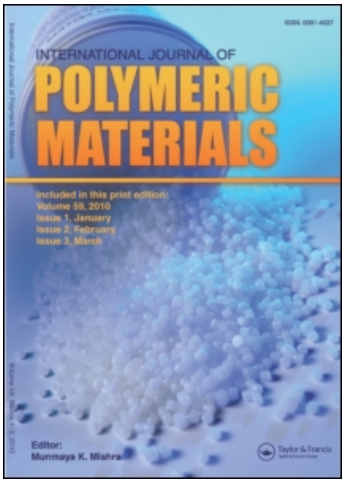

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Controlled delivery matrices are an alternative available to provide a better administration of drugs. Hydrogels have been used to produce these matrices due to the control of absorption and desorption rates of water into their molecular structure, which allows us to obtain various delivery profiles. Poly(vinyl alcohol) (PVA), a candidate matrix material, was physically modified through a solvation-desolvation process with acetone to change its crystallinity. Tolbutamide is a poorly water-soluble drug with a dissolution-rate-limited bioavailability. Thus, it was used as a model for this methodology. This physical method introduces crosslinks, which decrease the crystallinity of PVA in the order of 8% and has the advantage that there is no residual toxic chemical present in the hydrogel. Dissolution studies, carried out with the PVA-hydrogel (H) loaded with tolbutamide, allow us to state that 78% of drug release takes place in about 24 h which contrasts with the dissolution curves of tablets of tolbutamide and tolbutamide mixed with the PVA as powder both of which were used as comparative preparations.

Keywords: controlled delivery, nontoxic crosslinker, poly(vinyl alcohol) gel, tolbutamide

INTRODUCTION

Much of the current technology of controlled delivery in general is primarily based on polymers having various properties. In pharmacy, controlled-release formulations have been developed to improve the

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clinical efficacy of drugs having short half lives, as well as to increase patient compliance [1]. Tolbutamide, an antidiabetic drug (non-insulin-dependent diabetes mellitus), is a poorly water-soluble drug with dissolution rate of limited bioavailability. Poly(vinyl alcohol) is a water-soluble synthetic polymer used in sustained release formulations in the pharmaceutical industry for many years and is generally considered a nontoxic material [2].

For orally administered drugs, there are diffusional systems like matrix devices, where the drug is first dissolved or dispersed within the polymeric matrix which is usually in a glassy state. When the system is placed in the dissolution medium (e.g., water), the medium penetrates into the glassy region and the polymeric matrix begins to swell. In the presence of penetrant molecules, macromolecular chains gain mobility. Here, the swollen polymer is in a rubbery state, and the rubbery region permits the drug to diffuse [3].

It is known that the degree of crystallinity varies according to the chemical structure of the polymer [4] and with the degree of polymerization, while the properties of poly(vinyl alcohol) (PVA), which is a nontoxic highly hydrophilic material [5], depend upon the degree of polymerization and hydrolysis as well as the solubility [6].

Different methods can be used to cause structural changes. For instance, PVA gels have been prepared by using glutaraldehyde or formaldehyde as crosslinking agents [7], resulting in hydrogels which can swell. But unreacted crosslinking agents are often toxic. An alternative is the freezing-thawing method [8] in which aqueous PVA solutions result in three-dimensional networks held together by crystallites acting as physical crosslinkers. Mongia and Peppas [8,9] found that crystallite formation was a function of freezing time, thawing time and PVA solution concentration. It is worth noting that the limit of this method is that the drug must be soluble in water. Other methods apply irradiation [10] or combine the two last approaches [11], which highlight the analysis of the mechanical properties of the gels [12].

The aim of this work was to develop a matrix device for poor water-soluble drugs with dissolution rate limited bioavailability, using another physical and nontoxic method to modify the degree of crosslinking by crystallite formation in PVA and therefore, achieve a decrease in the crystallinity and increase the swelling ratio, which provides different characteristics of controlled release. The solvation-desolvation method presented here uses acetone as the solvent for tolbutamide (as a model) and as the crosslinking agent for the PVA as well, whose advantage is the absence of residual toxic chemicals in the hydrogel. The influence of the solution concentration of the

polymer and the amount of acetone on the yield of the hydrogel was also investigated.

MATERIALS AND METHODS

Analytical grade acetone was supplied by Baker. Tolbutamide was supplied by Kichari Phytochemicals International. Poly(vinyl alcohol), a 40% w/w solution with viscosity 28–32 cps 20°C, degree of hydrolysis 99.0% was from MCB. Deionized water was used for solutions as well as for swelling studies. Equipment consisted of a controlled bath recirculator (Lauda D6870), differential scanning calorimeter (DSC-7 Perkin Elmer) dissolutor VK 7000-Vankel, spectrophotometer UV-1201 (Shimadzu Model 35000-986) and tablet analyzer Mod VK-2000. The hardness was measured by means of durometer according to ASTM 2240-75.

Hydrogel Preparation (H)

A factorial design 2^2 was carried out using aqueous solutions of 12 and 20 wt% PVA, which were dissolved in deionized water at 68°C. Then these solutions were injected with 100 and 150 v/v% acetone A.R. to get the hydrogels, determining their drug loading capability and the amount of the hydrogels formed. The gels were transferred out of the vessels and dried at 37°C for 72 h in a glass mold as a die (Table 1). The experiments were carried out in duplicate.

Drug Into the PVA Hydrogel

5 mL of a tolbutamide solution 12 wt% by weight in acetone was prepared and injected to 2 mL of PVA solution, at both 12 and 20%

TABLE 1 2^2 Factorial design. Percent of the hydrogels obtained (%Y), and amount of tolbutamide incorporated (% drug) respecting the ratio used of PVA and acetone.

Sample	% solution of PVA[a]	% of acetone	Yield[b] (%)	% of drug
H1	12	100	97	82
H2	12	150	98	70
H3	20	100	95	77
H4	20	150	96	71

[a]At 68°C.
[b]Dried at 37°C for 72 hs.

in water. The hydrogel with tolbutamide was decanted and dried at 37°C for 72 h, in a glass mold as a die.

Percent of loading drug was determined from the difference between the original amount of the drug and the measure of the remaining drug in the solution of water-acetone by UV-analysis.

Differential Scanning Calorimetry Studies

Differential scanning calorimetry was performed by using a DSC-7 Perkin Elmer at a rate of 10°C/min, with a nitrogen purge. The flow rate of nitrogen was adjusted to 50 mL/min.

Crystallinity Measurement (%C)

The degree of crystallinity (on a dry basis) was calculated by comparing the heat required to melt the sample to the heat required to melt a 100% crystalline PVA sample (138.6 J/g) [9].

Percent Swelling Determination (%S)

One of the two most widely used methods for determining crosslinking density is solvent-induced swelling [13]. Here, water was used as the swelling solvent and the equation used to calculate the percent swelling was:

$$\%S = \frac{(Vf - Vi)}{Vi} \times 100$$

The dried sample's volume was determined by putting the sample into a burette (Vi). The sample was left in a tube with water in a thermostated bath at 37°C for 14 h, which was taken as the characteristic equilibrium swelling after a previous assay. Surface water was removed by patting samples with paper tissues before placing the sample again into the burette to read the final volume (Vf).

Dissolution Study

The study was carried out according to the U.S. Pharmacopoeia [14] in a VK 7000 dissolution testing station detecting tolbutamide at a wavelength of 228 nm. Dissolution test media was phosphate buffer pH7.4 at 37°C and paddles at 75 rev/min. Dissolution results are presented as the percentage of tolbutamide dissolved at certain time points along the whole profile.

Tablet of Tolbutamide (T1)

100 mg of tolbutamide was molded as a tablet at 1000 lb/in^2.

Tablet of Commercial PVA (T2 and T3)

100 mg of commercial PVA was molded as a tablet at 1000 and at 5,000 lb/in^2, respectively.

Tablet of PVA and Tolbutamide (T4)

46 mg of tolbutamide and 54 mg of commercial PVA was molded as a tablet at 1,000 lb/in^2.

RESULTS AND DISCUSSION

The results shown in Table 1 allow us to state that over the range of value in the experiment neither the amount of acetone nor the concentration of PVA solutions had a significant effect on the yield of the hydrogel. Based on the loaded drug, it seems to be a compromise between the polarities of PVA, the drug, and the solvents, since tolbutamide is very soluble in acetone and as it comes in contact with the PVA aqueous solution, both tolbutamide and PVA become less soluble. As expected, the higher volume of acetone used should speed up the entanglement of PVA, and as a consequence the amount of tolbutamide in the hydrogel will be limited. The conditions to prepare samples H2, H3 and H4 were discarded because even though the yields of hydrogel were similar H1 could incorporate the drug more efficiently with less consumption of acetone, and therefore it was used to perform the dissolution assays.

TABLE 2 Comparison of the percent of crystallinity (%C) and swelling (%S) among the hydrogel (H1), the commercial PVA and PVA molded at different pressures (T2 and T3).

Sample	PVA (mg)	Pressure (lb/in^2)	%C	%S
H1*	100	–	42.3	250[b]
PVA[a]	100	–	49.9	–
T2[c]	100	1000	51.0	200
T3[d]	100	5000	55.1	100

[a]Commercial powder.
[b]Soluble.
[c]Hardness 1.1 kp.
[d]Hardness 12.3 kp.
*Glass mold as die.

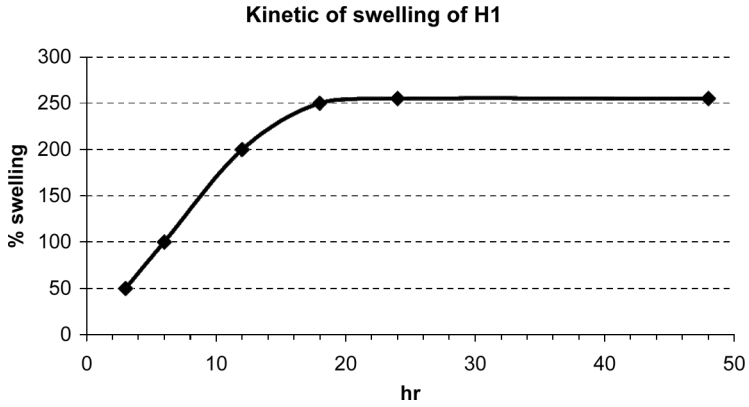

FIGURE 1 Kinetic of swelling of H1 in water.

To demonstrate the physical changes realized in sample H1 the degree of crystallinity was determined, as well as the percent of swelling, and they were compared with the data obtained from tablets T2 and T3, which were molded at 1000 lb/in^2 and 5000 lb/in^2, respectively. The crystallinity of the commercial PVA was also considered. As expected for H1, its crystallinity was reduced, which allowed the formation of a crosslinked network, whose effect can be seen in the swelling response (Table 2 and Figure 1). A picture of the H1 before and after the swelling is shown in Figure 2.

It was of interest to observe the effect of the pressure on T2 and T3, in which the crystalline structure of the polymer increased as the pressure increased and thus the percent of swelling decreased. Even though the hydrogel H1 and the tablet T2 showed a nearly same level

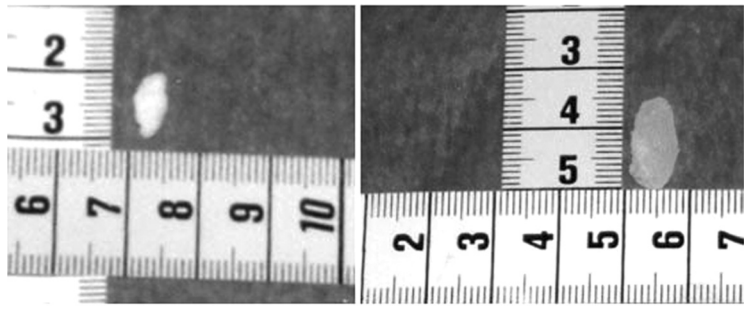

FIGURE 2 PVA hydrogel (H1) before (left) and after swelling (right) in water.

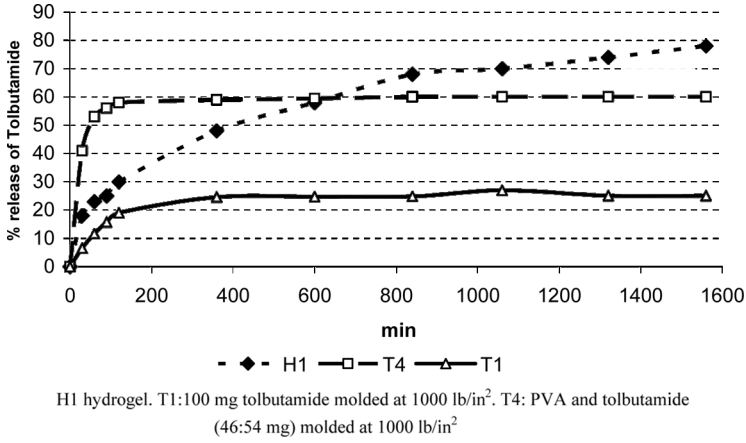

FIGURE 3 Dissolution profiles of the Hydrogel (H 1)(◆), Tablets (T1 (▽), T4 (□)). H1 hydrogel. T1: 100 mg tolbutamide molded at 1000 lb/in^2. T4: PVA and tolbutamide (46:54 mg) molded at 1000 lb/in^2.

of swelling, the latter has a drawback since its hardness (1,1 kp) produces an easily broken tablet.

Furthermore, the dissolution profiles in Figure 3 confirm the modification of drug release behavior as follows. The release profile of the tablet T4 is regular and at 90 min reaches 58% of the drug whereas T1 releases only up to 22% at 6 h. The H1 which was charged with

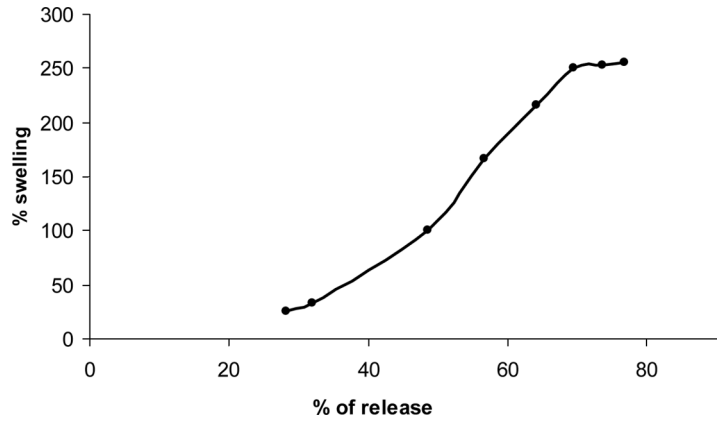

FIGURE 4 Ratio of tolbutamide release as a function of swelling of H1.

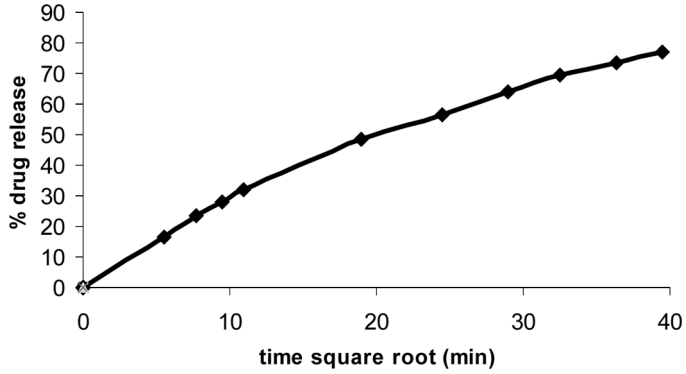

FIGURE 5 Ratio of tolbutamide release vs. time square root loaded in H1.

the drug displays a first discharge of 18% at 30 min, presumably as a result of some percentage of the drug which could not be incorporated into the hydrogel but onto its surface. In order to release 58% of the drug, H1 was six times slower than T4 and after that monotonically increased for 16 h reaching up to 78%. It is noteworthy to see that the release kinetics of the model drug was proportional to the percent of swelling of H1 as well as to the time square root which are properties found for polymer matrices used successfully in controlled-release devices [15] (Figures 4,5).

CONCLUSIONS

We present herein a fast, inexpensive and nontoxic physical method to introduce a physical crosslinking for PVA, which produces a hydrogel (H1) with less crystallinity, in the order of 8%, with no residual toxic chemical present in it and a swelling capacity of 250%. Furthermore, the method allows a very easy and efficient loading of the drug into the H1. The dissolution curve allows us to state that almost 78% of drug release takes place in about 24 hours and that the PVA as hydrogel improves not only the rate but the percentage release of tolbutamide compared with the tolbutamide tablets (T1), or the PVA-tolbutamide tablets (T4), which were used here as reference.

It is noteworthy to observe that the release kinetic of the model drug was proportional to the percent of swelling of H1 as well as to the time square root which are properties present in polymer matrices used successfully in controlled-release devices.

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