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Measurement of Diffusion Coefficients of Theophylline and Aminophylline in Carrageenan Gel

Yoshiaki Kawashima,*,[a] Teruyoshi Nasu,[b] Sumio Watanabe,[b] Yasuo Miyake[b] and Hideo Takenaka[a]

Gifu College of Pharmacy,[a] 5-6-1, Mitahora-higashi, Gifu 502, Japan and Eisai Co., Ltd.,[b] Kawashima-cho, Hashima-gun, Gifu 483, Japan

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Diffusion coefficients of theophylline and aminophylline in carrageenan gels of various concentrations at 37°C were measured by means of drug sorption and permeation tests using a diffusion cell. The permeation data were analyzed by Rogers' method and a lag time method. The diffusion coefficients determined by Rogers' method coincided reasonably well with those determined by means of the drug sorption test. They were 0.54 to 0.81×10^{-5} cm²/s and 0.43 to 0.86×10^{-5} cm²/s for theophylline and aminophylline, respectively. The diffusion coefficients determined by the lag time method were larger than those determined by the other methods. The diffusion coefficient of aminophylline was slightly larger than that of theophylline at the same initial concentration, *e.g.* 5.0×10^{-3} (g/ml). Ethylenediamine might loosen the carrageenan network, thus enhancing the diffusion of the drug. The diffusion coefficient was dependent upon the carrageenan concentration in the gel. The gel thickness had a less important effect on the diffusion coefficient, although the lag time greatly depended on it.

The diffusion coefficients were also determined by means of drug release tests using the same diffusion cell. When the drug was dispersed in the gel as a solution, the diffusion coefficient agreed fairly well with that determined in the sorption test. In carrageenan with dispersed solid particles, the drug transfer rate was enhanced by hydrodynamic flow from the voids left after dissolution of the particles in the gel.

Keywords——diffusion coefficient; theophylline; aminophylline; carrageenan gel; drug sorption and permeation test; drug release test; diffusion cell

Introduction

Many controlled drug release devices have been developed to prolong drug action or to prevent adverse effects of a drug due to local overdose.[1-4] Polymeric delivery devices are most common. The measurement of the diffusion coefficient of a drug in polymeric networks in a useful way to identify a suitable polymer material for such a device and to predict the drug release behavior from the resultant device.[5]

The objective of the present study was to develop a method for determining the diffusion coefficient of drug in a hydrogel, such as a polysaccharide gel, which is expected to be suitable for use in drug delivery devices because of a lack of antigenicity in general.[6,7] In this study, the diffusion coefficients of theophylline and aminophylline in carrageenan gel were determined by means of drug sorption and permeation tests and a drug release test from the gel. The diffusion coefficients determined by the three methods were compared and the characteristics of each method were explored. The effects of gel thickness, carrageenan concentration in the gel and drug loading in the gel on the diffusion coefficients were also clarified.

Experimental

Materials used——Carrageenan (Genugel LC, Copenhagen Pectin Factory Co., Lot. 126341) was used as a model material for a polysaccharide hydrogel, since it is widely used as a stable gel material in the food industry. A preliminary test by the present authors also suggested excellent gel performance. As model drugs, theophylline (Wako Pure Chemical Industries Ltd., Lot. DPM5563) and aminophylline (Maruishi

Pharm. Co., Lot. Z46219) were used. The materials were used as received.

Preparation of Carrageenan Gel——Carrageenan (10 to 20 g) was gradually dissolved in distilled water (180 to 190 ml) uniformly at 80°C over several hours. The weight loss due to evaporation of water during the dissolution procedure was compensated for by adding distilled water warmed to 80°C. The carrageenan solution was slowly and carefully poured into a cylindrical die (internal diameter 25 mm, thickness 5, 10 or 20 mm) mounted on a flat glass plate so as to exclude bubbles. A flat glass plate was mounted on the upper side of the die and the whole assemblage was stored in a refrigerator for an hour at 5°C for gelation. The gel diameter and thickness were assumed to be 25 mm and 5, 10 or 20 mm, respectively. The die filled with the gel was stored in a desiccator saturated with water vapor at 37°C for one hour, then the die was connected with the diffusion cells as shown in Fig. 1 for drug sorption and permeation tests. Carrageenan concentration in the gel was 6, 7 or 10% (w/v).

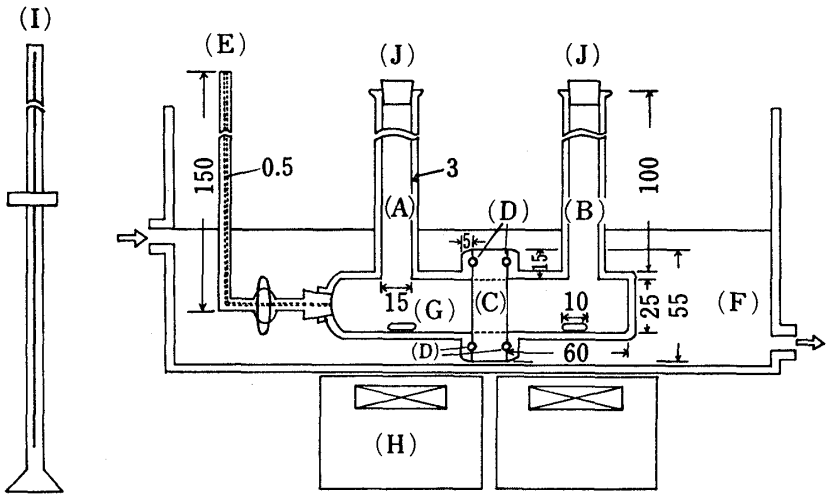

Fig. 1. Apparatus for Drug Permeation and Release Tests

Dimensions in the figure are in mm.

(A) donor cell.	(F) water bath.
(B) receptor cell.	(G) stirrer bar.
(C) stainless steel die.	(H) magnetic stirrer.
(D) O-ring.	(I) cathetometer.
(E) capillary tube.	(J) sampling tube.

Other carrageenan gels containing the drugs were prepared by dispersing the drug particles or the drug solution uniformly into 6% (w/v) carrageenan solution in a mortar warmed to 37°C. The carrageenan solution containing the drug was poured into the die (internal diameter 25 mm, thickness 10 mm), one side of which was sealed with an aluminium foil, and was gelled in the same way as mentioned above. These carrageenan gels were used for drug release tests.

Drug Sorption and Permeation Tests——The diffusion apparatus used in this study is shown in Fig. 1. The stainless steel cylindrical die (25 mm internal diameter, 5 to 20 mm thickness) filled with carrageenan gel was connected to two tubular glass cells (25 mm internal diameter) with a sampling tube. Flexible rubber O-rings were inserted between the die and the cells to prevent liquid leakage from the diffusion apparatus. One cell was equipped with an L-shaped capillary tube for monitoring changes in the level of solution in the cell during the diffusion test. The whole assemblage was placed in a water bath controlled at 37°C. The drug solution (35 ml) and distilled water (32 ml) were placed in the cell with an L-shaped capillary tube (donor cell) and in the other cell (receptor cell), respectively. The two liquids (pre-warmed at 37°C) were slowly placed in the cells alternately to keep the liquid levels in the cells nearly equal. By this procedure, the same hydrostatic pressure was applied on both sides of the gel. Two magnetic stirrers were used to agitate the liquids uniformly in the cells. Initial concentration of drug solution in the donor cell was 2.0×10^{-3} or 5.0×10^{-3} g/ml. Saturated solution and aqueous slurry of the drug were also used as donor solutions.

After the start of the diffusion test, at suitable intervals, 0.1 ml and 1.0 ml aliquots were withdrawn from the donor and the receptor cells, respectively. At the same time, the same volume of distilled water at the same temperature was added to the receptor cell to keep the solution volume constant. The volume loss of solution in the donor cell was considered to be negligible; this was confirmed by monitoring the water level in the L-shaped capillary tube. When the saturated drug solution was used as the donor solution, 0.5 ml was sampled from the donor cell and the volume loss was replaced with the saturated solution. When the donor solution was a suspension, sampling was done only from the receptor cell. Theophylline concen-

tration in the sample was determined spectrophotometrically at 270 nm in 0.1 N hydrochloric acid with a spectrophotometer (model 100-60, Hitachi Manufacturing Co.) as follows. The absorbance of carrageenan at 270 nm was calculated by multiplying the absorbance at 305 nm by the absorbance ratio at 270 to 305 nm (=1.50), since no absorbance of theophylline was observed at 305 nm. The net absorbance of theophylline was determined by subtracting the calculated absorbance of carrageenan from the overall absorbance observed at 270 nm. To examine the accuracy of the spectrophotometric analysis, a high-performance liquid chromatography (HPLC) analysis was also employed. The HPLC system consisted of a Shimadzu model LC-3A pump (Shimadzu Manufacturing Co.), a Shimadzu model SPD-2A spectrophotometric detector (Shimadzu Manufacturing Co.) operated at 254 nm and a Rheodyne model 7125 injector (Rheodyne Co.). All experiments were performed on a Nucleosil C_{18} column (10 μm, 4.6 mm i.d. × 250 mm, Machery-Nagel Co.) at ambient temperature. The eluent was 2% (v/v) acetic acid and 10% (v/v) acetonitrile in water, the flow rate was 3 ml/min and the injection volume was 80 μl. Caffeine was used as the internal standard. It was found that the two analytical methods gave essentially the same results. Therefore, spectrophotometry was adopted in the present study for convenience.

The amounts of theophylline absorbed into the gel and passed through the gel were determined by measuring the theophylline concentrations in the donor and the receptor cells.

Drug Release from the Gel——The die filled with the gel containing the drug, one side of which was sealed with aluminium foil, was connected to the diffusion cells. The carrageenan concentration in the gel was 6% (w/v) and the gel thickness was 10 mm. The drug concentration in the gel was 1.0, 2.0, 4.0, 10.0 or 20.0% (w/v). When the drug concentration was higher than 2.0% (w/v) for theophylline and 20.0% (w/v) for aminophylline, the drug existed as dispersed solid particles. Distilled water as a dissolution medium was placed in the cell facing the open side of the die containing the gel. At suitable intervals, 1.0 ml was sampled and the drug concentration was determined spectrophotometrically. At the end of the run, the whole gel was recovered and the drug remaining in the gel was determined.

Determination of Diffusion Coefficient of Theophylline in Water——Diffusion coefficients of the drugs in water at 37°C were determined by a diaphragm method.[8] The diaphragm used was made of sintered glass and the diffusion cell constant was 4.28. The diffusion coefficients of theophylline and aminophylline in water were found to be 1.14 and 0.91×10^{-5} (cm^2/s), respectively.

Theory

Drug Permeation through the Gel

In the case of diffusion of a drug through a thin film or membrane, a steady state in the film is reached after a time. The diffusion process in such a steady state is described by Fick's first law. In the present system, the steady state was hardly reached, since the gel was quite thick. In a non-steady state, the diffusion process is described by Fick's second law, represented by equation (1),

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{1}$$

Where D is the diffusion coefficient, C is the drug concentration in the gel, x is distance and t is time. Equation (1) can be solved by assuming suitable initial and boundary conditions.

Barrel[9] has obtained equation (4) by solving equation (1) under the initial and the boundary conditions represented by equations (2) and (3), respectively;

$$t = 0,\ C = C_0 \qquad 0 \leq x \leq l \tag{2}$$

$$\left.\begin{aligned} t > 0,\ C &= C_1 \quad \text{at } x = 0 \\ C &= C_2 \quad \text{at } x = l \end{aligned}\right\} \tag{3}$$

where C_1 and C_2 are constants, l is the gel thickness, and $x=0$ and $x=l$ represent the donor and the receptor faces of the gel respectively.

$$C = C_1 + (C_2 - C_1)\frac{x}{l} + \frac{2}{\pi}\sum_{n=1}^{\infty}\frac{C_2\cos n\pi - C_1}{n}\sin\frac{n\pi x}{l}\exp(-Dn^2\pi^2 t/l^2) + \frac{4C_0}{\pi}\sum_{m=0}^{\infty}\frac{1}{2m+1}\sin\frac{(2m+1)\pi x}{l}\exp\{-D(2m+1)^2\pi^2 t/l^2\} \tag{4}$$

The total amount of drug that passes through the gel into the receptor cell in time t, Q, is represented by equation (6), which is obtained by integrating the diffusion rate at $x=l$, $F_{x=l}$, with respect to t.

$$F_{x=l}=-D\left(\frac{\partial C}{\partial x}\right)_{x=l}=2C_1\sum_1^{\infty}\left(\frac{D}{\pi t}\right)^{1/2}\exp\{-(2m+1)^2l^2/(4Dt)\} \tag{5}$$

$$Q=D(C_1-C_2)\frac{t}{l}+\frac{2l}{\pi^2}\sum_1^{\infty}\frac{C_1\cos n\pi-C^2}{n^2}\cdot\{1-\exp(-Dn^2\pi^2t/l^2)\}$$
$$+\frac{4C_0l}{\pi^2}\sum_{m=0}^{\infty}\frac{1}{(2m+1)^2}\cdot\{1-\exp(-D(2m+1)^2\pi^2t/l^2)\} \tag{6}$$

When $C_0=C_2=0$, equation (6) is transformed into equation (7).

$$\frac{Q}{lC_1}=\frac{Dt}{l^2}-\frac{1}{6}-\frac{2}{\pi^2}\sum_1^{\infty}\frac{(-1)^n}{n^2}\exp(-Dn^2\pi^2t/l^2) \tag{7}$$

When a steady state is reached, equation (7) is transformed into equation (8).

$$Q=\frac{DC_1}{l}\left(t-\frac{l^2}{6D}\right) \tag{8}$$

The intercept, L, on the t-axis is the lag time for diffusion of the drug, represented by equation (9).

$$L=l^2/6D \tag{9}$$

One can determine the diffusion coefficient from the lag time obtained by extrapolating the Q *vs.* time curve at the steady state to $Q=0$.

Since the series in equation (5) converges rapidly for small t, Rogers *et al.*[10] took only the leading term and obtained equation (10).

$$\ln(t^{1/2}\cdot F)=\ln\{2C_1\left(\frac{D}{\pi}\right)^{1/2}\}-\frac{l^2}{4Dt} \tag{10}$$

A plot of $\ln(t^{1/2}\cdot F)$ *vs.* $1/t$ yields a straight line. From the slope of the straight line, the diffusion coefficient is determined.

Drug Sorption into the Gel[11]

Until a diffusing substance front in the gel reaches the receptor face of the gel, the diffusion process is assumed to be a drug sorption phenomenon by the gel. Crank has solved equation (1) under the initial and boundary conditions represented by equations (11) and (12) respectively, leading to equations (13) and (14);

$$t=0,\ C=C_0 \quad \text{at} \quad 0\leq x\leq l \tag{11}$$

$$\left.\begin{aligned} &t>0,\ C=C_1 \quad \text{at} \quad x=0\\ &\frac{\partial C}{\partial x}=0 \quad \text{at} \quad x=l \end{aligned}\right\} \tag{12}$$

$$\frac{C-C_0}{C_1-C_0}=1-\frac{4}{\pi}\sum_{n=0}^{\infty}\frac{(-1)^n}{2n+1}\exp\{-D(2n+1)^2\pi^2t/4l^2\}\cdot\cos\frac{(2n+1)\pi x}{2l} \tag{13}$$

$$\frac{M_t}{M_\infty}=1-\sum_{n=0}^{\infty}\frac{8}{(2n+1)^2\pi^2}\exp\{-D(2n+1)^2\pi^2t/4l^2\} \tag{14}$$

where M_t is the total amount of diffusing substance which has entered the gel in time t, and M_∞ is the corresponding quantity after infinite time. Equation (14) can be solved graphically for Dt/l^2 (Fig. 2). The diffusion coefficient can be obtained from the Dt/l^2 value corresponding to the measured value of M_t/M_∞ on the curve in Fig. 2.

Drug Release from the Gel

When the drug is released from one side of a gel containing uniformly dissolved drug under the sink condition, the initial and the boundary conditions for the drug diffusion in the gel are represented by equations (15) and (16), respectively,

$$t = 0,\ C = C_0 \quad \text{at} \quad 0 \leq x \leq l \tag{15}$$

$$\left.\begin{aligned} t > 0,\ C &= C_1 \quad \text{at} \quad x = 0 \\ \frac{\partial C}{\partial x} &= 0 \quad \text{at} \quad x = l \end{aligned}\right\} \tag{16}$$

where C_0 is the initial concentration of the drug in the gel and $C_1=0$. The above initial and boundary conditions coincide with the initial and boundary conditions given by equations (11) and (12). Therefore the solution to the diffusion equation (1) is given by equations (13) and (14). For small times, the equation corresponding to equation (14) is represented approximately by equation (17):[12]

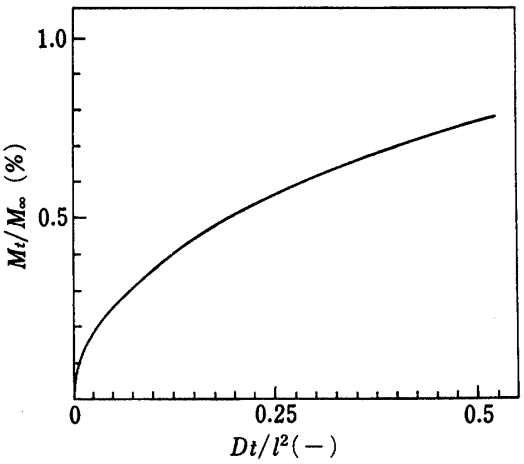

Fig. 2. Drug Sorption Curve of Drugs into the Gel from a Stirred Solution of Limited Volume

$$\frac{M_t}{M_\infty} = 2\left(\frac{Dt}{\pi l^2}\right)^{1/2} \tag{17}$$

where M_∞ is the initial drug loading in the gel. The diffusion coefficient is determined from the slope of the straight line obtained by plotting M_t/M_∞ against $t^{1/2}$.

When the drug exist as dispersed solid particles in the gel, the drug release process under the sink condition is described by the Higuchi equation (18),[13]

$$M_t = \{Dt(2M_\infty - Cs)Cs\}^{1/2} \tag{18}$$

where M_∞ is the drug loading in the gel and Cs is the drug solubility. The diffusion coefficient is also determined from the slope of the plot of M_t *vs.* $t^{1/2}$.

Results

Drug Sorption and Permeation through Carrageenan Gel

The amount of drug entering the receptor cell and the residual amount of drug in the donor cell are plotted against time as a function of carrageenan concentration in the gel in Fig. 3. As expected, the decreasing and the increasing rates of drug concentrations in the donor and the receptor cells, respectively, increased with decreasing carrageenan concentration in the gel. The lag time extended with increasing carrageenan concentration in

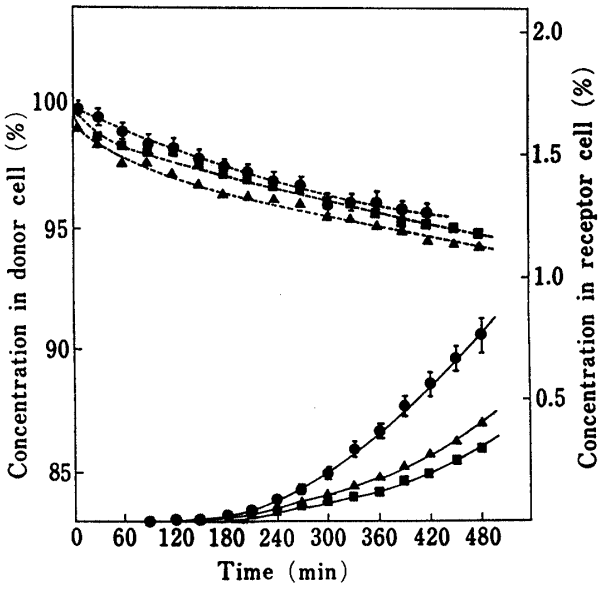

Fig. 3. Effect of Carrageenan Concentration on the Permeation of Aminophylline through the Gel

Solid and broken lines are percent of the drug permeated into the receptor cell and residual percent of the drug in the donor cell, respectively. Initial concentration of aminophylline was 5.0×10^{-3} g/ml.
Carrageenan concentrations: ●, 6% (w/v); ▲, 7%(w/v); ■, 10%(w/v).

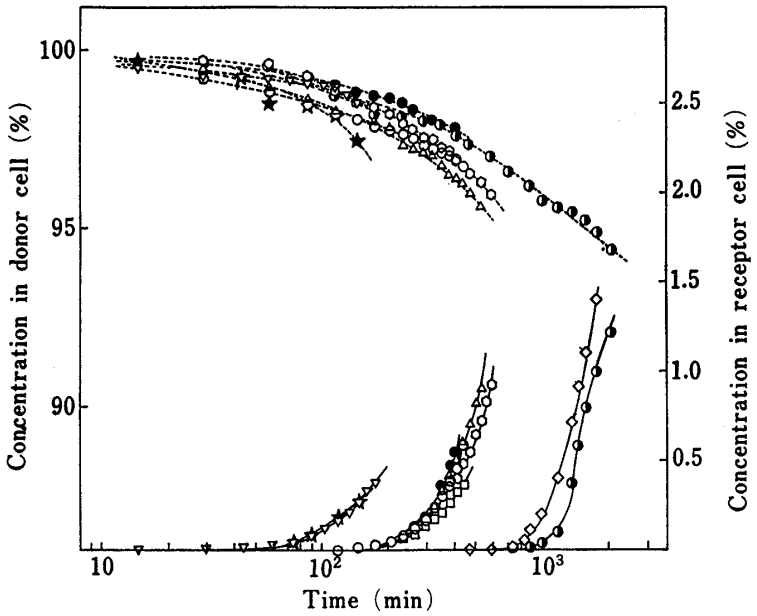

Fig. 4. Effects of Gel Thickness and Initial Drug Concentration in the Donor Cell on Drug Permeation through the Gel

Solid and broken lines are percent of the drug permeated into the receptor cell and residual percent of the drug in the donor cell, respectively. Carrageenan concentration was 6% (w/v).
Open symbols, theophylline;
Solid and semi-solid symbols, aminophylline.
★: 5.0×10^{-3} g/ml, 5 mm gel thickness.
▽: saturated solution, 5 mm gel thickness.
⬡: 2.0×10^{-3} g/ml, 10 mm gel thickness.
○, ●: 5.0×10^{-3} g/ml, 10 mm gel thickness.
△: saturated solution, 10 mm gel thickness.
□: suspension, 10 mm gel thickness.
◑: 5.0×10^{-3} g/ml, 20 mm gel thickness.
◇: suspension, 20 mm gel thickness.

TABLE I. Diffusion Coefficients of Theophylline and Aminophylline in Carrageenan Gel and Tortuosities of Carrageenan Gel

Experiment	Experimental conditions: Gel thickness (mm)	Carrageenan concentration (%(w/v))	Gel porosity (%)	Initial drug concentration (g/ml)	Theophylline: Permeation test: Lag time method[9] ($\times10^{-5}$ cm^2/s)	Theophylline: Permeation test: Rogers method[10] ($\times10^{-5}$ cm^2/s)	Theophylline: Sorption test[11] ($\times10^{-5}$ cm^2/s)	Aminophylline: Permeation test: Lag time method[9] ($\times10^{-5}$ cm^2/s)	Aminophylline: Permeation test: Rogers method[10] ($\times10^{-5}$ cm^2/s)	Aminophylline: Sorption test[11] ($\times10^{-5}$ cm^2/s)
I[a]	5	6	94.2	5.0×10^{-3}				1.1 (0.78)	0.70 (1.22)	0.61 (1.40)
	5	6	94.2	Saturated solution	1.0 (1.07)	0.54 (1.99)	0.55 (1.95)			
	5	6	94.2	Suspension	1.3 (0.83)	0.79 (1.36)				
	10	6	94.2	2.0×10^{-3}	1.2 (0.89)	0.66 (1.63)	0.71 (1.51)			
	10	6	94.2	5.0×10^{-3}	1.2 (0.89)	0.69 (1.56)	0.71 (1.51)	1.2 (0.71)	0.84 (1.02)	0.79 (1.08)
	10	6	94.2	Sasturated solution	1.2 (0.89)	0.75 (1.43)	0.74 (1.45)			
	10	6	94.2	Suspension	1.2 (0.89)	0.81 (1.33)				
	10	7	93.0	5.0×10^{-3}				1.1 (0.77)	0.68 (1.24)	0.67 (1.26)
	10	10	90.3	5.0×10^{-3}				1.0 (0.82)	0.51 (1.61)	0.43 (1.91)
	20	6	94.2	5.0×10^{-3}				0.8 (1.07)	0.86 (1.00)	0.63 (1.36)
	20	6	94.2	Sasturated solution	0.9 (1.19)	0.66 (1.63)	0.63 (1.70)			
	20	6	94.2	Suspension	0.9 (1.19)	0.77 (1.39)				
II[b]	Drug dissolved in the gel					0.79 (1.36)			0.57 (1.50)	
	Drug suspended in the gel					2.23 (0.48)			0.97 (0.88)	

a) Drug permeation test and sorption test.
b) Drug release test from the gel.
Numbers in parentheses are tortuosities.

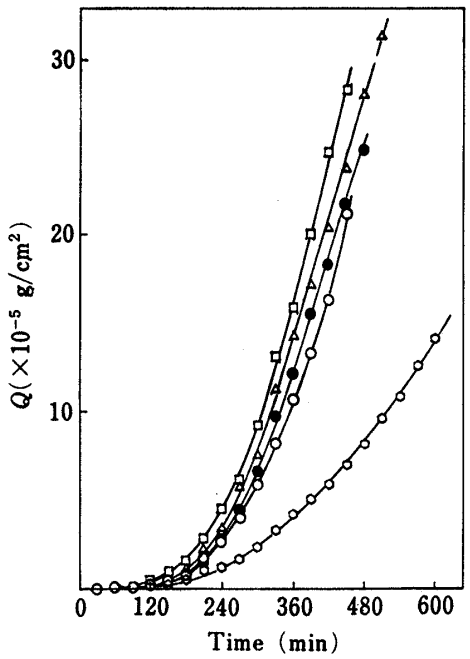

Fig. 5. Amounts of Drug Permeating through Unit Area of the Gel *vs.* Time

Carrageenan concentration and gel thickness were 6%(w/v) and 10 mm respectively.
Open symbols, theophylline;
Solid symbols, aminophylline.
○: 2.0×10^{-3} g/ml.
○, ●: 5.0×10^{-3} g/ml.
△: saturated solution.
□: suspension.

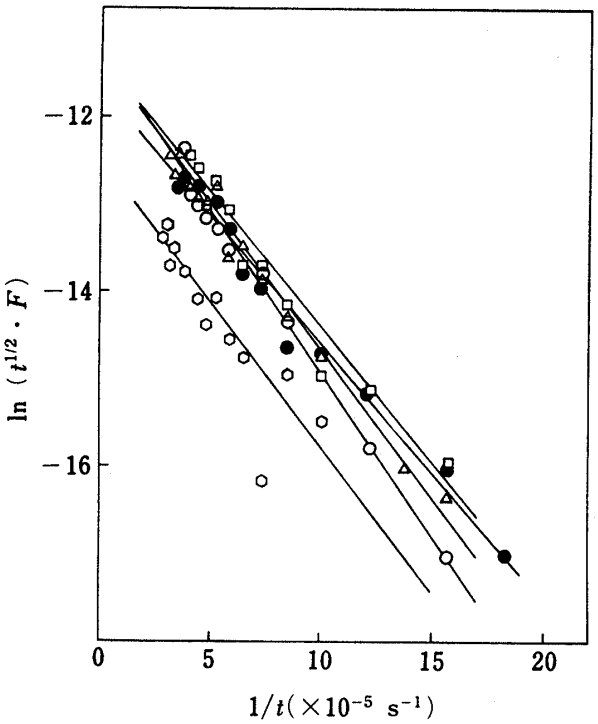

Fig. 6. Relationship between ln ($t^{1/2}\cdot F$) and $1/t$

Carrageenan concentration and gel thickness were 6% (w/v) and 10 mm, respectively.
Open symbols, theophylline;
Solid symbols, aminophylline.
Drug concentration in the donor cell:
○, 2.0×10^{-3} g/ml; ○, ●, 5.0×10^{-3} g/ml;
△, saturated solution; □, suspension.

the gel. Reproducibility of the data is represented by a standard deviation bar (n=4) for 6% (w/v) carrageenan concentration.

The effects of gel thickness on the drug permeation are shown in Fig. 4. Variation of the gel thickness was the most effective means to vary the drug release, variation of gel concentration or the initial drug concentration in the donor cell was less effective. With increasing gel thickness, the lag time extended extraordinarily and the rate of drug entry into the receptor cell decreased. Variation of the initial drug concentration in the donor cell had little effect on the drug entry into the receptor cell, as shown in Fig. 5.

According to Rogers' equation (10),[10] ln ($t^{1/2}\cdot F$) was plotted against $1/t$ as shown in Fig. 6. The drug diffusion rate (F) at the receptor face of the gel was obtained by differentiating the curve for the amount of drug passing through unit area of the graphically with respect to time A linear correlation was found between ln($t^{1/2}\cdot F$) and $1/t$ as can be seen in Fig. 6. The diffusion coefficient (D) was determined by substituting the slope of the straight line (tan α) in Fig. 6 into equation (19).

$$D = \frac{l^2}{4\tan\alpha} \tag{19}$$

The diffusion coefficient was also determined by substituting the lag time (L) obtained in Figs. 3, 4 and 5 into equation (20).

$$D = \frac{l^2}{6L} \tag{20}$$

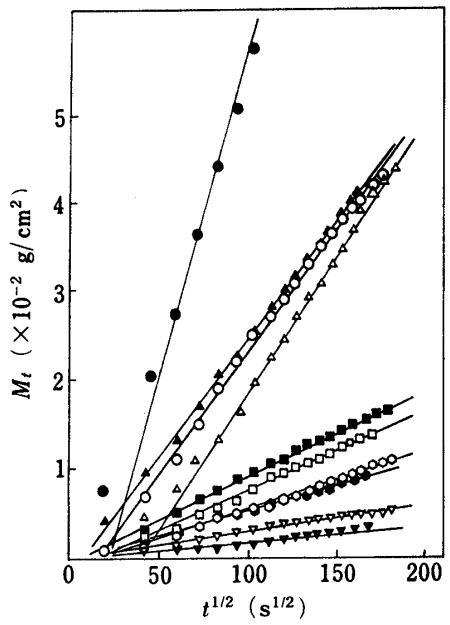

Fig. 7. Amounts of Drug released from the Gel *vs.* Time as a Function of Drug Loading

Open symbols, theophylline;
Solid symbols, aminophylline.
○, ●: 20.0% (w/v). ⬡, ⬢: 2.0% (w/v).
△, ▲: 10.0% (w/v). ▽, ▼: 1.0% (w/v).
□, ■: 4.0% (w/v).

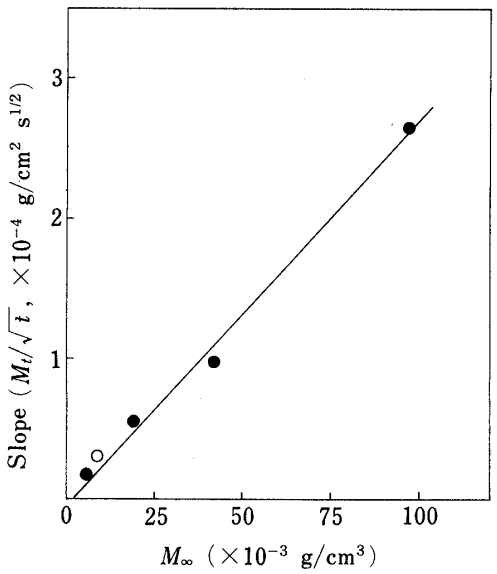

Fig. 8. Relationship between the Slope of the Straight Line ($M_t/\sqrt{t}$) in Fig. 7 and Drug Loading (M_∞)

○: theophylline, ●: aminophylline.

By substituting the experimental data, M_t/M_∞, within the lag time into the correlation curve of M_t/M_∞ *vs.* Dt/l^2. in Fig. 2, the diffusion coefficient of the drug was also determined. The diffusion coefficients determined by the above three methods are tabulated in Table I.

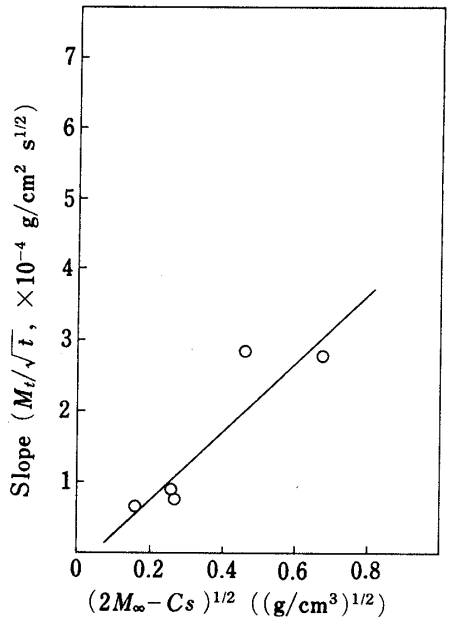

Fig. 9. Relationship between the Slope of the Straight Line ($M_t/\sqrt{t}$) and $(2M_\infty - Cs)^{1/2}$ for Gel Containing Solid Dispersed Theophylline

Drug Release from the Gel and Determination of the Diffusion Coefficient

Drug release data at the initial stage, in which the drug release was less than 20 to 30%, were employed to meet the initial and the boundary conditions represented by equations (15) and (16) for using equations (17) and (18). The amount of drug released (M_t) is plotted against the square root of time in Fig. 7. After a short induction time, all of the plots are linear, and the slope of the straight line increases with increase in the initial loading of the drug in the gel.

When the drug was dispersed in the gel as a solution, the slope of the straight line, $M_t/\sqrt{t}$ in Fig. 7, was plotted against the drug loading, M_∞, as shown in Fig. 8. For aminophylline, a straight line was obtained and the diffusion coefficient was obtained from the slope.

For the drug release from the gel containing

solid dispersed drug, $M_t/\sqrt{t}$ was plotted against $(2M_\infty - Cs)^{1/2}$ in Fig. 9. The diffusion coefficient was determined from the slope of the straight line. The diffusion coefficients determined from the drug release test are listed in Table I.

In the present experiment, the amount of drug that entered the receptor cell was less than 4% and the amount left in the donor cell was greater than 90% as shown in Figs. 3 and 4. Therefore it was assumed that the initial and boundary conditions represented by equations (2) and (3) were approximately established, *i.e.* $C_0=0$, $C_1=$ the initial concentration of drug in the donor cell and $C_2=0$. Before the drug passed through the gel, *i.e.* within the lag time, the initial and the boundary conditions represented by equations (11) and (12) were approximately established ($C_0=0$ and C_1 is the initial concentration of the drug in the donor cell). Therefore, the drug permeation and the drug sorption data in the present study were analyzed by employing the lag time equation (9), Rogers' equation (10) and the sorption equation (14) described previously.

Determination of Diffusion Coefficients of the Drugs in the Gel

The amounts of drug that permeated through unit area of the gel (Q) are plotted against time in Fig. 5. The amount of drug that entered the receptor cell in a given time was significantly affected by the initial concentration of the drug in the donor cell. With increasing initial drug concentration in the cell, the amount of drug that entered the receptor cell increased. When the drug suspension was in the donor cell, the greatest amount of drug passed through the gel. The lag time for the drug passing through the gel was almost independent of the initial drug concentration in the donor cell.

Discussion

Drug Permeation and Sorption Tests

Little change in the gel structure occurred during the drug sorption test, since the data were available immediately after starting the test. On the other hand, the data in the drug permeation test were only available after detectable amounts of drug had passed through the gel into the receptor cell. The diffusion coefficients determined by Rogers' method in the drug permeation test were in good agreement with those determined by the sorption method, although some discrepancies were apparent (Table I). This finding suggests that the structure change in the gel during the test was minor, if any. However, the diffusion coefficients determined by the lag time method deviated from those determined by the other methods as shown in Table I. This result indicated that the lag time determined in the test was shorter than the intrinsic value. In the present system, only a quasi-steady state was attained, and this may have resulted in the above deviation. Thus, it is important to ensure that the system has achieved a steady state if diffusion coefficient is to be determined by the lag time method.

The diffusion coefficients of theophylline in Table I appear to be concentration-dependent. The diffusion coefficients increased a little with increasing initial concentration of the drug in the donor cell. Interaction between theophylline and the gel is probably not responsible for the above concentration dependency, since no effect of carrageenan on the solubility of theophylline in water was found. The gel thickness was a less important factor affecting the diffusion coefficient, as shown in Table I, although the lag time greatly depended upon the gel thickness as shown in Fig. 4.

The diffusion coefficient of aminophylline in the gel at the initial drug concentration of 5.0×10^{-3} (g/ml) was found to be larger than that of theophylline, although the former was smaller than the latter in water. The gel concentration influenced the diffusion coefficient, as expected. The diffusion coefficients decreased with increasing carrageenan concentration. The pore volume filled with the solvent in the gel was measured by drying the gel, and the gel porosity was determined (Table I). The diffusion coefficient in the gel can be described

as a function of tortuosity (τ) and porosity (ε) in the gel, as in equation (21),

$$D = \frac{D^*\varepsilon}{\tau} \tag{21}$$

where D^* is the diffusion coefficient in water. The tortuosity increased with the carrageenan concentration. The tortuosity for the diffusion of aminophylline was smaller than for theophylline. It was reported that polysaccharide solution became less viscous alkaline.[14] In the present system, ethylenediamine might loosen the carrageenan networks, thus enhancing the diffusion coefficient of the drug.

Drug Release from the Gel

The diffusion coefficients determined in the drug release test (Fig. 8) agreed fairly well with those determined by means of the drug sorption test. Little concentration dependency of diffusion coefficient was found, as can be seen in Fig. 8. This might be due to the fact that the range of drug loading in the gel employed in the drug release test was rather narrow compared to those in the drug sorption and permeation tests.

The diffusion coefficient of theophylline in the gel containing dispersed drug particles (Fig. 9) was found to be larger than the others. This finding might be interpreted in terms of hydrodynamic flow from the voids left in the gel after the particels dissolved. The pressure difference between the internal void and the outer surface of the gel brought about by the agitation of the system could cause hydrodynamic flow from the void.[15] The drug is transferred by the flow as well as by the intrinsic diffusion, resulting in an increase of the apparent diffusion coefficient.

In conclusion, it appears that the simultaneous testing of drug sorption and permeation through a hydrogel is a useful method for measuring the diffusion coefficient of the drug in the gel.

References and Notes

1) V.H.L. Lee and J.R. Robinson, in "Sustained and Controlled Release Drug Delivery Systems," ed. by J.R. Robinson, Marcel Dekker Press, N.Y., 1978, Chap. 3.
2) M. Nakano, *J. Memb. Sci.*, **5**, 355 (1979).
3) J.W. McGinity, L.A. Hunke, and A.B. Combs, *J. Pharm. Sci.*, **68**, 662 (1979).
4) R. Langer, *Chem. Eng. Commun.*, **6**, 1 (1980).
5) D. Attwood, L. Johansen, J.A. Tolley, and J. Rassing, *Inter. J. Pharm.*, **9**, 285 (1981).
6) M. Nakano, K. Takikawa, and T. Arita, *Membrane*, **3**, 141 (1978).
7) M. Nakano, K. Takikawa, and T. Arita, *J. Biomed. Mater. Res.*, **13**, 811 (1979).
8) M. Nakagaki and S. Iwata, *Yakugaku Zasshi*, **82**, 1134 (1962).
9) R.M. Barrel, *Trans. Faraday Soc.*, **35**, 628 (1939).
10) W.A. Rogers, R.S. Buritz, and D. Alpert, *J. Appl. Phys.*, **25**, 868 (1954).
11) J. Crank, "The Mathematics of Diffusion," Clarendon Press, Oxford (1976), p. 47.
12) B.J. Poulsen, in "Drug Design Vol. IV," ed. by E.J. Ariens, Academic Press, N.Y., 1973, p. 158.
13) T. Higuchi, *J. Pharm. Sci.*, **50**, 10, 874 (1961).
14) A.M. Goldstein, E.N. Alter, and J.K. Seaman, in "Industrial Gum: Polysaccharides and Their Derivatives," ed. by R.L. Whistler and J.N. BeMiller, Academic Press, N.Y., 1973, p. 303.
15) J. Okada and Y. Kawashima, *Yakugaku Zasshi*, **88**, 729 (1968).