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A new ultrasonic method for the measurement of the diffusion coefficient of drugs within hydrogel matrices

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Summary

A new method for the determination of the diffusion coefficient within a solid matrix has been developed. The method is based on the simultaneous, automatic measurement of the ultrasonic velocity at two fixed positions within the solid matrix as a function of time. Application of the method to the diffusion of sodium chloride through dilute gelatin gels gave a diffusion coefficient in reasonable agreement with the literature value for the diffusion in pure water. Diffusion coefficients of 4.3 and 2.8×10^{-6} cm^2 s^{-1} were determined for the diffusion of the hydrochlorides of ephedrine and pethidine, respectively, through polyacrylamide hydrogels.

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 of 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). Neither 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 the surfaces can have different properties to the bulk material (Stilberberg, 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; Collett et al., 1981).

Ultrasonic techniques have been applied in our laboratory to the investigation of a variety of systems including polymer solutions (Rassing, 1979). Since it is now possible to measure the ultrasonic velocity automatically with high accuracy and since low energy sound waves allow a non-destructive investigation of the interior of a solid matrix which need not be transparent, it is considered that this technique might prove of value as an analytical tool with possible applications in pharmaceutical systems. In a previous communication (Dela et al., 1979) we introduced an ultrasonic velocity method by which the concentration of a drug inside a gel block could be measured in a non-destructive way. In the present paper this work is developed into a new method by which the diffusion coefficient of any water-soluble drug inside a solid gel matrix may be measured. The method is tested using a dilute gelatin gel, the structure of which is such as to offer little significant obstruction to free diffusion but which prevents mixing and streaming in the diffusing system. A polyacrylamide gel was selected as a suitable hydrogel for the study of the diffusion properties of drugs since the properties of this gel have been well documented and it has been previously used in the controlled release of drugs (Davis, 1974; Davis et al., 1972).

Background of 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 the isentropic compressibility of the system, respectively. If the system consists of several components the velocity becomes a function of the composition. 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 component 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 into Eqn. 1 gives:

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

where ϕ denotes the volume fraction of component 2 that is now referred to as the solute. If dilute solutions are considered, $\phi \ll 1$ and Eqn. 5 may be written as

$$U^{-2} = \alpha C + U_1^{-2} \tag{6}$$

where

$$\alpha = V_2^0[\beta_1(\rho_2 - \rho_1) + \rho_1(\beta_2 - \beta_1)] \tag{7}$$

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 the molar concentration of the solute by means of this equation. It can be readily shown that this treatment easily extends to a multicomponent system.

The diffusion cell

The cell is constructed in such a way as to make possible the measurement of sound velocity, and hence the molar concentration, as a function of time at two fixed positions within the gel block. Details of the construction are given in Fig. 1. The sound velocity is measured by means of the 'sing around' technique as described previously (Dela et al., 1979). In principle a sound 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 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 a NUS-Sonic Solution Monitor (NUSonics) with an attachment making it possible for the oscillatory to successively operate two sets of transducers conveniently placed across the solid matrix under investigation and to print the pulse repetition frequency at suitable time intervals with a desired accuracy. The equipment is able to detect velocity changes of 0.01%.

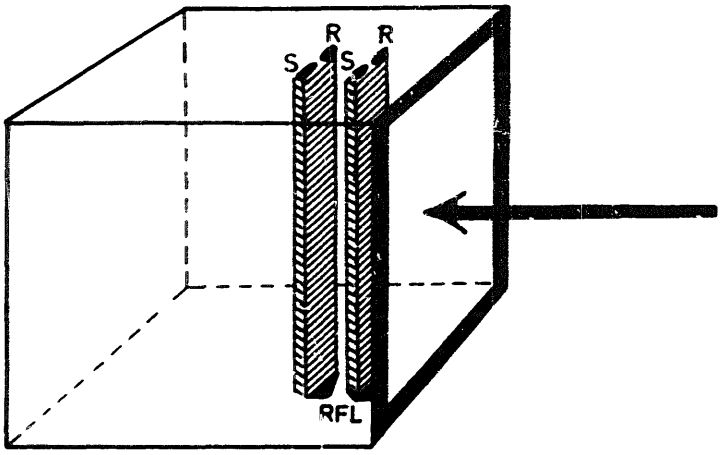

Fig. 1. The diffusion cell with dimensions 7×10×8 cm. S, sender transducer; R, receiver transducer, RFL, reflector. Two transducer sets are inserted at positions Δx cm apart. The shaded regions in the diagram indicate the layers in the gel block through which the sound wave travels and hence measures the diffusant concentration as a function of time. The cell containing a gel block is inserted in a solution containing the compound whose diffusion coefficient within the gel is required. Only the front face of the gel is exposed to the solution, the arrow indicates the direction of diffusion.

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.

$$\frac{\partial C}{\partial t} - D\frac{\partial^2 C}{\partial x^2} = 0 \tag{8}$$

Several mathematical solutions of Eqn. 8 have been applied to the experimental data (Johansen, 1981). The solution which most clearly describes the data over a wide concentration range is the well known solution to the diffusion equation,

$$C = C_0 \operatorname{erfc}\frac{x}{2\sqrt{Dt}} \tag{9}$$

where x denotes the diffusion distance and t, the diffusion time. Because of the large volume of solution surrounding the gel block and the low percentage of the total solute which diffuses into the gel, the initial concentration of solute C_0 in the surrounding solution is maintained effectively constant, which is a requirement for the application of Eqn. 9. The derivative of Eqn. 9 is

$$\frac{dC}{dt} = C_0\frac{q}{\sqrt{\pi}}t^{-3/2}e^{-q^2/t} \tag{10}$$

where

$$q = \frac{x}{2\sqrt{D}} \tag{11}$$

Eqn. 10 describes the slope of the experimentally obtained C vs t plots. A closer examination of Eqn. 10 shows that the actual value of the slope passes through a maximum at corresponding t and x values that satisfy the following equation

$$t_{max} = \frac{2}{3}\left(\frac{x}{2\sqrt{D}}\right)^2 \tag{12}$$

Furthermore it can be shown that the value of t_{max} is obtained as the abscissa time-value for the point on the curve corresponding to the ordinate value $C = 0.083C_0$. Making use of these observations leads to the following equation for the diffusion coefficient

$$D = \frac{(\Delta x)^2}{6t_1} F^2(t_1,t_2) \tag{13}$$

where

$$F(t_1,t_2) = \frac{t_1 + \sqrt{t_1 t_2}}{t_2 - t_1} \tag{14}$$

Eqn. 13 demonstrates that the calculation of the diffusion coefficient requires values for Δx, the distance between the two transducer sets, and also t_1 and t_2 which are the t_{max} values derived from the diffusion curves obtained from these two transducer sets at measuring sites 1 and 2, respectively. It should be noted that the experiment can be terminated when the concentration at the measuring sites is only about 10% of the initial outer concentration and also that the absolute distance from the gel–water interface is not required. This latter point demonstrates an important advantage of this technique since the interface between gel matrix and a solution is often difficult to define due to swelling of the gel.

In order to check the reliability of the diffusion coefficient determined by this technique, the diffusion of sodium chloride in a dilute gelatin gel was examined and the diffusion coefficient compared with the literature value in pure water.

Materials and methods

Materials

A 5% gelatin (Nordisk Gelatine) gel was used to test the operation of the cell. The hydrogel used for the study of drug diffusion was 9.15% w/w 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 diffusion cell by free-radical polymerization with ammonium persulphate (0.0625%) (BDH Chemicals) and triethanolamine (0.0625%) and allowed to equilibrate overnight with water at 288°K.

Sodium chloride (BDH Chemicals) was of analytical grade. Ephedrine hydrochloride (Sigma) and pethidine hydrochloride (May and Baker) conformed to the purity standards of the British Pharmacopoeia (99.0–101.0%).

Experimental procedure

Initial measurements of the sound velocity in the gels were recorded with the gels immersed in water, after which the water was replaced by a solution of the diffusant and measurements were taken for the required time interval as diffusion proceeded. Initial concentrations of 0.2 mol·dm^{-3} were used in the studies of the diffusion of ephedrine and pethidine. The initial sodium chloride concentration was 0.77 mol·dm^{-3} for diffusion into gelatin gels and 0.5 mol·dm^{-3} for diffusion into polyacrylamide gels. All measurements were taken at 288°K.

Results

Fig. 2 shows the reciprocal of the square of the ultrasonic velocity measured in aqueous solutions containing known concentrations of sodium chloride plotted as a

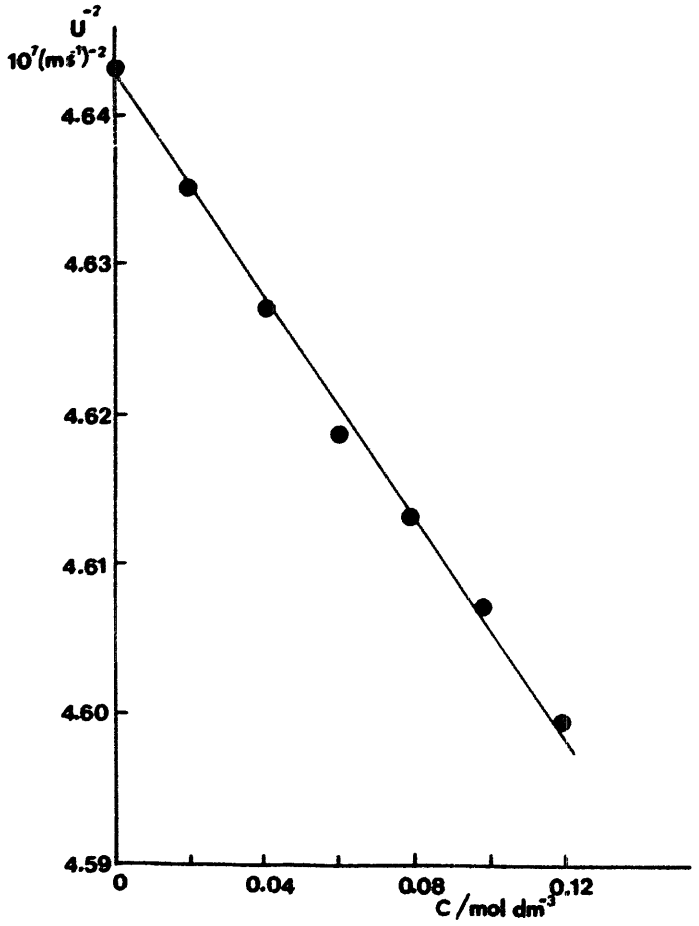

Fig. 2. Reciprocal of the square of the ultrasonic velocity, U, (at 4 MHz) versus the molar concentration of sodium chloride in aqueous solution.

function of sodium chloride concentration. The linear relationship between U^{-2} and C is in agreement with Eqn. 6. Typical curves of the time-dependent changes in concentration at the two measuring sites during the diffusion of sodium chloride are given in Fig. 3 over a time period of 90 h. Abscissa time-values t_1 and t_2 at ordinate values of $C = 0.083C_0$ were interpolated from the diffusion curves obtained at the two transducer sets and used to calculate the diffusion coefficients from Eqn. 13. Fig. 3 shows reasonable agreement between theoretical curves calculated from Eqn. 9 using this diffusion coefficient and the experimental data. Diffusion curves for 5% and 3% gels were superimposable supporting the proposition that the gel structure in these dilute gels causes no appreciable obstruction to the diffusion. The diffusion coefficient at 288°K calculated from Eqn. 13 was 1.3×10^{-5} cm$^2 \cdot$ s^{-1}, in reasonable

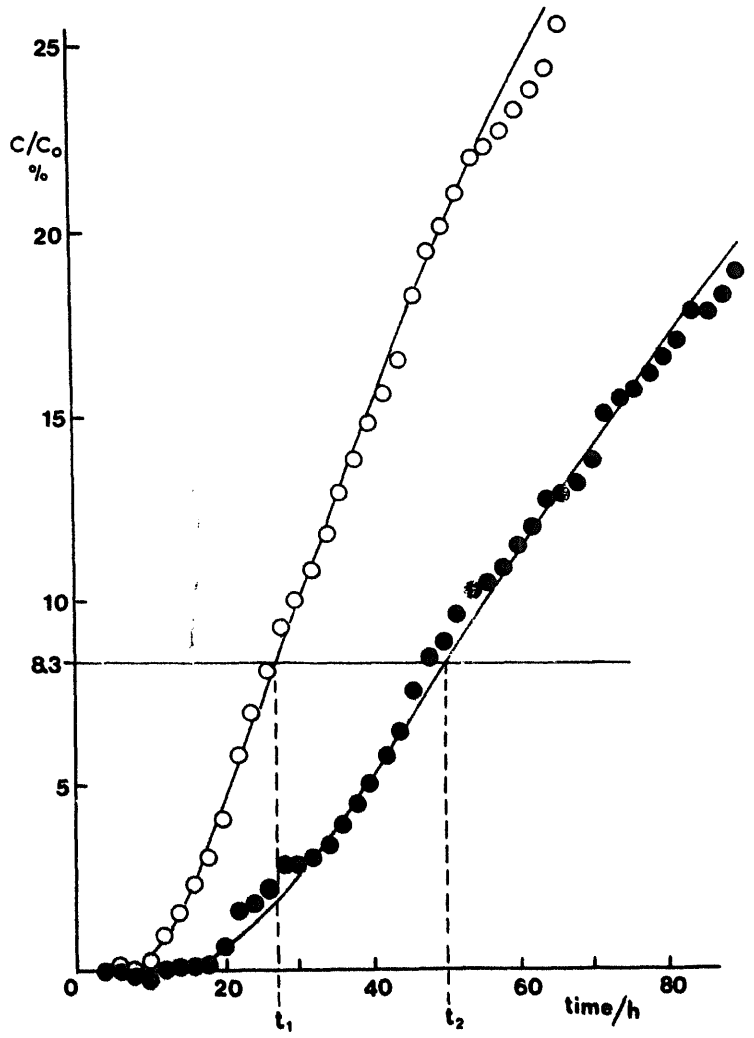

Fig. 3. Plot showing the typical time-dependence of the diffusant concentration at two fixed points, 1.0 cm, apart within the gel. Open and closed symbols represent experimental data obtained at measuring positions 1 and 2, respectively. The lines are theoretical curves predicted by diffusion theory (Eqn. 9). Values of t_1 and t_2 corresponding to ordinate values of $C = 0.083C_0$ are used in the calculation of D from Eqn. 13. The diffusant is sodium chloride with an outside concentration, C_0, of 0.77 mol$\cdot$dm^{-3} and the gel is 5% gelatin.

agreement with a literature value (Vitagliano and Lyons, 1956) of 1.490×10^{-5} $cm^2 \cdot s^{-1}$ for an average sodium chloride concentration of 0.08059 $mol \cdot dm^{-3}$ at a higher temperature (298°K). It seems reasonable to draw the conclusion that the experimental technique and computational procedure give reliable values for the diffusion coefficient.

Fig. 4 shows reasonable agreement between theoretical concentration–time curves derived from Eqn. 9 and experimental data for the diffusion of sodium chloride, ephedrine hydrochloride and pethidine hydrochloride within 9.15% w/w polyacrylamide hydrogels. The values of the diffusion coefficients as calculated from Eqn. 13 are 1.0×10^{-5}, 4.3×10^{-6} and 2.8×10^{-6} $cm^2 \cdot s^{-1}$ for sodium chloride, ephedrine hydrochloride and pethidine hydrochloride, respectively at 288°K.

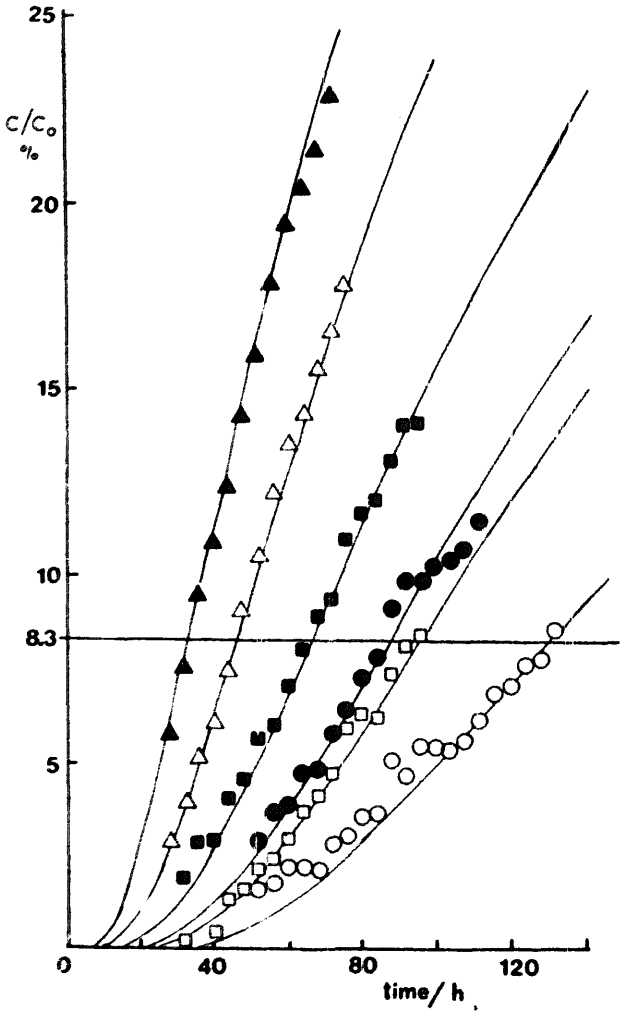

Fig. 4. Time dependence of concentration of (▲△) sodium chloride; (■□) ephedrine hydrochloride, and (●○) pethidine hydrochloride within a polyacrylamide gel (9.15% w/w) at position 1 (closed symbols) and position 2 (open symbols), 0.5 cm apart. The lines are theoretical curves predicted by diffusion theory (Eqn. 9) using the values of D given in the text.

Discussion

Fig. 3 shows that the solution to the one-dimensional diffusion equation given by Eqn. 9 describes the diffusion very precisely over a time interval well beyond that needed for the calculation of the diffusion coefficient by means of Eqn. 13. It was found, however, that divergence between the theoretical and experimental curves occurred when experiments were conducted over a long time scale (> 200 h). Since the measured concentration in such cases was always smaller than the predicted value, the phenomenon is attributed to deviations from one-dimensional diffusion and to problems arising in some experiments in maintaining the outer concentration and gel geometry constant over very long periods. Measurement of the ultrasonic velocity with the accuracy quoted in this paper requires a very constant temperature (Dela and Rassing, 1978). The temperature was recorded continuously using a digital thermometer and it was sometimes found necessary to correct for temperature fluctuations.

The sound frequency, 4 MHz, is so high that structural relaxation in the polymer material does not affect the sound velocity (Rassing, 1971) and consequently the change in the sound velocity is strictly related to the incoming diffusant. All compounds used fulfil Eqn. 6 over the concentration range used.

Conclusions

The ultrasonic velocity technique has proved to be a simple, effective and direct method of evaluating solute concentration as a function of time and distance inside a gel system. The change of concentration with time at fixed points in a gel is described by a standard solution to the diffusion equation. By manipulation of the equation a relation is obtained from which the diffusion coefficient can be calculated directly from the experimental data requiring only a knowledge of the distance between the two measuring points and the interpolation of two time values from the experimental diffusion curves. The experiments contain sufficient information when the concentration at the measuring points approaches 10% of the initial concentration. The method is non-destructive, measures the diffusion coefficient inside the gel and can be used for any water-soluble drug.

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