Fractal kinetics in drug release from finite fractal matrices

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We have re-examined the random release of particles from fractal polymer matrices using Monte Carlo simulations, a problem originally studied by Bunde *et al.* [J. Chem. Phys. **83**, 5909 (1985)]. A certain population of particles diffuses on a fractal structure, and as particles reach the boundaries of the structure they are removed from the system. We find that the number of particles that escape from the matrix as a function of time can be approximated by a Weibull (stretched exponential) function, similar to the case of release from Euclidean matrices. The earlier result that fractal release rates are described by power laws is correct only at the initial stage of the release, but it has to be modified if one is to describe in one picture the entire process for a finite system. These results pertain to the release of drugs, chemicals, agrochemicals, etc., from delivery systems. © *2003 American Institute of Physics.* [DOI: 10.1063/1.1603731]

INTRODUCTION

The problem of particle release from a matrix[1] has many applications in several areas, including pharmaceutics, particularly for the drug release from delivery systems. The basic question posed here is how do the drug molecules escape from a tablet or capsule that is taken orally and how are they delivered to the gastrointestinal (GI) tract. It is well known that the release mechanism is dependent on the device used, and thus there is no single answer to the question posed here. For immediate release formulations the entire quantity of solid drug particles becomes available for dissolution in the GI fluids upon disintegration of the device. On the other hand, for controlled release formulations, meaning a controlled release rate of drug over a time period, there are several mechanisms that can be envisaged.[2] According to the simplest mechanism the release device is gradually dissolved inside the GI tract and the drug molecules follow the same pattern. This is a simplified description of the model that describes release from swellable polymer devices known in the literature as case II release, a model that has been studied[3–6] by several groups, and recently by us[7] for the case of cylindrical devices with both axial and radial release. A second mechanism for the escape of drug molecules from the release device is through Fickian diffusion before the device is dissolved. For detailed studies of this model, see, for example, Refs. 8–10, and references included therein. This model has also been studied by means of Monte Carlo simulations.[1,11] A third possibility is that the release devise, as it is immersed in the GI tract fluids, it is penetrated by these fluids, creating areas of high diffusivity. Thus, the drug molecules can escape from the release device through diffusion from these high diffusivity ''channels.'' Now, the dominant release mechanism is diffusion, but in a complex disordered medium. The same is true when the polymer inside the release device is assuming a configuration resembling a disordered medium. This is a model proposed for HPMC matrices.[12] This last interesting possibility was first studied by Bunde *et al.*[1] and is also the subject of the present study. Of course, in realistic situations for controlled release formulations, it is expected that the above mechanisms coexist simultaneously. This fact usually complicates the analysis of experimental data. In such cases Monte Carlo simulations may be particularly useful.

In spite of the complexity of the phenomena involved in drug release mechanisms, the mathematical expressions used in pharmaceutics to describe the kinetics of drug release from a large variety of devices are rather simple, and they can be summarized briefly in three basic laws:

(a) The Higuchi law,[8]
$$M_t = A\sqrt{D(2c_o - c_s)t}, \tag{1}$$
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.

(b) The Peppas equation or the so-called power law,[9,10]
$$\frac{M_t}{M_\infty} = kt^n, \tag{2}$$
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 boundary of the system which can be related to the drug release mechanisms.

(c) The Weibull model,[13]
$$\frac{M_t}{M_\infty} = 1 - \exp(-at^b), \tag{3}$$
where α, b are constants. This model has the form of a stretched exponential and it is sporadically used in drug release studies in spite of its extensive empirical use in

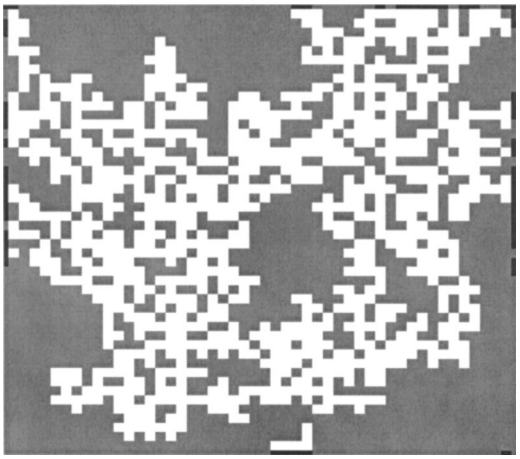

FIG. 1. A percolation fractal embedded on a two-dimensional square lattice of size 50×50. Cyclic boundary conditions were used. We observe, especially on the boundaries, that there are some small isolated clusters, but these are not isolated as they are actually part of the largest cluster because of the cyclic boundary conditions. Exits (release sites) are marked with dark color, while all gray color areas are blocked areas.

dissolution studies. It was recently used by us[7] to describe release results from Monte Carlo simulations with higher accuracy than any of the other semiempirical models.

An interesting problem comes up when the geometry of the release device is not a homogeneous, Euclidean space, but some irregular space, as, for example, a fractal. Several diffusion properties have to be modified when we move from Euclidean space to fractal and disordered media. The problem of the release rate from devices with fractal geometry was first studied by Bunde *et al.*[1] They specifically reported that the release rate follows a power law. An attempt to explain experimental results using the above result can be found in Rinaki *et al.*[14] In the present study, however, we show that the above approach of a power law is valid only in the initial stages of the release process. Our results show that the Weibull function is more appropriate for the entire duration of the release, and additionally it can describe release both from fractal as well as from Euclidean matrices, thus providing a more generalized picture. Furthermore, this functional form for the release is consistent with the theoretical predictions under the frame of fractal kinetics.

THEORY OF THE RELEASE PROBLEM

Our main goal is to study the escape of particles from a release device of fractal geometry. As such structure we use a percolation cluster at the critical point, assuming cyclic boundary conditions, embedded on a two-dimensional square lattice, as shown schematically in Fig. 1. The concentration of open sites is known to be approximately around $p=0.593$. Particles are randomly placed with a given concentration on the open sites only, and they perform independent random walks on the sites of the cluster. Our intent is to derive the details of the release problem, which can be used to describe release when particles escape not from the entire boundary but just from a portion of the boundary of the release device under different interactions between the particles that are present.

The release problem can be seen as a study of the kinetic reaction A+B→B, where the A particles are mobile, the B particles are static, and the scheme describes the well known trapping problem.[15] For the case of a Euclidean matrix the entire boundary (i.e., the periphery) is made of the trap sites, while for the present case of a fractal matrix only the portions of the boundary that are part of the fractal cluster constitute the trap sites. See Fig. 1 for a schematic. The difference between the release problem and the general trapping problem is that in release, the traps are not randomly distributed inside the medium but are located only at the medium boundaries. This difference has an important impact in real problems for two reasons:

(1) Segregation is known to play an important role in diffusion in disordered media. In the release problem the traps are ''segregated'' from the beginning, so we expect to observe important effects related to this segregation.
(2) The problem is inherently a finite size problem. Results that otherwise would be considered as ''finite size effects'' and should be neglected are in this case essential. At the limit of infinite volume there will be no release at all. Bunde *et al.*[1] found a power-law also for the case of trapping in a model with a trap in the middle of the system, i.e., a classical trapping problem. In such case, which is different from the model examined here, it is meaningful to talk about finite size effects. On the contrary, release from the surface of an infinite medium is impossible.

The fractal kinetics treatment of the release problem goes as follows: The number of particles present in the system (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 all molecules are homogeneously distributed over the percolation cluster. Later, due to the fractal geometry of the release system segregation effects will become important.[16] We expect that f will be a function of time, so that $f(t)$ will be used to describe the effects of segregation (generation of depletion zones) which is known to play an important role when the medium is disordered instead of homogenous.[16]

We thus expect a differential equation of the form,

$$\frac{dN}{dt} = -af(t)N \tag{4}$$

to hold, where α is a proportionality constant, $f(t)N$ denotes the number of particles that are able to reach an exit in a time interval dt, and the negative sign denotes that N decreases with time. This is a kinetic equation for an A+B→B reaction. We have absorbed the constant trap concentration [B] in the proportionality constant α. The basic assumption of fractal kinetics[16] is that $f(t)$ has a form $f(t)\sim t^{-m}$.

In this case Eq. (4) will be

$$\frac{dN}{dt} = -a\frac{N}{t^m}, \quad \frac{dN}{N} = -at^{-m}dt. \tag{5}$$

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

$$N = N_0 \exp(-\alpha t^b), \tag{6}$$

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

The form of Eq. (6) is a stretched exponential. In cases where a system can be considered as infinite (for example, release from percolation fractals from an arbitrary site located at the middle of the volume) then the number of particles N inside the system is practically unchanged. Treating N as constant in the right-hand side of Eq. (4) will lead to a power law for the quantity dN/dt. Since most physical problems belong to this class it is widely believed that release rate from fractal matrices follows a power law. In the case of release from the periphery and if we want to study the system until all particles have escaped, as it is often the case for practical applications, then Eq. (6) is of practical importance.

The above reasoning shows that the stretched exponential function Eq. (6), or Weibull function as it is known, may be considered as an approximate solution of the release problem. An alternative derivation of the Weibull function in dissolution studies has also been given.[17] 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 different interactions, by adjusting the values of the parameters α and b. We will use Monte Carlo simulation methods to calculate the values of the parameters α and (mainly) the exponent b.

METHODS

Following the procedure proposed by Bunde *et al.*,[1] we consider partially encapsulated percolation fractals on a square lattice, for which the percolation threshold[18] is $p_c = 0.593$. The fractal dimension of the percolation fractal is known to be 91/48. Calculations were preformed as described below. For each run we generate a new fractal matrix using the method of Hoshen and Kopelman,[19] assuming cyclic boundary conditions. We start with a known initial drug concentration $c = 0.5$ and with randomly distributed drug molecules inside the fractal matrix. We assume here that the drug molecules move inside the fractal matrix by the mechanism of diffusion. We also assume excluded volume interactions between the particles, meaning that two molecules cannot occupy the same site at the same time. The matrix can leak from the intersection of the percolation fractal with the boundaries of the square box where it is embedded (Fig. 1).

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. After each particle move (one Monte Carlo microstep) time is incremented. The increment is chosen to be $1/N$, where N is the number of particles remaining in the system. This is a typical approach in Monte Carlo simulations, and is necessary because the number of particles continuously decreases, and thus, the time unit (one Monte Carlo step) characterizing the system is the mean time required for all N particles present to move one step. We monitor the number of particles that are present inside the matrix as a function of time until a fixed number of particles (50 particles) remains in the matrix. Unless otherwise mentioned, we average our results using different initial random configurations over 100 realizations. We monitor the release rate dQ/dt by counting the number of particles that diffuse into the leak area in the time interval between t and $t+1$. This quantity is used to directly compare our results with those derived by Bunde *et al.*[1]

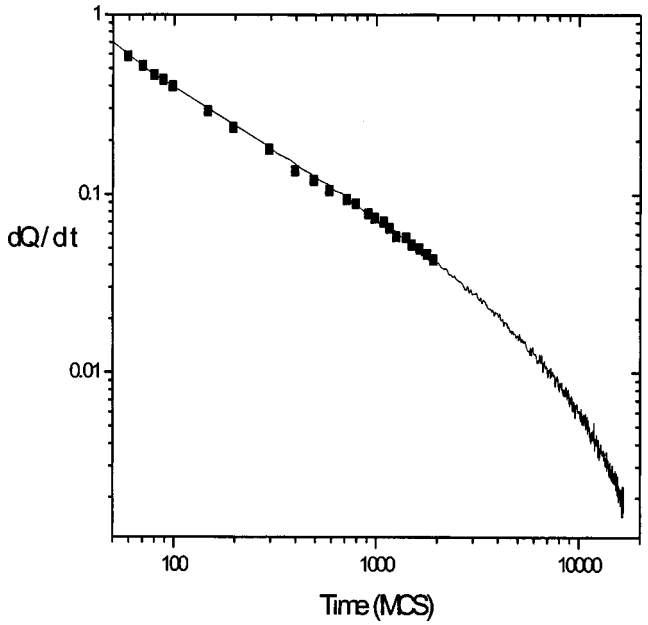

FIG. 2. Plot of the release rate $dQ(t)/dt$ vs time. Lattice size is 50×50 and the initial concentration of particles is $c = 0.50$. Points are the results given in Ref. 1, while the line is the result of the current simulation.

RESULTS AND DISCUSSION

Figure 2 shows simulation results (line) for the release of particles from a fractal matrix with initial concentration $c = 0.50$, on a lattice of size 50×50. The simulation stops when more than 90% of the particles have been released from the matrix. We see that this takes about 20 000 MCS. In the same figure we include the data by Bunde *et al.*[1] (symbols) which cover the range 50–2000 MCS. Because of the limited range examined in that study, the conclusion was reached[1] that the release rate dQ/dt is described by a power law, with an exponent value between 0.65 and 0.75. With the extended range examined here we see that this conclusion is not true, as in longer times dQ/dt deviates strongly from linearity, as a result of the finiteness of the problem.

In Fig. 3 we plot $N(t)/N_0$ as a function of time for several different lattice sizes. We fit the data with a Weibull function [Eq. (6)] where the parameter α ranges from 0.05 to

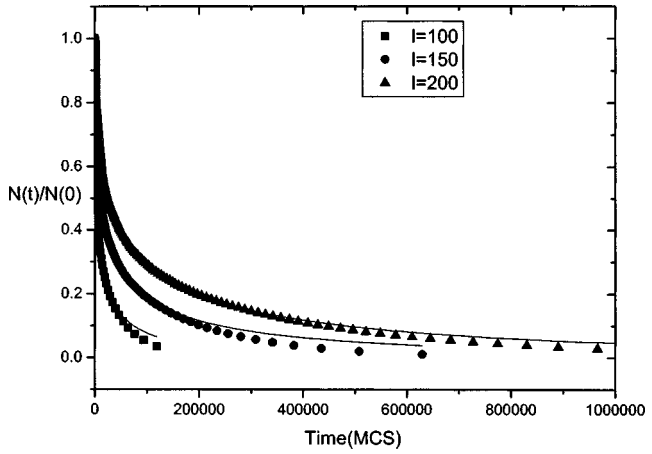

FIG. 3. Plot of the number of particles (normalized) remaining in the percolation fractal as a function of time t for lattice sizes 100×100, 150×150, and 200×200. $N(t)$ is the number of particles that remain in the lattice at time t and N_0 is the initial number of particles. Simulation results are represented by points. The solid lines represent the results of nonlinear fitting with a Weibull function.

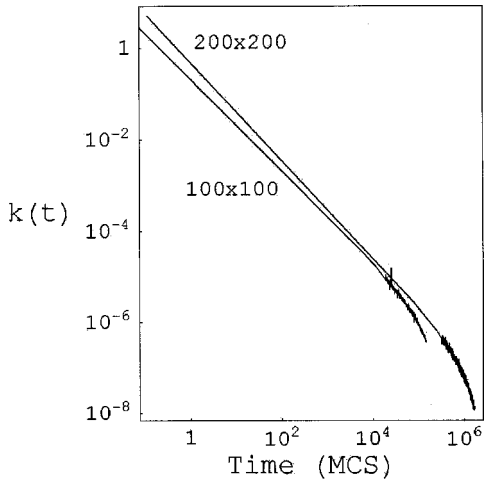

FIG. 4. Log–log plot of the function $k(t)$ [defined by Eq. (8)] as a function of time. The data describe fractal release from a percolation fractal embedded in square lattices of sizes 100×100 and 200×200 sites.

0.01 and the exponent b from 0.35 to 0.39. In all cases we have performed nonlinear curve fitting using the Levenberg–Marquardt algorithm.[20] In a previous publication[11] we have shown that Eq. (6) also holds in the case of release from Euclidean matrices. In that case the value of exponent b was found to be $b \approx 0.70$.

Bunde *et al.* report that "the nature of drug release drastically depends on the dimension of the matrix and is different depending on whether the matrix is a normal Euclidean space or a fractal material such as a polymer, corresponding to the fact that the basic laws of physics are quite different in a fractal environment."[1] This conclusion is accurate for infinite problems but has to be modified in case of problems where the finite size is inherent. The present results reveal that the same law describes release both from fractal as well as from Euclidean matrices. In the previous work the conclusion was reached by monitoring the release rate up to 2000 time steps. But in the fractal release case,[1] due to the slowing down of the diffusion process in the disordered medium the system was not monitored for sufficiently long times in order to reveal the complete nature of the release law. The release rate is given by the time derivative of Eq. (6). For early stages of the release calculating the derivative of Eq. (6) and performing a Taylor series expansion of the exponential will result in a power law for the release rate, just as Bunde *et al.*[1] have observed. In the present paper and in a previous publication concerning Euclidean matrices[11] we demonstrate that in all lattices the behavior can be approximated with a Weibull function. If we oversimplify the release problem by treating it as a classical kinetics problem, we would expect a pure exponential function instead of a stretched-exponential (Weibull) function. [The classical kinetics solution is derived by solving Eq. (4) in case of $f(t)=1$.] The stretched exponential arises due to the segregation of the particles because of the fractal geometry of the environment. Concerning the release from Euclidean matrices[11] we have demonstrated that the stretched exponential functional form arises due to the creation of a concentration gradient near the releasing boundaries. Note, however, that although the functional form describing the release is the same in Euclidean and fractal matrices, the value of the exponent b is, of course, different reflecting the slowing down of the diffusion process in a disordered medium.

In Fig. 4 we present an additional way to investigate the validity of the fractal kinetics assumption directly from Eq. (4). Let us indicate as $Q(t)$ the number of particles that are released from the matrix up to time t. Then, $Q(t)=N_0-N(t)$, where N_0 is the number of particles in the vessel at time $t=0$. Using the above notation Eq. (4) can be written as

$$\frac{dQ}{dt} = af(t)N(t) \Rightarrow \tag{7}$$

$$k(t) \equiv af(t) = \frac{dQ/dt}{N(t)}, \tag{8}$$

where we have defined a function $k(t)=\alpha f(t)$. We can use Eq. (8) in order to check the basic assumption of fractal kinetics, i.e., that $f(t)$ can indeed be approximated by a power law. We use the same Monte Carlo simulation data for $N(t)$. We perform a linear interpolation of these data followed by a numerical differentiation in order to calculate dQ/dt and plot the ratio $dQ/dt/N(t)$ as a function of time in logarithmic scale. The results for 100×100 and 200×200 lattices are shown in Fig. 4. To a large extent it can be regarded as a straight line and this supports the idea that choosing $f(t)$ as a power law is a good assumption.[21]

Our results reconcile with the approach of Bunde *et al.*[1] if we consider the following: We assume that the preexponential parameter α of the Weibull function is decreasing when the size of the lattice increases. The reason for this is explained in detail elsewhere,[11] but we can also see directly that $M_t \to 0$ as $\alpha \to 0$ for an infinite lattice or for a lattice with no leak sites at all, independently of the value of exponent b. Suppose that we consider release from two fractal lattices of different size, say 50×50 and 100×100, just as in the case of Fig. 4 of Bunde *et al.*[1] From what is stated above, we expect that in both cases $N(t)$ will be described by

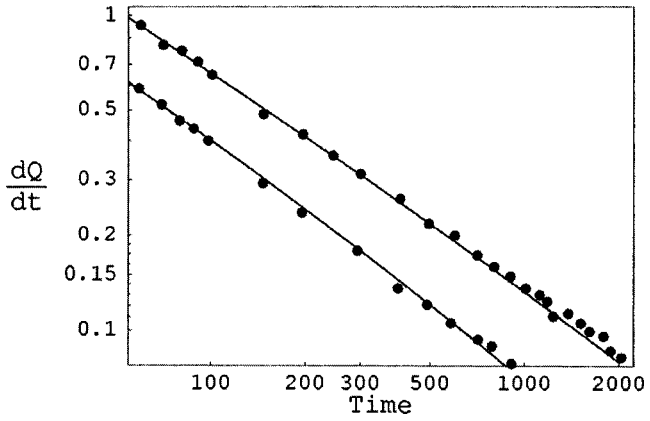

FIG. 5. Log–log plot of dQ/dt vs time, where $Q(t)=N_0-N(t)$ and $N(t)=\exp(-at^b)$, $a=0.04$ and 0.02 and $b=0.37$ in both cases (lines). Points represent the data of Bunde *et al.* (Ref. 1) for 50×50 and 100×100 matrices.

Eq. (6). We expect that the α values will differ, but the value of b will be approximately the same in both cases, of the order of $b=0.37$. We use the data of Bunde *et al.*[1] and fit them to the function dQ/dt (which is equal to $-dN/dt$) calculated using Eq. (6), and considering α to be an adjustable parameter. From the fit we find that $\alpha=0.04$ for the 50×500 and $\alpha=0.02$ for the 100×100 lattice. In Fig. 5 we include the data of Bunde *et al.*[1] as points, and the quantity dQ/dt using the above parameter values. We observe that dQ/dt follows a power law for the time range $t=50-2000$ MCS and that the exponents of the power law are within the range 0.65–0.75, exactly as in Bunde *et al.*[1] This is due to the fact that both results come from the derivative of a Weibull function with the same exponent but different pre-exponential terms.

CONCLUSIONS

We have described a model for drug release from a fractal matrix as a result of a diffusion process assuming excluded volume interactions between the drug molecules. Our work showed that:

(1) Similarly to the case of release from Euclidean matrices[11] release from a fractal matrix as a function of time is approximated by a Weibull (stretched exponential) function, which is theoretically predicted using the basic assumptions of fractal kinetics.[16]
(2) This behavior is similar to the release from a Euclidean matrix, apparently pointing to a universal release law given by the Weibull distribution. The difference between the two cases is only in the two prefactors.
(3) The power law [Eq. (2)] may be considered as an approximation of Eq. (6) for short times.

The above considerations substantiate the use of the Weibull function as a more general form for drug release studies. They may provide a valuable tool in decision making in pharmaceutics and other related fields, when facing the dilemma of whether one should invest in expensive micro or nanotechnology in order to achieve controlled release and importance of the trade off when decreasing the length of the release devices.

ACKNOWLEDGMENT

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[21] Technical Note: Reproduction of Fig. 4 can easily be done using the programming language *Mathematica*. Linear Interpolation of data points is easily done using the command Interpolation[ ] and using the option InterpolationOrder→1. The resulting *InterpolatingFunction* is differentiated using the command Derivative[ ]. Smoothing of the curve for the reduction of noise in plotting the final curve can be done either by adjusting the Interpolation order or by suitable use of the option PlotPoints of the LogLogPlot[ ].