Kinetic Degradation and Controlled Drug Delivery System Studies for Sensitive Hydrogels Prepared by Gamma Irradiation

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ABSTRACT: Ternary mixtures of *N*-vinyl-2-pyrrolidone/itaconic acid and gelatin were irradiated by gamma rays at 30 kGy/s and at ambient temperature to prepared poly (NVP/IA and G) hydrogels. Poly (NVP/IA) hydrogels were prepared in different compositions (NVP/IA) mole ratio, (100/0), (98/1.5), (96.5/3.5), and (93/7.0) at 30 kGy. Then adding gelatin at different content (5, 10, 15, 20) mg to the best composition (NVP/IA/H_2O) (93/7)% for the characterization of network structure of these hydrogels, kinetic swelling drug release behavior and Scan Electron Microscope was studied. The equilibrium degree of swelling for P(NVP/IA) and P(NVP/IA/G) copolymer and the swelling-degradation kinetics were also studies. According to dynamic swelling studies, both the diffusion exponent and the diffusion coefficient increase with increasing content of (IA), whereas, the addition of gelatin to (NVP/IA) composition by different content did not lead to any significant change in swelling percent. Also, the swelling behavior of copolymer hydrogels in response to pH value of the external media was studied, it is noted that the highest swelling values were at pH 4. The *in vitro* drug release behavior of these hydrogels was examined by quantification analysis with a UV/VIS spectrophotometers. Chlorpromazine hydrochloride was loaded into dried hydrogels to investigate the stimuli-sensitive property at the specific pH and the drug release profile of these pH-sensitive hydrogels *in vitro*. The release studies show that the highest value of release was at pH 4 which can be used for drug delivery system. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 112: 1745–1754, 2009

Key words: hydrogels; swelling kinetic; diffusion; degradation; drug delivery

INTRODUCTION

Hydrogels are one of the promising and versatile materials with enormous possibilities and potential. In particular, controlled release systems are capable of delivering drug at constant rate over an extended period of time.[1–3] Hydrogels are crosslinked polymeric networks that can imbibe large quantities of fluid. They represent an important group of biomaterials for the controlled release of a bioactive agents. Therefore, a thorough understanding of fluid-polymer interactions of such systems is critical for the development of these materials for biomedical applications. The release of a drug incorporated in a polymeric system takes place by migration of the solute to the medium that surrounds the system by molecular diffusion through the support or by diffusion through micropores of the polymeric matrix. This makes the solute solubility in the polymer an important factor in the control of its migration. Drug diffusion from monolithic systems can be analyzed using Fick's second law of diffusion. The systems of controlled release by diffusion are based on the principle of the permeability of the polymeric matrix after the swelling process in a hydration medium. The swelling kinetics and, therefore, the release rate depend on the matrix swelling degree.[4] The use of site-specific biodegradable polymeric systems as implantable controlled release drug delivery systems is desirable, since the devices are degraded and eliminated from the body. Because of the unique properties of hydrogels, the biodegradable hydrogels are expected to find wide application in the improvement of the existing dose form and the development of a new and better drug delivery system. The interpenetrating network structure (IPNs) of full and semi-IPNs hydrogels provides additional strength and new properties to drug carrier systems. The IPNs behave like composites and reflects combination properties of its ingredients. Depending on the network composition, the degradation and drug release behavior of the hydrogels can be varied from a few days to over a year without losing strength.[5] Chlorpromazine hydrochloride are used as an antipsychotic antiemetic. The drug have ahydrophobic part (tricyclic), and a hydrophilic part (*tert*-amine).

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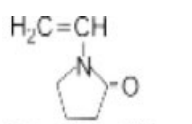
Most of the research on biodegradable drug delivery system has employed water-insoluble polymers such as poly(glycolic acid) or poly(lactic acid) and its derivative.[6–11] Not much work has been reported on biodegradable hydrogel systems using a combination of natural and synthetic polymer for the treatment of osteomyelitis.

In the present work, an attempt has been made to evaluate the effect of composition on IPNs based on poly(*N*-vinyl pyrrolidone/Itaconic/Gelatin) hydrogels on the equilibrium swelling and the effect of external stimuli such as pH on the equilibrium swelling, drug release, degradation and the loading of chlorpromazine hydrochloride as model drugs from and within hydrogels. The advantage of NVP is a great compatible with the human body. The advantage of IA is a great hydrophilicity-it has two COOH groups with different pKa values, so that very small amounts of IA, render good pH sensitivity to hydrogels. Gelatin has been chosen as the hydrogel polymer backbone in this study because of the following physicochemical properties of gelatin: (i) great capacity for modification at the number of amino groups, (ii) low level of immunogenicity and cytotoxicity, (iii) hydrogel formation by facile procedures,[7] and (iv) ability to degrade. Specifically, it has been explored modification of the gelatin backbone with *N*-vinyl pyrrolidone/Itaconic acid to alter the physicochemical properties of the gelatin, and to affect the subsequent release, degradation and solubility of model drugs from and within the hydrogel.[12]

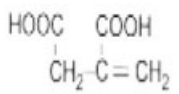
MATERIALS AND METHODS

Materials

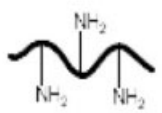
The *N*-vinyl-2-pyrrolidone (NVP) (Merch, Germany) of purity 99%, was used without further purification. Itaconic acid (IA) was obtained from Sigma Aldrich, while Gelatin was obtained from EL-Nasr for medical supplies, Cairo, Egypt. Chlorpromazine Hydrochloride (as drug model) were received from Arab drug company, Cairo, Egypt, of purity 99% and used without further purification. The other chemicals and phosphate buffers were reagent grade and used as received.



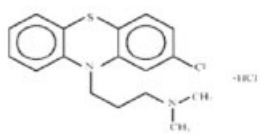
N-vinyl pyrrolidone



Itaconic acid



Gelatin


chlorpromazine hydrochloride

Preparation of hydrogels

Different commonomer compositions were prepared and subjected to gamma irradiation at 30 kGy in air at ambient temperature and fixed dose rate of 1.3 Gy/s. Three components were used in the prepration of poly (*N*-vinyl-2-pyrrolidone/Itaconic acid). Aqueous solutions of (NVP) and (IA) were prepared in 2 mL of distilled water and total volume 4 mL in different compositions (NVP/IA) mole ratios, 100/0.0, 98.5/1.5, 96.5/3.5, and 93/7.0. The Third component, gelatin was added to the selected composition (NVP/IA) (93/7.0) at different concentrations (5, 10, 15, and 20) mg.

Composition of gels

Irradiated mixture obtained in cylindrical shape cut into disks, dried in a vacuum oven at 50°C for 8 h to constant weight and subjected to soxhlet extraction with water as solvent for 8 h. The uncrosslinked polymer and/or residual monomer were removed with this extraction from the gel structure. Extracted gel were dried again in vacuum oven at 50°C for 8 h to constant weight then stored for later evaluations. The mole percentages of monomers in the hydrogel systems are given in Table I. The gel fraction yield in the hydrogel was determined from the following equation:

$$\text{Gel}(\%) = (W_g/W_o) \times 100 \quad (1)$$

where W_o and W_g represent the weights of dry hydrogel and gelled part after extraction, respectively.

The swelling/degradation kinetics studies

The prepared crosslinked gels were soaked in buffer solution of different pH values ranged from 2 to 8 at 25°C. Swollen gels weighed and the measurements were continued until a constant weight was reached for each sample. This weight was used to calculate the swelling ratio (*S*) from the following equation:

$$S\% = (W_s - W_g)/W_g \times 100 \quad (2)$$

where W_s and W_g are the weights of the swollen and the dry hydrogel, respectively. Dried hydrogels were placed in 50 mL of aqueous solutions of pH ranged from 1 to 8 at ambient temperature. Swollen hydrogels were weighed at interval times to characterize the swelling/degradation kinetics. Extreme care was taken to preserve the integrity of the hydrogels at every step in the weighing process. The swelling weight ratio at each time point for each hydrogel was calculated as: $(W_s - W_d)/W_d$, where W_s is the weight of the swollen gel/g and W_d is the original weight of the dry gel/g. The maximum swelling weight ratio that occurred over 8 weeks

TABLE I
The Hydrogel Composition, Gelation Percent Mole Percent of the NVP, IA, Gelatin Content

Group number	Hydrogel composition	NVP mole %	IA mole %	G mg	Gelation %
(I)	P(NVP)	100	0	0	93.43
	P(NVP/IA)-1	98.5	1.5	0	88.85
	P(NVP/IA)-2	96.5	3.5	0	77.33
	P(NVP/IA)-3	93	7	0	74.45
	P(NVP/IA)-4	90	10	0	76.96
(II)	P(NVP/IA/G)-1	93	7	5	88.29
	P(NVP/IA/G)-2	93	7	10	88.97
	P(NVP/IA/G)-3	93	7	15	91.05
	P(NVP/IA/G)-4	93	7	20	89.63

and the time was calculated (S_{max}; T_{max}) where S_{max} is the maximum swelling percent; T_{max} is the time of the maximum swelling. The last attainable swelling weight ratio (due to hydrogel dissolution) and the time it occurred was also calculated (S_{fail}; T_{fail}), where S_{fail} is the weight ratio at failure and T_{fail}; is the time to failure. The degradation % of the hydrogels has been calculated by the following equation:

$$\text{Degradation } \% = \left[(S_{max} - S_{fail}/S_{max}\right] \times 100 \quad (3)$$

Since both swelling and degradation are occurring from the onset of the study, the resulting change in the gravimetric measurement cannot differentiate the contribution of either phenomenon.[12]

Drug loaded and *in vitro* release studies

A known weight of dried hydrogel were loaded with a drug model chlorpromazine hydrochloride solution (100 mg/L) at different pH values from 1 to 8 and at room temperature. Based on the maximum swelling time (T_{max}), the hydrogel immersed for 8 days then taken out. The swollen hydrogel was placed in a vessel containing 50 mL of buffer solution at room temperature. At various times aliquots of 3 mL were drown from the medium to follow the drug release and placed again into the same vessel so that the liquid volume was kept constant. Chlorpromazine hydrochloride drug release was determined spectrophotometrically at 304 nm.

Ultra violet–visible spectrophotometer

The released amount of Chlorpromazine Hydrochloride was determined at 304 nm by using a double-beam UV visible Sp200, Pye-Unicam, England.

Scanning electron microscopy (SEM)

JEOL-SEM-25 Scanning Electron Microscope–Japan was used for investigating the pore structure of different hydrogels at high magnification and resolution by means of energetic electron beam. The hydrogels were dried, cated with gold under sputter.

RESULTS AND DISCUSSION

Composition of hydrogel

When pure *N*-vinyl pyrrolidone monomer has been irradiated with gamma rays, polymerization and crosslinking reactions takes place simultaneously. The total dose required for the onset of gelation was determined to be 30 kGy and the sensitizing effect of water for the gelation was very well demonstrated in many studies.[13] In this study for the prepration of hydrogels, the mixtures of group (I) (NVP/IA/H_2O) and group (II) (NVP/IA/G/H_2O) at different ratio were irradiated to 30 kGy with gamma rays. Table I summarizes the mole percentage of monomers in copolymeric gels and percentage gelation. It is noted that, increasing of mole percentage of IA in the initial mixture (caseI) causes change in the conversion from monomer to gel. These results indicate that IA acts as an effective chain transfer agent in the NVP hydrogel, where as, the addition of gelatin to NVP/IA/H_2O mixture by different content leads to a slight increase in gelation percent.

Swelling kinetics and diffusions

For the hydrogels such as NVP, the swelling is controlled by the hydrophilicity of the monomer or polymer. Where acidic or basic groups are incorporated, then the gels should exhibit pH swelling and deswelling.[13,14] The incorporation of acidic moieties into base polymeric structures for the synthesis of hydrogels have been mostly carried out by using mono, di or triprotic acid. The use of diprotic acids namely Itaconic acid, however, has been shown to impart additional advantages over monoprotic acids such as acrylic and methacrylic acids.[13,15] The hydrophilicity of NVP/IA is higher than NVP due to ionization of carboxylic group from IA. Figures 1 and 2 show the swelling curves of P(NVP/IA) and P(NVP/IA/G)

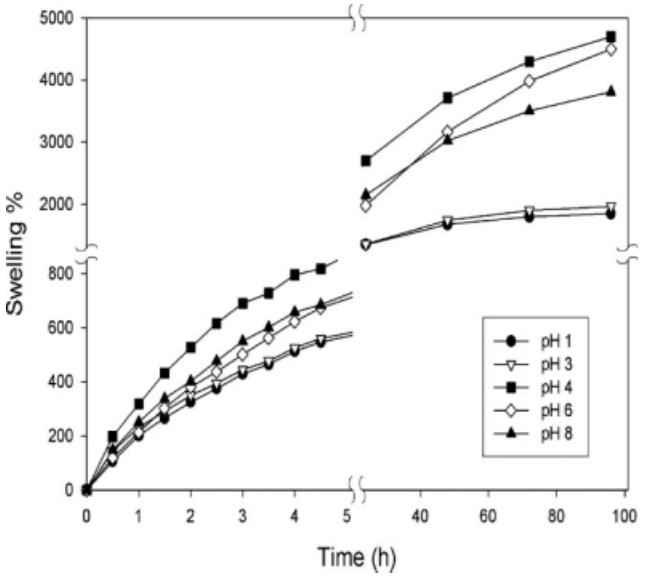


Figure 1 Change in S% and time (h) of P(NVP/Itaconic) hydrogels irradiated at 30 kGy at different composition: (100/0 ●, 98.5/1.5 ▽, 96.5/3.5 ■, 93/7 □, and 90/10 ▲).

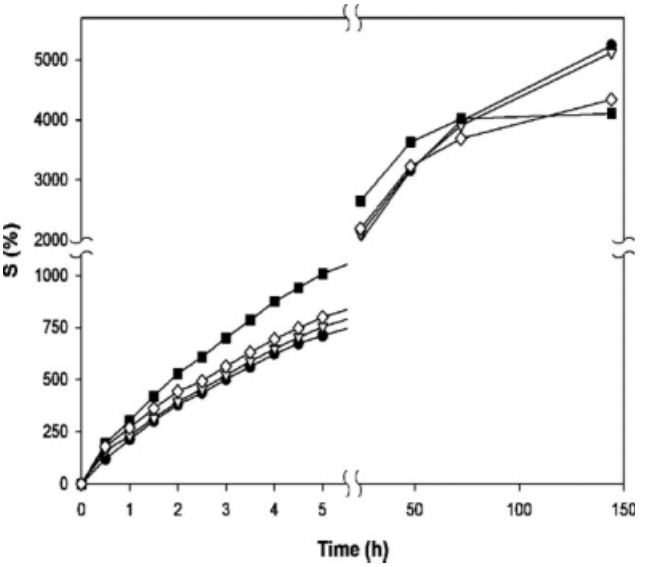


Figure 2 Change in S% and time (h) of P(NVP/Itaconic/Gelatin) hydrogels irradiated at 30 kGy at different composition: (93/7/5 mg ●, 93/7/10 mg ▽, 93/7/15 mg ■, and 93/7/20 mg □).

hydrogels in distilled water. Table II shows the values of the equilibrium swelling degrees of the radiation crosslinked NVP were lower than those of the radiation crosslinked NVP/IA hydrogels. The equilibrium swelling of NVP hydrogels increased with the addition of IA monomer due to increase the number of carboxylic group. Figure 1 shows also that, the values of S% increased with time but reached a constant value after a certain time. This value of swelling may be called equilibrium swelling (Seq %). It can also shows that, the equilibrium swelling percentage of P(NVP/IA) copolymeric hydrogels (at fixed irradiation dose) increases as the itaconic ratio increases up to 93/7 then decrease in 90/10 ratio, because the increase in the electrostatic interactions of the neighboring carboxylate groups in IA in the hydrogels. It can be seen that the percentage swelling of an ionic network very much depends on the concentration of ionizable groups in the network. Moreover the swelling degree dramatically decrease by increasing the (IA) content in the copolymer than 7% it may be due to the steric effect of the function group. As shown on the comparing Figures 1 and 2, the addition of gelatin which have a great capacity for modification at the level of amino groups, to NVP/IA hydrogel causes an increase in the swelling percent by increasing the gelatin content from 5 to 10 mg. The swelling percent was found to be 4500 for P(NVP/IA)-3 and increase to 5240 and 5120 for P(NVP/IA/G)-1 and P(NVP/IA/G)-2 respectively. These results may be attributed to highly swelling property of gelatin.[12]

The swelling controlled diffusion mechanism of the gamma crosslinked samples case I and II was determined by using the following equation.[16,17]

$$F = (M_t/M_\infty) = Kt^n \quad (4)$$

TABLE II
The Variation in the Equilibrium Swelling Degree and Diffusion Parameters of Different Hydrogels in Distilled Water (at 30 kGy)

Group number	Hydrogel composition	teq (h)	Seq %	Diffusion parameters		
				n	*K*	*D*
(I)	P(NVP)	120	1030	0.5	−1.1768	0.32
	P(NVP/IA)-1	96	1243	0.61	−1.7268	0.23
	P(NVP/IA)-2	264	4158	0.72	−2.7809	0.11
	P(NVP/IA)-3	96	4521	0.67	−2.1792	0.18
	P(NVP/IA)-4	96	2402	0.69	−1.9864	0.22
(II)	P(NVP/IA/G)-1	192	4462	0.77	−3.2529	0.07
	P(NVP/IA/G)-2	192	5510	0.74	−3.1055	0.08
	P(NVP/IA/G)-3	192	5182	0.8	−2.6804	0.14
	P(NVP/IA/G)-4	192	4208	0.68	−2.8083	0.09

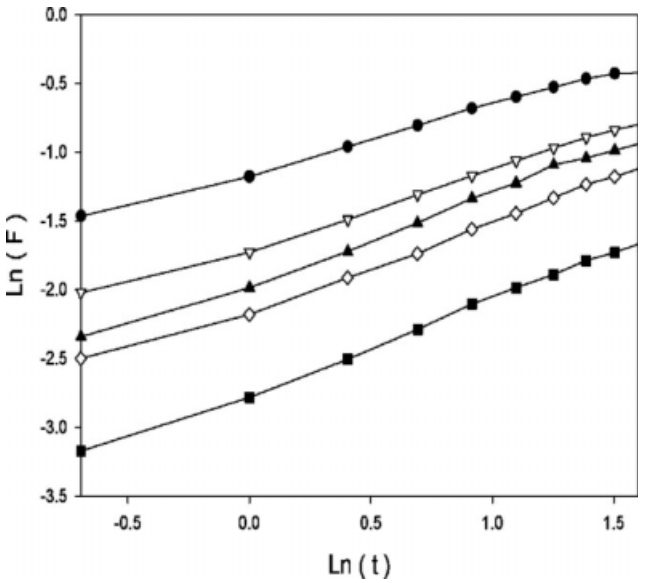


Figure 3 Fractional swelling of case (I) P(NVP/Itaconic) hydrogels irradiated at 30 kGy with time at different composition of (NVP/itaconic): (●, 100/0); (▽, 98.5/1.5); (■, 96.5/3.5); (□, 93/7); and (▲, 90/10).

In the above equation, F are fraction of swelling due to the water uptake M_t are the adsorbed water at time t and M_∞ are the adsorbed water at equilibrium, K is the swelling constant, and n is the swelling exponent. For disk-shaped samples, n is 0.5 if the swelling is by Fickian diffusion of water, n is between 0.5 and 1.0 for non-Fickian, n is 1.0 for case II diffusion, and n is greater than one for super case-II diffusion. This equation was applied to the initial stages of swellings, and plots of ln F versus ln t shown in Figures 3 and 4. The values of the exponent n and K were calculated from the slope and intercept of the lines, respectively, and are presented in Table II as a function of the hydrogel composition group I and II. The mechanism of swelling was a non-Fickian as the average swelling power was 0.64 for Itaconic acid ranged between 0 and 10 mol % which indicated that chain relaxation had little effect on the rate of swelling. For Gelatin content ranged from 5 to 20 mg, the mechanism of swelling was also a nonFickian diffusion as the average n value was 0.75 indicating that chain relaxation contributed to the rate of swelling. The range of n values observed can have great implications for applications in drug delivery systems and drug release. As the n value approaches one, the rate of swelling and the rate of release of the bioactive agent from the hydrogel becames constant.[18–22]

The values of K depend upon characteristics of the polymer network and the solvent. Since the type of solvent does not change (water), here K-values are the only function of polymer composition. According to eq. (4), the rate constant K depends upon the transport exponent n; so that a direct comparison of K values is possible only if the polymer networks have the same value of the transport exponent. The study of diffusion phenomena in hydrogels as the value in controlled diffusion process that it clarifies polymer behavior. For hydrogel characterization, the diffusion coefficient (D) of the cylindrical P(NVP/IA/G) hydrogels was calculated from the Fick' second low[23]:

$$F = 4\left(Dt/\pi r^2\right)^{1/2} \tag{5}$$

Here D is the apparent diffusion coefficient for the transport of the penetrant into the gel, t is the time and r is the radius of cylindrical polymer sample. For the hydrogels, the graphs of F versus $t^{1/2}$ are plotted and are shown in Figures 5 and 6. The linearity is obtained in the first stage of the process, corresponding to the values of $F < 0.5$ allow the calculation of the apparent diffusion coefficient from the slop of the straight line. The values of the diffusion coefficients of P(NVP/IA) and P(NVA/IA/G) hydrogels are listed in Table II. The table shows that the copolymer composition plays an important role on the values of the diffusion coefficient which found to be varied from 0.11 to 0.32 by increasing of Itaconic acid content in the hydrogels case (I). It also found to be varied from 0.07 to 0.136 by changing of Gelatin content in the hydrogels case (II).

Swelling/degradation kinetics

As the samples swell and degrade concurrently when exposed to the aqueous environment, the

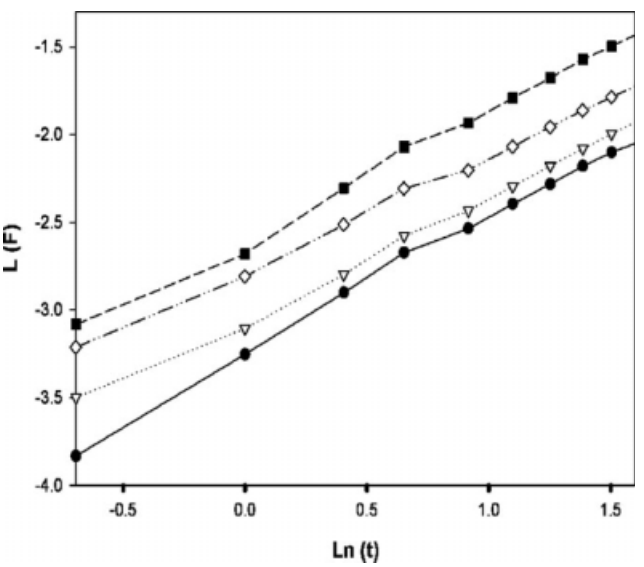


Figure 4 Fractional swelling of case (II) P(NVP/Itaconic/Gelatin) hydrogels irradiated at 30 kGy with time at different Gelatin concentration: (●), 5 mg; (▽), 10 mg; (■), 15 mg; and (□), 20 mg.

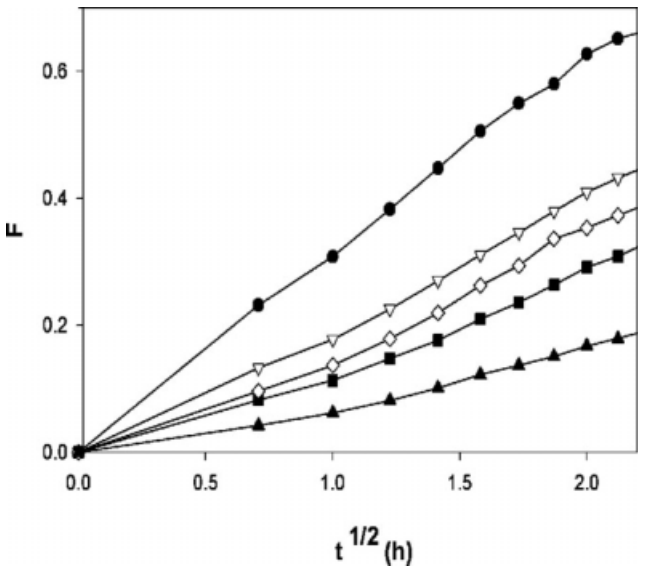


Figure 5 Fractional swelling (*F*) of P(NVP/Itaconic) hydrogels irradiated at 30 kGy versus ($t^{1/2}$) at different composition: (●, 100/0); (▽, 98.5/1.5); (■, 96.5/3.5); (□, 93/7); and (▲, 90/10).

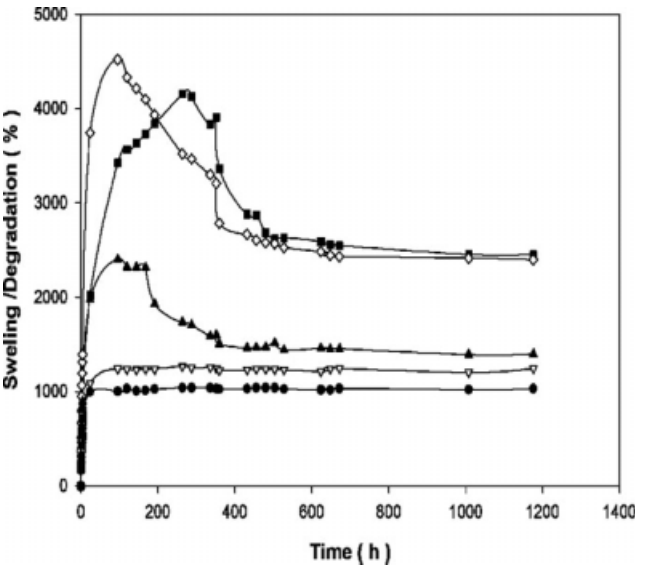


Figure 7 Swelling/degradation % of P(NVP/Itcaonic) hydrogels irradiated at 30 kGy with time: (●, 0% IT; ▽, 1.5% IT; ■, 3.5% IT; □, 7% IT; and ▲, 10% IT).

change in sample mass should be attributed to these two phenomena.[12] The representative swelling/degradation kinetics for P(NVP/IA) and P(NVP/IA/G) hydrogels at distilled water are shown in Figures 7 and 8. Where Figures 7 and 8 show that the swelling % of P(NVP/IT) and P(NVP/IT/G) hydrogels increase with time until to certain value of swelling (S_{max}) and begin to decrease due to the degradation process of the hydrogls. We noted also in Figure 7 that addition of itaconic onto the hydrogel composition increase the swelling values. But and as the increase of itaconic % increase the swelling % increase. In Figure 8 we noted that the increase of gelatin content in the hydrogels slightly increase in the swelling ratio. The values for defined kinetic parameters, S_{max}; T_{max}; S_{fail} and T_{fail}; for all levels of concentration of Itaconic acid and gelatin modification are shown in Table III, Case (I), the effect of IA modification within P(NVP) was evaluated. Swelling/degradation of P(NVP) with IA significantly increased S_{max} and S_{fail} but had no significant change in T_{max} and T_{fail}. The presence of IA in the

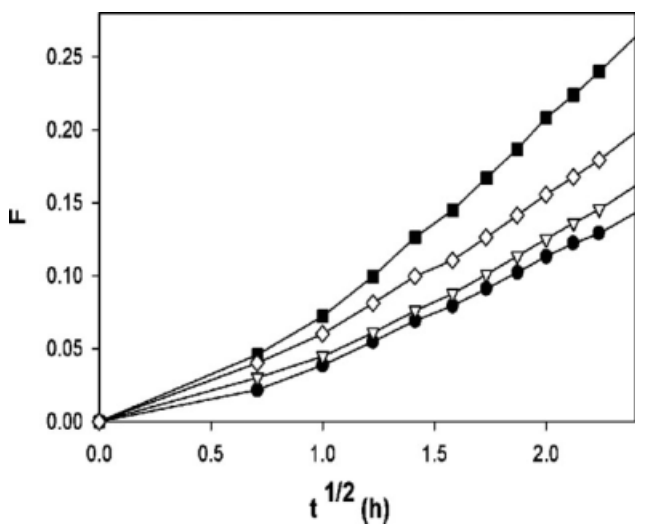


Figure 6 Fractional swelling (*F*) of P(NVP/Itaconic/Gelatin) hydrogels irradiated at 30 kGy versus ($t^{1/2}$) at different Gelatin concentration: (●), 5 mg; (▽), 10 mg; (■), 15 mg; and (□), 20 mg.

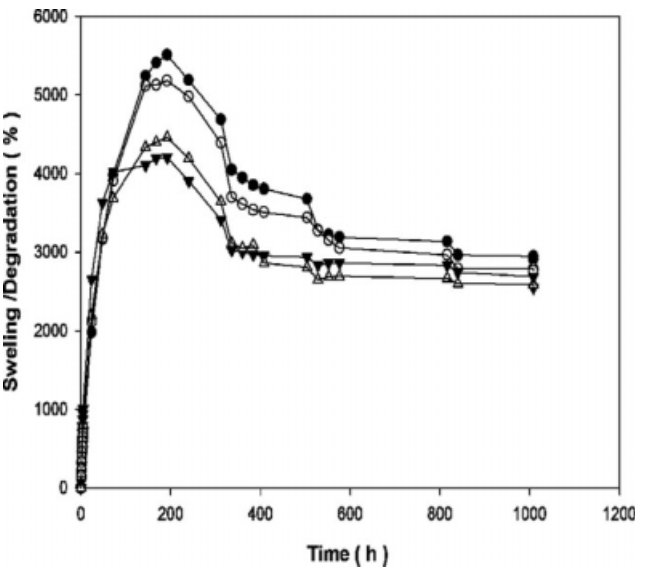


Figure 8 Swelling/degradation % of P(NVP/Itaconic/Gelatin) hydrogels irradiated at 30 kGy with time: (●, 5 mg Gelatin; ▽, 10 mg Gelatin; ■, 15 mg Gelatin; and □, 20 mg Gelatin).

TABLE III
Maximum Swelling Percent (R_{max}) and Time (T_{max}) for Different Hydrogels

Group number	Hydrogel composition	R_{max}	T_{max}	R_{fail}	T_{fail}	Degradation %
(I)	P(NVP)	1030.32	120	1029.63	1176	0.067
	P(NVP/IA)-1	1242.99	96	1244.15	1176	3.06
	P(NVP/IA)-2	4158.45	264	2454.59	1176	40.97
	P(NVP/IA)-3	4521.15	96	2445.17	1176	45.92
	P(NVP/IA)-4	2402.32	96	1398.78	1176	41.77
(II)	P(NVP/IA/G)-1	5510.01	192	2911.86	1008	47.15
	P(NVP/IA/G)-2	5181.87	192	2763.95	1008	46.66
	P(NVP/IA/G)-3	4207.68	192	2546.59	1008	39.48
	P(NVP/IA/G)-4	4462.49	192	2584.28	1008	42.09

P(NVP) gel increase the concentration of the ionizable group, thus increasing the hydrophilicity of the network and swelling capability of the resulting hydrogel. The proximity and prevalence of the ionic carboxylic groups in P(NVP/IA) would increase the electrostatic repulsion with the network, thereby increasing the distance between adjacent segment of the gel and the resulting volumetric potential for swelling S_{max} and S_{fail}.[12] The presence of IA in the hydrogel causes the increase of the degradation % of the P(NVP/IA) hydrogel. By increasing IA concentration within the hydrogel, the degradation % of the investigated hydrogel dramatically increases. Case (II), modification of P(NVP/IA) with Gelatin as by increasing the Gelatin content S_{max} and S_{fail} slightly decrease whereas T_{max} and T_{fail} has no change. Modification with Gelatin has been shown to increase the hydrolytic degradation of the hydrogel. Adding gelatin increases the degradation %, but increasing the gelatin % only has little effect on the degradation %.

Effect of pH of the surrounding medium

The copolymer composition influences significantly on the swelling behavior of the prepared hydrogels. Figure 9 represent the effect of pH on the kinetic swelling for poly(NVP/IA/G)-1 at 25°C andphosphate buffer solution at pH (1 to 8). Consistent with polyelectrolyte behavior, the functional groups responsible for swelling and involved in the hydrogel formation are the carboxylic groups of the itaconic acid and the amino groups of the *N*-vinyl pyrrolidone and gelatin.[24–26] As shown in Figure 9 the P(NVP/IA/G) hydrogel shows pH-dependant start above pH 3. At higher than pH 4, the hydrogel possesses abrupt change in the swelling percent and decrease by increasing the pH value. The above-mentioned results could be explained in the light of the ionization of ionic groups present in the network structure where, the swelling of the hydrogel increase due to first at pH 4, pH 6, the increase of charge repulsion of the dissociated carboxylic groups within the hydrogel.[27] and at second (pH > 6) the deprotonated of the amino group of *N*-vinyl pyrrolidone and gelatin at higher pH values (alkalin medium). At pH value less than pH 4, the carboxylic group are completely collapsed and also the amino groups.

Drug release

The release of a drug from a hydrogel network depends on the degree of swelling of the gels, which can be precisely controlled by a combination of pH sensitive gels for a given structure and the degree of crosslinking.[28] Poly (NVP : itaconic/gelatin) (97 : 3/15 mg) hydrogel was investigsted to determine the composition that exhibits appropriate pH sensitive for drug release delivery. The pH values in the physiological medium change from the highly acidic conditions in the stomach pH (1–3) to the almost

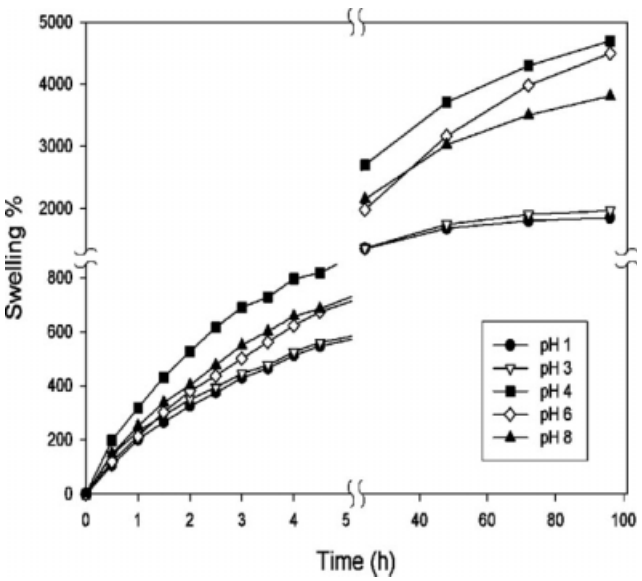


Figure 9 Change in the swelling percent of P(NVP/Itaconic/Gelatin) hydrogel in buffer solutions of different pH values against time.

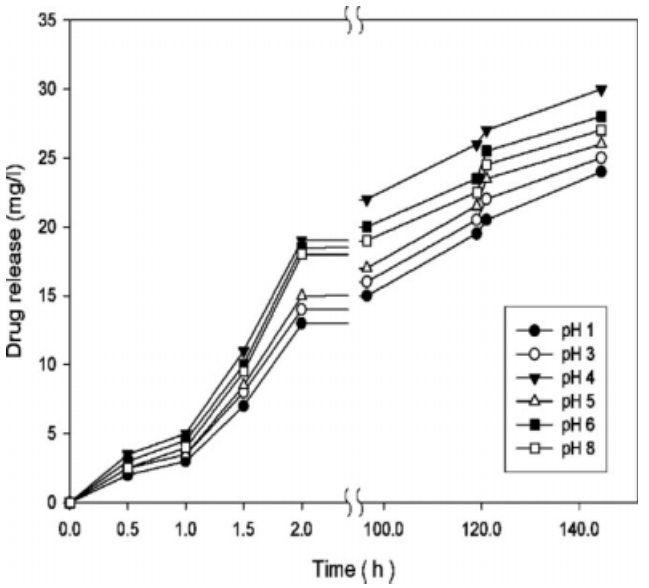


Figure 10 The effect of different pH phosphate buffer solutions on the release of drug from Poly (NVP : itaconic/gelatin) (97 : 3/15 mg) hydrogel.

neutral pH values in the small and large intestine, in the range of pH (6.63–7.49) and pH (6.37–7.04), respectively.[29] The data from the release curve of Figure 10 shows the effect of different pH phosphate buffer solutions on the release of drug from IPNS in water. The diffusion exponent for the drug release curve in water was found that, the hydrogels demonstrated a very high burst effect at pH (1, 3, 4, 5, 6, and 8) and almost 30% of loaded drug was released within 6 days in water. The highest burst effect at pH 4 > pH 6 > pH 8 which could be explained on the nature of bonding between chlorpromazine hydrochloride and gelatin chain of the hydrogels.[30–32] Due to the structure of chlorpromazine hydrochloride which contains a hydrophobic part (tricyclic), and a hydrophilic part (*tert*-amine), it's release depending upon the solution pH. The *tert*-amine becomes protonated or deprotonated by changing the pH of the surrounding medium, where by increasing the pH of the solution, the number of deprotonated of chlorpromazine hydrochloride

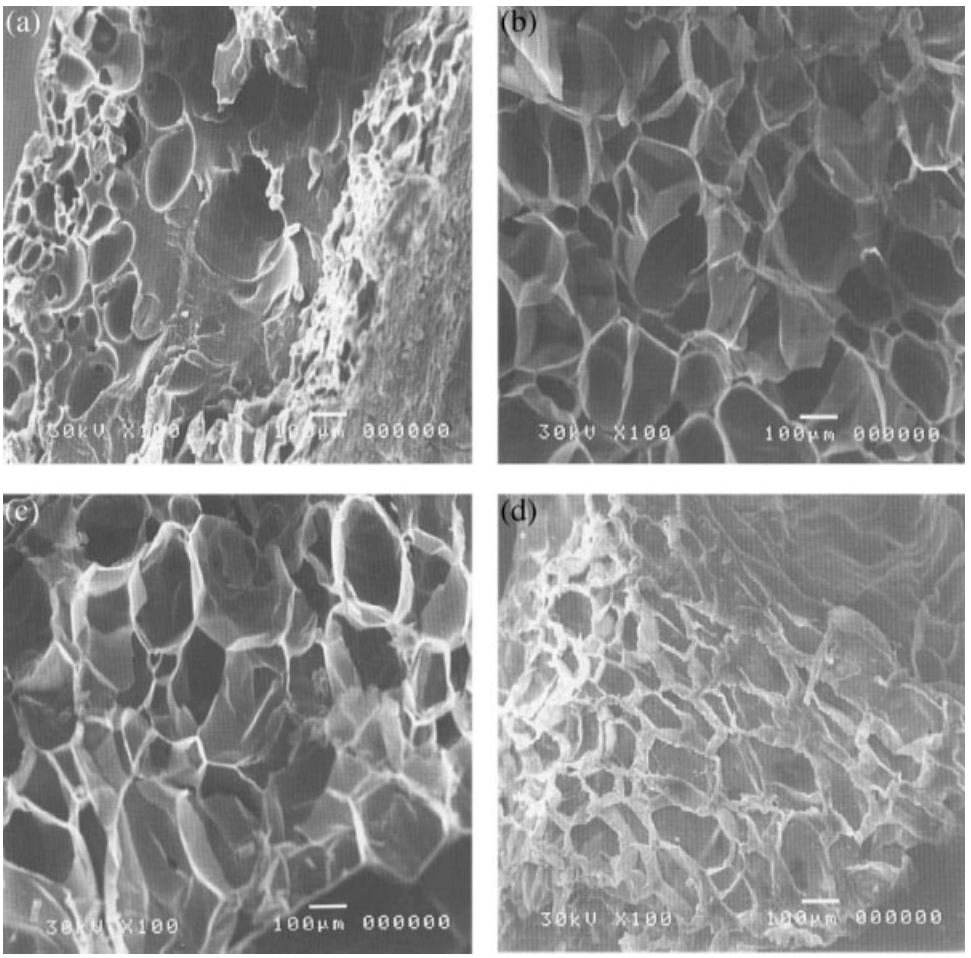


Figure 11 (a) Scanning electron micrographs of P(NVP) hydrogel prepared at gamma-irradiation dose 3 kGy. (b) Scanning electron micrographs of P(NVP/IA) (93 : 7) hydrogel prepared at gamma-irradiation dose 3 kGy. (c) Scanning electron micrographs of P(NVP/IA/G) (93 : 7/5 mg) hydrogel prepared at gamma-irradiation dose 3 kGy. (d) Scanning electron micrographs of P(NVP/IA/G) (93 : 7/15 mg) hydrogel prepared at gamma-irradiation dose 3 kGy.

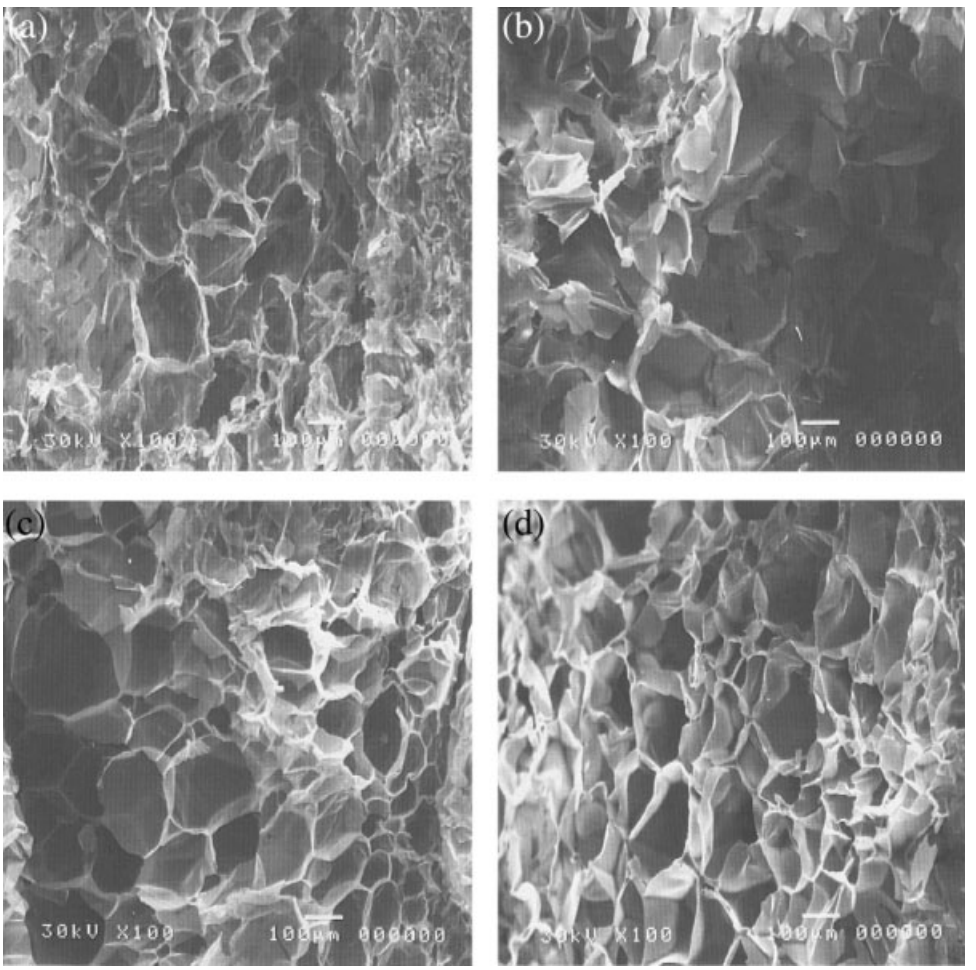


Figure 12 (a) Scanning electron micrographs of P(NVP/IA/G)-1 hydrogel (93 : 7/5 mg) at pH 3. (b) Scanning electron micrographs of P(NVP/IA/G)-1 hydrogel (93 : 7/5mg) at pH 4. (c) Scanning electron micrographs of P(NVP/IA/G)-1 hydrogel (93 : 7/5 mg) at pH 6. (d) Scanning electron micrographs of P(NVP/IA/G)-1 hydrogel (93 : 7/5 mg) at pH 8.

molecules increases. In all the samples, drug release has higher value as pH of the medium equal 4 to 8. This is in correlation which the percentage swelling which showed that water uptake by the hydrogels increased with increasing pH of the medium.[4]

Scanning electron microscopy (SEM)

The scan electron microscope shows the morphology and the pore size as the different composition of the hydrogels. It was carried out at equilibrium swelling and 25°C in phosphate buffer solution pH 6. Figure 11(a–d) represent the imaged hydrogel of P(NVP), P(NVP/IA) (93 : 7), P(NVP/IA/G) (93 : 7/5 mg) and (NVP/IA/G) (93 : 7/15 mg) shows the introducing of (IA) to (NVP) net work structure gel, increase the pore diameter of the hydrogel due to the presence of carboxylic group of itaconic acid. It can also observed that, the addition of gelatin molecule to P(NVP/IA) gel filled the hole of the gel pore and the filling of pore by gelatin molecule increase by increasing gelatin content which appeared as block pits when compared to the surface of [Fig. 11(c,d)].

The pore structure of the hydrogels prepared P(NVP/IA/G) (93 : 7)% and gelatin at 5 mg which swollen at different pH (were soaked) at 25°C in phosphate buffer solution with pH 3, pH 4, pH 6,pH 8 and dried at (−60°C) can be shown in Figure 12(a–d) and e respectively. We noted that the pore size of the hydrogels increase in pH 4 and pH 6 than in pH 3 and pH 8 this it may be due to the swelling in pH 4 > pH 6 > pH 8 > pH 3 due to the polyelectrolytic behavior swelling of hydrogels, it was found increase until reached to the maximum at pH 7,[33] This being due to the complete dissociation of acidic groups of itaconic acid at this pH value. The experimental data points and theoretical curves are very good accordance as it is seen from the Figure.

Figure 13(a,b) show the comparison between the swelled hydrogels pore size in pH 6 solution and the pore size of hydrogels after drug loading. Figure 13(b), showed the appearance of the drug as small white spots adsorbed on the hydrogel. These spots

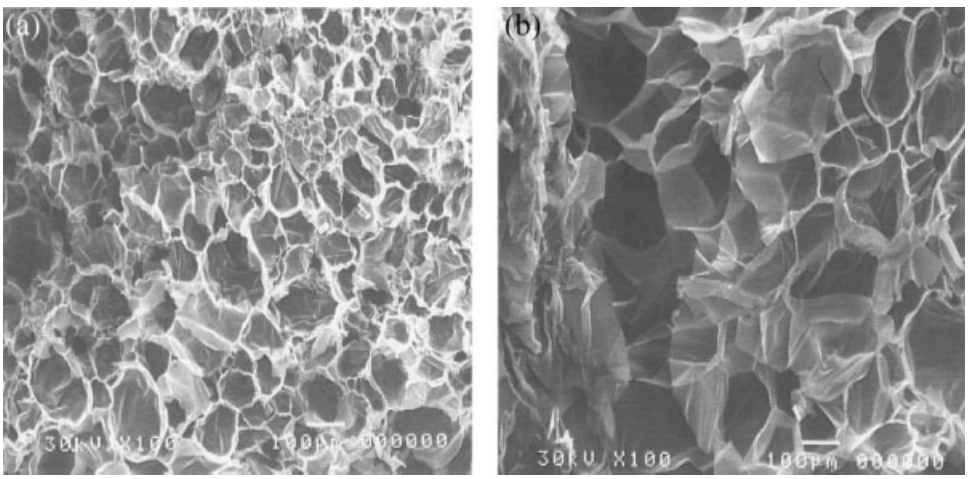


Figure 13 (a) Scanning electron micrographs of P(NVP/IA/G)-1 hydrogel at pH 6. (b) Scanning electron micrographs of P(NVP/IA/G)-1 hydrogel for drug loading by swelling.

indicate the existing of drug occupying the pore space of the hydrogels.

CONCLUSIONS

In this study the sensitive hydrogels with different compositions of P(NVP/IA/G) were prepared by using gamma irradiation. The kinetic study for swelling/degradation of the hydrogels indicated that the swelling % increases as the itaconic acid content increases in the mixture and the addition of gelatin in the hydrogel increases the swelling behavior The kinetic swelling/degradation behavior was found to be nonfickian diffusion ($0.5 < n < 1$). The diffusion exponent (n) and diffusion coefficient (D) for the hydrogels was studied. It was found that the dried hydrogels have stimuli-sensitive property at the specific pH. The release studies show that the drug release behavior of hydrogels is depend on the pH of the external medium, the highest value of release at pH 4. Thus the hydrogels prepared under this conditions can be used as drug delivery system.

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