Glutaraldehyde-Crosslinked Poly(vinyl alcohol) Hydrogel Discs for the Controlled Release of Antidiabetic Drug

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ABSTRACT: Hydrogel discs of poly(vinyl alcohol) loaded with glipizide, an oral antidiabetic drug, were prepared with glutaraldehyde (GA) as a crosslinker. Various formulations were prepared with various amounts of polymer, GA, and initial drug. The prepared hydrogel discs were characterized by thermogravimetric analysis, differential scanning calorimetric analysis, and X-ray diffractometry. The dynamic swelling behavior and drug-release patterns were dependent on the crosslink density. The hydrogel discs were capable of releasing drug for up to 24 h. The discs that were prepared with a higher concentration of GA released the drug more slowly. The release data were fitted to an empirical equation to determine the transport mechanism, which indicated a non-Fickian trend for drug transport.
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Key words: biomaterials; crosslinking; drug delivery systems; hydrogels

INTRODUCTION

Hydrogels are hydrophilic, crosslinked polymers made of synthetic or natural polymers that can absorb large amounts of water or biological fluids without dissolving because of the presence of crosslinks.[1] Hydrogels have been studied widely for controlled release applications because they are biocompatible and easy to prepare. The controlled release kinetics of entrapped drugs from such hydrogels can be monitored by crosslinking.[2] In general, hydrogels exhibit good biocompatibility. Their hydrophilic surface is characterized by a low interfacial free energy in contact with body fluids, which results in a low tendency for proteins and cells to adhere to these surfaces. Because of their high water content, hydrogels also possess a degree of flexibility similar to natural tissues, which minimizes potential irritation to surrounding membranes and tissues.[3,4] The ability of molecules of different sizes to diffuse into and out of hydrogels allows their possible use as drug-delivery systems for oral, nasal, ocular, rectal, vaginal, and transdermal routes of administration.[5–7] The entrapped drug within the hydrogel matrix concomitantly dissolves and diffuses through the swollen network into the surrounding aqueous environment.[8]

Poly(vinyl alcohol) (PVA) is a widely used hydrophilic polymer because of its processability, strength, pH, and temperature stability. As it is biodegradable, biocompatible, and nontoxic, it has a wide variety of pharmaceutical applications.[9] PVA-based hydrogels crosslinked with ethylenediaminetetraacetic dianhydride were prepared and tested for the release of methylene blue and methyl orange as model drugs. The model drugs were influenced both loading and release pattern.[10] Maleate-denatured PVA hydrogels were prepared by heat crosslinking and evaluated for drug-delivery applications. Various tablet formulations were prepared and tested for the swelling and release of *p*-acetamidophenol from tablets in buffer solutions.[11] Interpenetrating polymer network hydrogel microspheres of PVA and guar gum were prepared by crosslinking with glutaraldehyde (GA). Nifedipine, an antihypertensive, was drug-loaded into these interpenetrating networks before and after crosslinking and evaluated for swelling and drug-release patterns. The release of the drug depended upon the extent of crosslinking, the amount of drug loaded, and the method of drug loading.[12] Another study reported novel interpenetrating network microspheres of PVA and gellan gum for the controlled release application of carvedilol, an antihypertensive drug.[13]

GA is a common crosslinker used in polypeptide and protein crosslinking because of the high activity of its aldehyde groups, which readily form a Schiff base with amino groups of proteins/peptides. GA is also used as a crosslinking agent for PVA and some polysaccharides. Crosslinked PVA has been extensively studied as a controlled drug-delivery device.[14,15] However, a literature search suggested that

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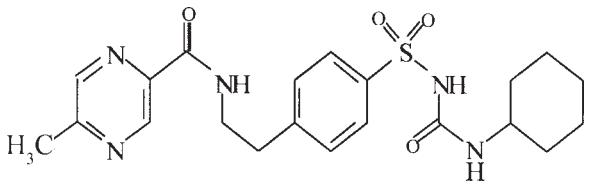

Figure 1 Chemical structure of glipizide.

there was no report on GA-crosslinked PVA-based hydrogel discs for the controlled release of glipizide.

The aim of this study was to develop PVA-based hydrogel discs with GA as a crosslinker for the controlled release of glipizide. Glipizide is an oral hypoglycemic agent widely used in the treatment of diabetes (see Fig. 1); it has a shorter plasma half-life of 3.4 h and undergoes first-pass metabolism.[16] Hence, to conquer this limitation, the development of a controlled release system is necessary. The prepared hydrogel discs were characterized by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and X-ray diffraction (XRD) studies.

EXPERIMENTAL

Materials

Glipizide was obtained from Wallace Pharmaceuticals (Mumbai, India). PVA (weight-average molecular weight = 125,000, 98% hydrolyzed) was purchased from Qualigens Fine-Chemicals (Mumbai, India). GA (25% v/v), sodium hydroxide, concentrated HCl, and methanol were purchased from S. D. Fine Chemicals (Mumbai, India). Double-distilled water was used throughout the study. All other chemicals were used without further purification.

Preparation of the hydrogel discs

An accurately weighed quantity of PVA was dissolved in distilled water at 70°C with a magnetic stirrer; the glipizide was uniformly dispersed in the polymeric solution with continuous stirring for 30 min. Different concentrations of GA and 1*N* HCl were added to the solution and stirred. Then, the mixture was immediately poured into a stainless steel mold and kept for 5 h at 37°C. After the formation of wet hydrogels, excess water was drained out, and the obtained hydrogel discs were taken from the mold and washed repeatedly with distilled water to remove unreacted GA. The complete removal of the unreacted GA was confirmed by a negative test from washings with Brady's qualitative reagent (2,4-dinitrophenyl hydrazine). The discs were dried at 40°C for 24 h and stored in a desiccator until further use. The formulation details are given in Table I.

Measurement of the disc size

The sizes of the discs were measured with a digimatic micrometer (MDC-25S Mitutoyo, Tokyo, Japan) with an accuracy of 0.001 mm. The average size of 50 discs per batch was calculated.

Estimation of the drug content

Known amounts of discs were added to 100 mL of United States Pharmacopoeia (USP) phosphate buffer at pH 7.4 for complete swelling at 37°C. The discs were crushed in a glass mortar with a pestle; the solution was then heated gently for 2 h to extract the drug completely and centrifuged to remove polymeric debris. The clear supernatant solution was analyzed for drug content with an ultraviolet–visible spectrophotometer (model Pharmaspec UV-1700, Shimadzu, Kyoto, Japan) at 276 nm. The average of three determinations was considered.

TGA

The samples were heated from 0 to 600°C at a heating rate of 10°C/min under a nitrogen atmosphere with a microcalorimeter (Dupont-9900, DuPont, USA), and thermograms were obtained.

DSC analysis

The samples were heated from 0 to 300°C at a heating rate of 10°C/min under an argon atmosphere with a microcalorimeter (DuPont-9900), and thermograms were obtained.

XRD studies

The spectra were recorded with a Philips PW-171 X-ray diffractometer (Philips, PW-1710, Almelo, The Netherlands). with Cu-NF filtered Cu Kα radiation. Quartz was used as an internal standard for calibration. The powder X-ray diffractometer was attached to a digital graphical assembly and a computer with a Cu-NF 25-kV/20 mA tube as a Cu Kα radiation source in the 2θ range 0–50°.

TABLE I
Composition of Hydrogel Discs

Formulation code	PVA (% w/v)	Drug (% w/w)	GA (% w/w)	1*N* HCl (mL)
HD1	5	20	10	0.5
HD2	10	20	10	0.5
HD3	12	20	10	0.5
HD4	10	20	20	0.5
HD5	10	20	30	0.5
HD6	10	30	20	0.5
HD7	10	40	20	0.5

TABLE II
Average Thickness, Diameter, Weight, Drug Content, M_c, dx, and n of the Hydrogel Discs

Formulation code	Average thickness (mm)	Diameter (mm)	Weight (mg)	Drug content (%)	M_c	$dx \times 10^3$	n	r
HD1	2.12 ± 0.58	6.23 ± 0.12	110 ± 0.85	75.61 ± 0.75	3762	2.53	0.64	0.97
HD2	2.34 ± 0.65	6.65 ± 0.23	110 ± 0.45	77.58 ± 0.41	3738	3.15	0.65	0.98
HD3	2.65 ± 0.48	6.89 ± 0.65	110 ± 0.85	79.29 ± 0.12	3725	3.89	0.71	0.98
HD4	2.21 ± 0.85	6.35 ± 0.45	110 ± 0.42	76.37 ± 0.38	3236	4.53	0.71	0.99
HD5	2.08 ± 0.75	6.12 ± 0.85	110 ± 0.85	74.17 ± 0.84	2615	5.62	0.73	0.99
HD6	2.35 ± 0.7	6.42 ± 0.47	110 ± 0.12	76.37 ± 0.71	2725	5.02	0.61	0.99
HD7	2.58 ± 0.85	6.54 ± 0.65	120 ± 0.75	75.52 ± 0.75	2865	4.85	0.56	0.99

r = correlation coefficient.

Dynamic swelling study

The dynamic swelling behavior of the discs was studied by mass measurement. An accurately weighed hydrogel disc was incubated with 25 mL of phosphate buffer solution at pH 7.4 and 37°C. We took the hydrogel disc out at different time intervals and carefully blotted it without pressing hard to remove the excess surface liquid. The swollen hydrogel disc was weighed with an electronic microbalance (model BL-220H, Shimadzu) with an accuracy of 0.001 mg.

In vitro drug-release study

An *in vitro* drug-release study was carried out with a USP-23 rotating paddle dissolution tester (Electrolab TDT-06P, USP, Mumbai, India). The dissolution was measured at 37.0 ± 0.5°C and a 100-rpm paddle speed. Drug release from the hydrogel discs was studied in 900 mL of acidic medium (pH 1.2) for 2 h and in alkaline medium (pH 7.4 phosphate buffer) until the end of the study. At predetermined time intervals, 5-mL aliquots were withdrawn and replaced with the same volume of fresh solution. The amount of drug released was analyzed with ultraviolet–visible spectrophotometer at λ_{max} (maximum wavelength) = 276 nm.

RESULTS AND DISCUSSION

The glipizide-loaded hydrogel discs of PVA were prepared with GA as a crosslinker. The method adopted was found to be satisfactory; the thickness, diameter, weight, and drug content of all of the discs were found to be uniform. When a dispersion of PVA–drug was brought in contact with GA, a bifunctional covalent crosslinking agent, it formed acetal structures between the —CHO groups of GA and the —OH groups of two PVA strands and, thus, formed hydrogels and made the matrix insoluble.

The average diameter of the discs was found to be in the range 6.12–6.89 mm, and the thickness was found to be 2.08–2.65 mm. As the concentration of PVA increased in the formulation, the size increased, whereas an increased concentration of GA decreased the disc size; this may have been due to the shrinking of the discs, which led to the formation of a smaller and rigid matrix at higher crosslink densities.[17] On the other hand, as the amount of glipizide increased, the disc size increased because glipizide might have occupied the interstitial spaces between the polymer segments.[18] The drug content of the discs was measured by the swelling method, and it was found to be in the range 74.18–79.29%. As the concentration of PVA increased, the drug content increased, which may have been due to the larger size of the discs, whereas the drug content decreased as the concentration of GA increased in the discs. This may have been due to the formation of a small and rigid matrix at higher crosslink densities (see Table II).

TGA

Typical thermograms of PVA, the drug-free disc HD2, and HD4 and HD5 are shown in Figure 2. The

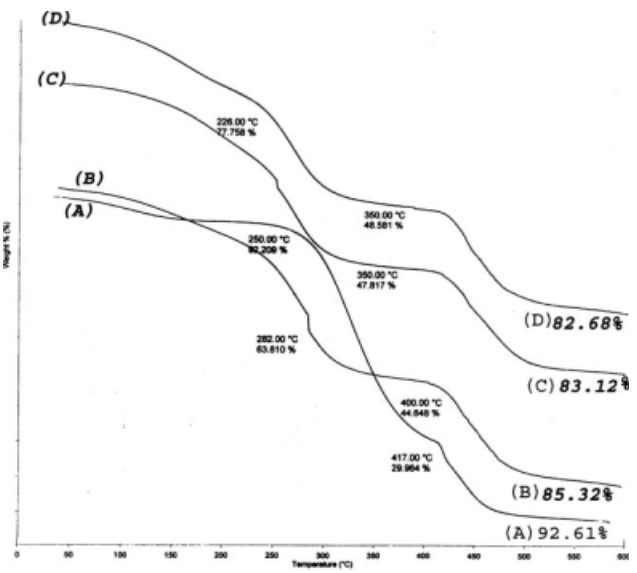

Figure 2 TGA thermograms of (A) PVA, (B) HD2 disc, (C) HD4 disc, and (D) HD5 disc.

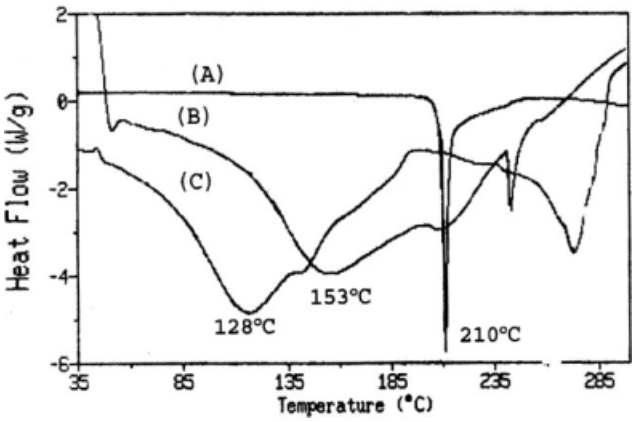

Figure 3 DSC thermograms of (A) glipizide, (B) drug-free HD2 disc, and (C) drug-loaded HD2 disc.

PVA started decomposing after 250°C; the rate of mass loss increased with increasing temperature. A sharp mass loss was observed between 250 and 417°C and at 600°C; only an 8% char yield was obtained. This may have been due to the decomposition of the polymer, and nearly 70% of PVA was degraded at 400°C. In the case of the hydrogel discs HD2, HD4, and HD5, the decomposition started at a higher temperature, and at 600°C, 15, 17, and 18% char values were obtained for the HD2, HD4, and HD5 discs, respectively. The mass loss was found to be constant, and the percentage residual mass of the hydrogel discs was higher than that of PVA. Thus, the thermal stability of the hydrogel discs was greater in comparison with PVA. In the hydrogel discs, because the polymeric chains were more closely tangled together because of the presence of crosslinks, the thermal stability of the hydrogels was higher. This also supported the fact that an increase in crosslinking increased the polymer chain rigidity.

DSC analysis

The DSC analysis of plain glipizide, the drug-free HD2 discs, and the drug-loaded HD2 discs was carried out, and the results are shown in Figure 3. The drug-free discs showed an endothermic peak at 153°C, which indicated the melting temperature of the polymer, whereas the drug-loaded discs showed an endothermic peak at 128°C. This decrease in the melting temperature may have been due to physical and morphological changes taking place in the polymer matrix after drug loading. After drug loading, the proportion of polymer per unit weight decreased, and this weakened the gel network structure and rigidity, which resulted in a decreased melting temperature. The plain glipizide showed a sharp endothermic peak at 210°C because of the melting of the drug, but this peak is absent in the drug-loaded discs, which indicated an amorphous dispersion of the drug in the hydrogel matrix.

XRD studies

The XRD studies were useful for investigating the crystallinity of the drugs after they were loaded into the dosage forms. The X-ray diffractograms of glipizide, drug-free HD6 discs, and drug-loaded HD6 discs are presented in Figure 4. Glipizide showed characteristic intense peaks between 2θ values of 17 and 30° because of its crystalline nature. In case of the drug-free HD6 discs, no characteristic peaks related to drug were noticed, whereas in the drug-loaded HD6 discs, some peaks of lower intensity were observed between 2θ values of 16 and 28°, which may have been due to the surface-adhered drug. The XRD peak always depends on the crystal size, but in this study, in the drug-loaded discs, the characteristic peaks of the drug overlapped with noise of the coated polymer itself. Furthermore, the loaded drug was amorphous, which was very difficult to measure at the detection limit of the crystal size in this case. This indicated that the drug was dispersed at the molecular level in the polymer matrix; this was also supported by DSC analysis.

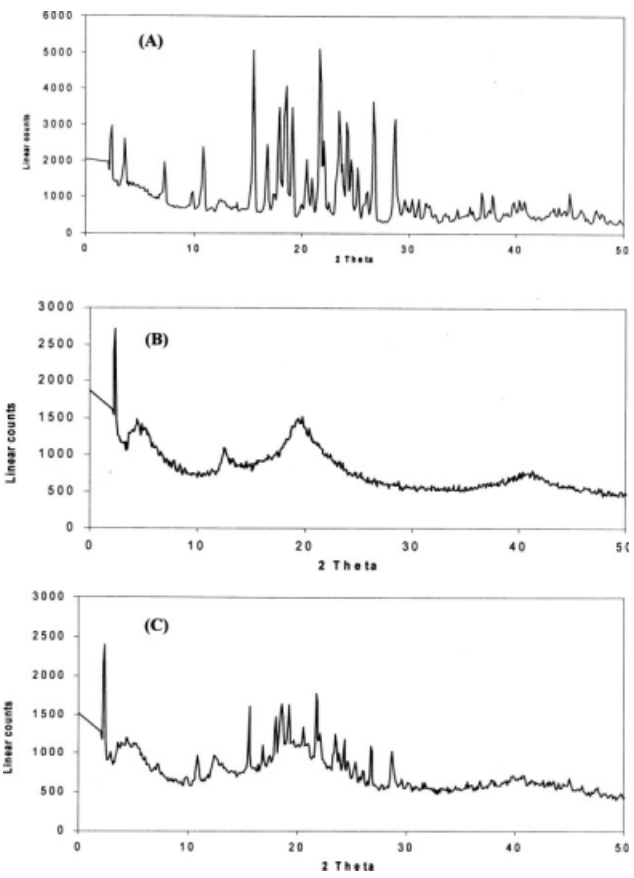

Figure 4 XRD diffractograms of (A) glipizide, (B) drug-free HD6 disc, and (C) drug-loaded HD6 disc.

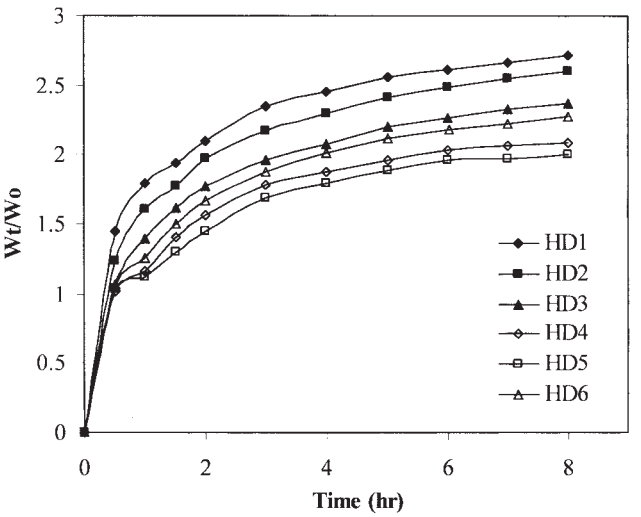

Figure 5 Swelling behavior of the hydrogel discs Wo = initial weight of discs; Wt = final weight of swollen discs at time *t*.

Dynamic swelling studies

The release of a loaded drug from a hydrogel matrix depends on the swelling behavior. As the hydrogel swells, the pores of the network open, and release of the solute occurs. Therefore, the dynamic swelling study of the prepared discs was carried out in phosphate buffer at pH 7.4, and the results are shown in Figure 5. The swelling behavior of the discs was expressed as the ratio of the initial weight of the discs to the final weight of the swollen discs as a function of time. The swelling of the discs depended on the concentration of PVA and the extent of GA crosslinking in the discs. The swelling of the discs decreased with increasing amounts of PVA and GA, which may have been due to the formation of a more rigid hydrogel network. At a low crosslink density (*dx*), the hydrogel network was loose with more hydrodynamic free volume and could absorb more of the solvent, which resulted in greater swelling.[19]

Molar mass between crosslinks (M_c) and *dx*

The ability of hydrogels to release drug is a function of *dx*. To determine the crosslinking of the polymer network, two important parameters were calculated, that is, M_c and *dx*, on the basis of the equilibrium swelling study. When a polymer is placed in a solvent, it swells until the elastic forces balance the osmotic forces that could dissolve the polymer. These elastic forces are inversely proportional to the molar mass of the polymer between the points of crosslinking. Thus, the molar mass between two junction points in a network would be rigid and exhibit limited swelling. When M_c is large, the network is more elastic and swells rapidly. The M_c values were calculated with the following equation:[13]

$$M_c = -\rho_p V_s \Phi^{1/3}[\ln(1-\Phi) + \Phi + \chi\Phi]^{-1}$$

where ρ_p and ρ_s are the densities of the polymer and solvent, respectively; Φ is the volume fraction of the polymer, V_s is the molar volume of the solvent, and Φ is the volume fraction of the polymer in the swollen state and was calculated as follows:

$$\Phi = \left[1 + \frac{\rho_p}{\rho_s}\left(\frac{M_a}{M_b}\right) - \frac{\rho_p}{\rho_s}\right]^{-1}$$

M_b and M_a are the masses of the polymer before and after swelling. χ can be calculated with the following equation:[20]

$$\chi = \beta + \left(\frac{V_s}{RT}\right)(\delta_s - \delta_p)^2$$

where β is a lattice constant, with a value that is taken to be 0.34; R is a molar gas constant; T is the temperature (K); and δ_s and δ_p are the solubility parameters of the solvent and polymer, respectively. For the analysis of the crosslinked structure of the hydrogels, *dx* was calculated with the following equation:[21]

$$dx = \left(\frac{1}{vM_c}\right)$$

where v is the specific volume of the polymer. The results of M_c and *dx* are presented in Table II. As the concentration of GA increased in the hydrogel, M_c values decreased and the network became denser, whereas the *dx* values increased with increasing GA concentration.

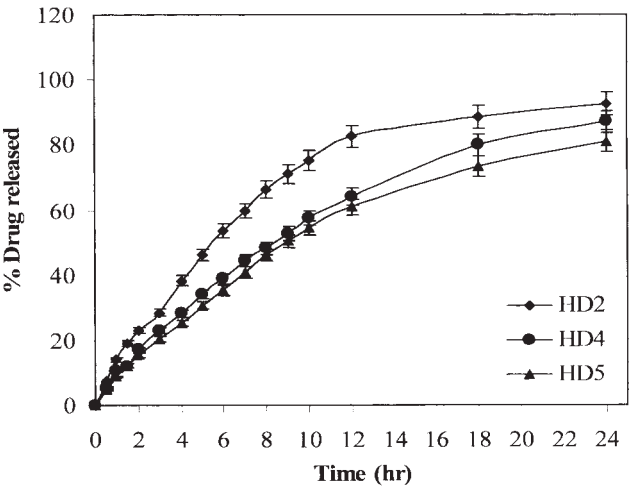

Figure 6 Effect of *dx* on glipizide release from the hydrogel discs.

In vitro drug release

The *in vitro* drug-release study indicated that the hydrogel discs were capable of releasing the drug for up to 24 h, depending on the formulation variables. The discs that were prepared with a higher concentration of GA released the drug more slowly (Fig. 6). This could have been due to the fact that at higher crosslinking, the free volume of the matrix decreased and thereby hindered the transport of drug molecules through the matrix. This could have also reduced the swelling and drug-release rate from the matrix. Also, the drug release decreased with increasing amount of PVA (Fig. 7), which may have been due to an increased diffusional path length for the solute. On the other hand, with all of the variables kept constant, an increase in the initial drug loading increased the drug release (Fig. 8). An increase in the initial drug load decreased the proportion of polymer per unit weight, and this weakened the gel network structure. Moreover, higher drug loading increased the free volume within the network and created a more tortuous path for water to penetrate through. Consequently, an increase in the initial drug loading increased the release of the drug.

To determine the drug-release mechanism in the hydrogel network, the release data was fitted to an empirical equation:[22]

$$\frac{M_t}{M_\infty} = kt^n$$

where M_t is the amount of drug released at time t, M_∞ is the total amount of the drug loaded, k is the rate constant, and the n values indicate the type of release mechanism. Values of n between 0.45 and 0.85 are an indication of both diffusion-controlled and swelling-controlled transport mechanisms (anomalous transport). Values above 0.85 indicate case II transport, which is related to polymer chain relaxation during swelling. The calculated n values, along with the correlation coefficients, are shown in Table II. The values of n depended on the concentration of PVA and dx; the n values increased with increasing concentration of PVA and GA. The calculated n values suggested that the mechanism of drug release followed non-Fickian/anomalous transport.

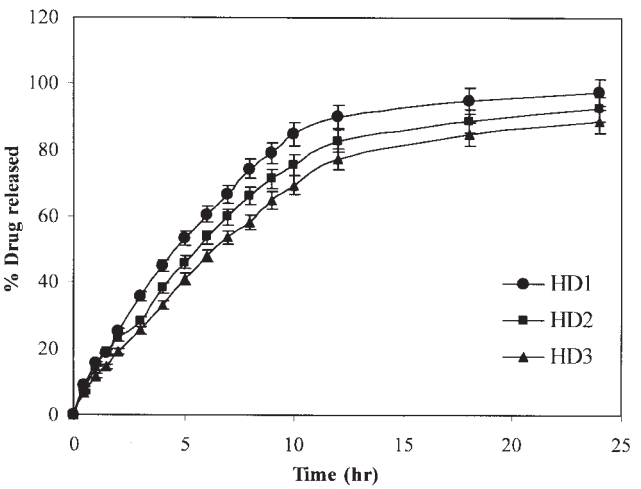

Figure 7 Effect of the polymer concentration on glipizide release from the hydrogel discs.

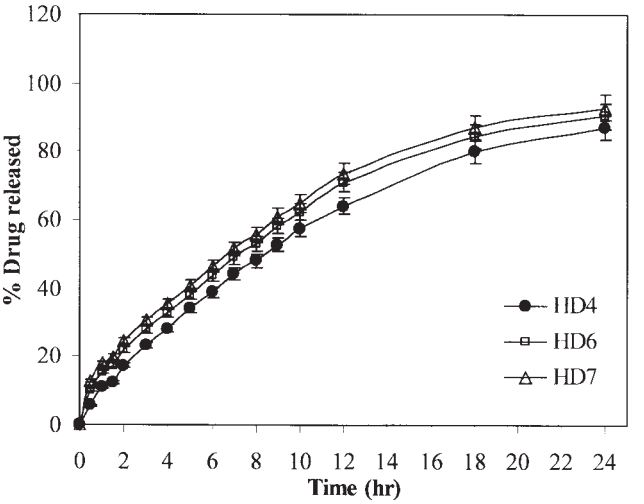

Figure 8 Effect of the initial drug loading on glipizide release from the hydrogel discs.

CONCLUSIONS

PVA-based hydrogel discs were prepared with GA as a crosslinker for the controlled release of glipizide. Uniform discs were produced with drug contents as high as 79% with low burst release rates. DSC and XRD studies confirmed the amorphous dispersion of the drug in the hydrogel matrix. The swelling of the discs and drug release depended on the extent of crosslinking and amount of PVA used in the formulation. The hydrogel discs were capable of releasing the drug for up to 24 h. The discs that were prepared with a higher concentration of GA released the drug more slowly. The drug-release rate and mechanism of drug release could be controlled by the hydrogel composition and crosslinking density. This study demonstrates the feasibility preparing PVA-based hydrogel discs that may be useful in controlled drug-delivery systems.

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