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Research paper

Swelling-controlled release system for the vaginal delivery of miconazole

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Abstract

Miconazole nitrate, a fungicidal, is effective for the local treatment of vaginitis. The objective of this project was to develop a swelling-controlled release delivery system for miconazole. An aqueous solution of 15% w/w poly(vinyl alcohol) was mixed with a specific amount of miconazole powder. The resultant mixture was cross-linked by freeze–thawing. The effect of the number of freeze–thawing cycles was studied at four levels. The effect of the presence of PEG was studied by mixing different concentrations of two different PEG. The swelling at the end of 48 h was significantly higher (32%) for the batch that underwent four cycles. The swelling within the first 15 min for the batches containing PEG1000 was approximately 9%. However, the swelling for the batches containing PEG1450, at much lower concentration, within the same period was between 10 and 19%. The drug release profiles up to 108 h were independent of the number of freeze–thawing cycles. The cumulative percent miconazole released, in the absence of PEG, (two, four, six, eight cycles) at the end of 108 h was between 30 and 35%. The drug release was lower for the batches containing PEG1000, irrespective of the concentrations, compared with the batches containing PEG1450. A comparison of the value of diffusional exponent (n) indicates the predominance of a Fickian diffusion mechanism of release from the hydrogels.

Keywords: Controlled release; Drug delivery; Freeze–thawing process; Polyvinyl alcohol; Miconazole; Dissolution

1. Introduction

Miconazole is an antifungal drug, which is used to treat topical fungal and yeast infections [1–3]. Miconazole is available as a 2% vaginal cream (Monistat-Derm) [4], 100-mg suppositories (Monistat 7) to be applied in the vagina at bedtime for 7 days, and 200-mg vaginal suppositories (Monistat 3) for 3-day therapy [5]. One of the most common problems with this drug is that patients often cease using it before the infection is completely eradicated, leading to reinfection. Development of a controlled release delivery system for miconazole would provide a long-term therapeutic concentration of the drug following a single dose leading to a complete eradication of the infection.

During the last three decades, considerable attention has been focused on the development of novel and controlled release drug delivery systems to provide a long-term therapeutic concentration of drugs following a single dose. Many controlled release drug delivery systems are based on hydrogels [6,7]. These are hydrophilic polymers that have been cross-linked by means of covalent bonds. These hydrogels, when placed in an aqueous environment, are able to swell rapidly and retain large volumes of water in their swollen structure [8]. Hydrogels prepared with poly(vinyl alcohol) (PVA) and its copolymers have been used extensively for the controlled release of numerous drugs [9–14]. These formulations are highly biocompatible [15,16]. PVA hydrogels are useful for the controlled delivery of both hydrophobic and hydrophilic drugs [17]. The linear PVA must be cross-linked in order to achieve controlled drug release [18]. The rate of drug release from these formulations is regulated by controlling the cross-linking density. An increase in cross-linking density results in a decrease in both the volume swelling and the rate of drug release [19,20]. Chemical cross-linking methods have a tendency to leave behind residual toxic chemicals. Moreover, the cross-linking agents used during the preparation may severely damage the active ingredients, specifically proteins and peptides. However, when aqueous solutions of PVA were exposed to a number of freeze–thaw cycles, crystallites form and the system behaves as if it has been chemically cross-linked [21,22]. The time of the freezing and thawing cycles was important in determining the final properties of the crystalline structure [23]. The crystallinity of the system increased with the increase of the time of the freezing cycle. The mechanical strength and swelling ratio of the hydrogels

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were dependent on the number of freeze–thaw cycles, the freezing time, the concentration of the PVA solution, and the molecular weight of the PVA. An increase of any of these parameters resulted in an increase of the mechanical strength and a decrease in the swelling ratio of the hydrogel [21].

The primary objective of this project was to develop a hydrogel formulation for the controlled delivery of miconazole. The specific objectives were to (1) study the effect of the number of freeze–thawing cycles and (2) study the effect of PEG. PEG is a hydrophilic excipient that is commonly used in the preparation of suppositories [24]. Based on the molecular weight, different grades of PEG are commercially available. Development of this miconazole hydrogel formulation would be beneficial over the current marketed preparations, which require once or twice daily dosing, for 3–5 days. In contrast, the hydrogel preparation will require only one dose for the entire course of treatment, assuming that the treatment will continue for 3–5 days. In addition, the soft and rubbery nature of the hydrogel will minimize mechanical and frictional irritation to the surrounding tissue.

2. Materials and methods

2.1. Materials

Miconazole nitrate, polyvinyl alcohol (average molecular weight 70 000–100 000; viscosity of a 4% aqueous solution at 20°C 11–14 cps), and polyethylene glycol (PEG, MW 1000 and PEG, MW 1450) were obtained from Sigma Chemical Co. St. Louis, MO).

2.2. Experimental design

The hydrogel was prepared by a freeze–thawing process in the absence of a chemical cross-linking agent. The effect of the number of freeze–thaw cycles was studied at four levels (two, four, six, and eight cycles). The effect of the presence of PEG was studied by mixing four different concentrations of two different PEG (MW 1000 and 1450).

2.3. Preparation of hydrogel

An aqueous solution was prepared by dissolving 3 g of PVA in 20 ml deionized water (15% w/w) at 90°C for 6 h. A specific amount (900 mg) of miconazole (with or without PEG) was added to the PVA solution (Table 1). A measured amount of the mixture (1.5 ± 0.1 g) was poured into a suppository mold (torpedo-shaped; 10×30 mm; Armstrong, NJ) and then frozen by cooling at -12°C for 15 h. The mixture was then allowed to thaw at room temperature for 8 h. This procedure constituted one full cycle. The samples were subjected to two, four, six, or eight freeze–thaw cycles. To study the effect of PEG all hydrogels were prepared, based on the results obtained from the preliminary experiments, using four freeze–thaw cycles.

2.4. Swelling characterization study

Swelling characteristics were evaluated through dynamic swelling studies. Each sample (torpedo-shaped; 10×30 mm) was weighed and then placed in 10 ml deionized water in a glass vial at room temperature. The samples were periodically weighed after removing the excess water on the surface with a filter paper.

$$\% \text{ Swelling} = \left[\frac{(W_t - W_i)}{W_i} \right] \times 100 \quad (1)$$

where, W_t is weight of the swollen sample at time t, W_i is initial weight of the sample.

2.5. Dissolution study

Dissolution of miconazole from the hydrogel (torpedo-shaped; 10×30 mm) was monitored using a Vankel dissolution apparatus (Vankel Industries, Edison, NJ). Deionized water (1000 ml) was used as the dissolution media and the

Table 1
Best fit parameters, k and n, based on equation $M_t/M_\infty = kt^n$, Using Marquardt–Levenberg algorithm

No. of freeze–thaw cycles	Formulations		Kinetic constant k (SE)	Diffusional exponent n (SE)
	PEG 1000 (%)	PEG 1450 (%)		
Two	–	–	5.4 (0.45)[a]	0.4 (0.02)
Four	–	–	6.1 (0.60)	0.4 (0.02)
Six	–	–	5.5 (0.33)	0.4 (0.02)
Eight	–	–	5.5 (0.34)	0.4 (0.02)
Four	1	–	5.3 (0.03)	0.5 (0.02)
Four	2	–	5.3 (0.23)	0.5 (0.01)
Four	3	–	5.1 (0.20)	0.5 (0.01)
Four	–	0.1	6.3 (0.33)	0.4 (0.01)
Four	–	0.3	5.9 (0.37)	0.5 (0.02)
Four	–	0.5	6.8 (0.40)	0.5 (0.01)
Four	–	1.0	7.7 (0.45)	0.4 (0.02)

[a] $n = 6$.

temperature was maintained at 37 ± 1°C. The USP II, rotating paddle dissolution method was used at a rotation speed of 50 rev./min. One-milliliter samples were collected at scheduled times by means of a filter pipette. Fresh double distilled water was added to the dissolution vessels (1 ml) to maintain sink conditions. Dissolution studies were performed independently for six samples from each batch.

At the end of the dissolution study, each sample was removed from the dissolution vessel and excess water from the surface was dried with a filter paper. Each sample was heated in a beaker (immersed in a water bath) at 60°C for 30 min. The un-cross-linked PVA solution was diluted with deionized water to measure the amount of miconazole present at the end of the dissolution study.

2.6. Analysis

The amount of miconazole dissolved at any time was determined by measuring the absorbance at 223 nm in a spectrophotometer (Beckman DU 640). The calculation for the amount of miconazole in the test samples was performed by intrapolation from a calibration curve. The calibration curve was prepared from a series of standard solution ranges from 1 to 50 μg/ml. All measurements were corrected for impurities resulting from the PVA and PEG.

2.7. Curve fitting

Curve fitting was performed using SigmaPlot graphic software package version (WIN 1.02) (Jandel Co., USA). The dissolution data obtained up to 108 h were fitted to Eq. (2) and the best-fit parameters (k and n) were calculated based on the Marquardt–Levenberg algorithm.

$$M_t/M_\infty = kt^n \quad (2)$$

where M_t/M_∞ is the fraction of drug released at time t, k is the kinetic constant of the system, and n is the exponent characteristic of the mode of transport.

2.8. Statistical analysis

The different formulations were evaluated by comparing the mean ($n = 6$) equilibrium swelling, mean ($n = 6$) time to reach equilibrium swelling and the mean ($n = 6$) release of miconazole at a specific time. A comparison between two formulations was performed by using a t-test. A comparison among three or more formulations was performed by one-way analysis of variance (ANOVA) followed by Student–Newman–Keul's multiple range test in the presence of a significant difference. The data analysis was performed using SAS software package. A P value of less than 0.05 was considered as evidence of a significant difference.

3. Results and discussion

The average weight of each sample was 1.5 (±0.1) g. The total amount of miconazole present in each sample was calculated by adding the cumulative amount of miconazole released at the end of the dissolution study with the residual amount present in each sample. The total amount of miconazole present in each sample was between 72.5 and 78.6 mg.

3.1. Effect of the number of freeze–thaw cycles

Effect of the number of freeze–thaw cycles was studied at four levels (two, four, six, and eight cycles). Fig. 1 shows the effect of the number of freeze–thaw cycles on the equilibrium swelling of the hydrogel. The initial swelling of the hydrogels at 15 min was not significantly different ($P > 0.05$). However, the batches that had undergone six and eight cycles showed consistently lower equilibrium swelling (19.1 and 21.8%, respectively) compared with the batch that had undergone four cycles (31.7%). The equilibrium swelling (23.7%) of the hydrogel that had undergone two cycles was significantly ($P < 0.05$) lower than the batch after four cycles, but not significantly different from the batches after six and eight cycles. This observation was different from the results reported by Hassan and Peppas [25]. Hassan and Peppas have reported that volume swelling ratio of hydrogel consistently decreases with the number of cycles. According to this observation our hydrogel that had underwent two cycles should have the maximum equilibrium swelling. This difference in observation was may be due to the partial dissolution of PVA in the hydrogel. Hassan and Peppas have also reported similar finding where PVA samples having undergone three cycles showed significantly higher dissolution compared with the samples

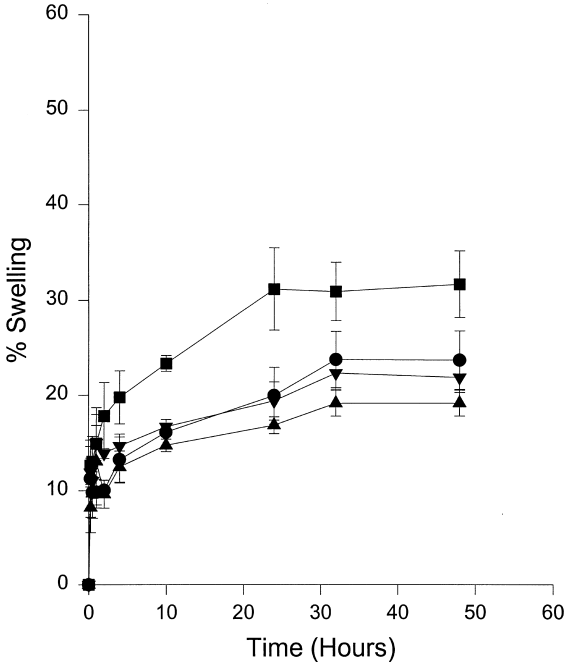

Fig. 1. Swelling kinetic study: effect of the number of freeze–thaw cycles. Two cycles (●); four cycles (■); six cycles (▲); eight cycles (▼).

after five, seven and ten cycles. The initial swelling of the batch after two cycles was 11.2% but the value decreases to 9.8% during the next 45 min. This decrease in value was may be due to a partial dissolution of PVA. In general, the results from this study showed that an increase in the number of freeze–thaw cycles reduces the equilibrium swelling of PVA hydrogel. This reduction in equilibrium swelling was due to an increase in the degree of crystallinity of the hydrogel.

Fig. 2 shows the effect of the number of freeze–thaw cycles on the dissolution of miconazole from the hydrogels. There was no significant ($P > 0.05$) difference in the cumulative percent release from one batch to the other. The mean amount of miconazole released from all four batches at 1 h was between 3.5 and 4.0%. The mean amount of miconazole released at the end of 3 days was between 29.4 and 34.2%. Drug release continued beyond 3 days. In general, the number of freeze–thaw cycles did not have any significant effect on the release of miconazole from the hydrogel. Fig. 3 shows effect of freeze–thaw cycles on the release rate of miconazole. There was no significant difference in release rate of miconazole from one batch to the other. The release rate varied from 3.5 to 3.9% per hour during the initial 30 min. The release rate declined by 50% within 3 h and continued doing so, eventually reaching 0.1–0.3% at the end of 3 days. The dissolution data obtained up to 108 h were fitted to Eq. (2) and the best-fit parameters (k and n) were calculated based on a Marquardt–Levenberg algorithm. The values of k and n are listed in Table 1. A comparison of the kinetic constant k indicates that there was no significant difference among these four formulations, although the value of k varies between 5.4 and 6.1. The value of n indicates the drug release mechanism. The value of n is 0.5 for Fickian diffusion and 1 for case II diffusion. A value of n greater than 0.5 but less than 1 indicates a non-Fickian or anomalous diffusion, which is a

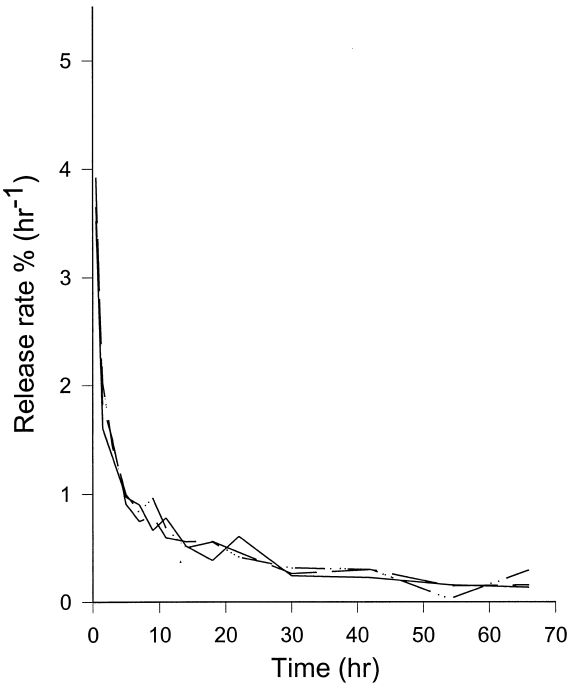

Fig. 3. Miconazole release rate versus time: effect of the number of freeze–thaw cycles. Two cycles (—); four cycles (···); six cycles (–···–); eight cycles (– –).

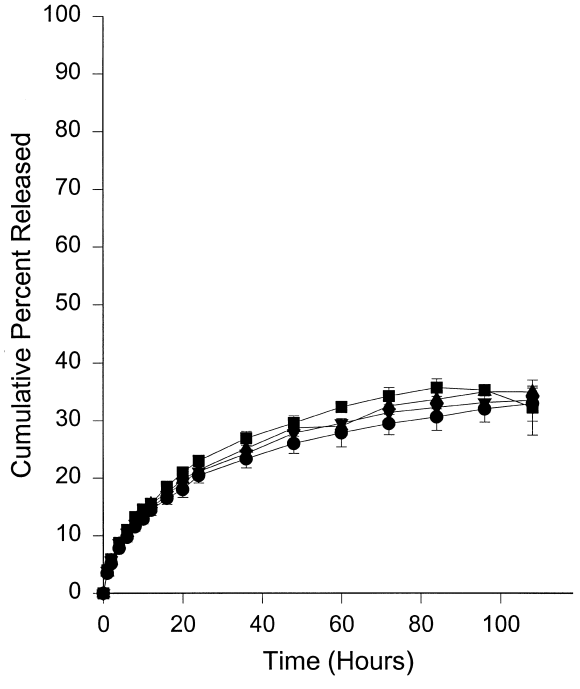

Fig. 2. Dissolution of miconazole: effect of the number of freeze–thaw cycles. Two cycles (●); four cycles (■); six cycles (▲); eight cycles (▼).

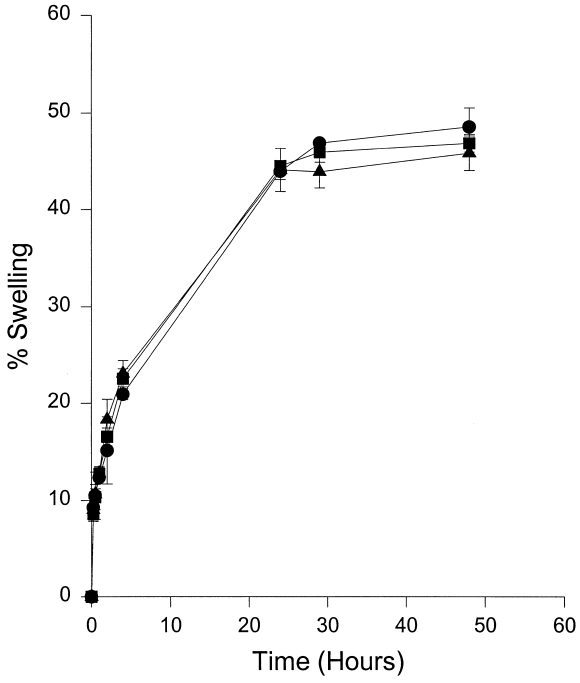

Fig. 4. Swelling kinetic study: effect of PEG 1000. 1% (●); 2% (■); 3% (▲).

mixture of Fickian and case II diffusion. When n is greater than 1 the drug release occurs through the super case II diffusion [26,27]. A comparison of the value of n in Table 1 indicates the predominance of a Fickian diffusion mechanism of release from all four hydrogels. In other words, the number of freeze–thaw cycles did not change the mode of transport of the drug.

3.2. Effect of PEG

PEG is a commonly used hydrophilic base for suppository. Two different PEG, PEG 1000 and PEG 1450, were used for these studies. Three different concentrations (1, 2, and 3%) of PEG 1000 and four different concentrations (0.1, 0.3, 0.5, and 1%) of PEG 1450 were used for these studies (Table 1). The maximum concentration for PEG 1450 was 1% because the hydrogels prepared with higher concentrations of this PEG were very viscous and difficult to pour in a suppository mold.

Fig. 4 shows the effect of PEG 1000 on the equilibrium swelling of the hydrogels. The initial swelling at 15 min of all three hydrogels varied between 8.7 and 9.3%. The equilibrium swelling of the hydrogels at 24 h varied between 44.0 and 46.7%. A comparison of these hydrogels was performed using initial swelling at 15 min and equilibrium swelling as the comparison parameters. There were no significant differences ($P > 0.05$) among all three hydrogels. Fig. 5 shows the effect of PEG 1450 on the equilibrium swelling of the hydrogels. The initial swelling at 15 min of all four hydrogels were significantly higher ($P < 0.05$) than the hydrogels prepared with PEG 1000. Within this group of four hydrogels, the one prepared with higher amount of PEG 1450 showed higher initial swelling than the one prepared with a lower amount of PEG 1450. The initial swelling varied between 10.2 and 18.8%. The equilibrium swelling of these four hydrogels at 24 h varied between 35.6 and 50.5%. There was no significant difference in equilibrium swelling between the hydrogels prepared with 0.1 and 0.3% PEG 1450. The difference in equilibrium swelling between the hydrogel prepared with 0.5 and 1.0% was also not statistically significant ($P > 0.05$). However, in general, an increase in the amount of PEG 1450 also increases the value of equilibrium swelling.

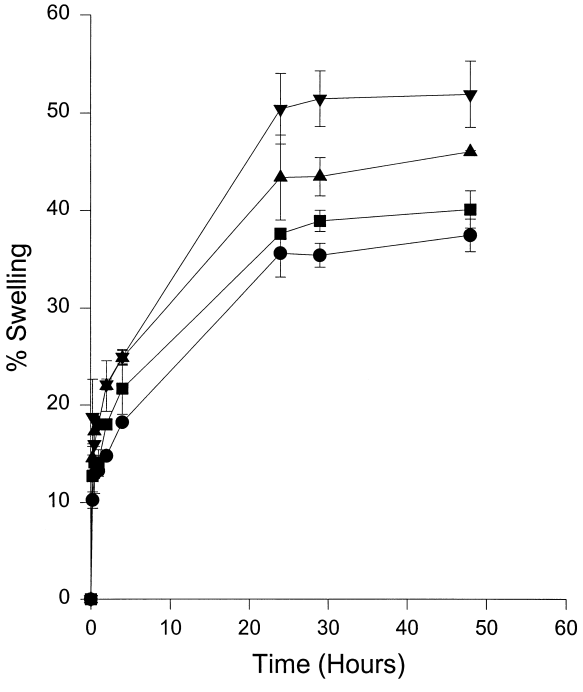

Fig. 5. Swelling kinetic study: effect of PEG 1450. 0.1% (●); 0.3% (■); 0.5% (▲); 1.0% (▼).

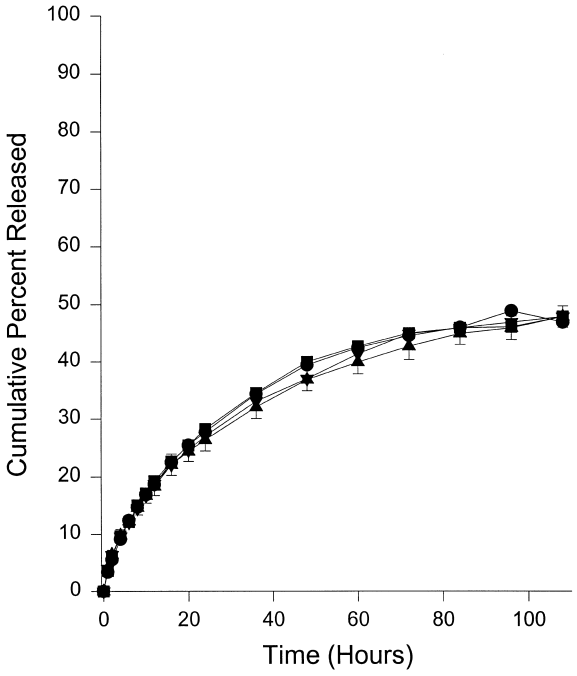

Fig. 6. Dissolution of miconazole: effect of PEG 1000. 1% (●); 2% (■); 3% (▲).

Fig. 6 shows the dissolution profiles of three hydrogels prepared with 1, 2, and 3% PEG 1000, respectively. There was no significant ($P > 0.05$) difference in the cumulative percent of miconazole released from one batch to the other. The mean amount of miconazole released from all three batches at 1 h was between 3.6 and 4.0%. The mean amount of miconazole released from all three batches at 3 days was between 42.6 and 44.9%. Fig. 7 shows the effect of PEG 1000 on the release rate of miconazole from the hydrogels. The initial release rate at 30 min varied between 3.6 and 4.0% per hour. The release rate decreased significantly with time, at the end of 3 h the release rate from all three batches was reduced by more than 50%. The release rate at the end of 3 days was between 0.2 and 0.3% per hour. In general, the presence of PEG 1000 in the hydrogels did not change the dissolution of miconazole or release rate of miconazole. Fig. 8 shows the effect of PEG 1450 on the dissolution profiles of the hydrogels. There was no significant difference ($P > 0.05$) in micona-

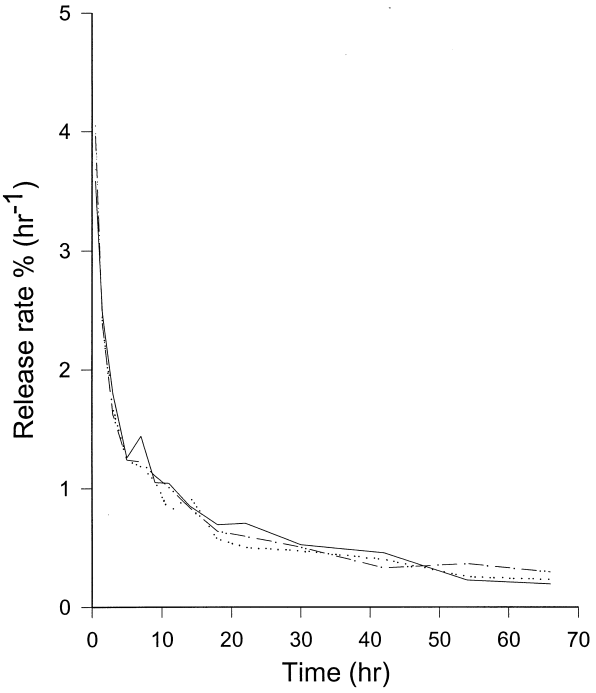

Fig. 7. Miconazole release rate versus time: effect of PEG 1000. 1% (–); 2% (···); 3% (–···–).

zole release at 1 h among all four hydrogels prepared with PEG 1450. The drug release varied between 3.9 and 5.1%. The cumulative percent miconazole released at the end of 3 days from the two hydrogels prepared with 0.1 and 0.3% PEG 1450 were significantly lower ($P < 0.05$) than miconazole released from the other two hydrogels prepared with 0.5 and 1% PEG 1450. The cumulative percent of miconazole released from the first two batches were 41.7 and 42.5%, respectively, whereas the cumulative percent of miconazole released from the two later batches were 51.6 and 50.4%, respectively. The presence of a higher amount of PEG 1450 increased the dissolution of miconazole up to 51%. Fig. 9 shows the effect of PEG 1450 on the release rate of miconazole with time. The initial release rate at 30 min from the hydrogels prepared with 0.1, 0.3, 0.5, and 1% PEG 1450 were 4.4, 3.9, 4.6 and 5.1% per hour, respectively. The release rate from all four hydrogels, at the end of 3 days, decreased significantly, reaching the values between 0.2 and 0.3% per hour. In general, the presence of 0.5 and 1.0% PEG 1450 increased the released rate slightly. Table 1 listed the best-fit parameters, k and n for the hydrogels. There was no apparent change when the value of k from all three hydrogels prepared with PEG 1000 were compared. However, the value of k increased slightly due to the presence of PEG 1450 in the hydrogels. This trend was more significant when the amount of PEG 1450 increased up to 1.0%. A comparison of the value of n indicates that there was no significant difference in diffusional exponent among the hydrogels prepared with PEG 1000 and PEG 1450.The value of n indicates the predominance of a Fickian diffusion mechanism of release from the hydrogels prepared with PEG. In other words, the presence of PEG did not change the mode of transport of the drug.

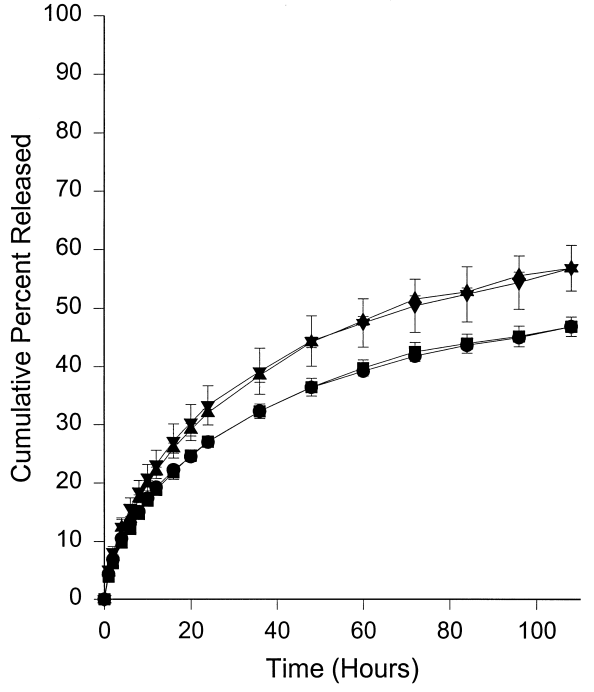

Fig. 8. Dissolution of miconazole: effect of PEG 1450. 0.1% (●); 0.3% (■); 0.5% (▲); 1.0% (▼).

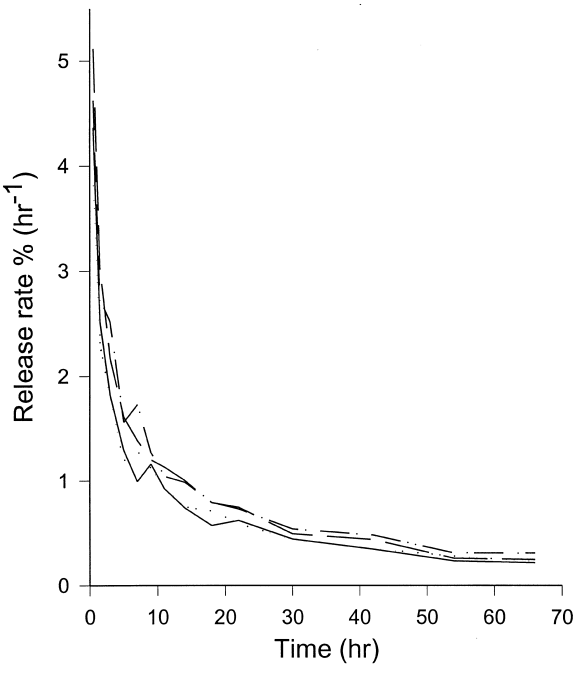

Fig. 9. Miconazole release rate versus time: effect of PEG 1450. 0.1% (–); 0.3% (···); 0.5% (–···–); 1.0% (–– ––).

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