Dissolution-Controlled Transport from Dispersed Matrixes

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Abstract □ A simplified mathematical model for dissolution-controlled transport from dispersed matrixes is presented. Analytical solutions have been obtained previously when solute diffusion totally controls the transport process. However, when solute dissolution offers the limiting resistance to mass transport, the solution reduces to a form where the mass released varies directly with time. Experimental release rates of a drug from a dispersed polymeric matrix into water were measured for a range of drug particle sizes in order to test the applicability of the proposed model; the agreement between theory and experimental is good.

Keyphrases □ Dissolution—transport from dispersed matrixes □ Matrixes—dispersed, dissolution-controlled transport □ Models, dissolution—dissolution-controlled transport from dispersed matrixes

The theory of diffusional release of a solute or therapeutic agent from a polymer matrix where the initial loading of solute is greater than the solubility limit was initially proposed by Higuchi (1). Several assumptions were made in this model: (*a*) the suspended solute is present as particles of diameter much smaller than the thickness of the matrix; (*b*) the receptor medium is immiscible with the matrix and serves as a perfect sink for the released solute; and (*c*) a pseudo steady-state condition exists during the transport process. More recently the pseudo steady-state assumption in Higuchi's model was reexamined (2) and it was concluded that an exact analysis offered some advantages under conditions of low solute loadings but became virtually identical with Higuchi's analysis for large solute loadings.

The Higuchi model has been applied extensively in the literature with favorable results (2–6). However, there have been several cases in which the drug release-rate kinetics from drug-dispersed matrixes are not adequately described by this model. The *in vitro* release rate of steroids from silicone elastomeric matrixes was studied (7), and it was found that their results were inconsistent with the Higuchi model. Based on the effect of concentration and particle size on the duration of drug release, a dissolution rather than diffusion-controlled mechanism was suggested. It was determined (8) that the release rate of salicylic acid from ointment bases did not follow the Higuchi model, and the discrepancy was related to an inadequate dissolution rate of the suspended particles. The release of benzocaine from ointment bases was determined (9) and it was found that the release rate was not proportional to the square root of drug concentration.

Several theories have been put forth for dissolution-controlled transport mechanisms. The area of drug release rate processes in biopharmaceutics was reviewed (10), in which dissolution mechanisms are considered as a heterogeneous reaction with mass transfer occurring through the movement of solute molecules from solid surfaces. The thermodynamics of drug release from polymeric matrixes was studied (11) and the process was depicted to involve three energy-activated steps: (*a*) dissociation of drug molecules from a crystal lattice, (*b*) solubilization of drug molecules in the polymer matrix, and (*c*) diffusion of drug molecules in the matrix. More recently a good mathematical model for drug release from suspensions was developed (12, 13), which is relatively complex and requires numerical techniques to obtain general solutions. In that study the dissolution rate of a drug in a vehicle and diffusion through the vehicle was related to drug distribution and cummulative drug uptake by a receptor phase. When dissolution is essentially nonexistent, it was found that the suspension behaved as a solution with respect to drug release, whereas when dissolution is slower than diffusion, the rate of dissolution markedly influenced the rate of drug release.

The purpose of the present study was to develop a simplified model for dissolution-controlled transport from dispersed matrixes. Analytical solutions to the complicated phenomenon of combined dissolution and diffusion mechanisms have been derived, and the results are related to experimental measurements.

THEORETICAL

A combined dissolution and diffusion-controlled transport system is shown in Fig. 1. As an approximation, the controlled release system is depicted in one dimension as a semi-infinite medium. The kinetics of dissolution is assumed to be given by an expression which is proportional

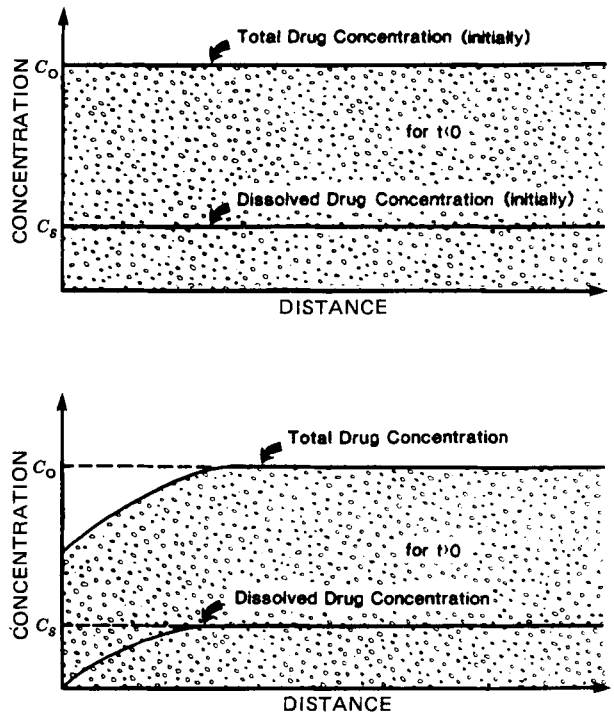

Figure 1—*Drug concentration profiles within the matrix.*

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to the difference between the solubility of the solute in the matrix and the actual concentration of the solute in the matrix at the point in space. Under these conditions, the equation incorporation of both dissolution and diffusion in the mass transport process can be given to a first approximation by (12, 14):

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} + K(C_s - C) \quad \text{(Eq. 1)}$$

where D is the solute diffusivity in the matrix, C is the concentration, C_s is the solute solubility, and K is the solute dissolution rate constant. The appropriate boundary conditions for dissolved solute with respect to time and distance are:

(*a*) $C = 0$ at $x = 0$ for all t;

(*b*) $C = C_s$ at $t = 0$ for all x.

Defining $\overline{C}$:

$$\overline{C} = C_s - C \quad \text{(Eq. 2)}$$

Equation 1 can be transformed to read:

$$\frac{\partial \overline{C}}{\partial t} = D\frac{\partial^2 \overline{C}}{\partial x^2} - K\overline{C} \quad \text{(Eq. 3)}$$

with boundary conditions:

(*a*) $\overline{C} = C_s$ at $x = 0$ for all t;

(*b*) $\overline{C} = 0$ at $t = 0$ for all x.

The analytical solution of Eq. 3 is given by (14):

$$\frac{\overline{C}}{C_s} = \tfrac{1}{2}\exp(-x\sqrt{K/D})\,\mathrm{erfc}\left(\frac{x}{2\sqrt{Dt}} - \sqrt{Kt}\right) + \tfrac{1}{2}\exp(x\sqrt{K/D})\,\mathrm{erfc}\left(\frac{x}{2\sqrt{Dt}} + \sqrt{Kt}\right) \quad \text{(Eq. 4)}$$

and

$$M_t = C_s\sqrt{D/K}\left[(Kt + \tfrac{1}{2})\,\mathrm{erf}\sqrt{Kt} + \sqrt{\frac{Kt}{\pi}}\exp - Kt\right] \quad \text{(Eq. 5)}$$

where M_t is the mass released per unit area at time t.

The total mass of solute per unit area is given by:

$$M_\infty = \frac{C_0 l}{2} \quad \text{(Eq. 6)}$$

where C_0 is the total solute loading and l is the thickness of the finite slab. The model assumptions will not be met when l is very small.

The fractional amount of solute released at any time t is now given by:

$$\frac{M_t}{M_\infty} = 2\frac{C_s}{C_0}\sqrt{\frac{D}{Kl^2}}\left[(Kt + \tfrac{1}{2})\,\mathrm{erf}\sqrt{Kt} + \sqrt{\frac{Kt}{\pi}}\exp - Kt\right] \quad \text{(Eq. 7)}$$

The ratio M_t/M_∞ can take values >1 for long enough time periods, since M_t is unbounded because of the semi-infinite medium assumption. The solution is only applicable when there is undissolved solute at every point. Thus, Eq. 7 is only valid for:

$$C_s Kt \le C_0 \quad \text{(Eq. 8)}$$

Under conditions when Kt assumes large values and solute dissolution is offering the limiting control to the transport process, Eq. 7 reduces to (12, 14):

$$\frac{M_t}{M_\infty} = 2\frac{C_s}{C_0}\sqrt{\frac{DK}{l^2}}\left(\frac{1}{2K} + t\right) \quad \text{(Eq. 9)}$$

In this case, the mass, M_t, varies linearly with time. However, under conditions when Kt assumes small values and solute diffusion is controlling mass transport totally, Eq. 7 reduces to:

$$\frac{M_t}{M_\infty} = 4\frac{C_s}{C_0}\left(\frac{Dt}{\pi l^2}\right)^{1/2} \quad \text{(Eq. 10)}$$

which is roughly similar to the solution originally obtained by Higuchi (1).

The release rate of solute for small times is given by:

$$\frac{dM_t/M_\infty}{dt} = 2\frac{C_s}{C_0}\sqrt{\frac{DK}{l^2}}\left(\mathrm{erf}\sqrt{Kt} + \frac{1}{\sqrt{\pi Kt}}\exp - Kt\right) \quad \text{(Eq. 11)}$$

Similarly, under conditions when Kt assumes large values and solute dissolution is offering the limiting control to the overall transport process, Eq. 11 reduces to:

$$\frac{dM_t/M_\infty}{dt} = 2\frac{C_s}{C_0}\sqrt{\frac{DK}{l^2}} \quad \text{(Eq. 12)}$$

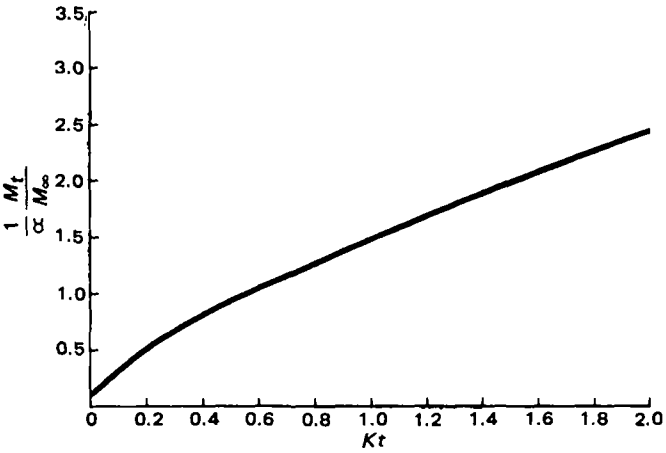

Figure 2—*Variation of* M_t/M_∞ *with* Kt ($\alpha = 2C_s/C_0\sqrt{D/Kl^2}$).

However, when Kt assumes small values and solute diffusion is controlling mass transport, Eq. 11 reduces to:

$$\frac{dM_t/M_\infty}{dt} = 2\frac{C_s}{C_0}\left(\frac{D}{\pi l^2 t}\right)^{1/2} \quad \text{(Eq. 13)}$$

The implications of Eqs. 7 and 11 can be seen in Figs. 2 and 3, where the cummulative mass released and the release rate are plotted as a function of Kt. The release rate is strongly dependent upon Kt in the region where $Kt < 0.3$, after which the release rate becomes almost independent of Kt.

EXPERIMENTAL

Preparation of Monolithic Systems—Solute-dispersed monolithic matrixes were prepared by a solvent casting procedure (15). Polyisobutylene and mineral oil were dissolved in heptane at room temperature and to this solution was added a drug of varied particle size so as to obtain a total solids content in the solution of ~25% by weight. At this concentration, the solution had a suitable viscosity to facilitate casting on a polyester substrate using a gardner knife set-up (15). The cast films were allowed to set at room temperature and subsequently oven dried at 50° to remove the residual traces of heptane. The residual solvent levels were always <100 ppm.

The thickness of the dried films were measured using a thickness gauge and were found to be relatively uniform (50 ± 5 μm). The drug content in the films was determined by dissolving the dried films in heptane followed by extraction into dilute sulfuric acid and subsequent analysis using liquid chromatography. The average particle size of the drug was obtained by specific surface area analysis using a gas absorption (Brunayer, Emmett, and Teller) technique (16).

Release Rate Determinations—The drug release rates as a function of time were determined using a special thermostated holder and bath assembly. The monolithic systems were attached to a suitable sample holder and suspended from a vertically reciprocating shaker such that each system was continuously immersed in a test tube containing 15 ml

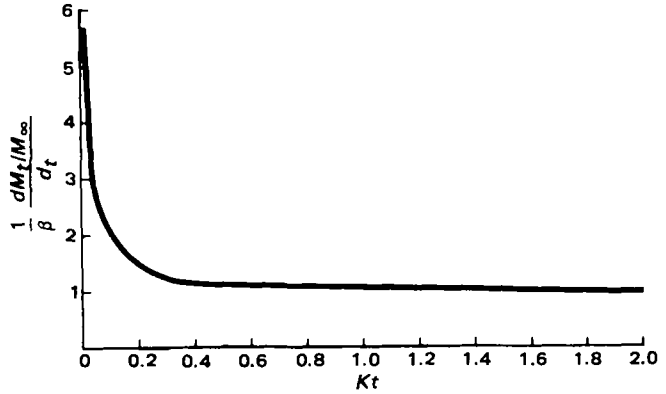

Figure 3—*Variation of* $dM_t/M_\infty/dt$ *with* Kt ($\beta = 2C_s/C_0\sqrt{DK/l^2}$).

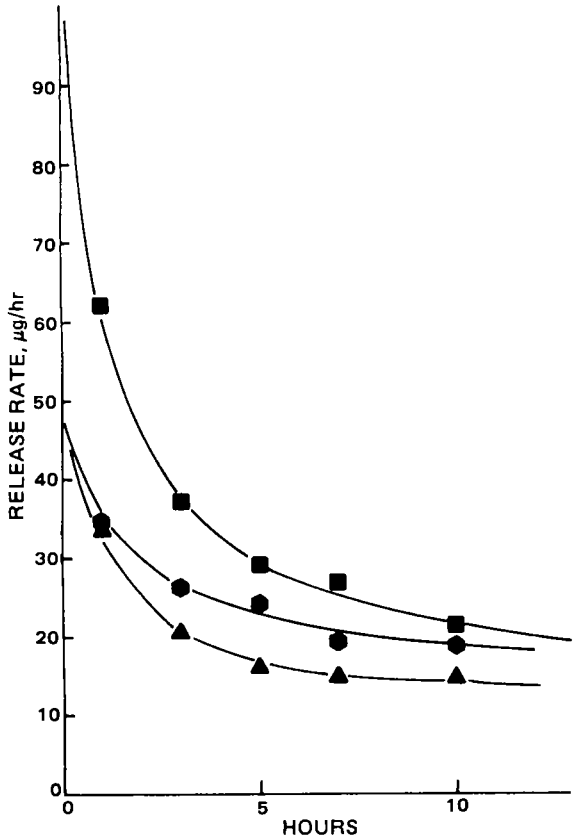

Figure 4—*Drug release rate* versus *time profiles. Key: (■) 2.5 μm; (●) 7.8 μm; (▲) 9.9 μm.*

of water equilibrated at 32.0 ± 0.3°. Agitation was at a frequency of 0.5 cycle/sec with an amplitude of 20–25 mm. At each time interval the systems were transferred to fresh tubes containing 15 ml of water preequilibrated to 32.0 ± 0.3°. Drug concentrations in the solutions were determined using liquid chromatography.

RESULTS

The *in vitro* drug release rate *versus* time profiles for the various monolithic systems are shown in Fig. 4. Three different average particle sizes were used: 2.5, 7.8, and 9.9 μm. The release-rate profile is dependent on particle size, increasing with decreasing particle size; however, the relative flatness of the pseudo steady-state portion of the curve improves markedly with increasing particle size. These results were analyzed using the typical Higuchi model, and assuming that drug diffusion is the controlling mechanism. The apparent drug diffusivity was computed utilizing (1):

$$\frac{1}{A}\frac{dM_t}{dt} = \left(\frac{DC_sC_0}{2}\right)^{1/2} t^{1/2} \qquad \text{(Eq. 14)}$$

where C_0 is the initial drug loading in the matrix.

The normalized flux, DC_s, as a function of drug particle size, is shown in Fig. 5. At the same drug loading, the value of DC_s decreases with increasing particle size, suggesting the presence of a secondary mechanism affecting drug diffusion. As infinite sink conditions were maintained during the release-rate measurements and boundary layer affects were held to a minimum by adequate stirring, drug particle dissolution was considered to be the secondary mechanism.

The apparent drug dissolution rate constant was computed following the procedure outlined in *Theoretical*, together with the normalization of drug diffusivity to zero particle size, *i.e.*, totally dissolved state. These results are presented in Fig. 6, where the dissolution rate constant is plotted as a function of drug particle size. It is apparent that the dissolution rate constant decreases with increasing particle size with a limiting value of $\sim 35 \times 10^{-7}$ sec^{-1} for an infinitely small particle size. Also shown in Fig. 6 is the limiting Sherwood Number (SH = kd/D) relationship normalized to 10 μm (17). The separation between the two lines is probably indicative of the deviation from infinite sink conditions maintained within the matrix.

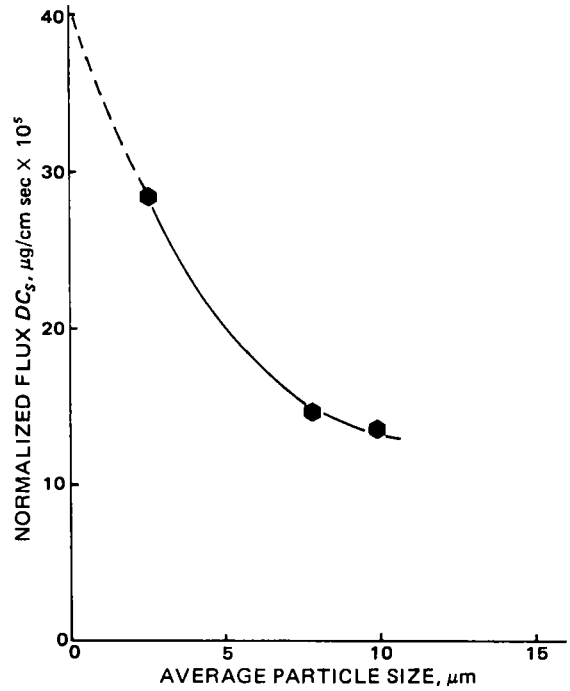

Figure 5—*Effect of particle size on normalized flux.*

CONCLUSIONS

A simplified model for dissolution-controlled transport from dispersed matrixes has been presented. Analytical solutions to the combined phenomenon of dissolution and diffusion mechanisms have been derived. At the limit when diffusion totally controls the mass transport, the solution reduces to a form with the mass released having a square-root dependency with time. However, when solute dissolution offers the

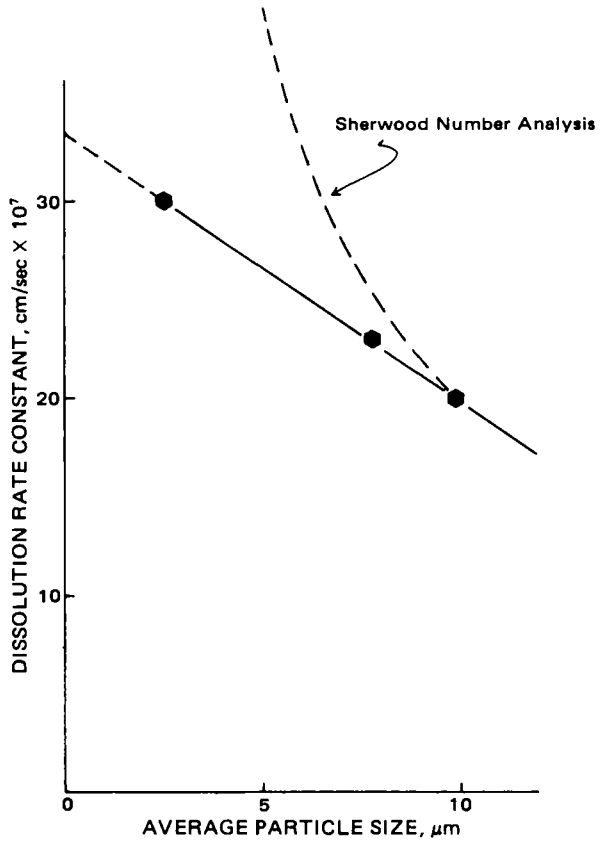

Figure 6—*Effect of particle size on dissolution rate constant.*

limiting resistance to mass transport, the solution reduces to form where the mass released varies directly with time. Under these conditions, the release rate of a dispersed solute would become time independent.

The simplified model can be viewed as an extension of the familiar Higuchi model (1) for drug release from ointments and suspensions. In the region of small time, the conclusions presented here are in agreement with previous studies (12, 13). However, the application of this model is considerably simplified compared to the system presented previously (12, 13), which is more complex and results in equations that do not predict a simple relationship between the various parameters.

Experimental release-rate measurements have been conducted with monolithic systems where the particle size of the dispersed solute has been varied. The results can be adequately analyzed using the proposed mathematical model and indicate that the mass transport resistance offered by particle dissolution increases with increasing particle size. However, the release rate approaches a pseudo steady-state and becomes time independent with this increasing resistance offered to the mass transport process by particle dissolution. This information can be utilized in the design and development of controlled-release formulations.

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Determination of Enviroxime in a Variety of Biological Matrixes by Liquid Chromatography with Electrochemical Detection

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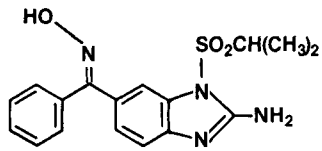
Abstract □ A simple and specific method has been developed for determination of enviroxime in biological samples. Enviroxime, a substituted benzimidazole, its coisomer zinviroxime, and the internal standard hexestrol were extracted from the samples with benzene. The benzene layer was evaporated and the residue was reconstituted and injected onto a liquid chromatograph. Reversed-phase chromatography on an octylsilane column with a 65% methanol–35% 0.14 *M* sodium acetate mobile phase separated the components. The compounds were detected electrochemically using a glassy carbon electrode held at +0.85 V. The assay could detect as little as 4 ng of enviroxime/ml of plasma, 15 ng/ml of nasal wash, and 20 ng/ml of urine or tissue homogenate. For plasma assays, the procedure was >97% accurate and had a relative standard deviation of <4%. This method has proven to be applicable and reliable for the determination of enviroxime in many types of biological samples. Several problems encountered during the routine use of electrochemical detection were explored and minimized.

Keyphrases □ Enviroxime—determination in a variety of biological matrixes by liquid chromatography with electrochemical detection □ Electrochemical detection—determination of enviroxime in a variety of biological matrixes by liquid chromatography □ Liquid chromatography—determination of enviroxime in a variety of biological matrixes with electrochemical detection

Enviroxime, anti-6-[(hydroxyimino)phenyl]methyl-1-(1-methylethyl)sulfonyl-1*H*-benzimidazole-2-amine (I), has been shown to be a highly specific inhibitor of the multiplication of rhinovirus in tissue cultures (1, 2):



I

Compound I has undergone extensive metabolic and toxicological studies in dogs and rats (3, 4) and is currently being evaluated as a treatment for the common cold (5).

In early work with I in dogs and mice, blood levels were determined using a plaque reduction assay. Plaque assays are nonspecific, since they are capable only of determining antiviral activity. To determine levels of I in the presence of the less active syn–oxime isomer, zinviroxime (II), it was necessary to develop a chemical assay. Initial experiments aimed at developing a GC assay for I and II indicated that such an approach was undesirable. Derivatization of the oxime group was required to make I and II volatile enough. However, such a derivatization eliminated the hydrogen bonding capability of this group and, thus, made the separation of I and II quite difficult. Recently, a method was reported which used high-performance liquid chromatography (HPLC) with UV detection for the determination

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