Interpenetrating Hydrogel Networks Based on Gelatin and Polyacrylamide: Synthesis, Swelling, and Drug Release Analysis

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SYNOPSIS

Interpenetrating hydrogel network has been synthesized from gelatin and polyacrylamide by cross-linking with their respective cross-linking agents. The swelling behavior of this Interpenetrating polymer network (IPN) system was analyzed in water and in citric acid–phosphate buffer solution at various pH. The effect of temperature on swelling behavior of these gels has been analyzed by variation from 25 to 60°C at physiological pH. The drug release behavior of these gels was also analyzed with temperature variation at physiological pH. © 1994 John Wiley & Sons, Inc.

INTRODUCTION

Hydrogels are cross-linked three-dimensional hydrophilic polymer networks that swell, but do not dissolve when brought into contact with water. Much attention has been directed in recent years at hydrogels that undergo large volume changes in response to small variation in external stimuli such as pH and temperature.[1,2] Temperature and pH have been the solution variables of great importance, because these variables change in typical physiological, biological, and chemical systems. Temperature- and pH-sensitive hydrogels have been suggested for use in a variety of novel applications including controlled drug delivery,[3,4] immobilized enzyme reactors,[5] and separation process.[6]

In the recent past, much of work has been carried out on the synthesis and characterization of pH- and temperature-sensitive hydrogels by copolymerization and cross-linking.[2,7-12] The Interpenetrating polymer network (IPN) technique has also been used in a wide range of other applications and several reviews have been published describing both applications and fundamental theory of IPNs.[13,14] Extension of this IPN technique to hydrogels have been reported.[15-17] IPNs are defined as a combination of two or more polymers, each in a network form, at least one of which is synthesized and/or cross-linked in the immediate presence of the other.[18]

In the IPN system, if only one polymer is cross-linked, then the network formed is a semi-IPN. If polymer I is cross-linked and polymer II is linear, then a semi-I-IPN is formed, while a semi-II-IPN is produced from a linear polymer I and a cross-linked polymer II.

Based on our studies on the synthesis and modification of hydrophilic polymers,[19-23] we report on the synthesis of IPNs based on gelatin and polyacrylamide. A wide range of pharmaceutical and medical applications of gelatin and polyacrylamide justify the synthesis of such a network. The primary purpose of this study is to characterize the swelling behavior of the IPN as a function of temperature and pH, as well as the analysis of model drug release behavior with variation of temperature.

EXPERIMENTAL

Materials

The raw materials used have been described in Table I. Acrylamide and bisacrylamide were recrystallized before use, and other materials have been used as received.

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Journal of Applied Polymer Science, Vol. 52, 837–846 (1994)
 CCC 0021-8995/94/070837-10

Table I Raw Materials Employed and Their Source

Case Number	Name and Description	Source
1.	Acrylamide (Aam)	J. T. Baker Chemical Co.[a]
2.	*N,N'*-Methylene bisacrylamide (BIS)	EASTMAN KODAK Co.[a]
3.	Gelatin (Gel) from porcine skin	Sigma Chemical Co.[a]
4.	Glutaraldehyde (GLA) (25% solution)	S. D. Fine Chemicals[b]
5.	Potassium persulfate (KPS)	S. D. Fine Chemicals[b]
6.	Sodium metabisulphite (SMB)	S. D. Fine Chemicals[b]
7.	Citric acid	S. D. Fine Chemicals[b]
8.	Sodium dihydrogen phosphate	S. D. Fine Chemicals[b]
9.	Bromo thymol blue (BTB)	S. D. Fine Chemicals[b]

[a] USA.
[b] India.

Synthesis of Hydrogels

Preparation of Full-IPN (GelX-PAamX)

The initial step is the dissolution of gelatin in hot distilled water for 5 min. To this, acrylamide and *N,N'*-methylenebisacrylamide solution are added and mixed thoroughly followed by the addition of calculated quantities of KPS, SMB, and 25% solution of GLA. The total mixture is stirred well quickly to avoid lumping, poured over a mercury pool, and set aside undisturbed. After the completion of polymerization and gelation, the firm gel, in the form of a thick sheet, is carefully dislodged from the surface of the mercury pool. Identical sizes of gel discs were made by punching the gel sheet with a cork borer of 3.3 cm diameter, and were dried in a dust-free glass chamber at room temperature. The actual composition of each gel is given in Table II.

Preparation of Semi-IPNs and Blend (GelX-PAam, Gel-PAamX and Gel-PAam)

The procedure adopted is the same as that for the full-IPN, except that in semi-I-IPN, bisacrylamide is deleted, and in the semi-II-IPN, GLA is omitted. For the blend, both cross-linkers are avoided.

The drug-loaded discs were made in the same way as mentioned above by the addition of a required

Table II Composition of Gelatin, Acrylamide IPN System

	Composition (g)							
System	GEL	GLA	Aam	BIS	KPS	SMB	H_2O	Gelation
Gel-PAam[a]	5	—	5	—	0.05	0.05	31.0	No
GelX-PAam[b]	5	0.1	5	—	0.05	0.05	31.0	Yes
GelX-PAamX[c]	5	0.1	5	0.1	0.05	0.05	31.0	Yes
Gel-PAamX[d]	5	—	5	0.1	0.05	0.05	31.0	Yes

[a] Gel-PAam.—It is a blend of polyacrylamide and gelatin.
[b] Gel-PAamX.—Semi-I-IPN, where only gelatin is cross-linked.
[c] GelX-PAamX.—Full-IPN where gelatin and polyacrylamide are fully cross-linked with their respective cross-linking agents.
[d] Gel-PAamX.—Semi-II-IPN, where only polyacrylamide is cross-linked.

amount of model drug (BTB) to the solution before polymerization.

Dynamic Swelling Studies

In each experiment, two preweighed, initially dry gel discs were placed in distilled water or buffer solution as per the requirement. Periodically, these samples were removed from the solution and weighed after excess surface water was removed by blotting with a laboratory tissue paper. The gel discs were returned to the solution immediately after weighing.

The swelling capacity of these gels were determined as per the following equation.

Grams of water per gram of polymer sample

$$= \frac{\text{Swollen weight} - \text{Dry weight}}{\text{Dry weight}}.$$

The penetration velocity (v) of buffer in each polymer was determined by weight gain method as described by Peppas and coworkers.[24,25] The penetration velocity was calculated from the slope of the initial portion of the penetrant uptake curve by using the equation

$$v = \frac{1}{2 \cdot \rho \cdot A^*} \frac{dwg}{dt} \qquad (1)$$

where v denotes the penetration velocity, dwg/dt denotes the slope of the weight gain versus time curve, and ρ denotes the density of water at 37°C. A^* denotes the area of the one face of the disc, and factor 2 accounts for the fact that penetration takes place through both sides.

The mass uptake of the swelling solution "Mt" as a function of time "t" was analyzed according to the equation[26]

$$\frac{Mt}{M\alpha} = Kt^n \qquad (2)$$

which could be used to find out the Fickian and nonFickian release behavior. $M\alpha$ is the mass uptake of solvent at equilibrium, "K" is a constant related to the characteristics of the macromolecular matrix, and "n" is the exponent describing the Fickian or Anomalous swelling mechanism. Using the natural logarithm of eq. (2)

$$\ln(Mt/M\alpha) = n \cdot \ln(t) \times \ln(K). \qquad (3)$$

"n" and "k" were calculated from the slope and intercept of plot of $\ln(Mt/M\alpha)$ against $\ln(t)$, respectively.

Using "n" and "K," the diffusion coefficient of solvent in the matrix could be calculated using the following equation.[27,28]

$$K = 4(D/\pi r^2)^n$$

$$4D^n = K(\pi r^2)^n$$

$$D^n = \frac{K}{4}(\pi r^2) \cdot \cdot \cdot \qquad (4)$$

where "D" is the diffusion coefficient and "r" is the radius of the gel disc.

In vitro Release Studies

The drug release experiments were carried out in 100 mL of 0.1 M citric acid–phosphate buffer at various temperatures. The polymer discs were immersed in the buffer medium, and the quantity of drug (Bromothymol Blue) released to the medium was followed by monitoring the UV absorbance of the buffer medium at λ_{max} = 616 nm with Shimadzu 160A UV spectrophotometer. The amount of active ingredient released "Mt" at a time "t" was determined using Beer–Lambert's Law. The total amount of drug incorporated in the disc was taken as "$M\alpha$."

RESULTS AND DISCUSSION

Effect of Cross-linking on Swelling

The presence of solvent surrounding the dry Gel/PAam gel plasticizes the polymer matrix and causes it to undergo a chain relaxation process and swelling. Water absorption of Gel/PAam matrix with time has been shown in Figure 1, which shows higher water absorption for GelX-PAam matrix than it does for Gel-PAamX and GelX-PAamX. Among the three systems, lower swelling associated with GelX-PAamX is expected to be due to the cross-linking of both the matrices. Between the two semi-IPNs, GelX-PAam exhibits higher swelling than does Gel-PAamX.

The advantage in using an Interpenetrating polymer network system is its enhanced physical integrity due to cross-linking. The blend of gelatin and polyacrylamide material, when it comes into contact with water, dissolves within 10 h, however, the GelX-PAam matrix remains undissolved for about 100 h, and, Gel-PAamX and GelX-PAamX remain as such even beyond 100 h. The sorption

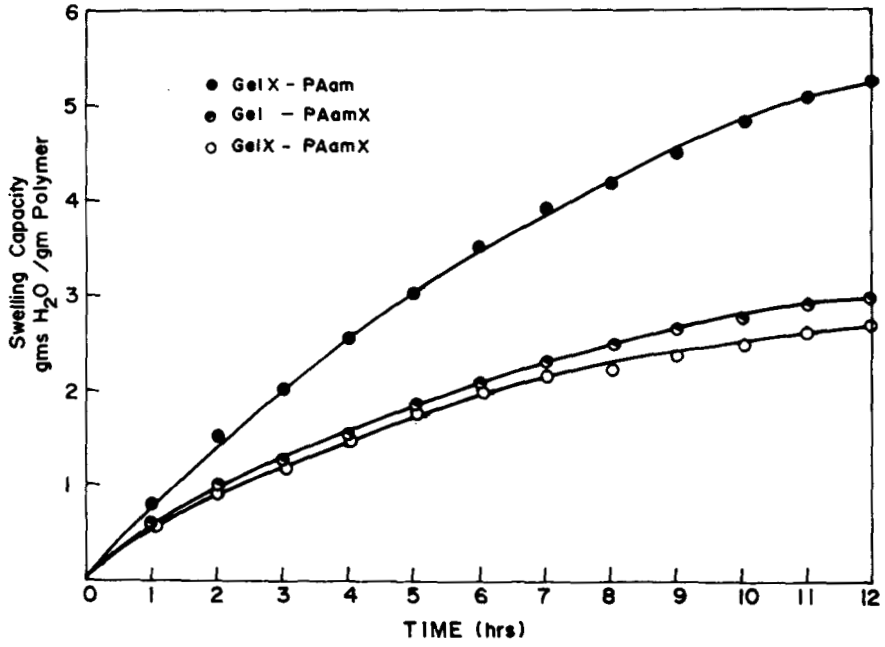


Figure 1 Swelling analysis of Gel/Aam IPN in water at 37°C.

kinetic data presented, clearly indicates that the structural variation of the hydrogel profoundly affects the water sorption kinetics.

Buffer Effect on Swelling Behavior

The influence of solution pH on water sorption kinetics of Gel/PAam IPN system in 0.1 *M* citric acid–phosphate buffer at physiological temperature are shown in Figures 2 and 3. The sorption kinetics are markedly influenced by variation of pH of the buffer. The sorption at low pH (pH = 2, pure citric acid) is significantly higher due to the presence of weak acid groups, because at low pH, the larger presence of carboxylic groups increases the diffusional flux of

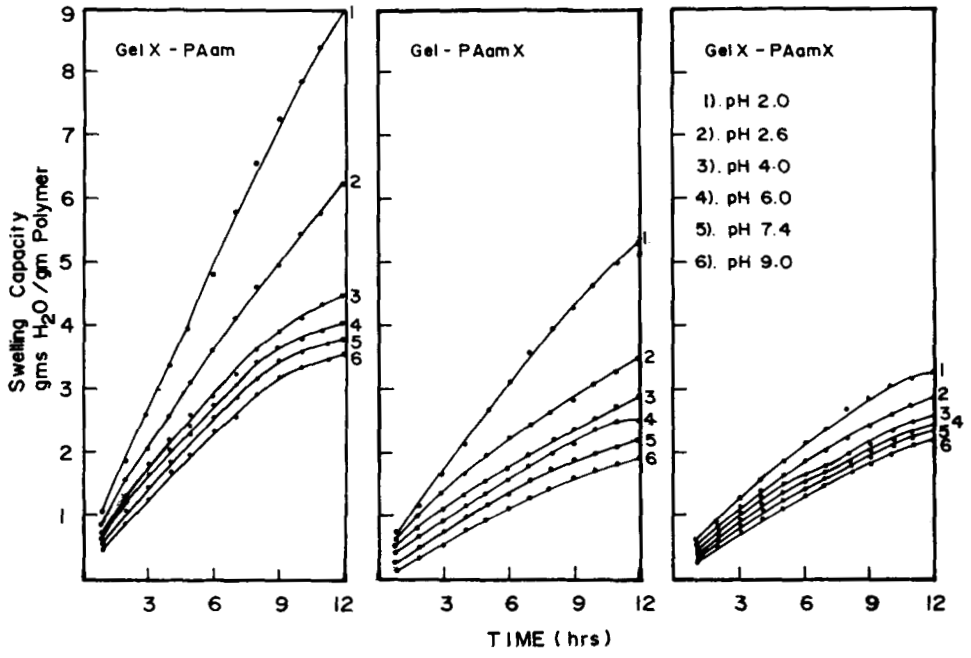


Figure 2 Effect of pH on swelling behavior of Gel/Aam IPN at 37°C.

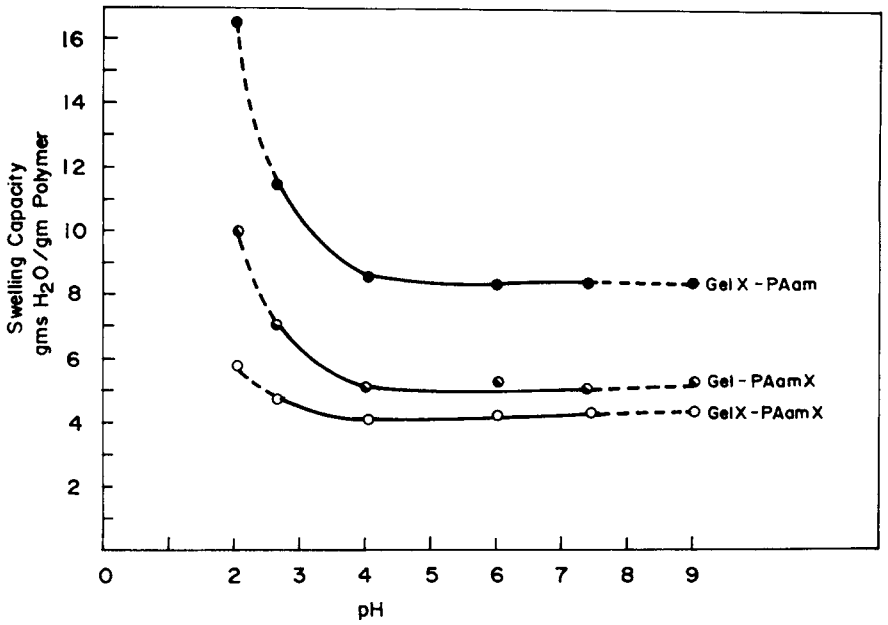


Figure 3 Effect of pH on swelling behavior of Gel/Aam IPN at equilibrium at 37°C.

the carrier species into the hydrogel (carboxyl groups are H^+ ion carriers). As the pH increases, the amount of acidic groups decreases, and the concentration of cations increases in the outer solution. Those cations will be attracted into gel and replace H^+ ions of the available carboxylic acid groups due to the possible hydrolysis of the polyacrylamide under the present temperature and pH. However, the supply of H^+ ions is limited. Eventually, all the available acid groups will be dissociated. So, there

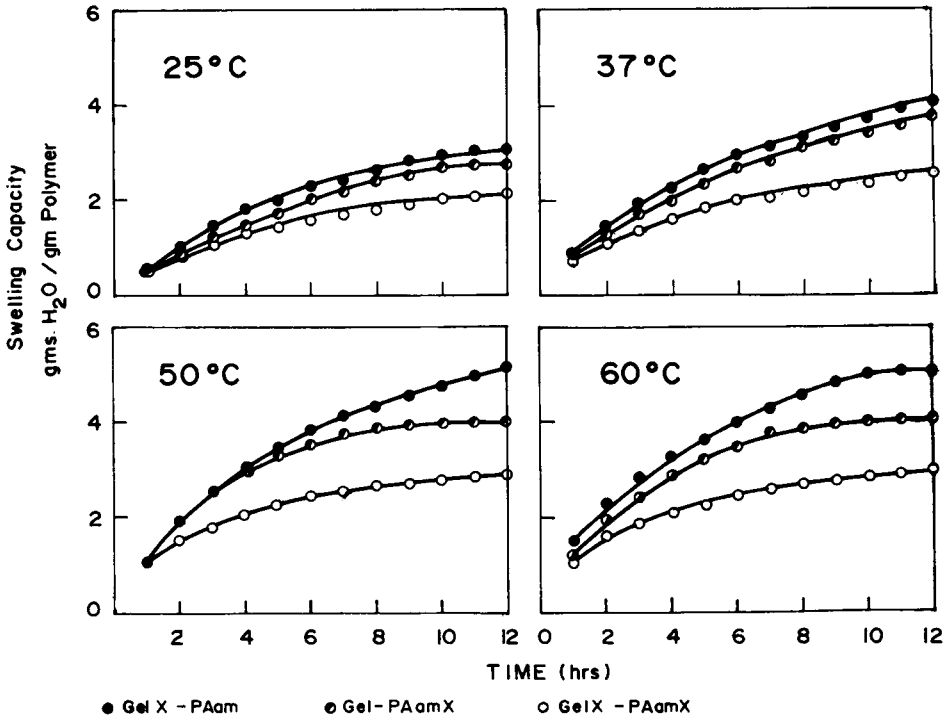


Figure 4 Effect of temperature on swelling behavior of Gel/Aam IPN at pH 7.4.

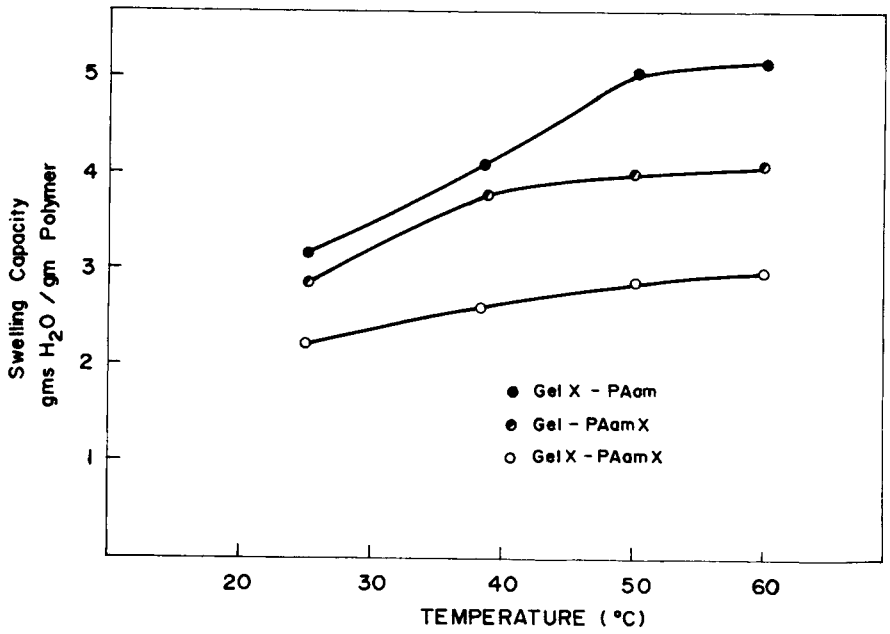


Figure 5 Effect of temperature on swelling behavior of Gel/Aam IPN at pH 7.4.

is no further decrease in the swelling behavior (at pH = 9, pure phosphate solution). In general, GelX-PAam exhibits higher swelling than does either Gel-PAamX or GelX-PAamX.

Temperature-dependent Swelling Behavior

The effect of temperature on swelling behavior of gelatin and polyacrylamide IPN hydrogel has been shown in Figures 4 and 5 by variation of temperature from 25 to 60°C at physiological pH. It is clear from these figures that, as the temperature increases, the swelling capacity also increases. The polymer matrix taken for swelling analysis is in the dry state initially and when it comes into contact with a buffer at physiological pH, it swells. As the temperature increases, the velocity of the swelling front also increases leading to faster swelling as well as higher polymer relaxation. Because of higher chain relaxation, the amide groups of polyacrylamide may become more prone for hydrolysis into acid groups.[29] The swelling capacity of the hydrogel remains con-

Table III Swelling Analysis of Gel/PAam IPN System in Buffer Solution Over a Period of 12 h

Temperature (°C)	System	Swelling Capacity (g H_2O/g POL)	Penetration Velocity ($\nu \times 10^5$ cm/s)	"n"	"k"	Diffusion Coefficient ($D \times 10^6$ cm^2/s)
25	GelX-PAam	3.13	0.95	0.55	0.26	8.01
	Gel-PAamX	2.88	0.91	0.62	0.22	9.81
	GelX-PAamX	2.18	0.79	0.52	0.29	6.19
37	GelX-PAam	4.08	1.13	0.54	0.27	7.84
	Gel-PAamX	4.05	1.11	0.58	0.23	7.67
	GelX-PAamX	2.58	0.85	0.50	0.31	5.78
50	GelX-PAam	5.13	1.56	0.45	0.45	8.98
	Gel-PAamX	4.00	1.52	0.48	0.40	8.71
	GelX-PAamX	2.90	1.01	0.36	0.33	6.94
60	GelX-PAam	5.16	1.41	0.49	0.32	6.65
	Gel-PAamX	4.06	1.23	0.50	0.34	7.63
	GelX-PAamX	2.93	0.91	0.37	0.41	2.04

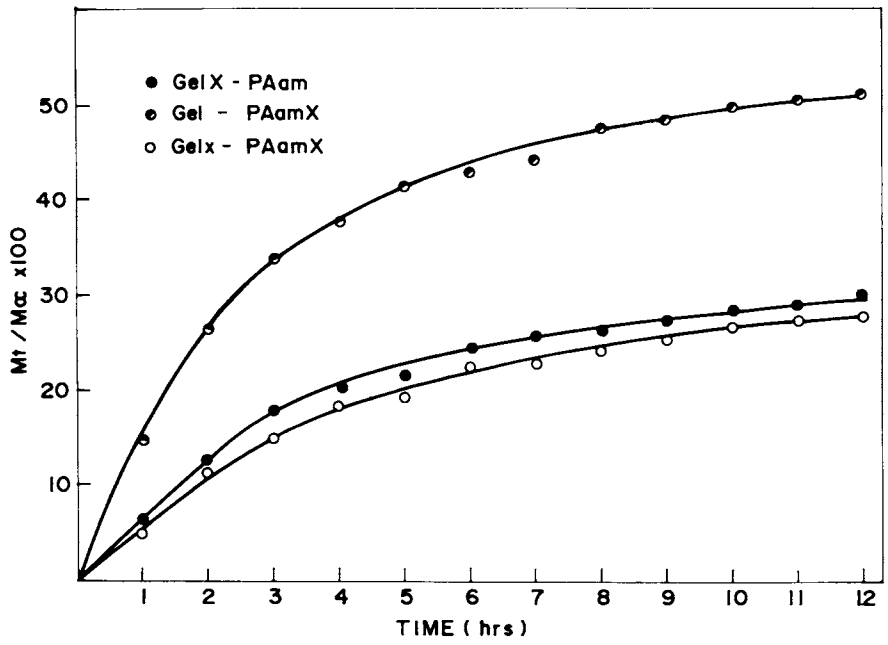


Figure 6 Drug release profile from Gel/Aam IPN at 25°C.

stant after 50°C, which may indicate that all the possible amide groups have been hydrolyzed.

Data shown in Table III indicate an increase in penetration velocity (v) and swelling capacity with an increase in temperature up to 50°C, beyond this they decrease. The swelling exponent "n" and constant "k" calculated using eq. (3) are presented in Table III. It is seen that, as the temperature increases the swelling exponent "n" decreases, suggesting a variation from nonFickian or anomalous ($n = 0.62$) diffusion to Fickian ($n = 0.5$) type. This may be due to the chain relaxation behavior of the network and a certain degree of hydrolysis of acrylamide groups. The diffusion coefficient of the swell-

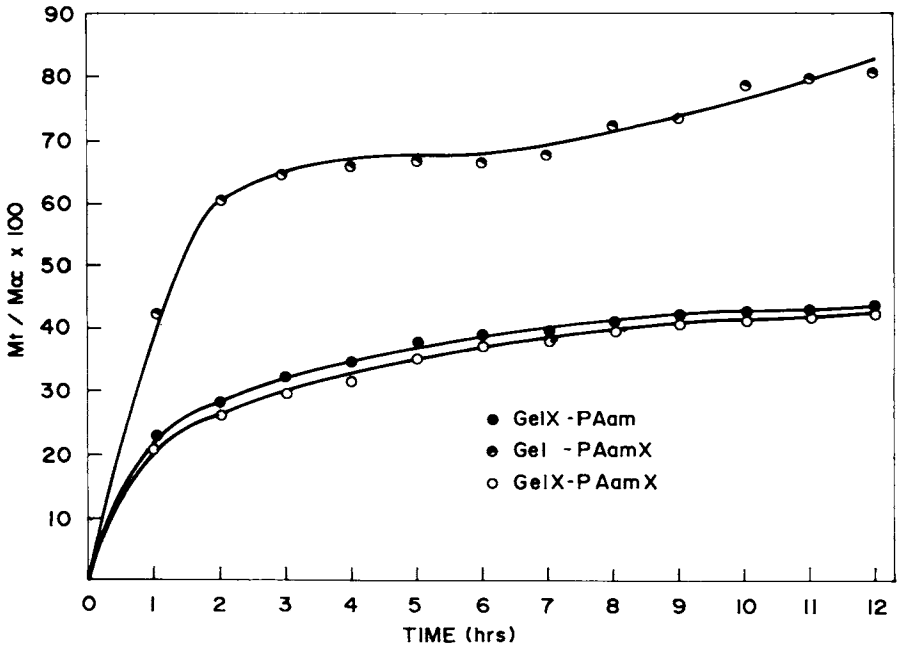


Figure 7 Drug release profile from Gel/Aam IPN at 37°C.

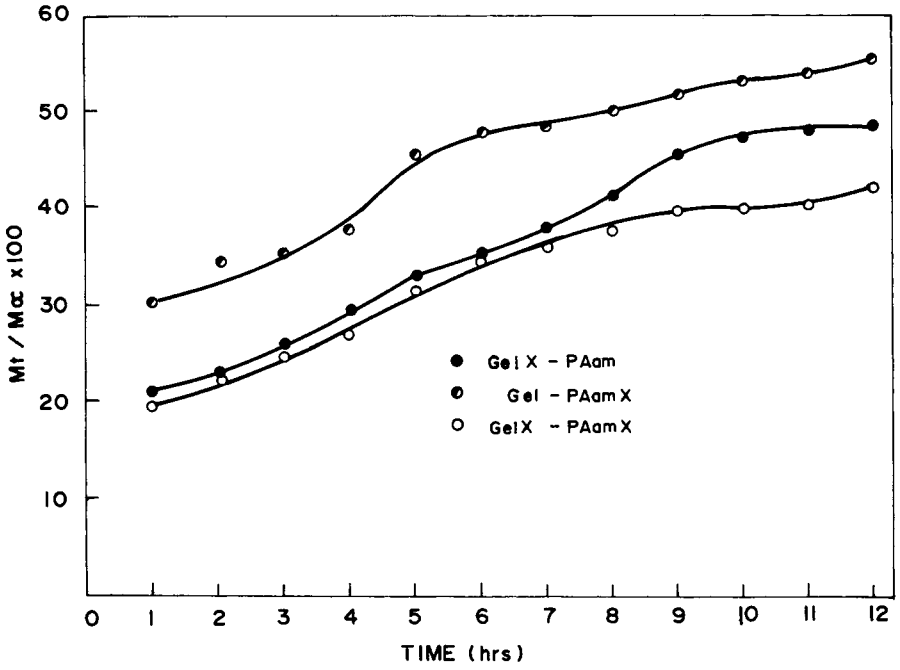


Figure 8 Drug release profile from Gel/Aam IPN at 50°C.

ing solutions calculated using eq. (4) are shown in Table III.

Drug Release Behavior

The model drug release behavior of gelatin and polyacrylamide IPN matrix is shown in Figures 6–10. When the drug-loaded polymer discs come into contact with buffer solution, the loaded drug at the surface of the disc gets released. With an increase in temperature, the trapped drug inside the matrix diffuses out of the device due to the increased chain relaxation. An increase in temperature from 25 to 37°C shows a higher and faster drug release. This

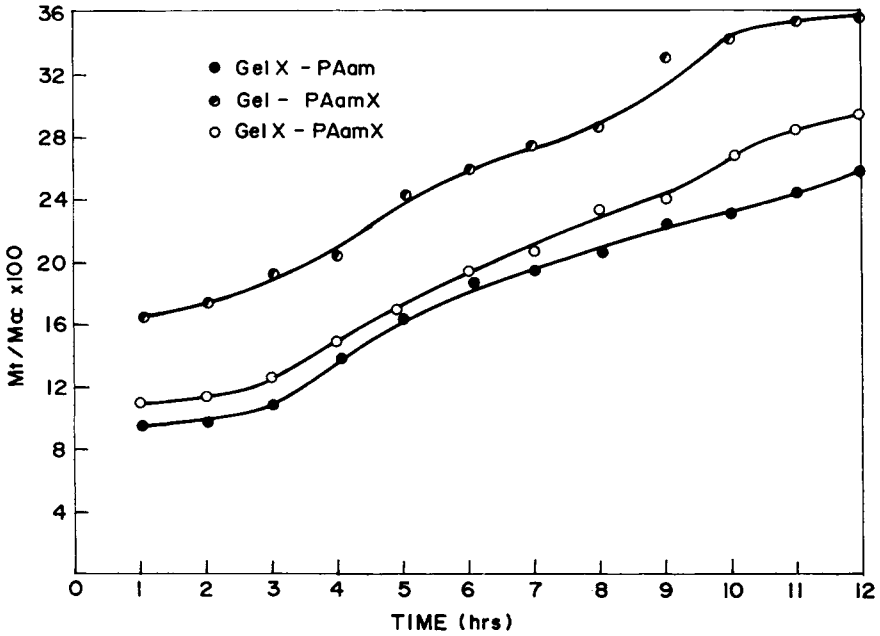


Figure 9 Drug release profile from Gel/Aam IPN at 60°C.

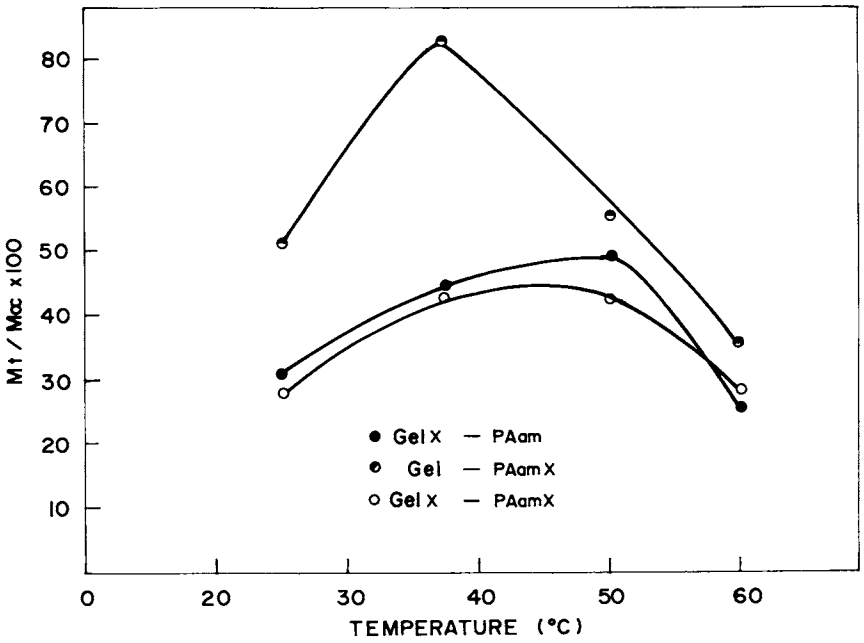
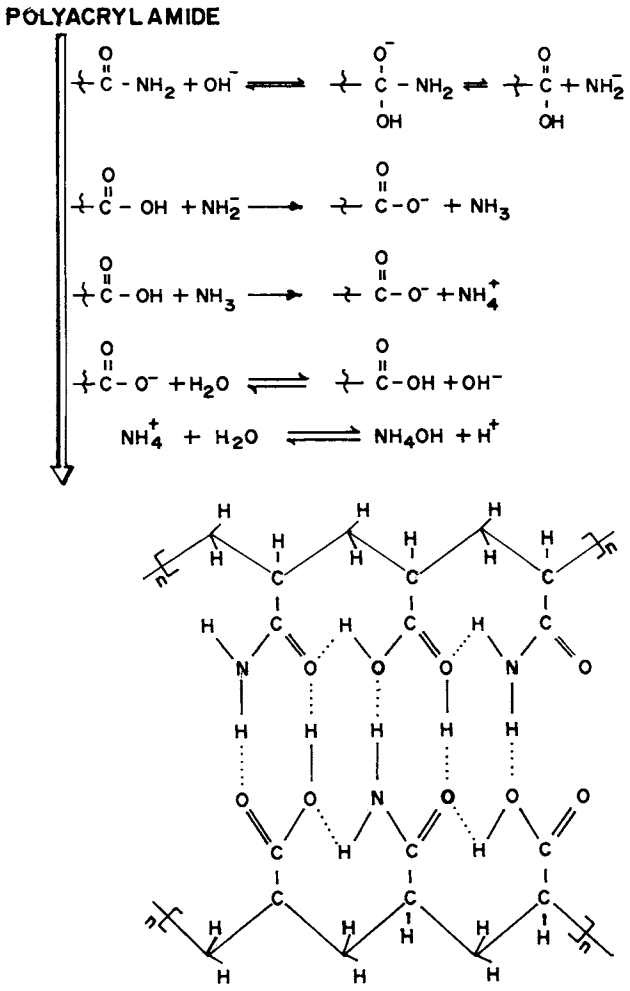


Figure 10 Effect of temperature on drug release profile of Gel/Aam IPN.



Scheme 1

may be due to the extensive swelling and chain relaxation. An increase in temperature beyond 37°C shows a decrease in drug release followed by erratic change. Under this pH, the increase in temperature may have accelerated the hydrolysis of acrylamide groups. So, the polymer matrix will have both acid and amide groups, and the possible interaction between acid and amide groups may lead to a formation of complex structures through hydrogen bonding,[30] which is shown in Scheme 1. Such a tight structure of the complex restricts the mobility of the polymer segments. So, the drug loaded inside the matrix can have only limited release. This may be the reason for the slow drug release beyond 37°C. Even though more swelling occurs with GelX-PAam than with Gel-PAamX, the drug release for the former is lower than for that of the latter for the same reason. It has been established that the gelatin and polyacrylamide IPN systems have a higher drug release rate at physiological temperature (37°C) and at physiological pH.

CONCLUSION

Hydrogels synthesized from gelatin and polyacrylamide in the form of interpenetrating polymer networks are found to have a higher drug release at physiological temperature and pH. This is a system where swelling is augmented with an increase in temperature and GelX-PAam exhibits more swelling than do Gel-PAamX and GelX-PAamX because of structural changes in the polymer network.

One of the authors (B.R.) thanks the University Grants Commission and, Council of Scientific and Industrial Research in India for the financial assistance.

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Received August 4, 1993
Accepted October 13, 1993