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Diffusional release of a solute from a porous polymeric matrix

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Summary

A diffusional model based on a moving boundary analysis (Miller and Peppas, 1983) for solute release from an inert porous polymeric matrix in which the solute initial loading is greater than its solubility limit, was experimentally validated using sodium salicylate ($< 30\ \mu m$) released from fused polyethylene disc matrices (1.27×0.16 cm, 0.245 g). The release kinetics were evaluated in an isotonic phosphate buffer, pH 7.4 at $37 \pm 0.1°C$ for two different loadings which gave final porosities of 0.49 and 0.60. The model parameters (C_s, ϵ, ρ, D') were independently determined and used to test the validity of the model against experimental results. An exponent of 1 was used for the porosity term (ϵ) instead of 2/3 as initially proposed by Miller and Peppas (1983) in the equation for the amount of solute released. The experimental cumulative amounts released were directly proportional to $t^{1/2}$ and the slopes correlated well, less than 8% relative error, with the theoretical values generated from the model. The results presented here demonstrate that the proposed equations an exact physical description of solute diffusional characteristics in a porous polymer, and can be used for the design of a particular system in order to achieve desired kinetics.

Introduction

The rationale behind the concept of controlled release of drugs has recently been discussed by Chien (1983). The reasons for using a controlled release formulation may be summarized as follows: to obtain a constant systemic blood level of a drug, to localize drug action at a particular body site and to improve patient compliance. Excellent reviews exist on the use of polymers for controlled release of drugs (Graham, 1978; Langer, 1980; Langer and Peppas, 1981), polypeptides and other macromolecules (Siegel and Langer, 1984). In the development and evaluation of controlled release systems, the research scientist can develop and use mathematical models to describe the release kinetics, to understand the release mechanisms, and to adjust the model parameters to achieve particular kinetics.

When modelling the release of highly water-soluble solute from a porous planar surface of a hydrophobic polymeric matrix, in which the solute initial loading is greater than its solubility limit, several assumptions are made: (1) the only mechanism responsible for mass transport is molecular diffusion (no convection); (2) diffusion of the solute in the matrix is unidirectional and occurs only through water-filled pores (> 100 Å); (3) the diffusion coefficient of the solute is represented by the integral diffusion coefficient; (4) the solvent in

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the release medium provides a perfect sink for the solute; (5) all the incorporated solute is available for diffusion; and (6) the solute particles are small relative to the distance of diffusion and are homogeneously dispersed in the matrix.

Models developed for the release of a highly water-soluble solute from a porous polymeric matrix, in which the solute loading is above its solubility limit in the dissolution medium, are the well known Higuchi (1963) model, the dissolution–diffusion (Gurny et al., 1982) model and the diffusional (Miller and Peppas, 1983) model including a moving boundary analysis. The boundary is the region where the undissolved and dissolved solute transition occurs. These porous systems are generally made by blending the bioactive agent with the polymer followed by their compression, or by dispersion in a solvent–polymer solution and subsequent solvent removal. When such systems are introduced in a solvent, the solvent penetrates the solute-filled pores by dissolving the solute, which is then released in the external medium by molecular diffusion. The boundary recedes as a function of time, at a rate which depends on tortuosity of the pores in the matrix, solute density, solubility and diffusion coefficient in the solvent. A general mathematical treatment of moving boundary problems for non-porous systems was given by Crank (1975) and a specific solution for porous systems was given by Miller and Peppas (1983). The Miller and Peppas model is an exact analytical solution to the diffusional problem when the dissolution rate of the solute is not a controlling parameter. This model has been developed by solving Fick's second law of diffusion and introducing a moving boundary condition. The model was evaluated by studying the release of albumin and theophylline from ethylene–vinyl acetate copolymer slabs. It has been suggested that it could be used to predict tortuosity values for certain types of controlled drug delivery polymeric systems, by fitting the release data to the moving boundary model. The model has not been validated by comparing experimental release rates with model predicted values, generated from all of the parameters determined from independent experiments. The D/τ value, where D is the solute diffusion coefficient in the solvent and τ is the tortuosity factor of the matrix, has not been determined. This D/τ term can be determined from sorption–desorption experiments (Desai et al., 1965). Additionally, it appears that the 2/3 exponent proposed for the porosity (ϵ) term, in the equation for the amount of solute released, can not account for the effective cross-sectional surface area available for diffusion, since this value for a porous solid, equals ϵ (Gray, 1968; Sherwood, 1975).

If this model is the exact mathematical expression of physical events occurring in the matrix, good agreement is expected between experimental release rates and model predicted values calculated from independently determined system parameters. Consequently, the purpose of this investigation was to provide experimental evidence as to whether or not the exactitude of the model can be confirmed using sodium salicylate (< 30 μm) released from one surface of fused polyethylene disc matrices. Model parameters were determined from independent experiments and used to generate plots of sodium salicylate cumulative amounts released as a function of $t^{1/2}$. The model and experimental release rates were compared and used to discuss the validity and applicability of the model.

Theoretical models

Higuchi (1963) proposed a relationship governing solute release from one surface of an insoluble inert porous matrix where the initial loading of the solute in the matrix is greater than its solubility limit. The mass of solute which has diffused out of the matrix at time t, is given by the following equation:

$$M_t = \sqrt{D' \cdot \epsilon \cdot C_s \cdot (2A - \epsilon C_s) \cdot t} \qquad (1)$$

where M_t is the total amount of solute released per unit area at time t, D' is the diffusion coefficient of the solute in the release medium divided by the tortuosity factor (τ), ϵ is the final volumetric porosity of the matrix, C_s is the solubility of the solute in the release medium, A is the solute concentration in the matrix and t, the time. Eqn. 1

is an approximate analytical solution of the problem, based on a pseudo-steady-state analysis which supposes a linear concentration gradient in the dissolved region. By solving Fick's second law of diffusion and introducing a moving boundary condition, Paul and McSpadden (1976) developed the exact analytical solution of the moving boundary problem for non-porous systems. The expression for M_t is:

$$M_t = \frac{2C_p}{\mathrm{erf}(\eta^*)}(D \cdot t/\pi)^{1/2} \quad (2)$$

where $\eta^* = x^*/2\sqrt{Dt}$, x^* is the moving front position, C_p is the solute solubility in the polymer and D is the diffusion coefficient of the solute in the polymer. The corresponding solution for porous systems was given by Miller and Peppas (1983):

$$M_t = \frac{2\epsilon^{2/3} \cdot C_s}{\mathrm{erf}(\alpha)}(D' \cdot t/\pi)^{1/2} \quad (3)$$

in which the moving front position can be determined by solving the following equation (Miller and Peppas, 1983):

$$\sqrt{\pi} \cdot \alpha \cdot \exp(\alpha^2) \cdot \mathrm{erf}(\alpha) = \frac{C_s}{\rho - C_s} \quad (4)$$

where $\alpha = x^*/2\sqrt{D' \cdot t}$ and ρ is the solute density. In Eqn. 3, a porosity term with a 2/3 exponent is proposed for the cross-sectional porous area available for diffusion per unit area exposed to the release medium. This two-dimensional cross-sectional "porosity" is identical to the volumetric porosity, ϵ (Gray, 1968; Sherwood, 1975), and therefore Eqn. 3 was then modified to introduce an exponent of 1 to the ϵ term:

$$M_t = \frac{2 \cdot \epsilon \cdot C_s}{\mathrm{erf}(\alpha)}(D' \cdot t/\pi)^{1/2} \quad (5)$$

Materials and Methods

Sodium salicylate [1] and polyethylene [2] were used as models for the solute and hydrophobic polymer, respectively. Sodium chloride, potassium phosphate monobasic and sodium phosphate dibasic were of reagent grade and used as is for buffer preparation [3].

For matrix preparation, the salicylate–polyethylene mixture was blended in a Turbula [4] mixer for 20 min and sieved (U.S. 50 mesh) twice to obtain an homogeneous mixture. An aliquot of this blend (0.250 g) was then transferred into a tempered steel die, 1.27 cm in diameter, pre-heated to 150°C for 30 min and heated for a further 15 min in order to melt the polyethylene.

The die containing the mixture was then transferred to a Carver laboratory press and compressed at 175 MPa for 2 min with the use of two stainless steel flat punches. A 30 min cooling period, at room temperature, was allowed after compression to permit polyethylene to solidify. The weight and thickness of each matrix were then measured and matrices were stored in total darkness.

The method of Desai et al. (1965) was used for the release experiments. In this method, one surface of the matrix is exposed to the release medium by using a wax-coated matrix mounted in a glass tube which is fixed to a petri dish covering a jacketed glass beaker. Agitation is provided by magnetic stirring. Single-face release of sodium salicylate from the porous matrices was carried out in 200 ml of an isotonic phosphate buffer, pH 7.4 at 37 ± 0.1°C under perfect sink condition and vigorous agitation. At pre-determined time intervals, 5 ml samples were withdrawn, diluted with the buffer, and sodium salicylate amount was determined spectrophotometrically [5] at 296 nm. Release medium volume was kept constant by introducing 5 ml of fresh buffer (37°C) after each sampling. Beer plots were prepared using a 10–80 $\mu g \cdot cm^{-3}$ sodium salicylate concentration range. No spectrophotometric interference, at 296 nm, was observed from buffer extracted polyethylene samples.

[1] Fisher Scientific Co., Fair Lawn, NJ, Lot 737013.

[2] Polyethylene powder, BDH Chemicals, Poole, U.K., Lot 15046.

[3] Buffer composition, per liter: 4.11 g NaCl, 1.90 g of anhydrous KH_2PO_4, 8.10 g of anhydrous Na_2HPO_4 and distilled water to 1000 ml.

[4] Type T2C.

[5] Cary, Model 118.

The solid sodium salicylate density (ρ) was determined pycnometrically using dichloromethane.

Matrix porosities were determined from the following expression:

$$\epsilon_{matrix} = (V_{matrix} - V_{PE})/V_{matrix} \quad (6)$$

where V_{matrix} is the matrix volume and V_{PE} is the polyethylene volume of the matrix, computed from its weight and density. Any residual air entrapped in the matrix is thus included in the value of ϵ.

Polyethylene density was determined as follows: 1 g was weighed, introduced in a tempered steel die, heated at 150°C for 1 h and then compressed at 702 MPa for 5 min. After a 30 min cooling period, the polyethylene disc was removed from the die, its thickness and diameter were accurately measured with a micrometer and used to calculate the matrix volume from which the density was determined.

Sodium salicylate solubility was determined as follows: in a thermostated beaker (37°C), a supersaturated sodium salicylate–buffer suspension was introduced and vigorously agitated. At set time intervals, samples were removed with a syringe, rapidly filtered through a 0.22 μm filter membrane [6] and assayed until a constant value was obtained. The syringe and filtering membrane were pre-equilibrated at 37°C to prevent rapid cooling of the suspension and consequently, sodium salicylate precipitation.

The D′ (D/τ) values were determined from sorption–desorption experiments (Desai et al., 1965). The emptied matrices were resaturated for 10 days in a 0.600 $g \cdot cm^{-3}$ sodium salicylate solution, at room temperature and in total darkness. Once the matrices were resaturated, they were carefully removed from their wax supports and rinced with distilled water to remove surface excess sodium salicylate. They were then embedded in fresh wax using the procedure of Desai et al. (1965) and immediately used for the release experiments using conditions previously described. These resaturated matrices released sodium salicylate according to the following expression (Desai et al., 1965):

$$M_t = 2\epsilon \cdot C_0 (Dt/r \cdot \pi)^{1/2} \quad (7)$$

where C_0 is the equilibrium sodium salicylate solution concentration, which was 0.600 $g \cdot cm^{-3}$. The D/τ value can be determined from the slope of a M_t vs $t^{1/2}$ plot, knowing ϵ and C_0, using Eqn. 7. The slopes were calculated from the $M_t/M_\infty < 0.4$ regions, where M_∞ is the total mass of sodium salicylate in the resaturated matrices.

Results and Discussion

Matrices were made with physical characteristics shown in Table 1. Densities (ρ) of solid sodium salicylate and polyethylene were 1.54 ± 0.02 $g \cdot cm^{-3}$ ($\bar{X} \pm S_{\bar{x}}$, $n = 3$) and 0.910 $g \cdot cm^{-3}$, respectively. Desai et al. (1966) reported a value of 1.57 $g \cdot cm^{-3}$ for sodium salicylate density. Solubility (C_s) of sodium salicylate was found to be 0.655 ± 0.006 $g \cdot cm^{-3}$ ($n = 3$).

Sodium salicylate and polyethylene powders were observed under an optical microscope and no particles greater than 30 and 20 μm were respectively found. The solute particles are therefore small relative to the distance of diffusion, except for the first few seconds of release. Fig. 1 shows a typical plot of sodium salicylate cumulative amount released as a function of $t^{1/2}$. The release rates, with their corresponding linear regression parameters, are found in Table 1. It can be seen that the results are consistent with Eqn. 5 which predicts a M_t vs $t^{1/2}$ linear relationship. This relationship was observed until approximately 75% of initial sodium salicylate quantity was released, after then a dispersed–dissolved system transition occurs. Experiments were pursued until more than 95% of sodium salicylate was released which is an indication that all of the solute was available for diffusion. Fig. 2 shows a typical plot of solute released from a matrix equilibrated with a 0.600 $g \cdot cm^{-3}$ sodium salicylate solution. The slope of this curve was computed and used to calculate the D′ value using Eqn. 7. Table 1 shows the specific values of D′ for all the matrices. It must be noted

[6] Millipore, HA filter.

TABLE 1

PHYSICAL AND KINETIC CHARACTERISTICS OF POROUS MATRICES USED IN THE STUDY

Matrix	I	II	III	IV	V	VI
Sodium salicylate (%w/w)	60	60	60	70	70	70
Weight (g)	0.224	0.243	0.246	0.246	0.247	0.243
Thickness (cm)	0.158	0.165	0.165	0.160	0.163	0.160
Volume (cm^3)	0.200	0.209	0.209	0.203	0.207	0.203
Porosity	0.508	0.489	0.483	0.601	0.607	0.605
Slopes $\times 10^4$ *(g · s* $^{-1/2}$*) and intercepts of* M_t *vs* $t^{1/2}$ *plots*						
Intercept	−0.0909	−1.53	1.29	−1.24	−0.396	1.51
Slopes						
Experimental	2.87	3.95	2.40	7.16	6.25	7.34
r^2(n) [a]	0.9988(17)	0.9994(22)	0.9998(28)	0.9994(24)	0.9992(24)	0.9998(24)
Model predicted [b]	3.22	3.89	2.25	6.75	5.59	6.71
$D' \times 10^7$ ($cm^2 \cdot s^{-1}$)	1.37	2.29	0.754	4.47	3.01	4.34
r^2(n) [c]	0.9990(14)	0.9992(14)	0.9997(17)	0.9995(10)	0.9988(12)	0.9984(10)

[a] n represents the number of points used for the calculations.

[b] Computed from Eqn. 5.

[c] Computed from a linear regression of M_t vs $t^{1/2}$ sorption–desorption release data. One set of release kinetics for each matrix.

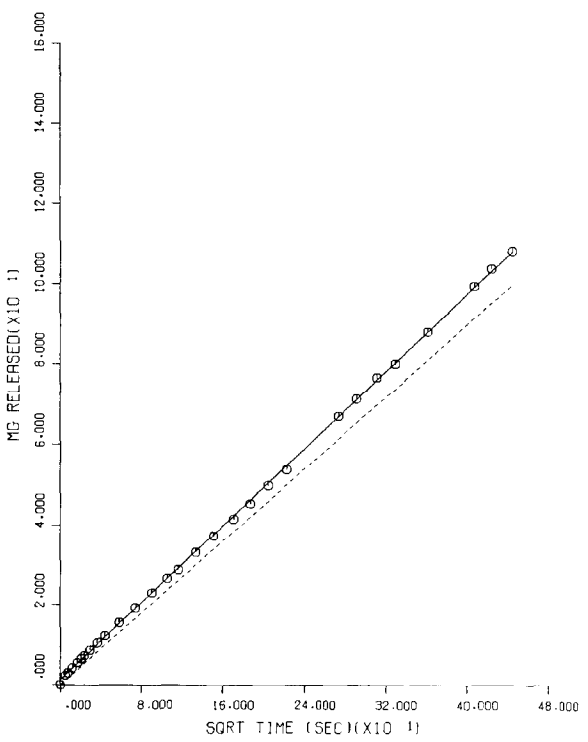

Fig. 1. Typical plot of sodium salicylate cumulative amount released as a function of $t^{1/2}$ for fused porous polyethylene disc matrix III. (O——O), experimental and (- - - - -), model predicted values.

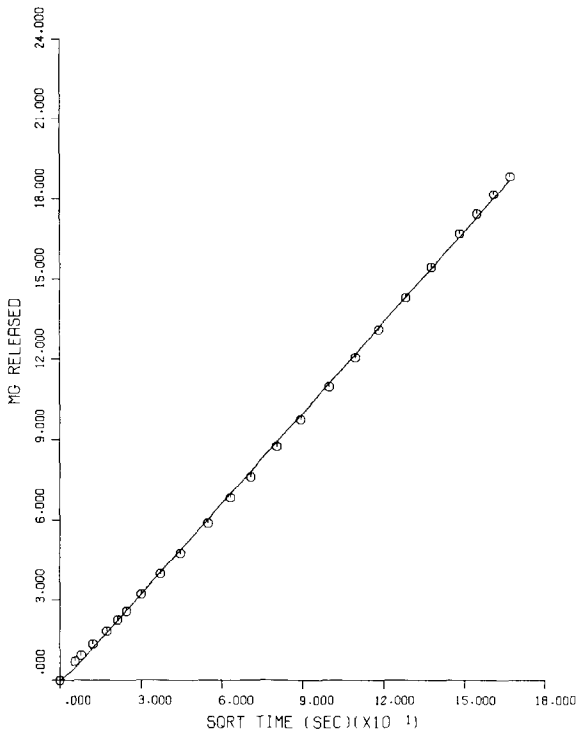

Fig. 2. Sodium salicylate release from fused porous polyethylene disc matrix III equilibrated with 60% sodium salicylate solution. Data were used for the calculation of D′. Matrix initially contained 60% w/w solid sodium salicylate that was leached completely according to that kinetics shown in Fig. 1.

that the D′ determined value is an average value since D is dependent on sodium salicylate concentration (Desai et al., 1966). Application of Eqn. 7 to the curve of Fig. 2 yields a mean value of D′, because the variable diffusion coefficient is averaged over the range of concentration existing in the matrix during the experiment, 0 at the surface and C_s at the moving front.

The Higuchi equation is essentially valid only if $A/\epsilon \cdot C_s \geqslant 3$–4 (Higuchi, 1963), otherwise the boundary moves too fast and the discrepancy between theoretical and experimental release values increases. $A/\epsilon \cdot C_s$ values for matrices I to VI ranged from 2.02 to 2.23 which indicated that Eqn. 1 is not the best equation to use. In fact, for non-porous systems, Paul and McSpadden (1976) reported that when the limit of $A \rightarrow C_s$, there is a 11.3% underestimation using the Higuchi equation developed for non-porous systems (Higuchi, 1963) and this difference can be eliminated if the exact analytical solution (Eqn. 2) is used. The Higuchi Eqn. 1 has the advantage to be simple to use, however, with microcomputers, solutions of Eqns. 4 and 5 can be easily obtained.

Table 2 shows a comparison of the experimental sodium salicylate release data with Eqns. 5, 3 and 1. It can be seen that the best description of experimental data is obtained with Eqn. 5 which uses the ϵ term with an exponent of 1 instead of 2/3 as proposed by Miller and Peppas (1983). This exponent of 1 is necessary, because the effective cross-sectional area available for diffusion in a porous solid per unit area exposed to the release medium, is equal to ϵ (Gray, 1968; Sherwood, 1975). When using the $\epsilon^{2/3}$ term, a great overprediction results, especially for the lower porosity matrices. This discrepancy is less pronounced for higher porosity discs since as ϵ increases, the difference between $\epsilon^{2/3}$ and ϵ, decreases. It is expected that for low porosity discs (0.3–0.5), the difference between predicted release rates using Eqns. 3 and 5 would be much higher, with Eqn. 3 giving an overprediction of experimental results. Except in the case of matrix I, Eqn. 5 gives an average 6.5% underestimation. It is believed that this underestimation could be due to a convective flow component, which is difficult to model, as a result of a solution density gradient inside the matrix pores.

In conclusion, the experimental release rates correlated very well, less than 8% relative error, with the moving boundary model and indicates that the model is the exact representation of physical events occurring in the matrices. The introduction of an exponent of 1 for the ϵ term (in Eqn. 5) instead of a 2/3 exponent initially proposed (Miller and Peppas, 1983) in the equation for the amount of solute released, to take into account the effective porous cross-sectional area, has improved the predictive capabilities of the moving boundary model. In the evaluation of controlled release systems, in vitro drug release experiments must be carried out (Langer and Wise, 1984) for any new system. Therefore, Eqns. 4 and 5 can be used to evaluate the effect of the model parameter values on release kinetics and used to design a particular system, if the prerequisites previously mentioned, are fulfilled. This model is especially useful for highly water-soluble solutes when the solute loading is not significantly greater ($A/\epsilon \cdot C_s \leqslant 3$–4) than the solute solubility in the matrix.

TABLE 2

COMPARISON OF EXPERIMENTAL SODIUM SALICYLATE RELEASE RATES WITH THE DIFFERENT MODELS

Matrix	$M/C_s \cdot (D' \cdot t)^{1/2}$						
	Experimental	Eqn. 5	% Error	Eqn. 3	% Error	Eqn. 1	% Error
I	1.18	1.33	+12.7	1.67	+41.5	1.12	−5.36
II	1.26	1.24	−1.59	1.58	+25.4	1.13	−10.3
III	1.33	1.25	−6.02	1.59	+19.6	1.14	−14.3
IV	1.64	1.54	−6.10	1.83	+11.6	1.39	−15.2
V	1.74	1.56	−10.3	1.84	+5.75	1.38	−20.7
VI	1.70	1.56	−8.24	1.84	+8.24	1.38	−18.8

References

Chien, Y.W., Novel Drug Delivery Systems, Marcel Dekker, New York, 1983, pp. 1–11.

Crank, J., The Mathematics of Diffusion, Clarendon Press, Oxford, 1975.

Desai, S.J., Simonelli, A.P and Higuchi, W.I., Investigation of factors influencing release of solid drug dispersed in inert matrices. J. Pharm. Sci., 54 (1965) 1459–1464.

Desai, S.J., Singh, P., Simonelli, A.P. and Higuchi, W.I., Investigation of factors influencing release of solid drug dispersed in inert matrices: II. J. Pharm. Sci., 55 (1966) 1224–1229.

Graham, N.B., Polymeric inserts and implants for the controlled release of drugs. Br. Polym. J., 10 (1978) 260–266.

Gray, W.A., The Packing of Solid Particles, Chapman and Hall, London, 1968, p. 129.

Gurny, R. Doelker, E. and Peppas, N.A., Modelling of sustained release of water-soluble drugs from porous, hydrophobic polymers. Biomaterials, 3 (1982) 27–32.

Higuchi, T., Mechanism of sustained-action medication, J. Pharm. Sci., 52 (1963) 1145–1149.

Langer, R., Polymeric delivery systems for controlled drug release. Chem. Eng. Commun., 6 (1980) 1–48.

Langer, R. and Peppas, N.A., Present and future applications of biomaterials in controlled drug delivery systems. Biomaterials, 2 (1981) 201–214.

Langer, R.S. and Wise, D.L., Medical Applications of Controlled Release, Vol. II, CRC Press, Florida, 1984, p. 26.

Miller, E.S. and Peppas, N.A., Diffusional release of water-soluble bioactive agents from ethylene-vinyl acetate copolymers. Chem. Eng. Commun., 22 (1983) 303–315.

Paul, D.R. and McSpadden, S.K., Diffusional release of a solute from a polymer matrix. J. Membr. Sci., 1 (1976) 33–48.

Sherwood, T.K., Pigford, R.L. and Wilke, C.R., Mass Transfer, McGraw Hill, New York, 1975, p. 40.

Siegel, R.A. and Langer, R., Controlled release of polypeptides and other macromolecules. Pharm. Res., 1 (1984) 2–10.