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Swelling Controlled Delivery of Antibiotic from a Hydrophilic Macromolecular Matrix with Hydrophobic Moieties

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Abstract: A hydrophilic macromolecular network containing hydrophobic moieties has been prepared by free radical copolymerization of acrylamide and styrene in the presence of poly(vinyl alcohol) (PVA) and its potential as controlled drug delivery carrier was evaluated with tetracycline as a model antibiotic drug. The amount of drug was assayed spectrophotometrically. The network was characterized by optical microscopy, infra-red spectroscopy and structural parameters such as average molecular weight between crosslinks (M_c), crosslink density (q) and number of elastically effective chains (V_e) were evaluated. It was found that with increasing concentration of PVA, ST and MBA in the hydrogel, the release rate initially increases but after definite concentrations of the above components the release rate falls. In the case of AM, release rate constantly decreases with increasing AM concentration in the hydrogel.

Keywords: hydrogel, poly(vinyl alcohol), swelling, release rate, kinetics.

Introduction

Hydrogels are three-dimensional covalently bonded hydrophilic macromolecular networks or interpenetrating polymer network (IPN) prepared by polymerization of vinyl monomer either alone or in the presence of an appropriate synthetic or natural hydrophilic polymer. These systems are also termed as 'hungry network' or 'intelligent polymers'[1] are among the best materials for a number of biomedical applications because of their certain unique biophysical properties such as ease of fabrication to various geometricals forms, soft and rubbery texture, living tissue like resemblance, unusual stability to biofluids, minimum mechanical irritation to surrounding tissue, etc. The water imbibing property of hydrogel is responsive not only to the chemical architecture of macromolecular matrices, but also to the surrounding conditions such as pH,[2] temperature,[3] ionic strength,[4] magnetic field, ultra-violet etc. Some of the significant application of hydrogels include artificial implants,[5] dialysis membrane,[6] drug delivery[7] as well as capacity to act as carrier of a variety of bioactive compounds like proteins,[8] agrochemicals,[9] low and high molecular weight drugs.[10] Such loaded polymeric carriers swell and subsequently deliver the entrapped compounds into the aqueous reservoirs when allowed to contact a still release medium.

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Tetracycline is one of the most abundantly tested and used antibiotics in the treatment of periodotal diseases. Clinical studies using tetracycline hydrochloride (TC) have shown that it has an effective spectrum of activity against many of anaerobic microbes associated with various periodontal diseases involving both adult and juvenile periodontitis patients.[11] However, the systematic use of antibiotics may cause several side effects (sensitivity, resistant, strains and superinfections) and the local administration of antibiotics has received considerable attention.[12] Looking to the pharmacological importance of TC release studies, we, in the present investigation, are reporting results on the controlled release of tetracycline entrapped in a hydrophilic macromolecular network of poly(vinyl alcohol) (PVA) and P(AM-*co*-ST).

Experimental

Materials. PVA (hot processed molecular weight; 40,000 g/mole, degree of hydrolysis-98.6%) was obtained from Burgoyne Burbidges & Co. (Bombay, India) and used without further purification. Acrylamide (AM, Research Lab, Poona, India) was crystallized twice from methanol (G.R.) and dried under vacuum over anhydrous silica for a week. Styrene (ST, Research Lab, Poona, India) was purified by washing sequentially with 10% NaOH, 2 N H_2SO_4 and finally with double distilled water. The monomer so purified was distilled under vacuum conditions. *N,N'*-methylene

bisacrylamide (MBA, Central Drug House, Bombay, India) employed as a crosslinking agent, potassium persulphate (Loba Chemie, India) as a polymerization initiators were used as received. Tetracycline capsules IP 250 mg (TC) was gifted from Jagsonpal Pharmaceuticals Ltd., India. All other chemicals used were of analytical grade and bidistilled water was used throughout the experiments.

Methods

Preparation of Macromolecular Hydrophilic Network. In the present study copolymerization of AM and ST was carried out in the presence of both PVA and MBA. Prior to performing experiments, the reactants were degassed by purging dry N_2 for 50 min. Then into a petridish (diam. 2', corning) were added 1.00 g PVA, 10.5 mM AM, 8.6 mM ST, 0.12 mM MBA and 1.11 M water.

The reaction mixture homogenized by manual mixing, deaerated by purging N_2 gas for 1 hr and covered with the lid and kept at 80 °C for 3 hrs. The hydrogel so formed were dried at 60 °C for 5 hrs. They were further purified by equilibrating them in bidistilled water for seven days. The equilibrated IPNs were cut into small identical circular pieces and dried at room temperature for one week.

Morphology. The film morphology was observed by optical microscope (NICON, E800 Eclipse).

Infra-red (IR) Spectral Analysis. The IR spectral analysis was carried out on a Perkin Elmer Spectrophotometer (FTIR, Paragon 1000, USA).

Swelling Measurements. The extent of swelling was determined by conventional gravimetric procedure. In brief, a preweighed piece (0.04 g) of hydrogel was immersed into a thermostated double distilled water bath and allowed to swell over the desired time interval. The swollen piece was then taken out and pressed gently between two filter papers to remove excess of water and finally weighed in a sensitive balance. The degree of swelling was expressed in terms of swelling ratio as given below,

$$\text{Swelling Ratio} = \frac{\text{Weight of the swollen gel}}{\text{Weight of dry gel}} \tag{1}$$

Loading of Drug. In the present study method of loading TC involves swelling of preweighed pieces of hydrogel into the TC solution of known concentration and then taking out and drying them at room temperature for 48 hrs. The following equation was used to calculate the percent loading,

$$\text{Percent Loading} = \frac{W_d - W_o}{W_o} \times 100 \tag{2}$$

where W_d and W_o are the weights (in mg) of TC loaded and dry hydrogel, respectively. By this technique even hydrophobic and non-functional drugs could be loaded into the releasing device.

Release Experiments. The dried and loaded piece of hydrogels were placed at a definite pH into a fixed volume (10 mL) of bidistilled water as a release medium and mildly shaken in thermostated shaker at 27 °C. The hydrogels were rapidly removed transferred into fresh water at predetermined time intervals. The amount of tetracycline was assayed spectrophotometrically.[13]

Release Kinetics. In order to have mechanistic insights into the drug transport processes the kinetic data of the swelling process was fit into the following power law equation,

$$\frac{W_t}{W_\infty} = kt^n \tag{3}$$

where k is a constant incorporating structural and geometric characteristics of the device, n is diffusional exponent and W_t and W_∞ are the amounts of drug released at time t and equilibrium time, respectively. For $n>0.5$, non-Fickian diffusion is observed, while $n = 0.5$ represents a Fickian diffusion mechanism. The value of $n = 1$ provides Case II transport mechanism in which drug releasing from hydrogel of slab geometry will be of zero order. It is notable here that eq.(3) is based on the assumption that release occurs as soon as the matrix is placed in contact with the fluid.

$$\frac{W_t}{W_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} exp\left\{\frac{-D(2n+1)^2\pi^2 t}{l^2}\right\} \tag{4}$$

The above equation is further simplified to the following early-time approximation,

$$\frac{W_t}{W_\infty} = 4\left(\frac{Dt}{\pi l^2}\right)^{0.5} \tag{5}$$

where D is the diffusion constant of the drug (cm^2s^{-1}) and l is the thickness of the dry and drug-loaded hydrogel slab. The eq. (5) clearly implies that from the early-time slope of the plot drawn between W_t/W_∞ and $(t)^{0.5}$ the value of D can easily be calculated for any fractional release vs $(\text{time})^{0.5}$ curve.

Penetration Velocity Measurements. The penetration velocity for each hydrogel composition was determined by the weight gain method as described by Peppas and Franson.[14] The penetration velocity was calculated from the slope of the initial portion of the penetrant uptake curve from the equation,

$$v = \left(\frac{dW_g}{dt}\right)\left(\frac{1}{\rho}\right)\left(\frac{1}{2A}\right) \tag{6}$$

where v denotes the penetration velocity, dW_g/dt denotes the slope of weight gain vs time curve, and ρ denotes the density of water. A denotes the area of one face of the slab and the factor 2 accounts for the fact that penetration takes place through both the faces. The penetration velocities calculated for different hydrogel compositions are listed in Table II.

Results and Discussion

Characterization of Hydrogel.

Morphology of Hydrogel: An optical micrograph of the prepared unloaded hydrogel is depicted in Figure 1(a). The photograph clearly shows the hydrophobic polymeric moieties due to irregular location of PST segments in the copolymeric chains of the network. The optical image also suggests that PST segments are unevenly distributed over the film surface. Another image of the film loaded with TC is also shown in Figure 1(b) which predominantly indicates the presence of hydrophobic microdomains. Moreover, the photograph shows small hairy cracks over the hydrogel film which may be explained by the fact that when the hydrogel is loaded by the hydrophilic TC drug, it is completely absorbed by the hydrophilic domain of the IPN whereas the hydrophobic regions of the film do not absorb the drug and as a result small hairy cracks are seen on the hydrogel surface.

IR Analysis of Hydrogel. The IR spectra of the end-polymer is depicted in Figure 2. The spectra clearly marks the presence of hydroxyls of alcohol at 3605 cm^{-1} (OH stretching), methylene (CH_2) twisting and wagging vibrations at 1392, 1371, 1359 and 1143 cm^{-1}, amide groups at 3563 cm^{-1} (NH stretching) and NH_2 bending vibrations at 1660, 1651 and 1633 cm^{-1}, respectively. In addition to the above mentioned peaks, the spectra also contains absorption bands at 1651, 1486 and 1462 cm^{-1} indicative of C=C skeletal in plane vibration due to phenyl ring.

The spectral analysis suggests for a grafted type of network structure in which crosslinked AM and ST chains are grafted onto the backbone of PVA via hydroxyls of the preformed polymer. On the basis of the spectral analysis, a scheme of reactions may be proposed for the formation of network as depicted in Figure 3.

Network Structure. Both theoretically[15] and experimentally[16] it has been demonstrated that polymer composition has profound effects on release profiles. For instance, the parameters of polymer network could retard solute diffusion, through three primary variables: the molecular weight between crosslinks, the equilibrium volume swelling ratio and the solute radius.

In the case of swelling-controlled release systems and hydrogels used for drug delivery, it is important not only that swelling increases progressively with time, but also that the

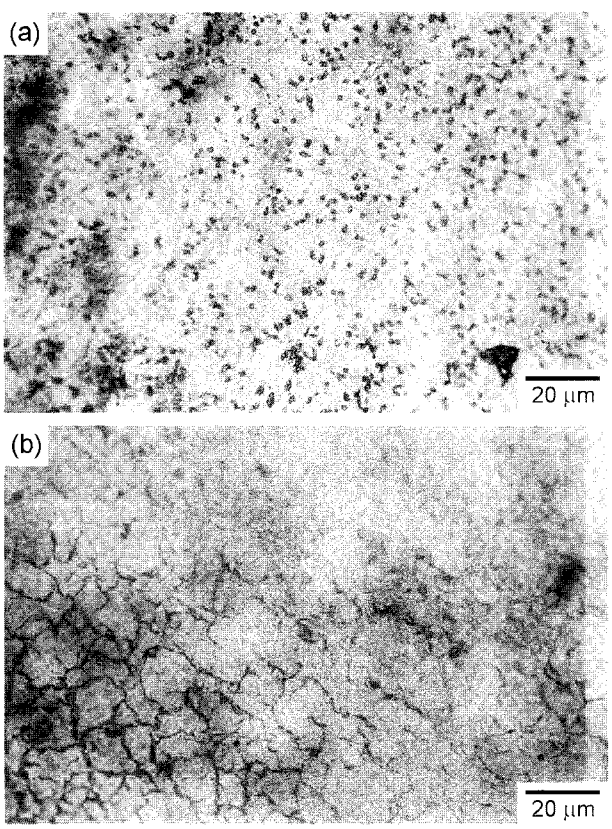

Figure 1. Optical microscope (a) unloaded network and (b) loaded network.

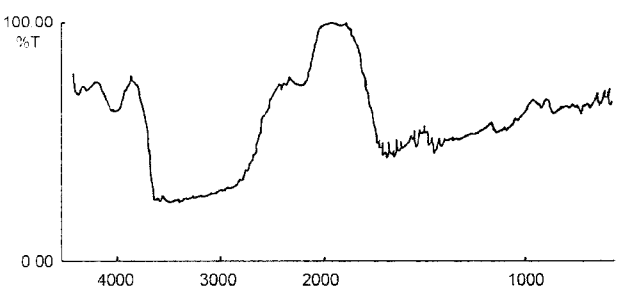

Figure 2. IR spectra of the macromolecular network.

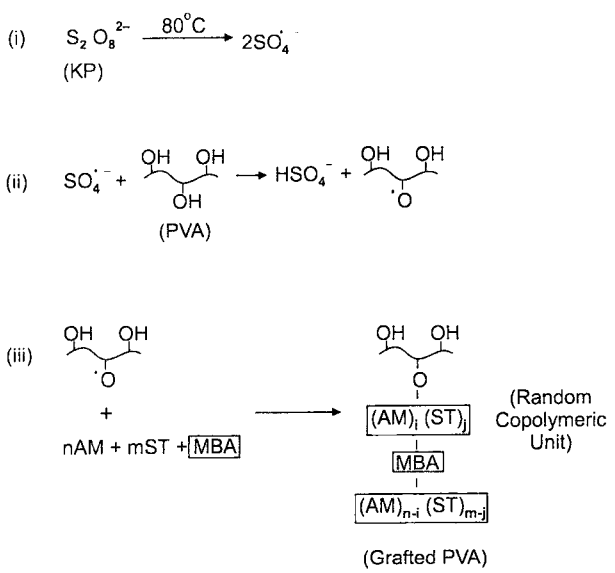

Figure 3. A proposed scheme of reactions for the synthesis of network.

mesh size of the device is able to molecularly accommodate the drug. Thus, the mesh size of a network is an important parameter for prediction of hydrogel (or IPN) permeability. The mesh size is directly controlled by the molecular weight between crosslinks (M_c) which is also a significant parameter in characterizing the crosslinked polymer network. The magnitude of M_c greatly affects the physical and mechanical properties of crosslinked network, its determination is of practical significance. Equilibrium swelling is widely used to determine M_c. Early research by Flory and Rehner laid the foundation for analysis of equilibrium swelling. According to the theory of Flory and Rehner, for a network

$$M_c = -V_1 d_p \frac{(V_s^{1/3} - V_s/2)}{ln(1-V_s) + V_s + XV_s^2} \tag{7}$$

where V_1 is the molar volume of water (mL · mol^{-1}), d_p is the polymer density (g · mL^{-1}), V_s is the volume fraction of polymer in the swollen hydrogel, X is the Flory-Huggins interaction parameter between solvent and polymer.

The swelling ratio (Q) is equal to $1/V_s$. Here, the crosslink density, q, is defined as the mol fraction of crosslinked units.[17]

$$q = \frac{M_o}{M_c} \tag{8}$$

where M_o is the molar mass of the repeating unit.

Other authors define a crosslink density, v_e, as the number of elastically effective chains, totally included in a network, per unit volume, v_e is simply related to q since

$$v_e = d_p N_A / M_c \tag{9}$$

where N_A is Avogadro number.

Since the network in the present study contains a copolymeric structure, the molar mass of the polymer repeat unit, M_o, can be calculated by the following equation.

$$M_o = \frac{n_{AM} \cdot M_{AM} + n_{ST} \cdot M_{ST}}{n_{AM} + n_{ST}} \tag{10}$$

where n_{AM} and n_{ST} are the mol. Number of AM and ST (mol) and M_{AM} and M_{ST} are the molar mass of AM and ST (g mol^{-1}) respectively.

The density of the polymer d_p was determined by pycnometry and found to be 1.2 g · cm^{-3}. Other parameters such as V_1 and X were noted from the literature.[18,19] Using eqs. (7), (8) and (9) the volume of M_c, q and v_e have been calculated for the hydrophilic network containing different amounts of AM, ST and MBA. The values summarized in Table I.

Mechanism of Drug Release. Hydrogels consist of macromolecular chains crosslinked to each other to create a tangled mesh structure, providing a matrix for the entrapment of drugs. When such loaded matrices come in contact with a thermodynamically compatible solvent, relaxation of polymeric chains take place. This happens when the characteristic glassy rubbery transition temperature of the polymer is decreased below the temperature of the experiment. Swelling is the macroscopic evidence of this transition. 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, including special Case II transport.[20]

In the present study, the IPN could be imagined to be made up of PVA and crosslinked P(AM-*co*-ST) chains. Into the free volumes available between the hydrogel chains are accommodated the TC molecules in the loaded gel. When the hydrogel contacts the release medium, the penetrant water molecules invade the hydrogel surface and, thus, a moving front is observed that clearly separates the unsolvated glassy polymer region ahead of the front from the swollen and rubbery hydrogel phase behind it.[21] Just ahead of the front, the presence of solvent plasticizes the polymer and causes it to

Table I. Structural Parameters of the Network of PVA and Poly(AM-*co*-ST) with Varying Composition

PVA	AM	ST	MBA	Average Mol. Wt. between Crosslinkers	Crosslink Density	Elastically Effective Chains
g		mM		M_c	$q \times 10^3$	$V_e \times 10^{-19}$
1.000	7.00	8.6	0.12	20,204	4.24	3.57
1.000	10.5	8.6	0.12	79,399	1.08	0.91
1.000	17.6	8.6	0.12	21,322	3.83	3.38
1.000	10.5	4.3	0.12	34,607	2.32	2.08
1.000	10.5	8.6	0.12	79,399	1.08	0.91
1.000	10.5	13.0	0.12	21,318	4.18	3.39
1.000	10.5	8.6	0.06	110,625	0.75	0.65
1.000	10.5	8.6	0.12	79,399	1.08	0.91
1.000	10.5	8.6	0.25	15,949	5.38	4.53

undergo a glass to rubber transition.[22] Now, the following possibilities arise :

(i) If the glass transition temperature of the polymer (T_g) is well below the experimental temperature, the polymer will be in the rubbery state and polymer chains will have a higher mobility that allows an easier penetration of the solvent into the loaded hydrogel and subsequently release of the drug molecules into the release medium.[23] This clearly results in a Fickian diffusion (Case I) which is characterized by a solvent (or drug) diffusion rate, R_{diff}, slower than the polymer relaxation rate, R_{relax} ($R_{diff} << R_{relax}$).

(ii) If the experimental temperature is below T_g, the polymeric chains of hydrogel are not sufficiently mobile to permit immediate penetration of the solvent in the polymer core. This gives rise to a non-Fickian diffusion process which includes Case II and anomalous diffusions respectively depending on the relative rates of diffusion and chain relaxation (for Case II, $R_{diff} >> R_{relax}$, and for anamolous, $R_{diff} \sim R_{relax}$). The whole mechanism is modelled in Figure 4.

Effect of Hydrogel Compositions on TC Release. Swellable hydrophilic macromolecular networks have been used for the purpose of prolonged drug delivery and drug targeting.[24] Delivery systems based on relaxing networks are capable of slow release of an imbedded drug, with release controlled by the rate of swelling and relaxation of the polymer chains.[25] As the swelling pattern of a hydrogel is primarily dependent on the composition of the network, the release profiles of drug are directly and substantially regulated by the chemical architecture of the loaded device. In the present study also the release of TC is influenced by varying composition of the IPN's as discussed below :

(i) Effect of PVA

It is an established[26] fact that the drug: polymer ratio is one of the important factors that significantly influences the release of a drug from the polymer matrices. In the present study the effect of PVA content of the network was investigated on the released amount of TC by varying the amounts of PVA in the feed mixture in the range 0.5 to 1.5 g. The results are depicted in Figure 5 which indicate that the

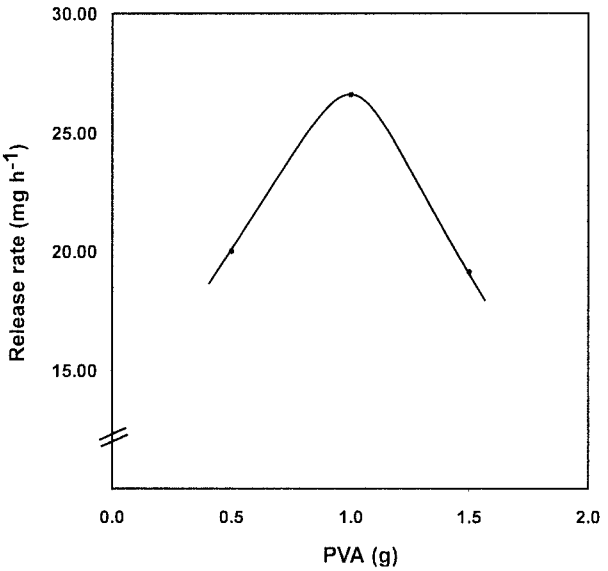

Figure 5. Effect of PVA content of the network on the release rate of TC at fixed composition of the hydrogel, [ST] = 8.6 mM, [AM] = 10.5 mM, [MBA] = 0.12 mM, [KP] = 0.12 mM, % Loading = 43.3, pH = 3.0, Temp. = 27±0.2 °C, Thickness = 0.051 cm.

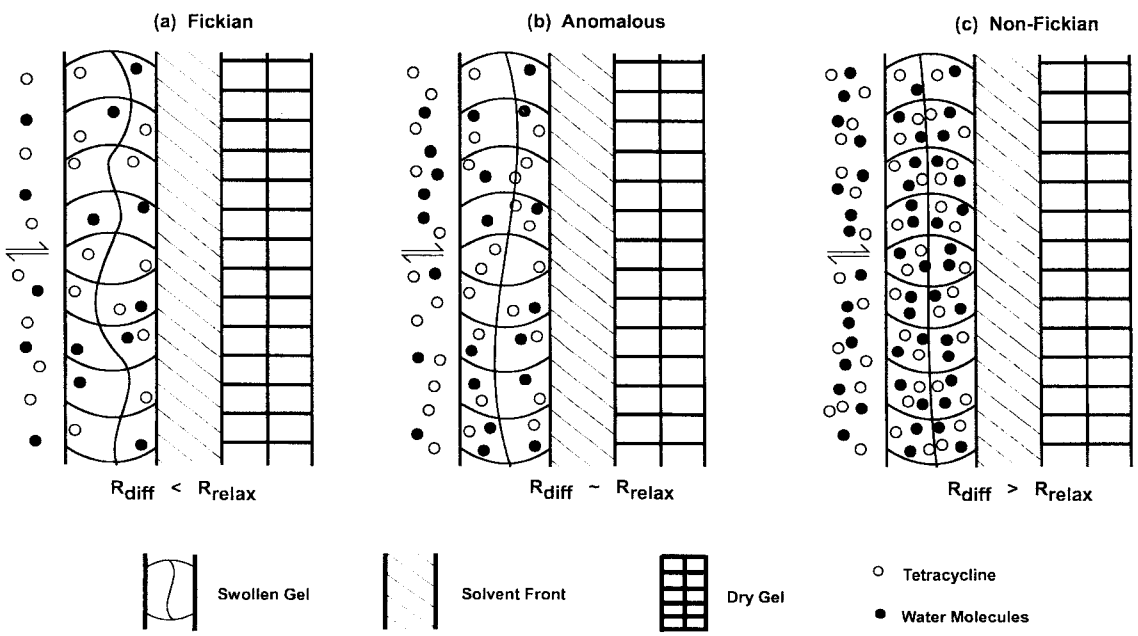

Figure 4. A hypothetical model depicting (a) Fickian, (b) anomalous, and (c) non-Fickian release of tetracycline.

release rate of TC increases upto 1.0 g of the PVA while beyond it a fall in the released amount is noticed. The reason for the observed initial increase is quite apparent as PVA is a hydrophilic polymer with distinct water associating properties and its increasing proportion in the hydrogel composition will result in a greater swelling of the network which, as a consequence, will deliver increasing release rate of the drug into the release medium. However, beyond a certain concentration of PVA (1.0 g) the network density becomes so high that incoming water molecules as well as outgoing TC molecules are prevented by the network chains and, therefore, the release rate decreases.

(ii) Effect of Styrene

The effect of increasing concentration of ST on the release behavior of TC has been examined by varying its concentration in the range 4.3 to 13.0 mM in the feed mixture of the hydrogel. The results are displayed in Figure 6 which indicate that with increasing proportion of ST in the hydrogel, the release rate of TC increases up to 8.6 mM of ST content while beyond 8.6 mM, a fall in release rate is noticed. The observed initial increase in release rate of TC may be explained by the fact that since ST is a hydrophobic and bulky. Moreover, its increasing concentration in the feed mixture results in a steric repulsion among the PST segments of the IPN chains which widens the mesh sizes of the network pores and thus facilitate the release of TC molecules. This obviously brings about an increase in release rate. This observation is further supported by the increasing diffusion constants of the TC as shown in Table II. However, beyond 8.6 mM of ST concentration the gel achieves greater hydrophobicity which because of lower water sorption results in a decrease in the release rate of TC. The results are further supported by the observed lower penetration velocity and diffusion constant values as summarised in Table II.

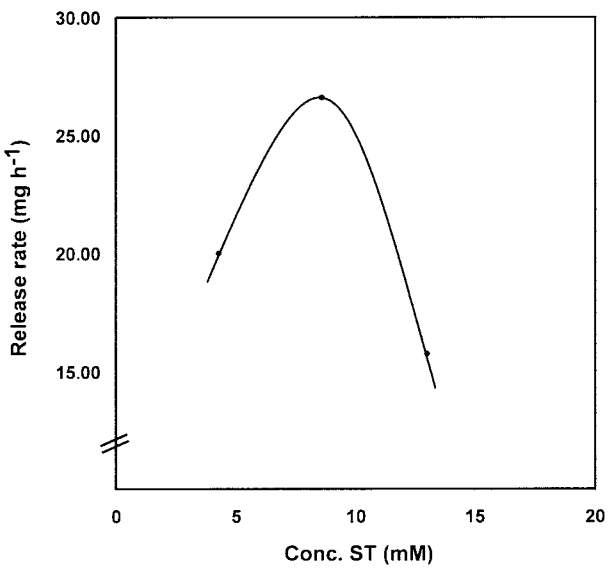

Figure 6. Effect of ST content of the network on the release rate of TC at fixed composition of the hydrogel, [PVA] = 1.0 g, [AM] = 10.5 mM, [MBA] = 0.12 mM, [KP] = 0.12 mM, % Loading = 43.3, pH = 3.0, Temp. = 27±0.2 °C, Thickness = 0.051 cm.

(iii) Effect of Acrylamide

The hydrophilic comonomer AM has been identified to have exerted a direct influence on the release profiles of the drug. In the present investigation the effect of AM variation on the release profile of TC has been studied by varying the monomer in the range 7.0 to 17.6 mM in the feed mixtures of the hydrogel. The results are shown in Figure 7 which indicate that with increasing AM content the release rate constantly decreases. The observed findings may be explained by the fact that increasing crosslinked PAM chains in the gel network brings about a compactness of the macromolecular chains in the hydrogel and this suppresses the release of TC molecules into the release medium.

It is clear from Table II that at higher AM content the diffusion constant of the drug has increased which is further supported by the observed increase in the penetration velocity of the moving front (water). It is also worth mentioning here that at higher AM content the network has low degree of water sorption which reveals that the drug molecules will not have to travel a longer path to come to the surface of the device and, therefore, an acceleration in the diffusivity of the TC molecules is expected. The phenomenon of time/position dependent diffusivity has been well cited in the literature.[27]

Table II. Data Showing the Variation of Penetration Velocity (v) for Swelling of IPN and Diffusion Constant (D) for Release of TC with Varying Composition of the IPNs

PVA (g)	ST (mM)	AM (mM)	MBA (mM)	Thickness (cm)	$v\times 10^5$ (cm/s)	$D\times 10^6$ (cm^2/s)
0.5	8.6	10.5	0.12	0.051	1.85	2.06
1.0	8.6	10.5	0.12	0.051	1.60	2.56
1.5	8.6	10.5	0.12	0.051	1.03	2.21
1.0	4.3	10.5	0.12	0.051	2.08	2.34
1.0	8.6	10.5	0.12	0.051	1.60	2.56
1.0	13.0	10.5	0.12	0.051	1.20	2.34
1.0	8.6	7.0	0.12	0.051	1.15	1.79
1.0	8.6	10.5	0.12	0.051	1.60	2.56
1.0	8.6	17.6	0.12	0.051	1.90	2.84
1.0	8.6	10.5	0.06	0.051	2.08	2.02
1.0	8.6	10.5	0.12	0.051	1.60	2.56
1.0	8.6	10.5	0.25	0.051	0.80	3.04
1.0	8.6	10.5	0.12	0.017	0.55	5.15
1.0	8.6	10.5	0.12	0.030	1.25	3.60
1.0	8.6	10.5	0.12	0.051	1.60	2.56

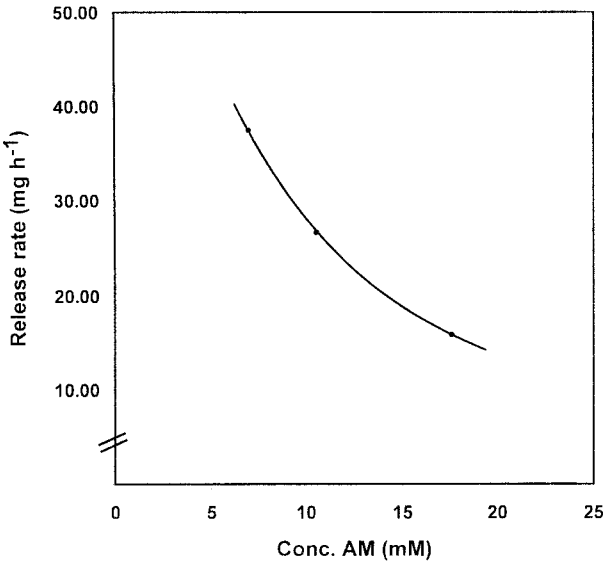

Figure 7. Effect of AM content of the network on the release rate of TC at fixed composition of the hydrogel, [PVA] = 1.0 g, [ST] = 8.6 mM, [MBA] = 0.12 mM, [KP] = 0.12 mM, % Loading = 43.3, pH = 3.0, Temp. = 27±0.2 °C, Thickness = 0.051 cm.

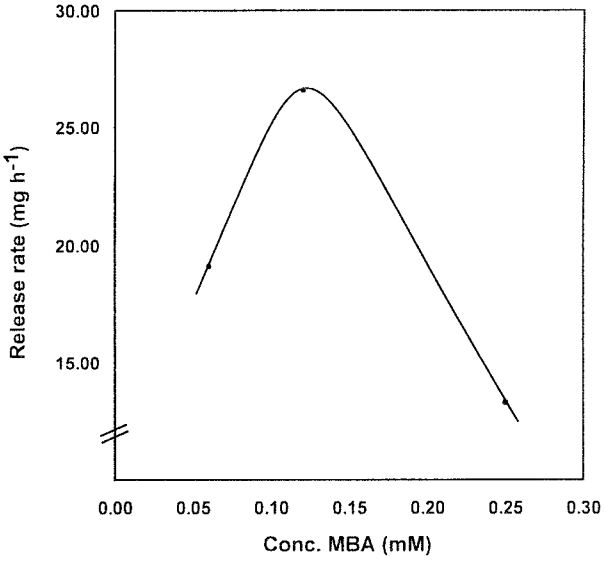

Figure 8. Effect of MBA content of the network on the release rate of TC at fixed composition of the hydrogel, [PVA] = 1.0 g, [ST] = 8.6 mM, [AM] = 10.5 mM, [KP] = 0.12 mM, % Loading = 43.3, pH = 3.0, Temp. = 27±0.2 °C, Thickness = 0.051 cm.

(iv) Effect of Crosslinker

The influence of increasing crosslinking of the hydrogel on the release behaviour was investigated by employing different amounts of crosslinking agent (MBA) while in the network preparation. When MBA was used in the concentration range 0.06 to 0.25 mM in the feed mixture of the network. It was observed that whereas the release rate increases up to 0.12 mM, concentration of MBA decrease in further release observed beyond 0.12 mM of crosslinker concentration. The observed increase in release may be attributed to the reason that since MBA is hydrophilic monomer, its increasing concentration in the feed mixture results in an enhanced hydrophilicity of network, which in turn increases the degree of water sorption and the release rate as well. However, beyond 0.12 mM of MBA is significant decrease may be explained on the basis of the fact that crosslink density increases to appreciable extent, therefore, swelling of hydrogels decreases which as a consequence slows down the release rate. The above explanation is further supported by the value of crosslink density summarised in Table I. It is clearly revealed by the table that when the concentration of MBA increases from 0.06 to 0.12 mM, the crosslink density increases by 50%, where as the further increase in crosslink concentration that is from 0.12 to 0.25 mM, the crosslink density increases by nearly 500%. This obviously support the explanation given in the preceding para.

Some authors[28] have reported an increase in the T_g of the polymer with increasing concentration of the crosslinker. This also results in a restrained mobility of the network chains and, therefore, slows down the swelling and the release processes. As can be seen in Table II, the penetration velocities of the solvent have also decreased with increasing concentration of the MBA, and hence this also supports the idea of slow penetration of water molecules into the IPN matrix.

Thickness Effect. In the present study, the influence of the surface area of the gel on the release kinetics has been observed by taking loaded hydrogels of varying thickness in the range 0.017 to 0.051 cm. The results are shown in Figure 9 which indicate that the release rate increases with decreasing thickness of the loaded hydrogel. The observed results are quite obvious as a thinner gel has a greater surface area and, therefore, will show a larger release. It has also been noted that the thinner gel attains equilibrium release at earlier times than the thicker gel does (not shown). Another reason could be that the thicker is the gel greater would be the force required to stretch it, as evident from the slower swelling of the thickest (0.051 cm) gel. The degree of swelling of a network is controlled by a combination of free energies of mixing between water and the hydrophilic polymer chains and by the elastic response of the rubbery network to the expansion due to water uptake. Similar type of results have also been reported by other workers.[29] The penetration velocities have also been calculated and summarized in Table II.

pH Effect. The effect of pH on the release pattern of TC has been studied by varying the pH of the release medium in the range 2.07 to 6.85. The results are depicted in Figure 10 which indicate that the amount and rate of release of TC decrease with increasing pH up to 4.05 while beyond 4.05,

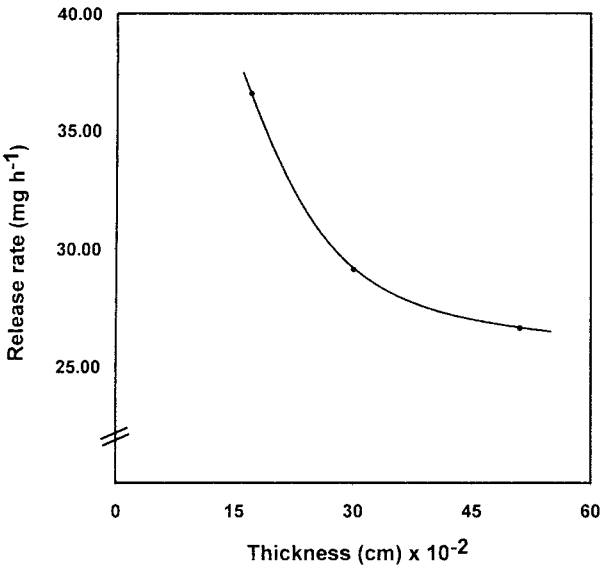

Figure 9. Variation of fractional release of TC with thickness of the hydrogel of fixed composition, [PVA] = 1.0 g, [ST] = 8.6 mM, [AM] = 10.5 mM, [MBA] = 0.12 mM, [KP] = 0.12 mM, % Loading = 43.3, pH = 3.0, Temp. = 27±0.2 °C.

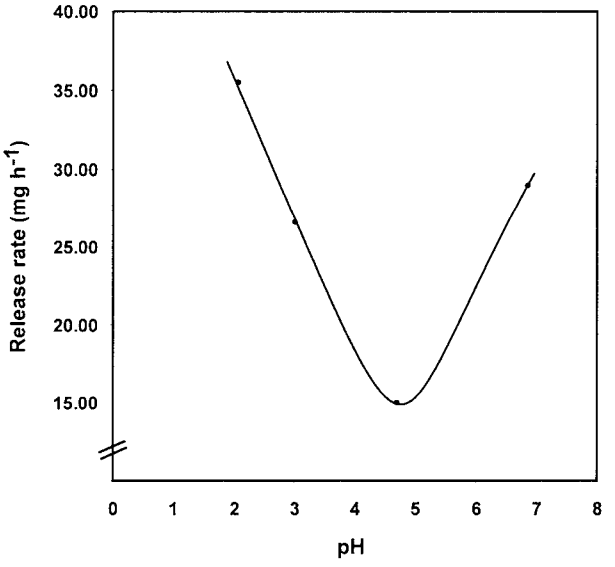

Figure 10. Effect of pH of the release medium on fractional release of TC through the hydrogel of fixed composition, [PVA] = 1.0 g, [ST] = 8.6 mM, [AM] = 10.5 mM, [MBA] = 0.12 mM, [KP] = 0.12 mM, % Loading = 43.3, Temp. = 27±0.2 °C, Thickness = 0.051 cm.

it increases. The results can be explained as below : tetracycline produces three acidity constants (Table III) in aqueous solutions of their acid salts as its molecule has three protonation sites as shown in Figure 11. Thus, in the acidic range at lowest pH, i.e. 2.07, the TC molecule becomes protonated

Table III. Actidity Constants for Tetracycline

Antibiotic	pKa_1	pKa_2	pKa_3
Tetracycline	3.3	7.7	9.5

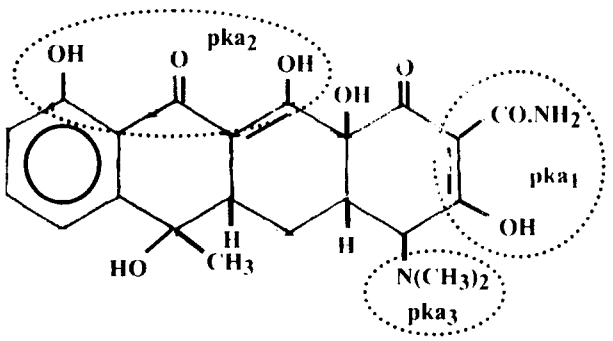

Figure 11. Structure of TC molecule.

and causes repulsion among the entrapped drug molecules within the gel network. This obviously results in a widening of the mesh sizes of the gel which facilitate release of the TC molecules into the release medium. Another reason for higher release at pH 2.07 may be that the amide groups of the PAM segments may also be protonated at low pHs and produce repulsion among the protonated segments within the gel network.

With increase in pH of the medium, H^+ ion concentration decreases which results in a less widening of network chains and as a consequence the release of TC falls. However, beyond pH 4.05, when pk_1 site of TC starts releasing protons within the network, the ionic concentration inside the gel increases which obviously results in an enhanced swelling of the network. The swollen network expels TC molecules into the release medium, thus bringing about an increase in the released rate and released amount of TC.

Analysis of Release Data. When the concentration of PVA increases in the gel in the range 0.5 to 1.5 g the release exponent decreases from super Case II to anomalous value as shown in Table IV. The results observed can be explained by the fact that at lower PVA content in the gel the free volumes in between the network chains will have large mesh-sizes and, therefore, the water sorption and subsequently the drug release would be faster displaying super Case II transport. However, upon increasing PVA content in the gel the diffusional exponent decreases to an anomalous value indicating a relaxation controlled nature of release process. This appears justified also as greater PVA content in the gel will result in dense network which permits slow relaxation of macromolecular chains.

When the amount of ST increases in the feed mixture of the gel in the range 4.3 to 13.0 mM, the diffusional exponent is found to increase in the anomalous region indicating that the release process becomes increasingly relaxation con-

Table IV. Data Showing the Variation of Diffusional (Release) Exponent n with Varying Composition of the IPNs

PVA (g)	ST (mM)	AM (mM)	MBA (mM)	Thickness (cm)	n	Swelling Mechanism
0.5	8.6	10.5	0.12	0.051	1.25	Super Case II
1.0	8.6	10.5	0.12	0.051	0.76	Anomalous
1.5	8.6	10.5	0.12	0.051	0.70	Anomalous
1.0	4.3	10.5	0.12	0.051	0.70	Anomalous
1.0	8.6	10.5	0.12	0.051	0.76	Anomalous
1.0	13.0	10.5	0.12	0.051	0.80	Anomalous
1.0	8.6	7.0	0.12	0.051	0.47	Fickian
1.0	8.6	10.5	0.12	0.051	0.76	Anomalous
1.0	8.6	17.6	0.12	0.051	0.82	Anomalous
1.0	8.6	10.5	0.06	0.051	1.27	Super Case II
1.0	8.6	10.5	0.12	0.051	0.76	Anomalous
1.0	8.6	10.5	0.25	0.051	0.66	Anomalous
1.0	8.6	10.5	0.12	0.017	0.48	Fickian
1.0	8.6	10.5	0.12	0.030	0.62	Anomalous
1.0	8.6	10.5	0.12	0.051	0.76	Anomalous

trolled. This can be explained by the fact that larger number of hydrophobic PST chains, because of their bulky sites, experience restriction in relaxation and as a result the release process becomes relaxation controlled.

In case of addition of hydrophilic monomer (AM) to the feed mixture of the gel in the concentration range 7.0 to 17.6 mM, the diffusional exponent n is found to increase from a nearly Fickian value of 0.47 to anomalous value of 0.82, thus implying a shift of release mechanism from diffusion controlled to relaxation controlled. The observed shift in release mechanism could be attributed to the fact that with increasing crosslinked PAM chains in the gel network, the relaxation process becomes less favourable thus making release of the TC as relaxation controlled.

The crosslinker also has a pronounced effect on the release mechanism. When the concentration of crosslinker (MBA) increases in the range 0.06 to 0.25 mM the diffusional exponent decreases from a super Case II value to anomalous value, thus implying that the release process acquires increasing chain relaxation controlled nature. However, at the lowest MBA content the observed super Case II value of the diffusional exponent suggests for a faster water sorption process which is found experimentally verified also.

The thickness of the loaded gel also influences the transport mechanism of releasing tetracycline. It is noticed that with increasing thickness of the gel the diffusional exponent increases from Fickian to non-Fickian (anomalous) value indicating for a shift of transport mechanism from diffusion controlled to relaxation controlled process. The numerical values of the diffusion constants (D) have also been calculated and summarized in Table III.

Conclusions

The copolymerization of AM and ST in the presence of a crosslinker and a preformed polymer such as PVA results in the formation of a IPN or hydrogel which shows potential to act as a vehicle for the controlled delivery of TC. The release rate of TC is greatly influenced by the chemical architecture of the gel. In the case of variation in the PVA content of the IPN the release rate initially increases while beyond an optimum PVA content a decrease in the release rate is noticed. When the concentration of ST varied in studied range, the release rate initially increases but after a definite concentration, it falls. On the other hand, increasing AM in the IPN results in constant decrease in release rate. A similar trend is also observed with increasing crosslinker (MBA) content of the IPN. The rate of release is also found to increase with decreasing thickness of the IPNs and increasing pH of the release medium. The release exponent (n), diffusion constant (D) and penetration velocity (v) also vary with varying IPN composition and experimental conditions.

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