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A new ultrasonic velocity scanning technique giving concentration–distance profiles and diffusion coefficient of drugs in gels

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Summary

A new diffusion cell for measuring the concentration–distance profiles of diffusing solutes in gel systems has been developed. The technique is based on the ultrasonic velocity at 4 MHz which by means of a scanning set-up is measured as a function of distance along a gel block (75 ml) placed in a specially designed cell. The technique has been applied to the diffusion of sodium chloride, glucose, sucrose, lidocaine hydrochloride, and mepyramine maleate in a 10% polyacrylamide gel with the following diffusion coefficients 11.3, 3.4, 2.7, 6.4 and $3.9 \times 10^{-6} cm^2 \cdot s^{-1}$, respectively.

Introduction

The transport of drugs and other molecules of biological relevance through solid matrices is a phenomenon of current interest, particularly with reference to the controlled release from polymeric devices. The use of hydrogels in controlled release therapy has been the subject of several reviews and symposia (Andrade, 1976; Tanquary and Lacey, 1974).

The diffusion coefficients of solutes in polymeric networks have been measured by techniques which generally involve the estimation of the amount of solute which diffuses out or into an implant, disc or layer of gel (Bottari et al., 1979) or the

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permeability of the solute through a thin membrane of the polymer (Zentner et al., 1979). None of these methods measure directly the diffusion properties within the gel and consequently the magnitude of the diffusion coefficient so obtained may depend on the geometry of the polymeric device, the solute loading of the polymer and probably several boundary effects. For studies with thin membranes the experimentally determined value of the diffusion coefficient very often depends on the method of formation of the membrane since surfaces can have different properties to the bulk material (Silberberg, 1976). Those non-destructive methods which are available for the determination of the concentration of solute throughout the gel network itself generally require radiolabelled solutes (Park and Hoang, 1979).

Ultrasonic techniques have been applied in our laboratory to the investigation of a variety of systems including polymer solutions (Rassing, 1979; Dela and Rassing, 1978). In a previous communication (Dela et al., 1979) we introduced an ultrasonic velocity method by means of which the concentration of a drug inside a gel block could be measured in a non-destructive way. Recently we presented a new method for determination of the diffusion coefficient within a solid matrix (Attwood et al., 1981). The method was used to determine the diffusion coefficient for the hydrochlorides of ephedrine and pethidine in a polyacrylamide hydrogel. The method makes use of the ultrasonic velocity measured at two fixed positions within the solid matrix as a function of time. Each experiment takes at least 35 h. Consequently the requirements of long time stability of the electronics and constant temperature are difficult to fulfil. A periodic variation in the temperature of $\pm 0.1°C$ has a large influence on the velocity and must be corrected for by measuring the temperature in the gel very accurately as a function of time. In order to avoid these complications we have developed a scanning technique which enables the ultrasonic velocity to be measured as a function of distance along a gel block that under controlled conditions has been exposed to a drug solution. The scanning procedure takes only a few minutes and hence problems with time stability of the electronics and temperature fluctuations are eliminated.

By means of this new technique that is presented in this paper we have extended our investigation of drug diffusion in polyacrylamide hydrogels.

Background to the method

The ultrasonic velocity, U, is given by the following equation

$$U^{-2} = \rho\beta \tag{1}$$

where ρ and β are the density and isentropic compressibility of the system, respectively. If a two-component system is considered under the condition of ideal mixing expressed as

$$V = n_1 V_1^0 + n_2 V_2^0 \tag{2}$$

where V denotes the total volume, V_1^0 and V_2^0 denote the partial molar volumes for

pure components 1 and 2, respectively, and n denotes mole amounts, then

$$\rho = \rho_1 + (\rho_2 - \rho_1)\phi \tag{3}$$

and

$$\beta = \beta_1 + (\beta_2 - \beta_1)\phi \tag{4}$$

Substitution in Eqn. 1 and neglecting higher-order terms gives:

$$U^{-2} = [\beta_1(\rho_2 - \rho_1) + \rho_1(\beta_2 - \beta_1)]\phi + U_1^{-2} \tag{5}$$

where ϕ denotes the volume fraction of component 2 that is now referred to as the solute. Eqn. 5 rewrites as:

$$U^{-2} = \alpha C + U_1^{-2}, \quad \alpha = V_2^0[\beta_1(\rho_2 - \rho_1) + \rho_1(\beta_2 - \beta_1)] \tag{6}$$

Eqn. 6 predicts a linear relationship between the molar concentration, C, and the reciprocal of the square of the ultrasonic velocity. Consequently the actual value of the ultrasonic velocity of a two-component system in the low concentration range translates easily into molar concentration of the solute by means of this equation.

The diffusion cell and the scanning device

The gel is formed in a brass mould (Fig. 1a) which incorporates a V-shaped base that acts as a sound wave reflector. During formation of the gel a lid is in position so

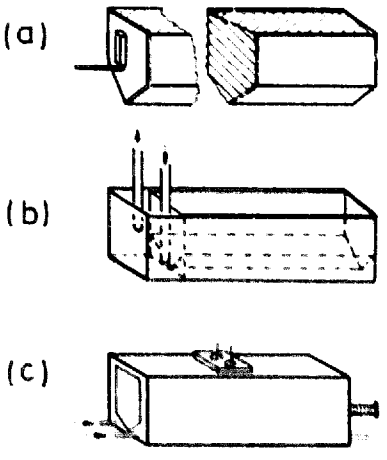

Fig. 1. a: the brass mould (length 20 cm, volume 75 ml) in which the gel is formed and which contains the gel during the diffusion and scanning procedures. b: the diffusion cell. Solution is pumped across the gel surface as the brass mould, with one end-plate removed, sits in the cell. c: the scanning carriage containing the sound transducers which sit on top of the gel surface. The screw moves the brass mould along under the sound transducers. The whole carriage is maintained at a temperature of 298K by circulating water.

that the gel is formed exactly the right height to allow contact with the sound transducers when the scanning takes place. This lid is also in position during the diffusion experiment where the mould is placed in a perspex diffusion cell (Fig. 1b), operated in a way that approximately 150 ml of drug solution is pumped from a reservoir through a coil immersed in the water bath to allow temperature equilibration and into the diffusion cell. The solution is removed from the top of the cell so that a constant flow of solution is maintained across the gel surface which is at one end of the brass mould. After a given diffusion time the brass mould is placed in the thermostatted carriage for the scanning studies (Fig. 1c). The lid is removed and the sound transducers are placed in direct contact with the gel surface. The carriage and hence the brass mould with the gel block is moved along under the sound transducers by means of a long screw, one revolution of the screw moves the cell 1 mm.

The sound velocity is measured by means of the "sing around" technique as described previously (Rassing, 1971). In principle the wave is transmitted through the solid matrix by means of two transducers, one operating as a sender and the other as a receiver. By means of an oscillator, the sending transducer is excited with a radio frequency signal of 4 MHz and a duration time of 3 μs. The resulting low amplitude sound wave produced in the system is reflected from the V-shape base of the cell and detected by the receiver which then creates a voltage which triggers the oscillator to produce a second frequency signal across the sender and so on. Thus the pulse repetition frequency in the circuit is related to the velocity of the sound wave that travels between the two transducers. The oscillator used is an NUS-Sonic Solution Monitor (NUSonics).

Computational procedure

The basis of the procedure used in the calculation of the diffusion coefficient, D, is the diffusion equation describing diffusion in one direction

$$\frac{\partial C}{\partial t} - D\frac{\partial^2 C}{\partial x^2} = 0 \tag{7}$$

The solution to the differential equation used to the determination of D is the well known "error function" solution,

$$C = C_0 \operatorname{erfc}\frac{x}{2\sqrt{Dt}} \tag{8}$$

where x denotes the diffusion distance and t, the diffusion time. Because of the large volume of solution that is circulated in the diffusion cell the initial concentration, C_0, in the diffusion chamber is maintained constant, which is a requirement for the application of Eqn. 8. The calculated diffusion coefficient is very sensitive to the absolute value of the diffusion distance, x. However, it is very difficult experimentally to place the gel block exactly in the same position in the scanning set up. Consequently the exact distance is not known. The distance read from the scanning set up is called x, and the correction to that value in order to obtain the absolute

distance is defined as Δx. For each scan we have: (neglecting the second-order term in Δx)

$$\left(\frac{x}{z}\right)^2 \frac{1}{4t} = -\Delta x \frac{x}{2tz^2} + D \tag{9}$$

if the diffusion is described by Eqn. 8. z is the value for which $\text{erfc}(z) = C/C_0$ for the given value of x. t is the time that the gel has been exposed to the drug solution in the diffusion cell. Eqn. 9 thus predicts a linear relation between two experimentally determined quantities. The slope gives the value Δx and the intercept gives the best value of the diffusion coefficient. In the calculation only C/C_0 values larger than 5% are used. Otherwise the uncertainty caused by fluctuations in the base line becomes dominant.

Materials and methods

The hydrogel used for the study of drug diffusion was 10% polyacrylamide (BDH Chemicals) gel cross-linked with 5% w/w of the total polymer weight of N,N'-methylene-*bis*-acrylamide (BDH Chemicals). The gel was prepared within the brass mould by free-radical polymerization with ammonium persulphate (0.045%) (Merck) and triethanolamine (0.045%) and allowed to equilibrate for 24 h with water at 298K.

Sodium chloride (Merck), D-glucose (Merck) and D-sucrose (Struers) were of analytical grade. Mepyramine maleate and lidocaine hydrochloride (Mecobenzon) conformed to the purity standards of the European Pharmacopoeia.

In the production of the gel, the brass mould was covered with a protective coating to avoid inhibition of the free radical reaction, which causes an imperfectly formed gel in the region of the walls.

For the diffusion of sodium chloride, D-glucose and D-sucrose, the cell containing the gel was placed in a large stirred volume of the diffusant at 298K. Initial concentrations and volumes of the diffusants were, respectively, 0.5 M and 5 dm^3 for sodium chloride, 0.5 M and 2 dm^3 for D-glucose, and 0.25 M and 2 dm^3 for D-sucrose.

Diffusion studies of the drugs, mepyramine maleate and lidocaine hydrochloride, in a 0.4 M solution at 298K were performed using the diffusion cell (Fig. 1b) where a smaller volume (0.15 dm^3) of solution was pumped across the front face of the gel.

It is necessary to establish that the ultrasonic velocity of the gel–drug system relates linearly to the concentration of drug within the gel. The calibration of sodium chloride concentration with ultrasonic velocity for an aqueous solution and a 10% polyacrylamide gel gives linear relationships according to Eqn. 6. As a further check of the relationship between the calibration coefficients in solution and gel systems, gels were allowed to equilibrate for two weeks with solutions of glucose and sucrose and the resulting frequency increase above the original gel value was compared with the frequency difference between the equilibrating solution and distilled water. The

TABLE 1

DIFFUSION COEFFICIENTS AT 298K

	Diffusion coefficients $\times 10^6$ ($cm^2 \cdot s^{-1}$)	
	10% P.A. gel	distilled water
Sodium chloride	11.3	14.9 [a]
Glucose	3.4	6.73 [b]
Sucrose	2.7	5.21 [c]
Lidocaine hydrochloride	6.4	
Mepyramine maleate	3.9	

[a] Vitagliano and Lyons, 1956.
[b] Gosting and Morris, 1948.
[c] Handbook of Chemistry and Physics, 1979.

increase in ultrasonic velocity due to the increase in concentration of the solute is the same for an aqueous solution as for a solute-containing gel.

The increase of the ultrasonic velocity at set points in the gel above that measured for the gel at that point at time, t = 0, is converted to a concentration value using the calibration coefficients produced from aqueous calibration curves.

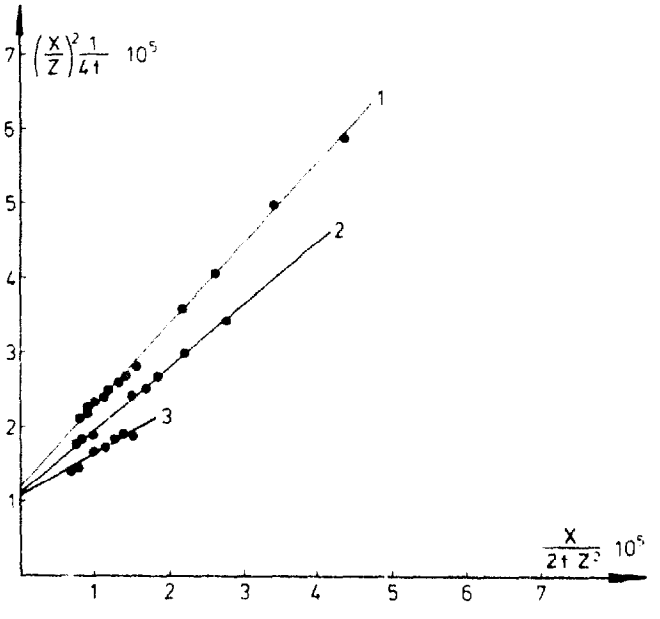

Fig. 2. Plot showing that the linear relation predicted by Eqn. 9 is fulfilled by the data. The points are calculated from concentration-distance profiles obtained from scans after: (1) 50 h; (2) 75 h; and (3) 100 h gel contact with the drug solution. The lines have about the same intercept which defines the diffusion coefficient. The diffusant is sodium chloride with an outside concentration, C_0, of 0.5 mol·dm^{-3} and the gel is 10% polyacrylamide.

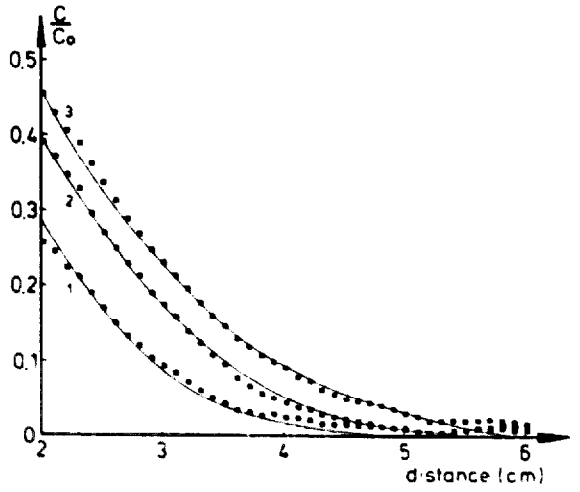

Fig. 3. Plot showing the typical concentration–distance profiles obtained from scans after: (1) 51 h; (2) 75 h; and (3) 99 h gel contact with the drug solution. The lines are the theoretical curves predicted by the diffusion theory (Eqn. 8) with the diffusion coefficient determined from Eqn. 9. The diffusant is lidocaine hydrochloride with an outside concentration, C_0, of 0.4 mol·dm^{-3} and the gel is 10% polyacrylamide.

Results

Diffusion coefficients for the solutes studied at selected times were calculated from plots according to Eqn. 9 and are given in Table 1. Data at different times give virtually the same intercept and slope values for each substance with the exception of sodium chloride which as shown in Fig. 2 has the same intercept value at different times but different slope values. This indicates that the Δx adjustment to the absolute distance increases with time. The exact significance of this increase is unknown but it could be due to some physical effect at the gel–solution boundary or to uncertainty in the definition of $x = 0$ at high concentrations of solute in the boundary layers. Fig. 3 shows typical concentration–distance profiles obtained for the diffusion of lidocaine hydrochloride.

Discussion

The diffusion coefficients calculated for the sodium chloride, D-glucose and D-sucrose in the 10% polyacrylamide gel are lower than those values in aqueous solution (see Table 1). This would be expected due to the obstruction that the polymer network offers to the diffusing molecules. The ratio of the diffusion coefficients of D-glucose to that of D-sucrose is the same in solution as in the gel. However, the ratios of their diffusion coefficients to that of sodium chloride are slightly lower in the gel than in water. There appears to be no particular relationship between the diffusion coefficient in the gel to that in solution. Some workers (White and Dorion, 1961; Brown and Chitumbo, 1975) have investigated such relationships between molecular size of the diffusing solute and pore size or gel concentration with

varying results, but the small number of substances studied and the single concentration of gel do not allow such calculations in the present study.

The technique and results presented here demonstrate the advantage of an ultrasonic velocity scanning technique and indicate the nature of the results that can be obtained. Thus the concentration profile within a matrix can be measured and the diffusion process and the effects of different conditions, boundaries and layers within the matrix can be evaluated.

Acknowledgement

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