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Controlled release of local anaesthetic agents from liquid–solid emulsion gels

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Summary

The release of lignocaine from emulsion films, made from gelatin and a homologous series of alkanols, is studied. The release profiles are modelled. Using the standard Higuchi square root of time diffusion equation, it is shown that the solution matrix model holds to different extents with the different alkanols, in line with the changes in the drug partition coefficient between the continuous and dispersed phases. Although suspension matrix models have been used for modelling drug release from emulsions, it is shown that this approach is also limited by the fact that as release proceeds, drug activity within the film decreases. The Bruggeman equation which takes account of the permeability coefficient of the drug in both continuous and dispersed phases was useful in predicting drug release at high partition coefficients but its value deteriorates badly as the partition coefficient decreased. Effective diffusion coefficients of lignocaine in the four alkanols are calculated and these show that no single model adequately predicts the observed values.

Introduction

The quantitative study of the release of drugs from emulsions has attracted only limited attention which is partly due to the complexity of these two-phase systems. The problems imposed by the presence of additives, notably surfactants, makes systematic variation of any given parameter difficult to study. Despite this, the use of emulsions as sustained-release systems has aroused the interest of various groups of workers (Windhauser et al., 1970; Brodin, 1975; Chien and Lambert, 1976;

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Abbreviations: Q_t, cumulative amount of drug released per unit area; Q_r, amount of drug remaining in unit area of matrix; D, diffusion coefficient as defined by Ficks law; D_e, effective (apparent) diffusion coefficient; $[C]_0$, total initial drug concentration; C_s, solubility of drug in continuous phase; $[C]_{aq}$, drug concentration in the aqueous (continuous) phase of emulsion; h, film thickness; t, time; P_e, effective permeability coefficient of heterogeneous medium; P_c, permeability coefficient of drug in continuous phase; P_i, permeability coefficient of drug in dispersed phase; V_i, volume fraction of dispersed phase; V_c, volume fraction of continuous phase; K, partition coefficient; k_B, Boltzmann's constant; T, temperature (K); n, coefficient of viscosity; r, radius of diffusing species; η_c, viscosity of continuous phase; η_i, viscosity of dispersed phase.

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Davis, 1981). However, in order to make the transition from sustained to controlled delivery it is necessary to develop suitable models for analysing the data when the formulation parameters are systematically changed. Two types of approache have contributed significantly to a better definition of release patterns from emulsions. The first involved studies on interface transport, such as those described by Brodin and other workers (Goldberg et al., 1967; Goldberg and Higuchi, 1969; Brodin, 1975). The second involves the investigative modelling of release data from idealised systems (Koizumi and Higuchi, 1968; Ghanem and Higuchi, 1969; Bikhazi and Higuchi, 1970; Bialik, 1985; Szust and Kubis, 1985). These approaches are of course complementary.

In this report, work aimed at producing controlled drug delivery systems for local anaesthetics is described. Release of local anaesthetics from emulsion devices consisting of oil droplets dispersed and entrapped in a solid gelatin matrix is studied and modelled, using equations proposed by other workers (Higuchi, 1958; Higuchi and Higuchi, 1960; Higuchi, 1962; Koizumi and Higuchi, 1968; Barrer, 1968; Broberg et al., 1982).

Two equations have generally been adopted for analysing drug release from emulsions. The first is the Higuchi equation (Eqn 1) for release of drugs suspended in ointment bases (Higuchi, 1961) while the second (Eqn 2) is the equation for medicament release from homogeneous ointment systems (Higuchi, 1962).

$$Q_t = D_e t(2[C]_0 - C_s)C_s \tag{1}$$

$$Q_r = h[C]_0\left[1 - \frac{8}{\pi^2}\sum_{n=0}^{\infty}\left(\frac{1}{2n+1}\right)^2 \times \exp\left(-\frac{D_e(2n+1)^2\pi^2 t}{4h^2}\right)\right] \tag{2a}$$

$$Q_r = h[C]_0\left[2\sqrt{\frac{D_e t}{h^2}}\left(\frac{1}{\sqrt{\pi}} + 2\sum_{n=1}^{\infty}(-1)^n \operatorname{ierf}\frac{nh}{2\sqrt{Dt}}\right)\right] \tag{2b}$$

Generally, approximations such as Eqn 3, the short-time approximation of Eqn 2 have been used (Higuchi, 1962; Ostrenga et al., 1971).

$$Q_t = 2[C]_0\left(\frac{Dt}{\pi}\right)^{1/2} \tag{3}$$

Eqn 1 has been further modified by Koizumi and others (1975) to account for the non-steady concentration gradient in the region where the solid drug has been depleted. Broberg and others (1982) adapted the modified equation for the emulsion case as follows:

$$Q_t = \left[D_e[C]_{aq}t\left(2[C]_0 - \tfrac{2}{3}[C]_{aq}\frac{[C]_0 - 0.88[C]_{aq}}{[C]_0 - 0.89[C]_{aq}}\right)\right]^{1/2} \tag{4}$$

This equation has been claimed to model diffusion from suspensions better than Eqn 3 and has therefore been included in this study for comparison.

Although several reports show good correlation between the experimental data and the data predicted by Eqn 3, it is clear that the concordance in results is only achieved because of specific characteristics of the systems studied and the use of these equations for portraying the complete release behaviours of emulsions in general will not always be successful. Unlike suspension systems emulsions have reservoir droplets in which drug activity decreases with drug depletion.

For predicting purposes, attempts have been made to adapt the equations for dielectric permeability of heterogeneous media to model the release behaviour of emulsions (Koizumi et al., 1975). Maxwell's equation for predicting dielectric behaviour of heterogeneous systems as expressed by the Wagner-Weiner equation (Eqn 5) and the Bruggeman equation (Eqn 6) have been explored for their potential usefulness in this respect.

$$\frac{P_e - P_c}{P_e - 2P_c} = \frac{P_i - P_c}{P_i - 2P_c}V_i \tag{5}$$

$$\frac{P_e - P_i}{P_c - P_i}\left(\frac{P_c}{P_e}\right)^{1/3} = V_c \tag{6}$$

Based on Maxwell's model (Maxwell, 1873), Eqns 5 and 6 assume the absence of interaction between neighbouring particles, which in the present study are the oil droplets making up the dispersed phase. To account for perturbation by neighbouring particles, Higuchi and Higuchi (1960) derived the following expression:

$$P_e = \left(\left[2P_c^2(1 - V_i) + P_c P_i(1 + 2V_i)\right] - \left[KP_c\left(\frac{P_i - P_c}{2P_c + P_i}\right)^2 (2P_c + P_i)(1 - V_c)\right]\right) \times \left[P_c(2 + V_i) + P_i(1 - V_c) - K\left(\frac{P_i - P_c}{2P_c + P_i}\right)^2 (2P_c + P_i)(1 - V_c)\right]^{-1} \tag{7}$$

In this study, only the permeability constant in the continuous phase was independently measured as described in the experimental section. The permeability constant in the dispersed phase was derived from the corresponding viscosity data using the Stokes-Einstein relationship (Eqn 8). Eqns 5 to 7 were therefore correspondingly transformed to Eqns 9 to 11 respectively.

$$D = \frac{k_B T}{6\pi\eta r} \tag{8}$$

$$P_e = \frac{P_c(1 + 2BV_i)}{1 - BV_i} \tag{9}$$

$$\frac{P_e - AP_c}{P_c(1 - A)} \cdot \left(\frac{P_c}{P_e}\right)^{1/3} = V_c \tag{10}$$

and

$$P_e = \frac{P_c\left[2(1 - V_i) + A(1 - 2V_i) - X\right]}{(2 + V_i) + A(1 - V_i) - X} \tag{11}$$

where

$$A = \frac{K_i \eta_c}{K_c \eta_i} \tag{12}$$

$$B = \frac{K_i/\eta_i - K_c/\eta_c}{K_i/\eta_i + 2K_c/\eta_c} \tag{13}$$

and

$$X = KB^2(2 - A)(1 - V_i) \tag{14}$$

Experimental

Materials

The alcohols, octanol (Fisons), nonanol (Sigma), decanol (BDH), undecanol (Sigma) and dodecanol (Fisons) were all analytical grade and were used without any further purification. Gelatin was kindly provided by Messrs. Alfred Adams, West Bromwich, U.K. The Bloom strengths of the gelatin quoted in the text were determined by the manufacturers. All HPLC solvents were HPLC grade.

Preparation of emulsion films

The initial step involved the formulation of an aqueous gelatin base. This was composed of 20% (w/w) 200 bloom gelatin in phosphate buffer (pH 7.0) prepared by melting at 60 °C the gelatin/water mixture previously matured for 1 h at room temperature. The molten gel was left at 60 °C for a further 2 h to rid it of air bubbles.

The oil-in-gel emulsions were prepared without the use of any additional surfactants since gelatin itself has sufficient emulsifying properties. The general procedure involved adding 10 g of the oleagenous phase (containing 1.5 g lignocaine base) pre-heated to 60 °C, to 40 g of the molten aqueous gel and stirring at 2000 rpm with a Heidolph RZR50 motor for 2 min.

Solid, circular films (diameter 7.0 cm) were cast between two flat stainless steel plates within a pre-set gap of approximately 0.7 mm. The correct thickness of the films was measured just before

the beginning of the release experiments using a Mercer dial gauge.

Release experiments

The film was clamped between a flat, circular perspex plate and a perspex ring, allowing one-sided exposure of 6.8 cm^2 area. A filter paper (Millipore SM 11307) and a wire mesh (40 mesh) were placed on top of the film before clamping so as to ensure no dissolution of the film during the release experiment. The clamped set was then immersed into a Quickfit dissolution vessel containing 500ml of pH 7.0 phosphate buffer pre-saturated with the appropriate alcohol at 25 °C. The receiving solution was stirred by a PTFE blade stirrer driven at 200 rpm by a Heidolph RZR50 stirrer motor at a height of 5 cm above the bottom of the vessel. Aliquots of 5 ml were withdrawn for analysis of lignocaine content at regular intervals, and were replaced by an equivalent volume of pure phosphate buffer. Calculations of the effective diffusion coefficients from the release data were based on Eqn 3.

Measurement of the diffusion coefficient of lignocaine in the gelatin gel

The release of lignocaine from homogeneous gelatin films (20% (w/w) 200 bloom gelatin in distilled water) was monitored using the same apparatus as described for emulsion films. The diffusion coefficient was calculated from the release data using Eqn 3.

Measurement of partition coefficients

100 ml phosphate buffer (pH 7.0) saturated with the appropriate alcohol and containing 200 mg of lignocaine (base) were added to 25 ml of the alcoholic phase (preweighed) which had also been saturated with the buffer at the appropriate temperature. The flask was then shaken in a thermostated water bath for 12 h, after which a sample of the aqueous phase was withdrawn and analysed for lignocaine content by UV spectrophotometry at 262 nm. The concentration of lignocaine in the oil phase was calculated by mass balance.

Assay of lignocaine in the release solutions

Lignocaine was assayed by HPLC during the release experiments. The column used was pre-packed, 10 cm. Altex Ultrasphere Silica column with an internal diameter of 0.5 cm. The mobile phase consisted of 15% isopropanol, 0.4% strong ammonia solution and 0.2% water in *n*-hexane pumped at a rate of 1 $ml \cdot min^{-1}$ by an Altex 100A double-piston pump. Detection and quantification was carried out using a Pye-Unicam LC UV detector set at 235 nm.

1 ml of the aqueous receiving phase was mixed with 1 ml each of 0.1 N sodium hydroxide, 0.2 mg/100 ml aqueous carbocaine solution as the internal standard and 1 ml of *n*-hexane. After vigorous shaking on a whirlimixer and centrifuging, 20 μl of the hexane layer were injected into the column for each assay.

Measurement of viscosity

These were determined at 25 °C using U-tube (Oswald's) viscometers. The calibration was done using an aqueous 80% glycerol solution whose viscosity and density values were obtained from standard references (Lange, 1979). Specific gravities of the alcohols were determined at 25 °C using a 25 ml specific gravity bottle, from which densities were calculated using distilled water at 25 °C as reference.

Results and Discussion

In the design of the controlled release films, it was thought necessary to identify parameters which could be systematically altered in the formulation in order to give optimal delivery rates of active ingredients in subsequent in-use situations. It was envisaged that after preparing the test formulations, these would be clinically tested and optimal delivery rates adjusted according to patient responses. Likewise, any subsequent toxicity problems could be overcome by substitution of the incriminated ingredient with an alternative possessing similar physicochemical properties. In the emulsion systems investigated, three basic parameters could be altered to give the desired release rate: the dispersed (oil) phase content, the drug content, or the polymeric continuous phase used. In this study, the parameter investigated was the oil-phase content, and systematic variation

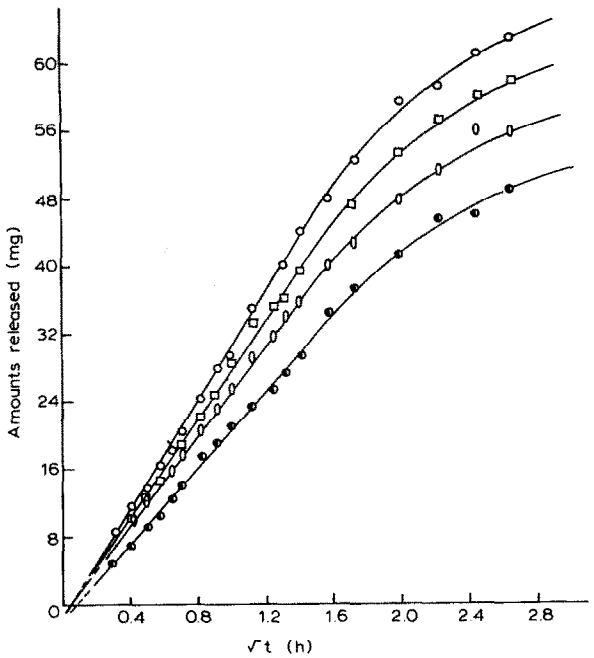

Fig. 1. The release of lignocaine (base) from thin alcohol-in-gel emulsion films (0.075 cm thickness) at 25°C. ○, octanol; 0, nonanol; □, decanol; and ○, dodecanol emulsions.

was achieved by using a series of homologous alcohols – octanol, nonanol, decanol and dodecanol.

Fig. 1 shows the release profile of lignocaine from the four kinds of alcohol emulsion film. Except for the type of alcohol used, all formulation parameters were maintained constant. Each film contained about 76 mg lignocaine. The plot of the amount released versus the square root of time shows that a linear relationship persists in the early stages of release but the extent seems to vary depending on the alcohol used. This is contrary to suggestions made by some investigators that the linear relationship should persist only to 30–50% of the total amount of the drug released. It can be observed that in the case of the dodecanol emulsion for example, the linear relationship persists to almost 60%, thus providing kinetics similar to homogeneous systems. This behaviour differs from that demonstrated by solid suspension systems in which the linear relationship is expected to persist as long as solid drug remains in the matrix (Higuchi, 1961).

Guy and Hadgraft (1981) have developed a model that can be used to simulate and compare sink and non-sink release of drugs from homogeneous matrices based on the solution of Fick's second law. A computer programme based on this model was written to simulate the complete release profiles on feeding the appropriate parameters. The programme was tested on the data for the release of lignocaine from homogeneous gelatin films, and the excellent fit to the observed profile under sink conditions is shown in Fig. 2. The programme was therefore used in this case to provide theoretical release profiles anticipated in case of homogeneous matrix systems with matrix parameters (diffusion coefficient, initial drug concentration and film thickness) similar to those of the emulsion systems under study. The diffusion coefficients used in this comparison were calculated from the emulsion release data using Eqn 3.

Fig. 3 compares the theoretical and observed profiles for the release of lignocaine from the alcohol emulsion gels. It can be observed that the

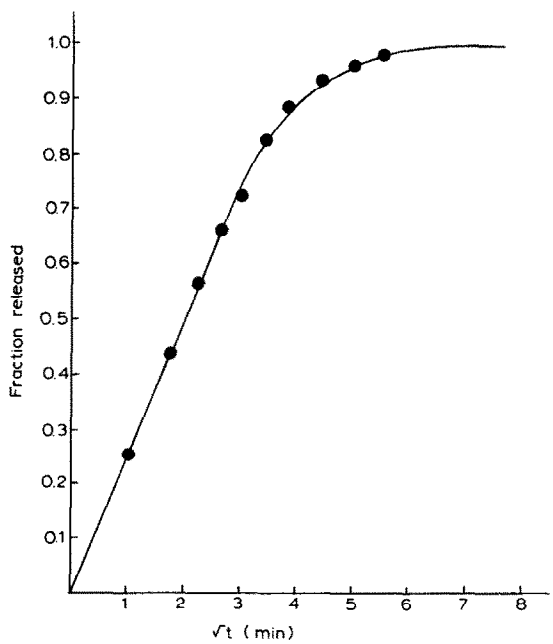

Fig. 2. Computer simulation of the release of lignocaine (base) from homogeneous matrices using the Guy and Hadgraft model (1981). Points are experimental and the line represents the computer predicted release.

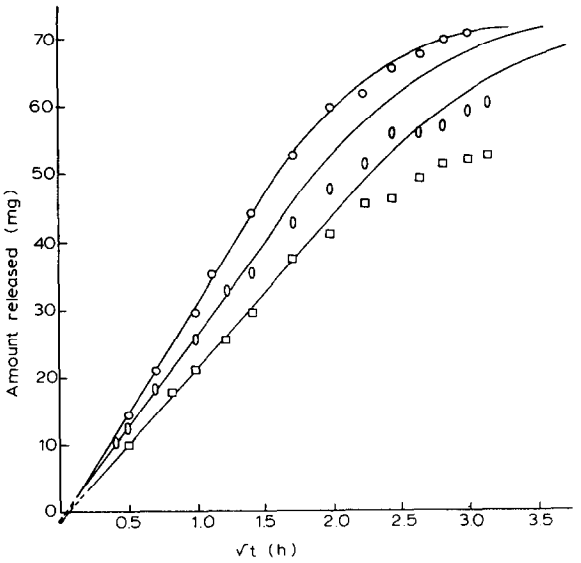

Fig. 3. Comparison of theoretical and experimental release profiles for the desorption of lignocaine from alcohol-in-gel emulsions at 25 °C. The theoretical profiles (solid lines) are computer simulated (see text). Points are experimental observations. □, octanol; 0, nonanol; and ○, dodecanol emulsion gels. (Data on release from decanol emulsions are not included in this graph for the sake of clarity.)

theoretical and observed release profiles for the dodecanol emulsion show good concordance. Deviation from the homogeneous-like release behaviour is observed in the other alcohol emulsion systems, apparently increasing in the order corresponding to decreasing number of carbon atoms in the alcohol molecules. Since the partition coefficient of lignocaine decreased with the number of alcohol carbon atoms (Fig. 4), it can be concluded that the extent of the initial $\sqrt{t}$ phase in emulsion systems depends on the partition coefficient of the drug between the two emulsion phases.

Most previous studies on the release of medicaments from emulsion systems have employed a semi-infinite layer and an oil sink as the receiver phase (Ostrenga et al., 1971; Broberg et al., 1982). Kinetic analysis has therefore been limited to the initial $\sqrt{t}$ phase only. Moreover, the oil phase is unsuitable for studies of thermodynamic processes, since such a system is essentially three phase with different partition coefficients at the dispersed/continuous phase interface and the continuous/receiver phase interfaces. Since the present study employs an oil-in-water emulsion releasing into an aqueous receiver phase, this complication does not arise. The deviations from the homogeneous-like release behaviour when the oil/water partition coefficient is high therefore reflects the gradual shift from sink to non-sink release behaviour. This is better illustrated in the semi-logarithmic plot of the release data (Fig. 5) which shows that there is a tendency to biphasic exponential release from the alcohol emulsions possessing high partition coefficients.

Although both the diffusion equations for homogeneous and suspension-type films have been used to describe release data from emulsions, it is clear that because the latter are neither homogeneous nor solid suspension systems, the diffusion coefficients calculated from the release data are

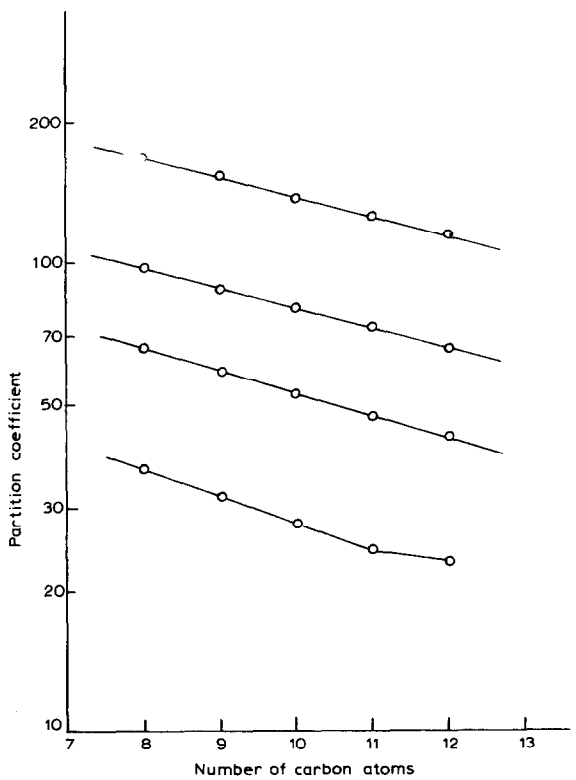

Fig. 4. The variation of partition coefficient of lignocaine between aliphatic alcohols and phosphate buffer pH 7.0 with temperature. (Partition coefficients calculated in terms of molal concentrations.)

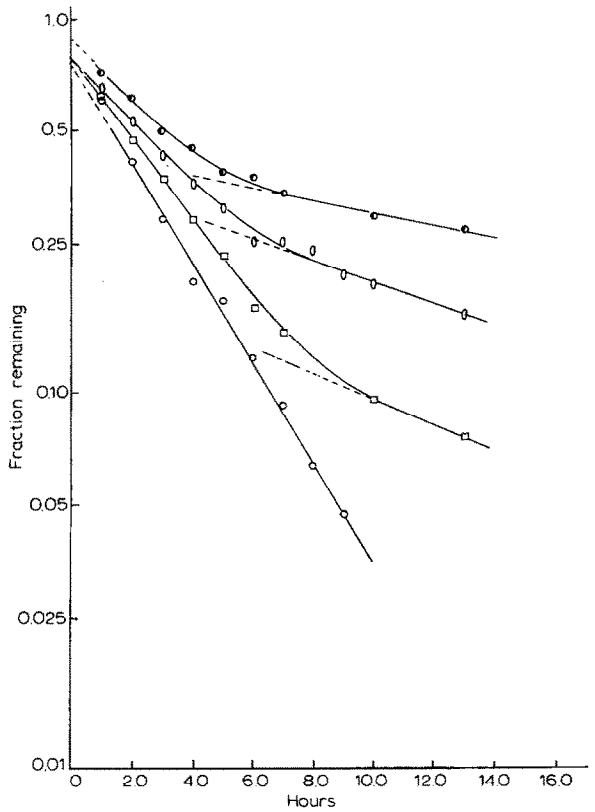

Fig. 5. The semi-logarithmic plot of the release of lignocaine (base) from alcohol-in-gel emulsions at 25°C. ○, octanol; 0, nonanol; □, decanol and ○, dodecanol.

not true diffusion coefficients but apparent diffusion coefficients, normally referred to as 'effective' diffusion coefficients. Clearly then, any adherence to Eqns 3 and 4 arise from constraints placed on the system under study. With this in mind, and for comparative purposes, the effective diffusion coefficients were calculated using both Eqns 3 and 4 and are presented in Table 1.

The use of the C_s term in Eqn 4 therefore seems to have serious implications on the value and meaning of the calculated effective diffusion coefficients. According to the original definition by Higuchi (Higuchi, 1962), the diffusion coefficient calculated using Eqn 3 is equivalent to the diffusion coefficient of a homogeneous system providing similar release behaviour to that of the emulsion. This is basically the same definition adopted by Maxwell while deriving the equation for the dielectric permeability of heterogeneous media (Maxwell, 1873). Since $[C]_0$ does not represent the true driving force for the release from emulsions, values of the effective diffusion coefficients calculated in this manner vary with the initial drug concentration ($[C]_0$). It has therefore been suggested (Broberg et al., 1982) that the modified suspension equation (Eqn 4) would provide a more realistic evaluation of the effective diffusion coefficient since it provides a constant value of the diffusion coefficient regardless of the initial drug concentration. However, on using this modified suspension equation, it is obvious that the Maxwell-Higuchi definition of the effective diffusion coefficient no longer applies. Ideally then, the diffusion coefficient calculated using Eqn 4 should be equal to that of the drug in the pure continuous phase of the emulsion. This assumes that diffusion in the continuous phase is the rate limiting step and that diffusion in the internal phase does not play any significant role in the control of the release process. This arises from the conditions imposed during the derivation of the suspension equation (Higuchi, 1961). It is not clear whether this condition was met in the previous study (Broberg et al., 1982). In this study, Eqn 4 provides different values of the diffusion coefficient for the alcohol emulsion systems (see Table 1). Both Eqns 3 and 4 are therefore unsatisfactory.

The partition coefficient of lignocaine in a homologous series of aliphatic alcohols, like other drug substances (Irwin and Li Wan Po, 1979), shows a semi-logarithmic relationship with the number of carbon atoms (Fig. 4). The deviation observed in case of dodecanol at 25°C in Fig. 4 can be attributed to the proximity of the experi-

TABLE 1

Comparison of the effective diffusion coefficients of lignocaine from alcohol emulsion gels as calculated using Eqns 3 and 4

Internal phase (Alcohol)	D_e (Eqn 3) $(m^2 \cdot s^{-1}) \times 10^{11}$	D_e (Eqn 4) $(m^2 \cdot s^{-1}) \times 10^{11}$
Octanol	11.408	108.58
Nonanol	15.939	131.92
Decanol	20.031	139.58
Dodecanol	23.178	148.94

mental temperature to the melting point of the alcohol. A similar deviation is obtained in the plot of the effective diffusion coefficient (as calculated using Eqn 3), against the number of alcohol carbon atoms (Fig. 6). Assuming that the actual driving force for the release process is the initial drug concentration in the continuous phase, it is expected that the effective diffusion coefficient should vary directly with the partition coefficient. Fig. 7 shows that there is a direct relationship between the effective diffusion coefficient and the partition coefficient. This relationship suggests that diffusion of the drug in the dispersed phase does not play a significant role in the control of the release process.

On the other hand, the equations adopted from dielectric permeability studies were specifically derived on the notion that the internal phase plays an equally important role in the overall behaviour. The results obtained in this study therefore suggest that there might be fundamental differences between the model employed in the case of dielectric permeability and the situation prevailing in pharmaceutical emulsion systems.

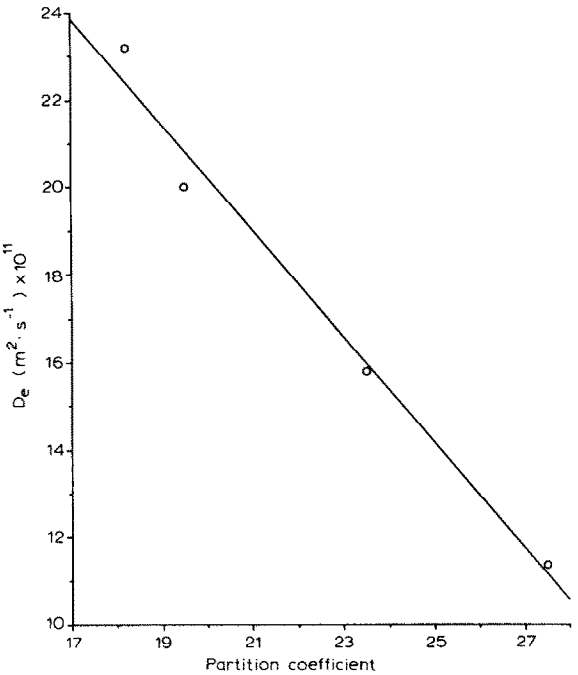

Fig. 7. The relationship between the effective diffusion coefficients and the partition coefficient of lignocaine in alcohol emulsion systems.

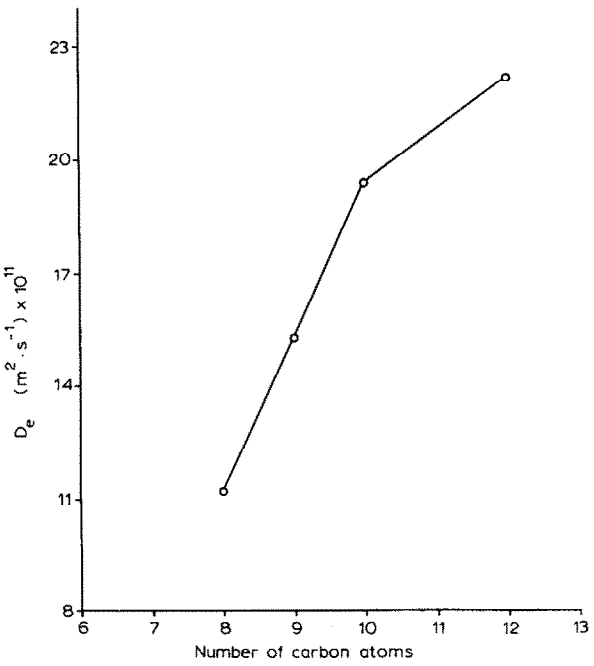

Fig. 6. The relationship between the effective diffusion coefficient (as calculated using Eqn 3) and the number of alcohol carbon atoms.

Since there are reports of the successful prediction of drug release from emulsion systems using the same dielectric permeability equations (Koizumi and Higuchi, 1968), attempts were made to study the usefulness of Eqns 5–7 in a system in which the internal phase is changed so as to vary the partition coefficient of the drug in the system. Table 2 gives the values of the diffusion coefficients calculated using Eqns 9–11. These values are plotted against their corresponding partition coefficients and compared to those calculated from experimental data using Eqn 3 (Fig. 8). It can be observed from Fig. 8 that no single equation provides satisfactory prediction throughout the entire range of partition coefficients. The Bruggeman equation seems to offer the best prediction at high partition coefficients but its concordance with observed values deteriorates badly as the partition coefficient decreases. This could be attributed to increased pertubation in emulsion systems with

TABLE 2

Calculated effective diffusion coefficient using the dielectric equations

Alcohol	$(m^2 \cdot s^{-1}) \times 10^{11}$			
	Bruggeman (Eqn 6)	Wagner-Weiner (Eqn 5)	Higuchi (Eqn 7)	Observed (Eqn 3)
Octanol	9.689	25.278	32.956	11.408
Nonanol	15.558	29.967	35.589	15.939
Decanol	28.417	30.911	37.244	20.031
Dodecanol	50.733	40.831	33.242	23.178

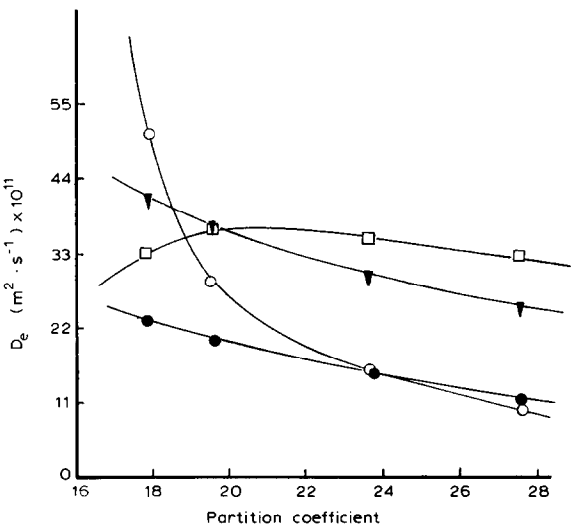

Fig. 8. Comparison of predicted and observed effective diffusion coefficients for lignocaine in alcohol emulsion systems. The effective diffusion coefficients are plotted against their respective alcohol/water partition coefficients. ○, Bruggeman; ▼, Wagner-Weiner; and □, Higuchis' equation. Shaded circles represent experimentally determined values.

low partition coefficients. Unreliability of these equations has also been reported in the case of prediction of dielectric permeability of heterogeneous media.

Conclusion

Emulsion systems have been investigated as controlled release delivery systems. Successful quantification of the release kinetics of medicaments from emulsion systems seem to be hindered by problems in basic modelling. The equation used by most investigators, i.e., that adopted from homogeneous systems, is useful only during the initial $\sqrt{t}$ phase. The extent of deviation seems to depend on the partition coefficient of the drug between the two emulsion phases. It follows therefore, that in cases where moderate to high partition coefficients exist, this equation would provide unrealistic values of the effective diffusion coefficient.

On the other hand, the suspension equation provided higher values of diffusion coefficients than the homogeneous equation. It is obvious from these results that the main restriction in the application of this equation is the lack of a proper definition of the effective diffusion coefficient, since it neither provides values of the diffusion coefficients equal to that of the drug in the pure continuous phase, nor does it fit the Maxwell-Higuchi definition of the effective diffusion coefficient of heterogeneous systems.

The role of thermodynamic partitioning in drug release from emulsion systems has been highlighted by the observation that drug release seems to be independent of diffusion in the dispersed phase. The unreliability of the dielectric permeability equations for prediction of drug release from emulsion systems observed in this study may therefore be a consequence of different modelling.

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