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Cross-linked Poly (vinyl alcohol) Hydrogel: Study of Swelling and Drug Release Behaviour

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ABSTRACT

Cross-linked poly (vinyl alcohol) (PVA) is a prolonged-release micromatrix, a hydrophilic polymer and a potentially interesting hydrogel, which is useful for drug delivery applications. As a part of drug development procedure the aim of this study was to investigate the effect of structural changes on drug release (theophylline) from this polymeric network. The studied parameters included: cross-linking agent (glutaraldehyde) concentration, PVA content of the films, theophylline percentage and their overall effect on swelling of the hydrogels, drug loading efficiency, diffusion and release characteristics of theophylline from PVA films. Changes in glutaraldehyde percentage (or cross-linking density) affected the swelling of the films. However, increasing PVA percentage caused more swelling. Drug loading efficiency was higher in gels with higher glutaraldehyde, PVA and theophylline percentages. Increasing contents of PVA and theophylline promoted the diffusion coefficient and drug release rate but glutaraldehyde had a reverse effect. The pH did not affect the swelling and diffusion coefficient. Water transport and drug release mechanism predominantly followed a Fickian model. It may be concluded that by changing the PVA structural parameters, a rate-controlled drug release is obtained.

Key Words: hydrogel, matrix, poly (vinyl alcohol), diffusion, swelling

INTRODUCTION

Hydrogels are gaining increasing popularity in the area of controlled-release drug delivery. These polymers are generally glassy in the dehydrated state but swell to become an elastic gel upon water penetration. The entrapped drug within the swelling matrix concomitantly dissolves and diffuses through the swollen network into surrounding aqueous environment. The rate of drug release from hydrogels is regulated by cross-linking density and the extent of swelling [1].

Poly (vinyl alcohol) (PVA) is a hydrophilic polymer with unique properties. It absorbs water, swells easily and it has extensively been used in controlled-

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release applications [2]. It has been used as a controlled drug delivery system for rectal propranolol, atenalol, indomethacin, phenylpropanolamine and emedastin/HCl [3–9]. Swelling characteristics of this hydrogel depends to the presence of salts and the degree to which the acetate groups are replaced by hydroxyl groups [9]. However, as this hydrogel is quite a hydrophilic system, it releases the drug with a relatively high rate. To prolong drug release from such system, its macromolecular structure should be modified. This can be done by cross-linking and reducing the macromolecular mesh size available for drug diffusion [10].

Increasing the cross-linking density decreases the volume swelling and drug release rate that is attributed to the decrease of diffusion coefficient of drug and solvent [11]. The type of drug release from these systems commonly follows according to Fickian transport.

Another approach for prolonging drug release from hydrophilic hydrogels is undergoing a glassy-to-rubbery state transition upon swelling by water penetration that modifies the type and drug release rate. Water uptake and drug delivery from swelling-controlled release systems can be described sufficiently by two dimensionless parameters for many solvent/polymer systems; the diffusional Deborah number, De, and the swelling interface number S_w. If the swelling process is dominated by either the relaxation time ($De >> 1$) or water diffusion ($De << 1$), the time dependence is Fickian. However, if De is on the order of 1, the two processes occur on the same scale, leading to anomalous transport behaviour [12].

Despite the growing interest in utilizing glassy PVA hydrogels as swelling-controlled delivery systems, the kinetics of swelling, drug diffusion and drug release through cross-linked PVA hydrogels have not been studied in details. The aim of this study was to investigate the effect of environmental conditions and network structure of PVA on its swelling, drug release and diffusion mechanism through it. Swelling measurements are relatively simple means to characterize cross-linked polymer networks and can be helpful in the interpretation of drug release and diffusional transport processes through the macromolecular material. It is obvious that by knowing these effective factors, modification of drug release from its micromatrices is possible.

MATERIALS AND METHODS

Materials

Theophylline as the model drug was kindly supplied by Amine Pharmaceutical Co. (Iran), PVA ($\overline{M}_n$ = 72000, and a degree of hydrolysis of 97.5–99.5% mole), methanol, sulphuric acid, glacial acetic acid and 25% aqueous solution of glutaraldehyde from Merck Chemical Co. (Germany). All other chemicals used were analytical grade obtained from Merck Co.

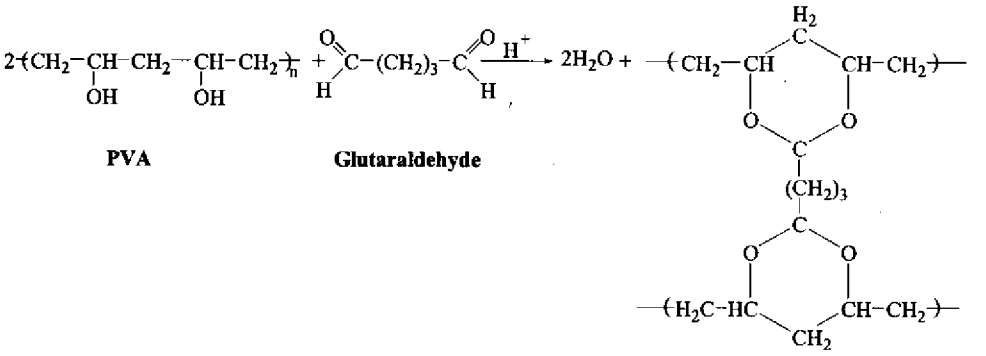
Methods

Cross-linking Procedure of PVA and Matrix Preparation

The method described by Korsmeyer and Peppas [11] was used. Briefly, a 10% PVA solution was prepared in hot water at 80–90 °C. After cooling to room temperature, 100 g of this solution was mixed with 20 g of a 50% aqueous solution of methanol, 30 g of a 10% aqueous solution of acetic acid and 10g of a 1% aqueous solution of sulphuric acid. Three different percentages of glutaraldehyde solution were used as cross-linking agent; 0.75, 1.00 and 1.25 % w/v. The reactants were stirred thoroughly and the mixtures were poured into petri dishes to obtain polymer disks. The petri dishes were sealed to prevent evaporation. After 12 h, the cross-linked hydrogels were cut into small slabs using a cork borer. The disks were swollen while stirred for 24 h in distilled water to extract any unreacted cross-linker and acids. The water was exchanged many times during this period. Finally, the gels were air-dried at room temperature for 24 h followed by a vacuum-drying cycle at 50 °C for another 24 h until reaching a constant weight. To study the effect of PVA concentration on different characteristics of the gels, the film containing 1.25% glutaraldehyde were prepared with 5, 10, 12.5 and 15% w/w PVA. The products of reaction of PVA with aldehydes are poly (vinyl acetal) resins [13]. The gelation of PVA by a dialdehyde (glutaraldehyde) is shown as the following [13] (Scheme I).

Drug Loading into Cross-Linked PVA Films

A 10 mg/mL solution of theophylline in 0.1N NaOH was used for loading the hydrogel disks. The disks were swollen and stirred by a Teflon bar in this



PVA **Glutaraldehyde** **Cross-linked PVA**

Scheme I

solution for 4 h. The disks were then air dried for 24 h and vacuum dried for another day at 50 °C. The crystallized drug over the surface of the disks was washed with water and then vacuum-dried again. Three different percentages of theophylline solution in 0.1N NaOH; 0.25, 0.50 and 1.00% w/v were used for loading the drug into the films of 10% w/w PVA with 1.25% w/v glutaraldehyde as cross-linker.

Drug Loading Efficiency

To determine the percentage of drug loaded in each hydrogel, the loaded disks were soaked in a 0.1 N NaOH solution, after 4 h the absorbance of the soaking medium was measured spectrophotometrically at 274 nm (Perkin-Elmer 550-SE, Germany).

Swelling Characteristics of the Films

The effect of pH, glutaraldehyde %, PVA content and drug loaded in the gels were studied on the swelling properties of the unloaded hydrogels. The swelling media were distilled water, phosphate buffer 0.2 M (pH 6.8), acetate buffer 0.2 M (pH 4.7), and hydrochloric acid 0.2 M buffer solution (pH 1.2). The ionic strength of the solutions was adjusted on by adding appropriate amounts of NaCl on 0.5. Each hydrogel disk was soaked in a proper medium at 37 °C which was stirred by a magnetic bar at 300 rpm and sorption of the aqueous medium was measured periodically by removing the disks, blotting excess surface solution and weighing by a Sartorius balance (model 2434) with a precision of 0.00001g. The swelling ratio was used as the criteria of swelling:

Swelling ratio or hydration: water/polymer (g/g) =

$$\frac{\text{swollen polymer weight - dry polymer weight}}{\text{dry polymer weight}} \qquad (1)$$

Diffusion Coefficient Measurements of Theophylline Through PVA Hydrogel

The effect of pH, PVA content of hydrogels, cross-linking agent concentration and theophylline percentage were studied on diffusivity of the drug through the gels. The disks were swollen to their equilibrium state at each studied pH and then placed between two cells of side-by-side diffusion cell (cell capacity was 3 mL and the surface area of the orifice was 0.81 cm^2). The donor cell was filled with 3 mL of a 0.25, 0.50 or 0.75% w/v of theophylline solution and the receptor cell with 3 mL of the studied medium used in the donor cell but without drug. The temperature of the cells was kept constant at 37 °C using a water pump bath. At predetermined time intervals 2.5 mL samples were taken and the absorbance was measured spectrophotometrically. The sink condition and the volume of the receptor cell were kept constant by adding

2.5 mL of fresh buffer after each sampling. The diffusion coefficients were calculated according to Fick's first law of diffusion [14].

$$dQ/dt = ADK_d (C_o - C)/h \quad (2)$$

In which dQ/dt is the mass transfer rate, A is the film surface area, h is the hydrogel thickness, C_o and C are drug concentrations in the donor and receptor cells, respectively.

Partition Coefficient Measurement of Theophylline

To calculate the partition coefficient of the drug through the hydrogel, the modified method of Sato and Kim [15] was used:

$$K_d = [V_s (C_o - C_s)]/V_m C_s \quad (3)$$

Where, V_s is the volume of solution, V_m the volume of polymer film, C_o the initial solute concentration and C_s the solute concentration in the solution at the equilibrium. The initial solute concentrations in the experiment were similar to those in the diffusion tests. C_s was measured spectrophotometrically until constant value was obtained. V_m was measured by eqn (4).

$$V_m = \pi r^2 h \quad (4)$$

Where the equilibrium thickness of hydrogel (h) was measured at the end of the test with a Digimatic thickness gauge, and r refers to the radius of the hydrogel.

Drug Release Studies

The paddle method dissolution apparatus rotating at 100 rev/min (Pharmatest, PTWS3) was used for the drug release experiments. All experiments were carried out in 250 mL phosphate buffer (pH 6.8) at 37±0.5 °C. Test sample of 5 mL were removed at specific time intervals and analyzed at 275 nm spectrophotometrically. Each sample was replaced by fresh buffer solution. The effect of glutaraldehyde, PVA and theophylline percentages was measured on the drug release from the hydrogels. Two parameters were used as the critical criteria for evaluation of release studies: $t_{50\%}$ (the time required to release 50% of the drug from hydrogels) and DE_{105} % (dissolution efficiency percentage after 105 min of release test that was calculated according to eqn (5) [16]):

$$DE(\%) = \frac{\int_0^t y\,dt}{y_{100}} \times 100 \quad (5)$$

Statistical Analysis

The experiments were conducted to one-way Anova test. (SPSS, computer program, version 10). Dunckan test was employed to evaluate the statistical differences between individual means. In all cases $P<0.05$ was accepted to denote significance.

RESULTS AND DISCUSSION

Swelling Properties of PVA Hydrogels

Table 1 shows the effect of pH on the swelling capacity of the cross-linked PVA (10%) hydrogel with 1.25 % glutaraldehyde. As this table shows there is not any significant difference between the swelling percentages of this hydrogel in different pHs. In other words this hydrogel is not a pH-sensitive polymer and does not respond to the environment stimuli. In all cases water transport fits with a Fickian mechanism (Table 1). Penetration of solvent into the polymer leads to its swelling which is involved with diffusion of solvent molecules through the polymer matrix, and local relaxation of polymer segments. For rapid relaxation rates, penetration speed is limited by diffusion process and the normal Fickian transport is observed. In this type of swelling mechanism, diffusion of water molecules inside the polymer is a rate-limiting step [12].

Considering that cross-linking of hydrogels is a way for reducing the molecular mesh size of the gel for drug diffusion [10], and prolong drug release may be achieved by decrease in the volume of the swelling of hydrogels [11], the effect of different ratios of glutaraldehyde/PVA was studied on the swelling characteristics of the PVA hydrogel. The effect of cross-linking concentration on the swelling properties of PVA hydrogel is shown in Figure 1. As this figure indicates

Table 1. Effect of pH on swelling percentage and water transport mechanism (from $M_t/M_\infty = kt^n$) of PVA (10%) hydrogel cross-linked with 1.25% glutaraldehyde after 180 min. (Diffusion coefficient measurement has been done on the loaded gels, while swelling studies on the unloaded hydrogels). The test repetition, n=3.

pH	Swelling (%) mean ± SD (n= 3)	n*	Diffusion coefficient (D) (cm^2/s) mean ± SD (n= 3)
1.2	75.29±0.09	0.124±0.003	$3.794 \times 10^{-6} \pm 0.15 \times 10^{-8}$
4.7	75.38±0.11	0.119±0.02	$3.799 \times 10^{-6} \pm 0.87 \times 10^{-8}$
6.8	75.09±0.06	0.12±0.023	$3.86 \times 10^{-6} \pm 5.51 \times 10^{-8}$
Water	75.36±0.16	0.128±0.05	$3.95 \times 10^{-6} \pm 3.24 \times 10^{-8}$

* Considering that in all studied pHs n value is <0.5, and water transport mechanism is described by a Fickian mechanism.

different ratios of glutaraldehyde/PVA show significant difference in their water uptake qualities ($P<0.05$). Chain entanglement along with increase in cross-linking agent concentration would result in a decreased network expansion (Figure 1). Lower glutaraldehyde/PVA ratios cause a significant increase in swelling properties ($P<0.05$). In general it may be concluded that by increase in the glutaraldehyde/PVA ratio, the cross-linking density increases and this in turn reduces the swelling or water uptake of the gels significantly.

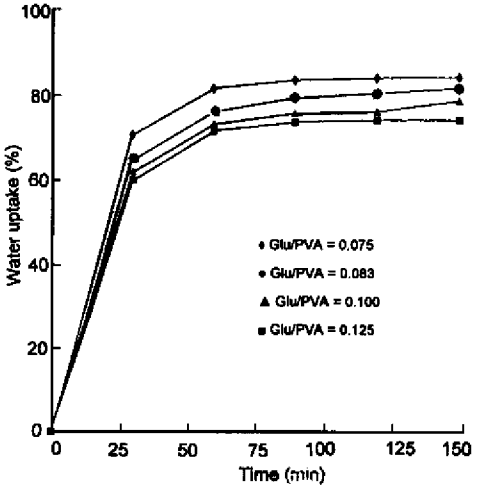


Figure 1. Effect of different ratios of glutaraldehyde/PVA (Glu/PVA) on the swelling isotherms of cross-linked PVA films in phosphate buffer solution (pH 6.8) (n=3).

Drug Loading in the Hydrogels

Table 2 shows the effect of different parameters on the loading percentage of theophylline in the hydrogels. As this table shows increasing the glutaraldehyde in the hydrogel from 0.75% to 1.25% increases the drug loading efficiency significantly ($P<0.05$). It seems that increasing the glutaraldehyde concentration has caused a better accommodation of the drug solution in the gels. PVA percentage in the hydrogel has a similar effect and increasing its content in the polymer increases the drug loading significantly ($P<0.05$). The amount of drug, which can be loaded into the polymeric material, depends on three parameters, namely, the drug solubility in the initial solution, the solvent volume fraction of the cross-linked hydrogel and the drug partition coefficient between the polymer and the solution. If the cross-linking density is relatively high such that the network cannot accommodate the entire volume of liquid, the solvent expels from the gel by contraction and this is known as syneresis [14]. As the results show no decrease in loading efficiency is noticed by increasing the cross-linking agent or PVA content of the gels. It seems that increasing these two parameters causes a better accommodation of drug and no syneresis has happened in the studied concentrations. Changing the drug concentration from 0.25 to 1.00% in the soaking medium of the gels also increases the loading efficiency significantly ($P<0.05$).

Diffusion and Release Studies

The effect of pH on the diffusion coefficient of

Table 2. Loading percentage (according to dry weight of the hydrogel) and release parameters of theophylline from drug loaded PVA hydrogels (n is obtained from equation $M_t/M_\infty = kt^n$).

PVA (%)	Glutaraldehyde (%)	Drug (%) (in the medium)	Loading (%)	$t_{50\%}$ (min)	DE_{105} (%)	n*
10	0.75	1	1.71±0.04	6.81±0.35	81.64±0.38	0.15±0.061
10	1	1	1.99±0.135	7.015±0.45	74.86±0.18	0.534±0.091
10	1.25	1	2.28±0.280	13.28±0.48	59.71±0.28	0.187±0.007
10	1.25	0.5	2.28±0.085	41.49±3.24	45.81±1.54	0.283±0.023
10	1.25	0.25	1.40±0.32	164.63±58.13	31.89±0.78	0.338±0.065
12.5	1.25	1	2.94±0.12	7.28±0.31	78.19±0.77	0.167±0.009
15	1.25	1	3.5±0.02	6.01±0.58	79.89±1.32	0.116±0.026

* Considering that in all studied cases $n \leq 0.5$, a Fickian drug release mechanism is obtained.

theophylline through cross-linked PVA hydrogel is shown in Table 1. As this table shows there is not any significant difference between the diffusivity of theophylline in different pHs. This result is in coincidence with swelling results and it confirms that PVA is not a pH-sensitive hydrogel.

Figure 2 indicates that increasing the glutaraldehyde % decreases the diffusion coefficient of theophylline through PVA hydrogel significantly ($P<0.05$). This is probably due to the reduced free space available for solute transport, which essentially depends on the network structure and can greatly change from one mesh to another in the network. Kim and Lee [17] also reported a similar behaviour for the cross-linked PVA beads.

Increasing the PVA content of the hydrogels from 10% to 15% produces a 4-fold increase in D, diffusion coefficient value (Figure 3). Higher swelling of the gels with lower glutaraldehyde / PVA ratios (Figure 1) can explain the increase of D value of the gels with higher PVA concentrations by the "free volume" theory [18]. This theory was suggested for solute permeation in hydrogel films. It assumes that: (1) solute diffuses only through aqueous regions, (2) the solute diffuses through "fluctuating pores" by successive jumps, and (3) the effective free volume available for transport is essentially the free volume of water in the gel.

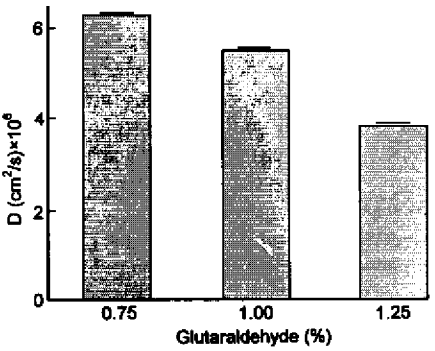


Figure 2. Effect of glutaraldehyde % on the diffusion coefficient (D) of theophylline through cross-linked PVA (10%) films in phosphate buffer (pH 6.8) (n=3).

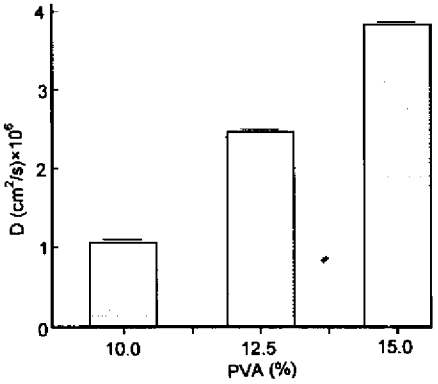


Figure 3. Effect of PVA content on the diffusion coefficient (D) of theophlline through cross-linked PVA films with glutaraldehyde in phosphate buffer (pH 6.8) (n=3).

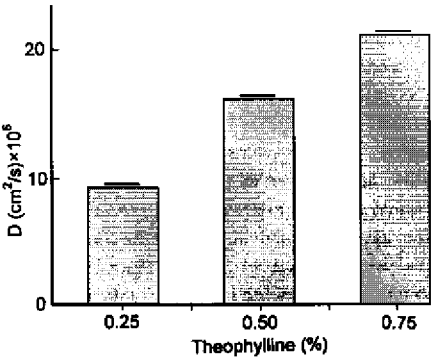


Figure 4. Effect of theophylline % on its diffusion coefficient (D) through cross-linked PVA (10%) films with 1.25% glutaraldehyde in phosphate buffer (pH 6.8) (n=3).

Figure 4 shows the effect of changes of the theophylline concentration in the diffusion cell, on the diffusivity of this drug through PVA hydrogel. The results show, that increasing the drug percentage causes a significant increase in the D value.

Drug release studies show a significant decrease in the theophylline release rate from PVA matrix by increasing the glutaraldehyde % (Figure 5), decreasing in PVA content (Figure 6) and drug loaded percentage in the hydrogel (Figure 7). A prolonging effect in $t_{50\%}$ and $DE_{105}\%$ of the drug release is obtained

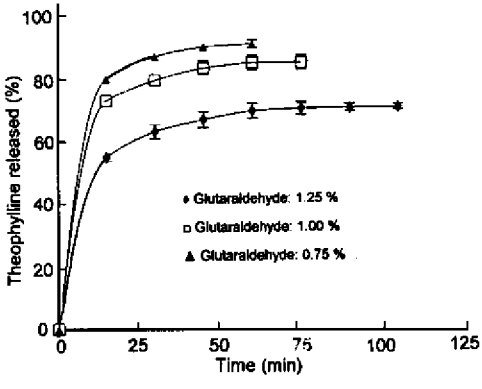


Figure 5. Effect of glutaraldehyde % on the drug release from cross-linked PVA (10%) films loaded with 1% theophylline in phosphate buffer (pH 6.8) (n=3).

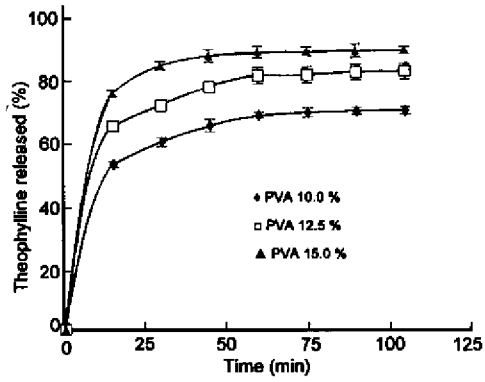


Figure 6. Effect of PVA content on the drug release from cross-linked PVA hydrogels with 1.25% glutaraldehyde and 1% loaded theophylline in phosphate buffer solution (pH 6.8) (n=3).

by increasing the glutaraldehyde %, which is related probably to increased chain entanglement and degree of cross-linking (Figure 5 and Table 2). The release of Santosol oil through PVA microcapsules showed the same pattern of release in the presence of different cross-linking agents [19].

From the release data it is obvious that cross-linking the linear PVA polymer along with PVA content are undoubtedly the most effective ways to

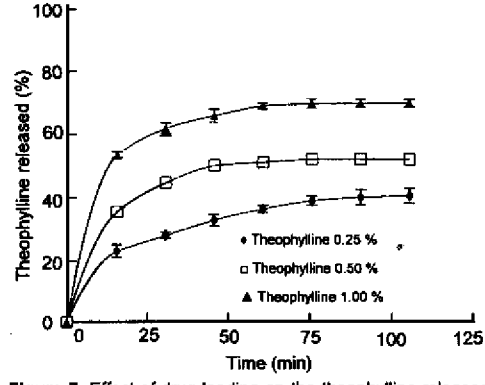


Figure 7. Effect of drug loading on the theophylline released from cross-linked PVA (10%) hydrogels with 1,25% glutaraldehyde in phosphate buffer solution (pH 6.8) (n=3).

reduce the transport rate of solute in this macromolecular material. Decreasing the glutaraldehyde/ PVA ratio in the hydrogels increased the swelling capacity of the matrix (Figure 1). Walker and Peppas [20] also found that increasing the mole fraction of HEMA as the more hydrophilic agent in the copolymers of HEMA/ EGDMA enhanced the swelling capacity of the hydrogel. This increase in PVA content causes the thicker wall formation of the matrix and so it prevents the drug solution transported out of the network and higher drug loading can be seen in the polymer with higher content of PVA (Table 2). Increasing the drug content, increases the rate of drug release [21, 22]. This observation has been confirmed by increasing the PVA content of the networks, which decreases the $t_{50\%}$ of drug release and the increase in $DE_{105}\%$ (Table 2).

From practical point of view, the amount of drug contained in a prolonged drug delivery system is an important aspect. As Table 2 shows increasing the theophylline concentration in the soaking medium, causes higher loading of drug in the hydrogel, increasing in the diffusion coefficient (Figure 4) and therefore the rate of drug release (Figure 7). Kim and Lee [17] reported that at loading levels below 17.8% of oxpernolol HCl in P(MMA/MAA) hydrogels, the drug shows an extended quasi-linear release, while at higher loading levels, it becomes faster and first-order in nature. Lee [23] found that the larger the initial load, the faster the solvent front penetrates the HEMA hydrogel. In loading above 18.8% of thiamine-HCl, a Fickian diffusion was reported while in lower loading an anomalous diffusion pattern was seen [22]. In this study theopylline loading, caused a faster release rate (Table 2) but in all cases a Fickian or diffusion mechanism was observed. In general it may be concluded that increasing the drug content in the hydrogel acts as a delivery force for the water uptake of the hydrogel which increases both drug release rate (Figure 7) and D value (Figure 4) of the drug. Decreasing the cross-linking density also increases the drug release rate (Figure 5). This effect can be seen also in Figure 6 in which in a constant concentration of cross-linking agent (1.25%), increasing the PVA concentration, decreases the cross-linking density which causes an increase in water uptake of the gels (Figure 1) and this in turn increases the drug release rate (Figure 6).

CONCLUSION

The aim of the present study was to investigate the swelling and drug release behaviour of cross-linked poly(vinyl alcohol) hydrogel. The structural characterization as well as the kinetics of swelling and drug release were studied as a function of PVA content, cross-linking density, and drug loading percentage. It was found that drug release from swellable PVA hydrogel could be controlled by cross-linking density, PVA content and drug loading percentage. In such networks, drug delivery and also water transport followed mainly a Fackian or diffusion controlled model. More Specifically, it was postulated that the drug release rate and diffusion coefficient increased by PVA content of the hydrogel and also by the amount of the loaded drug, while glutaraldehyde had a reverse effect. PVA content of the hydrogels also prompted the swelling. The gels showed no pH dependent swelling or drug diffusivity.

In conclusion, by changing the structural parameters of this hydrogel, a rate-controlled drug release may be achieved.

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