lower to higher. From the results it was observed that increase in the concentration of AA leads to the increased percent drug release. Table 3 indicates the amount of drug loaded and released.

3.3. Effect of Gelatin Concentration on Swelling of AA/Gelatin Hydrogels. Three formulations of AA/Ge hydrogels with varying concentration of gelatin (4.0 g, 5.0 g, and 6.0 g) keeping acrylic acid and EGDMA concentration constant (0.70% of AA) were synthesized and subjected to swelling studies in solutions of different pH values. Figure 5 shows the effect of gelatin concentration on dynamic swelling of these hydrogels. The numerical data showing effect of gelatin (U_1 to U_3) on swelling profile has been demonstrated in Table 2. The concentration of gelatin acts conversely on the swelling behavior as compared to acrylic acid content. The swelling coefficient of prepared hydrogels decreased with the increase in the concentration of gelatin. Below the PI (isoelectric pH) value, the gelatin chains remain protonated. As a result, the chains contain NH_3^+ ions, and the cationic repulsion between them could be responsible for their high swelling.

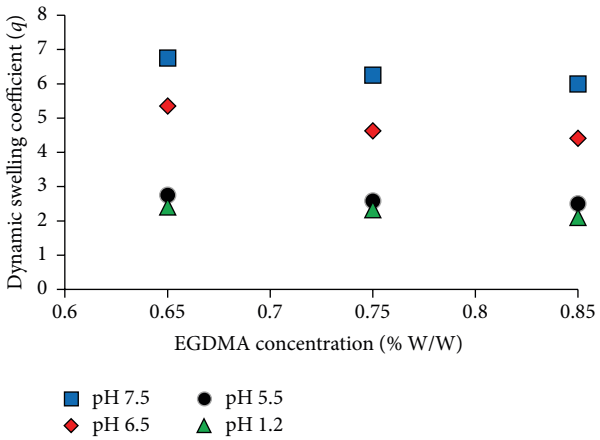


Figure 6: Dynamic swelling coefficient of AA/Gelatin hydrogels with different concentrations of EGDMA as cross-linking agent (0.65%, 0.75%, and 0.85% of acrylic acid) in 0.05 M USP phosphate buffer solutions of different pH values at 37°C.

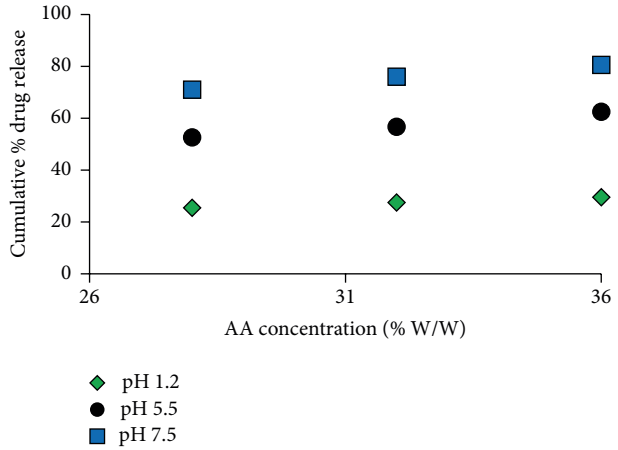


Figure 7: Cumulative % release of pheniramine maleate from AA/Gelatin hydrogels after 12 h using different concentrations of acrylic acid (28.0, 32.0, and 36.0 g) and EGDMA as cross-linking agent (0.7% of AA) at various pH values in 0.05 M USP phosphate buffer solutions.

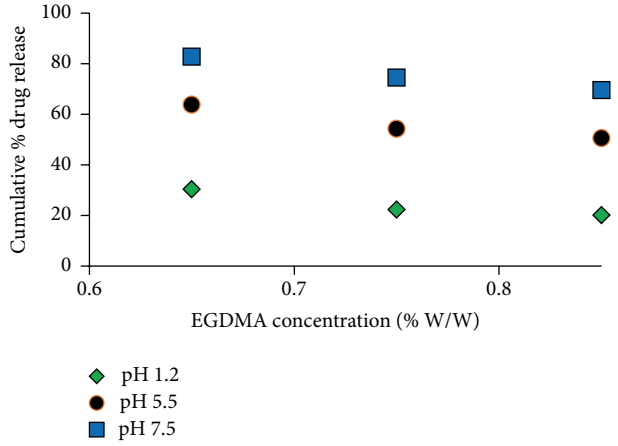


Figure 8: Cumulative % release of pheniramine maleate from AA/Gelatin hydrogels after 12 h using different concentrations of EGDMA as cross-linking agent (0.65%, 0.75%, and 0.85%) at various pH values in 0.05 M USP phosphate buffer solutions.

But the overall increase in gelatin contents has no significant effect on swelling because the percent swelling increased with increasing amounts of acrylic acid at all pH values, whereas increased gelatin content resulted in a decrease in percent swelling. Similar observations were made by Khan and Ranjha [22].

3.4. Effect of Degree of Cross-Linking on Swelling and on Drug Release of AA/Gelatin Hydrogels. The degree of swelling and drug release was also studied to be dependent on the concentration of cross-linking agent (EGDMA). In order to investigate the effect of EGDMA on swelling and release behavior of hydrogels, a series of three AA/Gelatin hydrogels (U_7–U_9) of different cross-linking agent concentration (0.65%, 0.75%, and 0.85% of AA) were prepared as shown in Table 2. In Figure 6 it was observed that swelling of gel decreased with increase of EGDMA concentration due to presence of more physical entanglements between hydrogels. The influence of increasing cross-linking can be described by decrease in mesh size of network. High cross-linked polymers are less acidic because carboxylate groups are concealed and higher cross-linking ratio reduces the process of ionization. It was observed that, at higher concentration of cross-linker, the relaxation of polymer chain decreased which is responsible for the less swelling of hydrogel. Same results were found by Shah et al. [23].

Drug release studies were performed in buffer solutions of different pH values (1.2, 5.5, and 7.5). The results from the study demonstrated that increase in EGDMA concentration will result in decrease in drug release % age due to the tighter hydrogel structure as shown in Table 3. Same observations were reported by Singh et al. [33]. Figure 8 indicates the effect of EGDMA concentration on cumulative % drug release in buffer solutions of various pH values.

3.5. Sol-Gel Analysis. To determine the uncross-linked fraction of the polymer in the hydrogel, sol-gel analysis was performed. It was found that gel fraction of hydrogels increased along with increased concentration of acrylic acid, gelatin, and cross-linker as shown in Table 4. Sol fraction of hydrogels was observed to decrease along the increased concentrations of gelatin, acrylic acid, and EGDMA. Dergunov et al. investigated the similar results [34]. Figures 9, 10, and 11 demonstrate the effect of gelatin concentration, AA concentration, and EGDMA concentration on gel fraction of hydrogel.

3.6. Porosity Measurement. From results in Table 4, it is observed that porosity increases by increasing the concentration of acrylic acid and gelatin due to increasing of viscosity of the hydrogel solution. Viscous solution efficiently prevents the bubbles from escaping from the solution that result in increase of porosity due to formation of interconnected channels. While increasing the EGDMA concentration porosity decreases due to increasing physical entanglement between

Table 4: Sol-gel fraction analysis and porosity measurement of different formulations of AA/Gelatin hydrogels.

Sample codes	Degree of cross-linking (EGDMA) % W/W	Gel fraction (%)	Sol fraction (%)	Porosity (%)
U_1	0.70	84.44	15.56	44.07
U_2	0.70	86.59	13.41	56.81
U_3	0.70	90.22	9.78	62.09
U_4	0.70	87.12	12.88	46.43
U_5	0.70	90.23	9.77	57.47
U_6	0.70	94.54	5.46	63.72
U_7	0.65	85.64	14.36	69.03
U_8	0.75	89.09	10.91	65.32
U_9	0.85	95.23	4.77	62.30

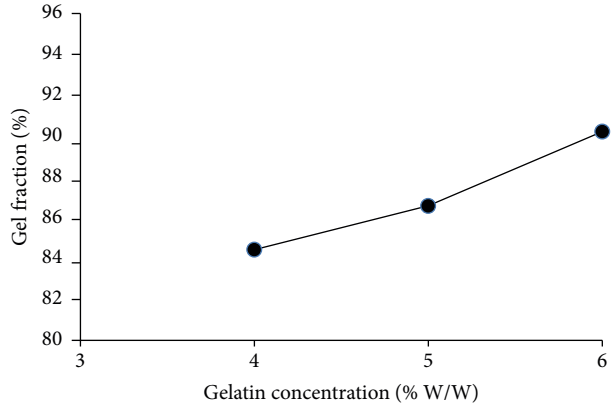


Figure 9: Effect of gelatin concentration on gel fraction of AA/Gelatin hydrogels.

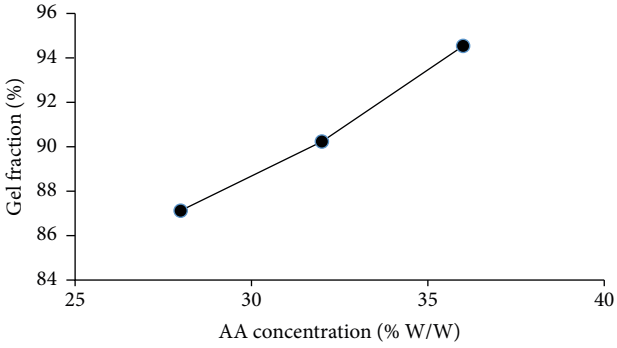


Figure 10: Effect of acrylic acid concentration on gel fraction of AA/Gelatin hydrogels.

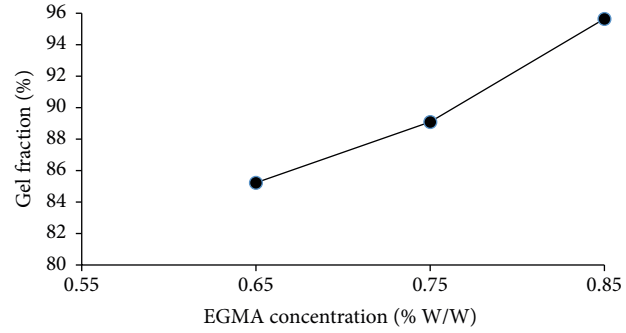


Figure 11: Effect of cross-linking agent concentration (EGDMA) on gel fraction of AA/Gelatin hydrogels.

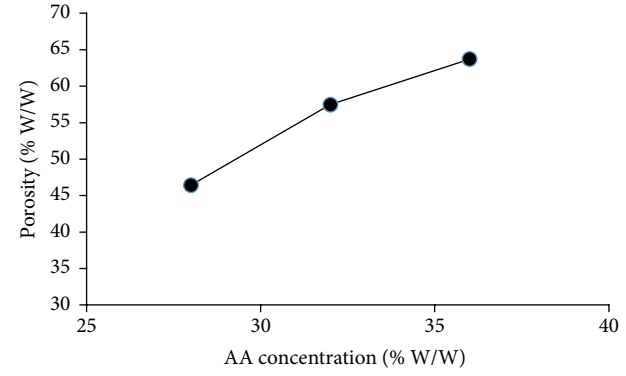


Figure 12: Effect of gelatin concentration on porosity of AA/Gelatin hydrogels.

acrylic acid and gelatin shown in Figures 12, 13, and 14. Increase in cross-linking agent concentration results in increase in entanglement between monomer and polymer which results in decreased porosity. Yin et al. observed the similar results [35].

3.7. Diffusion Coefficient of Polymers (D). During membrane permeation method or sorption and desorption phenomenon Fick's law of diffusion was used. To measure solute diffusion into hydrogel, diffusion coefficient is applied indirectly. Table 5 indicates that diffusion coefficient decreased with the increasing of acrylic acid concentration and gelatin concentration because swelling of polymer increases as the concentration of AA increases. Diffusion coefficient increased with increasing of cross-linking agent concentration.

3.8. Molecular Weight between Cross-Links (M_c) and Solvent Interaction Parameters (χ). It was observed that increase in the concentration of acrylic acid results in increased values of molecular weight between cross-links (M_c). Due to presence

Table 5: Flory-Huggins network parameters of AA/Gelatin hydrogel.

Sample codes	Degree of cross-linking (EGDMA) wt %	$V_{2,s}$	χ	M_c	M_r	Q	$D \times 10^{-5}$ ($cm^2 sec^{-1}$)
U_1	0.70	0.059	−0.520	949.945	106.527	8.917	0.2289
U_2	0.70	0.064	−0.522	856.917	113.876	7.524	0.3038
U_3	0.70	0.065	−0.522	858.763	120.869	7.105	0.3526
U_4	0.70	0.064	−0.527	918.091	130.723	7.023	0.3316
U_5	0.70	0.053	−0.518	1245.87	124.633	9.996	0.1559
U_6	0.70	0.052	−0.515	1291.54	119.702	10.79	0.1487
U_7	0.65	0.049	−0.516	1483.83	120.811	12.28	0.1301
U_8	0.75	0.066	−0.523	1031.95	120.878	8.532	0.2547
U_9	0.85	0.067	−0.523	804.943	120.949	6.659	0.4384

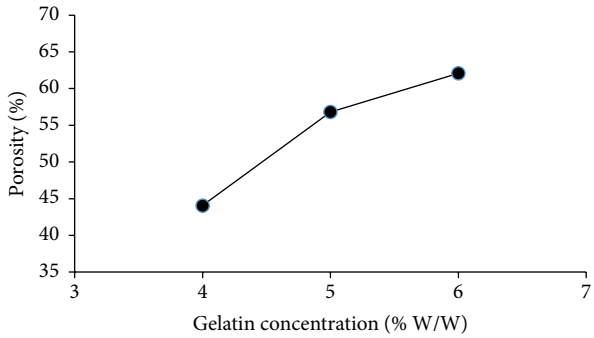


Figure 13: Effect of acrylic acid concentration on porosity of AA/Gelatin hydrogels.

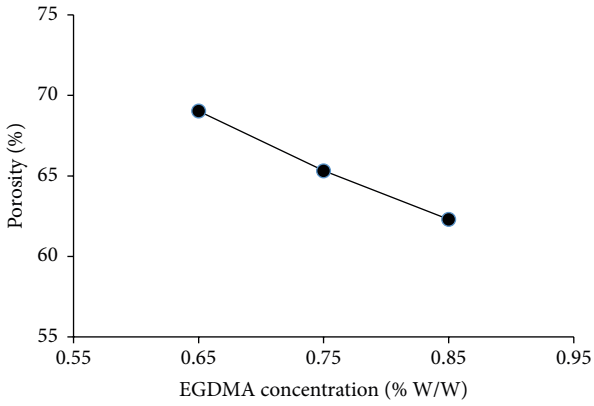


Figure 14: Effect of cross-linking agent (EGDMA) concentration on porosity of AA/Gelatin hydrogels.

of carboxylic groups in polymer chain of acrylic acid, higher swelling of polymer was reported. Cross-linked density (N) is also related to the values of acrylic acid and average molecular weight between cross-links as shown in Table 5. To check the effect of solvent interaction between polymer and solvent, the solvent interaction parameters (χ) were studied. In Table 5 it was reported that greater values of (χ) lead to the weaker interaction between polymer and solvent [36].

3.9. Drug Release Kinetics. Analysis of drug release pattern was studied in phosphate buffer solutions pH 1.2, pH 5.5, and pH 7.5. The data obtained was fitted in zero-order, first-order, Korsmeyer-Peppas, and Higuchi models to evaluate the drug release pattern as given in Tables 6 and 7. The method that best fits the release data was evaluated by the regression coefficient (r). A criterion for selecting the most appropriate model was based on the ideal fit indicated by the values of regression coefficient (r) near to 1. Values of regression coefficient (r) for zero-order and first-order models obtained from drug loaded AA/Ge hydrogels at varying content of acrylic acid and degree of cross-linking are given in Tables 6 and 7. For most of samples, the values of regression coefficient (r) obtained for zero-order release rate constants were found higher than those of first-order release rate constants. It is therefore attributed to the fact that drug release from the samples of varying monomeric compositions and degree of cross-linking are according to zero-order release. In Higuchi model the value of regression coefficient (r) at different monomeric composition and at different degree of cross-linking indicated that the drug release mechanism is diffusion controlled. Figures 15, 16, and 17 indicate the release profile of pheniramine maleate following zero-order release, first-order release, and Higuchi model from AA/Gelatin hydrogels (sample U_7). Effects of monomer concentration and degree of cross-linking on release exponent (n) values are given in Tables 8 and 9, respectively. All samples showed non-Fickian behavior [37].

4. FTIR Spectroscopy

In order to assess the functional groups in monomer and polymer (AA and Ge) and to confirm the formation of cross-linked networks from the hydrogels with EGDMA, samples were analyzed by Fourier transform infrared spectroscopy (FTIR). The FTIR spectra of gelatin, acrylic acid, AA/Gelatin hydrogel, AA/Gelatin drug loaded hydrogel, and pheniramine maleate are shown in Figure 18. In the FTIR spectra of gelatin as shown in Figure 18 (A), the absorption peak at 3321 cm^{-1} is attributed to N–H stretching. Peaks at 3060 and 2948 cm^{-1} are attributed to C–H stretching. The peak at 1664 cm^{-1} refers to the absorption band of amide I and at 1539 cm^{-1} shows the absorption band of amide II [38]. The FTIR spectra of pure AA are shown in Figure 18 (B). The absorption peak of acrylic acid at 3425 cm^{-1} corresponds to O–H stretching, 1691 cm^{-1} is for C=O stretching, 1573 cm^{-1}

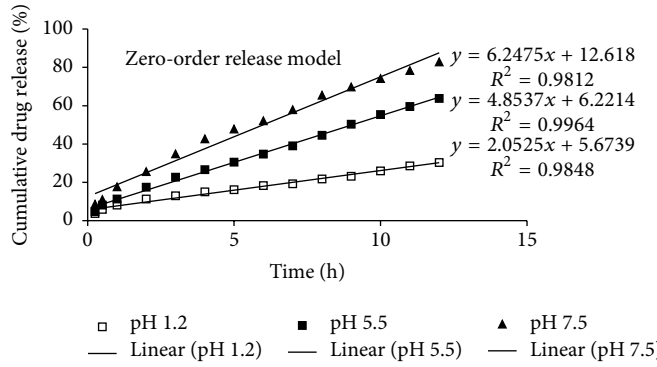


Figure 15: % Cumulative pheniramine maleate release versus time (zero-order release) from EGDMA cross-linked AA/Gelatin hydrogels.

Table 6: Effect of different concentrations of acrylic acid on drug release kinetics of AA/Gelatin hydrogels in solutions of different pH values using EGDMA as cross-linking agent (0.70% w/w).

Sample codes	AA contents (%)	pH	Zero-order kinetics		First-order kinetics		Higuchi model	
			K_o (h^{-1})	r	K_1 (h^{-1})	r	K_2 (h^{-1})	r
U_4	28	1.2	1.75	0.991	0.020	0.991	0.068	0.958
		5.5	3.945	0.997	0.057	0.990	0.157	0.958
		7.5	5.127	0.991	0.092	0.976	0.204	0.959
U_5	32	1.2	2.076	0.992	0.024	0.986	0.081	0.930
		5.5	4.149	0.994	0.063	0.995	0.167	0.979
		7.5	5.177	0.994	0.099	0.951	0.206	0.950
U_6	36	1.2	1.948	0.985	0.023	0.980	0.077	0.942
		5.5	4.401	0.995	0.071	0.986	0.177	0.971
		7.5	5.679	0.985	0.119	0.987	0.232	0.997

Table 7: Effect of degree of cross-linking on drug release kinetics of AA/Gelatin hydrogels in solutions of different pH values.

Sample codes	EGDMA contents (%)	pH	Zero-order kinetics		First-order kinetics		Higuchi model	
			K_o (h^{-1})	r	K_1 (h^{-1})	r	K_2 (h^{-1})	r
U_7	0.65	1.2	2.052	0.984	0.025	0.987	0.0833	0.976
		5.5	4.853	0.996	0.077	0.984	0.195	0.971
		7.5	6.247	0.981	0.134	0.988	0.083	0.976
U_8	0.75	1.2	1.423	0.980	0.016	0.984	0.057	0.973
		5.5	4.176	0.990	0.062	0.995	0.169	0.983
		7.5	5.121	0.989	0.097	0.966	0.211	0.993
U_9	0.85	1.2	1.412	0.977	0.016	0.983	0.058	0.993
		5.5	4.019	0.997	0.056	0.994	0.160	0.963
		7.5	5.251	0.992	0.090	0.989	0.212	0.978

is attributed to C=O bending in –COOH, and 1319 cm^{-1} is for C–C stretching. The FTIR spectrum of AA/Ge hydrogel is different than the spectra of pure Ge and AA as shown in Figure 18 (C). For AA/Ge hydrogel without drug, the vibration absorption peaks at 3060 and 2948 cm^{-1} have weakened or disappeared after chemical cross-linking with EGDMA. This weakening of absorption peak and change in C–C stretching in between 1200 and 1350 confirms the formation of hydrogel. From the FTIR spectra of drug loaded hydrogel shown in Figure 18 (D), it is clear that there is no prominent shift in the major peaks, which shows that there is no chemical interaction between polymers and drug loaded in hydrogel. Figure 18 (E) indicates the FTIR spectra of pure drug.

4.1. Scanning Electron Microscopy (SEM). The morphology of the interpenetrating hydrogels was studied by surface electron microscopy. Figures 19(a) and 19(b) indicate the surface morphology of unloaded and AA/Gelatin hydrogel sample loaded with pheniramine maleate. It was observed

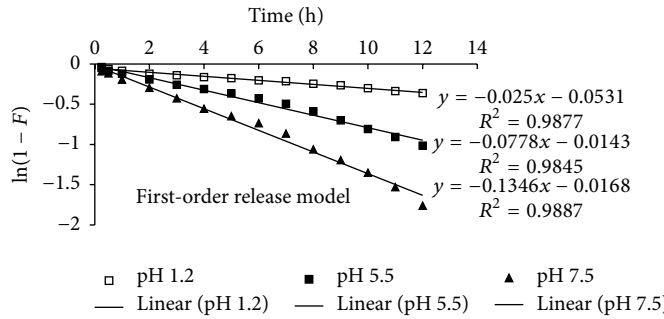


Figure 16: % log cumulative pheniramine maleate release (1 − F) versus time (first-order release) from EGDMA cross-linked AA/Gelatin hydrogels.

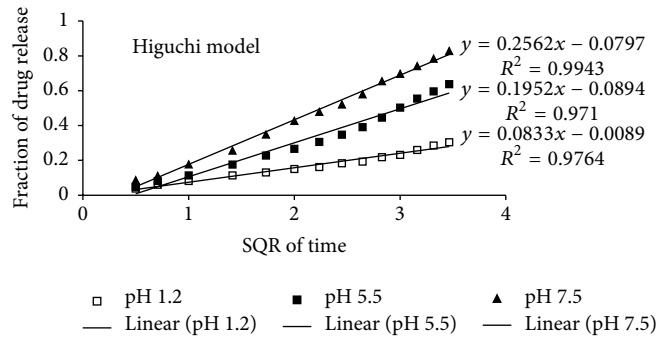


Figure 17: % cumulative pheniramine maleate release versus Sq. Rt. time (Higuchi model) from EGDMA cross-linked AA/Gelatin hydrogels.

Table 8: Effect of different concentration of acrylic acid on drug release mechanism of AA/Gelatin hydrogels in solutions of different pH values using EGDMA as cross-linking agent (0.7% of acrylic acid).

Sample codes	AA contents (%)	pH	Release exponent (n)	r	Order of release
U_4	28	1.2	0.7162	0.995	Non-Fickian
		5.5	0.9463	0.997	Non-Fickian
		7.5	0.9257	0.991	Non-Fickian
U_5	32	1.2	0.7532	0.994	Non-Fickian
		5.5	0.9832	0.994	Non-Fickian
		7.5	0.9573	0.992	Non-Fickian
U_6	36	1.2	0.7261	0.987	Non-Fickian
		5.5	0.8643	0.990	Non-Fickian
		7.5	0.8252	0.985	Non-Fickian

Table 9: Effect of degree of cross-linking on drug release mechanism of AA/Gelatin hydrogels in solutions of different pH values.

Sample codes	EGDMA contents (%)	pH	Release exponent (n)	r	Order of release
U_7	0.65	1.2	0.6242	0.981	Non-Fickian
		5.5	0.8345	0.996	Non-Fickian
		7.5	0.7752	0.984	Non-Fickian
U_8	0.75	1.2	0.7529	0.978	Non-Fickian
		5.5	0.8673	0.990	Non-Fickian
		7.5	0.7868	0.987	Non-Fickian
U_9	0.85	1.2	0.7591	0.992	Non-Fickian
		5.5	0.8765	0.994	Non-Fickian
		7.5	0.7847	0.979	Non-Fickian

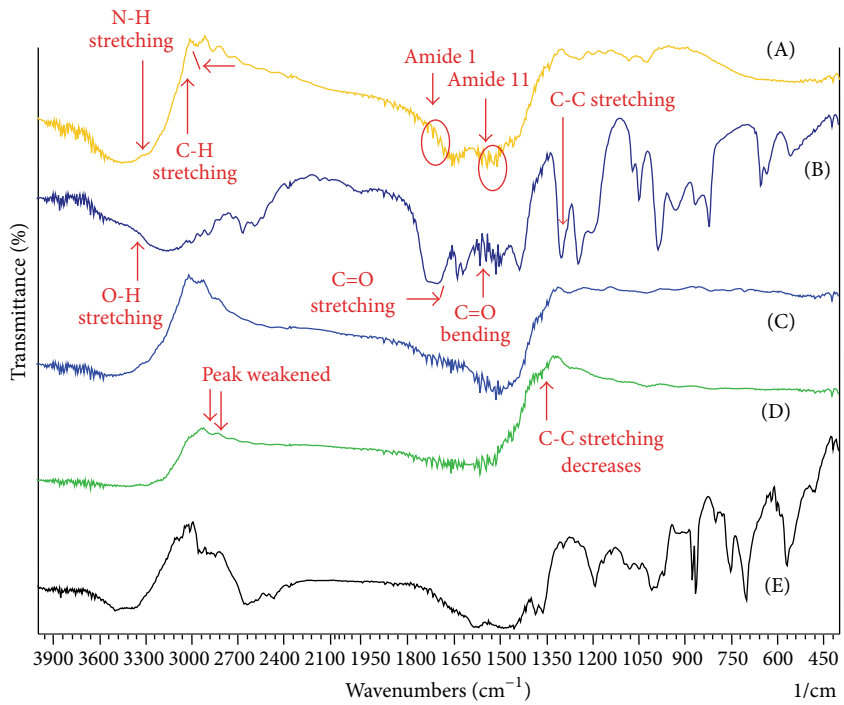
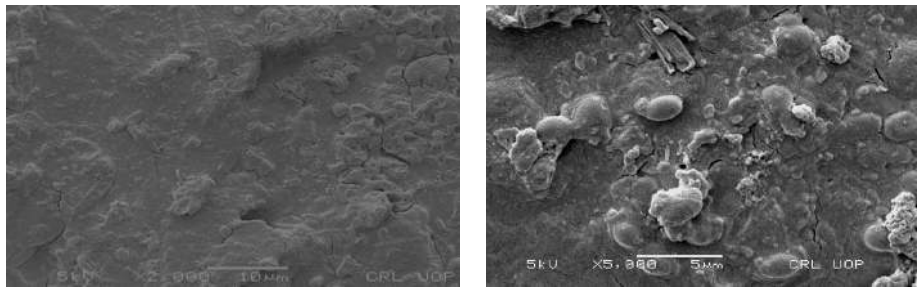


Figure 18: FTIR spectra of (A) pure gelatin, (B) acrylic acid, (C) unloaded AA/Gelatin hydrogel, (D) loaded AA/Gelatin hydrogel, and (E) pheniramine maleate.



(a) Unloaded (b) Loaded

Figure 19: Surface electron micrographs (SEM) of AA/Gelatin hydrogels of sample U_6: (a) magnification ×2000, (b) magnification ×5000.

that SEM graphs of the hydrogel sample contain pores, which facilitate the adherence of the drug into the interpenetrating network of the hydrogel. Figure 19(b) shows the dispersed white particles at high magnification throughout the hydrogel network which refers to the model drug loaded in these hydrogel samples.

5. Conclusion

In present study, pH sensitive cross-linked AA/Gelatin hydrogels were prepared by free radical polymerization using ethylene glycol dimethacrylate (EGDMA) as cross-linking agent as a carrier for water soluble drugs. To investigate the pH sensitive behavior, hydrogel samples were subjected to swelling experiments in USP phosphate buffer solutions of various pH values. Swelling of polymeric network was found affected by composition and pH of swelling medium. The swelling ratios of these hydrogels showed a regular variation with changing concentrations of the monomer, polymer, and cross-linking agent. The swelling ratios were found to decrease as the polymer and cross-linker concentration increased in the composition of samples. While with the increase of acrylic acid contents in the composition, the dynamic and equilibrium swelling ratio increased due to the electrostatic repulsion between carboxylate ions (COO^-) which leads to chains repulsion and in turn swelling of the network at higher pH values. The swelling and release of the drug decreased with increasing concentration of cross-linking agent due to the tighter hydrogel structure. The drug release from hydrogel is dependent upon the composition as well as the pH of swelling medium. In phosphate buffer of pH 7.5 the rate of drug release was faster as compared to other pH values. Gel fraction of the samples increased with the increasing concentration of monomer, polymer, and cross-linking

agent concentration. Porosity of the hydrogels increased with increasing contents of the acrylic acid and gelatin, while it decreases as the contents of EGDMA increased in the gels. Drug release mechanism was found to be non-Fickian for AA/Gelatin hydrogels. It was concluded that these polymeric networks are pH sensitive and are able to respond to the environmental conditions.

Conflict of Interests

The authors declare that they have no conflict of interests.

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