Journal of Macromolecular Science, Part A
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597274

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To cite this Article Abou Taleb, Manal F. , Ismail, Sahar A. and El-Kelesh, Nabil A.(2009) 'Radiation Synthesis and Characterization of Polyvinyl Alcohol/Methacrylic Acid-Gelatin Hydrogel for Vitro Drug Delivery', Journal of Macromolecular Science, Part A, 46: 2, 170 — 178
To link to this Article: DOI: 10.1080/10601320802594808
URL: http://dx.doi.org/10.1080/10601320802594808

Journal of Macromolecular Science®, Part A: Pure and Applied Chemistry (2009) **46**, 170–178

ISSN: 1060-1325 print / 1520-5738 online
DOI: 10.1080/10601320802594808

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Radiation Synthesis and Characterization of Polyvinyl Alcohol/Methacrylic Acid–Gelatin Hydrogel for Vitro Drug Delivery

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Received June 2008 and accepted July 2008

This paper describes the use of gamma radiation Co^{60} source as crosslinker for the preparation of gelatin based pharmaceutical hydrogels. Glutaraldehyde (GLU) (0.5% v/v) was incorporated after irradiation to crosslink the gelatin chains. Several samples of hydrogels P(PVA/MAA) were prepared by varying the ratio of PVA and MAA monomer. The swelling behavior of these hydrogels was investigated as a function of doses, concentration, copolymer composition (PVA:MAA ratio) and pH of the immersion medium. It was found that the swelling of test hydrogels was larger (8) in the alkaline medium than in the acid medium (3) and at pH 5.3 was the smallest (3). The characterizations of the hydrogels were performed by FTIR, SEM to evaluate the relationship of the structure and morphology of the hydrogels. The adsorption isotherm studies by batching techniques under the effect of different initial feed concentrations of drugs and MAA content of the adsorbent hydrogels will be investigated. Furthermore, for the evaluation of the pH effect on drug release from the prepared hydrogels, we studied chlortetracycline HCl and amoxicillin trihydrate release profiles at pH 2.2, 5.0 and 7.5. The pH-sensitivity of the novel polyelectrolyte complex would make an interesting drug delivery system.

Keywords: Hydrogel, gamma irradiation, swelling behavior, loading, drug release

1 Introduction

Many synthetic and naturally derived materials have been reported to form well-characterized hydrogels. Since natural polymers possess better biocompatibility, biodegradability, non toxicity and easily modified ability than various synthetic materials, more and more researches have focused on natural polymer-based hydrogels (1, 2) using polysaccharides, cellulose derivatives and proteins as drug carrier.

Polyvinyl alcohol PVA has several useful properties including non-toxicity, biocompatibility, high hydrophilic, fiber/film forming ability, and the chemical and mechanical resistance. It has been widely commercialized and studied in the chemical and medical industries for the productions of fibers, films, coatings, cosmetics, pharmaceuticals, and so on (3). PVA hydrogels are non-toxic, noncarcinogenic, have good biocompatibility, and have desirable physical properties such as rubbery nature and high degree of swelling in water (4). PVA must be crosslinked if it is to be used in biodegradable materials. PVA hydrogel has excellent transparency and is smooth as membrane, and it is also biologically inactive and biocompatible. It has attracted much attention to be widely used as a good material for temporary skin covers or burn dressings (5).

Gelatin is a biopolymer and is not found in nature, but it can be produced by acid or base hydrolysis of collagen. Moreover, due to the large number of functional side groups, gelatin readily undergoes chemical cross-linking, which is very important for its use as a biomaterial. These advantages made gelatin-based controlled release systems possess diverse applications in fields ranging from tissue engineering (6) to drug delivery and gene therapy (7). Gelatin is widely used for wound dressing and drug delivery because of its biocompatibility and biodegradability (8–13). However, the main limitation of gelatin for the preparation of sustained release hydrogel systems arises from its rapid dissolution in aqueous environments leading to fast drug release profiles at body temperature. In order to overcome this problem, chemical cross-linking procedures which form scarcely or non-soluble products and slow down the release of the loaded drug have been considered. Glutaraldehyde and formaldehyde were the most

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common cross-linking agents used in various gelatin-based biomaterial formulations due to its high efficiency of collageneous material stabilization (14, 15).

Irradiation of gelatin using gamma ray was first studied many years ago and it was reported that gelatin hydrogels as a biomaterials impregnated with the copolymer network structure can be functionalized as a drug delivery system (16, 17).

In the present work, γ-ray as a source of initiation and crosslinking was used to graft copolymerization of PVA and MAA onto gelatin to produce PVA/MAA/gelatin hydrogels which can be used as antibiotic drug carrier. The drug delivery will be estimated using Chlortetracycline HCl and Amoxicillin trihydrate. The effects of composition of the hydrogel structure on release of the amoxicillin and Chlortetracycline HCl drugs and their path ways have been followed and focused on well. Chlortetracycline HCl is mainly used in the treatment of Chlamydia, Vibrocholera, Acnc vulgaris, Gonorrhea, Syphilis, Prostitis and Sinusitis with a dosage 250 and 500 mg (three times per day). Amoxicillin (a-amino-hydroxybenzylpenicillin) was a semisynthetic, orally absorbed, broad-spectrum antibiotic, and treats bacterial infections caused by susceptible microorganisms. It is now widely used in a standard eradication treatment of gastric Helicobacter pylori infection combined with a second antibiotic and an acid-suppressing agent (18–20). Amoxicillin is stable in the presence of gastric acid and is rapidly absorbed after oral administration.

2 Experimental

2.1 Materials

Gelatin (Sigma–Aldrich Company), polyvinyl alcohol (PVA), and Methacrylic acid (MAA) of purity 99% (Merck, Germany) were used as received. Deionized water was used to prepare all hydrogels in this study. Chlortetracycline HCl (Sigma Chemical Co. USA) and Amoxicillin (Glaxo Smith Kline Co., British) were used in drug delivery. Structures of the drugs are shown below:

2.2 Hydrogel Preparation

PVA/MAA/gelatin copolymer hydrogels were prepared by gamma irradiation technique -induced copolymerization of aqueous solutions of 10 ml gelatin (3%) with 10 ml of monomer composition mixture as 2.5 mol% PVA (10 wt%) with 5 mol% of MAA (A_1) and other composition (A_2) with MAA 7.5 mol%. Each reaction mixture was purged with nitrogen for 8–10 min to expel oxygen from the reaction mixture and then transferred into glass tubes. The glass tubes were then sealed with Para film and placed in the gamma chamber. Polymerization was carried out at 2, 4, 5, 10 and 20 kGy, at a dose rate of 1.7 Gy/sec. After irradiation, samples were removed from the glass tubes and then immersed in glutaraldehyde (0.5% v/v) solution for 6 h. The samples thus obtained were washed thoroughly with distilled water for 1 week to remove the unreacted monomers/crosslinker.

2.3 Characterization

2.3.1. *FTIR spectroscopic analysis*

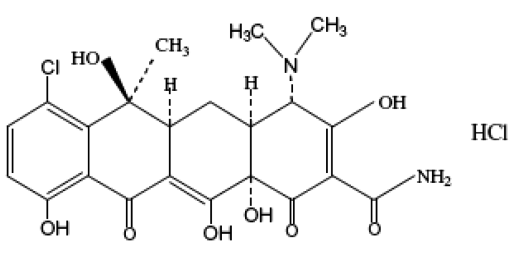
Spectra were recorded on Mattson 1000, Unicom infrared spectrophotometer Cambridge, England in the range from 400–4000 cm^{-1} using KBr pellets.

2.3.2. *Thermogravimetric Analysis*

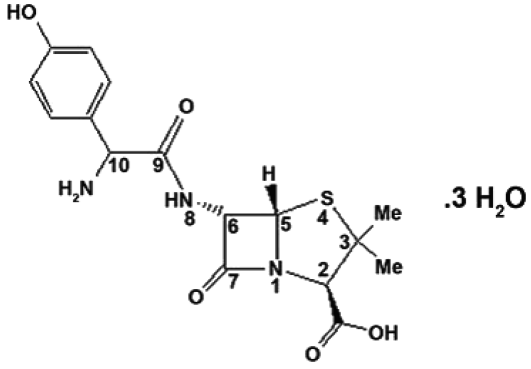
Thermogravimetric analyzer Shimadzu TGA system of Type TGA-50 was used in this study. The temperature range was from ambient to 500°C at heating rate of 10°C/min in nitrogen atmosphere 20 ml/min.

2.4 Surface Morphology (SEM)

For morphological characterization, hydrogels after swelling (equilibrium) in water were freeze-dried using a freeze drier (Christ, Germany, Alpha 1–2) at −52°C for



Chlortetracycline Hydrochloride



Amoxicillin trihydrate

6 h. Transverse sections were cut from freeze-dried film samples using a cold knife. Samples were then examined with a Jeol JSM-5400 scanning electron microscopy (SEM) (JEOL, Tokyo, Japan).

2.5 Water Uptake

Water uptake studies were carried out by immersing the dry prepared samples in a medium of varying pH, i.e., 0.2 M (citric acid/trisodium citrate) and 0.2 M (sodium dihydrogen phosphate/disodium hydrogen phosphate) were used to prepare buffer solution ranged from 3 to 5 and 6 to 8, respectively. 0.2 M HCl was used to prepare solutions of pH 1and 2 at 37 ± 1°C. Swollen samples were then taken out at regular intervals; the surface water was removed by filter paper and weighed again. The percent water uptake was calculated using the equation:

$$\text{Water uptake Percent} = (W - W_0)/W_0 \times 100 \quad (1)$$

Where W is weight of the swollen sample and W_0 is the weight of the dried sample the experiment was carried out until equilibrium was attained.

2.6 Measures of Water Retention by the Hydrogels

As a part of the characterization study, the water retaining capacity of hydrogels was investigated as a function of time at 30°C. Pieces of swollen hydrogels were put on Petri plates. The highly swollen hydrogels were weighed and the decreases in their weights measured as a function of time by gravimetry. The values of water retention (WR) were obtained by the following equation:

$$WR(\%) = (M_s - M_t)/M_s \times 100 \quad (2)$$

where M_s is the initial weight of the hydrogel in water and M_t is its weight after loss of water at each time

2.7 Drug Loading to the Polymer Matrix

The loading of a drug such as; amoxicillin trihydrate and chlorotetracycline hydrochloride onto hydrogels was carried out by swelling equilibrium method. The hydrogel was allowed to swell in the drug solution of known concentration for 24 h at 37°C and than dried to obtain the release device. The concentration of the rejected solution was measured to calculate percent entrapment of the drug in the polymer matrix.

2.8 Drug Release from Polymer Matrix

In vitro release studies of the drug were performed by placing the dried PVA/MAA/Gelatin hydrogels loaded with drug in definite volume of releasing medium at 37°C. The release studies for drugs were done in pH 2.2 buffer and pH 7.4 buffers. At a predetermined time, one milliliter sample was withdrawn to follow the release process. The concentration of amoxicillin trihydrate and chlorotetracyclin hydrochloride drugs was measured by UV spectroscopy (UNICAM UV/Vis Spectrometer. 1000 Model). After the complete release; the hydrogels were immersed in pH 3.0 buffer solutions and then, 0.1mol/l, HCl for 2 days to remove remaining drug may be loaded in the gel system.

The total uncertainly for all experiments ranged from 3 to 5%.

3 Results and Discussion

Although crosslinking of gelatin by gamma irradiation has been reported in the literature (21) in the present study leaching of gelatin was observed after irradiation, which was further confirmed by a ninhydrin test. For stabilization of the gelatin inside the polymer chains, glutaraldehyde was employed as a crosslinker.

3.1 Effect of Irradiation Doses in Swelling

The influence of irradiation dose on the water uptake percentage for the hydrogels prepared at different compositions, for PVA/MAA/gelatin hydrogels is shown in Figure 1. Meanwhile, the S_{max} in PVA/MAA/gelatin increases with an irradiation dose up to 4 kGy and thereafter it decreases. This phenomenon is attributed to the enhancement of the crosslinking process at higher doses resulting in lowering the free volume space where a gel network will be a denser network. Such a network may provide less "free volume" for water molecules to move and, as a consequence, the diffusion and swelling properties are hindered by a network structure formation. Similar behavior has been reported by Dergunov et al. (22) and Dipti et al. (23).

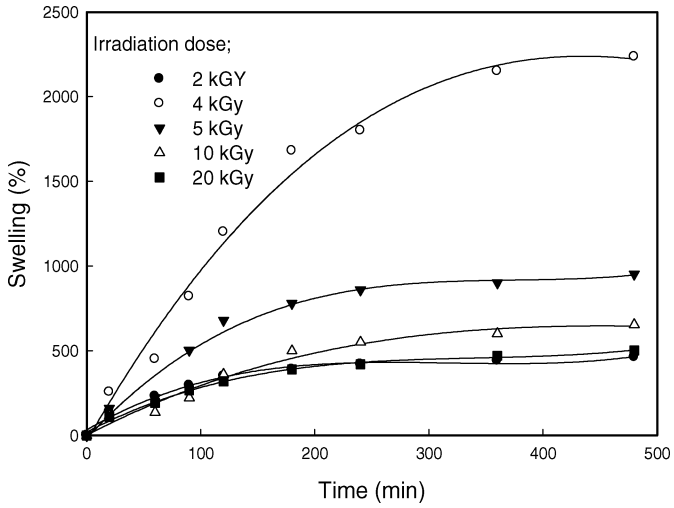


Fig. 1. Effect of irradiation dose on the swelling behavior of PVA/MAA/gelatin hydrogel(A_1) at mixture monomer (2.5/5 mol%) in phosphate buffer (pH 7).

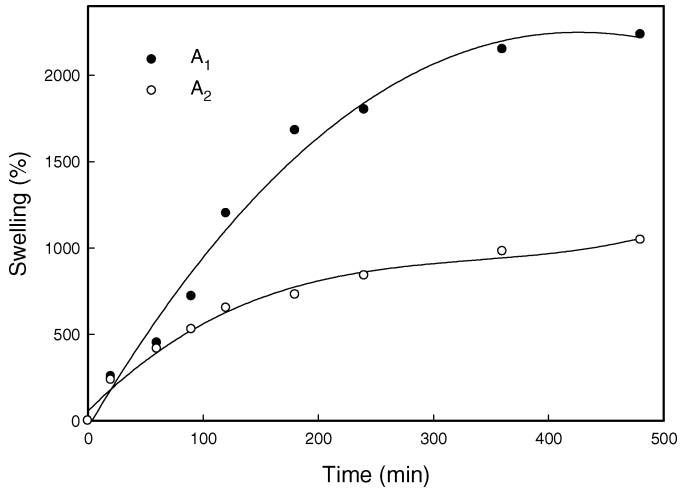


Fig. 2. Effect of monomer concentration on the swelling behavior in phosphate buffer (pH 7) at irradiation dose; 4 kGy.

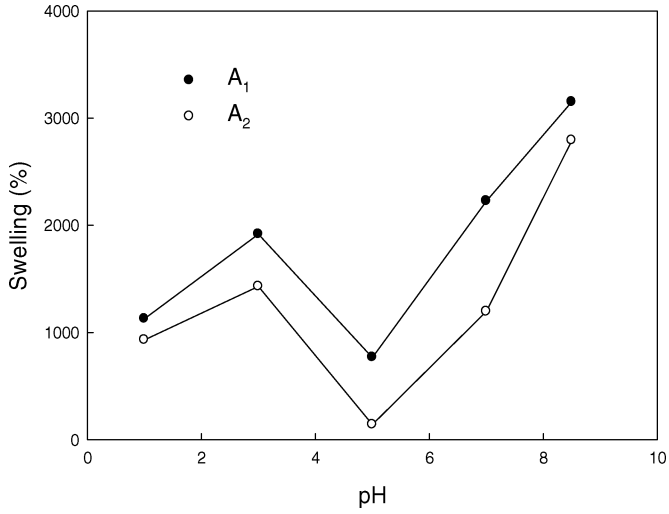


Fig. 3. Effect of pH on the swelling (%) for different PVA/MAA/gelatin composition at dose; 4 kGy.

One would expect a decrease in the swelling ratio with increasing dose; however, the increase observed at the beginning, from 2 to 4 kGy, could be due to the simultaneous degradation/crosslinking upon irradiation.

3.2 Effect of Monomer Concentration on Swelling

The influence of the swelling time on the equilibrium swelling for different PVA/MAA/gelatin hydrogels prepared at various comonomer compositions (A_1 and A_2) at pH 7 was investigated and was shown in Figure 2. As can be seen from this figure, swelling capabilities of all copolymer compositions are increased by increasing the time (min). The constant equilibrium swelling for two compositions was reached after 120 min. Furthermore, the results revealed that the increase in the MAA content in the initial comonomer feed solution (A_2) results in a hydrogel with a lower swelling behavior. The differences in the swelling behavior between A_1 and A_2 samples could be due to the loose and tight polymeric networks, respectively. In the A_2 samples, intermolecular hydrogen bonding between –COOH of MAA and -NH_2 of gelatin is expected, which might hinder the diffusion of water in the beginning due to the formation of a fine intermesh.

3.3 Effect of pH on the Equilibrium Swelling

The effect of equilibrium swelling behavior of PVA/MAA/gelatin hydrogels as a function of pH was studied and the results are presented in Figure 3. It can be seen that the swelling behavior of the produced copolymer is greatly influenced by its composition. In this system, a combination of attractive or repulsive electrostatic interactions and hydrogen bonding are the main reasons for existence of several phases observed in various environmental conditions.

PVA/MAA/gelatin hydrogels has both amine (gelatin backbone) and carboxylate (PMAA chains) as functional groups. Gelatin has an isoelectric point in the range of 4.0–5.0; below this value gelatin chains will be protonated (NH_3^+) and repulsion between them is responsible for higher water uptake (24, 25). PMAA contains carboxylic groups that become ionized at pH values above its pKa of 4.66.

Under acidic conditions, the swelling is controlled mainly by the amino group (NH_2) on the gelatin component. Therefore, it gets protonated and the increased charge density on the polymer should enhance the osmotic pressure inside the gel particles because of the NH_3^+ -NH_3^+ electrostatic repulsion. This osmotic pressure difference between the internal and external solution of the network is balanced by the swelling of the gel.

At pH range, 4–5 the majority of the base and acid groups are as NH_3^+ and COO^- or NH_2 and COOH forms, and therefore ionic interaction of NH_3^+ and COO^- species (ionic crosslinking) or hydrogen bonding between amine and carboxylic acid (and probably carboxamide groups) may lead to a kind of crosslinking followed by decreased swelling.

At pH above pKa (>5), the carboxylic acid groups become ionized and the electrostatic repulsive force between the charged sites (COO^-) causes an increase in swelling. Either protonated (NH_3^+) or deprotonated (COO^-) groups increase charge density on the polymer causing an enhancement of the osmotic pressure inside the gel particles because of the NH_3^+– $NH^+\hat{u}_3$ or COO^--COO^- electrostatic repulsion. This osmotic pressure difference between the internal and external solution of the network is balanced by the swelling of the gel. On the other hand, as the pH >5, an increase in swelling was observed. This could be due to the deprotonation of the acid groups found in the gelatin chains.

Some authors (26) have reported that the pH influence in the swelling of the ionic hydrogels, in this case the hydrogels with acid groups bonded to the polymeric chain, the ion H^+ can combine with OH^- ones present in the basic solutions to form H_2O. The charge is compensated by the cations joined with other hydroxylic groups that go into the polymeric network. A cationic concentration increase leads to an osmotic pressure increase and this pressure is responsible for the hydrogel swelling. When the recovery elastic force is equal to the osmotic pressure, the swelling equilibrium is reached (27).

3.4 Studies of Water Retention

The water retention (WR) of hydrogels was measured as a function of time. Kinetics curves of WR of the A_1 and A_2 hydrogels are displayed in Figure 4. The result showed that the decrease in weight was curvilinear with time up to 10 h and thereafter did not change significantly; evaporative loss was about 90% within 10 h. It is interesting that the water retention of hydrogels is inconsistent with the swelling behavior of the hydrogels.

In a previous study (25), pure gelatin possesses an excellent hydrophilic nature and the highest swelling value, while it shows the most rapid water loss rate. At the same time, the content of PVA/MAA/Gelatin exerts an obvious influence on water retention of the hydrogels.

We can observe that there is a slight difference in water retention between A_1 and A_2 gels, although the A_1 composite gel possesses a higher swelling value than A_2 gel. Even then, compared with pure gelatin, all composite hydrogels showed more excellent water retention.

It is interesting in the sense that, when used as wound coverings, they will be able to provide a moist environment to the wound surface for prolonged periods leading to better healing of the wounds.

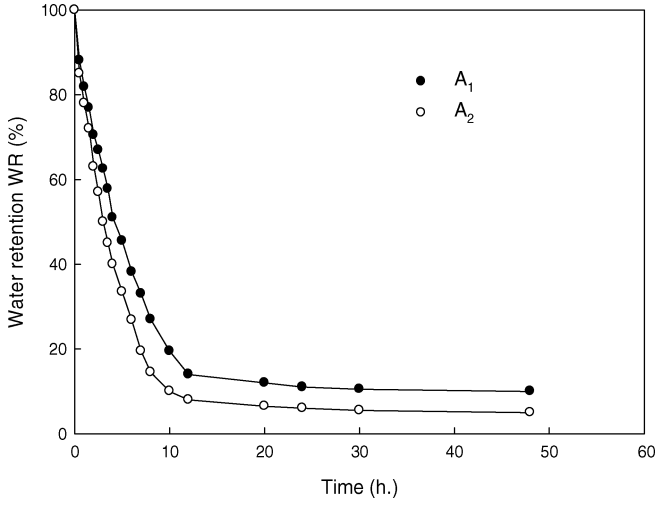


Fig. 4. The kinetics curves of water retention of the different PVA/MAA/gelatin composition at dose; 4 kGy.

3.5 Infrared Spectroscopy

FTIR spectrum (Fig. 5) shows the gelatin and hydrogel sample (A_1) PVA/MAA/gelatin. In the case of gelatin, it shows peaks at 3450 cm^{-1} and 3423 cm^{-1} due to NH stretching of secondary amide, C=O stretching at 1680 cm^{-1} and 1640 cm^{-1}, -NH bending between 1550 cm^{-1} and 1500 cm^{-1}, -NH out-of plane wagging at 670 cm^{-1}, and C-H stretching at 2922 cm^{-1} and 2850 cm^{-1}. The FTIR spectrum of PVA/MAA/gelatin copolymer (Fig. 5) contains all the characteristic absorption peaks of gelatin and, in addition, PVA, MAA characteristic functional groups bands, as well as OH-at 3500 cm^{-1} carbonyl C=O at 1750 cm^{-1} and also methyl group CH_3 at 2900 cm^{-1} of MAA. As there are no shifts of peaks of any group in the copolymer spectrum, it is confirmed that the copolymer structure is a valid with the absence of vinyl group at stretching vibration band at 1650 cm^{-1}which indicates a complete crosslinking.

3.6 Scanning Electron Microscopy

The SEM images were obtained to characterize the microstructure of the freeze-dried PVA/MAA/gelatin hydrogels and are presented in Figure 6. This suggests that the PVA/MAA/gelatin hydrogels matrices are porous, with a three-dimensional interconnected microstructure by virtue of the freeze-drying step (28) with the pores being the result of ice crystal formation, resembling other natural macromolecular hydrogel system structures. Additionally, the stronger wall appeared due to the rather orderly aggregates of the polymer chain segments in the interior of the PVA/MAA/gelatin hydrogels. The interconnection between pores could be assigned to the crosslinking network formation in gels.

3.7 Thermal Gravimetric Analysis (TGA)

The thermal stability of gelatin and PVA/MAA/gelatin copolymer was investigated using TGA (Figure 7). It is obvious that there is a significant change in the thermal stability of gelatin when polymerization with PVA and MAA takes place. At first step, the temperature increases up to 120°C with about 5% wt loss referring to evaporation of H_2O, NH_3 and CO_2 gases from the polymers. The second step for gelatin up to 180°C indicates its heat resistance and therefore, some deformation takes place with weight loss of about 10%, plus, over that it suffers from complete degradation at 300°C. The thermal stability of copolymer PVA/MAA/gelatin is higher than that of gelatin only. As the crosslinking in the copolymer with gelatin chains was increased, its thermal stability increased as well. The results show that the low thermal stability of gelatin accelerated the thermal degradation of MAA .It was reported that gelatin showed only one weight loss step at 200–280°C in the course of thermal degradation. A drop in thermal stability of the

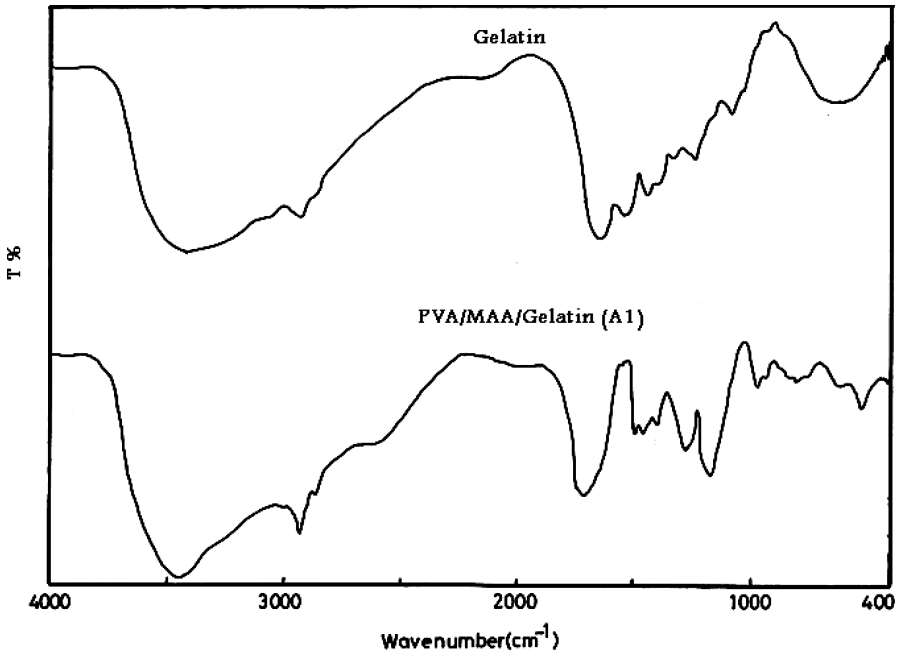


Fig. 5. FTIR spectroscopy of gelatin and PVA/MAA/gelatin (A_1) hydrogel.

gelatin rich hydogel can be attributed to the decomposition of the copolymer–gelatin structure.

3.8 Adsorption of Antibiotic Drugs on Hydrogel

For the investigation of cationic drug adsorption behavior of PVA/MAA/gelatin hydrogels with the different composition ratio A_1 and A_2, hydrogels were initially swollen in drug solution at pH 7.0 in a concentration range of 0.25–0.8 mg/ml. The studies were performed by using two different drug models: chlortetracycline HCl and amoxicillin. These molecules were selected because of their different molecular size, structural complexity, and hydrophilic/hydrophobic character.

In order to obtain adsorption isotherms of hydrogels, the mass of adsorbate per unit mass of adsorbent (q_e) was plotted vs. the equilibrium concentration of drug (C). q_e values are calculated from the following equation:

$$q_e = \left(\frac{C_i - C}{m}\right) \times V_t$$

Where q_e is in mg adsorbate per gram of dry adsorbent, C_i and C are the initial and equilibrium concentrations of adsorbate solution in mg/ml, V_t is the volume of solution treated in ml, and m is the mass of dry adsorbent, in g.

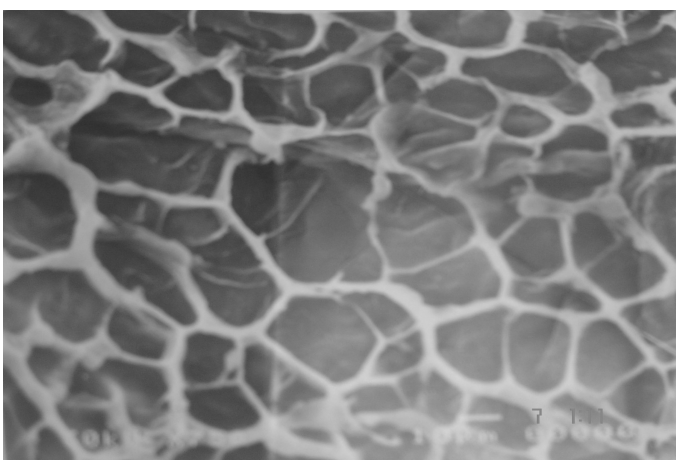


Fig. 6. SEM micrographs of freeze-dried of PVA/MAA/gelatin hydrogel composition (A_1) (magnification 750×) after equilibrium swelling.

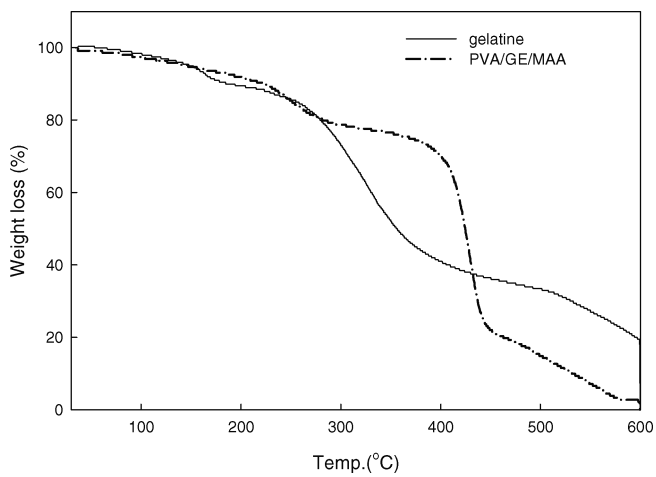


Fig. 7. TGA thermograms of gelatin and PVA/MAA/gelatin copolymer hydrogels.

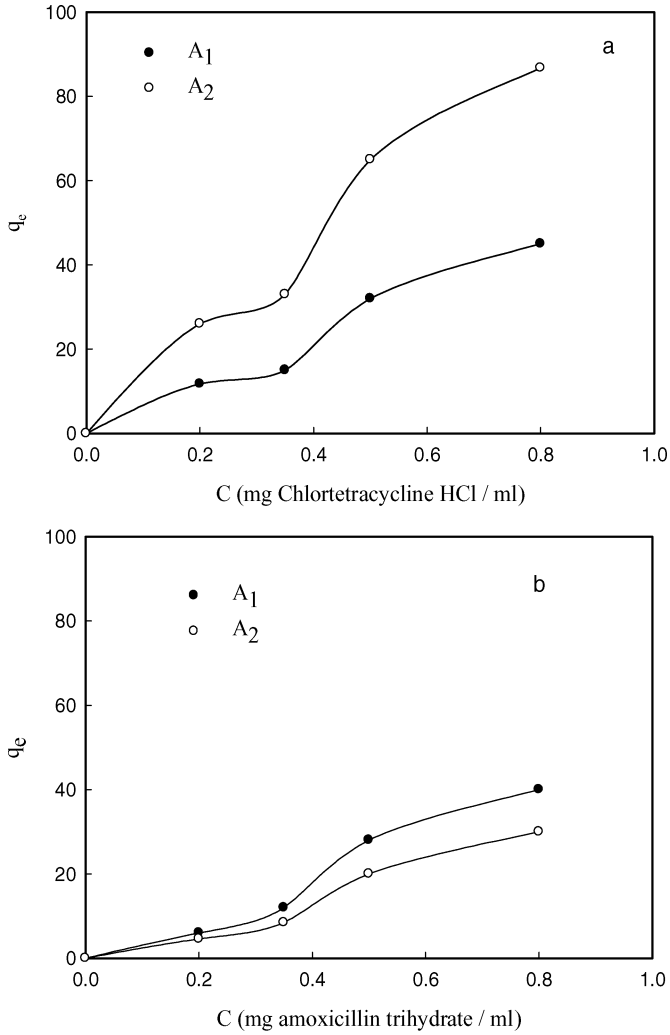


Fig. 8. Relationship between equilibrium concentration (C) of drugs and its amount of adsorption (mg/g) for different (PVA/MAA/gelatin) compositions at pH 7, at 37°C. a) Chlorotetracycline HCl; b) Amoxicillin trihydrate.

The total amount of drug adsorbed into 0.1 g of dry gel at different initial drug concentrations is given in Figure 8. As can be seen from this figure, the amount of the amoxicillin trihydrate drug taken, increased with a decrease in MAA content and initial drug concentration. The inverse correlation between the amoxicillin trihydrate drug loading and PVA/MAA/gelatin ratio was in agreement with the swellability results discussed above. The low loading efficiency indicates that the hydrogels are formed by tight networks that prevent drug diffusion into the matrix. The loading efficiency increased as the PVA/MAA/gelatin ratio decreased, confirming that loser matrices are generated by using low PVA/MAA/gelatin molar ratios. However, it should be kept in mind that the two drugs are a cationic molecule and repulsion charges with free amino groups of the hydrogel may interfere with the drug loading.

On the other hand, chlortetracycline HCl loading was found to increase proportionally with the MAA content in the hydrogel. The reason for this increase was attributed to the higher protic acid content of the gel system and specific bonding of a positively charged drug to partially ionized hydrogel and to the higher free volume available for diffusion.

As expected, the drug loading and the release profiles were strictly related to both matrix composition and drug physicochemical properties. Because of its high hydrophilicity and molecular weight, Amoxicillin expected to localize in the hydrated fraction of the matrices without significant interaction with the investigated hydrogels.

3.9 Release Dynamics of the Drugs

The release of water-soluble drugs, entrapped in hydrogels, occurs only after water penetrates the polymeric networks to swell and dissolve the drug, followed by diffusion along the aqueous pathways to the surface of the disc. The drug release is closely related to the swelling characteristics of the hydrogels, which in turn, is a, key function of the chemical architecture of the hydrogels. Figure 9 shows the cumulative release profile of chlorotetracycline hydrochloride and amoxicillin trihydrate from per grams of the drug loaded at various pH at 37°C as a function of time. The amount of drug release in pH 7.4 buffers was higher than the release medium of pH 2.2 and pH 5.0 buffer. Within 3 h, the release of chlorotetracycline HCl from A_1 hydrogel was 33 mg/g in pH 5.0, 110 mg/g at pH 2.2 and 230 mg/g at pH 7.4, also, the release of amoxicillin trihydrate from A_1 hydrogel was 10.5 mg/g in pH 5.0, 21.6 mg/g at pH 2.2 and 46 mg/g at pH 7.4. This suggests that the drug release profiles of (PVA/MAA/gelatin) hydrogels are pH-sensitive. This observation can be attributed to the opening up of pores and channels due to the swelling of the test hydrogel network increase (Fig. 3). The swelling of hydrogels (PVA/MAA/gelatin), increased when the pH of the medium changed from acidic to basic. At high pH values, it gets partially ionized, and the charged $-COO^-$ groups repel each other, leading to the higher swelling of the polymer and resulting in more drug release.

After an 8 h release, the cumulative investigated drugs release still maintained at a certain amount under three different pH conditions. This is because some drug molecules may be entangled within the hydrogel network, and those cannot be released unless polymer matrixes are degraded.

To study chlorotetracycline HCl and amoxicillin trihydrate transport mechanism from (PVA/MAA/gelatine) hydrogels, the experimental data have been further analyzed according to the following equation:

$$M_t/M_\infty = kt^n$$

In the above equations, M_t/M_∞ is the fraction of drug released (mg/g) at time t (min), k is a constant related to the properties of the drug delivery system, and n is the

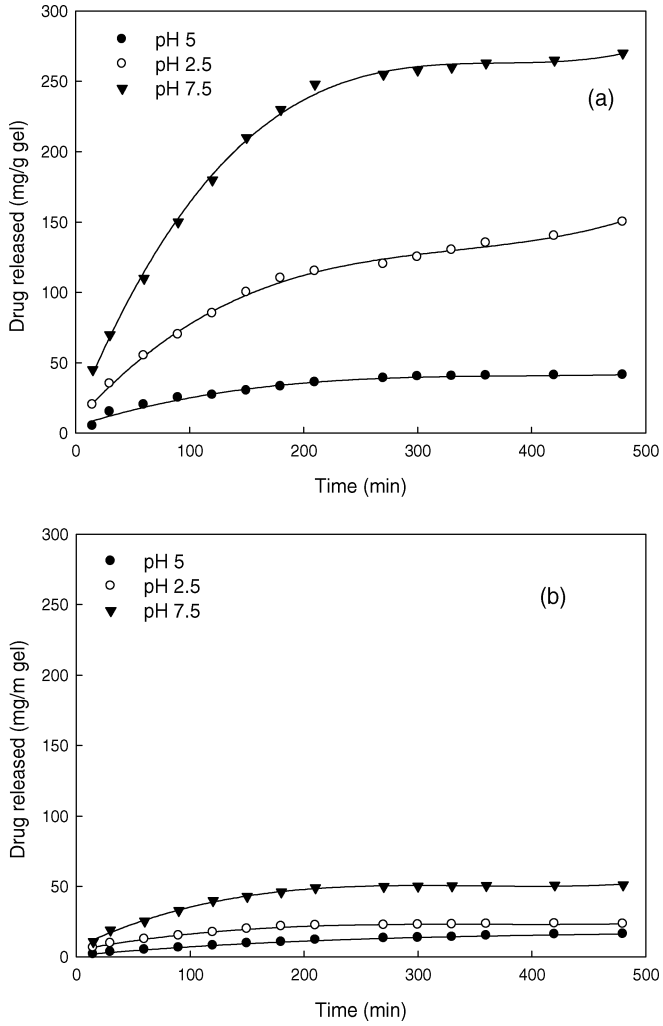


Fig. 9. The cumulative release profiles of Drugs from (PVA/MAA/gelatin) hydrogel (A_1) at various pH at 37°C. a) Chlorotetracycline HCl; b) Amoxicillin trihydrate.

diffusion exponent, which characterizes the drug release mechanism. A value of n of 0.5 indicates the drug release follows the Fickian diffusion; when $n = 1$, case II transport occurs; when $0.5 < n < 1$, anomalous transport is observed. The characteristics of a drug delivery system are evaluated using the first 60% release data in this paper. Values of the various parameters in pH 2.5, pH 5 and pH 7.5 media are shown in Table 1.

Table 1 shows that the number determining the values of the diffusional exponent n were found to be 0.637, 0.635, and 0.635 in the chlorotetracyclin HCl of pH 2.5, 5.0, and 7.5, respectively and in the case of amocicillin tihydrate n were found to be 0.525, 0.652 and 0.458 at pH 2.5, 5.0 and 7.5, respectively, this is over 0.5. Hence, the diffusion of water into the super water-retainer hydrogels is generally found to have a non-Fickian character (29). When the diffusion type is anomalous behavior, the relaxation and diffusion time are of the same order of magnitude. As solvent diffuses into the hydrogel, rearrangement of chains does not occur immediately.

Table 1. Kinetic constants (K), release exponents (n), correlation coefficients (r^2) following linear regression of release data of drugs from (PVA/MAA/gelatin) hydrogel (A_1) in different medium at 37°C.

	Drugs					
	Chlorotetracycline HCl			*Amoxicillin trihydrate*		
pH's	*n*	*k*	r^2	*n*	*k*	r^2
2.5	0.637	0.026	0.988	0.525	0.055	0.993
5	0.635	0.031	0.978	0.652	0.022	0.997
7.5	0.635	0.031	0.992	0.458	0.83	0.992

According to the above results, we believed that the chlorotetracyclin HCl and amocicillin tihydrate release mechanism can result from the superposition of various effects, such as swelling property of hydrogels, the solubility of the drug and erosion property of matrix; it is not necessarily based on a single factor.

4 Conclusions

The above studies demonstrate that the gamma irradiation technique can be used to prepared (PVA/MAA/gelatin) hydrogenls. The swelling degree was found to be dependent on dose, composition and pH of immersion medium. The swelling of hydrogel exhibited high sensitivity to pH. The study effect of H^+/OH^- concentration carried out at various pHs shows that the swelling of hydrogel causes several large volume changes. Ionic repulsion between charges groups incorporated in the gel matrix by an external pH modulation could be assumed as the main driving force responsible for such swelling changes. The release of chlortetracycline HCl and amocicillin tihydrate from the (PVA/MAA/gelatin) hydrogels, as studied at the physiological temperature of 37°C, exhibits a strong pH-dependent release behavior, thus offering minimum release at pH 5.0 and maximum release at pH 7–8. The pH-dependent release behavior is totally governed by the presence of –COOH groups along the macromolecular chains, which ionize at higher pH. The solubility of the drug, the degree of swelling of the hydrogels, and the ionic group content were found to influence predominantly the release profiles of drugs at various pH.

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