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Mechanism of sustained drug release in diffusion-controlled polymer matrix-application of percolation theory

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Abstract

This paper dealt with the controlled release of two kinds of drugs, 5-fluorouracil (5-FU) and hydrocortisonum (Hydro.) and loaded poly(ethylene-vinylalcohol) (EVAL), which composed 5-FU/EVAL and Hydro./EVAL matrix systems. The results were analyzed using the pseudo-steady-diffusion models coupled with the fundamental concepts of percolation theory. The percolation thresholds for the two systems were calculated, which could indicate the contribution of pore and matrix diffusion in controlled drug release.

Keywords: Controlled release; Percolation threshold; Pore diffusion; Matrix diffusion; Poly(ethylene-vinylalcohol)

1. Introduction

Diffusional release of biologically active molecules from porous polymeric systems is an important and commonly used method of achieving controlled release. There are several literature reviews concerning drug delivery systems that contain discussions of release from porous matrices (Siegel and Langer, 1984, 1990; Gurny et al., 1982). Several observations regarding the release mechanism are obtained from this study: (1) Drug release occurs primarily through a network of interconnected pores, which is created by solid drug particles that are initially loaded in the matrix. The pores are randomly situated within the matrix and communicate through narrow throats. Moreover, release is primarily through water which wets the pore network. When a drug can not access the matrix surface through the wetted pore network, it will not be released. (2) Release is primarily diffusion-controlled. (3) The drug is released much more slowly than would be expected from the simplest consideration of aqueous diffusion. Though pseudo-steady models (Higuchi,

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1961) and exact solutions (Miller and Peppas, 1983) for controlled release of drug from monolithic systems have been developed and used to test these observations, the predictive application of these models requires knowledge of the effective diffusion coefficient. Furthermore, the evidence of our study (Tongwen, 1995) showed that these models themselves could not successfully predict or explain the release processes of the Hydro./EVAL matrix system and 5-FU/EVAL system at high loading. To deal with these problems, we incorporate the concepts of percolation theory into pseudo-steady models in this research.

In recent years, some publications have presented the applications of percolation theory to drug release from matrix systems. Leuenberger et al. (1995) discussed the water-soluble drug/inert matrix system based on a 3-dimensional lattice and Bethe lattice percolation concepts, respectively. Adrover et al. (1996) proposed a percolation model for a swellable matrix system. Fernandez-Hervas et al. (1995) have determined the lower and upper percolation thresholds in matrix-type systems based on the percolation concepts. These applications have enabled new insights about the design and characterization of dosage forms and drug release properties. However, few of them are concerned with the system of matrix-pore diffusion and discussed the tortuosity factor in pore diffusion problems based on percolation concepts. Therefore, in this study, we intend to provide a very concise explanation of the most basic percolation concepts and results, to modify the above-cited pseudo-steady models by percolation concepts and to evaluate their utilities in Hydro./EVAL and 5-FU/EVAL matrix-type release systems.

2. Theoretical

2.1. Basic percolation concepts

Percolation theory, which is a mathematical tool that originally allows the prediction of morphogical and transport properties for heterogeneous materials or porous systems by the use of simple scaling laws, has received much attention from the pharmaceutical industry recent years (Leuenberger et al., 1995; Adrover et al., 1996; Fernandez-Hervas et al., 1995). It is based on the formation of clusters and on the existence of a site or bond percolation phenomenon (Stauffer and Aharony, 1985). For transport to take place through the matrix (or lattice), a continuous pathway of conducting sites (site percolation) that spans the matrix must be formed. At low porosities there will be so few conducting sites that a sample-spanning pathway will not exist. The porosity at which sample-spanning pore networks just to cease to exist is called the critical percolation threshold (ϵ_c). As the concentration of pores (sites) is increased, the sample-spanning clusters of conducting sites will form at ϵ_c and the transport across the matrix will become possible. For a matrix with a porosity that is larger than the percolation threshold, a fraction of the pore space will be connected to the outside medium through sample-spanning network and thus, is designated the volume fraction accessible (ϵ^a). The remainder of the pore space wil1 exist as isolated pockets and the volume fraction of these isolated pores is designated ϵ^i. The whole porosity of the matrix is the sum of ϵ^a and ϵ^i. According to percolation theory, one of the properties of ϵ^a is that it obeys the scaling law:

$$\begin{cases} \epsilon^a \propto (\epsilon - \epsilon_c)^\beta & \epsilon > \epsilon_c \\ \epsilon^a = 0 & \epsilon \leq \epsilon_c \end{cases} \quad (1)$$

where β is a universal constant, $\beta = 0.14$ for all two-dimensional (2-D) lattices, $\beta = 0.3$–0.4 for all three-dimensional (3-D) lattices (Stauffer and Aharony, 1985). The importance of these concepts to the release of drug from polymeric matrices is that the volume fraction accessible represents the fraction of pore space available to the surrounding medium and is, therefore, related to the fraction of drug loaded into the matrix that will eventually be released.

Another percolation parameter is the relative diffusivity (D). It is derived from the relative conductivity of composite materials and is defined as the dimensionless form of diffusivity, D_B/D_a, for steady-state diffusion through a porous system. Here, D_a is an aqueous medium diffusion coefficient. D_B is defined as the steady-state bulk diffusion coefficient of solute based on Eq. (2)

$$J_B = -D_B \frac{dC}{dx} \quad (2)$$

where J_B is the flux of steady-state bulk diffusion, C is the concentration of solute in the water-filled pores and x is the space co-ordinate in the transport direction.

It should be noted that the relative diffusivity is equivalent to relative conductivity and thus the dimensionless parameter D can be applied to either steady-state diffusion problems in porous materials or conductivity problems in heterogeneous materials. It is known to obey the conductivity scaling law (Stauffer and Aharony, 1985):

$$\begin{cases} D = \dfrac{D_B}{D_a} \propto (\epsilon - \epsilon_c)^{\mu} & \epsilon > \epsilon_c \\ D = \dfrac{D_B}{D_a} = 0 & \epsilon \leq \epsilon_c \end{cases} \quad (3)$$

where μ is also a universal constant, which depends only on spatial dimensions and is applicable to any percolation system regardless of its chemical, mechanical, structural morphological and statistical properties. It has the values of 1.3 for regular 2-D lattices and 2.0 for 3-D lattices (Stauffer and Aharony, 1985).

Therefore, the concepts and scaling laws in percolation theory may be directly incorporated into the quantitative transport model that describes the release profiles of water-soluble solutes from monolithic polymeric devices, when drug loading exceeds its solubility to assure steady-state diffusion.

2.2. Pseudo-steady-state solutions

The release mechanism of pore diffusion-controlled involves diffusion of the solute through water-filled pores within the matrix. The pore structure is generally derived from the dissolution process associated with the drug and the intrinsic pore spaces associated with the matrix. The volume fraction of drug loaded in matrix, i.e. the drug porosity, is defined as ϵ_d, the inherent porosity of the matrix (porosity before any dissolution) is defined as ϵ_i and the total porosity ϵ is thus, given by $\epsilon_d + \epsilon_i$. With the dissolution and release of drug from the matrix, the leached porous region of the matrix grows at the expense of the undissolved drug/polymer region. For a system in which the drug loading exceeds its solubility in medium, a moving boundary is generated by the dissolution of drug (Fig. 1), resulting in square root time release kinetics [11].

$$Q_t = \sqrt{D_e \epsilon C_a (2\epsilon_d \rho_d - \epsilon C_a)\, t} \quad (4)$$

where Q_t is the cumulative release amount of drug after time t per unit exposed area, C_a is the solubility of the drug in the aqueous solution, ρ_d is the solid-state density of the drug and D_e is the effective diffusion coefficient within the pores. The following relationships exist according to percolation concepts and the definition of D_B (Siegel, 1988):

$$D_B = D_e \epsilon^a = \frac{D_a \epsilon^a}{\tau^2} \quad (5)$$

where τ is the tortuosity factor. It is assumed that the porous structure in the release zone is due to both the dissolution of the solute and the inherent porosity of the matrix and that all accessible pores are wetted. Thus, only the drug particles accessible to the outside medium through the connected pore structure will contribute to transport in the matrix. In other words, those isolated drug particles can not contribute to transport. The available

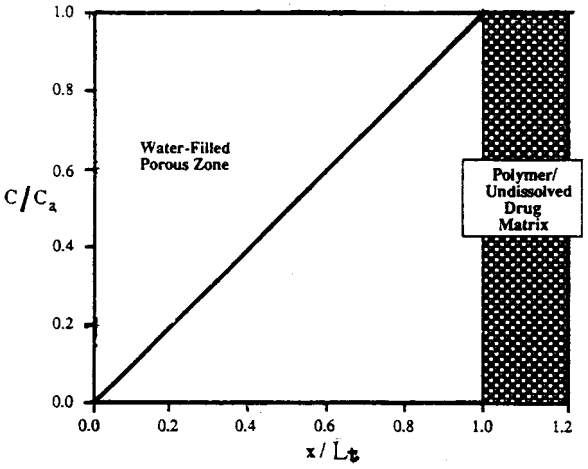

Fig. 1. Schematic diagram of pseudo-steady-state diffusion problem.

volume fraction of drug is defined as ϵ_d^a. Therefore, incorporating the percolation parameters and combining with Eqs. (5) and (4) is modified as below.

$$Q_t = \sqrt{D_B C_a [2\rho_d \epsilon_d^a - (\epsilon_d^a + \epsilon_i) C_a]\, t} \quad (6)$$

In other systems, such as 5-FU/EVAL matrix, as 5-FU is a hydrophilic drug with small molecular weight, the diffusion of 5-FU in matrix can not be negligible and the diffusion is both matrix and pore controlled. The volume fraction for drug diffusion through the matrix is $1-\epsilon$, while pore diffusion only takes place in the volume fraction of ϵ^a By means of concepts and methods, as described above, the following modified kinetics equation for matrix-pore bi-diffusion can be obtained (see Appendix A for the derivation).

$$Q_t = \sqrt{[2\rho_d \epsilon_d^a - (1-\epsilon) C_s - \epsilon^a C_a]\,[(1-\epsilon) D_m C_s + D_B C_a]\, t} \quad (7)$$

where D_m is the diffusion coefficient in the matrix, C_s is the solubility in the matrix. Therefore, by independently determining C_s, C_a, ρ_d, ϵ, D_a and D_m, the volume fraction of drug, ϵ_d^a and the bulk diffusion coefficient, D_B can be calculated at various porosities from the data of release test by pseudo-steady-state solutions (Eqs. (6) and (7)). Percolation parameters thus, can be evaluated based on the previously discussed scaling laws (Eqs. (1) and (3)).

3. Materials and methods

3.1. Materials

EVAL with VAL/E mole ratio of 56/44 is from Kori company (Japan), Hydro. and 5-FU are biochemical agents and from Shanghai (China) and *n*-propanol is analytically pure and used as received.

3.2. Preparation of monolithic matrix

The required amount of EVAL polymer was dissolved in composite solvent (*n*-propanol: water = 3:1) of correct volume and kept agitated for 3 h at 70°C, then the target drug (5-FU or Hydro.) was added and kept stirred for another 2 h to assure uniform mixing. The mixing solution was casted onto a glass dish at room temperature, allowing for the evaporation of solvents. After 12 h, it was transferred to a vacuum oven for complete evaporation of the solvent to obtain the matrix.

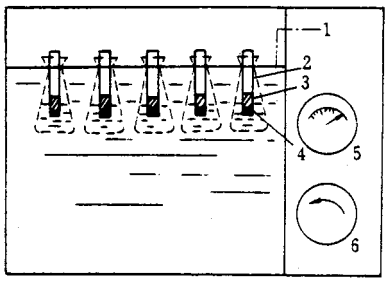

Fig. 2. Schematic diagram of apparatus for release test. 1, thermostatic vibrator; 2, glass tube; 3, wax; 4, tested matrix; 5, temperature adaptor; 6, vibrating speed adapter.

3.3. Release test

To measure the release rate or amount released, a volumetric flask (250 ml) adhering to a glass tube was filled with 50 ml of the medium (water) and was placed in a thermostatic vibrator maintained at 37°C. The matrix was put in the glass tube and was embedded in wax by coating the lateral and one of the flat sides with molten beeswax, thereby exposing only one flat surface for drug release (Fig. 2). Samples were withdrawn at specified time points and replaced with fresh water so that perfect sink conditions were maintained (Schwartz et al., 1968a). After proper dilution with water, these samples were assayed by UV spectrometry (5-FU, 265 nm; Hydro., 242 nm).

3.4. Determination of parameters

3.4.1. Solubility (C_a)

The solubility of the drug at 37°C in the extraction medium was obtained by shaking the

medium with excess solid drug in a sealed vial for 48 h. Aliquots from the solubility samples were filtered and the filtrate was analysed spectrometrically. A rapid filtering process was adopted to prevent the precipitation of drug from the saturated solution during filtration.

3.4.2. Drug-matrix partition tendencies (k_a)

Saturated solutions of the drug were shaken overnight at 37°C with finite volume of matrix materials. The concentration of drug in the medium at equilibrium was analysed spectrometrically and the concentration in the matrix was calculated by balance. Then k_a may be calculated from Eq. (8).

$$k_a = \frac{\text{concentration of drug in matrix at equilibrium}}{\text{concentration of drug in medium at equilibrium}} \quad (8)$$

The solubility of drug in matrix (C_s) was equal to C_a times k_a.

3.4.3. Porosity (ϵ)

As no other additive is added in our systems, the drug loaded and the air spaces make the contribution to the total porosity. From knowledge of the matrix volume, the densities of the drug and matrix material and the drug loading, porosity of air spaces (i.e. the inherent porosity, ϵ_i) and porosity of drug (volume fraction of drug, ϵ_d) could be carried out. The matrix volume was computed from its dimensions determined with a micrometer and the densities were determined with a Beckman air compression pycnometer.

3.4.4. Effective diffusion coefficient in medium (D_e)

The effective diffusion coefficient in medium was determined using the rotating disk method (Newman, 1966). Diffusion experiments were run at above 170 rpm and 37°C.

3.4.5. Diffusion coefficient in matrix (D_m)

The diffusion coefficient in matrix (D_m) was determined by permeating method (Siegel, 1986) and calculated using Eq. (9)

$$t_b = \frac{L_m^2}{3D_m} \quad (9)$$

where t_b is burst time and L_m is the thickness of the matrix.

The results were listed in Table 1 except for the porosities which are shown in Tables 2 and 3 for the two matrix systems, respectively.

4. Results and discussion

4.1. Hydro./EVAL matrix system

One of the powerful predictions that percolation theory makes is that the relationship between porosity and the bulk diffusion coefficient is described by the simple scaling law shown in Eq. (3). In order to test this scaling law, release profiles for the system of the Hydro./EVAL matrix were experimentally determined for a range of Hydro. loadings (ϵ_d values ranging from 0.00325–0.49961). Fig. 3 showed typical release profiles of Hydro. versus square root time for five different matrix porosities. The data were plotted against the square root time according to Eq. (6). The plateau region shown in Fig. 3 corresponded to complete extraction.

The percolation parameters, ϵ_d^a and the bulk diffusion coefficient (D_B) or relative diffusivity (D), were calculated from the plateau region and the slope of the released region, respectively. The relative diffusivity was determined by fitting the release data to Eq. (6), where C_a and D_a are independently determined constants. Then substituting the release data of the plateau region into the release equation, ϵ_d^a can be carried out. The values of D and ϵ_d^a determined in this manner are listed in Table 2.

Table 1
Some parameters of drugs investigated

	5-FU	Hydro.
C_s (mg ml^{-1})	7.8149	6.5811
C_a (mg ml^{-1})	12.9928	0.3029
D_m (cm^2 s^{-1})	2.78×10^{-8}	1.71×10^{-12}
D_a (cm^2 s^{-1})	3.127×10^{-5}	3.84×10^{-6}
k_a	0.6011	21.7233

Table 2
ϵ_d^a, D_B, τ et al. values determined as a function of drug loading for Hydro./EVAL system

Cd (mg^{-1} cm^3)	$\epsilon_d \times 10^3$	$\epsilon_d^a \times 10^3$	$D_B \times 10^6$ cm^2 s^{-1}	D	τ	$\epsilon \times 10^3$
2.97	3.25	0.11	2.14×10^{-9}	0.56×10^{-9}	6644.01	24.72
29.68	32.46	1.14	4.13×10^{-8}	1.05×10^{-8}	2266.3	53.93
59.35	64.92	64.83	2.32×10^{-3}	6.05×10^{-4}	11.950	86.39
118.7	129.84	129.81	0.0599	0.0156	3.114	151.31
148.38	162.30	162.50	0.1182	0.0308	2.443	183.77
178.08	194.76	194.81	0.1196	0.0510	2.059	216.23
237.44	259.68	259.75	0.4089	0.1065	1.625	281.15
256.93	280.80	280.76	0.5811	0.1513	1.413	302.27
329.95	360.60	360.63	0.8958	0.2333	1.280	382.07
384.39	420.10	420.06	1.2215	0.3181	1.178	441.57
429.93	469.87	469.93	1.6324	0.4251	1.075	491.34
457.14	499.61	500.03	1.9303	0.5027	1.018	521.08

By comparing the data ϵ_d^a with ϵ_d in Table 2 it is clearly seen that essentially all the Hydro. incorporated in the matrices was eventually released over the concentration range tested.

The evaluation of the results in Table 2 begins logically with a comparison of experimental results with theoretical calculations, based on percolation theory, for simple 3-D lattices. Theoretical estimations of the relative diffusivity (D) and volume fraction accessible (ϵ^a) have been determined using Monte Carlo simulation techniques for a wide range of simple lattices. A comparison of our experimental values of ϵ^a, where it is assumed $\epsilon^a = \epsilon_d^a + \epsilon_i$, with the theoretical profiles determined by Dean and Bird (1966) is shown in Fig. 4. It is obvious that the volume fraction accessible of the experimental matrix is significantly larger than that predicted for simple lattices at low porosities. The reasons may be: (1) practical matrix lattices don't distribute as uniformly as the theoretical ones; (2) for a practical matrix, even below the critical porosity, drugs on the surface can still be released and make an appreciable contribution.

The relative diffusivity for theoretical lattices have been studied by several researchers. Winterfeld (1986) has studied the cases of tetrakaidecahedral (14 nearest neighbors) and Voronoi (15.54 average neighboring sites) tessellations using two different techniques (resistor network approximation and finite element approximation). Kirkpatrick (1973) has determined the transport properties of the simple cubic lattice. Their results are shown in comparison with our experimental relative diffusivity results in Fig. 5. These comparisons indicated that the relative diffusivity of our experimental system approximately agreed with the case of Voronoi (15.54 average neighboring sites) tessellation.

The percolation threshold can be determined by fitting the relative diffusivity data in Table 2 to the scaling law shown in Eq. (3). For a practical release matrix, its geometry can be modelled with the help of a 3-D lattice and thus, the universal constant μ is assumed to be two, which is consistent with the literatures (Leuenberger et al., 1995; Dean and Bird, 1966; Winterfeld, 1986; Kirkpatrick, 1973). From Eq. (3), we have

$$D = m(\epsilon - \epsilon_c)^2 \tag{10}$$

where m is a proportionality constant. The plot of square root D versus porosities will be linear (Fig. 6). The value of m was determined to be 2.4 ± 0.01 and the ϵ_c was found to be $0.0705 \pm 0.0.05$ by using linear multiple regression.

The drug loading that corresponds to this ϵ_c is 44.84 mg/cm^3. Therefore, when drug loading is above this value, pore diffusion dominates the release process and in other cases, surface release may occur without appreciable contribution from pore diffusion.

Table 3
ϵ_d^a, D_B, τ et al. values determined as a function of drug loading for 5-FU/EVAl system

Cd mg^{-1} cm^3	$\epsilon_d \times 10^3$	$\epsilon_d^a \times 10^3$	$D_B \times 10^6$ cm^2 s^{-1}	D	τ	$\epsilon \times 10^3$
29.6	17.16	0.04	1.161×10^{-7}	3.91×10^{-9}	2868.17	30.52
118.7	68.4	0.17	5.713×10^{-6}	1.825×10^{-7}	669.33	81.76
178.05	102.95	102.14	0.013	4.30×10^{-4}	16.383	116.31
237.44	137.28	137.20	0.139	0.0045	5.808	150.64
296.81	171.60	171.71	0.398	0.0127	3.821	184.96
364.8	210.76	210.77	0.684	0.0218	3.204	224.12
491.23	283.80	283.76	2.364	0.0755	1.981	296.36
567.48	327.85	327.88	3.378	0.1079	1.777	341.21
641.13	370.40	370.25	4.782	0.1528	1.584	383.76
711.23	410.9	410.97	5.590	0.1786	1.372	424.26
783.06	452.4	452.39	7.861	0.2511	1.361	465.76

Another important parameter discussed here was τ, the tortuosity factor. τ was initially proposed by Higuchi (1963) and used to correct for the lengthened diffusional path caused by the necessary lateral excursions. In other words, it accounts for or corrects for the additional distance a particle must travel due to its circuitous path within the matrix. Thus, on the physical meaning, values of τ should not be larger than 100 and with the probable values of 1–10, for example, $\tau \approx 1$ for straight channel and $\tau \approx 3$ for capillary system (Desai et al., 1966). However, the studies of other systems (Desai et al., 1966; Schwartz et al., 1968b) demonstrated that τ was greater than 10^3–10^5. In these cases, the concept of the average tortuosity does not adequately describe physically the pathways and resistances for diffusion and a more reasonable explanation becomes expected. According to Eq. (5), τ can be calculated using the following equation in our paper

$$\tau = \sqrt{\frac{\epsilon^a}{D}} \tag{11}$$

The calculated values of τ were listed in Table 2 for this system. These values indicated that when

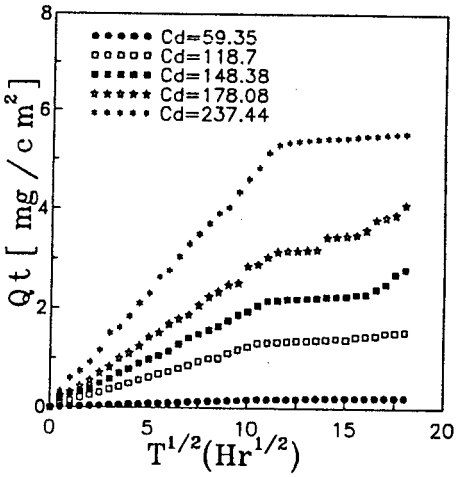

Fig. 3. Release amount of Hydro. from EVAL matrix for various initial loads.

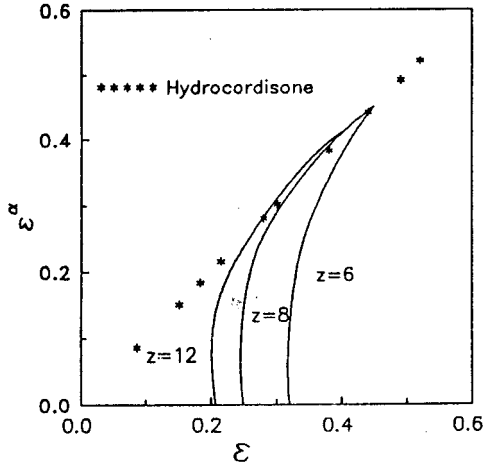

Fig. 4. Experimental ϵ^a values plotted against total porosity. Theoretical curves of ϵ^a (Dean and Bird, 1966) for simple cubic ($z = 6$), body-centered cubic ($z = 12$) lattices shown for comparison.

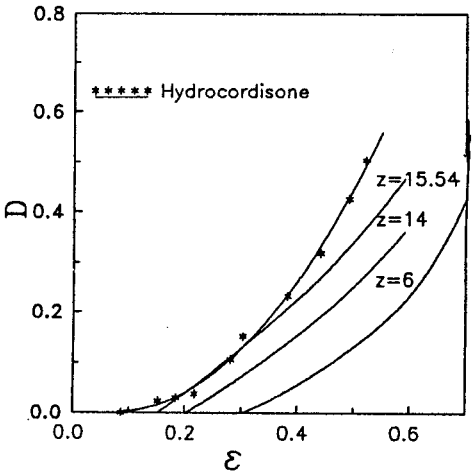

Fig. 5. Experimental D values plotted against total porosity for Hydro./EVAL system. Theoretical curves of D for the simple cubic ($z = 6$) (Fernandez-Hervas et al., 1995), tetrakaidecahedral ($z = 14$) (Winterfeld, 1986) and Voronoi ($z = 15.5$) (Winterfeld, 1986) lattices shown for comparison.

ϵ was above ϵ_c, τ had values ranging from 1 to 10 or so and when ϵ was below ϵ_c, τ had extremely large values. It was obvious that τ values had the meaning of modifying the diffusional path above the critical loading and thus, were reasonable. The unreasonable τ values resulted from the low drug loading, when no infinite cluster was formed and the drug particles

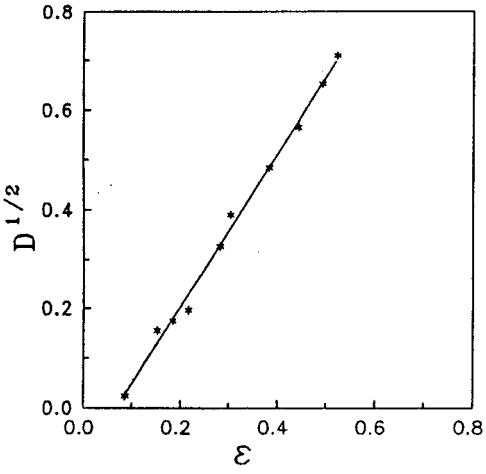

Fig. 6. $\sqrt{D}$ values plotted against total porosity for Hydro./EVAL system.

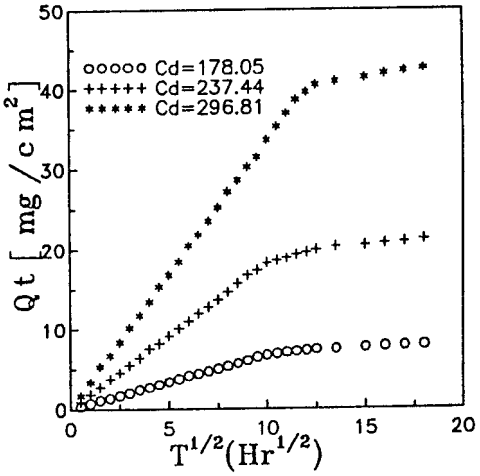

Fig. 7. Release amount of 5-FU from EVAL matrix for various initial loads.

were wrapped by matrix materials, as a result pore diffusion couldn't happen. It may be one of the reasons that the reported τ values in literature were significantly large.

4.2. 5-FU/EVAL matrix system

The release profiles of this system were shown in Fig. 7. Percolation parameters, ϵ_d^a and relative diffusivity D were obtained by the analogous method described above. In this system, as 5-FU is a hydrophillic drug with a small molecular weight, its diffusion in the EVAL matrix is both pore and matrix controlled (Tongwen, 1995) and thus Eq. (7) was used instead of Eq. (6) for this analysis. The results are shown in Table 3.

Obviously, 5-FU/EVAL system had a smaller D value at the same drug loading compared with Hydro./EVAL system, though the release amount of this system was much greater than that of the above-mentioned system from the experimental data. This is because the release amount of this system includes the contribution from both matrix diffusion and pore diffusion (based on Eq. (7)), while the calculation of D value is based only on the part of contribution from pore diffusion.

The plot of square D versus ϵ for this system was shown in Fig. 8. The values of m and ϵ can

be determined by the same regression to be 1.8 ± 0.1 and 0.1009 ± 0.0005, respectively. The ϵ_c for this system lost the meaning of percolation threshold, but it is able to label the beginning of the contribution from pore diffusion. The drug loading corresponding to this ϵ_c value is 151.45. Therefore, when drug loading is within this value, matrix diffusion dominates the release process and pore diffusion is negligible, otherwise both pore diffusion and matrix diffusion dominate the process.

The τ values for this system are shown in Table 3. It is observed that τ is less than 20 above the threshold, below this limit τ is significantly larger. This suggests that τ values are reasonable and possess the physical meaning of modifying the diffusional path when pore diffusion begins to contribute and if matrix diffusion controls the process, τ values are extremely large and unreasonable.

The results of the two matrix systems indicated that τ values were reasonable when pore diffusion began to contribute. Unreasonable τ values occurred below the threshold when surface release or matrix diffusion took place without appreciable contribution from pore diffusion.

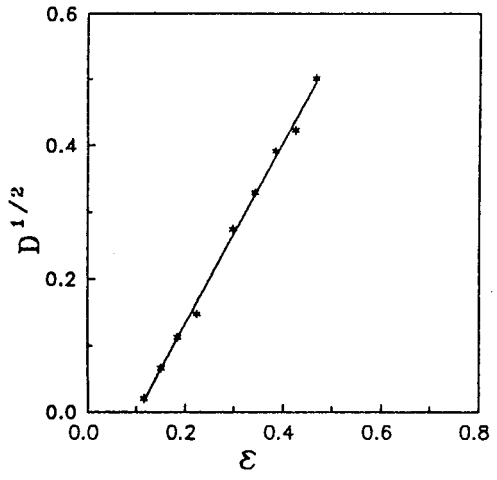

Fig. 8. $\sqrt{D}$ values plotted against total porosity for 5-FU/EVAL system.

5. Conclusions

The objective of this paper was to study the drug release mechanism for 5-FU/EVAL and Hydro./EVAL matrix systems. This objective has been accomplished using microscopic percolation concepts by establishing a modified pore diffusion model and a pore-matrix bi-diffusion model. These models could better address the problems that the simple diffusion model (Higuchi's model) could not solve as discussed in another paper (Tongwen, 1995). In addition, the limit of present models and their underlying problems were discussed in terms of the unreasonable τ values calculated by them. The results of this study indicated that for lipophilic drugs of moderate molecular size (MW > 300), such as Hydro., only pore diffusion could occur in EVAL matrix with a critical loading of 44.84 mg^{-1} cm^3. While for hydrophilic drugs of small molecular weight, such as 5-FU, both matrix diffusion and pore diffusion were important in the release process with a critical loading of 151.52 mg^{-1} cm^3. The calculated τ values had a reasonable explanation from our models.

Appendix A. Derivation of Eq. (7)

For the 5-FU/EVAL system, the diffusion is both matrix and pore controlled. The volume fraction for drug diffusion through matrix is 1-ϵ, while pore diffusion only takes place in the volume fraction of ϵ^a. Assumptions are made that both matrix diffusion and pore diffusion are steady-state and the medium keeps a perfect sink. According to Fick's law, the steady-state diffusional flux in the matrix, J_m is expressed as

$$J_m = (1-\epsilon) D_m \frac{dC_m}{dx} \tag{A1}$$

where D_m is diffusion coefficient in the matrix, C_m is the concentration in the matrix. Integration of this equation with the boundary conditions: $x = 0$, $C_m = 0$(perfect sink assumption) and $x = L_t$ (the released boundary), $C_m = C_s$, (drug solubility in matrix), yields

$$J_m = (1-\epsilon)D_m\frac{C_s}{L_t} \quad \text{(A2)}$$

The steady-state diffusional flux in the pores, J_p is

$$J_p = D_e\epsilon^a\frac{dC_p}{dx} = D_B\frac{dC_p}{dx} \quad \text{(A3)}$$

here D_e is effective diffusion coefficient within the pores, C_p is the concentration in the pores, ϵ^a and D_B are described in text in detail. Integration procedure is the same as the above except that C_a is in place of C_s and thus we have

$$J_p = D_e\epsilon^a\frac{C_a}{L_t} = D_B\frac{dC_p}{dx} \quad \text{(A4)}$$

The total flux per unit exposed area, J_t is

$$J_t = \frac{dQ_t}{dt} = J_m + J_p = \frac{(1-\epsilon)D_m}{L_t}C_s + D_B\frac{C_a}{L_t} \quad \text{(A5)}$$

L_t may be obtained by material balance for the released region. It is apparent that at time t, the release amount per unit area is

$$Q_t = (\rho_d\epsilon_d^a - \frac{1}{L_t}(1-\epsilon)\int_0^{L_t}C_m dx - \frac{1}{L_t}\epsilon^a\int_0^{L_t}C_p dx)\,L_t \quad \text{(A6)}$$

where ϵ_d^a is the available drug loading in place of ϵ_d based on percolation concepts. It should be noted that concentration distributions with distance in the pore and matrix are linear because of the assumption of steady state. Therefore, with the perfect sink assumption, the average concentrations in pore and matrix must keep the constant values of $C_a/2$ and $C_s/2$, respectively and Eq. (A6) becomes

$$Q_t = (\rho_d\epsilon_d^a - \frac{(1-\epsilon)C_s + \epsilon^a C_a}{2})L_t \quad \text{(A7)}$$

Differentiating by time t, one obtains

$$J_t = \frac{dQ_t}{dt} = \left(\rho_d\epsilon_d^a - \frac{(1-\epsilon)C_s + C_a\epsilon^a}{2}\right)\frac{dL_t}{dt} \quad \text{(A8)}$$

Substituting Eq. (A5) into Eq. (A8) and integrating for L_t and then substituting it back into Eq. (5), we can obtain

$$Q_t = \sqrt{[2\rho_d\epsilon_d^a - (1-\epsilon)C_s - \epsilon^a C_a][(1-\epsilon)D_m C_s + D_B C_a]t} \quad \text{(A9)}$$

This is the release kinetics model for the matrix and pore bi-diffusion.

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