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RELEASE OF THEOPHYLLINE FROM DRIED DOWN HYDROGELS BASED ON HYDROXYETHYL METHACRYLATE AND ACRYLAMIDE

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Hydrogels were chosen to assess their utilization for sustained release medication. The hydrogels based on hydroxyethyl methacrylate were synthesized and the maximum water uptake was varied by copolymerizing acrylamide and hydroxyethyl methacrylate. Methylene-bis-acrylamide was used as a crosslinking agent. Theophylline, used as the model drug, was incorporated in the hydrogels. The influence of selected hydrogel compositions and temperature effects on the release of theophylline from dried down drug loaded hydrogels was studied. The effect of storage on drug release was also investigated. No significant evidence of thermal instability was found on the drug after aging drug loaded polymer at 45°.

Key words : Hydrogels, Hydroxyethyl methacrylate, Acrylamide, Water, Theophylline, Hydrogel compositions, Temperature.

INTRODUCTION

Polymers are finding increasing applications in the controlled release of pharmaceuticals [1-3]. The mechanisms of drug release from various polymeric matrix systems have been extensively discussed [4, 5]. In polymeric controlled release system the drugs are released by diffusion, chemicals, swelling and magnetic processes. The most common mechanism is diffusion through hydrogels, whereby the drug migrates from its initial position in the plastic to the outer surface. Roseman and Higuchi [6] have proposed that under certain conditions the rate of diffusion from the surface of the matrix to the surrounding bulk solution makes a significant contribution to the total diffusional process. Haleblian [7] also suggested the possibility that the rate of solute transfer across the matrix-solution may control the release.

In the matrix or monolithic system where the drug is distributed uniformly throughout the polymeric matrix, the drug release does not follow zero-order [8]. Lee [9] has described an approach to zero-order drug delivery by immobilizing non-uniform drug distribution in hydrogels. In the presence of water, hydrogels can absorb a significant amount of water to form an elastic gel and at the same time release the dissovled drug by diffusion through the swollen region [10, 11]. In the present work the influence of hydrogel composition on the resulting release characteristics have been studied.

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EXPERIMENTAL

Materials. Acrylamide (AM) obtained from Merck was recrystalized from chloroform at room temperature. The melting point of recrystalized acrylamide was determined as 84° as compared to the reported 84.5° [12].

Hydroxyethyl methacrylate (HEMA), of Merck was dried by passing through a 40 cm column of anhydrous aluminium oxide. Azo-*iso*-butyronitrile (AIBN) and *N,N*-methylene-*bis*-acrylamide (MBAM) were used as received from Merck. All other reagent grade chemicals were of Merck origin.

Theophylline was used as a drug model and obtained from Sigma chemicals.

Composition of hydrogels. HEMA has lesser swellability than acrylamide [13, 14]. A series of HEMA hydrogels was prepared by varying the monomer feed ratio of HEMA and acrylamide, and by adding different amounts of cross-linking agent (MBAM) in the composition in order to have hydrogels of desired mechanical strength and swellability. The polymerization data of hydrogels under study are summarized in Table 1.

Table 1. Composition of Hydrogels.

Composition (Hydrogels)	HEMA (ml)	Acrylamide (g)	AIBN (g)	MBAM (g)
A	18.24	0	0.0197	0.1952
B	12.77	3.1986	0.0170	0.1686
C	9.12	5.3300	0.0152	0.0755

Azo-*iso*-butyronitrile (AIBN) was used as initiator (0.01% w/w of the bulk composition) and methylene-*bis*-acrylamide (MBAM) was included in the composition as crosslinking agent (0.5% and 1% w/w of the two monomers used in composition C, A and B respectively).

Preparation of hydrogels. Essentially the preparation of hydrogels consisted of mixing sequentially the required quantities of acrylamide, hydroxyethyl methacrylate and methylene-*bis*-acrylamide in a well dried two neck 250 ml quickfit flask preheated to 60° and connected to a vacuum system. Vacuum was necessary in order to remove air from the reaction flask to prevent formation of peroxy radicals. After the dissolution of ingredients, the AIBN (initiator) was added to the flask and the vacuum was resumed again quickly. The flask was kept heated at 60° till the solution became viscous. After disconnecting the vacuum, the contents of the flask were poured into a U-shaped poly propylene tubing tied in a stand for moulding and curing. The moulding was placed in an oven heated to 60° for five hours for curing. Then it was removed from the oven and cooled in a vacuum desiccator. The hydrogel was removed from the tube before use. The use of polypropylene tube made it possible to cast the hydrogels in cylindrical form.

Purification of hydrogels. Each hydrogel was cut into cylindrical pieces which were placed in the distilled water for 24 hours to extract any unreacted materials, or short chain fragments. The removal was monitored by UV spectrophotometer and after three days of washing there was no extractable coming out of the hydrogel. The swollen hydrogel was left to dry to constant weight under vacuum at 30° and stored in a desiccator over phosphorous pentoxide until used for experiments.

Drug incorporation in hydrogels. Theophylline was used as the model drug. Accuratley weighed pieces of hydrogel were immersed in a 0.8% w/v theophylline solution prepared in water and contained in a stoppered flask which was kept at room temperature for 48 hour. During this period the hdyrogel was allowed to equilibrate to ensure the uniform distribution of theophylline throughout the polymer. The swollen drug loaded hydrogel were wiped carefully with tissue paper and then dried at 40° in a vacuum oven. The dried hydrogel attained its original shape and dimensions.

In-vitro release studies. The *in-vitro* release of theophylline from the dry drug loaded hydrogel was studied by employing a rotating bottle dissolution apparatus similar to that described by Souder and Ellenbogen [15] and constructed by Emmay Enterprises, using distilled water as the release medium. The apparatus essentially consisted of a rotating machine with screw-tied clamps for holding eight 90-ml screw capped bottles along the rotating axis. A speed of rotation of 40 rpm and a water bath at 37° ± 1° were used. A piece of dry drug loaded hydrogel was placed in a round 90-ml screw capped glass bottle containing 60ml of distilled water. The bottles were rotated end-over-end in the water bath at the test temperature.

After an interval of one hour the entire liquid from each bottle was withdrawn in a conical flask for analysis. The contents of theophylline in the liquid was determined by the method given in B.P. 1980 [16]. The titration was carried by using micropipette of BHG Precicolor, West Germany. Release of drug was determined over an 8-hour period. After this, each hydrogel cylinder was crushed to a fine powder with the help of pestle and mortar. This powder was dispersed in the distilled water so as to make a slurry which after keeping for 24 hours was filtered through a Whatman filter paper. The remaining amount of theophylline in hydrogel was determined from the filtrate by the similar method [16], as mentioned before. Release studies were also carried at temperature of 37°, 50° and 60°.

Effect of storage on drug release. The storage stability tests were conducted on hydrogels stored in the capped vials under ambient conditions for 60 days.

Stability of theophylline. The stability tests of theophylline loaded in the hydrogel were also conducted by storing the dry drug loaded hydrogels in capped vials at 45° for seven days.

RESULTS AND DISCUSSIONS

In this study the cross-linked hydrogels with different composition of acrylamide and hydroxyethyl methacrylate (composition given in experimental section) having various amount of cross-linking agent, methylene-*bis*-acrylamide, were synthesized and evaluated for characteristics of *in-vitro* drug release. The swelling characteristics of the hydrogels would be published elsewhere.

The dry drug loaded hydrogels when imbibed by water, absorb a considerable amount of water to become an elastic gel and, simultaneously, release the dissolved drug by diffusion through the swollen region [10,11].

In the process of evaluation, the solvent (in this case water) penetrates a glassy hydrogel matrix loaded with drug and a clear discernible boundary separating an outer elastic swollen region from an un-penetrated glassy core was observed in the beginning which eventually disappeared and the whole hydrogel matrix became opaque, rubbery and swollen. This type of penetration and swelling usually undergo non-Fickian diffusion [17,18].

The weights of hydrogel cylinders used in the experiments were not precisely equal in all studies therefore, Mt/M_{∞} against time to obtain the comparable release curves, are presented in Fig. 1, where Mt is the amount of drug released at time t_0, (in minutes) and M_{∞} is the total drug uptake by the hydrogel at infinite time, that is, at drug equilibrium, when the weight of hydrogel and drug solution becomes constant.

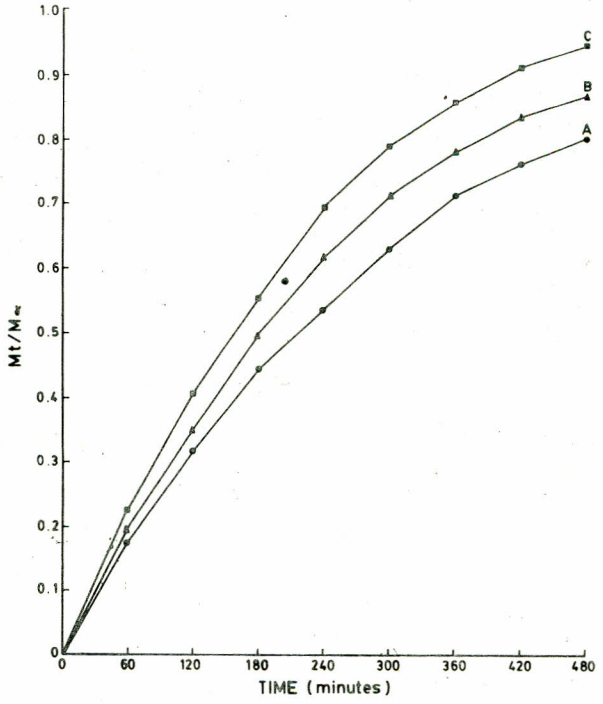

Fig. 1. Drug release of hydrogel A,B and C at 37°

Fig. 1 shows the in vitro release of drug from three compositions A,B and C at 37°. The apparent slope of the curves shows that the composition C releases drug more rapidly than that of hydrogel with composition A, whereas hydrogel with composition B gives intermediate release. This difference in release profile may be attributed to the amount of acrylamide and maximum uptake of water by hydrogel. The hydrogel A (100% HEMA) imbibed 137 %, hydrogel B 151 % (70 % HEMA + 30% AM) and hydrogel C (50 % HEMA + 50 % AM) 342 % water at 37°. As acrylamide is more hydrophilic than HEMA, therefore, by increasing the concentration of acrylamide, the swelling capacity of hydrogel increases. The ratio of acrylamide to HEMA used in the composition of A,B and C hydrogels is 0,3 and 5 respectively which is indicative of the drug release behaviour of the three hydrogels. In other words, higher feeds of HEMA follows the regular pattern of drug release, whereas higher feeds of acrylamide increase the drug release but suddenly the release slows down to constant. All the three curves (Fig. 1) exhibit an initially high drug release followed by a gradual decline. The onset increase is due to the surface area of the cylindrical hydrogel which when imbibed by swelling solvent diffuses out drug quickly, however the slow release at the later stage appears to be the result of increased diffusional distance and decreased area at the penetrating diffusion point.

Effect of temperature. Figs. 2a-4a depict the drug release pattern of hydrogels with composition A, B and C at temperature 37°, 50° and 60°. All the curves show

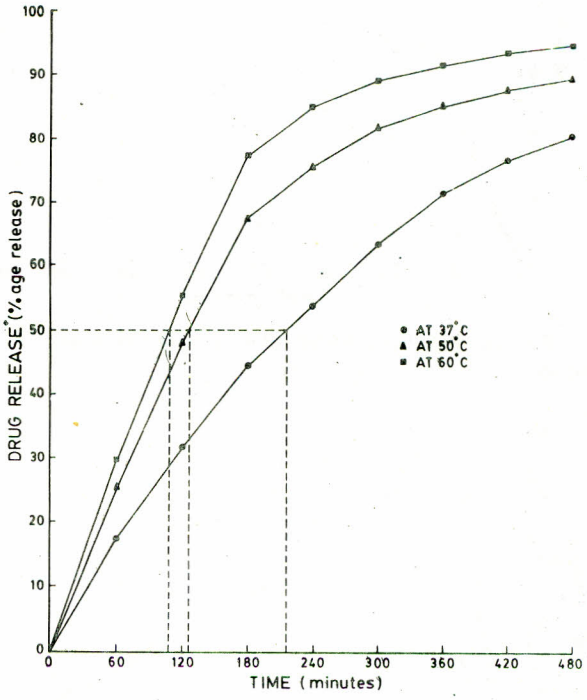

Fig. 2a. 50% Drug release plot of hydrogel A at 37°, 50° and 60°

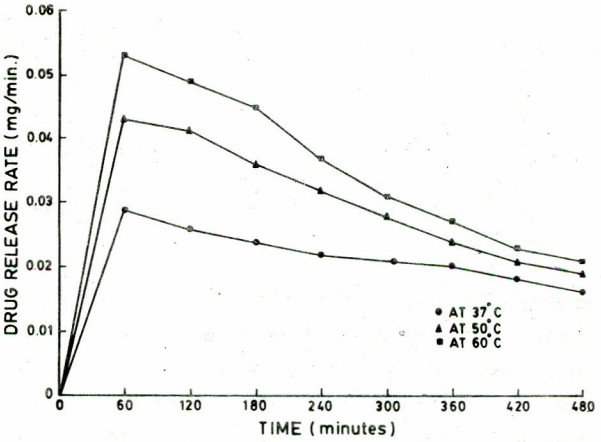

Fig. 2b. Drug release rate (mg/min.) of theophylline from hydrogel A at 37° and 60°.

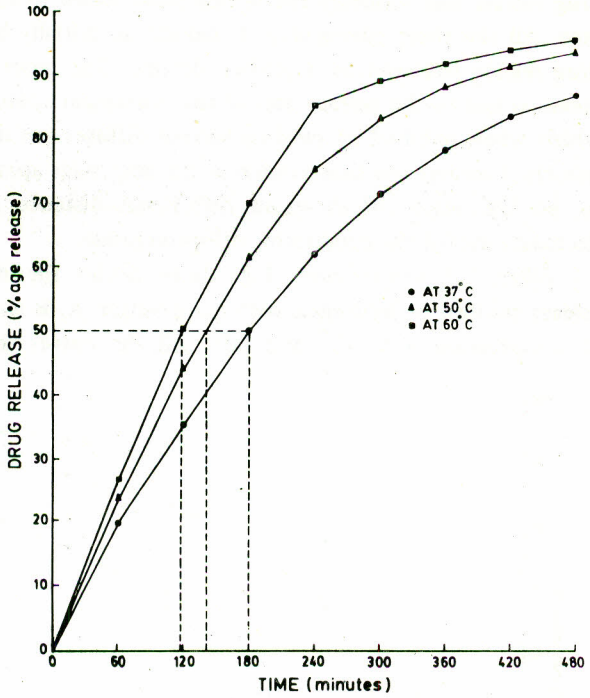

Fig. 3a. 50% Drug release plot of hydrogel B at 37°, 50° and 60°.

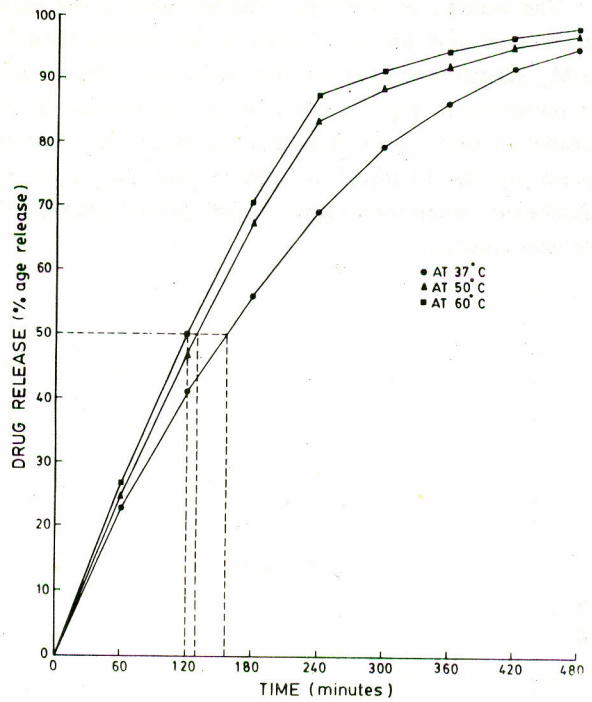

Fig. 4a. 50 % Drug release plot of hydrogel C at 37°, 50° and 60°.

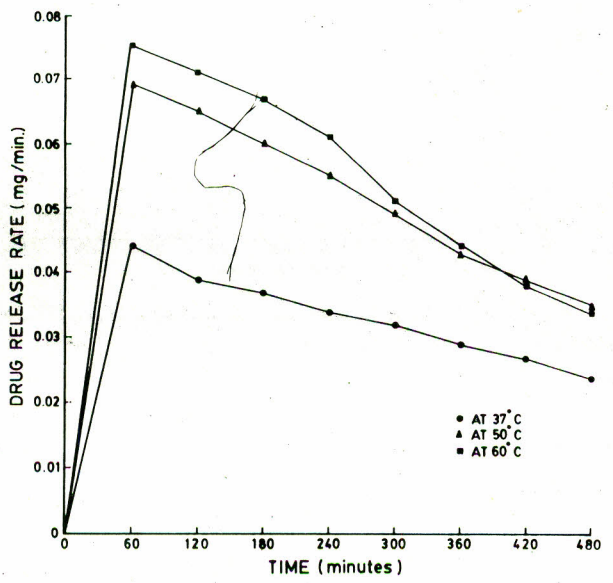

Fig. 3b. Drug release rate (mg/min) of theophylline from hydrogel B at 37°, 50° and 60o.

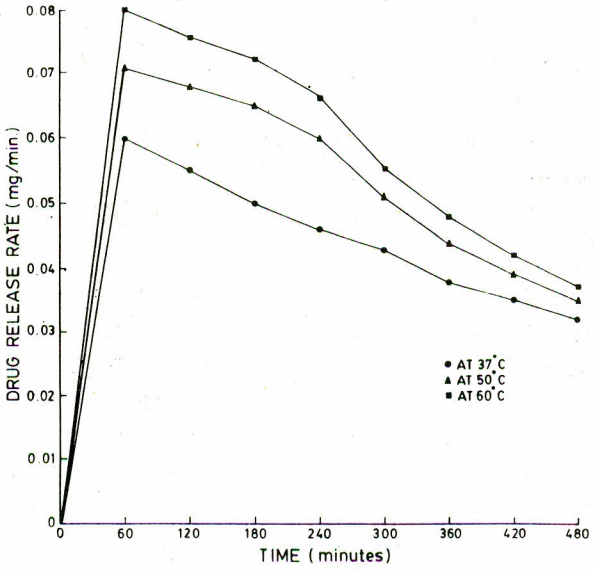

Fig. 4b. Drug release rate (mg/min.) of theophylline from hydrogel C at 37°, 50° and 60°

retarded first order dissolution but to variable extensts. At elevated temperature the drug release is higher followed by rapid decline which could be attributed to increasing pore size of hydrogel network due to extended molecular relaxation. Expansion of hydrogels may exert expansion in the inter-linking network with the result of higher drug release through such expanded surface. The existence of some molecular relaxation process in addition to diffusion is believed to be responsible for the observed non-Fickian behaviour [19,20]. As a result, an inflection point is built up in the drug release curves of higher temperatures. First-order release regions of upto 64 %, 75 % and 83 % of the total drug in hydrogels A, B and C respectively at 50°, and similarly 77 %, 85 % and 87 % of the total drug in hydro-

gels A,B, and C respectively at 60° are evident in curves of Figs. 2-4. Thus with the increase in temperature, considerable linearity in the cumulative release curves exists in all three hydrogels. The detailed released data are summarized in Table 2-4.

The drug release rate shows a progressively decreasing slope with increased drug release time as shown in Figs. 2b-4b. The fall in drug release rate is more at high temperature than at low temperature in each hydrogel. Among the three hydrogels, the A shows comparatively steady or constant release rate at 37°.

Further the half life of theophylline as function of temperature is plotted in Fig. 5. It is obvious that the release half-life is decreased with the increase in temperature which is an evidence of the release dependence on the temperature. It is evident that the release half-life is inversely proportional to the temperature i.e. higher the temperature the lower is the release half-life. The release half-life

Table 2. Drug release of theophylline from hydrogel A at 37°, 50° and 60°.

	37°C Weight of hydrogel (dry) = 253.8 mg Infinite theophylline uptake (M_∞) = 9.81 mg; (M)		50°C Weight of hydrogel (dry) = 267.3 mg infinite theophylline uptake (M_∞) = 10.54 mg		60°C Weight of hydrogel (dry) = 273.1 mg infinite theophylline uptake (M_∞) = 10.54 mg	
Time (min)	drug release Mt (mg)	Mt/M_∞	Drug released Mt (mg)	Mt/M_∞	Drug released Mt (mg)	Mt/M_∞
60	1.71	0.174	2.55	0.251	3.15	0.299
120	3.13	0.319	4.89	0.482	5.83	0.553
180	4.36	0.444	6.53	0.644	8.14	0.772
240	5.27	0.537	7.68	0.757	8.96	0.850
300	6.19	0.631	8.31	0.819	9.37	0.891
360	7.03	0.716	8.63	0.851	9.62	0.915
420	7.54	0.768	8.88	0.876	9.83	0.935
480	7.89	0.803	9.05	0.892	9.98	0.948

Table 3. Drug release of theophylline from hydrogel B at 37°, 50° and 60°.

	37°C Weight of hydrogel (dry) = 338.4 mg Infinite theophylline uptake (M_∞) = 13.31 mg		50°C Weight of hydrogel (dry) = 453.2 mg infinite theophylline uptake (M_∞) = 17.67 mg		60°C Weight of hydrogel (dry) = 444.3 mg infinite theophylline uptake (M_∞) = 17.67 mg	
Time (min)	drug release Mt (mg)	Mt/M_∞	Drug released Mt (mg)	Mt/M_∞	Drug released Mt (mg)	Mt/M_∞
60	2.62	0.197	4.15	0.235	4.47	0.262
120	4.70	0.353	7.83	0.442	8.55	0.501
180	6.65	0.499	10.86	0.614	11.98	0.701
240	8.26	0.620	13.30	0.753	14.59	0.854
300	9.52	0.715	14.73	0.834	15.21	0.891
360	10.49	0.788	15.60	0..883	15.69	0.919
420	11.16	0.838	16.18	0.916	16.06	0.941
480	11.59	0.870	16.59	0.939	16.34	0.956

Table 4. Drug release of theophylline from hydrogel C at 37°C, 50°C and 60°C.

	37°C Weight of hydrogel (dry) = 262.1 mg Infinite theophylline uptake (M_∞) = 16.05 mg		50°C Weight of hydrogel (dry) = 284.4 mg infinite theophylline uptake (M_∞) = 17.38 mg		60°C Weight of hydrogel (dry) = 294.8 mg infinite theophylline uptake (M_∞) = 18.24 mg	
Time (min)	drug release Mt(mg)	M_t/M_∞	Drug released Mt (mg)	M_t/M_∞	Drug released Mt (mg)	M_t/M_∞
60	3.62	0.225	4.27	0.245	4.78	0.262
120	6.57	0.409	8.12	0.467	9.13	0.500
180	9.00	0.560	11.65	0.670	12.90	0.707
240	11.08	0.690	14.47	0.832	15.92	0.872
300	12.75	0.794	15.34	0.882	16.63	0.912
360	13.81	0.860	15.99	0.920	17.20	0.943
420	14.96	0.915	16.48	0.948	17.59	0.964
480	15.22	0.948	16.83	0.968	17.87	0.979

Table 5. Drug release rate of theophylline at 37° from hydrogels, A,B and C stored for O day and 60 days at room temperature.

	Hydrogel A		Hydrogel B		Hydrogel C	
Time (Min.)	Release rate (mg/min) 0 d	Release rate (mg/min) 60 d	Release rate (mg/min) 0 d	Release rate (mg/min) 60 d	Release rate (mg/min) 0 d	Release rate (mg/min) 60 d
60	0.029	0.028	0.044	0.045	0.060	0.059
120	0.026	0.027	0.039	0.041	0.055	0.054
180	0.024	0.023	0.037	0.036	0.050	0.049
240	0.022	0.021	0.034	0.032	0.046	0.044
300	0.021	0.020	0.032	0.030	0.043	0.04
360	0.020	0.019	0.029	0.027	0.038	0.036
420	0.018	0.018	0.027	0.026	0.035	0.033
480	0.016	0.015	0.024	0.023	0.032	0.030

Table 6. Amount of theophylline in hydrogels stored at 45° for seven days.

No. of assay	% Drug present	% Drug calculated A	B	C
1	100	99.99	99.98	99.96
2	100	99.98	99.95	99.94
3	100	99.95	99.96	99.97
Average	100	99.97	99.96	99.96

in all three hydrogels differs from each other at any one temperature. It is attributed to the difference in composition of HEMA and acrylamide. Hydrogel A having nil acrylamide shows curve of very steep slope between temperature of 37° and 50° and then steepness is reduced between 50° and 60°. Hydrogels B and C having acrylamide in the ratio of 3 and 5 have close half-life at higher temperature (60°).

Presence of acrylamide in the hydrogels influences the diffusion rate of drug from them. The release of drug is increased with the increase in amount of acrylamide, thus the release half-life is decreased. Fig. 5 also depicits that all hydrogels behave in close similarity at high temperature (60° but in reverse order than that of low temperature (37°).

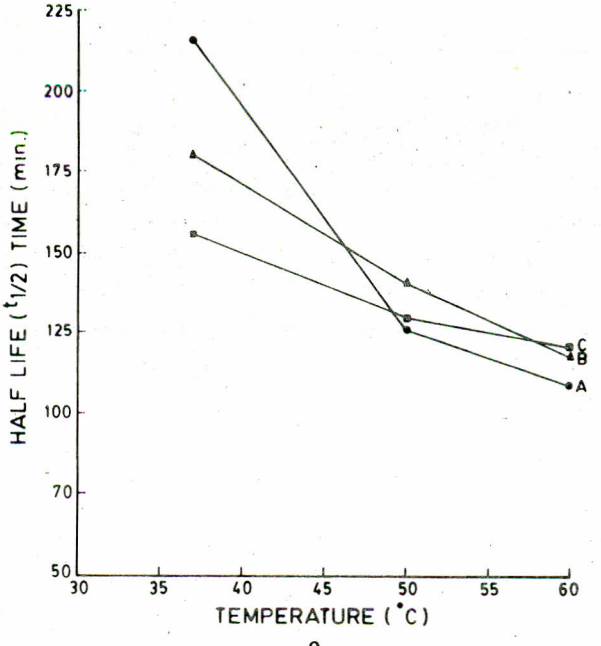

Fig. 5. $t_{1/2}$ VS temperature (°C) of hydrogels A, B and C.

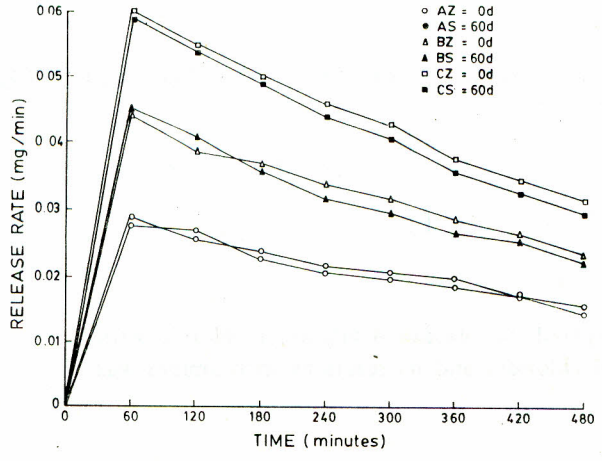

Fig. 6. Effect of storage time on release rate of theophylline.

The release of drug from the dry drug loaded hydrogel matrix occurs only when it is swollen in water. This is shown by the hydrogels stored for 60 days at ambient temperature (Table 5) followed by a release study at 37°. The release rates of theophyline from the respective hydrogels are plotted in Fig. 6. The comparison of curves indicates that there is insignificant change in the release rate of drug after sixty days of storage and the release pattern is also similar to that of 0 d storage. It is evident that the drug entrapped in hydrogel matrix is not released until the water penetrates into the hydrogel matrix at the time of imbibition.

The stability study was also conducted in order to evaluate the effect of hydrogel composition on theophylline. Table 6 shows the amount of theophylline present in dry drug loaded hydrogels evaluated after being kept at 45° for 7 days. The degree of deterioration of theophylline in the hydrogels is negligible. It indicates that the ingredients of hydrogels, being inert materials, have no degradation effect on theophylline.

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