INTERPENETRATING NETWORK HYDROGEL DISCS OF POLY(VINYL ALCOHOL) AND POLY(VINYL PYRROLIDONE) FOR CONTROLLED RELEASE OF AN ANTI-DIABETIC DRUG

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Abstract

In the present investigation, hydrogel based interpenetrating network (IPN) discs of poly(vinyl alcohol) and poly(vinyl pyrrolidone) loaded with an anti-diabetic drug, glipizide were prepared by chemical crosslinking method. The prepared discs were characterized by thermogravimetric analysis (TGA), differential scanning calorimetric analysis (DSC) and X-ray diffractometry (XRD). The swelling behavior and drug release were dependent upon the crosslink density. The IPN hydrogel discs were capable of releasing drug up to 24 h. The discs which were prepared with higher concentration of glutaraldehyde released the drug more slowly. The release data were fitted to an empirical equation to determine the transport mechanism, which indicated the non-Fickian trend for drug transport.

Rezumat

În studiul de faţă au fost preparate discuri de hidrogel cu reţea de interpenetrare din polivinil alcool şi polivinil pirolidonă, pentru eliberarea antidiabeticului oral glipizidă, prin mecanismul de *crosslinking*. Caracterizarea discurilor s-a realizat prin analiză termogravimetrică, calorimetrie diferenţială şi difractometrie cu raze X. Rezultatele privind cedarea substanţei active au descris o ecuaţie empirică pentru determinarea mecanismului de transport, indicând o eliberare de tip non-Fick.

Keywords: Hydrogel discs, Interpenetrating polymer network, Glipizide, Drug release.

Introduction

Hydrogels are termed as hydrophilic, crosslinked polymers made of synthetic or natural polymers that can absorb large amounts of water or biological fluids without dissolving due to the presence of chemical or physical cross-links. In chemically crosslinked hydrogels, covalent bonds

are present between different polymer chains, while in physically crosslinked hydrogels, dissolution is prevented by ionic interactions, hydrophobic associations or hydrogen bonds [1,2,3]. The hydrogels have found widespread applications in the field of pharmaceuticals. 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 [4,5,6]. The entrapped drug within the matrix dissolves and diffuses through the swollen network into surrounding aqueous environment. The rate of drug release from hydrogels can be regulated by cross-link density and extent of swelling. Increasing the crosslinking density it decreases the volume of swelling and the drug release rate that are attributed to the decrease of diffusion coefficient of drug and solvent [7].

The hydrophilic polymers, which even though exhibit some limitations in their reactivity and processibility, have been used for the preparation of hydrogels following modification by cross-linking, blending etc. Many attempts have been made to conquer such limitations by modification of polymers. Among these, development of interpenetrating polymer network (IPN) structures has attracted attention [8,9]. Hydrogel IPNs used as controlled release systems are capable of delivering drugs at constant rate over an extended period of time. IPN hydrogel has more complicated network structures than a homo-hydrogel and possesses improved mechanical properties. In such systems, the extent of crosslinking can be monitored to control the drug release [10,11,12].

Poly(vinyl alcohol) (PVA) is a widely used hydrophilic polymer because of its processibility, strength, and pH, as well as temperature stability. As it is biodegradable, biocompatible and non-toxic, it has a wide variety of pharmaceutical applications [13]. The IPN microspheres of PVA and gellan gum [14], PVA and guar gum [15] prepared by emulsion crosslinking have been reported for controlled release of drugs. However, hitherto we are not aware of the report on PVA and poly(vinyl pyrrolidone) (PVP) IPNs for the controlled release of glipizide, hence the present study was aimed to develop and evaluate the novel hydrogel based IPN discs using PVA and PVP by chemical crosslinking method for the controlled release of glipizide. Glipizide is an oral anti-diabetic drug having a shorter plasmatic half life of 3.4 h and it undergoes first pass metabolism [16]. Hence, to conquer this limitation, development of controlled release system is necessary. The prepared IPN hydrogel discs were characterized by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and x-ray diffraction (x-RD) studies.

Materials and Methods

Materials

Glipizide was obtained from Wallace Pharmaceuticals (Mumbai, India). Poly(vinyl alcohol) (PVA) was purchased from Qualigens fine-chemicals (Mumbai, India). Poly(vinyl pyrrolidone) (PVP) was purchased from Himedia laboratories (Mumbai, India). Glutaraldehyde (GA; 25% v/v), sodium hydroxide, conc. 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 IPN discs

The accurately weighed quantities of PVA and PVP (total polymer concentration 10% w/v) were dissolved in distilled water at 70 ^{o}C using a magnetic stirrer; the glipizide was uniformly dispersed in polymeric solution with a continuous stirring for 30 min. The different concentrations of glutaraldehyde (GA) and 1 N HCl were added to the solution and stirred. Then the mixture was immediately poured in a stainless steel mold and kept for 5 h at 37 ^{o}C. After the formation of wet hydrogels, excess water was drained out, and the obtained hydrogel discs were taken from the mold, washed repeatedly with distilled water to remove unreacted GA. The complete removal of the unreacted GA was confirmed by the negative test of the washings with Brady's qualitative reagent. The discs were dried at 40 ^{o}C for 24 h and stored in a desiccator until further use. The formulation details are given in Table I.

Table I

Composition of IPN hydrogel discs

Formulation Codes	PVA (% wt/vol)	PVP (% wt/vol)	Drug (% wt/wt)	GA (% wt/wt)
HDP 1	8	2	20	5
HDP 2	6	4	20	5
HDP 3	4	6	20	5
HDP 4	5	5	20	5
HDP 5	5	5	40	5
HDP 6	5	5	20	10

Measurement of disc size

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

Estimation of drug content

The known amounts of discs were added to 100 mL USP phosphate buffer of pH 7.4 for complete swelling at 37 ^{o}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 the drug content using an UV-visible spectrophotometer (Model Pharmaspec UV-1700, Shimadzu, Japan) at 276 nm. The average of three determinations was considered.

Thermogravimetric analysis (TGA)

The samples were heated from 0-600 ^{0}C at a heating rate of 10 ^{0}C/ min under nitrogen atmosphere using micro calorimeter (Dupont-9900 USA) and the thermograms were obtained.

Differential scanning calorimetric (DSC) analysis

The samples were heated from 0-300 ^{o}C at a heating rate of 10^{o}C/min under argon atmosphere using a microcalorimeter (DuPont-9900, USA) and then thermograms were obtained.

X-Ray diffraction (XRD) studies

The spectra were recorded using a Philips, PW-171, x-ray diffractometer with Cu-NF filtered CuKα radiation. Quartz was used as an internal standard for calibration. The powder x-ray diffractometer was attached to a digital graphical assembly and computer with Cu-NF 25 KV/20 mA tube as a CuKα radiation source in the 2θ range 0-50^{o}.

Swelling studies

The swelling behavior of the IPN discs was studied by mass measurement. Accurately weighed hydrogel disc was incubated with 25 mL phosphate buffer solution pH 7.4 at 37 ^{o}C. The hydrogel disc was taken out at different time intervals and blotted carefully without pressing hard to remove the excess surface liquid. The swollen hydrogel disc was weighed using the electronic microbalance (Model BL-220H, Shimadzu, Japan) having an accuracy of 0.001 mg.

***In vitro* drug release**

In vitro drug release study was carried out using a USP-23 rotating paddle dissolution tester (Electrolab TDT-06P, (USP), Mumbai, India). The dissolution was measured at 37.0 ± 0.5 ^{o}C and 100 rpm paddle speed. Drug release from the hydrogel discs was studied in 900 mL acidic medium (pH 1.2) for 2 h and in alkaline medium (pH 7.4 phosphate buffer) till 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 using an UV-visible spectrophotometer at 276 nm.

Results and Discussion

Preparation of IPN discs

The glipizide loaded IPN hydrogel discs of PVA and PVP were prepared by chemical crosslinking and molding method. The method adopted was found to be satisfactory; thickness, diameter, weight and drug contents of all the discs were found to be uniform. When a polymeric solution of PVA-PVP was brought in contact with GA, a bi-functional covalent crosslinking agent, it forms an acetal structure between the –CHO groups of GA and –OH groups of two PVA strands, thus forming an IPN including PVP and making the matrix insoluble.

The average diameter of discs was found to be in the range of 8.23 to 9.36 mm and thickness was found to be 3.56 to 4.32 mm. As the concentration of PVP was increased in the formulation, the size was increased, whereas increased concentration of GA decreased the disc size, this may be due to shrinking of discs leading to the formation of smaller and rigid matrix at higher crosslink densities. A similar result has been reported earlier at higher cross-link densities [17]. Also, by increasing the amount of glipizide, an increase in size was observed, which is in agreement with the previously published results [18]. The drug content of the discs was measured by swelling method and it was found to be in the range of 87.81 % to 95.05 %. As the concentration of the PVP was increased, the drug content was increased, whereas it was decreased as the concentration of GA was increased in the discs (Table II).

Table II

Thickness, diameter, weight, drug content and release parameter (*n*) of the IPN hydrogel discs

Formulation codes	Average thickness (mm) ± *SD*	Diameter (mm) ± *SD*	Weight (gm) ± *SD*	Drug content (%)± *SD*	*n*	*r*
HDP1	3.56 ± 0.42	8.23 ± 0.44	0.15 ± 0.95	87.81 ± 0.85	0.712	0.982
HDP2	3.98 ± 0.12	8.86 ± 0.75	0.16 ± 0.75	90.40 ± 0.46	0.591	0.980
HDP3	4.12 ± 0.85	9.23 ± 0.85	0.16 ± 0.85	95.05 ± 0.85	0.501	0.974
HDP4	4.02 ± 0.13	9.05 ± 0.95	0.16 ± 0.96	93.19 ± 0.25	0.528	0.979
HDP5	4.32 ± 0.15	9.36 ± 0.12	0.16 ± 0.52	94.37 ± 0.16	0.501	0.978
HDP6	3.85 ± 0.85	8.81 ± 0.36	0.16 ± 0.12	89.12 ± 0.85	0.854	0.978

'n' indicates the release mechanism and '*r'* indicates the correlation coefficient

TGA

Typical thermograms of PVA, PVP, disc HDP4 and disc HDP6 are shown in Figure 1. TGA of PVA has shown a mass loss of 92.6% at the end of 600 ^{o}C, while PVP has shown 98.6% mass loss. Whereas, in the case of thermograms of IPN discs, the initial mass loss was small and constant, at the end of 600 ^{o}C, 88.9% and 87.8% mass loss was exhibited by HDP4 and HDP6 discs respectively. Thus, the thermal stability of IPN hydrogel is high in comparison with PVA and PVP. In the case of IPN, since the polymeric chains are more closely tangled together, thermal stability of IPN is higher than those of other polymers. This indicates the formation of IPN including PVA and PVP.

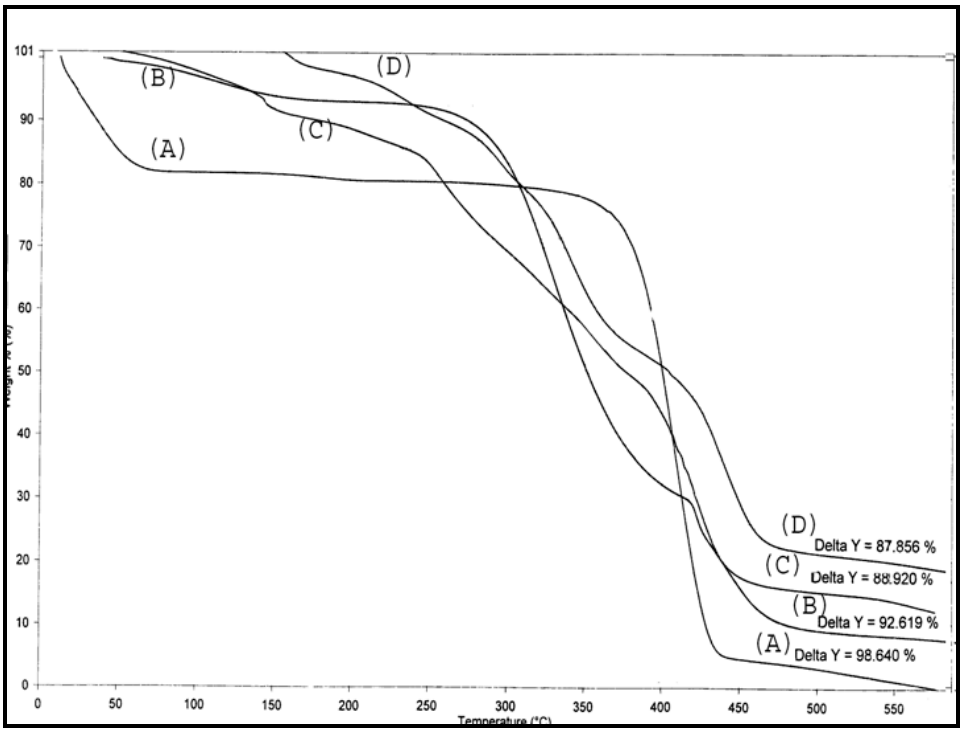

Figure 1

TGA thermograms of PVP (A), PVA (B), HDP4 disc (C) and HDP6 disc (D)

DSC analysis

The DSC analysis of pure glipizide, drug-free HDP5 discs and a drug-loaded HDP5 discs was carried out and the results are shown in Figure 2. The drug-free disc has shown an endothermic peak at 142 ^{o}C, whereas drug-loaded disc showed an endothermic peak at 125 ^{o}C. This decrease in

the temperature may be due to physical and morphological changes taking place in the matrix after drug loading. The plain glipizide has shown a sharp endothermic peak at 210 ^{o}C due to melting of the drug, but this peak is not seen in the drug-loaded discs indicating that the drug was uniformly dispersed in the IPN matrix.

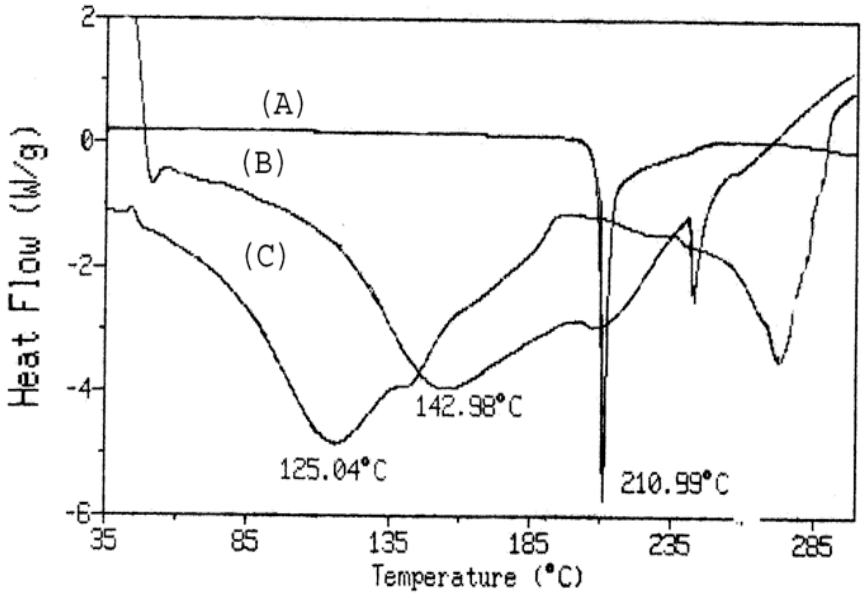

Figure 2
DSC thermograms of glipizide (A), drug free HDP5 disc (B) and drug loaded HDP5 disc (C)

XRD studies

The x-ray diffraction studies are useful to investigate the crystallinity of the drugs after loading into the dosage forms. The x-ray diffractograms of glipizide, drug free HDP5 discs and drug-loaded HDP5 discs are presented in Figure 3. Glipizide has shown characteristic intense peaks between the 2θ of 17^{o} and 30^{o} due to its crystalline nature. Whereas, in the case of drug loaded discs, no intense peaks related to drug were noticed between the 2θ of 17^{o} and 30^{o}. This indicates the amorphous dispersion of the drug after loading into IPN discs.

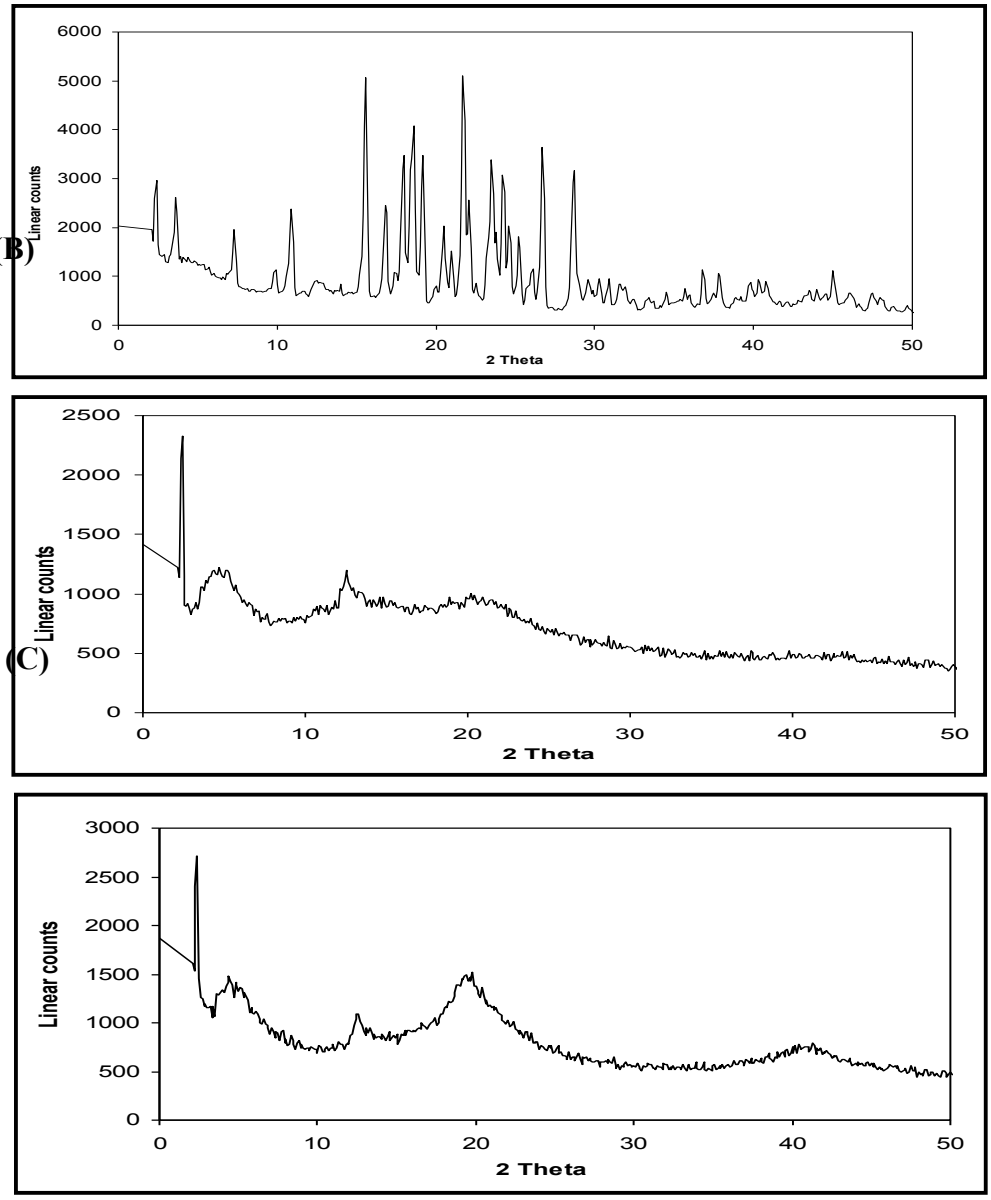

Figure 3
XRD analysis of glipizide (A), drug free HDP5 disc (B)
and drug loaded HDP5 disc (C)

Swelling studies

The release of drug from hydrogel matrix depends on the swelling behavior. As the hydrogel swells, the network pores open and drug release occurs. The swelling behavior of discs was expressed as the ratio of initial

weight of discs to the final weight of swollen discs as a function of time (Figure 4). The swelling of IPN discs depends upon the concentration of PVP and extent of GA crosslinking in the discs. The swelling of the discs increased with an increasing amount of PVP and swelling decreased with an increasing amount of GA which may be due to the formation of more rigid hydrogel network. At low crosslink density, the hydrogel network is loose with more hydrodynamic free volume and can absorb more of the solvent resulting in higher swelling [19].

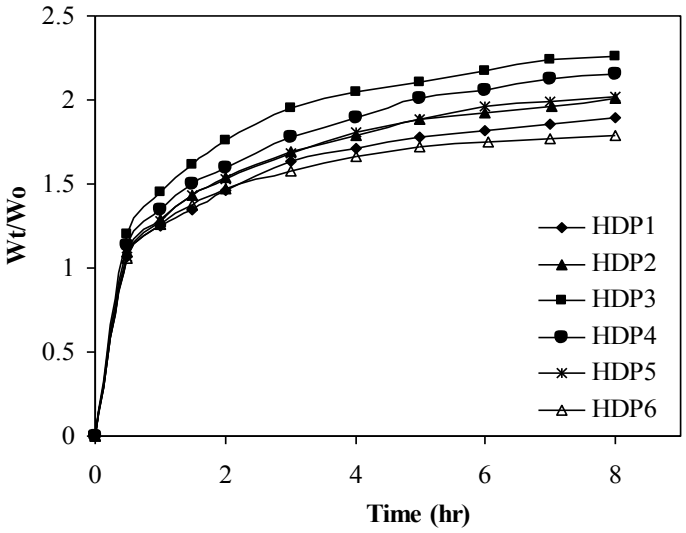

Figure 4
Swelling behavior of IPN hydrogel discs

***In vitro* drug release**

The *in vitro* drug release study indicated that the IPN discs were capable of releasing drug up to 24 h depending upon the formulation variables. Drug release was higher for the discs having higher amount of PVP as compared to those having lower amount of PVP (Figure 5). This may be due to higher swelling of IPN discs at higher amount of PVP in the IPN discs. The discs prepared with a higher concentration of GA released the drug more slowly (Figure 6). This could be due to the fact that at higher crosslinking, free volume of the matrix will decrease, thereby hindering the transport of drug molecules through the matrix. This could also reduce the swelling as well as drug release rate from the matrix. On the other hand, keeping all the variables constant, increase in initial drug loading increased the drug release (Figure 7). An increase in initial drug load decreases the proportion of polymer per unit weight and this weakens the gel network

structure. Moreover, higher drug loading increases the free volume within the network and creates a more tortuous path for water to penetrate through. Consequently, increase in initial drug loading increases the release of drug.

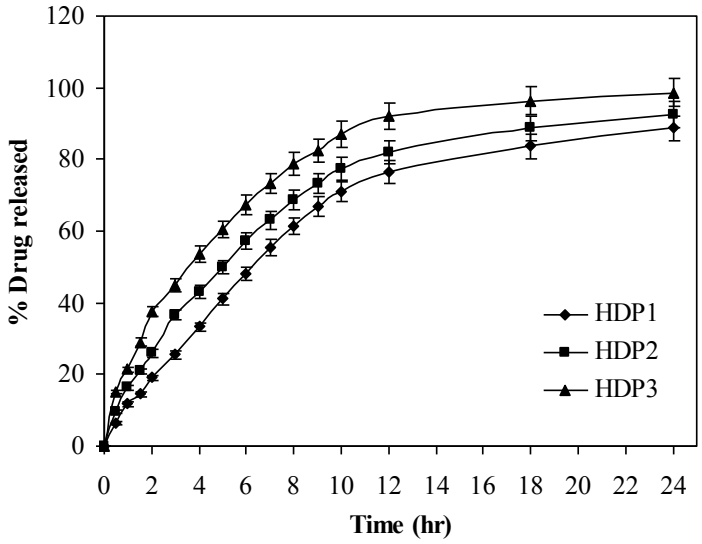

Figure 5
Effect of PVP on glipizide release from IPN hydrogel discs

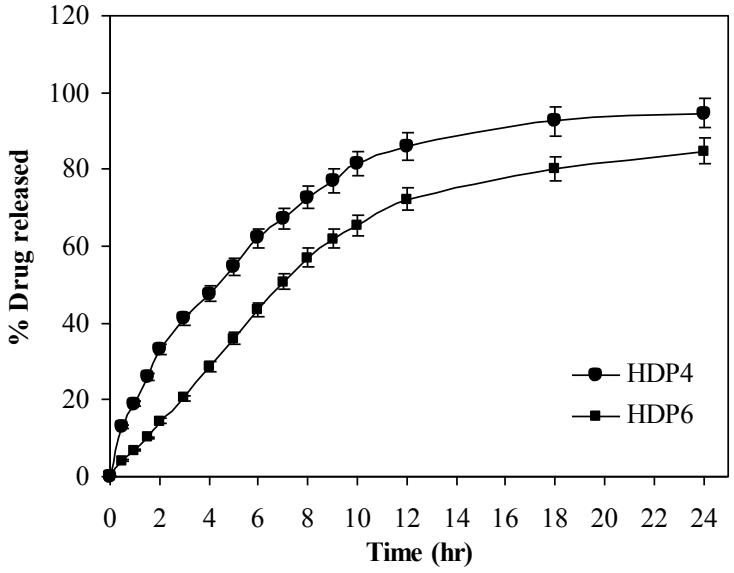

Figure 6
Effect of crosslinking on glipizide release from IPN hydrogel discs

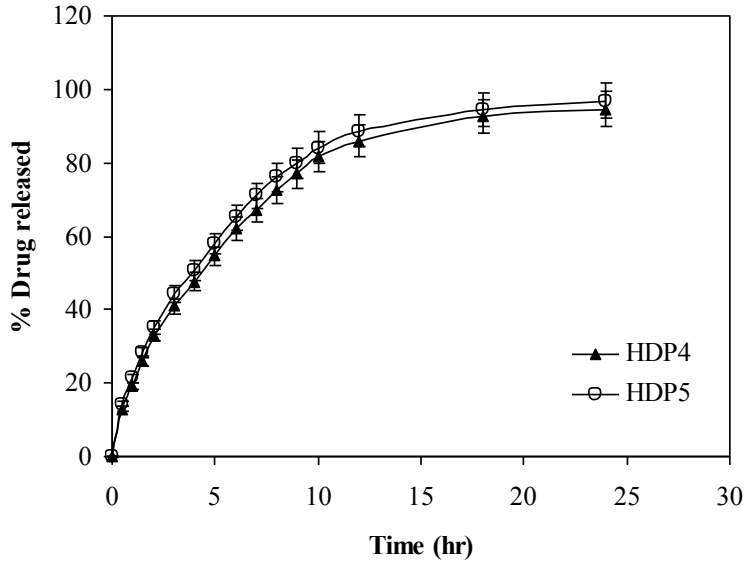

Figure 7

Effect of initial drug loading on glipizide release from IPN hydrogel discs

To understand the drug release mechanism in the hydrogel network, the release data were fitted to an empirical Eq. 1 [20]:

$$\frac{Mt}{M\infty} = Kt^n \quad (1)$$

In which M_t is the amount of drug released at time t, and M_∞ is the total amount of drug loaded, n values are the indication of the type of release mechanism. The calculated n values along with the correlation coefficients have been shown in Table 2. The values of n depend upon the extent of crosslinking and increases with increase in crosslinking. The calculated n values suggest that the mechanism of drug release followed a non-Fickian transport.

Conclusions

The IPN hydrogel discs of PVA and PVP were prepared by chemical crosslinking and molding method for the controlled release of glipizide. Uniform discs were produced with drug content as high as 95%. The TGA study confirmed the IPN formation; DSC and XRD analysis confirmed the uniform dispersion of the drug in IPN matrix. Swelling of the IPN discs and

drug release depend upon the extent of crosslinking and amount of PVP used in the formulation. The IPN hydrogel discs were capable of releasing drug up to 24 h. The discs prepared with higher concentrations of GA released the drug more slowly. This study indicates that the drug release rate and mechanism of drug release could be controlled by hydrogel composition and extent of crosslinking, which is important for application of the prepared IPN hydrogels for controlled drug delivery.

Acknowledgements

One of the authors (Prof. R. V. Kulkarni) is grateful to Vision Group on Science and Technology, Government of Karnataka, India for the financial support through a major grant under K-FIST (Level 2) programme. Authors are also thankful to Dr. B. G. Mulimani, Vice Chancellor, BLDE University and management of BLDE Association, Bijapur for providing the necessary facilities to carry out this work.

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Manuscript recieved: April 6th 2012