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RELEASE OF THEOPHYLLINE FROM FULLY SWOLLEN HYDROGELS BASED ON HYDROXYETHYL METHACRYLATE AND ACRYLAMIDE

M. HAFEEZ KHAN, M. AMIN AND M. ZULFIQAR*
Faculty of Pharmacy, University of Punjab, Lahore, Pakistan

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Release of uniformly dispersed theophylline in fully swollen hydrogels based on hydroxyethyl methacrylate and acrylamide was studied. The fractional drug release followed a direct time relationship instead of a $t^{0.5}$. The effect of monomers composition and different drug concentrations to control diffusivity of a drug from fully swollen cylindrical hydrogels was also investigated.

Key words: Release, Theophylline, Swollen hydrogels.

Introduction

Water swellable crosslinked polymers are called hydrogels which can be prepared from many chemical substances e.g. gelatin [1], polysaccharide, crosslinked polyacrylamide polymers [2,3], polyelectrolytes complexes [3] and polymers or copolymers derived from polymethylacrylic esters containing one hydroxyl group at the side chain [4-6]. These hydrogels can be fabricated into a wide range of sizes and shapes to suit the location in the body and then release the contained active drug at predetermined rate to the surrounding tissues. An advantage of hydrogels, being permeable to water and small ions or molecules, provides a mean for making compositions of drugs and polymeric materials for controlled release of drugs.

These hydrogels in the form of fully preswollen drug containing spheres, cylinders or slabs provide monolithic delayed release devices which normally follow the well described fractional release proportional to $t^{0.5}$ [7,8].

The purpose of the present work is to show the effect of chemical composition and different drug concentrations on the release profiles from the samples of fully swollen hydrogels.

Experimental

Preparation of hydrogels. Hydrogels used in this study comprise of acrylamide and hydroxyethyl methacrylate in different ratio and crosslinked with methylene-bis-acrylamide. The hydrogels are coded as A,B and C which represent acrylamide and hydroxyethyl methacrylate in the ratio of 0:10, 3:7 and 5:5 respectively. The synthesis of these hydrogels have been described elsewhere [9].

Drug incorporation in hydrogels. Hydrogels were purified by using the earlier described procedure [9]. The weighed purified hydrogels were immersed in distilled water contained in a stoppered flask and allowed to swell for 48 hr. at 37° [9]. Each swollen hydrogel was wiped carefully with tissue paper, its diameter was measured using a cathetometer and then cut 2 cm cylindrical pieces, which were accurately weighed. The swollen hydrogel cylinders were dipped separately in 50 ml solutions of 0.2, 0.4 and 0.6% w/v of theophylline contained in stoppered flasks at 37° and allowed to equilibrate for 48 hr. in order to ensure uniform distribution of the drug in the polymer matrix. The swollen drug loaded hydrogel was wiped lightly with tissue paper so as to remove any solution adhering to the outer surface of the hydrogel cylinder.

Drug release studies. A rotating bottle dissolution apparatus similar to that described by Souder and Ellenbogen [10] was employed in drug release evaluation. A piece of fully swollen drug loaded hydrogel was placed in a round 90 ml screw capped glass bottle containing 60 ml of distilled water. The contents of each bottle were withdrawn at an interval of 60 min. Release of the drug was carried out for an 8 hr. period. The amount of theophylline released during each time was determined by the method described earlier [11].

Results and Discussions

The hydroxyl group in hydroxyethyl methacrylate and amide in acrylamide are capable of hydrogen bonding. This property can affect the swelling of hydrogels as well as the release profile of the contained drug as compared with similar non-interacting materials [12].

Theophylline (M.W. 193.18), used as a model drug, has a moderate solubility in water (1 in 120) and display no significant tendency to interact with hydrogels. It was, therefore, chosen as a suitable drug/polymer combination for evaluating release profiles. It is pointed out in literature [13] that the polymers are reluctant to uptake concentrated solutions as compared to pure water, which is obvious due to the influence of solvation effect of water. Therefore, the different concentrations of theophylline used in the experiments were kept below 1% w/v to ensure uniform dispersion of the solute in the pre-swollen hydrogels.

*Department of Chemistry, Quaid-i-Azam University, Islamabad, Pakistan.

The typical fractional release profile of theophylline from the fully swollen hydrogel A having been immersed in conc. 0.2 w/v of the drug is depicted in Fig. 1. The release profile shows that the amount of drug released in time t, Mt, does not follow a $t^{0.5}$ relationship as would be expected for devices subject to diffusion control [7,8]. On the other hand, fractional release gives better relationship against time t for the values of Mt/M upto 0.5 beyond that release gradually slows down. The release pattern obtained from our fully swollen hydrogels is almost similar to release profile normally obtained by others [14,15] from dried down hydrogel devices.

Effect of monomers composition. An effect of the composition as well as of the structure of the three systems of hydrogels is important to explain the dissolution release rates observed. Figure 2 indicates the release of theophylline from the hydrogels A (100% HEMA + 0% AM), B (70% + 30%) and C (50% HEMA + 50% AM) in conc. 0.2% w/v of the drug. These release profiles are indicative that half life of theophylline is 217 mins for C, 250 min. for B and 290 mins for A. It is also obvious that the total amount of drug released within the total experimental time (480 min.) from the hydrogels A, B and C is 62.4, 71.6 and 83.2% respectively. This data demonstrate that the hydrogel A released the minimum quantity of the drug and gave a much slower and more prolonged release rate of the drug and left a substantial residue of the drug in the hydrogel after 8 hr. of elution. Whereas the hydrogel C released the maximum quantity of the drug. As a result of these observations, the most obvious effect influencing the release is the composition of monomers of which the hydrogels are composed of. The decrease in the half life of theophylline as a function of acrylamide contents in the hydrogels may be attributed to the fact that acrylamide contains a potential polar group in the chain and due to which possesses considerable sorptive capacity. The swelling experiments to be reported elsewhere showed that maximum uptake of hydrogel A was found to be 137%, B 151% and C 343% at 37°. The equilibrium water contents of hydrogels which can be varied by either monomers composition or by crosslinking, appears to be the principal limiting factor in the release of drug.

Drug concentration effect. The fully swollen hydrogels were immersed in aqueous solutions of 0.2, 0.4 and 0.6% w/v of theophylline for examining the effect of drug concentrations relative to hydrogels. Table 1 indicates the half life of theophylline from the three hydrogels in different concentrations of theophylline. It can clearly be seen from Table 1 that the release variation of theophylline from 0.2, 0.4 and 0.6% w/v in hydrogel A reveals decreased half- life of 292, 250 and 226 min. respectively. Similar variation in half life of the drug for hydrogels B and C were observed.

Figure 3 depict the drug release rates from the three

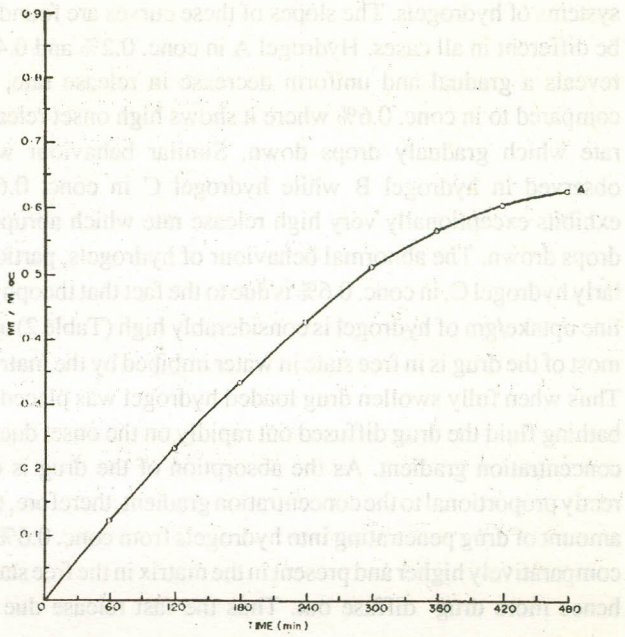

Fig. 1. Release of theophylline from fully swollen hydrogel A dipped in conc. 0.2% w/v solution at 37°.

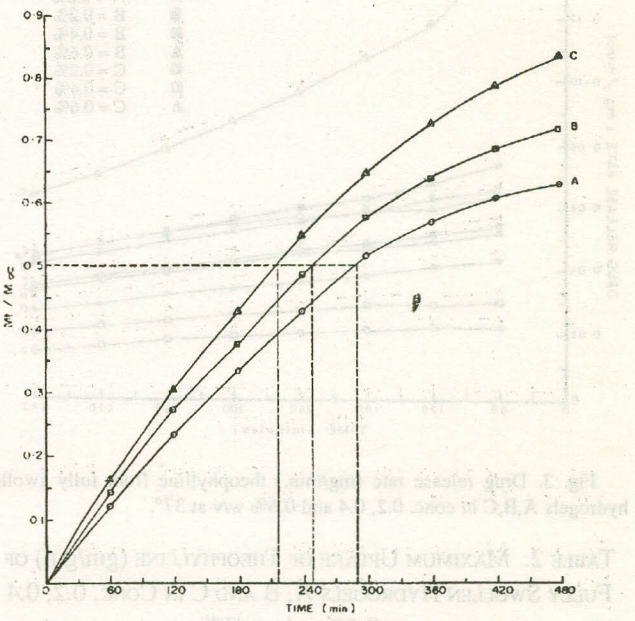

Fig. 2. 50% drug release plot of fully swollen hydrogels A,B and C at 37° dipped in conc. 0.2% w/v theophylline.

TABLE 1. HALF-LIFE $t_{1/2}$ (min.) VERSUS THEOPHYLLINE CONCENTRATION OF HYDROGEL A, B AND C (FULLY SWOLLEN) AT 37°.

Drug conc. (w/v) (%)	$t_{1/2}$ (Half-life) A (min.)	B (min.)	C (min.)
0.2	292	249	218
0.4	250	206	179
0.6	226	178	128

systems of hydrogels. The slopes of these curves are found to be different in all cases. Hydrogel A in conc. 0.2% and 0.4% reveals a gradual and uniform decrease in release rate, as compared to in conc. 0.6% where it shows high onset release rate which gradualy drops down. Similar behaviour was observed in hydrogel B while hydrogel C in conc. 0.6% exhibits exceptionally very high release rate which abruptly drops drown. The abnormal behaviour of hydrogels, particularly hydrogel C, in conc. 0.6% is due to the fact that theophylline uptake/gm of hydrogel is considerably high (Table 2) and most of the drug is in free state in water imbibed by the matrix. Thus when fully swollen drug loaded hydrogel was placed in bathing fluid the drug diffused out rapidly on the onset due to concentration gradient. As the absorption of the drug is directly proportional to the concentration gradient, therefore, the amount of drug penetrating into hydrogels from conc. 0.6% is comparatively higher and present in the matrix in the free state, hence more drug diffuse out. Thus the fast release due to

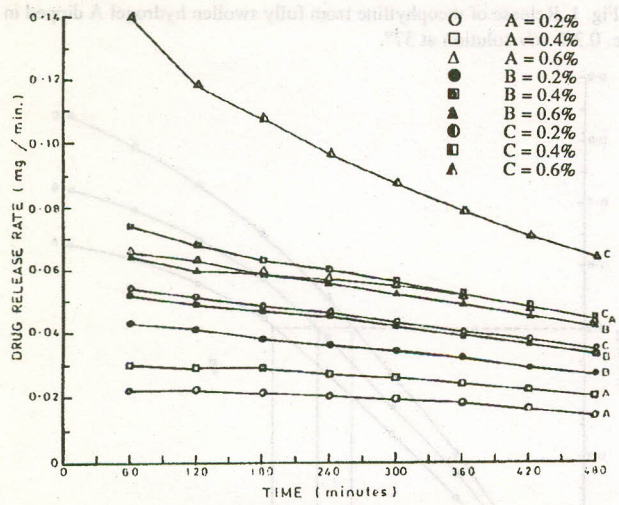

Fig. 3. Drug release rate (mg/min.) theophylline from fully swollen hydrogels A,B,C in conc. 0.2, 0.4 and 0.6% w/v at 37°.

TABLE 2. MAXIMUM UPTAKE OF THEOPHYLLINE (gm/gm) OF FULLY SWOLLEN HYDROGELS A, B AND C IN CONC. 0.2, 0.4 AND 0.6% W/V AT 37°.

Drug conc. (w/v) (%)	Theophylline uptake by hydrogels A (gm/gm of hydrogel)	B (gm/gm of hydrogel)	C (gm/gm of hydrogel)
0.2	0.0290	0.0362	0.0495
0.4	0.0355	0.0383	0.0564
0.6	0.0536	0.0609	0.0774

higher drug concentration may be attributed to the principle that the concentration gradient at the original boundry is decreasing function of time which approaches zero as desorption approaches completion. Since the amount of drug passing the boundry plane in a given time depends upon the concentration gradient the time required to release drug from the hydrogel in higher concentration is less.

The present studies show that release profile from the fully swollen hydrogels based on hydroxyethyl methacrylate depends on (i) the drug concentration and (ii) the composition of the hydrogel which determines the water uptake and consequently the diffusion of the drug through the matrix.

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