The Determination of Diffusion Coefficients in Semisolids by Fourier Transform Infrared (FT-IR) Spectroscopy

Dale Eric Wurster,[1,2] Varaporn Buraphacheep,[1,2] and Jatin M. Patel[1,3]

Received June 9, 1992; accepted September 29, 1992

A Fourier transform infrared (FT-IR) spectrometer with a horizontal attenuated total reflectance (ATR) cell was used to determine the diffusion coefficients of several liquids in two semisolid materials. The experimental setup was that of a system with one open and one closed boundary wherein the open boundary was maintained at constant concentration. While the liquid of interest was diffusing through the film of ointment, the concentration of liquid at the film surface in contact with the ATR crystal was determined at various times by means of IR absorption measurements. The depth of penetration of the IR radiation into the sample was approximately 0.6–0.9 μm at the wavelengths of analysis. Since the ointment thickness was 157 μm, it was reasonable to assume that only the penetrant reaching the lower boundary was being measured. The values of the diffusion coefficients were then calculated using an equation that appropriately modeled the aforementioned conditions. The liquids tested exhibited diffusion coefficients in anhydrous lanolin and in polyethylene glycol ointment that ranged from 0.56 to 7.2 × 10^{-7} and 0.68 to 5.7 × 10^{-7} cm^2/sec, respectively. The expected molecular weight dependency was observed.

KEY WORDS: attenuated total reflectance; diffusion coefficient; Fourier transform infrared spectrometer; semisolid.

INTRODUCTION

The transport of drugs within semisolid materials has been a subject of interest for many years. This interest has increased with the advent of topical drug delivery and controlled-release dosage forms employing polymeric gel systems. Although drug transport is frequently characterized in terms of the diffusion coefficient, the evaluation of this parameter in these systems is not trivial, and much effort has been devoted to the development of suitable techniques.

If the ointment base is composed of molecules whose size is comparable to or smaller than the drug molecule, the value for the diffusion coefficient is approximated by the Stokes–Einstein equation (1). This equation relates the diffusion coefficient to the molecular radius of the diffusant, the viscosity of the semisolid material, and the temperature of the system. However, this equation is limited to infinitely dilute solutions, and in most cases, modifications of this equation are needed to obtain reasonable estimates (2).

Lueck *et al.* (3,4) were among the first to develop a method to measure the permeability of semisolid materials. A diffusion cell having two reservoirs was used and a film of ointment supported by two rigid films was placed between the two reservoirs. A solution of penetrant was introduced into the donor reservoir, while the receptor reservoir contained an equal volume of solvent. At appropriate time intervals, samples were withdrawn and analyzed for penetrant content.

Wahlgren *et al.* (5) and Addicks *et al.* (6) employed a column which was functionally unlimited in length. The method actually employed two long columns of equal length, which could be glass cylinders or syringes. One column was filled with a gel containing the drug at a concentration of C_0. The second column was filled with a gel that did not contain drug. The second column was placed on top of the first one with the two free surfaces in contact. After time t, the two columns were separated and the gel segments were sliced off and weighed. Each segment was analyzed for the concentration of the drug.

Determination of the diffusion coefficient from drug release data has been a frequently used method. The relevant mathematical relationships were developed and investigated by W. I. Higuchi, T. Higuchi, and others (7–12). Typically, the diffusion apparatus for studying drug release employed a cell which was filled with the ointment. This cell was then placed in a water bath (13,14). The ointment surface was occasionally covered with a membrane that did not hinder the overall rate of release but protected the surface of the ointment (15–19). Samples were taken at various times and analyzed for the amount of drug released.

Attwood *et al.* (20) and Tolly and Rassing (21) used an ultrasonic scanning technique to measure the concentration profiles of diffusing solutes in gels. A calibration plot of the solute concentration versus the reciprocal of the square of the ultrasonic velocity was constructed, and a linear relationship between the two terms was obtained. The diffusion cell contained the gel block, of which only the front surface of the gel was exposed to the drug solution. The exposed surface was maintained at C_0. The velocity of an ultrasonic wave within the gel block was measured simultaneously at two fixed positions for several different times. The calibration plot was used to convert the ultrasonic velocity in the diffusion system to the concentration. The solute concentration was then plotted against time and the diffusion coefficient was estimated.

The method presented in this paper employed a Fourier transform infrared spectrometer (FT-IR) equipped with a horizontal attenuated total reflectance (ATR) cell. This new method is advantageous in that no solvent is required for liquid penetrants, the equipment is generally available, and the relatively thin film of ointment makes the determination reasonably fast.

MODEL CONSIDERATIONS

The experimental setup was considered to be a system with one open and one closed boundary. The planar ointment film had a finite thickness, h, and was initially at a concentration of liquid equal to zero at all positions. The bottom surface of the film was in contact with an impermeable material, the ATR crystal, and its top surface was in contact with an amount of liquid sufficient to provide a constant concentration, C_0, at all times during the experiment (Fig. 1). In this system, it can be seen that the rate of diffu-

[1] University of Iowa, College of Pharmacy, Iowa City, Iowa 52242.
[2] To whom correspondence should be addressed.
[3] Present Address: Bristol-Myers Squibb, Evansville, Indiana.

0724-8741/93/0400-0616$07.00/0

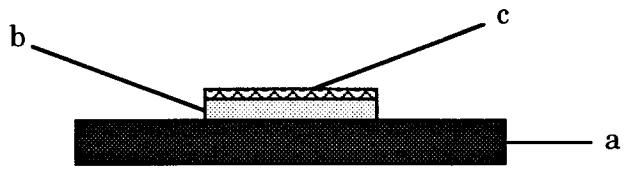

Fig. 1. Schematic for a diffusion system with one open and one closed boundary. a, impermeable material; b, semisolid; c, liquid.

sional mass transport varied continuously since the concentration difference between the two boundaries decreased continuously. The initial conditions (when $t = 0$) were $C = 0$ at the ointment–impermeable material boundary, $x = 0$ and $C = C_0$ at the ointment–liquid boundary, $x = h$. The boundary conditions for this system were $\partial C/\partial x = 0$ at $x = 0$ and $C = C_0$ at $x = h$. Using Fick's second law, a diffusion equation was derived that satisfied both the initial and the boundary conditions (22,23). The result was the following equation:

$$\frac{C}{C_0} = 1 - \frac{4}{\pi}\sum_{n=0}^{\infty}\frac{(-1)^n}{2n+1}\exp\left(\frac{-D(2n+1)^2\pi^2 t}{4h^2}\right)\cos\frac{(2n+1)\pi x}{2h} \quad (1)$$

where C is the concentration of liquid at time, t, and position, x, in the planar film, and D is the diffusion coefficient of the liquid in the film. The change in concentration with time at any position within the film could be described by Eq. (1).

MATERIALS AND METHODS

Materials

Anhydrous lanolin (Ruger Chemical Co., Inc., Hillside, NJ) was used as received. Polyethylene glycol (PEG) ointment was prepared by heating 129.5 g of PEG 400 (Ruger Chemical Co., Inc., Hillside, NJ) and 70 g of PEG 3350 (Amend Drug & Chemical Co., Irvington, NJ) in a beaker suspended in a 70°C water bath until the PEG 3350 melted. Upon melting, the PEG mixture was allowed to cool slowly. The mixture was stirred continuously during this cooling process.

Test liquids were pyridine (Aldrich Chemical Company, Inc., Milwaukee, WI), benzaldehyde (Fisher Scientific, Fair Lawn, NJ), acetophenone (Aldrich Chemical Company, Inc., Milwaukee, WI), methyl salicylate (Eastman Kodak Company, Rochester, NY), and 4-chloro-4'-fluorobutyrophenone (Aldrich Chemical Company, Inc., Milwaukee, WI).

Experimental Procedure

The ATR cell was placed in the sample compartment of the FT-IR spectrometer (Nicolet 5DXB, Madison, WI). The zinc selenide crystal employed had a 45° angle of incidence to the IR beam. A template was made by punching a 7.94-mm hole in a piece of 0.157-mm-thick Teflon (Berghof/America, Inc., Raymond, NH). This template was mounted on the surface of the zinc selenide crystal of the ATR cell (Spectra Tech, Inc., Stamford, CT). The background spectrum was obtained from the coaddition of 10 scans taken at a 2-cm^{-1} resolution and a detector gain of 2. The hole in the template was filled with the desired ointment using a syringe. The ointment was manipulated to ensure that there were no entrapped air bubbles and then the excess ointment was removed using a razor blade. A smooth film of the ointment remained, which had a thickness equal to the thickness of the template. The same ointment was then used to form a ridge around the perimeter of the hole. A 20-μL aliquot of the neat test liquid was placed on the ointment film, and the film was covered with a small beaker to prevent evaporation of the liquid. The diagram for this diffusion experiment is shown in Fig. 2. The temperature was 20 ± 0.5°C, with 1°C being the largest temperature difference occurring between runs. After the liquid was put on the ointment film, spectra were collected using the same instrument conditions as were used for the background spectrum. Spectra were usually obtained every 60 sec and spectral collection was continued well into the plateau region to ensure that the concentration changes and the equilibrium state were properly represented. The actual length of time over which spectra were collected was dependent upon the particular liquid being studied and ranged from 1500 sec for pyridine in anhydrous lanolin to 7400 sec for 4-chloro-4'-fluorobutyrophenone in anhydrous lanolin. These times could have been reduced since the plateau values were reached at 1000 and 6000 sec, respectively. Importantly, excess liquid was always visible on the film surface at the end of the experiment.

Analysis of the Spectra

The sample spectra were evaluated using the integrated absorbances of the selected peak regions. The regions of analysis for pyridine, benzaldehyde, acetophenone, methyl

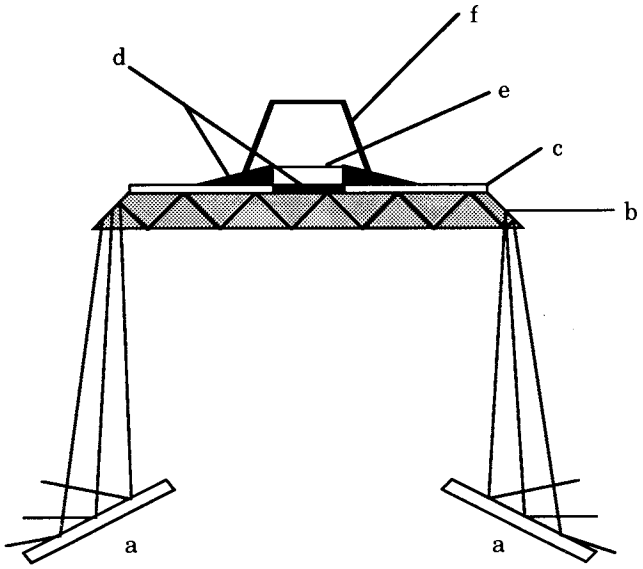

Fig. 2. The experimental system for determining the diffusion coefficient of a liquid in a semisolid material. An FT-IR spectrometer with a horizontal ATR cell is used. a, mirrors in the horizontal ATR accessory; b, internal reflection element of the horizontal ATR accessory; c, Teflon template; d, ointment; e, test liquid, f, beaker.

salicylate, and 4-chloro-4′-fluorobutyrophenone were 1432.5–1443.5, 1192.0–1212.0, 1672.0–1696.5, 1276.9–1345.5, and 1590.0–1603.0 cm^{-1}, respectively. The values of the integrated absorbance were plotted against time.

Preparation of the Standard Curve

Varying amounts of each test liquid were mixed with portions of the desired ointment. Each mixture was loaded into the template as described previously. The sample spectra for the various concentrations were obtained as previously described except that spectra were not obtained as a function of time. The reason that standards prepared in this manner were appropriate for the diffusion experiment is explained later.

RESULTS AND DISCUSSION

The horizontal ATR cell is a very useful device for the analysis of thin films of solid or semisolid materials. The cell consists of two planar mirrors aligned obliquely and the internal reflection crystal (Fig. 2). The sample is placed on the crystal in such a manner that intimate contact is achieved. For samples such as formed tablets, physical weighting may be required. Due to the high refractive index of the crystal, the internal reflectance creates an evanescent wave which extends beyond the surface of the crystal into the sample. The evanescent wave interacts with the sample and a spectrum is obtained. The depth of penetration (d_p) of the IR radiation into the sample depends on many factors, such as the wavelength of the radiation, the refractive index of the crystal, the refractive index of the sample, and the angle of incidence of the beam at the surface of the crystal. In general, the depth of penetration of the wave from an internal reflection element into the sample is small, and for most materials, d_p is approximately equal to 0.1 λ (24).

In this study, a horizontal ATR cell was employed to analyze quantitatively the amount of liquid diffusing through a thin film of semisolid. The depth of penetration of the IR beam into the ointment was only 0.6–0.9 μm with the 45° zinc selenide crystal and the wavelengths of radiation employed. This value is very small compared to the thickness of the ointment film (157 μm). It is therefore reasonable to assume that the sample spectra obtained were the spectra of the liquids at the lower film surface; that is, only the penetrant at the lower surface of the ointment film was being measured. This assumption, which is of obvious importance to the diffusion experiment itself, also allowed mixtures to be prepared for standard curve construction that were homogeneous with respect to penetrant concentration.

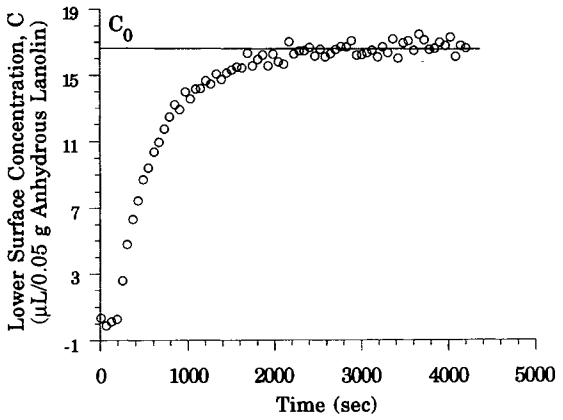

Fig. 4. Plot of the time dependence of the lower film surface concentration for methyl salicylate in anhydrous lanolin. C_0 was the maximum concentration.

Figure 3 shows the standard curve of integrated absorbance versus the concentration of methyl salicylate in anhydrous lanolin. Ideally, the integrated absorbance would be linearly related to the concentration, since integrated absorbance can be viewed as the summation of all of the individual Beer–Lambert law relationships that could be obtained over the wavelength range. However, absorption bands in the IR frequently exhibit deviations from the Beer–Lambert law. Such an instance is shown in Fig. 3. When this problem was encountered, as it was for acetophenone, methyl salicylate, and 4-chloro-4′-fluorobutyrophenone, a mathematical function was employed that better fit the calibration data. While a quadratic equation was used to fit the calibration data in these cases, no physical meaning was ascribed to its use.

Equation (1) is the diffusion equation that best modeled

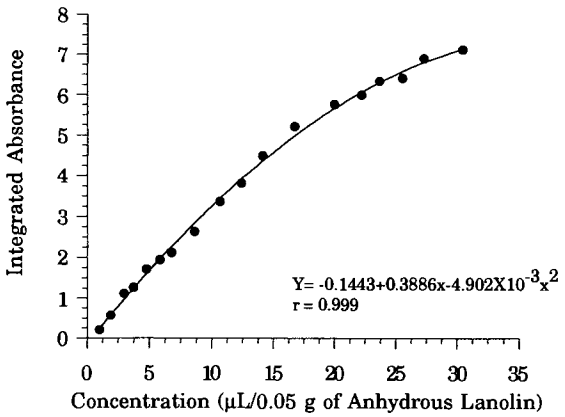

Fig. 3. The standard curve of integrated absorbance versus methyl salicylate concentration in anhydrous lanolin. The region of the IR spectrum over which integration was performed was 1276.9–1345.5 cm^{-1}.

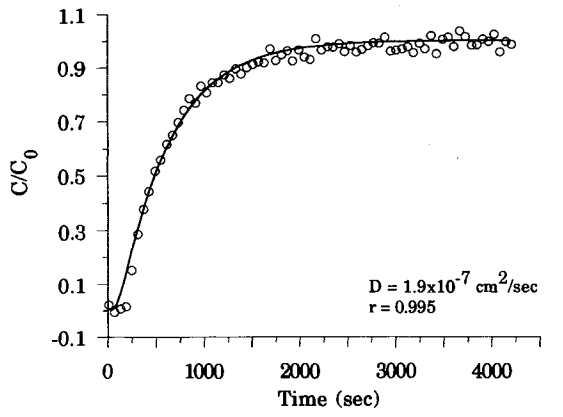

Fig. 5. Plot of the lower film surface concentration of methyl salicylate in anhydrous lanolin versus time. Open symbols represent experimental data. The line is the fitted curve obtained from the diffusion equation (3).

Table I. Average Diffusion Coefficients[a] of Various Compounds in Two Semisolid Materials

Diffusant	MW	$D \times 10^7$ cm²/sec (mean ± SD) In anhydrous lanolin	$D \times 10^7$ cm²/sec (mean ± SD) In PEG ointment
Pyridine	79.10	7.2 ± 0.5	5.7 ± 0.3
Benzaldehyde	106.13	2.5 ± 0.2	2.7 ± 0.5
Acetophenone	120.15	2.0 ± 0.1	1.7 ± 0.3
Methyl salicylate	152.15	1.8 ± 0.2	1.20 ± 0.08
4-Chloro-4'-fluorobutyrophenone	200.64	0.56 ± 0.03	0.68 ± 0.06

[a] Calculated from three sets of data. All correlation coefficients were better than 0.97, and 26 of 30 were better than 0.98.

the experimental conditions. Since the diffusant concentration at the lower surface ($x = 0$) was determined, the diffusion equation for evaluating the diffusion coefficient then became:

$$\frac{C}{C_0} = 1 - \frac{4}{\pi}\sum_{n=0}^{\infty}\frac{(-1)^n}{2n+1}\exp\left(\frac{-D(2n+1)^2\pi^2 t}{4h^2}\right) \quad (2)$$

The two unknowns in this equation were the diffusion coefficient, D, and the concentration of diffusant at the upper surface, C_0. C_0 was taken to be the diffusant concentration at the point where the diffusant concentration in the film remained constant with respect to time. The rate of change of concentration, $\partial C/\partial t$, would, obviously, be zero at this point. Thus, extrapolation of the plateau in the plot of concentration versus time to the y axis yielded the value of C_0 (Fig. 4). Importantly, there was still excess liquid at the surface when C_0 was achieved.

The remaining variable, D, could then be determined. After examining the series in Eq. (2), it was found that only six terms were needed for accurate results:[4]

$$\frac{C}{C_0} = 1 - \frac{4}{\pi}\left(e^{\frac{-D\pi^2 t}{4h^2}} - \frac{1}{3}e^{\frac{-9D\pi^2 t}{4h^2}} + \frac{1}{5}e^{\frac{-25D\pi^2 t}{4h^2}} - \frac{1}{7}e^{\frac{-49D\pi^2 t}{4h^2}} + \frac{1}{9}e^{\frac{-81D\pi^2 t}{4h^2}} - \frac{1}{11}e^{\frac{-121D\pi^2 t}{4h^2}}\right) \quad (3)$$

The value of D was then obtained from Eq. (3) using a nonlinear least-squares regression analysis program to obtain the best fit to the C/C_0 vs time data. Figure 5 shows both the experimental data and the fitted curve for the diffusion of methyl salicylate through anhydrous lanolin. The correlation coefficient for this fit was 0.995 and the diffusion coefficient yielded by the fit was 1.9×10^{-7} cm²/sec. Each liquid and ointment pair was analyzed in the same manner. The average diffusion coefficients obtained using this method are presented in Table I. Theoretically, the values of diffusion coefficients in liquids are about 10^{-5} cm²/sec (25). Diffusion coefficients in the gel phase are much lower than those in the bulk liquid, which is likely due to a change in the local viscosity (26). It would be expected that the D values in nongel semisolids would also be lower than the D values in liquids. The diffusion coefficients of the five compounds in anhydrous lanolin and in PEG ointment were determined to be in the ranges of $0.56–7.2 \times 10^{-7}$ and $0.68–5.7 \times 10^{-7}$ cm²/sec, respectively. Thus, the diffusivity values obtained in this study would appear to be quite reasonable.

It is known that the diffusion coefficient depends on diffusant radius. A molecule with a small radius diffuses more rapidly than a molecule with a large radius if there is no interaction between the diffusants and the barrier or no difference in interaction between the diffusants and the barrier. As expected, pyridine, which is the smallest molecule, exhibited the largest diffusion coefficient in both anhydrous lanolin and PEG ointment. The higher molecular weight molecules, which are benzaldehyde, acetophenone, methyl salicylate, and 4-chloro-4'-fluorobutyrophenone, had smaller diffusion coefficients which decreased in the aforementioned order. Therefore, the rank order of the diffusion coefficients of these compounds followed theory.

While it is worthwhile to compare the values of the diffusion coefficients obtained by this method with values obtained by other techniques, such information seems to be scarce. For instance, no diffusion coefficients are available in the literature for any of these compounds in anhydrous lanolin. In a study by Al-Khamis *et al.* (18), the estimated values of the diffusion coefficients of methyl salicylate in various molecular weight polyethylene glycols were determined from drug release data. The effective diffusion coefficients were found to be 1.80×10^{-7} and 0.20×10^{-7} cm²/sec in PEG 600 and PEG 2000, respectively. In this work, the diffusion coefficient of methyl salicylate in PEG ointment, which was a mixture of PEG 400 and PEG 3350, was 1.20×10^{-7} cm²/sec (Table I). This value seems to be in very good agreement with the previously published results.

[4] The difference between the D values obtained by including six and seven terms in Eq. (2) and then using nonlinear least-squares regression analysis to fit the model to the experimental data was less than 0.01%.

REFERENCES

1. W. I. Higuchi. Diffusion in ointment bases. *Proc. Am. Assoc. Coll. Pharm.* 13:162–173 (1961).
2. E. L. Cussler. *Diffusion: Mass Transfer in Fluid Systems*, Cambridge University Press, New York, 1984, pp. 118–123.
3. L. M. Lueck, D. E. Wurster, T. Higuchi, A. P. Lemberger, and L. W. Busse. Investigation and development of protective ointments. I. Development of a method for measuring permeation of mechanical barriers. *J. Am. Pharm. Assoc.* 46:694–698 (1957).

4. L. M. Lueck, D. E. Wurster, T. Higuchi, K. F. Finger, A. P. Lemberger, and L. W. Busse. Investigation and development of protective ointments. II. Influence of partition coefficient and thickness. *J. Am. Pharm. Assoc.* **46**:698–701 (1957).
5. S. Wahlgren, A. L. Lindstrom, and S. E. Friberg. Liquid crystals as a potential ointment vehicle. *J. Pharm. Sci.* 73:1484–1486 (1984).
6. W. Addicks, N. Weiner, G. Flynn, R. Curl, and E. Topp. Topical drug delivery from thin applications: Theoretical predictions and experimental results. *Pharm. Res.* 7:1048–1054 (1990).
7. W. I. Higuchi and T. Higuchi. Theoretical analysis of diffusional movement through heterogeneous barriers. *J. Am. Pharm. Assoc.* **49**:598–606 (1960).
8. W. I. Higuchi. Analysis of data on the medicament release from ointments. *J. Am. Pharm. Assoc.* 51:802–804 (1962).
9. T. Higuchi. Rate of release of medicaments from ointment bases containing drugs in suspension. *J. Pharm. Sci.* **50**:874–875 (1961).
10. T. Koizumi and W. I. Higuchi. Analysis of data on drug release from emulsions. II. Pyridine release from water-in-oil emulsions as a function of pH. *J. Pharm. Sci.* 57:87–92 (1968).
11. T. Koizumi and W. I. Higuchi. Analysis of data on drug release from emulsions. III. Boundary effect on pyridine release from water-in-oil emulsions as a function of pH. *J. Pharm. Sci.* 57:93–97 (1968).
12. T. Yotsuyanagi, W. I. Higuchi, and A. Ghanem. Theoretical treatment of diffusional transport into and through an oil-water emulsion with an interfacial barrier at the oil-water interface. *J. Pharm. Sci.* 62:40–43 (1973).
13. F. Bottari, V. Carelli, G. Di Colo, M. R. Firinu, and E. Nannipieri. A method for studying drug complexation in semisolid vehicles. *Farmaco* 33:3–21 (1978).
14. V. Carelli, G. Di Colo, E. Nannipieri, M. F. Saettone, and M. F. Serafini. Release of drugs from ointment bases. *Farmaco* 32:591–610 (1977).
15. N. F. Billus and N. K. Patel. Experiments in physical pharmacy V. In vitro release of medicament from ointment bases. *Am. J. Pharm. Educ.* 34:190–196 (1970).
16. F. Bottari, G. Di Colo, E. Nannipieri, M. F. Saettone, and M. F. Serafini. Influence of drug concentration on in vitro release of salicylic acid from ointment bases. *J. Pharm. Sci.* 63:1779–1783 (1974).
17. F. Bottari, G. Di Colo, E. Nannipieri, M. F. Saettone, and M. F. Serafini. Release of drugs from ointment bases. II. In vitro release of benzocaine from suspension-type aqueous gels. *J. Pharm. Sci.* 66:926–931 (1977).
18. K. Al-Khamis, S. S. Davis, J. Hadgraft, and S. Mills. The determination of thermodynamic activity by gas chromatography head space analysis and its use in studying release of drugs from topical preparations. *Int. J. Pharm.* 10:25–28 (1982).
19. F. Bottari, V. Carelli, G. Di Colo, M. F. Saettone, and M. F. Serafini. A new method for determining the diffusion coefficients of drugs in semisolid vehicles from release data. *Int. J. Pharm.* 2:63–79 (1979).
20. D. Attwood, L. Johansen, J. A. Tolley, and J. Rassing. A new ultrasonic method for measurement of the diffusion coefficients of drugs within hydrogel matrices. *Int. J. Pharm.* 9:285–294 (1981).
21. J. A. Tolley and J. Rassing. A new ultrasonic velocity scanning technique giving concentration-distance profiles and diffusion coefficients of drugs in gels. *Int. J. Pharm.* 14:223–230 (1983).
22. M. H. Jacobs. *Diffusion Processes,* Springer-Verlag, New York, 1967, pp. 47–53.
23. J. Crank. *The Mathematics of Diffusion,* 2nd ed., Oxford University Press, New York, 1975, pp. 47–49.
24. P. R. Griffiths and J. A. de Haseth. *Fourier Transform Infrared Spectrometry,* John Wiley & Sons, Inc., New York, 1986, pp. 191–194.
25. E. L. Cussler. *Diffusion: Mass Transfer in Fluid Systems,* Cambridge University Press, New York, 1984, p. 105.
26. W. Brown and K. Chitumbo. Solute diffusion in hydrated polymer networks. Part 2. Polyacrylamide, hydroxyethylcellulose and cellulose gels. *J. Chem. Soc. Faraday Trans. I* 71:12–21 (1975).