On controlled diffusion-limited drug release from a leaky matrix

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How fast can drug molecules randomly escape from a polymer matrix? This important question is of both scientific and practical importance, as increasing emphasis is placed on design considerations that can be addressed only if the physics of drug release is better understood. We study this problem using high accuracy Monte Carlo computer simulations. We find that the nature of drug release depends drastically 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. We also find the surprising result that drug release is the same for noninteracting particles as it is for particles with hard-core excluded volume interactions, suggesting that the nature of the matrix is more important than the nature of the interactions among the drug particles in determining drug release.

I. INTRODUCTION

During the last decade there has been great interest in developing systems for controlled delivery of drugs and other bioactive substances.[1,2] Many schemes have been devised, several of which involve diffusion of the bioactive material out of an inert polymer matrix within which it initially has been dispersed. The simplest of these utilize uncoated polymer matrices containing the embedded drug.[3] Other techniques involve covering most of the matrix with an impermeable material that acts as a barrier to diffusion, and the active substance escapes through surface pores or cavities that are left uncoated.[2,4]

An understanding of controlled drug release requires, as a prerequisite, a theory of how the escape rate depends on the size and geometry of the uncoated surface and also how it depends on the dimension, size, and structure of the polymer matrix. To this end, we studied several models of drug release. We describe Monte Carlo computer simulations of diffusion for three cases. Our purpose here is to discuss general features of these models and to present results of the simulations. We find that there are well-defined scaling laws whose specific form depends on the model in question.

The simplest model for a drug release system is a $L \times L \times L$ cubic box with a single square hole or "absorbing patch" of size $l \times l$. These are thus two independent variables that can be changed systematically, L and l. Our goal is to calculate the drug release rate $\dot{Q} = dQ/dt = \dot{Q}(L,l)$. The drug particles are generally presumed to move by diffusion on a lattice and when a drug particle reaches the hole, *release* occurs. We also consider a more sophisticated model in which the *Euclidean* lattice is replaced by a *fractal* polymer matrix.[5] This is motivated by the fact that real polymers involve conformations that can be of noninteger dimension (e.g., a swollen chain has fractal dimension $d_f \cong 5/3$).[6] For the sake of specificity, we consider here the percolation model for polymer gelation,[7] for which $d_f = 91/48 \cong 1.896$ in two dimensions.

For both the regular lattice and the fractal matrix model, we studied two cases: (i) the ideal case where the diffusing particles do not interact with one another; and (ii) a more realistic case where the diffusing particles interact by means of a hard core interaction.

DRUG RELEASE FROM ONE-, TWO-, AND THREE-DIMENSIONAL MATRICES: MODEL 1

We first consider a three-dimensional lattice in the form of a cube with L^3 sites. We next specify the size $l \times l$ of the absorbing patch that occurs on the surface, which can range from a single site ($l = 1$) to the entire surface ($l^2 \sim L^2$). Next, we randomly choose sites, excluding absorbing or "leak" sites. We occupy them with particles, avoiding double occupancy, until a fixed initial drug concentration is reached. The diffusive escape process is simulated by selecting a particle at random and moving it to a randomly selected nearest neighbor site. If this site is outside the system, the move is always rejected. If this site is already occupied, there are two possibilities: (i) for hard core interactions the move is rejected; (ii) for noninteracting particles the move is allowed so that more than one particle can occupy the same site. A particle is removed from the lattice as soon as it migrates to a site lying within the leak.

After each trial, the time is incremented. The increment is chosen to be $1/N_s$, where N_s is the number of particles remaining in the system, since the unit time characterizing

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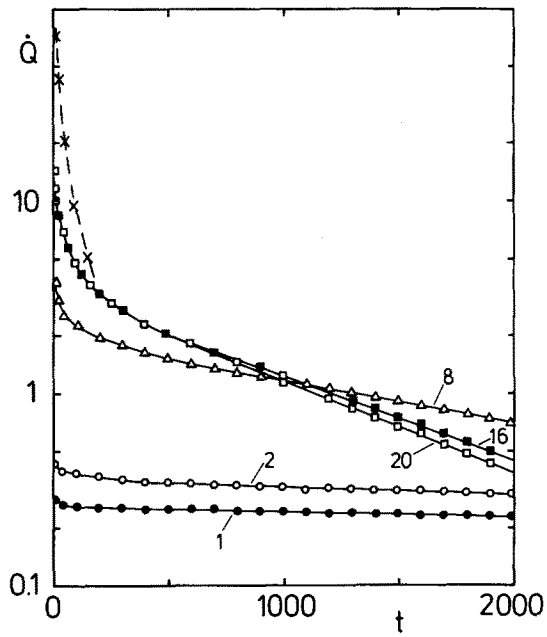

FIG. 1. Escape rate Q vs t for an $L = 20$ box with a surface leak of size $l \times l$, for various values of l. The curve designated by $(\times\times\times)$ pertains to the case where the entire boundary of the box is leaky, i.e., where the leak consists of all six sides of the box. The initial concentration is $c = 0.5$ for all curves.

this system is the mean time required for every one of the N_s particles to be offered the possibility of moving one step. We then count the number of particles diffusing into the leak in the time between t and $t+1$ and denote this quantity by $\dot{Q} = dQ/dt$, where $Q(t)$ is the number of particles that diffuse into the leak up to time t. Typically we consider t ranging up to 2000 time steps and we average $\dot{Q}$ over 10^3 runs.

Figure 1 shows, for hard core interactions, the escape rate as a function of time for a cube of size $20\times20\times20$ for several leak sizes $l = 1, 2, 8, 16, 20$. In each case the initial concentration of diffusing particles per lattice point c is chosen to be $c = 0.5$. We find that for large t, $\dot{Q}$ is given approximately as $\dot{Q}(t) \sim \exp(-\Gamma t)$, where Γ increases as the size of the leak increases. The results were essentially identical for the interacting and noninteracting cases, a finding consistent with recent observations on similar two-dimensional lattice models for drug escape.[8] In fact, it can be shown rigorously (see the Appendix) that the form of the time evolution of $Q(t)$ is identical for interacting and nondistinguishable hard core particles, regardless of the size of the leak and the geometry of the lattice. In contrast, when we have a mixture of different types of particles, where one type can escape and the other cannot, the hard core interaction influences the escape rate. In $d = 2$ and $d = 3$ mainly the amplitude of the rate is changed, while in $d = 1$ a characteristic new time dependence is observed.[9,10]

In Fig. 2(a) we show Γ for $c = 0.5$, computed from the data given in Fig. 1, as a function of l/L, for $L = 10$, 15, and 20. In Fig. 2(b), we show these data plotted in scaled form, namely $L^2\Gamma$ vs l/L. From the remarkable degree of data collapse, it is apparent that $\Gamma(L,l)$ obeys the scaling equation

$$\Gamma(L,l) = L^{-2} h(l/L). \tag{1}$$

Therefore we can describe the escape of diffusing particles

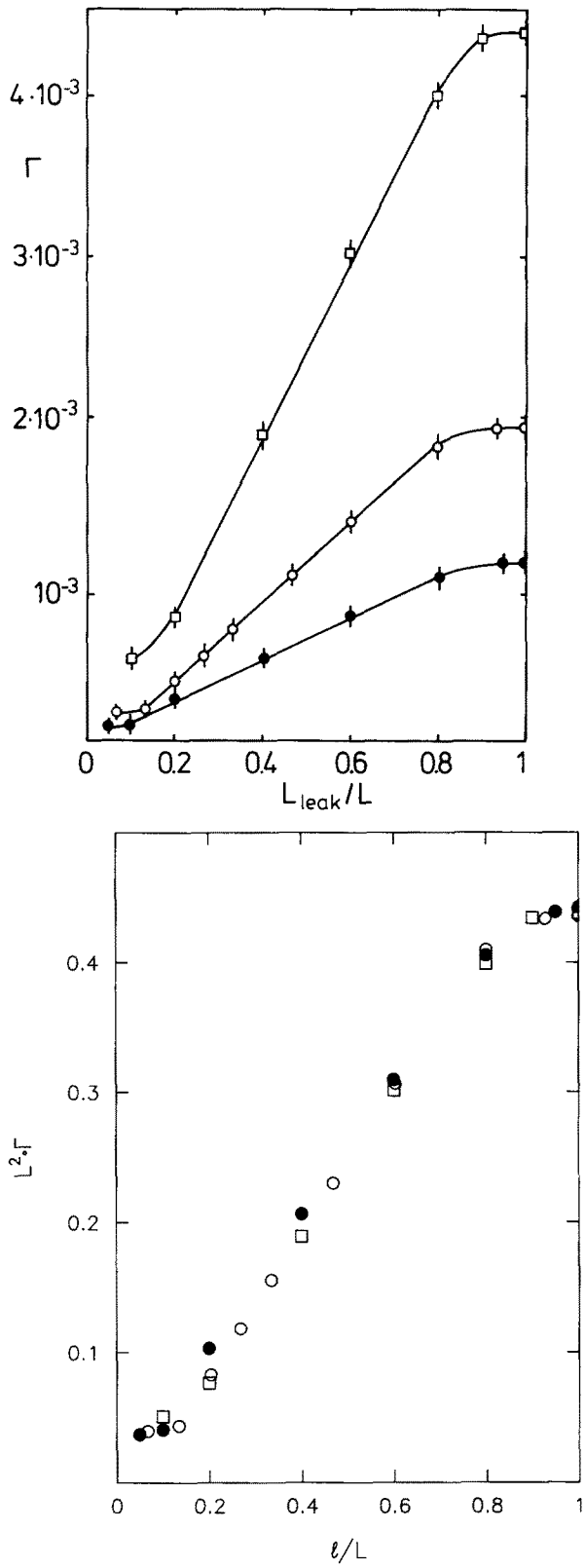

FIG. 2. (a) $\Gamma = d \ln \dot{Q}/dt$ vs l/L, for $L = 20$ (●), $L = 15$ (○), and $L = 10$ (□). (b) The same data of part (a), except plotted in a form designed to test the scaling equation (1), $l^2\Gamma$ vs l/L. We observe that the data "collapse" onto a single curve supports general scaling ideas.

from three-dimensional boxes of length L with a leak of length l by

$$\dot{Q}(t) \sim \exp[-(\alpha t/L^2) h(l/L)]. \tag{2}$$

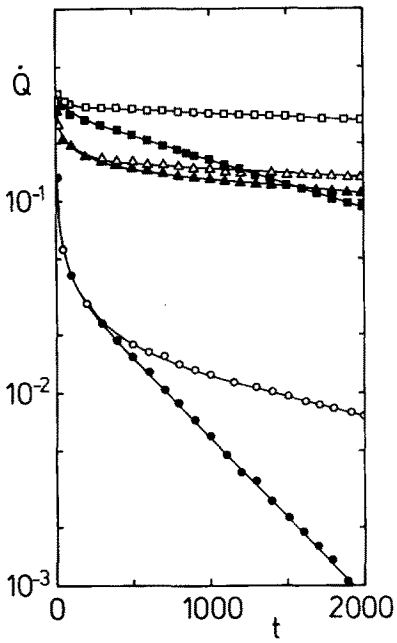

FIG. 3. Escape rate $\dot{Q}$ vs t for one randomly chosen hole. Comparison of rates in different dimensions [$d=1$: $L=50$ (●) and $L=100$ (○); $d=2$: $L=50$ (▲) and $L=100$ (△); $d=3$: $L=10$ (■) and $L=20$ (□)]. Initial concentration is $c=0.5$.

The coefficient α has the physical units of a diffusion constant.

Over much of its range, the function $h(x)$ is found to be linear in $x=l/L$, i.e.,

$$h(l/L)\sim l/L. \tag{3}$$

Therefore, if we fix the absolute size of the leak, but change the container size L, the first order release rate $\Gamma\equiv d(\ln \dot{Q})/dt$ varies approximately as $\Gamma\sim L^{-3}$. This is the theoretically expected result. On the other hand, it varies as $\Gamma\sim L^{-2}$ if the ratio l/L is held fixed. Note that the slope of $h(x)$ decreases strongly if x tends to 0 or 1. For fixed L the release rate remains practically constant for $l<0.1L$ or $l>0.9L$. In contrast to the dependence shown in Eq. (3), the first order release rate for similar two-dimensional models was found[8] to scale as $l^{0.67}$. Thus the exponent depends on the dimensionality of the system, as in the case for exponents in critical phenomena.[11]

Equation (2) holds for large times, while for small times the release rate seems to follow a power law. For example, for $l=L$, we find $\dot{Q}(t)\sim t^{-1/2}$. The crossover time above which $\dot{Q}$ is determined by Eq. (2) decreases with decreasing size of the leak and seems to approach zero for $l/L\to 0$, as is clear in Fig. 3.

What is the dependence of the release rates on the matrix dimension d? To answer this question, we studied d-dimensional cubes containing *one* hole, chosen randomly. Our analysis (Fig. 3) shows that

$$\dot{Q}\sim f_d(t)\exp[-\alpha_d(L)t/L^2], \tag{4}$$

where $\alpha_d(L)$ is a smoothly varying function of L, with $\alpha_1(L)=\text{const}$, $\alpha_2(L)\sim 1/\ln L$, $\alpha_3(L)=1/L$. The prefactor $f_d(t)$ tends to a constant for $t\gtrsim L^2/\alpha_d(L)$. For intermediate times, $1\ll t\ll L^2/\alpha_d(L)$, we find that $f_1(t)\sim t^{-1/2}$ and

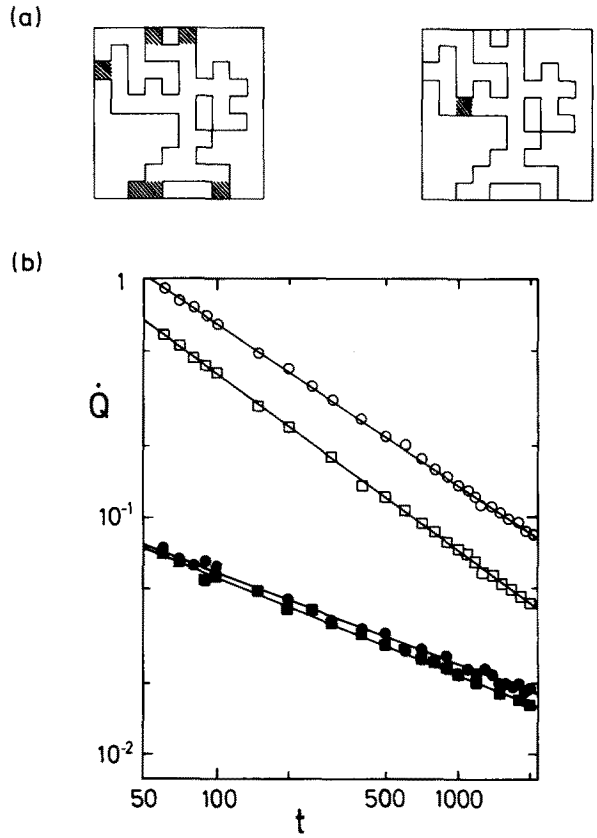

FIG. 4. (a) Illustration of a percolation fractal on a square lattice with two types of leaks (shadowed sites). On the left, the leak consists of the cut (intersection) of the percolation fractal with the boundary of the box, while on the right the leak is a randomly chosen site on the fractal. (b) Escape rate $\dot{Q}$ for percolation fractals for a square box of edge L. Upper curves: the leak consists of the cut ("intersection") of the percolation fractal with the boundary of the square lattice $L=50$ (□) and $L=100$ (○). Lower curves: the leak is a single randomly chosen fractal site $L=50$ (■) and $L=100$ (●).

$f_3(t)=\text{const}$, while $f_2(t)$ shows a more complicated behavior involving logarithmic terms, viz. $f_2(t)\sim[(\ln t)^{-1}-(\ln t)^{-2}]$. Note that since $f_3(t)=\text{const}$, for $\alpha_3 t\ll L^2$ the release rate in three dimensions is constant, in contrast to the case when $d=1$ or $d=2$. For a detailed mathematical study of the escape rate in finite lattices with a single hole, we refer to Ref. 12. A mathematically exact solution of the general problem of particles moving on a lattice in the presence of several trapping sites is available[13] as is that for the case of imperfect trapping.[14] These, however, are quite awkward to evaluate when $d>2$.

DRUG RELEASE FROM A FRACTAL MATRIX: MODEL 2

Another element that strongly influences the escape rate is the structure of the polymer matrix within which the drug is embedded. In order to illustrate the possible complexity that one might encounter when studying this factor, we consider partially encapsulated *percolation fractals* on a square lattice [Fig. 4(a)] for which the percolation threshold is $p_c=0.593$[15]; this is a commonly studied model for a branched polymer near the gel point.[7] On a fractal, the mass M depends on the radius r as $M\sim r^{d_f}$, and for percolation the fractal dimension is $d_f=91/48$. Calculations were performed as described above except that, for each run, a new

fractal matrix was generated using the method of Hoshen and Kopelman.[16] Again, the initial site occupancy of particles on the fractal was taken to be $c = 0.5$.

We calculated the escape rate for two types of leak: In case (i), the leak consists of the intersection of the percolation fractal with the boundary of the square box [Fig. 4(a) and the upper two curves of Fig. 4(b)]. In case (ii), the leak consists of a randomly chosen hole [see Fig. 4(a) and lower two curves of Fig. 4(b)]. In both cases the escape rate follows a power law $\dot{Q} \sim t^{-\gamma}$, where γ decreases slightly as the box size increases. In case (i), the absolute rate is larger (for any given time) when the box size is larger. This behavior is in accord with increased total initial number of particles in the larger box and concomitant increase in the surface area through which those particles can escape. The exponent γ varies roughly from 0.75 to 0.65 when L increases from 50 to 100. In contrast, when the leak consists of a randomly chosen hole, both the exponent γ and the absolute rate depend only weakly on L: $\gamma = 0.40 \pm 0.03$ for $L = 50$; $\gamma = 0.39 \pm 0.03$ for $L = 100$. As before, hard core interactions do not affect the escape rates.

DISCUSSION

In summary, we have studied by computer simulation the escape rate of diffusing particles from one-, two-, and three-dimensional boxes as well as from percolation fractals. We have investigated how the escape rate is changed systematically when we change the spatial dimension and the size of the box as well as the size of the leak. In all cases, we found simple systematic behavior of the escape rate. From a practical standpoint, these results may guide the development of simple systems for controlled drug release. Recent developments in controlled-release technology have emphasized heterogeneous systems where both the effective volume of the polymer matrix and the rate of release of drug into that volume change with time (e.g., a growing hemispheric interface between concentrated and dilute regions of drug).[17] We anticipate that high-accuracy Monte Carlo simulations will prove to be a very useful tool in guiding the efficient design of many types of practical controlled-release devices.

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APPENDIX

In this appendix, we discuss conditions under which the trapping rates for diffusing noninteracting and hard core particles become identical.

Consider a d-dimensional matrix of length L containing L^d sites with M traps at sites $\{\mathbf{l}_T\} \equiv \{\mathbf{l}_T^{(1)}, \mathbf{l}_T^{(2)}, \ldots, \mathbf{l}_T^{(M)}\}$. Initially, at $t = 0$, N_0 particles are distributed randomly at those sites $\mathbf{l}$ which are no traps, $\mathbf{l} \neq \{\mathbf{l}_T\}$. For noninteracting particles, the probability $n_{\mathbf{l}}(t+1)$ that a given site $\mathbf{l}$ of the box is occupied by any particle after $t+1$ time steps is governed by the evolution equation

$$n_{\mathbf{l}}(t+1) = n_{\mathbf{l}}(t) - \sum_{\delta} w_{\mathbf{l},\mathbf{l}+\delta} n_{\mathbf{l}}(t) + \sum_{\delta} w_{\mathbf{l}+\delta,\mathbf{l}} n_{\mathbf{l}+\delta}(t) \tag{A1a}$$

for $\mathbf{l} \neq \{\mathbf{l}_T\}$, and

$$n_{\mathbf{l}}(t) \equiv 0 \tag{A1b}$$

if $\mathbf{l}$ is a trap site. Here $w_{\mathbf{l},\mathbf{l}+\delta}$ is the transition rate of a particle from site $\mathbf{l}$ to the nearest neighbor site $\mathbf{l}+\delta$. The sums in Eq. (A1) run over all nearest neighbors δ of site $\mathbf{l}$. If all transition rates are identical, Eq. (A1) reduces to the diffusion equation in the continuous limit. We assume that the transition rates obey the rules

$$w_{\mathbf{l},\mathbf{l}+\delta} = w_{\mathbf{l}+\delta,\mathbf{l}} = \alpha \quad (\mathbf{l} \neq \{\mathbf{l}_T\}, \mathbf{l}+\delta \neq \{\mathbf{l}_T\}) \tag{A2a}$$

if a particle moves between two regular sites $\mathbf{l}$ and $\mathbf{l}+\delta$, and

$$w_{\mathbf{l},\mathbf{l}+\delta} = \gamma \quad (\mathbf{l} \neq \{\mathbf{l}_T\}, \quad \mathbf{l} \in \{\mathbf{l}_T\}) \tag{A2b}$$

if a particle attempts to move from a regular site $\mathbf{l}$ to a trap site $\mathbf{l}+\delta$. Moreover,

$$w_{\mathbf{l},\mathbf{l}+\delta} = 0, \tag{A2c}$$

if $\mathbf{l}$ is a trap site. If $\mathbf{l}+\delta$ is outside the box the transition rate is zero by definition. In Eqs. (A2a) and (A2b) we have assumed that there is only one type of regular sites where the particles can move. If we have a mixture of two types of sites with different potential energy, then forward and backward jumps do not have the same probability, as has been assumed in Eq. (A2a). Moreover, if we have distinguishable particles, only one type of particles can be trapped, then Eq. (A2c) does not hold.

Equation (A1) can be easily generalized to hard core particles. Now a particle only can jump between two sites if the attempted site is empty. Therefore, the transition rates $w_{\mathbf{l},\mathbf{l}+\delta}$ and $w_{\mathbf{l}+\delta,\mathbf{l}}$ are modified by factors $[1 - n_{\mathbf{l}+\delta}(t)]$ and $[1 - n_{\mathbf{l}}(t)]$, respectively. Then the evolution equation for hard core particles becomes ($l \neq \{l_T\}$)

$$n_{\mathbf{l}}(t+1) = n_{\mathbf{l}}(t) - \sum_{\delta} w_{\mathbf{l},\mathbf{l}+\delta} [1 - n_{\mathbf{l}+\delta}(t)] n_{\mathbf{l}}(t) + \sum_{\delta} w_{\mathbf{l}+\delta,\mathbf{l}} [1 - n_{\mathbf{l}}(t)] n_{\mathbf{l}+\delta}(t)$$

which can be rewritten as

$$n_{\mathbf{l}}(t+1) = n_{\mathbf{l}}(t) - \sum_{\delta} w_{\mathbf{l},\mathbf{l}+\delta} n_{\mathbf{l}}(t) + \sum_{\delta} w_{\mathbf{l}+\delta,\mathbf{l}} n_{\mathbf{l}+\delta}(t) + \sum_{\delta} n_{\mathbf{l}}(t) n_{\mathbf{l}+\delta}(t) (w_{\mathbf{l},\mathbf{l}+\delta} - w_{\mathbf{l}+\delta,\mathbf{l}}). \tag{A3}$$

For $\mathbf{l} \in \{l_T\}$, Eq. (A1b) holds. It is easy to verify that the last sum in Eq. (A3) vanishes identically for the transition rates (A2a)–(A2c) in connection with Eq. (A1b). Then the evolution equations for $n_{\mathbf{l}}(t)$ in the noninteracting limit as well as for hard core particles become identical. If we start from the same initial configuration we are led to exactly the same values for $n_{\mathbf{l}}(t)$ as a function of time in both cases. Averaging over many initial configurations gives the final distribution function $P(\mathbf{l},t)$. The mean number of surviving particles at time t is given by

$$S(t) = \sum_{\mathbf{l}} P(\mathbf{l},t)$$

and thus must be identical for hard core particles and nonin-

teracting particles. Therefore also the trapping rates are identical in both cases. This conclusion holds under the condition that Eqs. (A2a)–(A2c) are valid, which has been discussed above.

If we consider partially encapsulated percolation fractals [see Fig. 4(a)], Eqs. (A2a)–(A2c) have to be supplemented by the condition that the probability to be outside the fractal is zero. Accordingly the transition rate from a site inside the fractal to a side outside the fractal (which is not a trap site) must be zero. In this case, Eq. (A3) also reduces to Eq. (A1b) and the mean number of surviving particles at time t, and consequently the trapping rates, is identical for hard core and noninteracting particles. Equation (A3) can also be extended to systems with long range interactions.[18] Then $w_{l,l+\delta}$ depends on the whole actual configuration of particles at time t and Eq. (A3) does not reduce to Eq. (A1a). In this case we expect, that the interaction will strongly influence the trapping rate.

[1] *Controlled Release of Bioactive Materials* edited by R. W. Baker (Academic, New York, 1980).
[2] R. S. Langer, Drug Therapy **31**, 217 (1983).
[3] R. S. Langer and J. Folkman, Nature **263**, 797 (1976).
[4] R. S. Langer, Chem. Eng. Commun. **6**, 1 (1980).
[5] B. B. Mandelbrot, *The Fractal Geometry of Nature* (Freeman, San Francisco, 1982).
[6] P. G. de Gennes, *Scaling Concepts in Polymer Physics* (Cornell University, Ithaca, 1979).
[7] D. Stauffer, J. Chem. Soc. Faraday Trans. **2**, 72 (1976); Pure Appl. Chem. **53**, 1479 (1981).
[8] A. C. Balasz, D. F. Calef, J. M. Deutch, R. A. Siegel, and R. S. Langer, Biophys. J. **47**, 97 (1985).
[9] A. Bunde, S. Havlin, R. Nossal, and H. E. Stanley, Phys. Rev. B **32**, 3367 (1985).
[10] Also, for particles interacting via long range forces, for example, Coulomb interaction, dipole–dipole interaction, etc., we expect strong effects of interaction on the release rate.
[11] H. E. Stanley, *Introduction to Phase Transitions and Critical Phenomena*, 2nd ed. (Oxford University, Oxford 1971).
[12] G. H. Weiss, S. Havlin, and A. Bunde, J. Stat. Phys. **40**, 191 (1985).
[13] E. W. Montroll, J. Phys. Soc. Jpn. Suppl. **26**, 6 (1969).
[14] R. J. Rubin and G. H. Weiss, J. Math. Phys. **23**, 250 (1982).
[15] D. Stauffer, *Introduction to Percolation Theory* (Taylor and Francis, London, 1985).
[16] J. Hoshen and R. Kopelman, Phys. Rev. B **14**, 3438 (1976).
[17] D. S. T. Hsieh, W. D. Rhine, and R. Langer, J. Pharm. Sci. **72**, 17 (1983).
[18] A. Bunde and W. Dieterich, Phys. Rev. B **31**, 6012 (1985).