Heterogeneous Model of Drug Release from Polymeric Matrix

S. K. CHANDRASEKARAN ˣ **and R. HILLMAN**

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Abstract □ The kinetics of drug release from a polymeric matrix originally proposed by Higuchi were extended for the case of high drug loading (relative to the solubility of the drug in the polymer). The model of a granular matrix in which an effective porosity and tortuosity are assumed to modify the normal Higuchi kinetics is reviewed. A new model, which allows the prediction of the kinetics of drug release from properties of the polymer and drug, is based on the assumption that the permeability of the dispersed matrix is a function of drug loading.

Keyphrases □ Release rates—heterogeneous model of drug release from polymeric matrix □ Kinetics—heterogeneous model of drug release from polymeric matrix □ Diffusion—heterogeneous model of drug release from polymeric matrix

The kinetics of release of a solute dispersed in a polymeric matrix are of general interest in the controlled delivery of drugs (1). When the total loading of the solute (dissolved plus dispersed), C_0, is higher than its solubility in the matrix, C_s, the kinetics of release have been described by Higuchi (2). In this model, when the matrix is placed in an infinite sink, it is assumed that solid drug dissolves and diffuses from the surface layer of the matrix; when this layer becomes exhausted of drug, the next layer begins to be depleted.

BACKGROUND

In a planar system, the release of solute per unit time, dM_t/dt, is described by:

$$\frac{dM_t}{dt} = A\left[\frac{D(2C_0 - C_s)C_s}{t}\right]^{1/2} \quad \text{(Eq. 1)}$$

where A is the area of the slab, D is the diffusivity of the drug in the matrix, C_0 is the drug loading, and C_s is the solubility of the drug in the matrix at time t.

When the drug loading becomes much greater than the solubility and a granular matrix (with the possibility of interparticle contact) is formed, Eq. 1 usually is modified to give (2–4):

$$\frac{dM_t}{dt} = A\left[\frac{\frac{\epsilon}{\tau}D(2C_0 - \epsilon C_s)C_s}{t}\right]^{1/2} \quad \text{(Eq. 2)}$$

which becomes:

$$\frac{dM_t}{dt} = A\left(\frac{2\epsilon DC_0C_s}{\tau}\right)^{1/2} t^{-1/2} \quad \text{(Eq. 3)}$$

in the case where $C_0 \gg \epsilon C_s$. Thus, Eq. 1 is modified by an effective porosity, ϵ, which can be related to the volume fraction of drug in the matrix, and an effective tortuosity, τ, which describes the tortuous diffusion path a solute molecule must follow. In addition, the D value is taken as the diffusivity of the solute in the receptor solution. In other words, it is assumed that the solute is released by leaching through channels that are formed in the continuous matrix.

When Eq. 3 is rewritten as:

$$Q = Kt^{-1/2} \quad \text{(Eq. 4)}$$

with:

$$Q = \left(\frac{1}{A}\right)\frac{dM_t}{dt} \quad \text{(Eq. 5)}$$

and:

$$K = \left(\frac{2\epsilon DC_0C_s}{\tau}\right)^{1/2} \quad \text{(Eq. 6)}$$

it can be seen that this model predicts that the release rate constant changes in proportion to the square root of the initial drug loading, C_0. The ratio ϵ/τ then expresses the fractional area available for release.

There are several conceptual and practical drawbacks to the model. One would expect that by introducing flux enhancers or increasing the amount of drug in the matrix, the structure of the matrix, and, hence, the diffusivity of the drug in the matrix should be changed. In this model, the diffusivity is assumed to be independent of the drug concentration. Practically, it is difficult to measure the tortuosity and porosity of a polymer matrix. It is far more desirable to relate drug release to the molecular weight of the drug, the loading of drug in the matrix, and the diffusivity of the drug in pure polymer, all easily obtainable properties.

Davis (5) proposed an equation relating the diffusivity of several drugs in polyacrylamide and povidone gels based on the concentration and molecular weight of the drug in the polymer matrix and the diffusivity of the drug in the receptor solvent. The diffusion coefficient of the drug in the polymer, D_p, is related to the diffusion coefficient of the drug in pure solvent, D_0, by:

$$\log D_p = \log D_0 - k_sP \quad \text{(Eq. 7)}$$

where P is the volume percent of polymer and k_s is defined by:

$$k_s = -\frac{d \log D_p}{dP} \quad \text{(Eq. 8)}$$

and can be shown empirically to be a function of the molecular weight of the solute, M:

$$k_s = k_1 + k_2M \quad \text{(Eq. 9)}$$

Combining Eqs. 7 and 9 gives:

$$D_p = D_0 \exp[-(k_1 + k_2M)P] \quad \text{(Eq. 10)}$$

where k_1 and k_2 are empirical constants.

Davis pointed out that the logarithmic relationship between the diffusivity and the polymer concentration could be anticipated from previous work (6) on porosity in polymer networks. Thus, the exponential term in Eq. 10 could be redefined as porosity, which is defined by the space available for collision-free diffusion. The fundamental drawback in Davis' work is that it is based on an empirical correlation where four constants must be determined experimentally.

An attempt was made in this study to develop a heterogeneous model of drug diffusion from a dispersed polymer matrix for which fewer experimental measurements related directly to fundamental physicochemical properties are required.

THEORY

The polymer matrix is visualized as a heterogeneous system consisting of a continuous (polymer) phase with a discontinuous drug phase as

Table I—Release Rate Constant (K') for Salicylic Acid at Various Drug Concentrations (C_0) in a Polyethylene Glycol–Ethylcellulose Film

Drug, mg/ml	Release Rate Constant, mg/36 cm²/min$^{1/2}$	
	Calculated	Measured (3)
55	0.3	0.25
100	0.6	0.65
200	1.45	1.4
300	2.63	2.7
350	3.36	3.65

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Table II—Release Rate Constant (K') for Salicylic Acid at Various Drug Concentrations (C_0) in an Ethylcellulose Film

Drug, mg/ml	Release Rate Constant, mg/36 cm²/min$^{1/2}$	
	Calculated	Measured (3)
55	0.1	0.1
100	0.2	0.2
200	0.47	0.4
300	0.86	0.6

Table III—Release Rate Constant (K') for Tripelennamine at Various Drug Concentrations (C_0) in a Polyethylene Glycol–Ethylcellulose Film

Drug, mg/ml	Release Rate Constant, mg/36 cm²/min$^{1/2}$	
	Calculated	Measured (3)
55	0.1	0.1
100	0.2	0.3
200	0.47	0.7
300	0.86	1.2
400	1.45	1.99
450	1.8	2.45

particles dispersed uniformly throughout the matrix. Initially, the particles will be assumed to be a uniform array of spheres in the matrix. This assumption allows use of Maxwell's work on the conductivity of a dilute suspension of homogeneous nonpolarizable spheres (7). These assumptions are made to reduce the many particle problem to the case of one particle in a homogeneous field. This work also has been extended to the thermal conductivity of heterogeneous mixtures (8).

From Fick's law, the permeability of a dispersed polymer matrix can be expressed by:

$$P = \frac{D_p V_p \left(\frac{dc}{dx}\right)_p + D_d V_d \left(\frac{dc}{dx}\right)_d}{V_p \left(\frac{dc}{dx}\right)_p + V_d \left(\frac{dc}{dx}\right)_d} \qquad \text{(Eq. 11)}$$

or:

$$P = \frac{D_p V_p F_p + D_d V_d F_d}{V_p F_p + V_d F_d} \qquad \text{(Eq. 12)}$$

where:

$$F_d = \left(\frac{dc}{dx}\right)_d \qquad \text{(Eq. 13)}$$

$$F_p = \left(\frac{dc}{dx}\right)_p \qquad \text{(Eq. 14)}$$

Equation 11 expresses the permeability (P) as a function of the volume fraction of polymer (V_p) and drug (V_d), the diffusivity of the drug through the pure polymer phase (D_p) and the dispersed polymer phase (D_d), and the overall concentration gradient (F_p and F_d) in the two phases.

From Maxwell's work, the average gradient ratio for spheres can be expressed as:

$$F_d = \left[1 + \left(k\frac{D_p}{D_d} - 1\right)V_d\right]^{-1} \qquad \text{(Eq. 15)}$$

assuming $F_p = 1$. Substituting Eq. 15 into Eq. 12 and rearranging terms yield:

$$\frac{P}{P_p} - 1 = 3V_d\left[\frac{(kD_d/D_p) + 2}{(kD_d/D_p) - 1} - V_d\right]^{-1} \qquad \text{(Eq. 16)}$$

where P is the net normalized permeability of the dispersed matrix, P_p is the normalized permeability of the polymer matrix, V_d is the volume fraction of dispersed particles, and k is the partition coefficient.

With the assumption that $kD_d/D_p \gg 1$, Eq. 16 reduces to:

$$\frac{P}{P_p} = \frac{1 + 2V_d}{1 - V_d} \qquad \text{(Eq. 17)}$$

The volume fraction of the dispersed particles can be related to the total loading of particles by:

$$V_d = \frac{C_0}{\rho} \qquad \text{(Eq. 18)}$$

Table IV—Release Rate Constant (K') for Tripelennamine at Various Drug Concentrations (C_0) in an Ethylcellulose Film

Drug, mg/ml	Release Rate Constant, mg/36 cm²/min$^{1/2}$	
	Calculated	Measured (3)
55	0	0
100	0	0
200	0.2	0.2
300	0.37	0.4
400	0.59	0.5
450	0.74	0.7

Table V—Release Rate Constant (K') for Caffeine at Various Drug Contents in an Ethylcellulose Film

Drug, % w/w	Release Rate Constant, mg/7.95 cm²/sec$^{1/2}$ × 10³	
	Calculated	Measured (9)
2	5.0	4.9
5	7.5	7.6
10	11.5	20.4
15	15.5	31.0

Table VI—Release Rate Constant (K') for Salicylic Acid at Various Drug Contents in an Ethylcellulose Film

Drug, % w/w	Release Rate Constant, mg/7.95 cm²/sec$^{1/2}$ × 10³	
	Calculated	Measured (9)
5	6.9	6.3
10	10.3	7.6
15	14.0	16.8

where ρ is the density of the dispersed phase.

Equation 17 now becomes:

$$\frac{DC}{D_p C_p} = \frac{\rho + 2C_0}{\rho - C_0} \qquad \text{(Eq. 19)}$$

where D_pC_p is the normalized permeation rate in the pure polymer (*i.e.*, very low solute loadings) and DC is the normalized rate in the dispersed matrix at a particle loading of C_0.

The basic Higuchi model now may be modified for the release of drug from a dispersed polymer matrix to account for the change in diffusivity. Again, the basic Higuchi model can be written as:

$$\frac{1}{A}\frac{dM_t}{dt} = \left(\frac{2DC_0C_s}{t}\right)^{1/2} \qquad \text{(Eq. 20)}$$

Accounting for the effect of the addition of a dispersed phase by substituting Eq. 19 into Eq. 20 yields:

$$\frac{1}{A}\frac{dM_t}{dt} = \left[2D_pC_pC_0\left(\frac{\rho + 2C_0}{\rho - C_0}\right)\right]^{1/2} t^{-1/2} \qquad \text{(Eq. 21)}$$

The release rate constant, K', for a porous matrix becomes:

$$K' = \left[2D_pC_pC_0\left(\frac{\rho + 2C_0}{\rho - C_0}\right)\right]^{1/2} \qquad \text{(Eq. 22)}$$

and:

$$\frac{1}{A}\frac{dM_t}{dt} = K't^{-1/2} \qquad \text{(Eq. 23)}$$

Thus, the release rate of drug from a porous matrix can be calculated from the density of the dispersed phase, the drug loading, and the permeability of the drug in the pure polymer.

RESULTS AND DISCUSSION

There are few data in the literature on the incorporation of a drug or a solute at high loadings into polymeric films or matrixes. Samuelov *et al.* (3) recently published data on the release rate characteristics of salicylic acid and tripelennamine from polyethylene glycol–ethylcellulose films as a function of solute loading, and an attempt was made to utilize their data to test the validity of the proposed model. The release rate constant, K', was computed using Eq. 22, and the results of these computations as a function of solute loading are presented in Tables I–IV.

The release rate constants measured by Samuelov *et al.* (3) also are shown.

The release rate constants for salicylic acid in polyethylene glycol–ethylcellulose and pure ethylcellulose films are shown in Tables I and II. The density of the salicylic acid was taken as 1.443 g/cm^3, and the normalized permeation rate, D_pC_p, of salicylic acid in the polymer was calculated from the lowest solute loading (55 mg/ml) and used in all subsequent computations. The agreement between the release rate constants determined experimentally and those calculated from the model is good.

Similarly, the release rate constants for tripelennamine in polyethylene glycol–ethylcellulose and pure ethylcellulose films are presented in Tables III and IV. The normalized permeation rate of tripelennamine in the polymer was calculated from the lowest solute loading (55 mg/ml), and the density of the dispersed solute was taken as 1.35 g/cm^3. The agreement between theory and experiment again is good.

Friedman *et al.* (9) prepared timed-release dosage forms using ethylcellulose as the polymeric matrix and salicylic acid and caffeine as model drugs. They determined drug release rates for different initial drug concentrations, and their experimental results are presented in Tables V and VI. The values of the release rate constant, K', computed using Eq. 22 also are shown. The diffusivity in the polymer of caffeine and salicylic acid was 2.26×10^{-11} and 1.96×10^{-11} cm^2/sec, respectively. The agreement between the release rate constants determined experimentally and those calculated from the model is good.

There is a good correlation between the model predictions and the measured release rate constants for the drugs. The deviation at very high drug loadings (>30%) can be attributed to interparticle contact. The interparticle contact leads to the formation of channels in the membrane through which the drug can be leached. Therefore, a model of a porous network must be applied. However, up to this limit, the release of drug can be predicted simply from a knowledge of drug loading, drug density, and the permeation rate of the drug in the pure polymers (very low loadings). Comparison of Tables I and II or Tables III and IV shows that plasticized films (with polyethylene glycol) have significantly higher release rate constants than do pure ethylcellulose films. Thus, the diffusivity and solubility of the drug are altered by the addition of plasticizers. The theory could be suitably modified to predict the release rate based on flux enhancer content and will be the subject of a subsequent communication.

Clearly, many properties of the polymer matrix can influence the permeation of drug including the geometry of the dispersed phase (shape, size, and size distribution), the composition of the dispersed phase, and interactions between the phases. However, the simplified model proposed here apparently gives a good correlation to experimental evidence.

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Synthesis and Evaluation of Substituted Quinazolone Derivatives for Antibacterial, Antifungal, and Antiacetylcholinesterase Activities

ANIL K. SEN GUPTA ˣ and HEMANT K. MISRA

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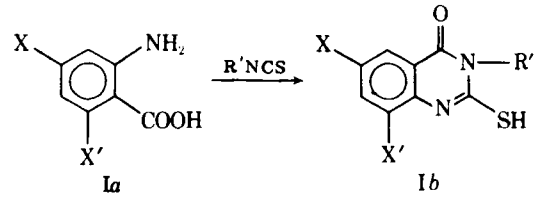
Abstract □ The synthesis of new 6-bromo- and 6,8-dibromo-2-[*N*-(2′-alkyl-1′,3′,4′-thiadiazol-5′-yl)carbamoylmethylthio]-3-aryl/cyclohexyl-4-(3*H*)-quinazolones is described. The synthesized derivatives were screened for antibacterial, antifungal, and antiacetylcholinesterase activities *in vitro*. Most of the compounds exhibited significant biological activity. The relation between their biological activity and chemical structure was studied.

Keyphrases □ Quinazolones—substituted derivatives, synthesis and evaluation for antibacterial, antifungal, and antiacetylcholinesterase activities □ Antibacterial activity—evaluation of substituted quinazolone derivatives □ Antifungal activity—evaluation of substituted quinazolone derivatives □ Antiacetylcholinesterase activity—evaluation of substituted quinazolone derivatives

Various quinazolone derivatives were investigated recently for biological and pharmacological activities such as antibacterial (1–4), antifungal (5, 6), antitubercular (7), antiamoebic (8), antiviral (9), anti-inflammatory (10), anticonvulsant (11, 12), hypotensive (13), and sedative (14, 15) activities. Parmar and coworkers (16, 17) reported the antiacetylcholinesterase activity of quinazolone derivatives.

Since the 1,3,4-thiadiazole nucleus already is well known for its biological activity (18–20), it was decided to combine different 5-chloroacetylamino-2-alkyl-1,3,4-thiadiazole



Ia Ib

X = Br, X′ = H
X = X′ = Br

Scheme I

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