Release and Diffusion of Sulfamethoxazole Through Acrylamide-Based Hydrogel

A. K. BAJPAI, M. RAJPOOT

Bose Memorial Research Laboratory, Govt. Autonomous Science College, Jabalpur—482 001, India

Received 25 February 2000; accepted 13 September 2000

ABSTRACT: Two polymeric hydrogels (xerogels) containing poly(vinyl pyrrolidone) (PVP)-crosslinked polyacrylamide and poly(vinyl alcohol) (PVA)-crosslinked polyacrylamide were loaded with the sulfamethoxazole drug and their swelling and drug-release dynamics were investigated at a fixed pH and at room temperature (27°C). The effects of various factors such as the composition of the xerogel, crosslinking density, and drug loading were studied on the swelling and drug-release pattern of the xerogels. The kinetic parameters such as the diffusion exponent (n), diffusion constant (k), and diffusion coefficient (D) were also evaluated and analyzed. The percent drug released by these xerogels was also compared to that by the crosslinked gelatin gels. © 2001 John Wiley & Sons, Inc. J Appl Polym Sci 81: 1238–1247, 2001

Key words: Poly(vinyl) pyrrolidone; Poly(vinyl alcohol); Acylamide; Release; Sulfamethoxazole

INTRODUCTION

Hydrogels are a unique class of polymeric materials which imbibe a significant amount of water into their internal molecular structure and maintain their permanent shape. In the dry state (xerogel) when contact with a thermodynamically compatible solvent (normally aqueous), they undergo a glassy-to-rubbery transition[1] and this property accounts for a great number of applications in biomedical and pharmaceutical fields.[2–5] Some prominent biomedical applications of hydrogels include soft contact lenses, artificial corneas, soft tissue substituents, and burn dressings. Furthermore, the application of hydrogels to a variety of substrates leads to the production of thermoresistant coatings, catheters, and blood detoxicants. Finally, hydrogels may be impregnated with biologically active agents, such as antibiotics, enzymes, contraceptives, drug antagonists, anticoagulants, and anticancer drugs and may serve as systems for the controlled release of the agents absorbed over a prolonged time period at a specific site of the body. Thus, one of the most potential applications of a hydrogel in pharmacy is the controlled drug-delivery system (CDDS),[6–8] where the dry-loaded polymer delivers a regulated amount of an entrapped drug into the surrounding receptor medium. This situation is normally demanded in therapeutic applications where only the necessary dose of the drug is needed for a certain purpose. Although a large variety of natural polymers such as cellulose, gelatin, collagens, and chitosan[9] has been employed as drug carriers, however, synthetic macromolecular systems have certain advantages also as they offer a wide choice for alteraion of their drug-release characteristics through manipulation of the chemical architecture of the hydrogel.[10] It is also required that apart from a desirable drug-release mechanism the hydrogel must also be nontoxic and mechanically good enough. Poly-

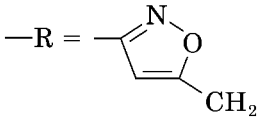
Correspondence to: A. K. Bajpai.

Journal of Applied Polymer Science, Vol. 81, 1238–1247 (2001)

mers like poly(vinyl alcohol) (PVA) and poly(vinyl pyrrolidone) (PVP) meet these requirements very well.

Normally, there are two methods for the loading of hydrogels as drug carriers. In one method, the hydrogel monomer is mixed with the drug, an initiator, and a crosslinker and allowed to polymerize, trapping the drug within the matrix.[11] In the second approach, a preformed hydrogel is allowed to swell to equilibrium in a suitable drug solution and then the drug-loaded hydrogel is dried and the device is obtained.

Although extensive release studies have been reported on the variety of drugs,[12–16] however, sulfonamide drugs have drawn little attention from researchers. Sulfa drugs, known also as sulfonamides (NH_2—C_6H_4—SO_2NHR), are antibacterial chemicals. To cure the bacterial infectious cells, they neither interfere with the development of specific antibodies as a response to infection nor are the antigenic properties of the infective organism significantly affected. These drugs act on the bacteria bacteriostatically or germicidaly and have no effect on the smooth muscles, heart, blood pressure, or respiration.[17] Thus, due to their physically inert nature, the sulfonamaid compounds have received much attention in medical science. Looking to the potential utility of sulfonamides, the present study aimed at reporting the results of the controlled-release behavior of a model sulfa drug, sulfamethoxazole (SM), where



through a polymeric hydrogel of crosslinked polyacrylamide and PVA and PVP.

EXPERIMENTAL

Acrylamide (Libichem Ltd., U.K.) was recrystallized twice from methanol (A.R.) and dried over a vacuum at 84°C for 1 week. PVP (MW ca. 40,000; BDH Chemicals Ltd. Poole, England), PVA (MW ca. 50,000, Kuraray Co. Ltd., Japan), gelatin (Aldrich), *N*-*N*′-methylenebisacrylamide (MBA; Wako Pure Chemical Co. Ltd. Osaka, Japan), glutaraldehyde (Aldrich), and potassium persulfate (KPS; Fluka Chemical Co. Buchs, Switzerland) were used as received. SM (mp 166°C) was obtained from Fisher Scientific Co. (New Jersey, USA) and used without any purification. Other chemicals used were of A.R. grade, and throughout the experiment double-distilled water was used.

Gel Preparation

The gel was prepared by free-radical polymerization of acrylamide in the presence of PVA (or PVP) and a crosslinking agent. In brief, the percent composition of the feed mixture and the method may be described as below:

Into a 4-inch diameter Petri dish were placed SM (3.4% w/v), AM, and PVA (2.85% w/v of each), KPS (0.28% w/v), and MBA (0.14% w/v) and the mixture was kept at 80°C for 10 min so that the whole solution was converted into a gel type of a solid mass. The gel so-formed was dried at 60°C for 24 h. In a similar way, the hydrogels (xerogel) of PVP were also prepared.

For preparing a gelatin-based xerogel, 1.25 g of gelatin was dispersed in 30 mL of water at 60°C and the solution was crosslinked by adding 5 mL of glutaraldehyde in the presence of 1.5 g of SM. The gel so-formed was dried at 80°C overnight to obtain a thin film of the xerogel.

Release and Swelling Measurements

To perform swelling and drug-release experiments, preweighed (0.1 g) squared-shaped (1.0 × 1.0 × 0.045 cm) pieces of the gel were left in different beakers containing 50 mL of water at the required pH (7.2) and ionic strength (0.01*M* NaCl). The release of SM in the external solution was monitored, performing several identical experimental runs simultaneously and by taking a 5.0-mL aliquot from each solution at different time intervals and estimating the SM colorimetrically[18] as given below:

In a Corning flask, 2.0 mL of the drug solution was taken and to that was added 15.0 mL of the buffer solution (pH 3.0) followed by the addition of 2.0 mL of a freshly prepared 0.2% 4-*N*-methylaminophenol sulfate solution and 3.0 mL of a potassium dichromate solution. The solution was further diluted to 25.0 mL by distilled water in a standard flask and the amount of the drug determined by a calibration curve.

The swollen samples were also weighed at various time intervals after pressing the swollen pieces gently between two filter papers to remove

the excess water from the hydrogel surface. The swelling ratio (S.R.) was calculated using the following formula:

$$\text{S.R.} = \frac{\text{weight of swollen gel}}{\text{weight of dry gel}}$$

As the swelling of the gel and release of SM occur simultaneously, the loss in weight of the swollen gel due to SM release was compensated by adding the released amount of SM to the weight of the swollen gel. All experiments were done in replicate numbers and the results found were quite reproducible.

RESULTS AND DISCUSSION

Mechanism of Drug Release

Recent years have witnessed considerable efforts in understanding the mechanism of drug release from hydrogel matrices.[19] McNeill and Graham[20] considered a water-swollen hydrogel as a two-component system which may be imagined as a physically strong polymer network structure between the strands of which are water-filled permeation channels. The water may be structurally bound to the polymer or of a modified water structure or similar to normal water in the pure free state. The water occupies the permeation channels when the water-soluble solutes diffuse out to the external receptor medium from within the gel. It is also known that the swelling properties of a crosslinked polymer are controlled by the combination of free energies of mixing between the solvent and polymer chains and by the elastic response of the network to a volume increase due to solvent sorption.[21] At equilibrium, the elastic response of the network exactly offsets the swelling potential of the solvent within the network.[22] A free-volume theory assumes that the free volume of the water present in the hydrogel is available for the diffusion of water-soluble solutes.[23] The theory implies that the free volume in a polymer may be thought of as the volume fraction of molecular sieve holes available for diffusion. It has also been described that the release of a water-soluble active agent from a hydrogel carrier in the form of a slab is to a large part determined by the water content of the hydrated polymer.

It is thus clear that when a drug-delivery system comes into contact with a solvent, relaxation of polymer chains takes place. This happens when the characteristic glassy–rubbery transition temperature of the polymer is decreased below the temperature of the experiment. The dissolved drug diffuses into the external-receiving medium, crossing the swollen polymeric layer formed around the matrix. Depending on the rate of the swelling process, the associated drug release may be Fickian or non-Fickian.[24] The whole mechanism of drug release is modeled in Figure 1.

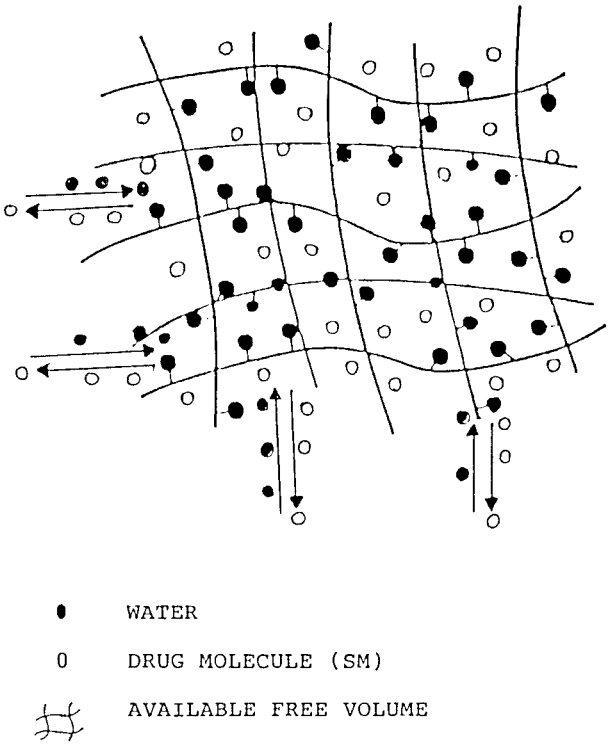


Figure 1 Model depicting release of drug (SM) from swollen hydrogel.

Kinetics of Swelling and Release

In evaluating the potential of a polymer device for drug delivery, by far the most important period is from the beginning until the half-life time. Most release systems slow down exponentially in the later slopes to a rate which may be therapeutically ineffective. It is, therefore, more beneficial to concentrate on the behavior of the first 50–60% of the total drug released.

Theoretically, the driving force for diffusion is the gradient of chemical potential; however, it is more usual to consider the diffusion process in terms of the concentration gradient, dc/dx,[25]

$$J = -D(dc/dx)$$

Table I Diffusion Coefficient (*D*) for PVA and Diffusion Exponent (*n*) and Diffusion Constant (*k*) for PVP and PVA Hydrogels of Four Different Amounts of Acrylamide at [PVP]/[PVA] = 2.85 g % (w/v), [SM] = 2.85 g % (w/v), [MBA] = 0.14 g % (w/v), and Temperature of 27 ± 0.2°C

Amount of Acrylamide (g %, w/v)	PVP		PVA		
	k	*n*	*k*	*n*	*D* ($cm^2\ s^{-1}$) $\times 10^{-7}$
1.43	0.04	0.61	0.03	0.48	38.51
2.85	0.07	0.63	0.07	0.49	40.89
4.28	0.12	0.63	0.11	0.49	42.08
5.71	0.01	0.60	0.01	0.48	34.14

where J is the flux of a mobile component across the plane of an unit area and D is the diffusion coefficient.

Although diffusion within a film is random and three-dimensional, diffusion across the film/sink interface is effectively one-dimensional and perpendicular to the surface. If a hydrogel film is equilibrated with a drug by soaking the drug hydrogel (xerogel) in an aquous solution of the drug, the film can act as a vehicle for subsequent release of the drug when it is transferred to an aqueous sink. Release of the solute from a slab can be regarded as one-dimensional if it takes place predominantly from the two main surfaces, and according to Crank,[26]

$$M_t/M_\infty = 1 - \sum_{n=0}^{\infty} \{8/(2n+1)^2\pi^2\} \times \exp\{-D(2n+l)^2\pi^2 t/4t^2\}$$

where M_∞ is the total drug content; M_t, the amount desorbed at time t; l, the film thickness; and n, an integer. This equation can be reduced to a simplified form still 99% accurate:

$$M_t/M_\infty = 4\left(\frac{Dt}{\pi l^2}\right)^{0.5}$$

for $0 \le M_t/M_\infty \le 0.6$.

These are early-time equations. Crank also derived equations for the second half of the release, termed the late-time equations. For the slab,

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2} \cdot \exp\left[\frac{\pi^2 Dt}{l^2}\right]$$

A more realistic view can be constructed about the release mechanism when the release and swelling data are analyzed in light of the following equation:

$$\frac{W_t}{W_\infty} = kt^n$$

where W_t/W_∞ is the fractional release at time t and k is a rate constant. The exponent n is an important indicator of the mechanism of transport and, in general, has a value between 0.5 and 1.[27] When $n = 0.5$, the release is taken to be Fickian. When $n = 1$, the release is zero order, that is, a constant with time. In between these values, that is, $0.5 < n < 1$, the release is described as anomalous. The closer n is to 1, the closer is the release pattern to a steady-state release. When $W_t/W_\infty = 0.5$, t is the half-life, another extremely useful parameter in comparing systems. It is noteworthy here that an anomalous release pattern is an indication of the contribution of non-Fickian processes such as polymer-chain relaxation toward the drug-release mechanism. The kinetic results are presented in Tables I–III and their significance is discussed in the last section.

Effect of PVA and PVP

A hydrogel is often sensitive to the external environment in the swelling system as well as to its

Table II Diffusion Coefficient (*D*) for PVA and Diffusion Exponent (*n*) and Diffusion Constant (*k*) for PVP and PVA Hydrogels of Four Different Amounts of Crosslinker, MBA, at [PVP]/[PVA] = 2.85 g % (w/v), [SM] = 2.85 g % (w/v), [AM] = 4.28 g % (w/v), and Temperature of 27 ± 0.2°C

Amount of Crosslinker (g %, w/v)	PVP		PVA		
	k	*n*	*k*	*n*	*D* ($cm^2\ s^{-1}$) $\times 10^{-7}$
0.07	0.25	0.57	0.11	0.50	29.38
0.14	0.30	0.60	0.27	0.51	36.92
0.21	0.28	0.56	0.19	0.51	32.95
0.28	0.20	0.56	0.06	0.49	25.01

Table III Diffusion Coefficient (D) for PVA and Diffusion Exponent (n) and Diffusion Constant (k) for PVP and PVA Hydrogels of Four Different Amounts of Loaded Drug (SM) at [PVP]/[PVA] = 2.85 g % (w/v), [MBA] = 0.14 g % (w/v), [AM] = 4.28 g % (w/v), and Temperature of 27 ± 0.2°C

Amount of Loaded Drug (g %, w/v)	PVP		PVA		
	k	n	k	n	D ($cm^2\ s^{-1}$) $\times 10^{-7}$
2.85	0.10	0.58	0.07	0.49	23.82
3.57	0.14	0.58	0.10	0.49	25.41
4.28	0.20	0.60	0.16	0.50	28.58
5.00	0.30	0.62	0.27	0.52	30.57

chemical composition. In the present study, the effects of variation in the amounts of PVA and PVP in the hydrogel were investigated on their swelling and release behavior by varying the amounts of PVA and PVP in the feed mixtures in the range 1.42–5.70% (w/v). The results indicate that with increasing amounts of PVA and PVP the swelling ratio and fractional release increase, while beyond a definite amount of PVA (2.85% w/v) and PVP (2.85 w/v), both start decreasing. The results are quite expected also and may be attributed to the fact that as these polymers are hydrophilic in nature their increasing amounts will certainly result in a greater swelling and drug release. However, beyond an optimum concentration of these polymers, the macromolecular chains become more crowded in the hydrogel and thus reduce the available free volume between the polymer segments. This obviously lowers the swelling ratio and drug release to a considerable degree. The results also indicate that the PVP gels exhibit a greater swelling and drug release than that of the PVA gels, which is obvious also, as, because of the well-known binding property of PVP chains, they bind to themselves with a greater number of SM molecules and thus produce greater swelling and drug release.

Effect of Monomer

When the concentration of acrylamide is varied in the feed mixtures in the range 1.0–6.0 g % (w/v), the swelling ratio and drug released increase to 4.28% of acrylamide and, thereafter, a decrease is observed with further increase in the amounts of

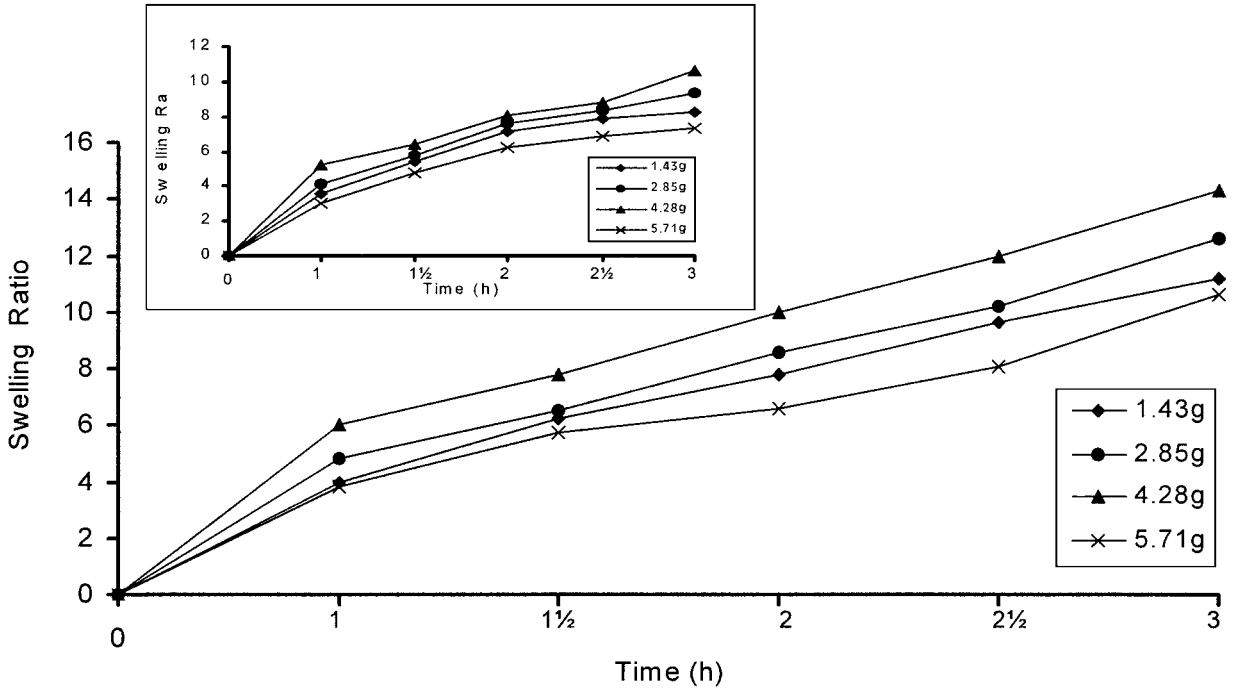


Figure 2 Effect of varying amounts of acrylamide (%, w/v) in PVP xerogel on water-sorption kinetics at [PVP] = 2.85 g % (w/v), [SM] = 2.85 g % (w/v), [MBA] = 0.14 g % (w/v), and temperature = 27 ± 0.2°C. Inset picture shows similar results with PVA xerogel.

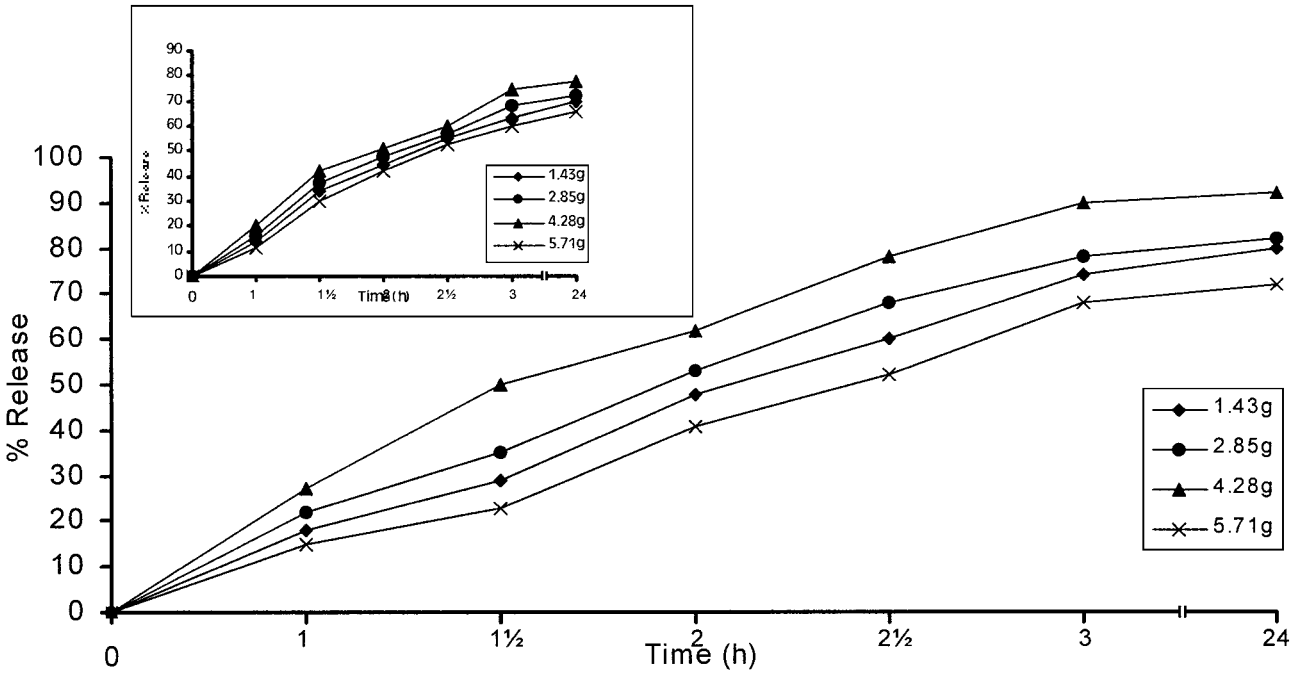


Figure 3 Effect of varying amounts of acrylamide (%, w/v) in PVP xerogel on release of SM at [PVP] = 2.85 g % (w/v), [SM] = 2.85 g % (w/v), [MBA] = 0.14 g % (w/v), and temperature = 27 ± 0.2°C. Inset picture shows similar results with PVA xerogel.

acrylamide (as shown in Figs. 2 and 3). The results are quite usual as increasing amounts of acrylamide, a hydrophilic monomer, will result in a greater number of hydrophilic polyacrylamide chains and this, in turn, results in a larger swelling and drug release. However, beyond 4.28 g acrylamide, the macromolecular chains become dense and, thus, the penetrant water molecule has difficulty entering the hydrogel and, consequently, the swelling and release of the drug molecules decrease. The monitoring of swelling and release processes was carried out for 3 h only, as beyond this period, the swelling and the drug release did not increase significantly.

Effect of Crosslinking Density

The effect of the degree of crosslinking on the swelling ratio and drug release was investigated by adding 0.05–0.3 g % (w/v) of MBA to the feed mixture of the polymerization recipe. The results are shown in Figures 4 and 5, which indicate that, initially, the swelling ratio and drug release increase to 1.43 g % of the crosslinker, while beyond this optimum concentration of the crosslinker, both the swelling rate and the drug release decrease. The cause of the initial increase is quite obvious, as with increasing MBA, which is itself a hydrophilic monomer, the swelling ratio will also increase and this will also bring about a proportional increase in the drug release. Beyond an optimum concentration of the crosslinker, the number of crosslinks increases so much that penetration of the water molecules and the diffusion of the drug molecules become difficult.

Another explanation for the observed decrease in the swelling ratio and drug release may be that increasing the crosslinking ratio lowers the average molecular weight between the crosslinks and this, consequently, reduces the free volume accessible to the penetrant water molecules. Similar results were also noticed by other workers.[28]

Effect of Drug Loading

An important aspect in the use of hydrogels as drug vehicles is the effect of the drug-loading level on the drug-release rate. For this purpose, various amounts of SM in the range 2.85–5.0 g % (w/v) were added to the feed mixture of the hydrogel synthesis and, in this way, increasing doses of the drug were loaded onto the xerogel. The results are depicted in Figures 6 and 7, which indicate that with increasing drug loading the swelling ratio and drug release increase and become optimum for 5.0 g % of the loaded drug. The results are

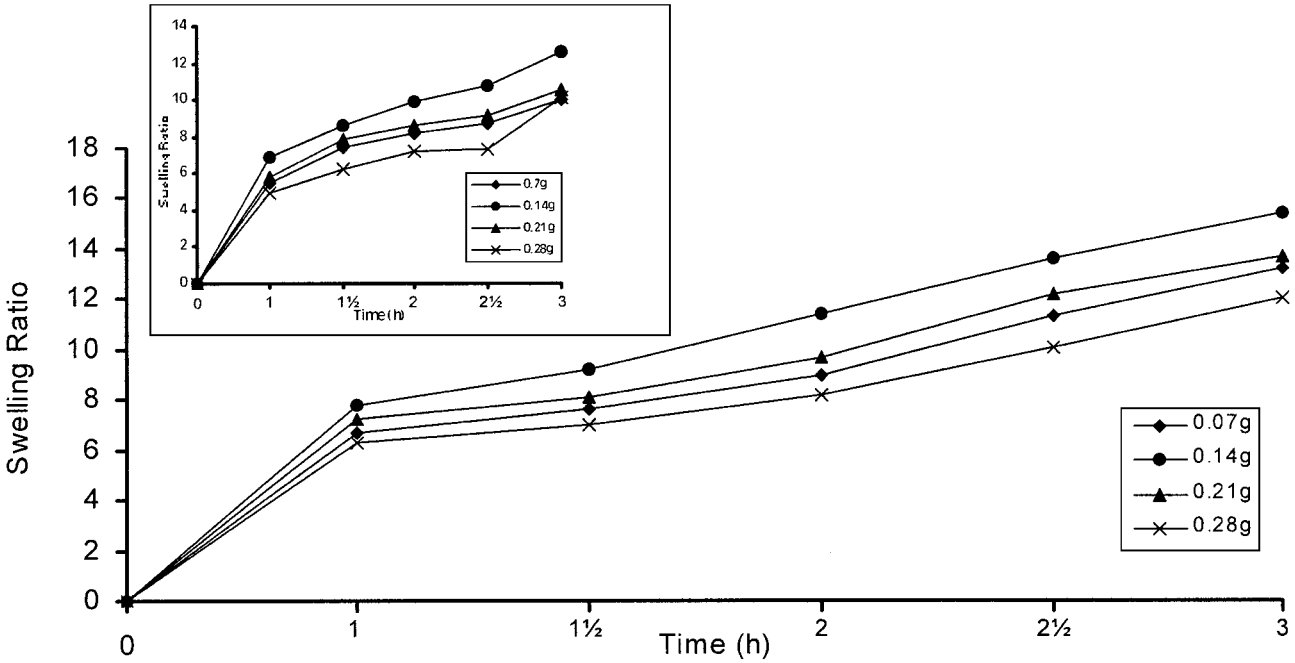


Figure 4 Effect of varying amounts of crosslinker, MBA (%, w/v) in PVP xerogel on water-sorption kinetics at [PVP] = 2.85 g % (w/v), [SM] = 2.85 g % (w/v), [AM] = 4.28 g % (w/v), and temperature = 27 ± 0.2°C. Inset picture shows similar results with PVA xerogel.

quite expected, as the larger is the initial load, the faster is the movement of the solvent front penetrating the surface of the xerogel slab.[29] A greater swelling with larger drug loading may be attributed to the fact that the polar SM molecules cause greater interaction with the penetrant water molecules and thus produce a larger chain relaxation within the xerogel.

Analysis of Kinetic Results

Tables I–III present data on the kinetics constants of swelling and diffusion processes at varying additions of acrylamide, SM, and the crosslinker (MBA), respectively. It is worth mentioning here that in the case of PVP-based gels the swelling and release processes were found to follow a non-Fickian type of behavior ($n > 0.5$) so that the values of the diffusion constants (D) were computed only for PVA-based gels.

It is clear from Table I that on increasing the amount of acrylamide in the PVP xerogel the value of n slightly increases from 0.61 to 0.63, indicating that the diffusion is of an increasing non-Fickian value. Further, a decrease in the value of n implies a decreasing tendency of chain relaxation, and also due to an increasing number of polyacrylamide chains, their relaxation may be hindered because of the crowding of macromolecular chains in the xerogel. On the other hand, the PVA xerogel shows a good Fickian behavior. This may be due to the lesser relaxational tendency of the PVP chains because of H bonding in the xerogel.

The effects of the crosslinker on the values of n and D are summarized in Table III. The results indicate that, initially, the value of n increases with an increasing amount of crosslinker (to 0.14 g %) in the PVP xerogel and then it decreases. The reason for the observed results is quite obvious, as with an increasing MBA concentration, the diffusion becomes more anomalous, implying that the process of diffusion is increasingly contributed to by the chain relaxation. However, beyond an optimum concentration of the crosslinker (0.14 g %), the relaxation of polymeric chains becomes difficult because of high crosslink density in the network and this results in a lower swelling and drug release as well. As observed previously, a full Fickian behavior is also seen with the PVA xerogel.

As evident from Table II, the swelling exponent n continues increasing with an increasing loading of the SM drug in the PVP xerogel. This obviously

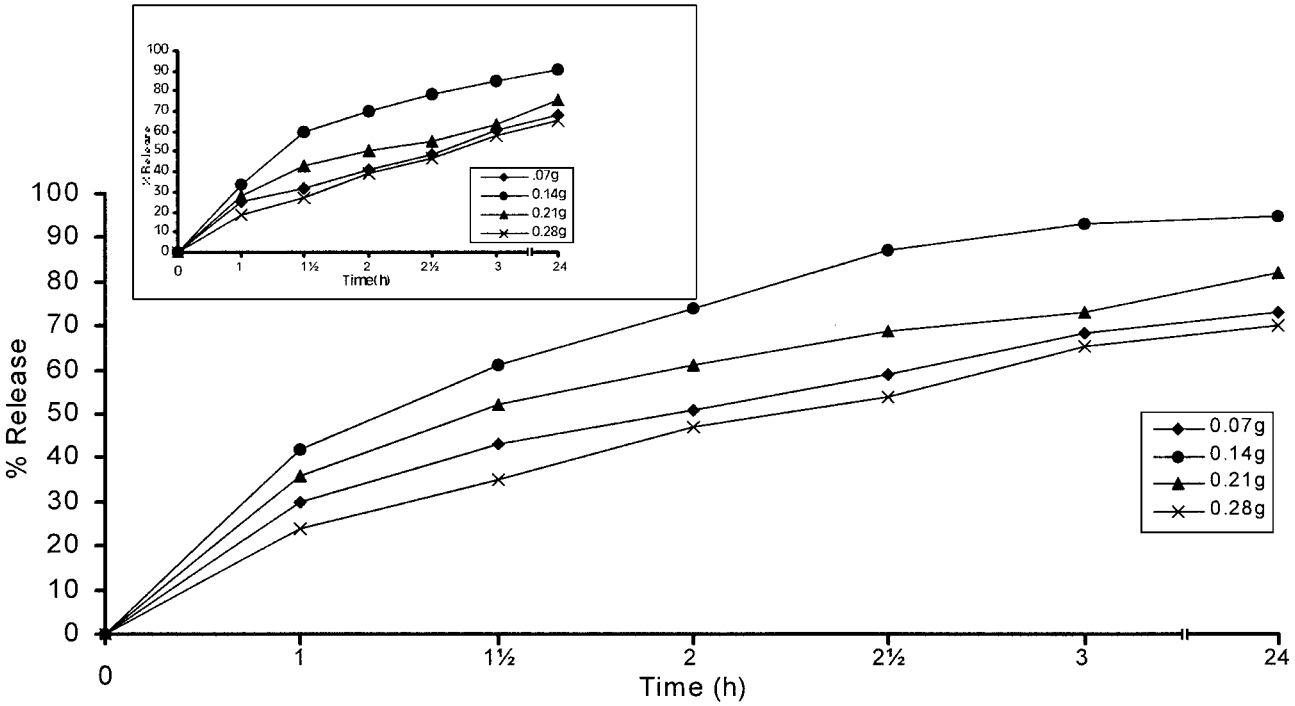


Figure 5 Effect of varying amounts of crosslinker MBA (%, w/v) in PVP xerogel on release kinetics of SM at [PVP] = 2.85 g % (w/v), [SM] = 2.85 g % (w/v), [AM] = 4.28 g %, and temperature = 27 ± 0.2°C. Inset picture shows similar results with PVA xerogel.

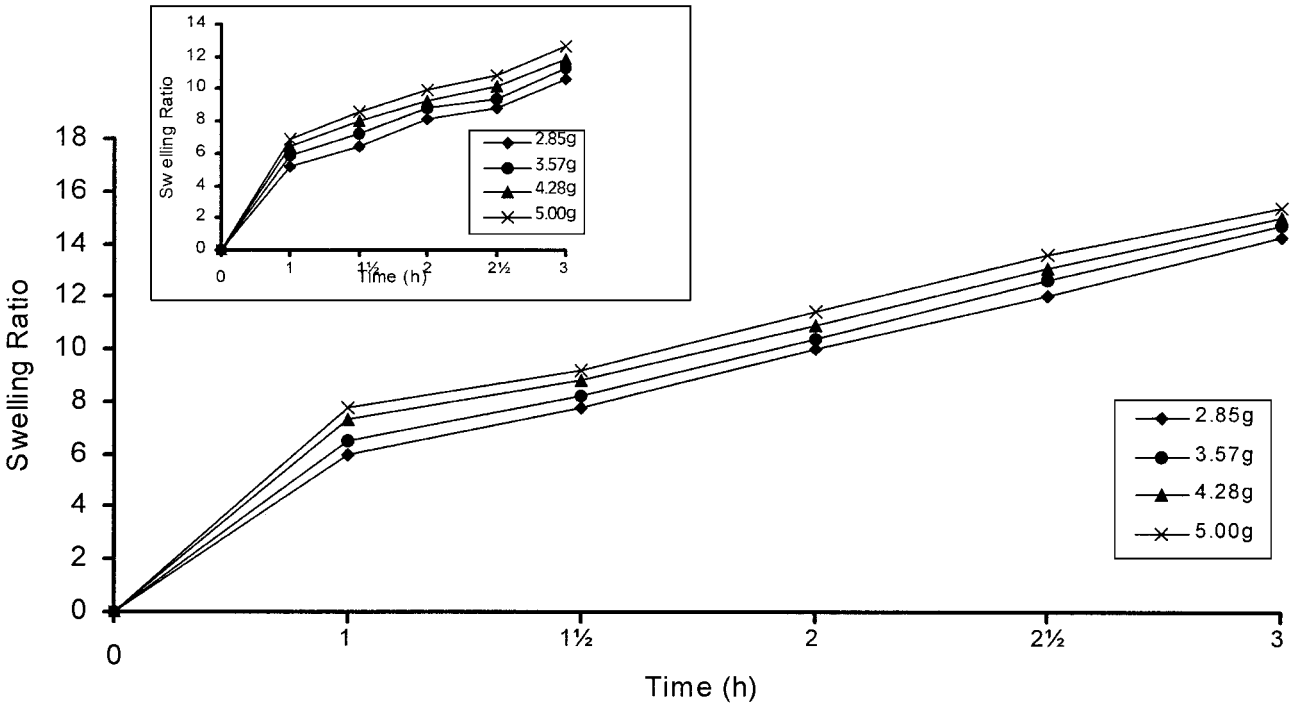


Figure 6 Effect of varying amounts of loaded drug (SM, %, w/v) in PVP xerogel on water-sorption kinetics at [PVP] = 2.85 g % (w/v), [MBA] = 0.14 g % (w/v), [AM] = 4.28 g %, and temperature = 27 ± 0.2°C. Inset picture shows similar results with PVA xerogel.

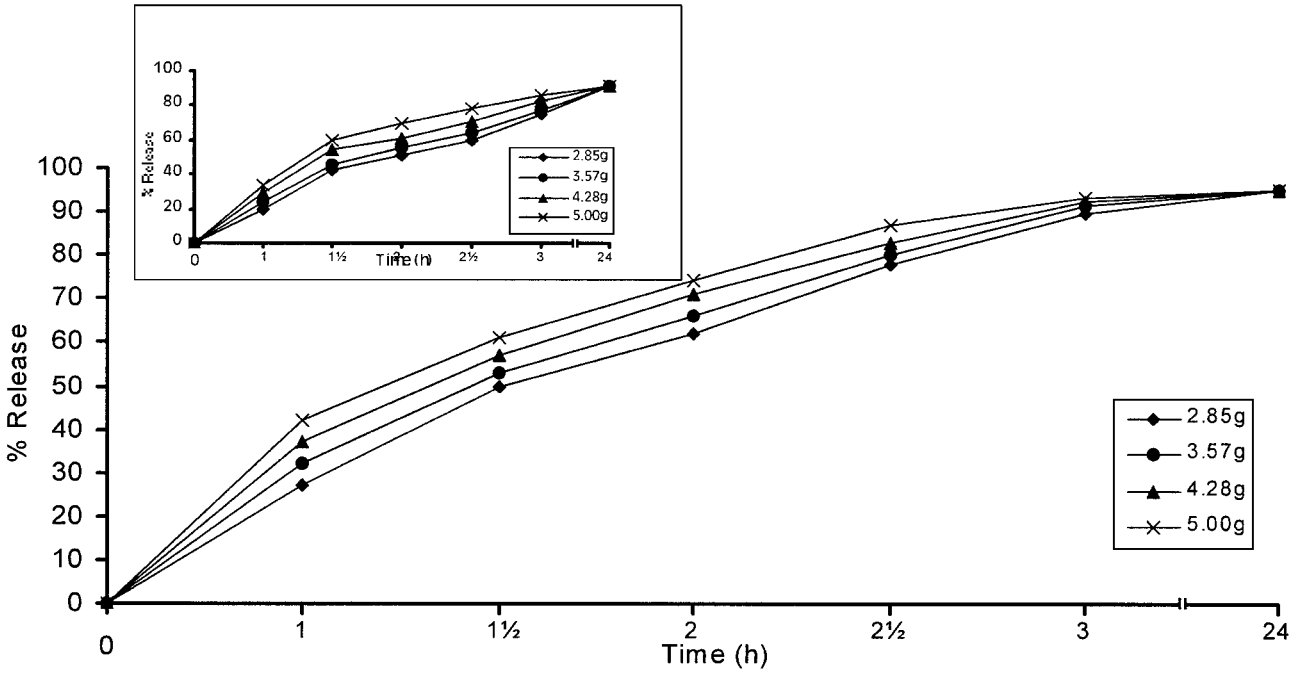


Figure 7 Effect of varying amounts of loaded drug (SM, %, w/v) in PVP xerogel on release kinetics of SM at [PVP] = 2.85 g % (w/v), [MBA] = 0.14 g % (w/v), [AM] = 4.28 g %, and temperature = 27 ± 0.2°C. Inset picture shows similar results with PVA xerogel.

implies an increasing chain relaxation of the macromolecular chains, which may be attributed to the fact that with greater drug loading of the xerogel the free volume between the polymer chains is occupied by the drug molecule and their interaction with water molecules facilitates the relaxation process and accounts for an increasing non-Fickian process. On the contrary, with the PVA xerogel, the diffusion appears to obey Fickian kinetics.

Drug Release Through Gelatin Gel

When the release of SM is carried out with crosslinked gelatin gels (pieces of same dimension as of PVP/PVA-based gels), it is found that about 80% of the drug was released in just 50 min, while to release to the same extent, the PVP and PVA xerogels required more than 180 min. This obviously proves the controlled-release property of the prepared xerogels.

CONCLUSIONS

PVP-based polyacrylamide hydrogel (xerogel) exhibits greater swelling and drug release than those shown by PVA-based polyacrylamide hydrogels. The swelling ratio and SM (drug) release vary with varying amounts of the PVP, PVA, acrylamide, crosslinking agent, and drug loadings. It was observed that the drug release approaches a more non-Fickian to a less non-Fickian behavior with an increasing amount of the monomer in the PVP xerogel, an initially a less non-Fickian to a more non-Fickian pattern with increasing amounts of the crosslinker, and beyond a 1.43 g % concentration of the crosslinker, a reverse trend is observed and also less non-Fickian to more non-Fickian behavior with increasing loading of the drug. In all PVA gels, a Fickian behavior is observed for the SM release. The xerogels prepared were found to show a better controlled-release property over that of the crosslinked gelatin xerogels.

REFERENCES

1. Colombo, P. Adv Drug Deliv Rev 1993, 11, 37.
2. Lelah, M. D.; Cooper, S. L. Polyurethanes in Medicine; CRC: Boca Raton, FL, 1986; p 57.
3. Peppas, N. In Hydrogels in Medicine and Pharmacy; Peppas, N., Ed.; CRC: Boca Raton, FL, 1986.

4. Clayton, A. B.; Chirla, T. V.; Lou, X. Polym Int 1997, 44, 201.
5. Akala, E. O.; Kopeckova, P.; Kopeck, J. Biomaterials 1998, 19, 1037.
6. Andreopoulos, A. G.; Plytaria, M. J Biomater Appl 1998, 12, 291.
7. Peppas, N. A.; Wright, S. L. Macromolecules 1996, 29, 8798.
8. Rao, K. V. R.; Devi, K.; Buri, P. J Control Rel 1990, 12, 133.
9. Dutta, P. K.; Viswanathan, P.; Mimrot, L.; Kumar, M. N. V. R. J Polym Mater 1997, 14, 351.
10. McNeili, M.; Graham, N. B. J Biomater Sci Polym Ed 1993, 4, 305.
11. Song, S. Z.; Kim, S. H.; Cardinal, J. R.; Kim, S. W. J Pharm Sci 1981, 70, 216.
12. Lee, P. I. Int Symp Control Rel Bioact Mater 1982, 9, 54.
13. Knepp, V. M.; Szoka, F. C.; Guy, R. H. J Control Rel 1990, 12, 25.
14. Shah, S. S.; Kulkarni, M. G.; Mashelkar, R. A. J Control Rel 1990, 12, 155.
15. McNeill, M. E.; Graham, N. B. J Biomater Sci Polym Chem Ed 1993, 5, 111.
16. Bruck, S. D. In Controlled Drug Delivery—Basic Concepts; Bruck, S. D., Ed.; CRC: Boca Raton, FL, 1983; p 11.
17. Ghose, R. In Pharmacology Materia Medica and Therapeutics; Biswas, S. K., Ed.; Hilton: Calcutta, India 1957.
18. Krishna, R. R.; Shastri, C. S. P. Talenta 1967, 26, 861.
19. Kim, S. W. In Bioactive Polymer Systems; Gebelein, C. G.; Carraher, C. E., Eds.; Plenum: New York, 1985; p 143.
20. McNeill, M. E.; Graham, N. B. J Biomater Sci Polym Chem Ed 1996, 7, 953.
21. Flory, P. J.; Rehner, J., Jr. J Chem Phys 1943, II, 512.
22. Good, W. R.; Mueller, K. In Controlled Release of Bioactive Materials; Baker, R. W., Ed.; Academic: New York, 1980; p 155.
23. Yasuda, H.; Lamaze, C.; Ikenberry, L. D. Makromol Chem 1968, 118, 19.
24. Peppas, N. A.; Franson, N. M. J Polym Sci Polym Phys Ed 1983, 21, 983.
25. Florence, A. T.; Attwood, D. In Physicochemical Principles of Pharmacy; Macmillan: Hong Kong, 1981.
26. Crank, J. The Mathematics of Diffusion; Clarendon: Oxford, 1956.
27. Ritger, P. L.; Peppas, N. A. J Control Rel 1987, 5, 37.
28. Cohn, D.; Aronhime, M.; Abdo, B. J Macromol Sci—Pure Appl Chem A 1992, 29, 841.
29. Kim, S. W.; Bae, Y. H.; Okano, T. Pharmaceut Res 1992, 9, 283.