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Controlled Release of a Digestive Enzyme from a Swellable Semi-interpenetrating Polymer Network (IPN)

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ABSTRACT

A novel interpenetrating polymer network (IPN) of poly(ethylene glycol), poly(vinyl alcohol) and poly(acrylamide) was prepared and its potential for sorption and delivery of diastase, a digestive enzyme, was evaluated. The effects of experimental parameters such as varying chemical composition of the IPN, percent loading of diastase, pH and temperature of the release medium and molecular weight of PEG were investigated on the release dynamics of the diastase. On the basis of Fick's equation the diffusional exponent (n) and diffusion constants (D) were evaluated for different IPN compositions. From the kinetic parameters data, an attempt was made to explore the nature of the mechanism of the release process of diastase. The IPNs were characterized by IR analysis and examined for zero-order release behavior of loaded enzyme.

Key Words: IPN; Polymeric; Diastase; Release; Kinetics.

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INTRODUCTION

Discovery of a new class of polymeric substances commonly known as hydrogels or fascinatingly coined as 'intelligent' or 'smart polymers' was a result of the attempts made for the development and use of materials in biomedical and biotechnological applications,[1] such as drug delivery systems,[2] soft contact lenses[3] and as artificial implants.[4] Other practical applications include the use of hydrogels as flocculants for treatment of sludge,[5] release of essential oils,[6] release of agrochemicals,[7] etc.

A wide range of bioactive molecules like proteins, peptides and enzymes are commercially available as drugs. Many of these are stable only under physiological applications and their therapeutic application is severely limited by their short half lives *in vivo*. Several attempts have been made to deliver the polypeptide molecule through polymer matrices, but these have limitations on appropriate delivery, biological activity, etc. In recent years, many biologically active peptides, proteins and enzymes for therapeutic use have been artificially produced by genetic engineering techniques. Thus, considerable research effort is now being invested in techniques to control release and delivery of these high molecular mass compounds.[8]

Controlled release of macromolecular drugs is not as easy as that of the low molecular weight drugs for certain reasons. For instance, the molecular size of the macro drug is a decisive factor in hindering the diffusion and release from hydrophilic networks.[9] Another critical consideration, especially in protein delivery from the hydrogel system, is the potential for protein denaturation in the device.[10] One more problem is the retention of bioactivity of peptides and proteins when loaded into the polymeric hydrogel devices.[11] Thus, the area of controlled delivery of macromolecular drugs possesses challenges and, therefore, deserve much more attention.

One of the goals of controlled delivery systems is obtaining therapeutically optimum drug concentration in the plasma through zero order release. This obviously yields a constant release rate for a prolonged time. Therefore, Case II transport, in which transport rates are independent of time, has been investigated by many researchers[12] in attempts to create long term drug delivery devices. Several efforts to achieve zero-order drug delivery have been made including creative device geometries, front synchronization[13] and parabolic initial drug concentration profiles.[14] Swelling-controlled hydrogels and membrane reservoir devices have so far shown the most promise.

Thus, motivated by the efforts put into designing a zero-order release carrier, we, in the present work, are reporting results on the controlled release of diastase from a swellable hydrophilic semi-interpenetrating polymer network (IPN) of polyvinyl alcohol, polyethylene glycol and polyacrylamide. The choice of constituent polymers for constructing the device rests upon the fact that both PVA and PEG are water soluble, non-carcinogenic, non-toxic and biocompatible polymers and have been extensively used in biomedical and pharmaceutical fields.[15–17] The diastase, on the other hand, has been selected as a model macromolecular drug as it is a well-known digestive enzyme that changes starch into simpler, more soluble sugars. Starch from potatoes, grains and other vegetables can cause thick viscous occlusions when left undigested. Thus, it has a vital role in regulating digestion process. Moreover, along with other nutrients, the diastase has frequently been put together in various digestive formulations.[18]

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EXPERIMENTAL

Materials

Polyethylene glycol (PEG) (400, 600, 6000 mol wt) were obtained from Wilson Laboratories, Bombay, India and used as received. Polyvinyl alcohol (hot processed, 98.6% acetalized, 30,000 mol wt) was obtained from Burgoyne Burbidges and Co. India, and used without any pretreatment. Acrylamide (Research Lab, Poona, India) was crystallized twice from methanol (GR) and dried under vacuum over anhydrous silica for a week. N,N′-methylene bisacryalmide (MBA) (Central Drug House, Bombay, India) was employed as a crosslinking agent while potassium persulphate (Loba Chemie, India) as a polymerization initiator. Diastase was obtained in powdered form (Research Laboratory, Mumbai) with an activity of 1300 IU/g and used as such.

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Preparation of IPN

The IPNs of varying composition were prepared by the free radical polymerization method as described in our earlier communications.[19] In brief, into different petridishes (4 inch diameter, Corning) were added PVA (0.75–1.5 g), acrylamide (AM) (10.5 mM–28 mM) PEG (0.22 g–1.32 g), MBA (0.006 mM–0.038 mM), potassium persulphate (KPS) (0.003 mM) and water (1.1 M). The mixtures (20 ml) were homogenized and kept at 70°C for 4 h so that the entire mass converted into thin white circular films. The films were cut into pre-weighed pieces of equal dimensions (1 cm × 1 cm) and equilibrated with bidistilled water for a week. The swollen hydrogel pieces were then dried at room temperature for 72 h and weighed again. This process was continued till the constant weight of IPNs were obtained. This clearly assured a complete removal of unreacted chemicals and monomers from the hydrogels.

Swelling Kinetics and Subsequent Loading of Diastase

The loading of diastase was performed by allowing the hydrogel to swell in the bioactive solution till equilibrium, and then drying to obtain the release device. In a typical experiment a pre-weighed dry piece of the hydrogel was allowed to swell in 5 ml diastase solution (0.3% w/v) till equilibrium. The progress of hydrogel swelling was monitored by recording weights of swollen gels at different time intervals. The swelling process was characterized by the parameters given below;

$$\text{Swelling Ratio} = \frac{W_s}{W_d} \tag{1}$$

The swelling IPNs after having attained a state of equilibrium were removed from enzyme solutions and then dried at room temperature for 72 h. The following equation was used to

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calculate the amount of loaded enzyme (mg/g),

$$\text{Loaded enzyme} = \frac{W_d - W_o}{W_o} \tag{2}$$

where W_d and W_o are the weights (in mg) of the enzyme loaded and dry gels respectively.

Release Experiments

The dried and loaded IPNs (0.1 g) were placed into a definite volume (5 ml) of double distilled water as the release medium. After different time intervals, 0.5 ml aliquot of the release medium was withdrawn and the amount of released diastase was estimated spectrophotometrically (Systronics, Model No. 106, India).[20]

Kinetic Analysis of Release Data

The potentiality of a drug delivery system is normally evaluated on the basis of first 50–60% release performance of the device as beyond this level therapeutically ineffective amounts of drug are present in the blood plasma. If a hydrogel film is equilibrated with a drug by soaking the hydrogel in an aqueous 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 solute from slab can be one dimensional if it takes place predominantly from the two main surfaces and according to Crank[21]

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \left\{ \frac{8}{(2n+l)^2 \pi^2} \right\} \exp\left\{ \frac{-D(2n+l)^2 \pi^2 t}{4l^2} \right\} \tag{3}$$

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

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

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

The following equation was used to study the release mechanism when the release and swelling data are analyzed:

$$\frac{M_t}{M_\infty} = K\, t^n \tag{5}$$

where M_t/M_∞ is the fractional release at time t and K is a rate constant. The exponent n is an indicator of mechanism of transport and has a value between 0.5 and 1. When $n = 0.5$ release is described as Fickian. When $n = 1$, the release is zero order, i.e., constant with time. In between these values, i.e. $0.5 < n < 1$, the closer is the release pattern to steady state release. When $M_t/M_\infty = 0.5$, t is the half life which is another extremely significant

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parameter in comparing systems. In the light of Eqs (4) and (5), the released data will be analyzed.

RESULTS AND DISCUSSION

Characterization of Network

Prior to discussing the results obtained, it is worth to characterize the structure of the prepared hydrogel.

IR Spectral Analysis

The IR spectra of the hydrogel is shown in Fig. 1. The spectra clearly marks the presence of hydroxyls of alcohol at $3650\,cm^{-1}$ (O–H stretching), amide group at $3424\,cm^{-1}$ (N–H stretching), $1596\,cm^{-1}$ (N–H bending), and 1656 (C═O stretching). In addition to the above observed peaks, the IR spectra also confirms the presence of poly(ethylene glycol) (PEG) in the semi-IPN as evident from the observed absorption bands at $1351\,cm^{-1}$ (interaction between O–H bending and C–O stretching), and $1026\,cm^{-1}$ (asymmetrical C–O–C stretching). The spectra also contains characteristic vibrational modes at 699 and $761\,cm^{-1}$ which are due to out-of-plane C–H bending vibrations.

Network Studies

The characterization of crosslinked polymer is measured by an important structural parameter M_c, the average molar mass between crosslinks, which is directly related to crosslink density. The magnitude of M_c affects the physical and mechanical properties of crosslinked polymers and its determination has wide range of practical significance. Equilibrium swelling is widely used to determine M_c. Early research by Flory and Rehner laid the foundation of the analysis of equilibrium swelling. According to the theory of Flory and Rehner, for a perfect network

$$M_c = -V_1 d_p \frac{(V_s^{1/2} - V_{s/2})}{\ln(1 - V_s) + V_s + \chi V_s^2} \tag{6}$$

where M_c is the number average molar mass of the chain between crosslinks. V_1 is the molar volume, d_p is the polymer density ($g\,ml^{-1}$), V_s is the volume fraction of polymer in the swollen gel, and χ is the Flory–Huggins interaction parameter between solvent and polymer.[22]

The swelling ratio is equal to $1/V_s$. Here, the crosslink density q is defined as the mole fraction of crosslinked units.

$$q = M_o/M_c \tag{7}$$

where M_o is the molar mass of the repeating unit.

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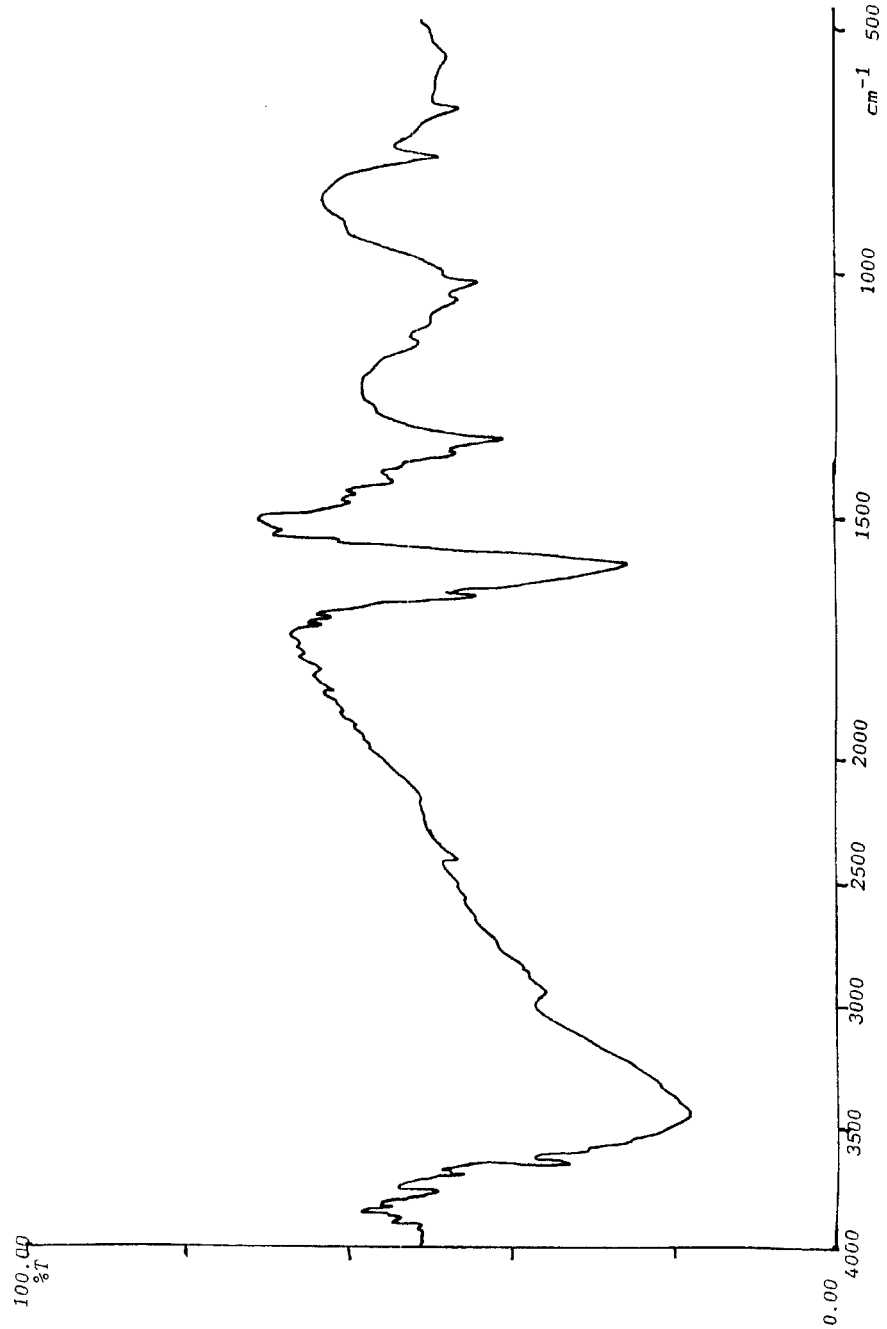

Figure 1. IR spectra of the IPN.

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Some other authors defined a crosslink density, V_e, as the number of elastically effective chains, totally included in a perfect network, per unit volume, V_e is simply related to q since

$$V_e = d_A N_A / M_c \tag{8}$$

The value of V_1, d_p and X were taken from related literature.[23,24]

The values of M_c, q and V_e of the networks have been calculated and summarized in Table 1 for varying compositions in the hydrogel.

Appearance of the IPN

In the dry state, the IPN was like a smooth thin film, which upon swelling changed into a semi-transparent enlarged mass as is evident from the photograph shown in Fig. 2.

Dynamic Release Model

When a drug loaded dry hydrogel comes into contact with a thermodynamic compatible solvent, relaxation of polymeric chains takes place. This happens when the characteristic glass transition temperature of the polymer is decreased below the temperature of the experiment. The dissolved drug releases into the external release medium crossing the swollen polymeric layer formed around the matrix. Now, the following possibilities could arise.

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Table 1. Network parameters of the IPNs of different compositions.

PEG (g)	PVA (g)	AM (mM)	MBA (mM)	KPS (mM)	M_c	$q \times 10^3$	$V_e \times 10^{-20}$
0.22	0.75	14	0.006	0.003	5536	12.8	10.4
0.55	0.75	14	0.006	0.003	14180	5.0	4.07
0.88	0.75	14	0.006	0.003	18510	3.83	3.12
1.32	0.75	14	0.006	0.003	21360	3.32	2.7
0.55	0.50	14	0.006	0.003	10152	6.9	5.69
0.55	0.75	14	0.006	0.003	14180	5.0	4.07
0.55	1.00	14	0.006	0.003	17036	4.16	3.3
0.55	1.50	14	0.006	0.003	20111	3.5	2.8
0.55	0.75	10	0.006	0.003	2477	28.6	23.3
0.55	0.75	21	0.006	0.003	14180	5.0	4.07
0.55	0.75	28	0.006	0.003	8173	8.6	7.0
0.55	0.75	14	0.012	0.003	6671	10.6	8.6
0.55	0.75	14	0.025	0.003	14180	5.0	4.07
0.55	0.75	14	0.038	0.003	7370	9.6	7.8
0.55	0.75	14	0.012	0.003	5575	12.7	10.3
0.55	0.75	14	0.038	0.003	3904	18.1	14.8

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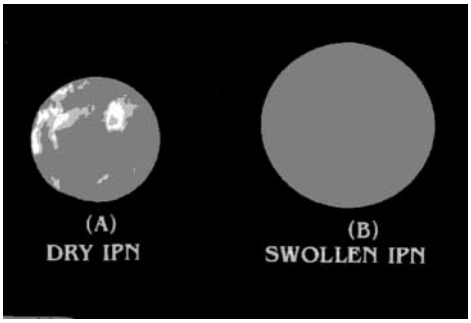

Figure 2. A photograph displaying dry and swollen IPNs.

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 the polymer chains will have a greater mobility that allows an easier penetration of the solvent.[25] This clearly results in a Fickian diffusion (Case I), which is characterized by the solvent diffusioin rate; R_{diff}, slower than the polymer relaxation rate R_{relax} ($R_{diff} \ll R_{relax}$). Thus, a greater chain-relaxation rate implies that the network chains undergo a greater loosening thus assuming a wave type shape as shown in Fig. 3(a).

If the experimental temperature is below T_g, the polymer chains may not be sufficiently mobile to permit immediate penetration of the solvent in the polymer case. This gives rise to non-Fickian diffusion process which includes Case II diffusion and anomalous diffusion depending on the relative rates of diffusion and chain relaxation (for Case II, $R_{diff} \gg R_{relax}$ and for anomalous $R_{diff} \sim R_{relax}$). The possibility when the rate of chain relaxation is smaller than that of diffusion of solvent molecules is depicted in Fig. 3(b) which indicate that the network chains acquire less wave-type shape thus exhibiting a smaller degree of loosening. This obviously results in a non-Fickian water transport mechanism.

Both the possibilities of diffusional and relaxation controlled release process of the IPN are shown in Fig. 3(a) and (b), respectively.

Effect of Composition on Loading

The IPNs of different compositions were prepared by varying the amounts of PEG, PVA, AM and MBA in the feed mixture and the enzyme was loaded by equilibrating them in the enzyme reservoir. The following discussion clearly reveals that the chemical architecture of the IPN has a pronounced effect on the percent loading of the diastase. The observed results are summarized in Table 2 and may be interpreted as below.

When the amount of PEG is increased in the feed mixture in the range of 0.22 g–1.32 g, there is observed an increase in the percent loading. The results may be explained by the fact that; increasing molar concentration of PEG results in the longer chain length of PEG between crosslink, achieved by decreasing the amount of the crosslinking agent,

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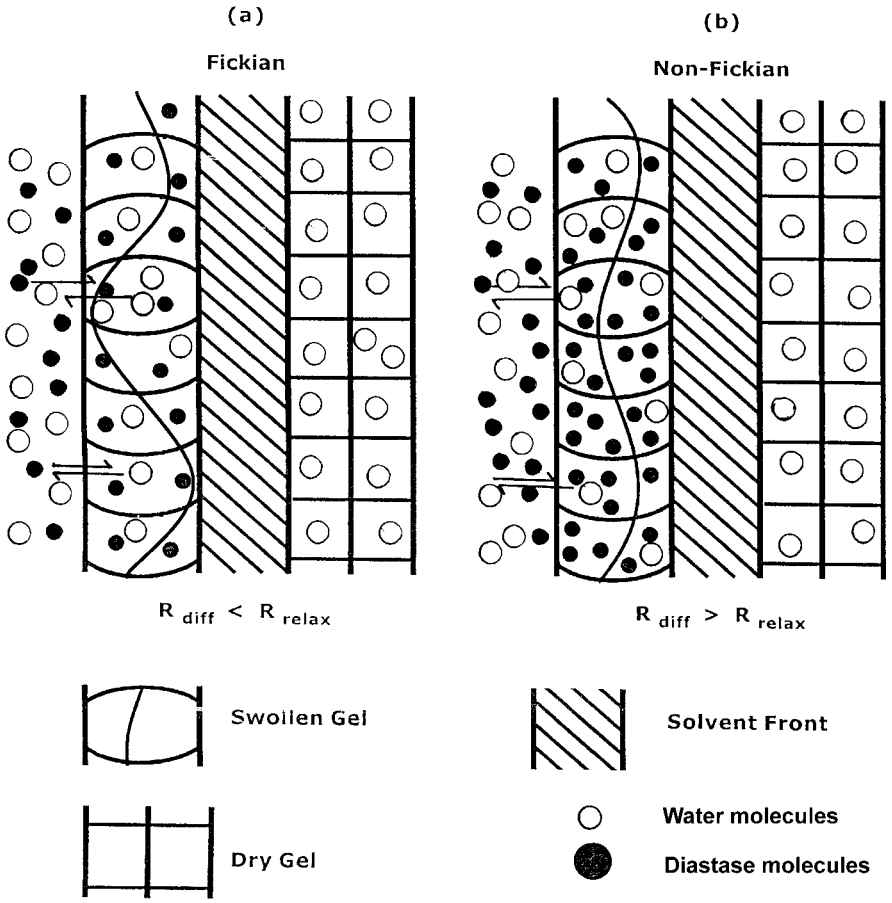

Figure 3. A proposed model of the IPN depicting the enzyme transport mechanism (a) Fickian, (b) non-Fickian.

thereby increasing the mesh size of the free volumes available in between the macromolecular chains which allow the penetration of the enzyme molecules into the network of the hydrogel. This ultimately results in a higher percent loading of the enzyme.

Similar type of results have been observed when the hydrophilic polymer PVA increases in the feed mixture in the range 0.75 g–1.5 g. The results may be explained by the fact that increasing concentration of PVA increases the hydrophilicity of the gel, thereby a greater percent loading since the enzyme diastase being water soluble is bound strongly to the molecules of water.

The influence of AM concentration on the amount of loaded diastase has been investigated by varying the AM concentration in the feed mixture in the range 10.5 mM–28 mM. The results are summarized in Table 2 which reveal that in the range 10 mM–14 mM of AM the amount of diastase loaded increases while beyond 14 mM a decrease

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Table 2. Data showing the variation of percent loading of diastase with varying composition of the IPNs.

PEG (g)	PVA (g)	AM (mM)	MBA (mM)	KPS (mM)	Amount of diastase loaded %
0.22	0.75	14	0.006	0.003	14.0
0.55	0.75	14	0.006	0.003	22.6
0.88	0.75	14	0.006	0.003	26.8
1.32	0.75	14	0.006	0.003	30.0
0.55	0.50	14	0.006	0.003	20.0
0.55	0.75	14	0.006	0.003	22.6
0.55	1.0	14	0.006	0.003	24.0
0.55	1.5	14	0.006	0.003	28.0
0.55	0.75	10	0.006	0.003	19.0
0.55	0.75	14	0.006	0.003	22.6
0.55	0.75	21	0.006	0.003	19.8
0.55	0.75	28	0.006	0.003	17.4
0.55	0.75	14	0.006	0.003	22.6
0.55	0.75	14	0.012	0.003	22.0
0.55	0.75	14	0.025	0.003	19.5
0.55	0.75	14	0.038	0.003	17.0

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is observed. The observed results could be attributed to the swelling results of IPNs (Fig. 4) which also imply that the swelling ratio increases in the range 10 mM–14 mM, while beyond 14 mM, a fall in the swelling ratio is noticed.

The results may be explained by the fact that in the range 10 mM–14 mM the swelling increases because of increasing hydrophilicity of the IPNs, while beyond that the polymeric network becomes so compact that entrance of penetrant water and enzyme molecules is restrained and the swelling ratio as well as the amount of loaded diastase decreases.

On varying the crosslinker (MBA) in the range 0.006 mM–0.38 mM in the feed mixture of the gels, there was a significant fall in the swelling of the IPNs and, therefore, the percent loading decreases. This may be explained by the fact that on increasing the crosslinker content there is a prominent decrease in the free volumes available between the chains of the macromolecular network and thus the loading of enzyme decreases.

Results on Diastase-Release

Effect of Percent Loading

In the present work, the diastase was loaded into IPNs to different extents by allowing the IPNs to swell in the diastase solution of concentration varying in the range 1.0–5.0 mg/mL. The release results are displayed in Fig. 5, which reveal that the released amount of diastase increases with increasing percentage loading in the range 12.8–31.4%. The observed increase in the release rate may be attributed to the fact that a larger loading of the IPN facilitates a faster movement of the solvent front that penetrates the surface of the loaded IPN slab.[26]

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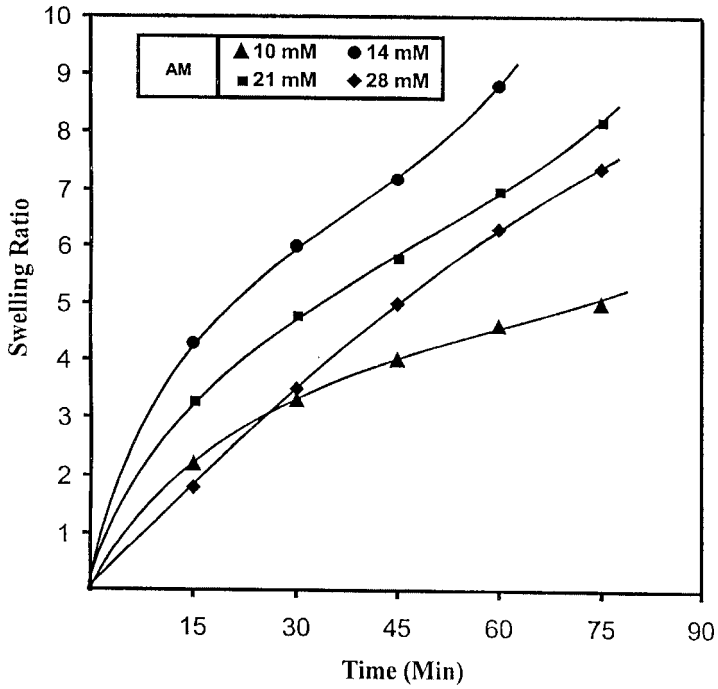

Figure 4. Effect of variation in AM content of the IPNs on the swelling ratio for a given composition of the IPN. [PEG] = 0.55 g, [PVA] = 0.75 g, [MBA] = 0.006 mM, [KPS] = 0.003 mM, pH = 7.4, Temp. = 27°C, %Loading = 22.6.

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Another reason for the observed increase may be that at higher loading of diastase on the IPN's the pores of the polymeric network get saturated with the enzyme thus resulting in an expansion of the pore volumes. This obviously enhances the release rate of the diastase.

The release profiles also present a typical feature that at higher loading of the IPNs, a major fraction of diastase is released just within 10 min. This is known as 'burst effect' and is probably due to transport of loaded diastase to the surface during drying of the IPNs. What actually happens is that drying of the loaded IPN starts at the surface and water from the interior of the gel is pulled along with the drug to the surface by capillary forces. Thus, loaded diastase accumulates close to the surface which in the absence of specific-polymer-enzyme interaction which is manifested by 'burst effect' during release in aqueous medium.

Effect of Composition of Hydrogel

Effect of PEG

When the amount of PEG is varied in the feed mixture of the IPN in the range 0.22 g–1.32 g, the release profiles are greatly affected as shown in Fig. 6. The results clearly reveal

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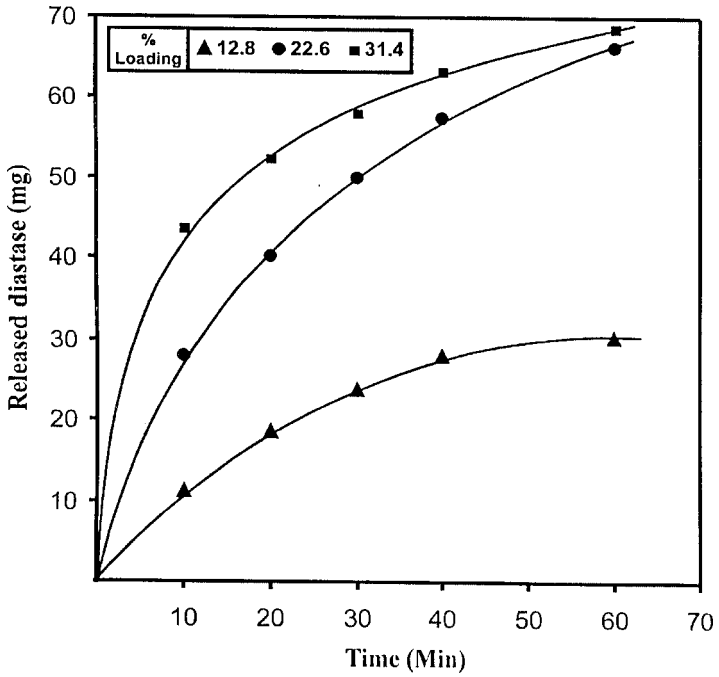

Figure 5. Effect of %loading of diastase on its release profiles for a given composition of the IPN [PEG] = 0.55 g, [AM] = 14 mM, [MBA] = 0.006 mM, [KPS] = 0.003 mM, pH = 7.4, Temp. = 27°C.

that the fractional release increases with increasing amount of PEG in the range 0.22 g–0.55 g while a drop in release of diastase is noticed beyond 0.55 g of PEG content in the IPN. The observed results are consistent to the swelling results of the same IPNs. The observed increase in released diastase may be attributed to the fact that because of hydrophilic nature of PEG, its increasing content in the IPNs results in a higher sorption which consequently leads to larger release of diastase. However, beyond the PEG content of 0.55 g, the decrease observed in both the swelling and release may be due to the reason that at higher content of PEG, the crosslink density of the network becomes so compact that water molecules experience difficulty in penetrating the gel. This obviously brings about a fall in the degree of swelling of the loaded IPN and this consequently also lowers the fractional release of diastase.

The fractional release curves also indicate that whereas the IPNs with high PEG content do not show any tendency to display zero order release behavior, at the lowest PEG content (0.22 g), a zero-order release behavior is noticed. The observed zero-order release implies that a constant amount of diastase is delivered into the release medium with increasing release time. The observed zero-order at lowest PEG content may be explained by the fact that because of the low PEG content the hydrophilicity of IPN is not much greater and, therefore, the IPNs show a lower degree of water sorption. Thus, because of lower swelling of the IPN, the rate of fractional release is also suppressed showing a constant delivery for a longer period. This clearly suggests that the release pattern of

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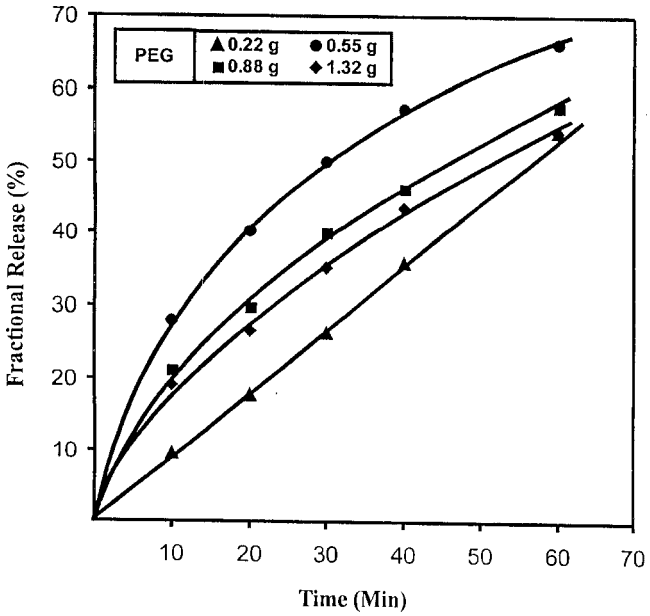

Figure 6. Effect of variation in PEG content of the IPNs on the fractional release diastase for a given composition of the IPN [PVA] = 0.75 g, [AM] = 14 mM, [MBA] = 0.006 mM, [KPS] = 0.003 mM, pH = 7.4, Temp = 27°C, %Loading = 22.6.

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diastase is identical to the swelling response of the IPN. This obviously becomes a pre-requisite of the zero-order release behavior.

The release profiles also display that up to 30% of diastase is released in just 10 min, which could be attributed to a phenomenon known as 'burst effect' as reported by many workers.[27] In analyzing the plot it is, therefore, more accurate to interpret the profile from the time t' when the burst is finished through to the time when the hydrogel is fully swollen.

The general equation for release modified for the burst effect until time, t', is now[28]

$$\frac{100M_t}{M_\infty} = \frac{100M_{t'}}{M_\infty} + k(t-t')^n \tag{9}$$

where $100\,M_t/M_\infty$ is the percentage of the total drug released by time, t'. This equation should fit the release profile until the late time transition, i.e., after more than 50% of the total has been released. The value of n is obtained from the gradient of a log–log plot of M_t/M_∞ vs. t from t' to $t_{0.60}$, the sixty percent life time. The n values have been summarized in Table 3.

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 stages (even reservoir can no longer provide a constant concentration) to a rate which may be therapeutically ineffective. The results clearly reveal that at low and high PEG content of the IPNs the half life of diastase is found

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Table 3. Data showing the kinetic parameters of the release of diastase through the IPNs of different compositions.

Hydrogel composition							
PEG (g)	PVA (g)	AM (mM)	MBA (mM)	KPS (mM)	n	$D \times 10^5\ cm^2\ min^{-1}$	Release mechanism
0.22	0.75	14	0.006	0.003	0.50	2.34	Fickian
0.55	0.75	14	0.006	0.003	0.48	2.17	Fickian
0.88	0.75	14	0.006	0.003	0.52	1.9	Fickian
1.32	0.75	14	0.006	0.003	0.45	1.66	Fickian
0.55	0.50	14	0.006	0.003	1.0	1.66	Case II
0.55	0.75	14	0.006	0.003	0.48	2.17	Fickian
0.55	1.0	14	0.006	0.003	0.48	3.4	Fickian
0.55	1.5	14	0.006	0.003	0.48	3.4	Fickian
0.55	0.75	10	0.006	0.003	0.50	2.08	Fickian
0.55	0.75	14	0.006	0.003	0.48	2.17	Fickian
0.55	0.75	21	0.006	0.003	0.49	1.91	Fickian
0.55	0.75	28	0.006	0.003	0.45	2.01	Fickian
0.55	0.75	14	0.006	0.003	0.48	2.17	Fickian
0.55	0.75	14	0.012	0.003	0.45	1.9	Fickian
0.55	0.75	14	0.025	0.003	0.46	2.06	Fickian
0.55	0.75	14	0.038	0.003	1.0	4.1	Case II

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between 50 min to 60 min while at optimum concentration of PEG (0.55 g) the half life was 30 min only. A smaller half life time for 0.55 g PEG could be attributed to the observed burst effect which is not so prominent at other PEG concentration. The release profiles do not indicate any zero-order delivery.

Effect of PVA

In the present study, the amount of PVA has been varied in the range 0.50 g–1.5 g in the reaction mixture of the IPNs and the obtained release results are depicted in Fig. 7. The results clearly imply that the fractional release significantly increases with increasing PVA content (0.50 g–1.0 g) and at highest PVA concentration (1.5 g) it almost remains unaffected. The observed increasing fractional release is quite obvious and has been explained in the beginning of the para. It is also clearly depicted in the figure that at lower concentration of PVA (0.5 g), a zero-order release behavior is obtained, i.e., the fractional release remains almost constant with increasing time. On the other hand, a burst effect is noticed at upper concentrations of PVA. The observed zero order release at low PVA content of the IPN can be explained on the basis of the water sorption behavior of the gel. When the swelling zone travels across the gel at a constant rate, solvent uptake is proportional to time and zero order kinetics are predicted if diffusate release follows the rate of swelling.[29] In several cases the release has been related to the rate of solvent uptake.[30]

It is also clear from the release profiles shown that half life of diastase increases with decreasing PVA content of the gel. A plot drawn between log $t_{1/2}$ and log [PVA] yields

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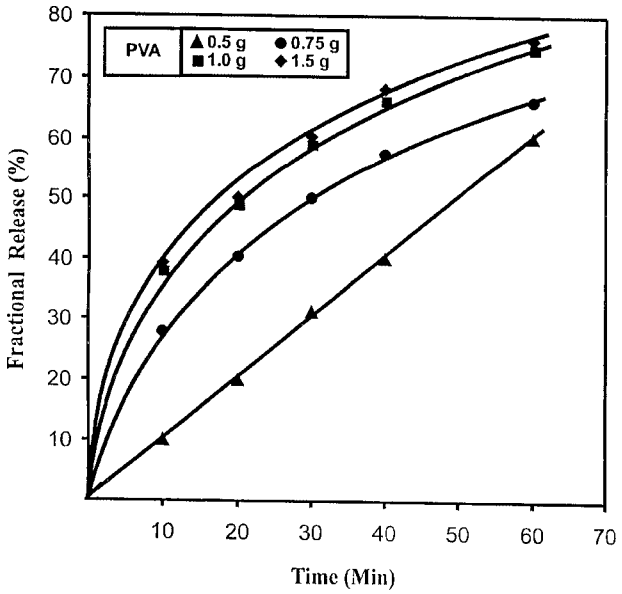

Figure 7. Variation in the fractional release of diastase with varying PVA content of the IPNs for a given composition of the IPN. [PEG] = 0.55 g, [AM] = 14 mM, [MBA] = 0.006 mM, [KPS] = 0.003 mM, pH = 7.4, Temp. = 27°C, %Loading = 22.6.

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a straight line (Fig. 8) which indicate that there is a direct, but reciprocal relationship between the half life of the entrapped enzyme and PVA content.

Effect of Acrylamide

Influence of increasing concentrations of acrylamide (AM) on the fractional release profiles of diastase are shown in Fig. 9 which clearly reveal that with increasing AM content in the IPNs, a decrease in fractional release is noticed. The reason for the observed decrease in release profiles can be understood by the fact that increasing AM in the feed mixture of the IPNs enhances the crosslink density of the network (Table 1) which results in a lower degree of water sorption. It is now obvious that since the IPN under investigation is a swelling controlled release system, a decrease in swelling will lead to a lower release of entrapped diastase.

The release profiles also exhibit a burst effect which is more pronounced at lower concentration of AM (10.5 mM) and gradually decreases with increasing AM concentration. The decrease observed in extent of initial 'burst' is directly related to the swelling of the IPNs in diastase solution during while loading the later onto the device.

Another remarkable feature visible in the release profiles is that a nearly zero-order release kinetics is obtained up to 30 min at highest concentration (28.1 mM). This could be explained on the basis of the swelling behavior of the loaded IPN which is depicted in Fig. 4. It is clear from the swelling ratio vs time curves that at lower concentration of AM

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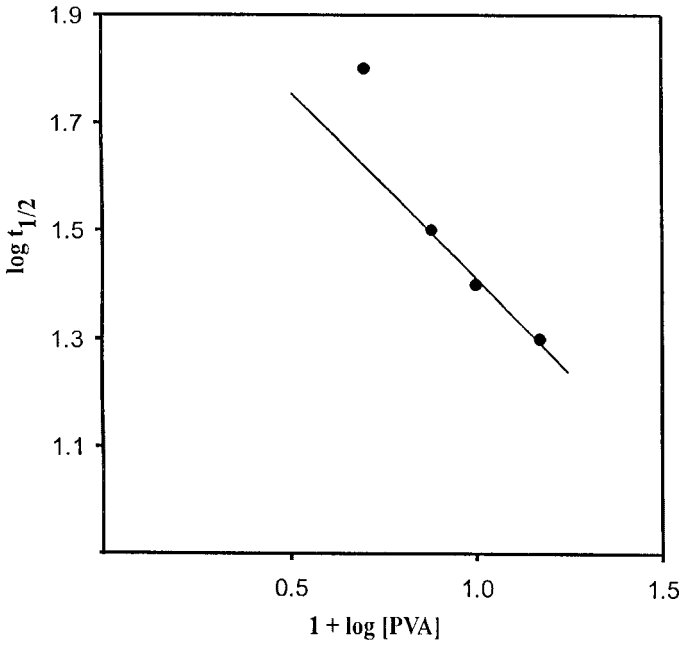

Figure 8. A double logarithmic plot drawn between concentration of PVA and half life of releasing diastase for a given composition of the IPN. [PEG] = 0.55 g, [AM] = 14 mM, [MBA] = 0.006 mM, [KPS] = 0.003 mM, pH = 7.4, Temp. = 27°C, %Loading = 22.6.

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the swelling ratio increases with time in exponential way while at higher AM (28.1 mM), it varies linearly. In other words, the solvent zone penetrates steadily into the loaded matrix and as a consequence the release of diastase also occurs in accordance with the swelling pattern. This obviously produces a zero-order release behavior.

It is also noticed that half life period of diastase also increases with increasing AM concentration (Fig. 10) and there is a linear relation between log $t_{1/2}$ and log [AM], thus suggesting a direct dependence of half life period of enzyme on AM concentration.

Effect of Crosslinker

One of the most effective ways to modify both water sorption and release characteristics of a hydrogel is to change crosslink density of the matrix by employing varying concentrations of the crosslinking agent.[31] In the present investigation, the effect of crosslinker on the release profiles of diastase has been investigated by varying MBA in the concentration range 0.006–0.038 mM in the feed mixture. The results are shown in Fig. 11 which clearly indicate that on increasing MBA in the studied range the fractional release is appreciably reduced. The observed decrease in fractional release is due to the fact that increasing MBA in the IPN results in an increase in crosslink density of the gel which gives rise to a compact network of macromolecular chains. This compactness not

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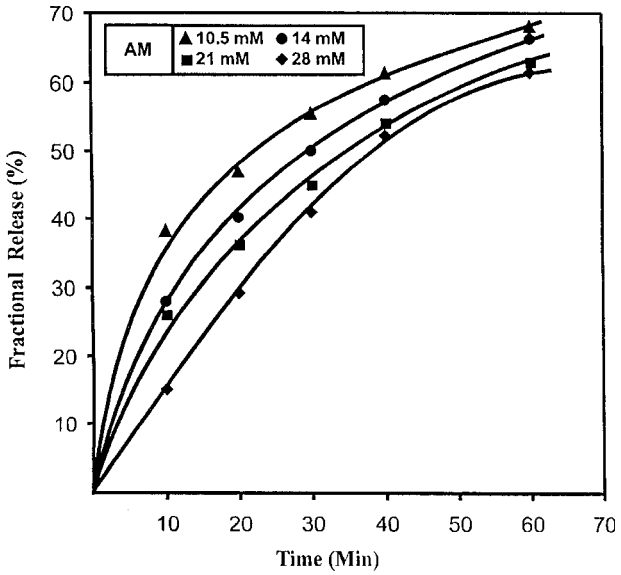

Figure 9. Effect of variation in AM content of the IPNs on the fractional release of diastase for a given composition of the IPN. [PEG] = 0.55 g, [PVA] = 0.75 g, [MBA] = 0.006 mM, [KPS] = 0.003 mM, pH = 7.4, Temp. = 27°C, %Loading = 22.6.

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only restrains the mobility of network chains (chain relaxation) but also slows down the diffusion of water molecules into the gel and subsequently that of diastase molecules from within the gel into the release medium. This obviously results in a fact in both the swelling of the IPN and fractional release of diastase. It is also clear from the release profile curves that at low concentration of MBA a burst effect is observed while with increasing crosslinker in the IPN the burst effect decreases and ultimately at highest concentration of MBA (0.038 mM) it completely disappears. The observed change in burst effect may be explained by the fact that at low MBA, the mesh size of the free volume available between the network chains is large, thus easily allowing the entrapped diastase molecules to release out quickly. On the other hand, at higher concentration of crosslinker due to a decrease in mesh size of the available free volumes, the diastase molecules experience difficulty in releasing out of the gel, thus avoiding the chance of a burst effect.

It is an important observation from the release profiles shown in Fig. 11 that at highest MBA concentration the release process followed a fairly zero-order kinetics. The possible reason for the observed zero-order behavior may be that at highly crosslinked state the hydrogel may not swell significantly and, therefore, the diastase molecules do not have to travel a larger distance within the gel to come out on the surface. This clearly reveals that diffusion constant of the releasing diastase molecules remain almost constant with release time.

The release profiles also show that the half life period of diastase also increases with increasing concentration of crosslinker. When a plot is drawn between log $t_{1/2}$ and log [MBA], a straight line is obtained which establishes a direct relation between the half life

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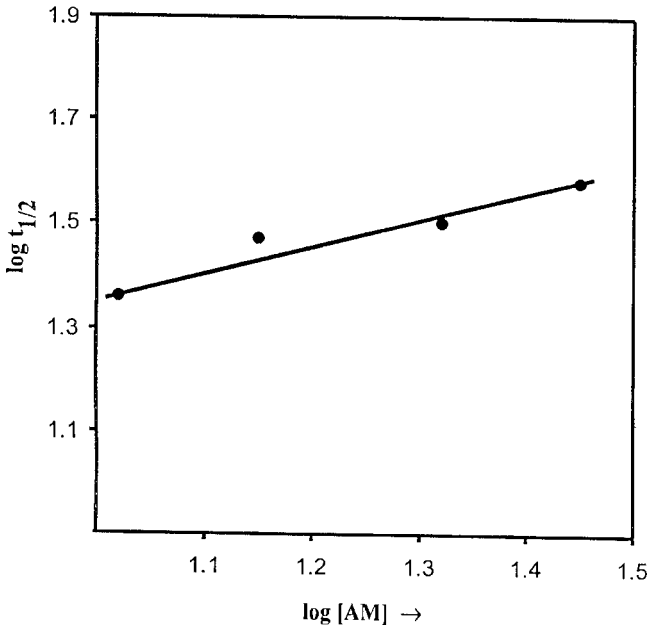

Figure 10. A double logarithmic plot between concentration of AM and half cycle of releasing diastase for a given composition of the IPN. [PVA] = 0.75 g, [PEG] = 0.55 g, [MBA] = 0.006 M, KPS = 0.003 mM, pH = 7.4, Temp. = 27°C, %Loading = 22.6.

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and crosslink density (or concentration). This obviously provides a tool to regulate the half-life period of the entrapped bioactive agent.

Effect of pH

pH responsive macromolecular devices have been most frequently used to develop controlled release formulations for oral administration which remains the most clinically acceptable way of drug-delivery. Oral administration of macromolecular drugs remains a significant challenge because peptides and proteins are susceptible to hydrolysis and digestion by the acid and enzymes in the gastrointestinal (GI) tract. Also, the bioavailability of orally delivered peptides and proteins is very low due to poor membrane permeability.[32] Thus, to improve therapeutic efficiency and to reduce or eliminate side effects of oral controlled drugs, it is reasonable to deliver drugs to specific regions of the GI tract.

Several methods of targeting the specific regions have been used or proposed. Two of these, i.e., utilization of pH changes within the GI tract[33] and exploitation of bacterial enzymes localized within the colon[34] are of current interest in controlled drug delivery systems.

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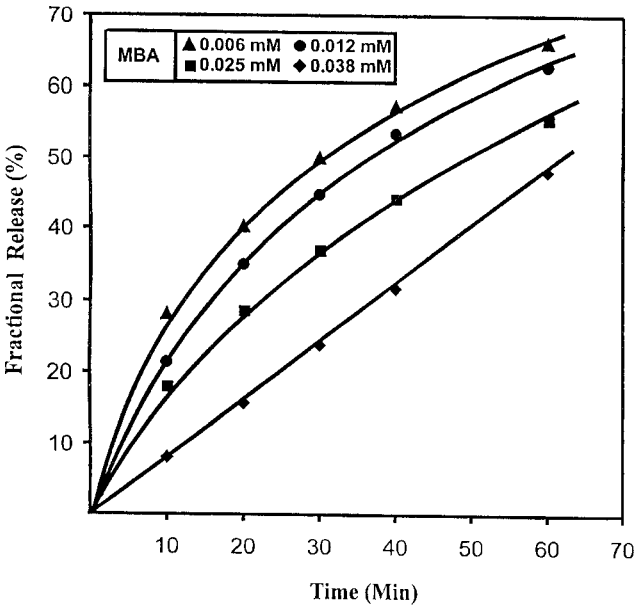

Figure 11. Effect of crosslinker (MBA) content of the IPNs on the fractional release of diastase for a given composition of the IPN. [PEG] = 0.55 g, [PVA] = 0.75 g, [AM] = 14 mM, [KPS] = 0.003 mM, pH = 7.4, Temp. = 27°C, %Loading = 22.6.

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In the present investigation, the release dynamics of the diastase has been observed under varying pH conditions as found in the GI tract [eg., saliva (in mouth) 6.7, stomach (gastric juice) 1.0, and small intestine 7.5 to 8.6]. The wide range of pH allows a specific drug to be delivered to a targeted site only. For example, the pH in the stomach (<3) is quite different from the neutral pH in the intestine and this pH difference could be used to prevent release of foul-tasting drugs into the neutral pH environment of the mouth while using polycationic hydrogels as drug carrier.[35] Similarly, a polyanion hydrogel which shows a minimal swelling at acidic pH (such as in stomach) could be of potential use to deliver drugs to the intestinal tract due to increase in pH leading to ionization of the carboxylic groups.[36]

In the present study, where a non-polyelectrolyte hydrogel is being used, the release profiles of diastase are shown in Fig. 12 which clearly indicate that the fractional release constantly increases with increasing pH of the release medium. The results imply that at neutral and alkaline pHs, the fractional release of diastase is much more faster than that at the acidic pH. The observed results are most desirable, also as the release of diastase, a well known digestive enzyme, must occur at mouth and intestinal regions of the GI tract where the pHs are neutral and slightly alkaline, respectively. The increase in fractional release with increasing pH may be explained by the fact that in the medium of neutral to alkaline pH, the amide groups ($-CONH_2$) of PAM are weakly hydrolyzed to carboxylic groups ($-COOH$) which in alkaline conditions yield carboxylate ions ($-COO$) thus imparting negative charge to macromolecular chains of the semi-IPN. The presence of $-COOH$ groups were further confirmed by potentiometric titration method and

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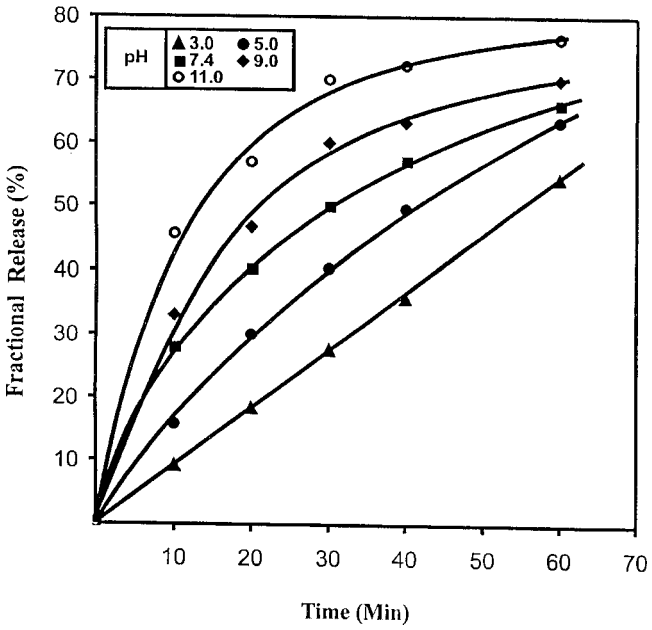

Figure 12. Effect of pH of the release medium on the fractional release of diastase for a given composition of the IPN. [PVA] = 0.75 g, [PEG] = 0.55 g, [AM] = 14 mM, [MBA] = 0.006 mM, [KPS] = 0.003 mM, Temp. = 27°C, %Loading = 22.6.

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the degree of hydrolysis of the hydrolyzed semi-IPNs was found to be 2.8 and 7.2% at pH 9.0 and 11.0, respectively. These charged chains being repulsive in nature undergo rapid relaxation, thus permitting water molecules to enter easily into the loaded IPN which, in turn, delivers the entrapped diastase into the release medium. It is also to be noted here that as pH of release medium increases, the burst effect also increases which could be due to the larger swelling of the IPN in the enzyme solution.

The release profiles also indicate that a zero-order release behavior is obtained in acidic range of pH, i.e. at pH 3.0 and pH 5.0. The observed zero-order may be attributed to the reason that in acidic medium the IPNs swell to a lower extent so that the solvent zone penetrates at a steady rate into the gel and as a consequence the release of diastase follows the same order of velocity. This obviously explains the zero order release in acidic pH range.

The half-life period of diastase is also found to increase with decreasing pH of the release medium and a linear dependence is obtained when a plot is drawn between log $t_{1/2}$ and log pH as shown in Fig. 13. Thus, the half-life period of the loaded drug may be fairly predicted at various parts of the GI tract on the basis of the respective pH.

Effect of Temperature

In the present study, the temperature of release medium has been varied in the range 10 to 40°C and its effect on the fractional release of diastase has been investigated.

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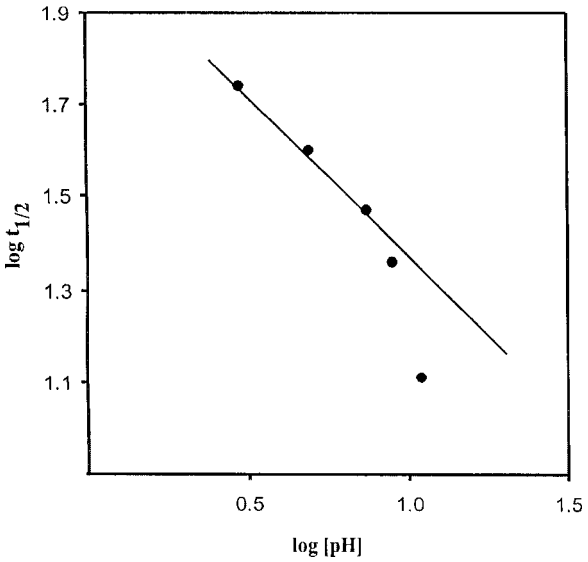

Figure 13. A double logarithmic plot between pH and half life of releasing diastase for a given composition of the IPN. [PEG] = 0.55 g, [PVA] = 0.75 g, [AM] = 14.0 mM, [MBA] = 0.006 mM, [KPS] = 0.003 mM, Temp. = 27°C, %Loading = 22.6.

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The results are displayed in Fig. 14, which indicate that with increasing temperature the fractional release of diastase decreases.

The observed decrease in fractional release may be attributed to the fact that with increasing temperature, the hydrogen bonds between the water molecules and network chains get broken thus converting 'bound water' to free water'[37] which because of faster relaxation of polymer chains is forced out. This obviously results in a lower degree of swelling. Since the present release system is a swelling controlled type, clearly the fractional release of diastase molecules will also be reduced. From the obtained release profiles it can also be seen that a prominent 'burst effect' appears at the lowest temperature of studied range and the 'burst effect' decreases with increasing temperature. A greater burst effect at lower temperature, as mentioned earlier, is also due to a higher degree of sorption of the IPN in diastase solution.

Another significant finding is that at higher temperature (40°C) the release profile follows a fair zero-order release behavior. This clearly shows that at higher temperature the swelling and release processes proceed with constant velocities with linear dependence on each other. It is also clear from the Fig. that the half-life period of diastase significantly increases with increasing temperature of the release medium.

To analyze the temperature effect, the Gibbs–Helmholtz equation can be applied according to which[38]

$$\frac{\mathrm{d}\ \ln(W_\infty)}{\mathrm{d}(1/T)} = -\Delta H_m/R \tag{10}$$

where R is a gas constant and ΔH_m is the enthalpy of mixing between the gel and infinite

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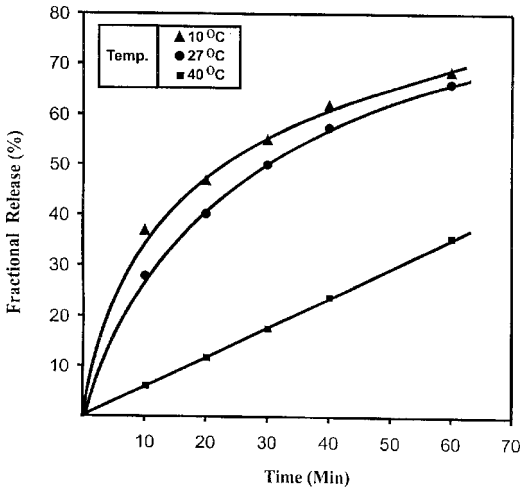

Figure 14. Effect of temperature on the fractional release of diastase for a given composition of the IPN. [PEG] = 0.55 g, [PVA] = 0.75 g, [AM] = 14 mM, [MBA] = 0.006 mM, [KPS] = 0.003 mM, pH = 7.4, %Loading = 22.6.

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amount of water. When W_∞ (equilibrium sorption) is plotted against reciprocal of temperature (1/T), a straight line with positive slope is obtained (Fig. 15) which implies for an exothermic process. The value of ΔH_m was calculated to be -0.14 kJ/mol.

Molecular Weight Effect

There are many parameters that are used to control the release rate of drug from polymeric systems. There are polymer hydrophilic/hydrophobic balance, crosslink density, device geometry and size and molecular weight of polymer. In the present study the effect of molecular weight on release profiles of diastase has been observed by using PEG of molecular weights 400, 600 and 6000, respectively. The results obtained are shown in Fig. 16, which indicate that with increasing molecular weights of PEG the fractional release significantly decreases. The results can be explained as below.

In the present study, the IPN could be considered as a network of PEG, PVA and crosslinked PAM chains entangled into one another via physical forces. When the molecular weight of PEG increases, the degree of entanglement also increases which enhances the number of pseudo-crosslinks in the network. The low molecular weight polymer has fewer crosslinks, the polymer chains are mobile, hence, this polymer matrix will relax rapidly, thus releasing the entrapped diastase with a faster rate. Another possibility with low molecular weights PEG is that because of the smaller dimension of polymer chains, the degree of entanglement will be low and some of the PEG chains are most likely to leak out of the IPN matrix. This will certainly result in the formation of a porous network through the pores of which the entrapped diastase molecules may release out with a faster rate as shown in Fig. 17.

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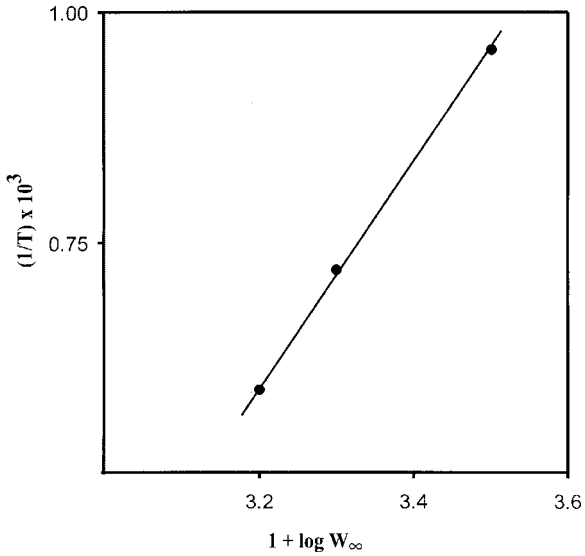

Figure 15. A plot drawn between $1 + \log (W_\infty)$ and 1/T for evaluation of enthalpy of mixing ΔH_m for a given composition of the IPN. [PEG] = 0.55 g, [PVA] = 0.75 g, [AM] = 14.0 mM, [MBA] = 0.006 mM, [KPS] = 0.003 mM, pH = 7.4, Temp. = 27°C, %Loading = 22.6.

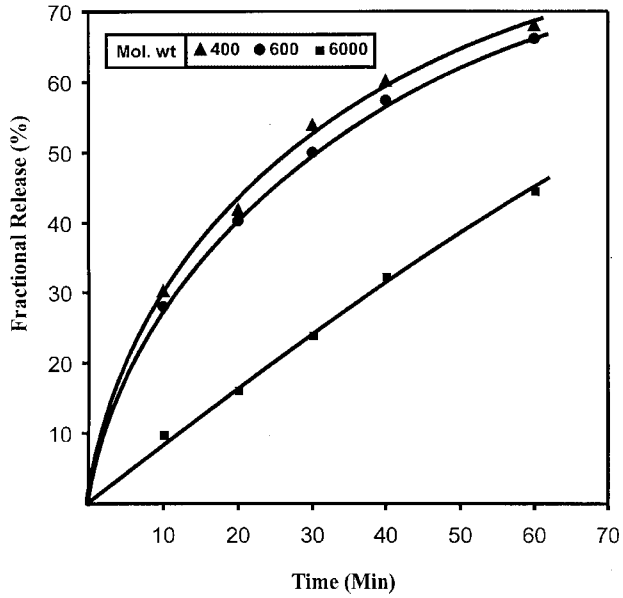

Figure 16. Effect of molecular weight of PEG on the fractional release of diastase for a given composition of the IPN. [PEG] = 0.55 g, [PVA] = 0.75 g, [AM] = 14 mM, [MBA] = 0.006 mM, [KPS] = 0.003 mM, pH = 7.4, Temp. = 27°C, %Loading = 22.6.

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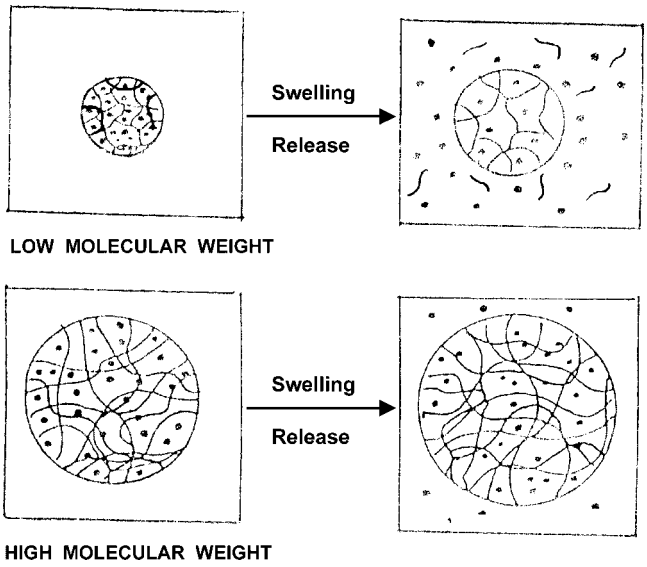

Figure 17. A model depicting the influence of molecular weight on the release of diastase.

The whole release mechanism has been depicted through a hypothetical scheme as shown in Fig. 17. The high molecular weight polymer, on the other hand, possesses a greater extent of physical crosslinking of the polymer chains which result in the formation of a three dimensional network which greatly restricts the mobility of the polymer chains. Furthermore, the macromolecular mesh size or the free space available for diffusion of diastase and water molecules is reduced and this gives rise to a slow releasing system as shown in Fig. 17. In such a system, the release mechanism generally involves movement of the drug through a complex porous path in the polymer matrix. If the polymer erodes, this will affect the pore structure and accelerate the release.[39] It is also clear from the release profiles that no 'burst effect' is observed with high molecular weight polymer. This could be due to the reason that because of a greater number of pseudo-crosslinks, the degree of swelling of the IPN will be low in the diastase solution and, therefore, the burst effect will also be absent.

This can also be seen from the release profiles that a zero order release behavior is exhibited by the IPN of higher molecular weight polymer (PEG). The reason for the observed behavior is quite obvious as in a highly crosslinked matrix both the swelling and release processes shall be slower and will have constant swelling and release rates. On the other hand, in a less crosslinked IPN, i.e., of lower molecular weight PEG, because of greater swelling in release medium the diastase molecules will have to travel an increasingly lengthier path and, therefore, a constant amount of diffusate cannot be delivered for the studied span of time.

Analysis of Dynamic Release Data

It is a well established fact that the release process basically results from the swelling of the loaded device in the release medium. In the present study, the release data has been

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treated with Eqs. (4) and (5), and the evaluated kinetic constants such as diffusion constant D and diffusional exponent n have been summarized in Table 3. Now, the summarized data may be analyzed to provide some information about the mechanisms of release process, as explained below.

When the amount of PEG increases in the concentration range 0.22 g–1.32 g in the feed mixture of the loaded IPN, the diffusional exponent n varies in the Fickian range (except for 0.22 g) as shown in Table 3. This clearly reveals that with increasing PEG in the IPN's, the enzyme transport mechanism remains Fickian in nature. The observed results may be explained by the fact that greater PEG content in the gel restrains the diffusion of releasing diastase molecules and, therefore, the release process remains diffusion controlled. However, at lowest PEG content the IPN is least hydrophilic and therefore shows less affinity to invading water molecules. Thus, because of low water sorption the glass transition temperature (Tg) may not decrease substantially, and the release process becomes relaxation controlled, i.e., Case II transport.

On varying the amounts of PVA in the feed mixture of the IPN in the range 0.50 g–1.5 g, the fractional release of enzyme is found to increase while a decrease is observed in the diffusional exponent n from Case II to Fickian value. In other words, the release process changes from relaxation controlled to diffusion controlled. The observed shift may be explained by the fact that increasing PVA content enhances the compactness of the network and, therefore, slows down the diffusion of diastase molecules. This clearly results in a diffusion controlled release of enzyme.

The data summarized in Table 3 also indicate that with increasing acrylamide content in the hydrogel in the range 10.5 mM to 28 mM, the diffusional exponent remains in the Fickian region, thus rendering the release mechanism to diffusion controlled. The observed results can be attributed to the fact that with increasing acrylamide content in the hydrogel the number of crosslinked polyacrylamide chains increases which because of reduced molecular weight of polymer chains (Table 1) decreases the free volumes available within the network. This results in a slow diffusion of diastase molecules into the release medium and thus the process remains diffusion controlled.

On increasing the concentration of cross-linker (MBA) in the range 0.006 mM to 0.038 mM in the IPN, the diffusional exponent n is found to remain in the Fickian region and tends to attain a Case II value. The observed results can be explained by the fact that with increasing crosslink density in the IPN's, the mesh size of network decreases which slows down the diffusion of releasing diastase molecules. Thus, the release process remains diffusion controlled. However, at the highest concentration of crosslinker the network becomes so highly crosslinked that the relaxation of macromolecular chains is restrained and a Case II transport condition (or zero order) is achieved.

CONCLUSION

The semi-IPNs prepared by polymerizing acrylamide in the presence of PEG and PVA display a fair potentiality to release the enzyme diastase from within their macromolecular matrices. The loading of diastase is found to be greatly influenced by the chemical composition of the gel. It is found that with increasing amounts of PEG, PVA

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and AM in the IPNs, the percent loading increases. The fractional release of diastase also increases with increasing percent loading of the enzyme.

The release profiles of diastase are greatly influenced by the chemical architecture of the IPNs. It is found that on increasing the amount of PEG in the feed mixture in the range 0.22 to 0.55 g, the fractional release of diastase increases while beyond 0.55 g, a decrease in release rate is observed. Moreover, a 'burst effect' is noticed when PEG is present in the IPNs in the range 0.55–1.32 g. It is also found that at the lowest PEG content (0.22 g) the release becomes zero order.

In the case of an increase in PVA content, the fractional release is found to increase and a zero-order release is achieved at lowest PVA content.

When AM and MBA contents are increased in the IPNs, a decrease in fractional release is noticed and for their greatest concentrations, a zero-order delivery of diastase is noticed. Most of the release profiles with higher fractional release rate show a 'burst effect'.

The release profiles are greatly influenced by pH of the release medium. It is found that the fractional release increases with increasing pH. A zero-order release behavior is obtained at the lowest pH (3.0).

Other factors such as temperature of the release medium and molecular weights of PEG are also found to suppress the fractional release of diastase at higher temperature (40°C) and molecular weight (6000) the release of diastase follows a zero-order delivery.

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