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Diffusion studies of methotrexate in Carbopol and Poloxamer gels

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Abstract

The diffusion properties of methotrexate (MTX) in two hydrogels, Carbopol 934 (Carbopol) and Poloxamer 407 (PF-127), were compared with those in PEG 1500 and white petrolatum ointments in order to evaluate various factors governing the diffusion of MTX in different semisolid vehicles. A new membraneless method, which employed an MTX gel as the donor phase, was used for the measurement of the diffusivity of MTX in the vehicles. The flux of MTX in the hydrogels was at least 20-fold faster than those found in the ointments. The diffusion coefficients (D) of MTX were 3.58 (± 0.31) $\times 10^{-6}$ cm^2/s in the 2% Carbopol gel and 1.03 (± 0.01) $\times 10^{-6}$ cm^2/s in the 25% PF-127 gel at 34°C, despite similar bulk viscosities of the two gels. The activation energies for the diffusion of MTX in the Carbopol and PF-127 gels were 6.13 kcal/mol and 5.56 kcal/mol respectively, which were in the same order of magnitude as the diffusion of the small molecules in water, indicating that microviscosity rather than bulk viscosity of the gel was primarily responsible for the diffusion of MTX in the gels. D values of MTX in the PF-127 gel were significantly accelerated at higher temperatures, despite increased bulk viscosity of the gels due to the reverse thermal gelation property of PF-127. The diffusivity of MTX was the inverse function of polymer concentration, over the range of 20–30% of PF-127 and 1–3% of Carbopol at 34°C. Significant effects of pH and drug concentration on the diffusivity of MTX in the Carbopol gels were observed, while no such effects were found in the PF-127 gels. © 1998 Elsevier Science B.V.

Keywords: Methotrexate; Diffusion; Poloxamer 407; Carbopol 934; Gel

1. Introduction

Methotrexate (MTX) has been used in the management of psoriasis for decades and various dosage forms, such as ointments, creams and gels, were investigated to improve the therapeutic effi-

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cacy of the drug after topical administration (Rees et al., 1967; Weinstein et al., 1989; Hwang et al., 1995). Since MTX is an acidic compound (pK_{a_1} = 3.76, pK_{a_2} = 4.83 and pK_{a_3} = 5.32) with low solubility in lipophilic bases, hydrogels may be an excellent vehicle for topical delivery of this drug. Among various hydrogel bases, Carbopol and Poloxamer 407 (PF-127) are commonly used in cosmetic and pharmaceutical products because of their high stability, compatibility and low toxicity. Carbopol 934 is a hydrophilic polyacrylic acid polymer and its carboxyl groups become highly ionized after neutralization, forming a gel due to electrostatic repulsion among charged polymer chains (Goodrich, 1995; Flory et al., 1953; French et al., 1995). Unlike Carbopol, PF-127 is a surface-active polyoxyethylene–polyoxypropylene–polyoxyethylene block copolymer, which forms two distinct amphiphilic regions after hydration. The polar regions are strongly compatible with water, while the other portion forms a hydrophobic cluster (Chen-Chow and Frank, 1981). The partition of drugs between these two segments of the polymer network is known to influence the diffusion and release of drugs from PF-127 gels (Chen-Chow and Frank, 1981; Suh and Jun, 1996).

For the development of effective topical formulations, it is important to determine the diffusion properties of drugs in the semisolid vehicles, especially when the release of drugs at the application site is likely to be rate-limited by the diffusion of drugs in those vehicles. A review of the literature indicated that little is known about the relationship between the retention and release of drugs in the vehicle and their therapeutic efficacy after topical administration. Although most topical formulations consist of rather simple components, the ability of a vehicle to release drugs at the local site is limited by numerous factors such as drug-vehicle, drug-skin and vehicle-skin interactions (Katz and Poulsen, 1971). The diffusion coefficient of drugs is one of the essential parameters governing drug transport and has often been measured as the important indicator for drug release and retention in various topical preparations. In this paper, the diffusivity of MTX in the four different semisolid vehicles was measured by a modified membraneless method, in which a 25% PF-127 gel containing saturated MTX was used as the donor phase. In addition, the effects of temperature, pH, drug concentration and polymer content on the diffusion properties of MTX in the Carbopol and PF-127 gels were investigated in order to develop an effective semisolid topical formulation of MTX for the treatment of psoriasis.

2. Experimental

2.1. Materials

Carbopol 934 NF (Goodrich, Cleveland, OH) and Poloxamer 407 (BASF, Parsippany, NJ) were used as received. MTX was obtained from American Cyanamid (Pearl River, NY). Other chemicals were purchased from commercial sources. Water was distilled and treated with a Millipore purification system (Continental Water Systems, El Paso, TX).

2.2. Preparation of gels

Carbopol gels (1, 2 and 3% w/w) were prepared using the previously reported method (Barry and Meyer, 1979). An appropriate amount of Carbopol powder was slowly added into water under constant stirring with a glass rod. After the mixture had been kept at ambient temperature for 24 h, a small amount of 0.5% (w/w) triethanolamine was added and well mixed until the gel was formed. A few drops of 2 M sodium hydroxide or 2 M phosphoric acid were added to adjust the pH of the gels between pH 5 and 7. The gels were left overnight at ambient temperature and the final pH values were 5.1, 6.0 and 7.1.

PF-127 gels (20, 25 and 30% w/w) were prepared using the method described by Schmolka (Schmolka, 1972). A weighed amount of PF-127 powder was mixed into cold water under agitation with a glass rod. The mixture was stored at 4°C for 24 h and became a clear liquid. The desired pH value of the gel was achieved by adding a small volume of 2 M sodium hydroxide or 2 M phosphoric acid solution to the cold PF-127 solu-

tion. The gel was formed when the PF-127 solution was left at room temperature for over 30 min. The donor gel containing MTX (3 or 0.05% w/w) was prepared by thoroughly mixing a known amount of MTX into a 25% PF-127 liquid in an ice-water bath and leaving the solution at room temperature until a gel was formed. The donor gel pH was adjusted to be the same as that of the receptor gel.

2.3. Measurement of diffusion coefficient

In order to establish the validity of the MTX gel as the donor phase in the membraneless method, the diffusion coefficients (D) of MTX in the Carbopol gel were measured using both an MTX gel and an MTX solution as the donor phase.

Donor phase as a gel: 3-ml empty plastic syringes with the top removed were filled with approximately 2 g of the Carbopol gels (1, 2 and 3% w/w) from the open ends, with the plungers in the pulled-out position. After filling the empty syringes with liquid PF-127 (20, 25 and 30% w/w), the syringes were covered with parafilm and kept in the open-end up position at room temperature overnight to form a semi-solid gel. Approximately 3 g of the MTX donor gel in PF-127 (3 or 0.05% w/w) was placed in a glass test tube which had a slightly wider diameter than that of the syringe. After covering the blank gel surface with a piece of filter paper (Whatman Qualitative Filter Paper), the syringe containing the blank gel (2 g) was inserted into the test tube, so that the donor and blank gel surfaces were contacting each other with the filter paper serving as a barrier.

After incubating the syringe sets for 24 h in an oven at the experimental temperature (23, 34 or 45°C), the receptor phase in the syringe was separated from the donor phase. The gel in the syringe was slowly pushed out with the plunger so that approximately 0.1 ml of the gel could be obtained from each push. A total of 14 slices of uniform thickness (1.7 mm) were sequentially cut, removed and weighed. Each gel slice was completely dissolved in 5 ml of pH 7 phosphate buffer (0.01 M) with vortexing and MTX concentration in each sample was quantitated by a spectrophotometric method at the wavelength of 300 nm. The diffusion coefficients of MTX in white petrolatum and PEG 1500 ointments were similarly determined following the procedures as described for the gels.

The D value of MTX in each slice of the vehicle was calculated independently, using Eq. (1) (Upadrashta et al., 1993; French et al., 1995):

$$\frac{C_i}{C_0} = 1 - erf\left(\frac{x_i}{2\sqrt{D_i t}}\right) \quad (1)$$

where C_i and C_0 are the concentrations of MTX in the individual slice and the donor–receptor interface respectively, x_i is the distance from the gel surface to the center of each slice and t is the diffusion time. C_0 could be regarded as the solubility of the drug in the receptor gel, but is not directly measurable in this system. Therefore, for the initial calculation of D_i, C_i in the first slice was assumed to be C_0. The 'true' C_0 at $x = 0$ was estimated from the diffusion profile by extrapolating to the donor-receptor interface using the mean of the calculated D_i values and Eq. (1). The 'true C_0' was then used for more accurate calculation of D_i. Finally, the D value of MTX in the vehicle was obtained as the mean of recalculated D_i values obtained for each slice. This method was previously employed to determine the diffusivity of various compounds in semisolid vehicles (French et al., 1995; Upadrashta et al., 1993; Sjoberg et al., 1996).

The diffusion mechanism of MTX in the gel was evaluated using Eq. (2):

$$\ln\left(\frac{\sqrt{\pi d}\sum C_i}{2C_0\sqrt{D}}\right) = n \ln t \quad (2)$$

where d is the thickness of gel slice and n is the coefficient which must be equal to 0.5 if the diffusion flux is to be of Fickian diffusion.

Donor phase as a solution: As described in previous papers (French et al., 1995; Upadrashta et al., 1993), the plastic syringe (3 ml) with the top removed and the plunger in place was filled with a blank gel (2 g) and covered with a piece of filter paper. The syringe in an open-end down position was immersed about 1 cm deep into a 100 ml

Table 1
Diffusion coefficients and n values of methotrexate in various vehicles at 34°C

Donor phase	Receptor phase	pH	D (cm^2/s) $\times 10^6$	n
Solution[a]	1% Carbopol gel	5.1	4.47 ± 0.32	0.500 ± 0.002
Gel[b]	1% Carbopol gel	5.1	4.29 ± 0.29	0.499 ± 0.001
Gel[b]	2% Carbopol gel	7.1	1.41 ± 0.23	0.499 ± 0.001
Gel[b]	25% PF-127 gel	5.1	1.03 ± 0.01	0.499 ± 0.005
Gel[b]	25% PF-127 gel	7.1	1.13 ± 0.13	0.502 ± 0.001

[a] Saturated MTX solution.
[b] 3% MTX in 25% PF-127 gel.

saturated aqueous solution of MTX in a 200 ml beaker which was stirred with a magnetic bar. The pH of the solution was the same as that of the blank gel. The remaining procedures for the calculation of D have been described in the previous section.

All of the diffusion experiments were triplicated and data were presented as the mean $\pm$ S.D. Statistical significance ($p < 0.05$) was determined using the Student's t-test.

3. Results and discussion

3.1. Measurement of diffusion coefficient

The release of drugs from semisolid vehicles on the skin primarily depends upon two major factors: diffusivity and thermodynamic activity of drugs in the vehicle. In the literature, various membrane and membraneless diffusion methods have been reported for the determination of diffusivity of drugs in semisolid matrices. Due to some inherent limitations of the membrane method, such as the effect of the membrane on diffusion of drugs, the membraneless method, in which the receptor phase is directly contacted with an immiscible donor liquid, has been employed (Chen-Chow and Frank, 1981; Park and Van Houng, 1979; Poulsen et al., 1968). The diffusion coefficient of drugs has also been measured using the membraneless method, in which a syringe is filled with a blank gel which acts as a receptor phase and is vertically positioned into a saturated solution of the diffusant as a donor phase (Upadrashta et al., 1993; Schantz and Lauffer, 1962). Using this method, a recent study determined the diffusion coefficient of benzoic acid in Carbopol gels (French et al., 1995). However, the use of an aqueous solution as the donor phase was not completely satisfactory for the measurement of diffusivity of MTX in PF-127 gels because of high miscibility of the gels in the donor solution. Therefore, the diffusion coefficient of MTX in the two hydrogels was determined in this study using the syringe method, in which a 3% (w/w) MTX suspension in a PF-127 gel was used as a donor phase. As shown in Table 1, the diffusivity of MTX measured in the Carbopol gel using either the saturated MTX solution ($D = 4.47 \times 10^{-6}$ cm^2/s) or the 3% MTX gel ($D = 4.29 \times 10^{-6}$ cm^2/s) as the donor phase was found to be almost identical, indicating the usefulness of the gel as a donor phase. For the accurate measurement of the D values using Eq. (1), it is important to maintain C_0 constant during the diffusion process. The use of a PF-127 gel containing an excess amount of MTX ensured the constant C_0 in the donor phase. A similar method was recently reported by Sjoberg et al. (1996).

3.2. Effect of vehicles on diffusion

The effect of different vehicles on the release and retention of drugs in the skin has been widely investigated to optimize the percutaneous absorption and duration of efficacy of drugs after topical administration (Chambin-Remoussenard et al., 1993; Hilton et al., 1994). In the present paper, white petrolatum and PEG 1500 ointments were employed as oleaginous and water soluble bases respectively, in order to compare the diffusion properties of MTX among various vehicles.

Fig. 1 shows the concentration/distance profiles of MTX in the Carbopol and PF-127 gels, as compared to those in the ointments. It was found that diffusion of MTX into the ointment bases was very slow. At the end of 24 h of diffusion, MTX was found only in the first slice (1.7 mm depth) of the petrolatum base, while diffusion of MTX had occurred through the first three slices (5.1 mm depth) of the PEG 1500 base. However, over the same period, the diffusion distances of MTX into the 25% PF-127 and 2% Carbopol gels were extended over 18 mm and 24 mm depth, respectively. Moreover, the concentrations of MTX in the first slice of the two hydrogels were at least 20-fold higher than those in the ointments. These results are strongly indicative of the significant effect of the vehicle on the diffusion and release of drugs from different semisolid vehicles, which could also possibly influence the percutaneous absorption and duration of efficacy of drugs in topical formulations. Previous papers (Weinstein et al., 1989; Hwang et al., 1995) have shown that the efficacy and duration of antipsoriatic agents largely depended on the type of vehicles used. Although oleaginous bases have been widely used as a vehicle for antipsoriatic medication, the present paper indicates that hydrogels may be the vehicle of choice for MTX in the consideration of fast drug release at the target site. Even though a thin film is formed over skin after topical application of a semisolid formulation, a substantial diffusion of drugs has to occur to reach the skin surface prior to entering the skin layers. The fast release of drugs at the receptor sites may be a desirable feature for antipsoriatic drugs to induce maximal pharmacological action without being prematurely wiped off from the applied site.

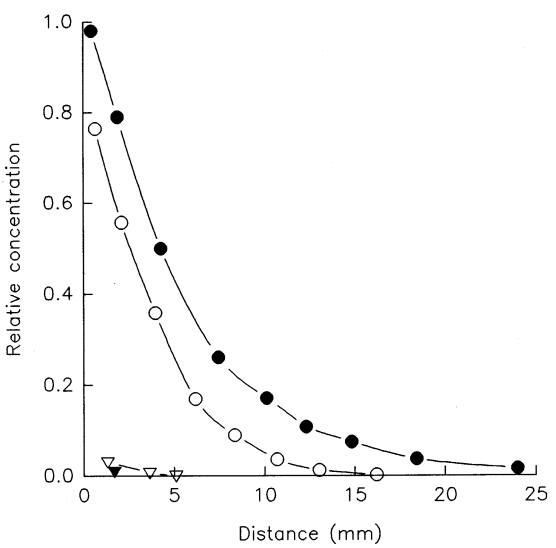

Fig. 1. Diffusion profiles of MTX in various vehicles at 34°C. (●) 2% Carbopol gel; (○) 25% PF-127 gel; (▽) PEG 1500 ointment; (▼) white petrolatum.

3.3. Effect of temperature on diffusion

The temperature of human skin is known to vary widely in response to fluctuation of external as well as internal factors and thus the release of drugs from topical vehicles on the skin could be altered accordingly. In view of the Stokes–Einstein equation ($D = kT/6\pi a\eta$), diffusion coefficient (D) is linearly related to the absolute temperature (T). In this experiment, the diffusion flux of MTX in the Carbopol and PF-127 gels was measured at three temperatures (23, 34 and 45°C) and pH 7.1. It was found that when the temperature was elevated from 23 to 45°C, the D values of MTX increased from 0.94×10^{-6} to 1.86×10^{-6} cm^2/s in the 2% Carbopol gel and from 0.82×10^{-6} to 1.56×10^{-6} cm^2/s in the 25% PF-127 gel. As previously discussed by several authors (Chen-Chow and Frank, 1981; Al-Khamis et al., 1986; Suh and Jun, 1996), microviscosity of the gel, which represents the viscosity of the entrapped aqueous phase in the polymer network, was primarily responsible for determining the diffusion of various drugs in the polymer gels. Based on the Arrhenius plot, which is a linear correlation between the logarithm of D values and reciprocal of absolute temperature as shown in Fig. 2, the activation energies (ΔE) for the diffusion of MTX were 6.13 kcal/mol in the Carbopol gel and 5.56 kcal/mol in the PF-127 gel, which are closely related to the activation energies (5 kcal/mol) reported for the diffusion of small molecules in water (Flynn et al., 1974). The similarity of the ΔE values of MTX found in the two hydrogels with those of the diffusion of other small

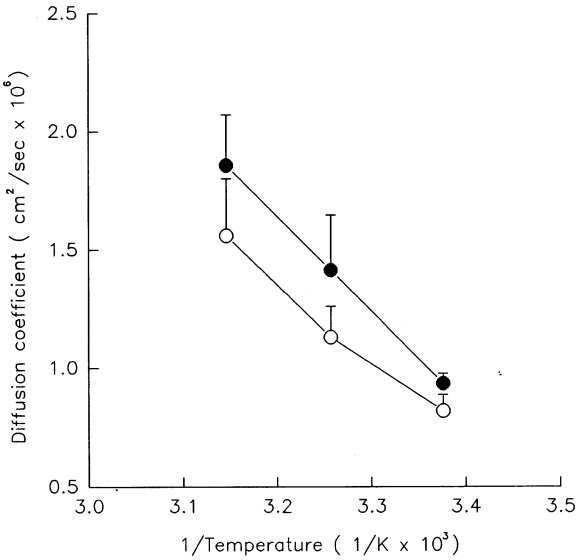

Fig. 2. Diffusion coefficient of MTX in gels as a function of the reciprocal of absolute temperature. (●) 2% Carbopol gel; (○) 25% PF-127 gel.

molecules in water, were strongly indicative of the important role of microviscosity in the diffusion of MTX. A slightly higher ΔE in the Carbopol gel than that in the PF-127 gel could be attributed to the effect of electrostatic interaction between MTX and Carbopol at pH 7.1.

Bulk viscosities of the gels were measured at the three temperatures as shown in Table 2. As expected, the viscosity of the Carbopol gels decreased at higher temperatures. However, a significant increase of the viscosity of the PF-127 gel from 39 600 to 53 000 cps was observed between 23°C and 45°C due to the reverse thermal gelation property of PF-127. Despite the net increase of bulk viscosity over this temperature range, the D values of MTX were also increased two-fold. This apparent deviation of the effect of bulk viscosity of the PF-127 gel on the D values of MTX at higher temperatures also suggested that factors other than bulk viscosity of the gel were involved in controlling the diffusion of MTX in the gels. It was shown that microviscosity of several Carbopol gels measured by the dynamic light-scattering method was considerably lower than their bulk viscosity (Al-Khamis et al., 1986). According to this paper, microviscosity of the 1% Carbopol 940 gel at pH 7.2 was 20.58 cps, while bulk viscosity of a Carbopol gel at pH 7 found in another paper (Goodrich, 1995) was nearly 75 000 cps. Chen-Chow and Frank (1981), after finding higher D values of lidocaine in more viscous PF-127 gels at elevated temperatures, proposed that diffusivity of lidocaine in these gels was largely dependent on microviscosity of the aqueous channels in the gel matrix. The lack of correlation between bulk viscosity of the gels and the diffusion coefficients of ketoprofen (Chi and Jun, 1991) and naproxen (Suh and Jun, 1996) in the PF-127 gels was also found. The present paper further supports the important role of microviscosity of the gel in determining diffusivity of small organic molecules in hydrophilic gels.

Table 2
Temperature effect on the viscosity[a] of Carbopol and PF-127 gels

Gel	Viscosity (cps) $\times 10^{-3}$		
	23°C	34°C	45°C
2% Carbopol	48.2	44.8	42.5
25% PF-127	39.6	49.6	53.0

[a] Measured with Brookfield Calculating Digital Viscometer (Model DV-II) attached to a cylindrical spindle # 7 at 50 rpm.

3.4. Effect of polymer content on diffusion

It was shown in the following equation (Schantz and Lauffer, 1962) that when diffusion of drugs occurs primarily through the aqueous channels in the gels, their diffusivity is an inverse function of polymer content: $D_g = D_w/(1 + k\phi)$, where D_g and D_w are the diffusion coefficients of drugs in the gel and water respectively, ϕ is the volume fraction of the polymer and k is the adsorption constant of the diffusant per unit volume of gel. In this paper, the effects of polymer concentration in the gel on diffusion of MTX and bulk viscosity of the gels were studied at 34°C. Table 3 shows that D values of MTX linearly ($r^2 > 0.99$) decreased with increasing Carbopol concentration in the range of 1–3%, which is in close agreement with the effect of Carbopol content on diffusivity of salicylates as previously

Table 3
Diffusion Coefficients of MTX in gels of different concentrations and their viscosity at 34°C and pH 5.1

Gel (%)	$D(cm^2/s) \times 10^6$	$\eta(cps) \times 10^{-3}$
Carbopol		
1	4.29 ± 0.29	32.4
2	3.58 ± 0.31	40.5
3	3.11 ± 0.09	44.7
PF-127		
20	1.40 ± 0.08	20.1
25	1.03 ± 0.01	49.6
30	0.77 ± 0.12	74.2

shown (Al-Khamis et al., 1986). The diffusion coefficient of MTX in the PF-127 gels at 34°C also decreased linearly ($r^2 > 0.99$) as polymer concentration increased from 20 to 30%. However, the relationship among the temperature, polymer content and diffusivity of drugs would be more complicated if the polymer exhibits the reverse thermal gelatin property, as discussed in the previous section.

3.5. Effect of pH on diffusion

The pH of vehicle has been shown to be one of the major variables that could influence diffusivity of drugs in semisolid vehicles (Chen-Chow and Frank, 1981; French et al., 1995; Suh and Jun, 1996). In this paper, the effect of gel pH on diffusion of MTX was determined in the two hydrogels between pH 5.1 and 7.1, which covered the pH range of normal skin. As shown in Fig. 3, the diffusion coefficients of MTX in the 2% Carbopol gel linearly decreased from 3.58×10^{-6} cm^2/s at pH 5.1 to 1.41×10^{-6} cm^2/s at pH 7.1, indicating that diffusivity of MTX was smaller at the pH where both MTX and Carbopol were highly ionized. It was previously shown (Goodrich, 1995) that ionization of carboxyl groups in the Carbopol molecule at pH 7 resulted in uncoiling of the polymer chains and forming a rigid gel, thus affecting diffusion of drugs in the polymeric matrix. In this study, bulk viscosity of the gel was found to slightly increase from 40 500 cps at pH 5.1 to 44 800 cps at pH 7.1. Therefore, a higher D value at a lower pH was probably due to incomplete uncoiling of the polymer chains, resulting in an increased amount of free water and thus expanding the aqueous channels in the gel.

Fig. 3 shows that diffusion of MTX in the PF-127 gel was independent of the gel pH between 5.1 and 7.1. Since PF-127 is a nonionic surfactant and both ionized and unionized MTX are insoluble in lipid, the degree of ionization of MTX at different pH values may not have a significant effect on diffusivity of MTX in the gel due to minimal micellar interaction between MTX and PF-127. The previous (Chen-Chow and Frank, 1981; Chi and Jun, 1991; Suh and Jun, 1996), as well as the present data, suggested that diffusion of lipophilic drugs, such as lidocaine, indomethacin, ketoprofen and naproxen, is highly dependent upon the pH of the vehicle, while diffusion of polar compounds, such as benzocaine and MTX, is less affected by the gel pH. These findings are strongly indicative of the presence of different diffusion pathways for the ionized and unionized drug molecules in the gel.

3.6. Effect of donor phase concentration of MTX on diffusion

Since diffusivity of drugs in hydrogels could be affected by drug loading (Wood et al., 1982;

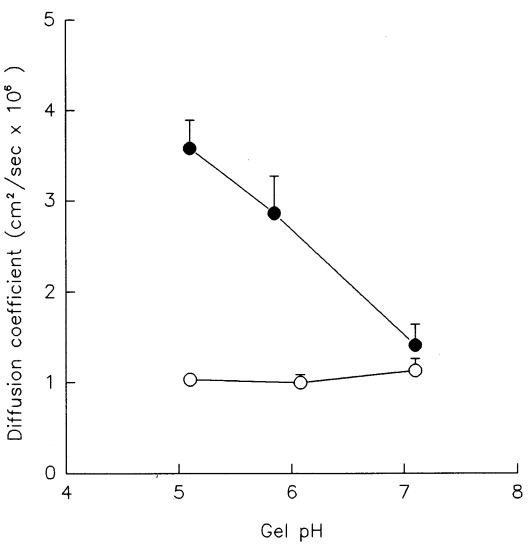

Fig. 3. Effect of pH on the diffusion coefficient of MTX in gels at 34°C. (●) 2% Carbopol gel; (○) 25% PF-127 gel.

Table 4
Effect of drug concentration in donor vehicle on the diffusion of MTX in gels at 34°C

	MTX Concentration (%)	D (cm^2/s) $\times 10^6$	
		pH 5.1	pH 7.1
2% Carbopol gel	0.05	1.46 ± 0.21	0.99 ± 0.15
	3.0	3.58 ± 0.31	1.41 ± 0.23
25% PF-127	0.05	1.04 ± 0.15	0.96 ± 0.18
	3.0	1.03 ± 0.01	1.13 ± 0.13

Al-Khamis et al., 1986), the effect of MTX concentrations in the donor gel on the diffusivity of MTX was investigated. As shown in Table 4, the diffusion coefficient of MTX in the 2% Carbopol gel was significantly increased both at pH 5.1 (2.5-fold) and at pH 7.1 (1.4-fold), when the donor gel containing 3% MTX rather than 0.05% MTX was used. The greater effect of drug loading on diffusivity of MTX at pH 5.1 than at pH 7.1 could be attributed to the changes of both drug concentration and vehicle pH. The effect of drug concentration on the diffusion of MTX observed in this study was consistent with the previous data (Wood et al., 1982; Al-Khamis et al., 1986). Al-Khamis et al. (1986) found that the apparent diffusion coefficients of salicylates in the Carbopol gels increased with increasing drug concentration, which was attributed to the change in the gel structure caused by the presence of the compounds. An earlier paper by Wood et al. (1982) also showed large D values of salicylic acid in a polyHEMA gel at higher drug concentrations.

Unlike the Carbopol gels, the effect of MTX concentrations in the donor phase on the diffusivity of MTX was not observed in the PF-127 gels, as shown in Table 4. This result indicated that MTX was free to diffuse through aqueous channels in the gel, due probably to lack of interaction between the polymer and MTX at both high and low MTX concentrations in the donor phase. Gelation of PF-127 is thought to have resulted from large chain friction and entanglement among polymer molecules in aqueous media, due to an increased hydrophobic association among the dehydrated micelles (Rassing et al., 1984; Vadnere et al., 1984). Therefore, this relatively nonpolar polymeric network of the PF-127 gel has not apparently caused a significant molecular interaction with highly polar MTX that could have affected its diffusivity in the gel.

In summary, the new membraneless method using a polymeric gel as the donor phase was employed to measure the diffusion coefficients of MTX in different semisolid vehicles. The higher flux of MTX in Carbopol and PF-127 gels than in PEG 1500 and white petrolatum ointments suggested that hydrogels may be the vehicle of choice for fast release of MTX after topical application. The activation energies of MTX in both gels were close to those of the small molecular diffusion in solution, reflecting the low diffusion barrier of the gels for MTX. The diffusivity of MTX was significantly affected by vehicle pH and MTX concentrations in the Carbopol gels, but not in the PF-127 gels. The following observations supported the view that microviscosity rather than bulk viscosity of the gels was the primary factor which affected the diffusion coefficient of MTX: (1) similar activation energies were found between the diffusion of MTX in the gels and that of the small molecules in water; (2) higher D values of MTX were obtained despite increased bulk viscosity of the PF-127 gels at elevated temperatures; and (3) a small decline in D values of MTX occurred, despite a large increase in the bulk viscosity of the PF-127 gels at higher polymer concentrations.

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