A Reappraisal of Drug Release Laws Using Monte Carlo Simulations: The Prevalence of the Weibull Function

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Purpose. To verify the Higuchi law and study the drug release from cylindrical and spherical matrices by means of Monte Carlo computer simulation.

Methods. A one-dimensional matrix, based on the theoretical assumptions of the derivation of the Higuchi law, was simulated and its time evolution was monitored. Cylindrical and spherical three-dimensional lattices were simulated with sites at the boundary of the lattice having been denoted as leak sites. Particles were allowed to move inside it using the random walk model. Excluded volume interactions between the particles was assumed. We have monitored the system time evolution for different lattice sizes and different initial particle concentrations.

Results. The Higuchi law was verified using the Monte Carlo technique in a one-dimensional lattice. It was found that Fickian drug release from cylindrical matrices can be approximated nicely with the Weibull function. A simple linear relation between the Weibull function parameters and the specific surface of the system was found.

Conclusions. Drug release from a matrix, as a result of a diffusion process assuming excluded volume interactions between the drug molecules, can be described using a Weibull function. This model, although approximate and semiempirical, has the benefit of providing a simple physical connection between the model parameters and the system geometry, which was something missing from other semiempirical models.

KEY WORDS: drug release; Monte Carlo simulations; power law; Weibull function.

INTRODUCTION

The modeling of drug release from delivery systems is important for our understanding and elucidation of the transport mechanisms and allows the prediction of the effect of the device design parameters on the drug release rate. Hence, the development of new pharmaceutical products is highly facilitated because the desirable release kinetics can be predicted in advance and thus be better achieved. Despite the complexity of the phenomena involved in drug release mechanisms, the mathematical models commonly used to describe the kinetics of drug release from a large variety of devices are two simple expressions, the Higuchi law and the power law.

The Higuchi law (1) states that

$$M_t = A\sqrt{D(2c_o - c_s)t} \tag{1}$$

where M_t is the cumulative amount of drug released at time t, A is the surface area of the controlled release device exposed to the release medium, D is the drug diffusivity, and c_o and c_s are the initial drug concentration and the drug solubility, respectively. This law is valid for systems where the drug concentration is much higher than the drug solubility.

The power law (2) states that

$$\frac{M_t}{M_\infty} = kt^n \tag{2}$$

where M_t and M_∞ are the amounts of drug released at times t and infinity, respectively; k is an experimentally determined parameter, and n is an exponent that depends on the geometry of the system; it can be related to the drug release mechanisms (3,4). Equation 2 is extensively used because of this property.

In addition to the above two equations, various approaches have been developed that are based on the geometry of the device and the physicochemical drug properties, and they provide a comprehensive, mechanistic interpretation of the drug release kinetics (5–10). One should also add that zero-order release kinetics can be considered as a special case of the power law [it is called Case II transport for polymeric controlled release devices (3)] and is often a desirable feature. (For a detailed presentation and comparison of the most commonly used drug release models, see Refs. 10 and 11.) Finally, the Weibull function (12) is sporadically used in drug release studies (13) in spite of its extensive empirical use in dissolution studies (14):

$$\frac{M_t}{M_\infty} = 1 - \exp(-a\,t^b) \tag{3}$$

where a and b are constants. This model has the form of a stretched exponential function. It describes experimental dissolution data (14) quite well, but up to now there is no physical reasoning for it or a physical meaning of the constants a and b. In this paper we intent to provide such a physical meaning for the use of Eq. 3.

It is well known that diffusion plays a significant role in drug release mechanisms, irrespective of the geometry and composition of the devices. The problem of release kinetics with Fickian diffusion and no interaction between drug molecules has analytic solutions (15) for various device geometries. These solutions are almost always in the form of infinite series that are very weakly converging for short times, a fact that makes them practically unusable. Moreover, there is no known analytic solution when interactions between drug molecules are taken into account. These observations, coupled with the approximate character (1–4) and the empirical use (13) of the models in drug release studies, prompted us to reexamine the release kinetics utilizing Monte Carlo simulations based on the random walk model of Fickian diffusion with excluded volume interactions, i.e., we assume that moving particles behave like hard spheres that collide and with no possibility for a sphere to penetrate into another. Similar Monte Carlo techniques have been used recently in several other diffusion problems in biopharmaceutics with very satisfactory results (16,17). To this end, we first studied drug release kinetics for a system complying with the constraint assumptions of the Higuchi law. We subsequently studied the general problem of release kinetics of drug particles randomly

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distributed in cylinders of various heights and diameters assigned to various numbers of leaking sites on the external surface of the cylinders. We have finally used the same computational tools for study of spherical release devices.

THEORY OF THE RELEASE PROBLEM

Our main goal is the escape of particles from a release device. We treat vessels of various shapes. As a starting point let us consider a cylindrical device. The direct way to study the problem is by solving the diffusion equation. Fu *et al.* (5) described the analytic solution of Fick's second law for cylindrical geometry, considering mass transfer in three dimensions. Their basic result is that

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{h^2 r^2} \sum_{m=1}^{\infty} a_m^{-2} \exp(-D a_m^2 t) \sum_{n=1}^{\infty} \beta_n^{-2} \exp(-D \beta_n^2 t), \quad (4)$$

where $\beta_n = (2n+1)\pi/2h$, a_m are the roots of the equation $J_0(ra) = 0$, and J_0 is the zero-order Bessel function. Here, h denotes the half-length, and r the radius of the cylinder. Note that for small t the series is very slowly converging. Even keeping 100 terms in the above series still it is not a good enough approximation for short times. For long times all terms with high values of a_m and β_n decay rapidly, and only the term with the lowest value survives. The series reduces to a simple exponential after some time. The above solution is valid when the diffusion coefficient is assumed to be constant and when particles escape from the entire surface of the cylinder. As we have pointed out, Eq. 4 is quite difficult to use, and therefore empirical models, like the power law (Eq. 2), are used instead.

Our intent is to derive a simple approximate solution of the release problem that can be used to describe release even when particles escape not from the entire surface but from just a portion of the surface of the release device (not necessarily a cylindrical device), and even when interactions between the particles are present.

We assume that particles are moving inside the vessel in a random way. If the number of particles that exist in the vessel at time t is N, we expect that the particle escape rate will be proportional to the fraction f of particles that are able to reach an exit in a time interval dt, i.e., the number of particles that are sufficiently close to an exit. Initially the molecules are homogeneously distributed over the matrix. Later, as a result of the release, a concentration gradient will arise with fewer molecules at the boundary of the release system and a maximum at the central position. Concerning the form of f, at this point we note that it should be a function of time. We thus expect a differential equation of the form

$$\frac{dN}{dt} = -a\, f(t) N \quad (5)$$

to hold, where a is a proportionality constant, fN denotes the number of particles that are able to reach an exit in a time interval dt, and the negative sign means that N decreases with time. If we assume the presence of interactions between the particles, this is an additional constraint implying that f should be a function of time. The reason is that as time elapses a large number of particles leave the vessel, and the rest can move more freely. This has to be included somehow in the equation, and the way we propose to do this is through f. In general we expect that in both cases Eq. 5 will be valid, but the functional form of $f(t)$ may be different depending on the type of intermolecular interactions. In order to find an approximate solution of the release problem, one has to start with a specific functional form for $f(t)$.

A plausible assumption is to consider that $f(t)$ has a form $f(t) \sim t^{-m}$. For $m = 1/2$ we see that $N(t) \propto \sqrt{t}$ (as a short-time approximation[4]), exactly as predicted by the Higuchi law (1). For $m = 0$, we obtain, again as a short-time approximation, the result $N(t) = N_o - A\, t$ corresponding to "ballistic" exit (zero order kinetics). The above imply that choosing $f(t) = t^{-m}$ is quite reasonable. In this case Eq. 5 will be

$$\frac{dN}{dt} = -a \frac{N}{t^m} \qquad \frac{dN}{N} = -a\, t^{-m}\, dt \quad (6)$$

Integrating both sides we find that $\ln N = -a\, t^b + c$ where $b = 1 - m$, and the above is also written as

$$N = N_0 \exp(-\alpha\, t^b), \quad (7)$$

where we have used the initial condition that $N(t = 0) = N_0$.

Note the following limiting case: Suppose that $f(t) = t^{-m}$ and that $m = 0$. Then from Eq. 5 we have

$$\frac{dN}{dt} = -aN \qquad \frac{dN}{N} = -a dt \quad (8)$$

We obtain the result that $N = N_0 \exp(-\alpha\, t)$, which is similar to the asymptotic result derived by Fu *et al.* (5) for pure Fickian diffusion inside a cylinder for long times.

The above reasoning shows that the stretched exponential function Eq. 7, or Weibull function as it is known, may be considered as an approximate solution of the release problem. We expect that it can be used to model release results in the presence or absence of interactions.

It is clear that using this rationale it can not be proven that the Weibull function is the best choice[5] for approximating the release results. There exist several different choices for the form of $f(t)$, and some of them might be better than the Weibull equation. The advantage of this choice is that it is general enough to allow us to describe release from vessels of various shapes, in the presence or absence of interactions, by adjusting the values of the parameters α and b. Our simulation results, as well as several experimental results, show that it is indeed a good choice. We will use our simulation results to derive a systematic way to calculate the values of the parameters α and b and gain some physical insight for the behavior for different vessel shapes and sizes.

[4] There are two ways to calculate a short-time approximation for the solution of Eq. 5. The direct way is to make a Taylor expansion of the solution. The second, more physical way is to realize that for short initial time intervals the release rate dN/dt will be independent of N. Thus, the differential Eq. 5 can be approximated by $(dN/dt) = -c\, f(t)$. Both ways lead to the same result.

[5] Actually it is not the best choice. There is an obvious weakness of the Weibull. The release rate dN/dt is singular at $t = 0$. The same, however, is true for the Higuchi law and the power law as well. We prefer to keep the functional form of $f(t)$ as simple as possible, despite this weakness. Our simulation results support this choice.

The above reasoning is quite important because it provides a physical model for the use of the Weibull function in order to fit experimental release data, and it elucidates some aspects of this empirical model, which is already sporadically used in release studies (13) without any justification of its physical origin.

METHODS

Our main methodology is based on Monte Carlo simulations performed on the systems that we are examining. Briefly, this method is based on considering finite-size systems made up of a specified number of units. These systems are statistically averaged over a large number of configurations in order to mimic correctly the system behavior. All decisions are taken by the use of random numbers drawn from a uniform random number distribution, a function that is inherent nowadays in all computers. Thus, the system dynamics can be inferred by the resulting configurations. Each decision corresponds to an arbitrary time unit (called Monte Carlo Step, MCS), which may eventually be shown to correspond to a real time unit.

Higuchi Law Simulations

In order to mimic the conditions of the Higuchi law, we constructed a one-dimensional matrix of 200 sites. Each site is labeled with the number of particles it currently hosts. Initially all sites have 10 particles. We assume that drug molecules move inside the matrix by the mechanism of Fickian diffusion. The diffusion process can be simulated using the random walk model (18–20). We also assume that the molecules cannot move to a site unless this site is empty. Thus, the system is expected to behave as if its "drug concentration" (10 particles per site) is much higher than its "solubility" (1 particle per site), which is the basic assumption made in the theoretical derivation of the Higuchi law. The matrix can leak only from the site at its edge.

The diffusive escape process is simulated by selecting a particle at random and moving it to a randomly selected nearest neighbor site. If the new site is an empty site then the move is allowed, and the particle is moved to this new site. If the new site is already occupied, the move is rejected. A particle is removed from the lattice as soon as it migrates to the leak site; see Fig. 1 for a schematic.

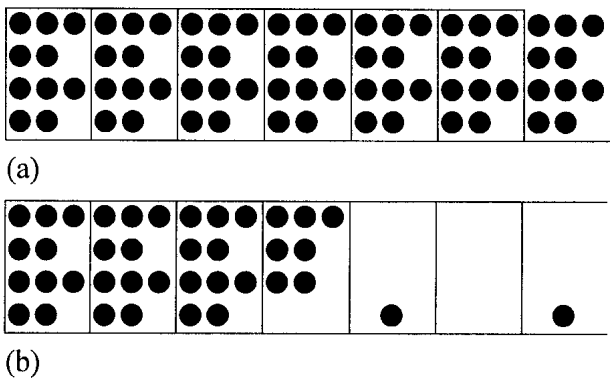

Fig. 1. Schematic of a system that is used to follow the Higuchi law. (a) Initial configuration of the system; (b) evolution after time *t*. Particles are allowed to leak only from the right side of the system.

After each particle move, time is incremented. The increment is chosen to be *1/N*, where *N* is the number of particles remaining in the system. This implies that the unit time characterizing the system is the mean time required for every one of the *N* particles to be offered the possibility of moving one step. This is a typical approach in Monte Carlo simulations (18). We monitor the number of particles that are present inside the cylinder as a function of time until the cylinder is completely empty of particles.

Simulations for the General Problem of Drug Release from Cylinders

We assume here that the drug molecules move inside the cylinder by the mechanism of Fickian diffusion. We also use excluded volume interactions between the particles. This means that each molecule occupies a volume V where no other molecule can be at the same time. We start with a known initial drug concentration and with randomly distributed drug molecules inside the cylinder.

We first consider a three-dimensional lattice in the form of a cube with L^3 sites. We next define inside this cubic lattice a cylinder. A site is uniquely defined by its 3 indices *i,j,k* (coordinates). We label sites as follows (r is the radius of the cylinder):

If $i^2 + j^2 < (r - 1)^2$ then it belongs to the interior of the cylinder and it can host drug molecules. If, on the other hand, $i^2 + j^2 > r^2$ then it is outside the cylinder; it is marked as a restricted area, and particles are not allowed to go there; see Fig. 2 for a schematic. Finally, we label leak sites. We can label as leak sites as many surface sites as we want. For example, in order to obtain the results presented in Fig. 4, we labeled as leak sites the sites with indices $(r - 1)^2 \leq i^2 + j^2 \leq r^2$, thus defining a cylinder leaking from its round surface but not from its top or bottom, whereas in Fig. 6 we label all surface sites as leak sites. The simulation method proceeds as follows: We place a number of particles randomly on the sites of the cylinder, according to the initial particle concentration

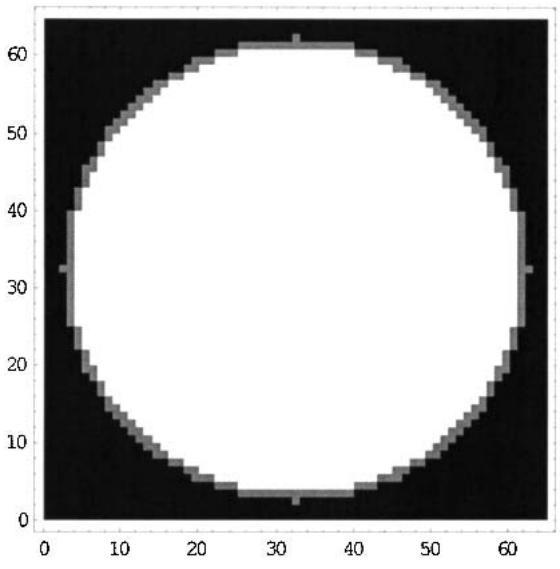

Fig. 2. A cylindrical cross section with radius $r = 30$ sites. The dark area is restricted to particles. The gray area indicates the leaking sites. The white area is where the drug particles are initially located. Each site in the white area can be either occupied or empty.

c, avoiding double occupancy. For example $c = 0.5$ means that 50% of the sites are initially occupied by particles, and the rest are empty. The diffusion process is simulated by selecting a particle at random and moving it to a randomly selected nearest neighbor site. If the new site is an empty site, then the move is allowed, and the particle is moved to this new site. If the new site is already occupied, the move is rejected (since we assume excluded volume interactions). A particle is removed from the lattice as soon as it migrates to a site lying within the leak area. We count time using the same method as in the previous section (Higuchi law simulation). We average our results using different initial random configurations but the same parameters.

Simulations for the Drug Release Problem from Spherical Matrices

The simulation technique used is the same as above, the only difference being that now sites with indices $i^2 + j^2 + k^2 > r^2$ are considered outside of the sphere and marked as a restricted area while leak sites are those whose indices satisfy the inequalities

$$(r-1)^2 \le i^2 + j^2 + k^2 \le r^2.$$

RESULTS AND DISCUSSION

Our simulation results verify the Higuchi law. In Fig. 3 we show the function $(1 - N/N_0)$ vs. time. The slope of the line is equal to 0.51, which is very close to the value 0.50 expected by the Higuchi law. We observe that the Higuchi law (1) and the Weibull function are apparently quite different in form. The Higuchi law is valid for very dense systems. Figure 3 demonstrates that the Higuchi law can be derived from our simulation model as a "short" time case (60% of the release data) of such a system. This approximation is in good agreement with the analysis of Siepmann and Peppas (10).

We now use the theoretically derived Weibull function in combination with our simulation results in order to:

a. Check if the Weibull can describe the simulation data.
b. Obtain some physical insight for the meaning of the Weibull parameters α and b.
c. Discuss the relevance of the power law to the Weibull function model.

Figure 4 shows our simulation results for four cylinders of different sizes. In all cases it is possible to achieve a quite accurate fitting of the simulation results for $N(t)$ using the stretched exponential law. It turns out that the stretched exponent b takes values in the range 0.69 to 0.75. Figure 5 shows that the fitting is very accurate, especially at the beginning, and it remains quite good until all of the drug molecules are

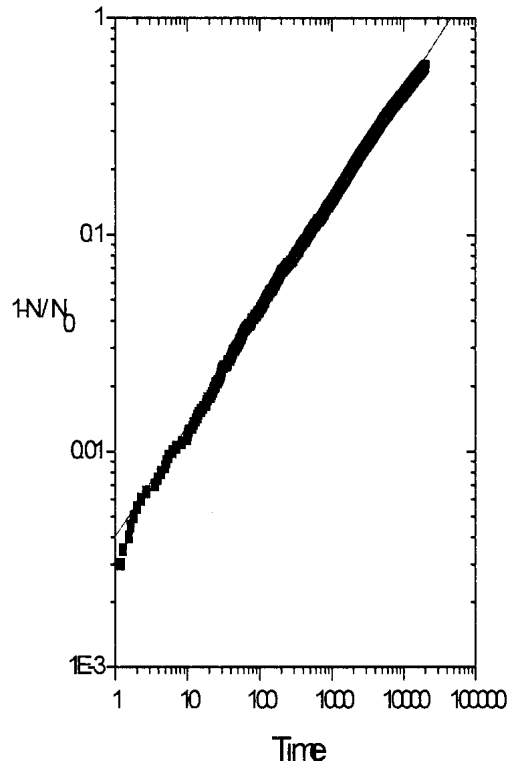

Fig. 3. Log-log plot of $1 - N/N_0$ vs. time (Monte Carlo units). We present simulation results (points) and linear fitting (solid line). The slope of the line $n = 0.51$ corresponds to the exponent of the Higuchi law. The theoretical prediction is 0.50. We plot the initial 60% of the release data.

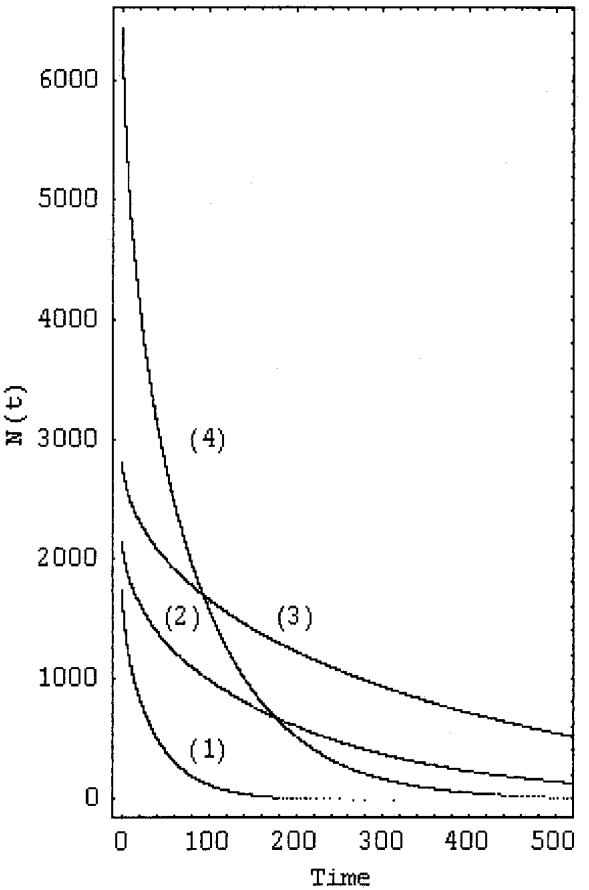

Fig. 4. Number of particles inside a cylinder as a function of time. (1) Cylinder with height of 31 sites and diameter 16 sites. Number of drug molecules $N_0 = 1{,}750$. (2) Cylinder with height 7 sites and diameter 31 sites. Number of drug molecules $N_0 = 2{,}146$. (3) Cylinder with height 5 sites and diameter 41 sites. Number of drug molecules $N_0 = 2{,}843$. (4) Cylinder with height 51 sites and diameter 21 sites. Number of drug molecules $N_0 = 6{,}452$.

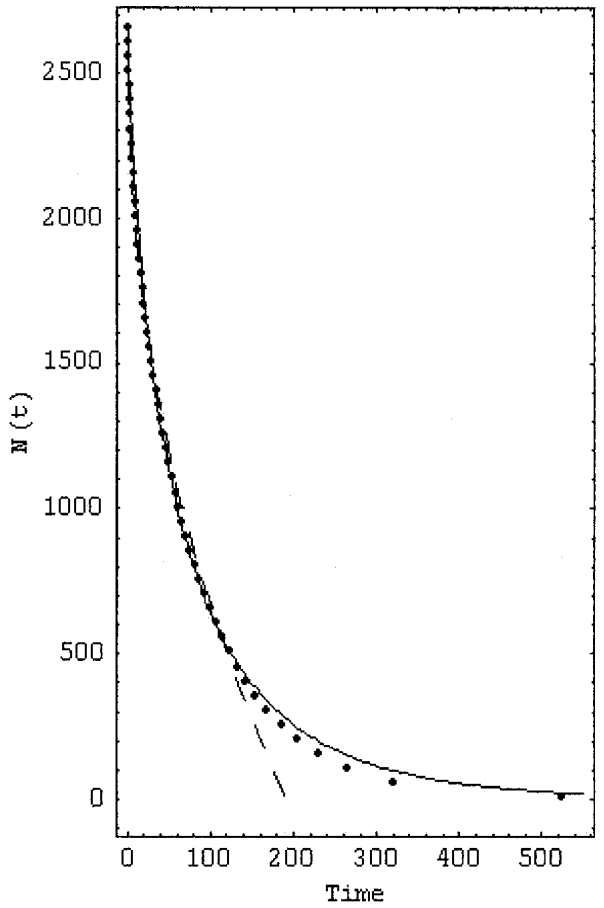

Fig. 5. Number of particles inside a cylinder as a function of time. Dotted line, simulation for cylinder with height 21 sites and diameter 21 sites; number of drug molecules $N_0 = 2{,}657$. Thin solid line, plot of curve $n = 2{,}657 \exp(-0.049\, t^{0.72})$ (Weibull model fitting). Dashed line, plot of curve $n = 2{,}657(1 - 0.094\, t^{0.45})$ (power law fitting). Weibull function describes simulation data more accurately till the end of the release.

released. We may summarize our results as follows. The number of particles that have escaped from a matrix is equal to

$$Q(t) = N_0 - N(t) = N_0\,(1 - \exp(-\alpha\, t^b)) \tag{9}$$

where α and b are parameters that have to be experimentally determined. We have been able to verify the above relation using Monte Carlo simulations by assuming that the particles perform a random walk inside the matrix and by taking into consideration excluded volume interactions. References 21 and 22 include experimental data fitted to Weibull functions. In Ref. 21 the authors explicitly study release from coated theophylline particles and present results from an experimental drug release study for different values of coating and plasticizer added to the coating polymer. The values of b exponent are in all cases in the range of 0.54 to 1.18, depending on the amount of coating and plasticizer. The higher value is found in the absence of plasticizer and coating, and it can be explained if we take into account that in this case there is an additional release mechanism related to the erosion of the release device and the penetration of water into the release capsule. When a film coating and the proper amount of plasticizer cover the release device, this second release mechanism ceases to be important, and the release is more or less Fickian. In these cases the experimentally determined exponents are within the range predicted in our simulations.

As already indicated in the theory section, Ritger and Peppas (3,4) have proposed the power law model, which is believed to describe accurately the release at short times. According to that model release is described by Eq. 2. This power law model is being successfully used in order to describe Fickian release. It is valid when the exponent n has values close to 0.5. For Case II release, n must be around 1.0, and anomalous diffusion prevails for $0.5 < n < 1$. It is easy to show that the two models (Eqs. 2 and 9) coincide for small values of t. For small values of x we can use the approximation $e^{-x} \sim 1 - x$ (Taylor expansion). From Eq. 9, setting $x = at^b$, one gets (for small values of $\alpha\, t^b$)

$$Q(t)/N_0 = 1 - (1 - a\, t^b) = a\, t^b \tag{10}$$

which has the same form as the power law model. (Note that $Q(t)/N_0$ is directly linked to M_t/M_∞.) For this approximation to hold, the quantity (at^b) has to be small. This does not mean that t itself must be small. As long as α is small, t may take larger values, and the approximation will still be valid. Published results using the power law (13,23) calculate the value of the power law exponent using data up to point when 60% of the release is completed. The small time approximation is not valid for such long time intervals (more terms should be considered in the Taylor expansion of e^{-x}). Thus, the values of the power law parameters from results (13,23) will not be the same as the Weibull function parameters in case one uses the Weibull function to describe the same experimental data.

Figure 5 shows simulation results and fittings with the Weibull and the power law model. Obviously, the Weibull model describes quite well all release data, whereas the power law diverges after a certain point in time. Of course, both models can describe equally well experimental data for the initial part of the release curve.

In Fig. 6 we present results of a release simulation in which we have allowed the cylinders to leak from their entire surface, i.e., round, top, and bottom parts. The two cylinders have similar specific surface, i.e., surface-to-volume ratio. In fact, one has a specific surface equal to 0.271 and the other equal to 0.277. They can both be fitted to a Weibull function, and as anticipated, the Weibull parameters are also almost the same in both cases (namely $\alpha = 0.073$ and $b = 0.71$ for the first case and $\alpha = 0.074$ and $b = 0.71$ for the second case).

The parameters α and b are somehow connected to the geometry and size of the matrix that contains the particles. To investigate this connection we performed release simulations for several cylinder sizes and for several initial drug concentrations. We fitted our results using the Weibull function model. We denote as N_{leak} the number of leak sites and N_{total} the total number of sites. In the continuum limit the ratio N_{leak}/N_{total} is proportional to the leak surface of the system. Plots of α vs. N_{leak}/N_{total} (Fig. 7) are independent of the initial drug concentration and are straight lines, so we may assume that α in our model is proportional to the specific leak surface. In Fig. 7 the slopes of curves are in the range of 0.30 to 0.35 (values of a linear fitting). Further, if we impose that $a(0) = 0$ the corresponding slopes are in the range 0.26 to 0.30. The value of the slope can be explained as follows, using the mathematical model presented in the theoretical section. In order

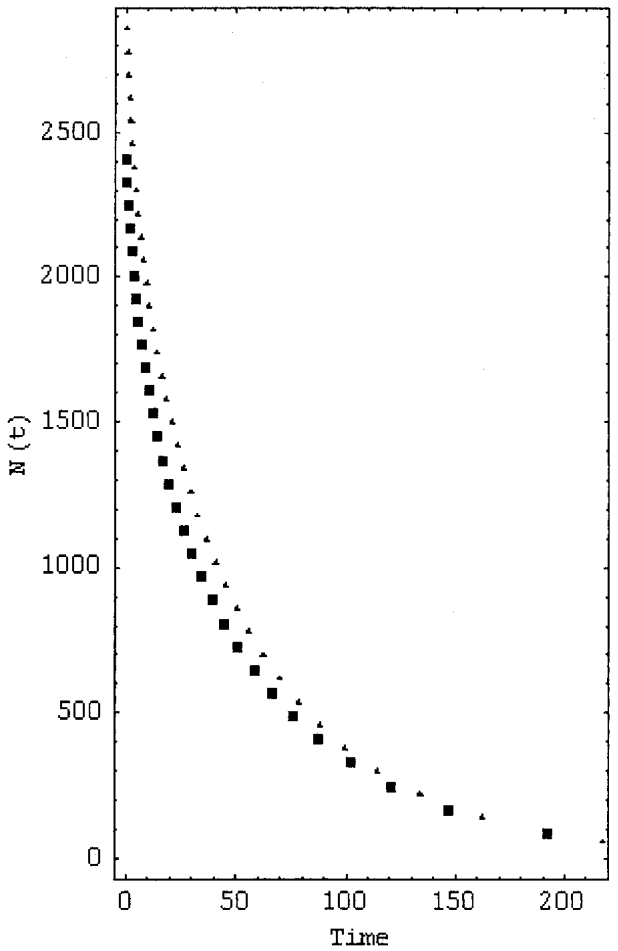

Fig. 6. Number of particles inside a cylinder as a function of time. The cylinder is allowed to release from its round surface, top and bottom. Triangles, cylinder with height $h = 31$ sites and diameter $d = 19$ sites; number of drug molecules $N_0 = 2{,}857$. Squares, cylinder with height $h = 21$ sites and diameter $d = 21$ sites; number of drug molecules $N_0 = 2{,}404$. Both cylinders have almost the same specific surface. Fitting of the Weibull function to data gives the same values for parameters α and b as anticipated ($\alpha = 0.07$, $b = 0.71$ in both cases.)

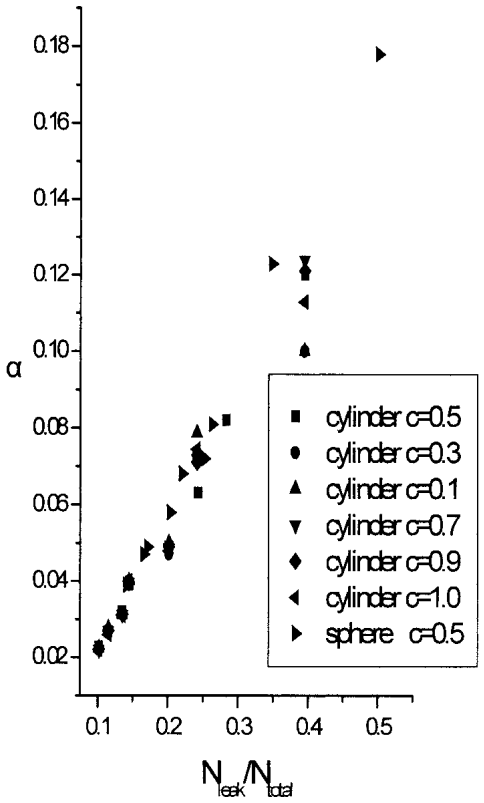

Fig. 7. Parameter α vs. N_{leak}/N_{total} for various initial drug concentrations c. Slope of the curves is ~0.28 in all cases. Note that higher values of N_{leak}/N_{total} correspond to smaller cylinder sizes. Computational errors become more significant when cylinder size is decreased.

to derive the Weibull distribution, we assumed Eq 5. From the simulation we found that $a\ N = 0.28(N_{leak}/N_{total})$. Assuming a uniform distribution of particles, N_{leak}/N_{total} is the probability that a particle is at a site that is just one step from the exit. Thus, (N_{leak}/N_{total}) is the mean number of particles that are able to escape at a given instance. Because there are six neighboring sites in the three-dimensional space, the probability that a particle will make the escaping step is 1/6 (~0.17). It is quite close to the 0.28 value of the simulation. The difference results from the fact that the distribution of particles is not uniform because of the concentration gradient that is created near the exits.

We plot b vs. N_{leak}/N_{total} (Fig. 8). Notice again that the slope of b is practically independent of the initial concentration. Considering it to be a straight line, we find that $b = 0.65 + 0.4\ N_{leak}/N_{total}$. We see that there are two terms contributing to b. One depends on the N_{leak}/N_{total}, and the other does not. Actually b is expected to be proportional to the specific surface because a high specific surface means that there are a lot of exits, so finding an exit is easier. The constant term is expected to depend on the ability of the particles to move inside the matrix, the interaction between the particles, etc.

In Figs. 7 and 8 we have also included the parameters α and b resulting from our simulation method for spheres (instead of cylinder) with initial drug concentration $c = 0.5$. As we can see, the simulation results imply that the parameter α seems independent of the geometry of the device. For the parameter b we see that although the slope seems independent of the geometry, the y-intercept is slightly less for a sphere than for a cylinder. This fact is in agreement with Siepmann and Peppas's (10) remarks for the power law model, where the power law exponent for a sphere is slightly less than that for a cylinder.

An interesting question now arises: If we know the properties of the polymer matrix and the properties of the drug molecule, is there a way to calculate the parameters of the Weibull model? We note that computer simulations use a Monte Carlo length and time scale. In order to study a cylinder we divide it in small cells. Because we study Fickian diffusion, each cell length can be considered to be equal to the mean free path Δl of the molecules (We do not know the mean free path, but a good approximation is to consider it of the same order of magnitude as the intermolecular distances of the matrix). The same holds for the time scale, which we may consider equal to the mean free time τ. Thus, a procedure to estimate release from cylinders is the following.

First, one may estimate the mean free time knowing the mean free path and the diffusion coefficient by the definition

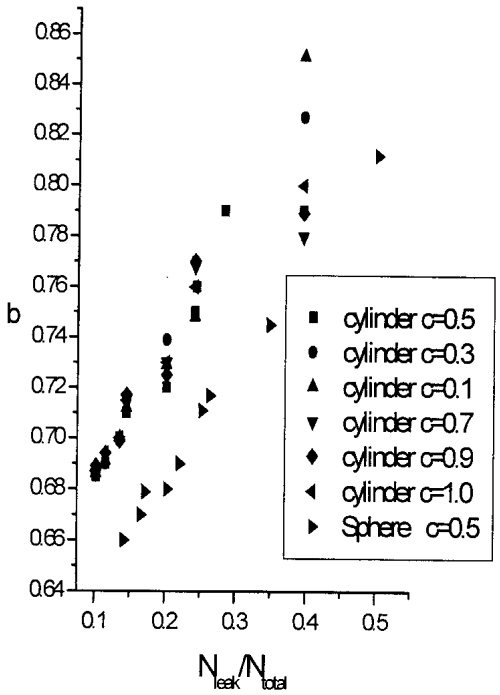

Fig. 8. Parameter b vs. N_{leak}/N_{total} for various initial drug concentrations c. Note that higher values of N_{leak}/N_{total} correspond to smaller cylinder sizes.

$$D = \frac{(\Delta l)^2}{2\tau}. \tag{11}$$

It is difficult to calculate or measure the mean free path exactly. However, reasonable approximations can be done, as pointed out above.

Second, we calculate

$$\frac{N_{leak}}{N_{total}}$$

using

$$\frac{N_{leak}}{N_{total}} = \frac{S}{V}\Delta l$$

where S/V is the specific surface of the cylinder.

Third, knowing

$$\frac{N_{leak}}{N_{total}}$$

we calculate the α and b parameters using the above derived relationships.

Finally, the release from a cylinder may be estimated as follows:

$$\frac{M_t}{M_\infty} \approx 1 - exp\left(-0.28\,\Delta\ell\frac{S}{V}\left(\frac{t}{\tau}\right)^{0.65+0.4\Delta l\frac{S}{V}}\right) \tag{12}$$

We can now answer several interesting questions. For example, we can predict the effect that an increase in temperature will have on the release. An increase in temperature will increase the drug particles' average speed and thus will decrease the mean free time τ. Thus, the release will be faster, and we may use Eq. 12 to estimate quantitatively how much faster. Of course, temperature has many other effects on real matrices. However, the Weibull model, as presented here, is the only semiempirical model that takes into account the simplest temperature effect. This is an advantage compared to the widely used power law model. Surely there are limitations in using Eq. 12 for practical purposes because there are no published values of the mean free path and mean free time of diffusive movement of drugs inside polymer matrices, and such measurements are not easy to perform. Also, for each particular geometry, the apparent specific surface S/V will be different from the actual active specific surface, first, because of the surface microstructure, and second, because of the possibility that some surface elements do not serve as leak sites. Equation 12 simply provides a link between the Weibull model and the physical kinetics of the release procedure.

CONCLUSIONS

We derived the Higuchi law as a limiting case of the diffusion process for a very dense system using Monte Carlo simulations. We have described drug release from a cylindrical matrix as a result of a diffusion process assuming excluded volume interactions between the drug molecules using Eq. 7, in which α is strongly dependent on the specific surface of the matrix, and b is subject to two influences. The more significant is the one resulting from the particle interactions and their ability to move inside the matrix, and a weaker contribution is that from the specific surface. Our simulation results reveal that:

1. Both α and b are very weakly dependent on the initial concentration of particles.
2. The power law may be considered as a short-time approximation of Eq. 3.

The above results substantiate the use of the Weibull function in drug release studies (13) and underline the role of the specific surface during the release processes. The role of the specific surface is not new (24). Its importance is known from experimental data and verified from our simulation results. But the other existing semiempirical models do not explicitly predict a dependence of their parameters on the specific surface.

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