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Research Article

Diffusion in Porous Materials Above the Percolation Threshold

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The diffusion of water-soluble solutes in water-soaked porous media was studied by following the release of benzoic acid from poly(vinyl stearate) matrices. The results were analyzed using a pseudo-steady-state diffusion model coupled with the fundamental concepts of percolation theory. The results of the study indicated that the relationship between the bulk diffusion coefficient of benzoic acid in the polymer matrix and the porosity was well described by percolation scaling laws. A very low percolation threshold (0.07) was experimentally observed for this system.

KEY WORDS: diffusion; percolation theory; matrix release; percolation threshold; conductivity; scaling laws.

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 reviews in the literature concerning drug delivery systems that contain discussions of release from porous matrices (1–4). Pseudo-steady-state (5) and exact solutions (6,7) for diffusional release of drugs from monolithic systems have been developed and experimentally tested. Although the mathematical models presented in the literature have been successful in modeling the time course of drug release, the predictive application of these models requires knowledge of the effective diffusion coefficient. Percolation theory is a mathematical tool that allows the prediction of morphological and transport properties for heterogeneous materials or porous systems by the use of simple scaling laws. Our research is concerned with diffusional release from porous, polymeric monolithic slabs where the drug load exceeds its solubility limit. The purpose of this research is to apply percolation theory to the general problem of diffusion in porous materials and to test the mathematical models developed against experimental diffusion coefficients of benzoic acid in a porous polymer matrix.

In the original work by Higuchi (5,8), a pseudo-steady-state solution was described for the release of a water-soluble drug from solid particles of the drug randomly dispersed in a solid matrix. It has been shown (1) for mechanisms involving diffusion retardation, as illustrated by Higuchi's system, the effective diffusion coefficient within the pores can be correctly defined as shown in Eq. (1):

$$D_e = \frac{D_{aq}}{\tau^2} \tag{1}$$

where D_{aq} is the aqueous diffusion coefficient and τ is the tortuosity. The tortuosity factor in Eq. (1) is an empirical correction factor that is obtained from curve fitting and has been shown to have no physical meaning (1). A more satisfactory description of the effective diffusion coefficient is required before the relationship between pore structure and release rates in porous systems is understood.

Early theoretical attempts at relating the rate of diffusional release from polymeric matrices to pore structure were made by T. Higuchi and W. Higuchi (9). A two-phase model, where the pore structure was pictured to consist of an assembly of small channels connected to large pores, was developed and tested by Schwartz *et al.* (10). This model was successful in predicting diffusion coefficients as a function of drug load. The relationship between pore structure and transport has recently been explored for systems with large pores interconnected by smaller throats (11–13).

While the above-cited work regarding the mechanism of diffusion through porous polymeric matrices has made significant contributions in relating pore structure and porosity to diffusion, no simple general model has resulted. It is shown here that percolation theory can be used to describe and predict quantitatively transport properties in porous polymeric materials as a function of porosity by employing scaling laws. These scaling laws take the form

$$\frac{D_B}{D_{aq}} \propto (\emptyset - \emptyset_c)^{\mu}, \qquad \emptyset > \emptyset_c \tag{2}$$

$$\frac{D_B}{D_{aq}} = 0, \qquad \emptyset \leq \emptyset_c \tag{3}$$

where D_B is the steady-state bulk diffusion coefficient of the solute through the matrix, $\emptyset$ is the porosity, $\emptyset_c$ is the percolation threshold, and μ is a universal scaling constant. It is shown later that the percolation threshold is a function

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of pore structure and that μ is a universal constant dependent only on the spatial dimension. The bulk diffusion coefficient, D_B, is not the same as the effective diffusion coefficient, D_e, defined earlier [Eq. (1)]; however, a relationship does exist between the two coefficients.

The concepts of percolation theory are directly incorporated into a quantitative transport model that describes the release profiles of water-soluble solutes from monolithic polymeric devices, where drug load exceeds drug solubility. We have also experimentally tested the application of percolation theory to the diffusional release of water-soluble solutes from porous polymeric matrices using a benzoic acid/poly(vinyl stearate) model system.

THEORETICAL BASIS

Percolation Theory

An understanding of the diffusional transport of solute through porous systems requires consideration of the geometrical and topological characteristics of the microenvironment within the porous material. Through the use of percolation theory (14–16), a morphological description of disordered media can be accomplished as follows. If a porous material is subdivided into many small spaces (or sites) and one labels the occupant of each subdivision as conducting (water-filled pores within the polymeric matrix) or nonconducting (solid particles of the polymer), it is then possible to use percolation theory to describe the important transport and geometrical properties of the material.

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 cease to exist is called the critical percolation threshold ($\emptyset_c$). As the concentration of pores (sites) is increased, sample-spanning clusters of conducting sites will form at $\emptyset_c$ and transport across the matrix will become possible. For a porous material with a porosity that is larger than the percolation threshold, a fraction of the pore space will be connected to the outside environment through sample-spanning networks and the remainder of the pore space will exist as isolated pockets. The volume fraction of isolated pores is designated $\emptyset^i$, and the fraction of space occupied by sample-spanning pore networks is designated the volume fraction accessible ($\emptyset^a$). Thus, the porosity of a material can be divided into the sum shown in Eq. (4):

$$\emptyset = \emptyset^i + \emptyset^a \tag{4}$$

One of the properties of $\emptyset^a$ is that it obeys the scaling law:

$$\emptyset^a \propto (\emptyset - \emptyset_c)^\beta, \qquad \emptyset > \emptyset_c \tag{5}$$

where β is a universal constant ($\beta \cong 0.3$–0.4 for three-dimensional lattices) (14,16,17). 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 environment and is, therefore, related to the fraction of drug loaded into the matrix that will eventually be released.

Scaling Laws for Conductivity and Definition of Diffusion Coefficients

The application of percolation theory to diffusional problems has its origins in the earlier application of this theory to the effective conductivity of composite materials. If we imagine a composite material composed of conducting sites (copper particles) and nonconducting sites (particles of insulating material), it is easy to see that when a voltage is applied across the material, current flows only between those sites occupied by the copper particles. For current to flow across the composite material, sample-spanning clusters of copper particles must exist. Below the critical percolation threshold the composite acts as an insulator, and above it acts as a conductor. It might seem that the relative conductivity, Σ (the conductivity of the composite divided by the conductivity of copper), would simply follow the scaling law shown in Eq. (5). It has been experimentally determined, however, that the scaling law for volume fraction accessible greatly overestimates the magnitude of the relative conductivity. This can be explained by the fact that the volume fraction of conducting particles accessible to current flow is not a good descriptor of the effectiveness of current transport. A typical sample-spanning cluster of copper particles would contain numerous dead-end branches that would not contribute to current flow but would be accessible. Thus, a different scaling law is defined for conductivity in composite materials and is shown below in Eq. (6):

$$\Sigma \propto (\emptyset - \emptyset_c)^\mu \tag{6}$$

where $\emptyset$ is the volume fraction conducting. The scaling law shown in Eq. (6) has been successfully applied to several conductivity problems in heterogeneous materials (18–20). In addition, theoretical networks (tessellations) have been studied using various numerical techniques and the relationship between the conductivity and the volume fraction conducting has been established (21,22).

The connection between diffusion and electrical conduction in heterogeneous materials is well established and there is a direct parallel between these apparently different processes (14,23). Straley has shown that the steady-state diffusion problem is analogous to bulk electrical conductivity. Thus, the bulk diffusion coefficient (D_B) of a solute through a porous material (percolating lattice) at steady state is defined as shown in Eq. (7). The same scaling law for conductivity [Eq. (6)] can be used to relate diffusion with porosity [Eqs. (2) and (3)]. It should be noted that the steady-state flux (J_B) described in Eq. (7) is the flux through a unit surface area of the bulk material and is not the flux of solute through a pore. The analogy between conductivity and steady-state diffusion allows the application of the extensive theoretical and experimental results concerning conductivity in heterogeneous materials to problems of diffusion in porous systems. Thus, we define all diffusion problems in this work in terms of the bulk diffusion coefficient, D_B.

$$J_B = -D_B \frac{dC}{dx} \tag{7}$$

For non-steady-state analysis, a diffusion coefficient describing diffusion within the pore must be used. The problem of non-steady-state release from monolithic devices has been correctly defined in terms of diffusion within the pore (1). The diffusion coefficient (D_e) defined by Siegel describes transport of solute in all pore spaces (both accessible and isolated). This definition of the diffusion coefficient will be valid for non-steady-state transport when the volume fraction isolated is small. The steady-state flux through a composite material, using D_e, is shown in Eq. (8):

$$J_B = -D_e\emptyset \frac{dC}{dx} \tag{8}$$

A diffusion coefficient (D_e') can also be defined for diffusion within sample-spanning pores only. This diffusion coefficient, D_e', is useful for the definition of non-steady-state problems where there is a significant amount of the pore space that is isolated. The steady-state flux using D_e' is given by Eq. (9):

$$J_B = -D_e'\emptyset^a \frac{dC}{dx} \tag{9}$$

As is obvious from Eqs. (7), (8), and (9), there is a simple steady-state relationship between these three different diffusion coefficients. This relationship has been discussed by Straley (23) and Stauffer (14). We can define the bulk diffusion coefficient in terms of the two pore diffusion coefficients as shown in Eq. (10). For a steady-state diffusion problem, the use of any one of the three different definitions is correct, as long as the proper flux equation is applied. For transient diffusion problems, however, selection of the proper diffusion coefficient is crucial.

$$D_B = D_e\emptyset = D_e'\emptyset^a \tag{10}$$

With these basic definitions of diffusion coefficients in place, a dimensionless representation can be defined equivalent to relative conductivity. The dimensionless form for steady-state diffusion through a porous system is defined as the relative diffusivity, D, and is shown in Eq. (11). 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.

$$D = \frac{D_B}{D_{aq}} \tag{11}$$

The value of D falls to zero as porosity approaches the percolation threshold ($\emptyset_c$) from above and reaches a maximum of one as porosity approaches one from below. For values of porosity below the percolation threshold there are no sample-spanning pathways, and thus the bulk diffusion coefficient of a solute in such a material will be zero. The relative diffusivity is known to obey the conductivity scaling law [Eq. (6)] and was introduced earlier in Eqs. (2) and (3). The universal conductivity constant (μ) is thought to be approximately 1.7 to 2.0 in three dimensions (17,24).

Pseudo-Steady-State Solution

It is well established that for the release of many water-soluble solutes from polymeric matrices, the mechanism of release involves diffusion through water-filled pores within the matrix. The pore structure within a compressed composite of water-soluble drug and hydrophobic polymer is generally derived from the dissolution process associated with the drug and the intrinsic pore spaces associated with the matrix. The volume fraction of benzoic acid is defined as $\emptyset_d$, the inherent porosity of the matrix (porosity before any dissolution) is defined as ϵ, and the total porosity is thus given by $\emptyset_d + \epsilon$. 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 load exceeds the product of the drug's water solubility and total porosity of the matrix, a moving boundary is generated by the dissolution of drug, resulting in square root time release kinetics. The mathematical solution of this type of transport problem is well documented (1,5–8,25); therefore, the detailed steps in the mathematical derivation of the model presented here are not shown. What is presented here is the formulation of the problem in terms of percolation concepts.

The physical situation within a polymeric matrix after partial extraction of drug is represented in Fig. 1. The region where $x < 0$ is the stirred aqueous medium. Since convection dominates the transport process in this region, it is assumed that there is negligible external mass transfer resistance (the validity of this assumption is discussed in the experimental section). The region where $0 < x < \xi(t)$ is the region of the matrix that contains dissolved solute and aqueous medium, resulting in a water-filled porous zone. It is assumed that the porous structure in the water-filled porous zone is due to both the dissolution of the water-soluble solute and the inherent porosity of the matrix and that all accessible pores are wetted. Only the benzoic acid particles accessible to the outside environment through the connected pore structure will contribute to transport in the matrix. In other words, those benzoic acid particles isolated in a sea of poly(vinyl stearate) will not be able to diffuse through an intercon-

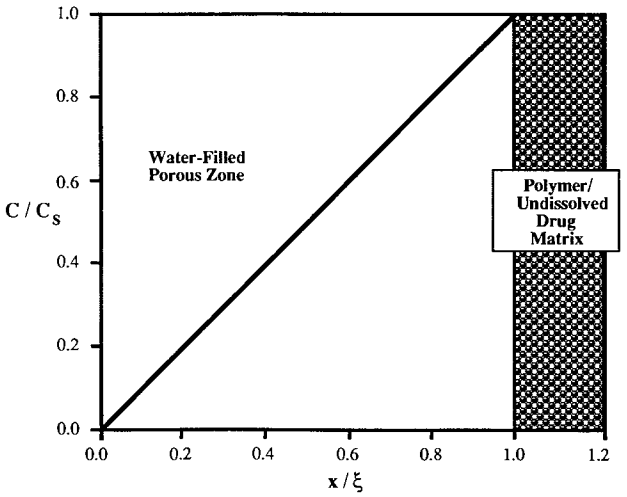

Fig. 1. Schematic diagram of pseudo-steady-state diffusion problem for the benzoic acid/poly(vinyl stearate) matrix system.

nected pore structure and thus cannot contribute to transport. The accessible volume fraction of benzoic acid is defined as $\emptyset_d^a$. The boundary that interfaces the water-filled porous zone and the undissolved drug/polymer matrix is at $\xi(t)$ and is moving with time in the positive x direction. The region where $x > \xi(t)$ is the polymer/undissolved drug matrix. In this section of the tablet it is assumed the diffusion coefficient of the drug is negligibly small since the porosity attributed to this region is below the percolation threshold. The critical diffusion step takes place in the water-filled porous zone, where the transport process can be described by Eq. (12):

$$J_B = \frac{dM_t}{Sdt} = \frac{dQ}{dt} = -D_B \frac{dC}{dx} \tag{12}$$

where C is the concentration of the solute (benzoic acid) in the water-filled pores, M_t is the amount of drug released, S is the surface area of release, and Q is the amount of benzoic acid released per unit area of surface exposed to the dissolution medium (M_t/S). The solution to this equation in terms of percolation parameters is given in Eq. (13). The derivation of this result is similar to that provided by T. Higuchi (5,8) and is therefore not restated. Modifications were simply made in terms of percolation concepts.

$$Q = \sqrt{D_B C_s [2\emptyset_d^a \rho - (\emptyset_d^a + \epsilon) C_s] t} \tag{13}$$

where C_s is the saturated solubility of the water-soluble solute and ρ is its solid-state density.

A plot of the amount released *versus* square root time will therefore be linear, with a slope equal to

$$\text{slope} = S\sqrt{D_B C_s [2\emptyset_d^a \rho - (\emptyset_d^a + \epsilon) C_s]} \tag{14}$$

Therefore, by experimentally determining C_s, ρ, ϵ, S, and $\emptyset_d^a$, values of the bulk diffusion coefficient, D_B, can be obtained at various porosities. From the values of D_B and the experimentally determined value of D_{aq}, percolation parameters can be evaluated based on the previously discussed scaling laws [Eqs. (2) and (3)].

MATERIALS AND METHODS

Benzoic acid (99%+ gold label purity) and poly(vinyl stearate) were obtained from Aldrich Chemical Company. The benzoic acid and poly(vinyl stearate) powders were micronized by Sturtevant Mill Company. Approximately 1 kg of benzoic acid was micronized at a feed rate of 2.3 kg/hr in a 4-in. micronizer lined with polyurethane rubber. Approximately 100 g of poly(vinyl stearate) was micronized at a feed rate of 6 g/min in a 2-in. micronizer. The particle size distributions of the resulting powders were determined using dot counting logic (26). Scanning electron micrographs (Jeol JSM-35C) were taken of samples of the micronized benzoic acid and poly(vinyl stearate) powders and mean projected area diameters were determined. The true densities of benzoic acid and poly(vinyl stearate) were determined at room temperature using helium pycnometry.

The dissolution system used for the diffusion studies consisted of a six-spindle dissolution apparatus and autosampler (Distek Inc.). A Carver Laboratory press, Model C, was used to compress the micronized materials into disks within dies. Sets of type 316 stainless steel and Hastelloy alloy G-3 dies were manufactured for the release experiments. It was found that the Hastelloy dies resisted corrosion during the diffusion experiments to a much greater degree than the 316 stainless-steel dies. The Hastelloy steel dies were manufactured with 0.5-mm-deep by 0.5-mm-wide grooves, spaced 1.5 mm apart within the die to prevent slippage of the matrix and to retard any flow of dissolution medium along the sides of the die. The internal radius of each die was 0.64 cm.

Sample concentrations were determined by high-performance liquid chromatography (HPLC). The HPLC system consisted of a Beckman Model 160 UV detector equipped with a 254-nm filter, a Model 110 pump, a Rheodyne 7120 injection valve (20-μl injection loop), an Altex Ultrasphere ODS (5 μm, 4.6-mm × 25-cm) column and matched precolumn, and a Kipp and Zonen BD 40 chart recorder. The mobile phase used for analytical determinations was composed of 65% methanol, 34% Type II water, and 1% glacial acetic acid. Quantification of sample concentrations was accomplished by comparing peak heights of samples and standards using an internal standard method employing 4-fluorobenzoic acid as the internal standard.

The solubility of benzoic acid at 37°C in pH 2.0 buffer with and without 0.5 m*M* Aerosol OT was obtained by shaking excess solid in sealed vials for 48 and 96 hr. Aliquots from the solubility samples were filtered (Gelman 0.45-mm filter) and then neutralized with high-purity methanol. The internal standard (4-fluorobenzoic acid) was then added to the samples prior to their dilution with the mobile phase. The concentration of benzoic acid in the solubility sample was subsequently determined using the liquid chromatographic method described above.

The diffusion coefficient of benzoic acid was determined using the rotating disk method (27). The experimental conditions used for the determination of the diffusion coefficient were 37°C, pH 2.0, with and without 0.5 m*M* Aerosol OT, and rotational speeds of 50, 100, and 150 rpm.

Benzoic acid/poly(vinyl stearate) matrices were prepared by mixing the two powders and then compressing the blend in a tablet die. Two types of blending procedures were used. For one set of experiments, the powders were simply mixed in porcelain evaporating dishes. In the second set of experiments the mixing procedure involved screening the powders through a 20-mesh (841-μm) screen, blending the screened powders in a sealed vial, screening the blend through a 20-mesh screen, and finally, blending the mixture a second time. It was determined that the second mixing procedure resulted in more reproducible release profiles. Approximately 500 mg of each blend was accurately transferred to separate tablet dies (type 316 dies for the first set of experiments and Hastelloy dies for the second set) and compressed at 10 kN on the Carver press. Volumes of the matrices were calculated from the physical dimensions of each of the compressed disks.

Release experiments were carried out in a Distek 2000 dissolution apparatus with autosampler (Distek Inc., Somerset, NJ) at 37°C in pH 2.0 HCl acid buffer, containing the internal standard (4-fluorobenzoic acid) and 0.25 to 0.5 m*M* Aerosol OT [below the critical micelle concentration (28)]. The medium was degassed by heating to 50°C. The benzoic

acid/poly(vinyl stearate) matrices, compressed within the steel dies, were rotated at 100 rpm.

By using the analysis of Levich (29) concerning mass transfer to a rotating disk, and combining this result with the work of Paul and McSpadden (6) concerning the effect of external mass transfer resistance, it was determined that the external mass transfer resistance at the disk interface is negligibly small under the experimental conditions utilized.

Samples were withdrawn at specified time points and analyzed using the internal standard method described previously. After withdrawal of each sample, the volume of the withdrawn solution was replaced with fresh dissolution medium.

RESULTS

One of the crucial experimental goals of this work was to match the particle size of the hydrophobic polymer with that of the water-soluble solute in order to generate a simple heterogeneous structure. Both the poly(vinyl stearate) and the benzoic acid powders were micronized and the particle size distributions were determined from electron micrographs using dot counting logic. The resulting statistical estimates, listed in Table I, illustrate the fact that the two materials are of comparable particle sizes. Densities were determined by helium pycnometry and the values for benzoic acid and poly(vinyl stearate) are also listed in Table I. The volume fraction of space occupied by benzoic acid and the pore space intrinsic to the undissolved matrix were calculated using the density values listed in Table I, the weight fractions of poly(vinyl stearate) and benzoic acid incorporated in each matrix, and the volume of each matrix. It was found that the porosity intrinsic to the undissolved matrix was 0.021 ± 0.007 (90% confidence) based on the evaluation of 12 matrices over a wide range of benzoic acid loadings. From these experimental results, the intrinsic porosity of the matrix was taken to be 0.02. The volume fraction of benzoic acid for each matrix evaluated is listed in Table II.

The solubility and aqueous diffusion coefficient of benzoic acid in pH 2.0 buffer are the important experimental solution properties required for the predictive application of Eq. (13). The aqueous solubility of benzoic acid at pH 2.0 and 37°C was determined with various concentrations of Aerosol OT (0.00, 0.25, 0.50, and 0.75 m*M*). No significant differences in solubility were observed among the solutions. The solubility of benzoic acid was determined to be 4.6 ± 0.1 mg/ml based on 22 experimental determinations.

The diffusion coefficient of benzoic acid in pH 2.0 aqueous solution (with and without 0.50 m*M* Aerosol OT) at 37°C was determined using the rotating disk method. Diffusion experiments were run at 50, 100, and 150 rpm and the resulting flux data were evaluated using the relationship published by Newman (30) [Eq. (15)]. The analysis was done using Newman's work because it provides a somewhat more accurate estimate than the conventionally used solution developed by Levich for the rotating disk. Using the experimental results of the rotating disk experiment the aqueous diffusion coefficient of benzoic acid was determined by numerically solving Eq. (15):

$$J = \frac{0.6205\, C_s Sc^{2/3}\, (\omega\nu)^{1/2}}{1 + 0.298\, Sc^{-1/3} + 0.14514\, Sc^{-2/3}} \qquad (15)$$

where ω is the rotation speed as radians per second, ν is the kinematic viscosity, and Sc is the Schmidt number (ν/D_{aq}). There were no significant differences found in diffusion coefficients determined in solutions with or without Aerosol OT. The experimental value of D_{aq} was found to be 1.29 ± 0.05 × 10^{-5} cm²/sec, as determined from six independent experiments. The experimental value of the aqueous diffusion coefficient of benzoic acid in water determined from the rotating disk experiment agreed within 5% of predicted coefficients using the correlations of Wilke (31) and Wilke and Chang (32).

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. (2). In order to test this scaling law, benzoic acid release profiles were experimentally determined for a range of benzoic acid loads (ϕ_d values ranging from 0.16 to 0.50). Figure 2 shows typical release profiles of benzoic acid *versus* square root time for three different matrix porosities. The data are plotted against the square root of time according to Eq. (13). The plateau region shown in Fig. 2 corresponds to complete extraction.

The percolation parameters, ϕ_d^a and the relative diffusivity, were calculated from the plateau region and the slope of the releasing region, respectively. The relative diffusivity (D) was determined by fitting the release data to Eq. (13),

Table I. Mean Projected Particle Diameter with 95% Confidence Limits[a] and Densities of Micronized Benzoic Acid and Poly(Vinyl Stearate)

Component	Mean projected area diameter (μm)	Density (g/cm³)
poly(vinyl stearate)	10.3 ± 0.2	0.979
benzoic acid	12 ± 4	1.266

[a] Confidence limits are calculated based on the standard error of the mean.

Table II. Experimental Volume Fraction Accessible and Relative Diffusivity Values Determined as a Function of Drug Load

ϕ_d	ϕ_d^a	$D_B \times 10^6$ (cm²/sec)	D
0.16	0.16	0.49	0.038
0.21	0.21	0.75	0.058
0.24	0.24	1.16	0.090
0.26		1.14	0.089
0.29	0.28	1.77	0.14
0.30		1.70	0.13
0.33	0.34	2.13	0.17
0.35		2.97	0.23
0.37	0.38	3.20	0.25
0.38		3.49	0.27
0.42	0.42	4.26	0.33
0.46		5.03	0.39
0.47	0.47	5.03	0.39
0.50		6.19	0.48

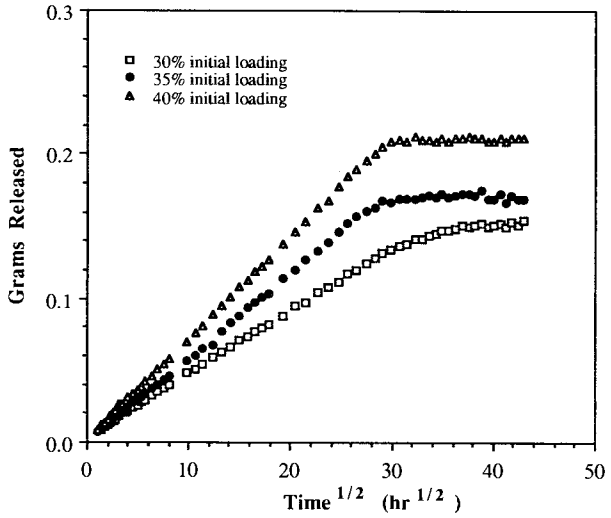

Fig. 2. Grams of benzoic acid released from poly(vinyl stearate) matrix system for various initial loadings (30, 35, and 40% benzoic acid by weight).

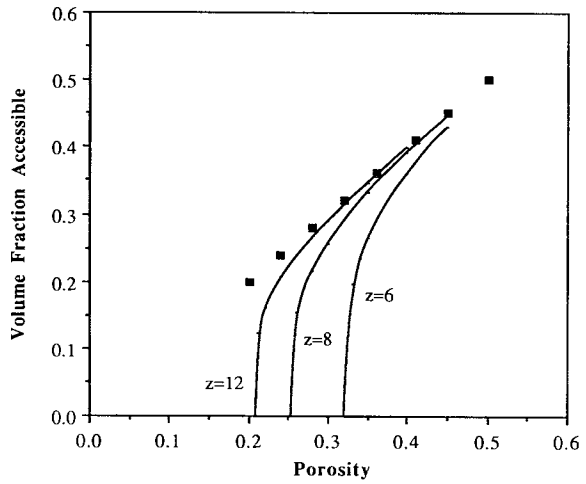

Fig. 3. Experimental $\emptyset^a$ values plotted against porosity. Theoretical curves of $\emptyset^a$ (taken from Ref. 33) for the simple cubic (z = 6), body-centered cubic (z = 8), and face-centered cubic (z = 12) lattices shown for comparison.

where C_s and D_{aq} are independently determined constants. The values of D and $\emptyset_d^a$ determined in this manner are listed in Table II. From the data in Table II it is clearly seen that essentially all the benzoic acid incorporated in the matrices was eventually released over the concentration range tested.

DISCUSSION

The evaluation of the results in Table II begins logically with a comparison of experimental results with theoretical calculations, based on percolation theory, for simple three-dimensional lattices. Theoretical estimates of the relative diffusivity and volume fraction accessible have been determined using simulation techniques for a wide range of simple lattices. The calculation of the volume fraction accessible for simple lattices (simple cubic, body-centered cubic, and face-centered cubic) has been accomplished by Dean and Bird (33) using Monte Carlo techniques. A comparison of our experimental values of $\emptyset^a$, where it is assumed $\emptyset^a = \emptyset_d^a + \epsilon$, with the theoretical profiles determined by Dean and Bird is shown in Fig. 3. It is quite clear that the volume fraction accessible of the experimental matrix is significantly larger than that predicted for simple lattices at low porosities.

The relative diffusivity for theoretical lattices has been studied by several researchers. Winterfeld (34) has determined the "volume fraction effective" (equivalent to our terminology of relative diffusivity) as a function of the volume fraction conducting for tetrakaidecahedral (14 nearest neighbors) and Voronoi (15.54 average neighboring sites) tessellations (site percolation) using two different techniques (resistor network approximation and finite element approximation). The transport properties of the simple cubic lattice have been determined by Kirkpatrick (21) and the results of both groups are shown in comparison with our experimental relative diffusivity results in Fig. 4.

These comparisons indicate that both the relative diffusivity and the $\emptyset^a$ of our experimental system are significantly larger than can be explained by simple lattices. By fitting the relative diffusivity data in Table II to the scaling law shown in Eq. (2), the percolation threshold was determined using nonlinear multiple regression. Because the parameter μ in Eq. (2) is assumed to be universal, the fitting of the experimental data to the scaling law was greatly simplified by treating μ as a known constant. Pandey *et al.* (35) have determined from careful Monte Carlo studies of cubic lattices that μ is 2.0 ± 0.2, whereas Harris (17) has estimated μ to be 1.85 ± 0.15 from an extensive literature survey. For our analysis we assume a value 2.0 for μ, which is consistent with the literature. The relative diffusivity data in Table II were fit using nonlinear regression (SYSTAT, Inc., Evanston, IL) to Eq. (16):

$$D = m(\emptyset - \emptyset_c)^{2.0} \tag{16}$$

where m is a proportionality constant. The value of m was determined to be 2.3 (standard error of 0.1) and the estimate of $\emptyset_c$ was found to be 0.07 (standard error of 0.01). The

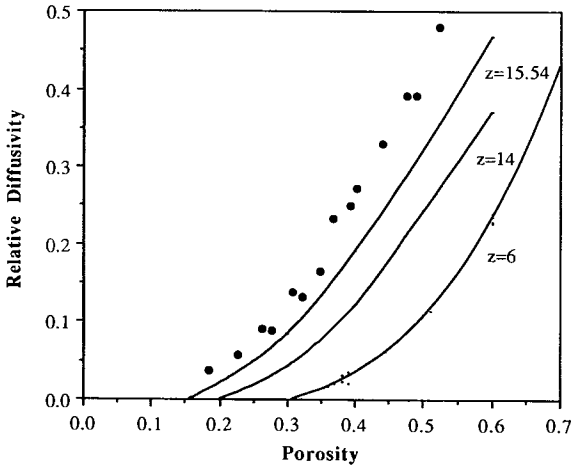

Fig. 4. Experimental D values plotted against porosity. Theoretical curves of D for the simple cubic (z = 6) (21), tetrakaidecahedral (z = 14) (34), and Voronoi (z = 15.5) (34) lattices shown for comparison.

excellent fit of experimental data to Eq. (16) is shown in Fig. 5.

The low experimental percolation threshold is difficult to explain in terms of conventional three-dimensional lattices, and thus, an alternative hypothesis concerning pore structure was tested. It was proposed that osmotic pressure gradients might alter pore structure by creating and connecting additional pore spaces for diffusion. If additional pore spaces were formed via this mechanism, a significantly lower percolation threshold would be observed experimentally. To test this hypothesis, release experiments were performed in media (adjusted with KCl) which were isosmotic with a saturated solution of benzoic acid. Thus, release rates were determined for matrices run in osmotically matched media and these rates were compared to release rates of benzoic acid in media that were not osmotically matched. The slopes for the amount of solute released *versus* square root of time for the two different sets of release experiments are shown in Table III. Clearly there is no significant difference in the rates of release at low porosities for matrices run in osmotically matched and unmatched media. We therefore infer that osmotic pressure effects are not the cause of the experimentally observed low percolation threshold and that an alternative explanation must be found.

Surface release of benzoic acid from the matrices could also be a contributing error in the evaluation of $\emptyset_c$. However, since the square root time release kinetics were constant over the entire time scale investigated, the mechanism of release occurring throughout this time course must be unvarying. This observation therefore supports the conclusion that surface release does not significantly contribute to the value obtained for the percolation threshold of this system.

The coordination number of a site (the number of nearest neighbors) in a three-dimensional lattice is a key concept relating the effect of pore structure to the percolation threshold. For example, a simple cubic lattice has six nearest neighbors and a percolation threshold of 0.312 (36), while a face centered cubic lattice has a coordination number of 12 and a percolation threshold of 0.20 for site percolation (37).

Table III. Comparison of Benzoic Acid Release Rates into Osmotically Matched and Unmatched Buffer Solutions[a]

Drug load ($\emptyset_d$)	Slope of mass released *versus* square root time ($g\ sec^{-1/2} \times 10^5$)	
	Unmatched solution (pH 2 buffer)	Isosmotic solution (pH 2 buffer + KCl)
0.21	5.5 ± 0.1	5.6 ± 0.1
0.26	7.6 ± 0.5	7.5 ± 0.2
0.30	9.9 ± 0.7	9.8 ± 0.2
0.38	16 ± 1	12.7 ± 0.3

[a] The buffer solution is considered matched if it is isosmotic with a saturated solution of benzoic acid.

This illustrates that the larger the coordination number of the lattice, the smaller the percolation threshold. Figure 6 is a plot of the percolation threshold as a function of porosity for several three-dimensional lattices. In order to estimate the number of nearest neighbors corresponding to the experimental percolation threshold, the data in Fig. 6 were fitted to the empirical expression shown in Equation (17), where σ is a fitted coefficient and z is the coordination number.

$$\emptyset_c = \frac{1}{1 + \sigma z} \tag{17}$$

The value of σ was determined to be 0.356 (standard error of 0.005). Solving for the coordination number corresponding to a percolation threshold of 0.07, it was determined that z = 37 for the experimental system studied here. Thirty-seven is a large number in comparison with the coordination numbers of the cubic, tetrakaidecahedron, and Voronoi lattices. This finding of a large coordination number is indicative of a complex shape of a typical site within the benzoic acid/poly(vinyl stearate) matrix investigated.

The large experimental coordination number could indicate that the benzoic acid particles are not randomly mixed on the microscopic scale. The present evidence for this hy-

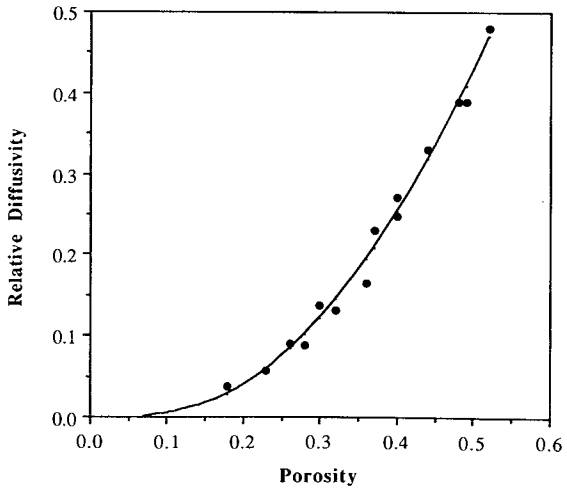

Fig. 5. Scaling law [Eq. (16)] fit to experimental values of D. Experimental critical percolation threshold was determined to be 0.07 ± 0.02.

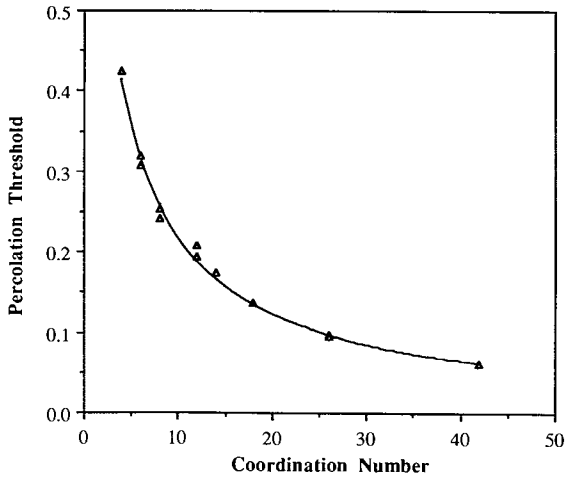

Fig. 6. Critical percolation threshold plotted against coordination number for a wide range of theoretical lattices (data taken from Refs. 33, 36, and 37). Fitted curve from Equation (17).

pothesis consists of the observed percolation threshold and the sensitivity of release rates to the experimental mixing procedure. If the local positions of benzoic acid particles are affected by the presence or absence of other benzoic acid particles, a nonrandom distribution of particles and pores will result.

An example of the effect of a nonrandom distribution of conducting sites on the percolation threshold comes from the thermal transport literature. There is evidence in the literature of structures with very low percolation thresholds (38,39). These structures with very low percolation thresholds tend to be ordered, in that the microscopic arrangement of the particles is not random, even though the system is well mixed. For example, aluminum oxide fleece shows a percolation threshold of approximately 3% and aerogels exhibit similarly low percolation thresholds. Both materials (aluminum oxide fleece and aerogels) show network structures. The reason for such low threshold values in fleece and aerogels is that the sites are not randomly dispersed; instead they are ordered on the microscopic level. This structural organization leads to sample-spanning clusters at very low densities of conducting sites.

Analysis to date has been based on the assumption that diffusion occurs only through the porous network produced by the intrinsic porosity and the dissolution of the benzoic acid particles. If diffusion was taking place directly through the poly(vinyl stearate) polymer, a very low percolation threshold and consequently high coordination would be observed. Low molecular weight chains of the polymer and the presence of amorphous regions within the polymer structure would facilitate diffusion through the polymer chains and possibly explain the current experimental observations. The micronization procedure could reduce the percentage crystallinity of the polymer and therefore impart a more amorphous nature to the polymer. Water uptake within these amorphous regions would serve to greatly enhance the transport of benzoic acid through the matrix.

The percolation models described here are site models and the experimental evidence presented in this analysis would indicate that the average site within the matrix must have a large number of nearest neighbors. It is interesting to note that a bond model of the Voronoi tessellation gives a percolation threshold of 0.082 (24), which is also not statistically different from the experimentally determined percolation threshold. Thus, the bond percolation threshold for the Voronoi tessellation is very close to the experimentally observed percolation threshold.

We hypothesize that the low percolation threshold evaluated for our system is due to either one or both of the following explanations: (i) the benzoic acid particles may not be randomly dispersed on a microscopic scale but, rather, form ordered clusters large enough to span the matrix even at low concentrations; or (ii) benzoic acid is diffusing directly through the poly(vinyl stearate) due to low molecular weight polymer chains or a low degree of crystallinity. Future research will focus on the elucidation of the physical structure of the porous matrix and the existence of network structures, characterization of the physical properties of the polymer, and evaluation of transport properties through the polymer.

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