THE ROLE OF POLYMER MATRIX STRUCTURE AND INTERPARTICLE INTERACTIONS IN DIFFUSION-LIMITED DRUG RELEASE

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ABSTRACT A lattice random-walk model is used to simulate diffusion in a porous polymer. This model may be useful for the practical design of drug-release systems. Both interacting and noninteracting particles (random walkers) were allowed to diffuse through a pore with a single exit hole. It was found that the specific interactions among the diffusing particles have little influence on the overall release rate. Diffusion through more complicated structures was investigated by simulating the diffusion of particles through two pores connected by a constricted channel whose length and width were varied. The overall rate of release was found to be proportional to the width of the constricted channel. When the length of the channel was greater than or equal to the length of the pore, the rate of release was also inversely proportional to the channel length. From a practical standpoint, release rates can be decreased (and times for release increased) by one or two orders of magnitude by decreasing the width and expanding the length of the interconnecting channels in the polymer matrix.

INTRODUCTION

Simulation of flow through porous media has seen applications to many fields. Recently, this approach has been used to describe the controlled release of drugs from polymeric systems (Siegel R., and R. Langer, manuscript submitted for publication). Langer (1976, 1982) has reported a method of incorporating powdered drugs during polymer casting that creates a series of interconnecting chambers (pores) and channels through which dissolved drugs can then diffuse. The drugs are not able to diffuse through the polymer backbone and the drug diffusion through the porous media is observed to be extremely slow. The significance of this method is that it extends the biological lifetime of many drugs, in particular, polypeptides, from minutes to days. For example, release for over 100 days from 1 mm thick polymer-drug slabs has been demonstrated for over 50 different drugs (Langer, 1982). (Identical release rates are observed whether these tests are done in vitro or in vivo [Brown et al., 1983].) Such release is over two orders of magnitude slower than would be predicted by diffusion through simple porous structures. However, Siegel and Langer (1984) have shown (via scanning electron microscopy) that the pores are connected via narrow channels or constrictions, whose radii are small compared with the pore radii but large compared with the dimensions of the drug. Here we analyze the effect of some parameters of the polymer matrix structure, such as the length and width of the connecting channels (constrictions), that contribute to the slowness of the transient kinetics.

To better understand the behavior of these systems, we use a mathematical model. Our objectives are twofold; first to validate (and hence understand) intuitive concepts of how the release kinetics should depend on geometric parameters (for example, pore size and channel length), and second to discover the role of interparticle interactions, specifically repulsive, excluded volume effects. Specifically, we have investigated the release rate for particles from a variety of simple, model geometries: pores with various exit-hole sites, and connected pores with a variety of connecting channel sites and exit holes. If we were solely interested in our first objective, the method that comes first to mind is to solve the diffusion equation, with appropriate boundary conditions to model walls and pores. Since analytic solutions cannot be found for these complicated geometries, it is necessary to proceed numerically (see Crank, 1975, for example). However, because of our second objective, understanding the role of interparticle interactions, we have taken the approach of random-walk simulations. The advantage of this microscopic approach is that it avoids the question of the correct form of diffusion

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equation (i.e., how does the bulk-diffusion coefficient depend on concentration, on walls, etc.) and that it permits future re-refinement that includes other effects, e.g., specific chemical binding. The disadvantage of the simulation approach is that one must average over many runs, hence limiting the size and complexity that can be investigated. An intriguing prospect is to combine this microscopic modeling with the theory of random networks to model macroscopic timed-release slabs.

In general, we find that the simulation results support intuitive results concerning diffusive release. However, one surprising feature is that the release-rate results for interacting or noninteracting particles are very similar. We comment on the reason for this similarity and note that further work is needed to fully understand its generality.

Previous attempts to model drug diffusion in polymeric systems have focused on flow through homogeneous material in simple geometries (slab, cylinder, sphere) (Baker and Lonsdale, 1974). Very little theoretical work has been done on diffusion of drug through a porous polymer (Peppas, 1983). Recently, however, Siegel and Langer (manuscript submitted for publication) have computed first-passage times via a Monte Carlo method for diffusion through a single pore with connecting channels of variable size. This model allows one to consider the complicated geometries involved, as well as incorporate the non–steady-state aspect of this problem, i.e., there is no continuous influx of drug (only a finite amount is cast into the polymer). In this report, we employ a simpler lattice random walk that easily allows us to construct more complicated geometries than previously considered.

To understand diffusion through porous media, one needs to consider not only flow out of a single pore but also flow between pores. Here, we examine the rate of diffusion through two pores and the tunnel connecting them, extracting generalizations that can characterize flow through an entire porous network.

We note that aspects of the model may also be applicable to other problems of biophysical interest. For example, it may be useful in describing the mechanics of exocytosis, i.e., the emptying of secretory vesicles such as the chromaffin granules in the cells of the adrenal medulla. Here, isolated intracellular secretory granules migrate and fuse to the enclosing plasma membrane. At the site of attachment, the fused membranes burst and thus create a site through which the granule contents are released (Pollard et al., 1979).

METHODS

Single Pore

Figs. 1 and 2 show models of the various structures we examined. The single pore (Fig. 1) consists of a 10 × 10 lattice, bounded by four reflecting walls. The dimensions were chosen to be an order of magnitude larger than the particles, yet small enough to be computationally convenient; in the Results section we briefly describe the effects of this choice. One of these walls contains an absorbing hole, providing the site through

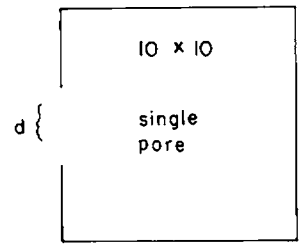

FIGURE 1 A diagram of the single pore is shown.

which the walkers can diffuse out of the pore (and into connecting channels). A variable number of particles (random walkers) are initially placed on the lattice. The diffusion process is modeled by nearest-neighbor hopping. At each time step there is a candidate move for each particle (if we permit the walker to stay in place with probability $[1/(Z + 1)]$, where Z is the number of nearest neighbors, the time scale will simply be increased by a factor of $[(Z + 1)/Z]$ or 5/4 for two dimensions.)

We adopt two sets of rules to govern the movement of each walker. In the first case, the particles are noninteracting. Each particle can land on a nearest-neighbor site whether that site is occupied or not. Hence, more than one particle can occupy a given lattice site. In the second case, we model interacting walkers with the following algorithm. At step n each particle is assigned (randomly) a direction, and a list of new particle locations is generated. If any particle attempts to move to an occupied site (occupied at step n), the move is rejected and the particle does not move. The list of new locations is then scanned to see if two or more particles are attempting to move to the same site; all such moves are rejected. Certain possible correlated motions of two or more walkers are not possible within this rule, such as a string of adjacent walkers hopping in the same direction. It is, however, the simplest possible scheme that allows interacting random walkers to attempt to move at each time step. It is important to stress that the algorithm we have adopted for interacting walkers is not unique. The rules adopted here exclude particular moves depending upon the location of all walkers prior to making the next step. An alternative algorithm can be based on the sequential move of individual walkers, which means that the configurations that arise depend upon the order in which the moves occur. The observed difference between the dynamics of interacting and noninteracting walkers will depend upon the precise algorithm adopted for the interaction.

The sets of rules for interacting and noninteracting walkers we adopt here can be thought of as corresponding to two different interpretations of the lattice sites. If we regard the sites as cells with a large volume compared with that of a molecule, clearly more than one particle may occupy a cell. If the molecules are as large as the cells, then there is an

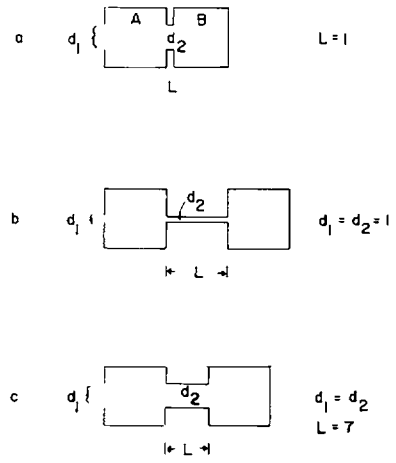

FIGURE 2 The various two-pore geometrics are examined.

excluded volume effect. The noninteracting case also corresponds to running 100 single-particle simulations, averaging over all possible initial locations.

In both cases, the number of walkers left in the pore after every hundred steps (up to 10,000 steps) is calculated. This was done at different degrees of lattice saturation (loadings), namely 100%, 67%, and 50% occupation. For the latter two cases, the particles were initially randomly distributed and 500 runs were carried out for all of the above loadings. Varying the initial concentration serves as a model for mixing the drug molecules with some inert molecules in the initial construction.

Of further interest regarding the single-pore geometry is how the rate of diffusion varies with the diameter, d (see Fig. 1), of the absorbing hole. Although solution of the diffusion equation for a rectangular box with variable hole width d is technically possible, it requires more numerical work than simple simulation. Thus the simulations provide a valuable methd of obtaining qualitative trends. Specifically, we allow d to vary from 1 to 10 lattice sites (the latter corresponding to an entire wall). 500 iterations, with an initial loading of 100 walkers, were carried out for each hole width d and the number of walkers remaining in the pore were calculated.

Two Pores

We have also considered the case of two pores connected by a tunnel whose length and width are varied (see Fig. 2). The pores themselves are kept the same size as in the previous single-pore example, 10 × 10 lattice units. The first case considered is two pores connected by a tunnel whose length is 1 lattice spacing. The openings at d_1 and d_2 are varied in size in the following manner. (*a*) d_1 is equal to 1 lattice spacing, whereas d_2 varies from 1 to 8, and (*b*) d_1 equals d_2 and both vary from 1 to 8 (Fig. 2 *a*). Example (*a*) mimics the situation where networks of pores empty and interconnect through tunnels of different width. Note that the direction of flow is predominantly from chamber *B* to chamber *A*; chamber *B* would correspond to a pore at the innermost layer of the polymer matrix.

Next we consider two pores connected by a channel whose width is 1 lattice spacing and whose length is varied from 1 to 30 lattice units (Fig. 2 *b*).

The final case considered has two pores interconnected by a tunnel 7 units long, but whose width varies from 1 to 10 lattice spacings (Fig. 2 *c*). All calculations were carried out on fully saturated lattices (100 walkers in each pore); in addition, all available lattice sites in the tunnels were occupied. Here, 100 iterations were performed on each configuration examined. This corresponds to ~10,000 iterations for a single random-walk particle.

We have investigated the simplest two-dimensional (planar) models. In general, there are certain pathological aspects of two-dimensional random walks [such as log(n) corrections] (Barber and Ninham, 1970) that could cause problems in applying the results of the two-dimensional model directly to three-dimensional systems. We do not believe there will be significant qualitative differences in our conclusions between two and three dimensions. Any results that we believe will be significantly different, we will comment directly on here. Finally, this model is only applicable to circumstances where the diffusing species are small compared with the characteristic pore structure. When this is not the case, other approaches such as the reptation method (de Gennes, 1971) may serve as more appropriate models for the diffusion.

RESULTS

Single Pore

Fig. 3 presents the number of particles remaining in the 10 × 10 pore, $N(t)$, (with 1 exit hole, 1 lattice-spacing wide) as a function of time for both interacting and noninteracting species; we see that both the interacting and noninteracting case lead to almost identical decay in total population $N(t)$. The apparent origin of this surprising result is that on the average (averaging over many runs), the probability that a given site is occupied at a given time does not depend strongly on the movement rules, and properties such as $N(t)$ only depend on the probability that sites are occupied. A mathematical explanation for this behavior is offered in the Appendix. Other properties, such as tagged-particle (tracer) diffusion coefficients may be expected to be different for the two cases. Another surprising feature of these simulations is displayed in Fig. 4. The concentration of drug decays exponentially with time over the entire time range of our simulations, indicating an effective first-order release rate.

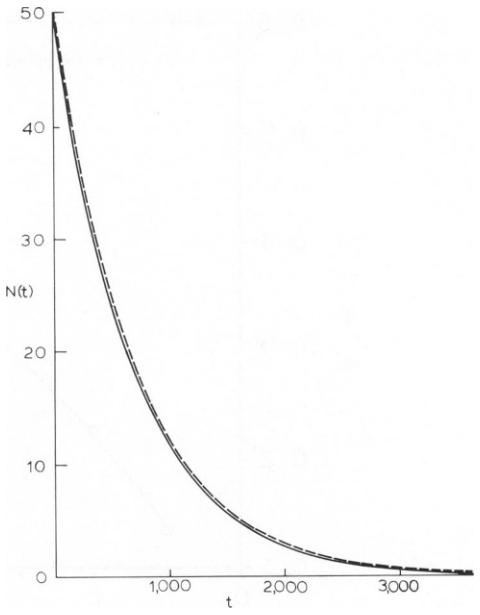

FIGURE 3 $N(t)$ vs. t for both interacting (solid line) and noninteracting (dashed line) species are shown. The degree of lattice saturation equals 50%.

Another question of importance concerning the single-pore model is how this first-order release rate varies with the aperture or exit hole size. Fig. 5 reveals the normalized rate of release vs. the hole diameter. The release rate is

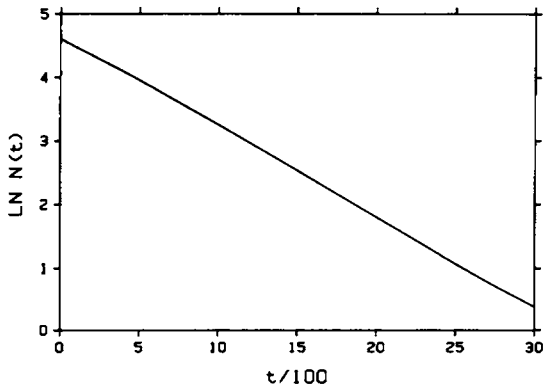

FIGURE 4 The ln $N(t)$ vs. t for an original configuration of 100 random walkers in a 10 × 10 pore with an exit hole 1 lattice-unit wide is shown.

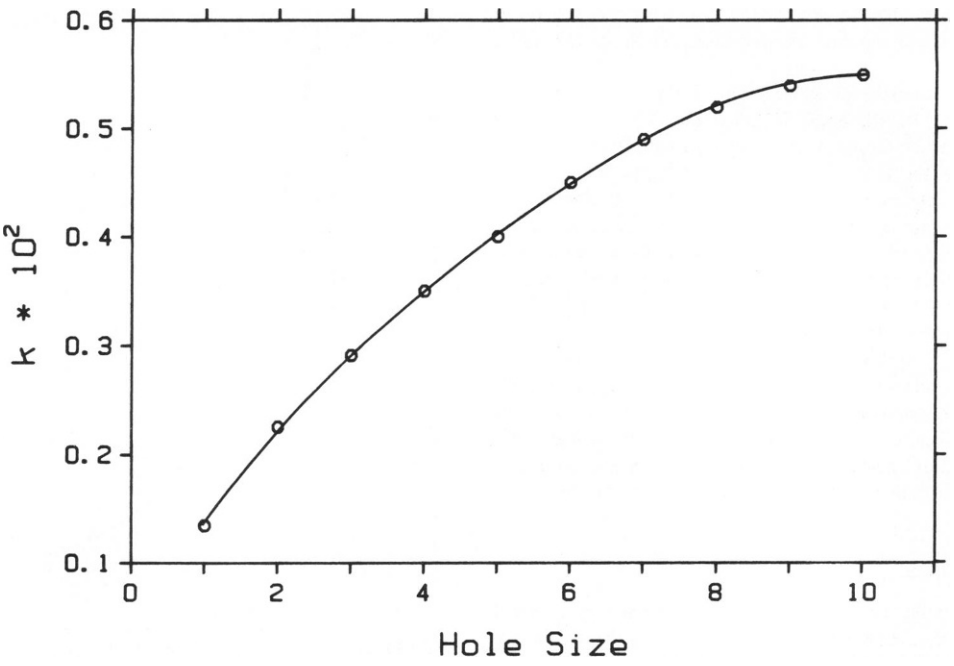

FIGURE 5 The magnitude of the release rate, k, vs. the hole size for a single pore, where the hole size was varied from 1 to 12 lattice units is shown.

seen to increase approximately $k \propto n^{\beta}$, where n is the number of lattice spacings in the hole and β is found to be ~0.67. If the hole were behaving as n independent small holes, we would simply find k proportional to n. Clearly there is a screening effect; two adjacent traps screen the number of walkers that fall into the other (Samson and Deutch, 1977). This exponent can be expected to depend on the dimensionality of the system, and hence may not be what would be observed in a three-dimensional timed-release experiment.

Two Pores

We next present the results for two pores connected by a constricted channel whose length is 1 lattice unit. Fig. 6 contrasts the population vs. time for 200 particles leaving a single large (12 × 24) chamber (through an aperture 1 lattice-unit wide) with these results for 201 particles leaving from chambers interconnected by a tunnel 1 lattice-unit long. Here, the tunnel width, d_1, and exit hole diameter, d_2, are also equal to 1 lattice spacing (Fig. 2 *a*). It is apparent that even this single, short channel retards the rate of drug release. By examining the slope of ln N vs. t for both configurations, we see the release rate has been retarded by approximately a factor of two-thirds due to the presence of the constricted channel.

We next consider the case where $d_1 = d_2$ and both are varied from 1 to 8 lattice units. Here we have labeled the particles originally in the chamber containing the exit hole as species 1 and those located in the other chamber as type 2 particles. Fig. 7 reveals $N(t)$ vs. t for both species. The most striking feature of this result is that <10% of the type 2 species leave through the exit hole before 90% of the type 1 particles exit. This is true over the range of $d_1 = d_2$ values. Thus, there is little mixing of the two species and subsequently little competition between the different particles for positions near the exit hole. Hence, it appears that chambers connected by a constricted tunnel act sequentially. Note that though type 1 particles decay exponentially,

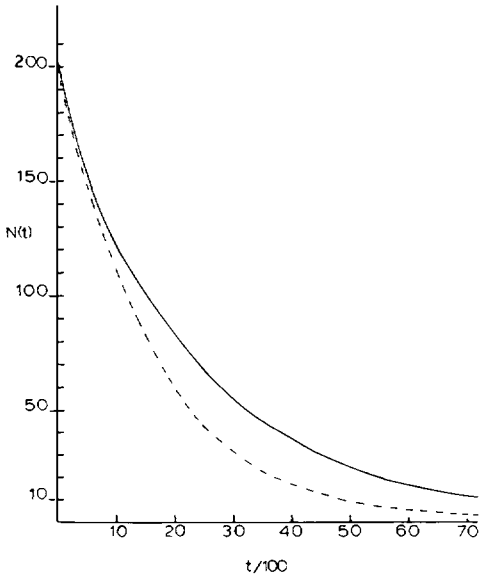

FIGURE 6 $N(t)$ vs. t for 200 particles leaving one large (12 × 24) chamber (dashed line) and for 201 particles leaving from two chambers interconnected by a tunnel a single lattice-unit long (solid line) are shown.

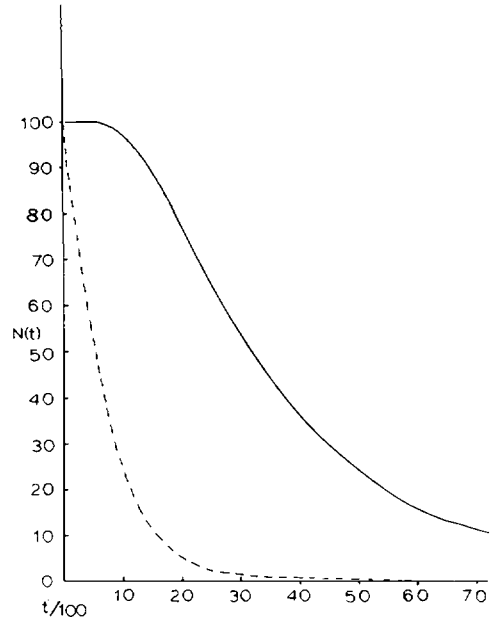

FIGURE 7 $N(t)$ vs. t for both type 1 (dashed line) and type 2 (solid line) particles are shown. Here $d_1 = d_2 = 1$ and L, the length of the tunnel, equals 1.

only the long time behavior of type 2 particles is characterized by exponential decay.

Finally, as expected, faster release rates are obtained for this configuration when the diameter of both the exit hole and the interconnecting tunnel are increased. Fig. 8 shows $N(t)$ vs. t for the following cases: (*a*) $d_1 = d_2 = 1$ and (*b*) $d_1 = d_2 = 7$ lattice units. Since the majority of the type 1 species have left the system in a short time, the rate of release at long times will be characterized by the exponential decay of the type 2 species. In this time region (approximately after 1,000 steps), there exists a linear relationship between the release rate and the width of the interconnecting tunnel (for tunnel widths >2 lattice units). (See Fig. 9). Thus, when $d_1 = d_2$, flow from the second pore is the rate-limiting step.

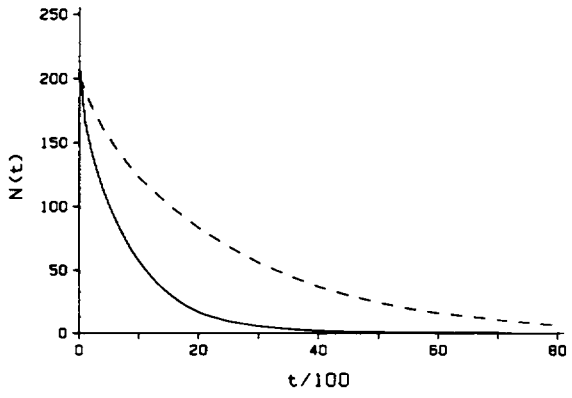

FIGURE 8 $N(t)$ vs. t for the sum of type 1 and type 2 particles for (*a*) $d_1 = d_2 = 1$ (dashed line), and (*b*) $d_1 = d_2 = 7$ (solid line), and $L = 1$ are shown.

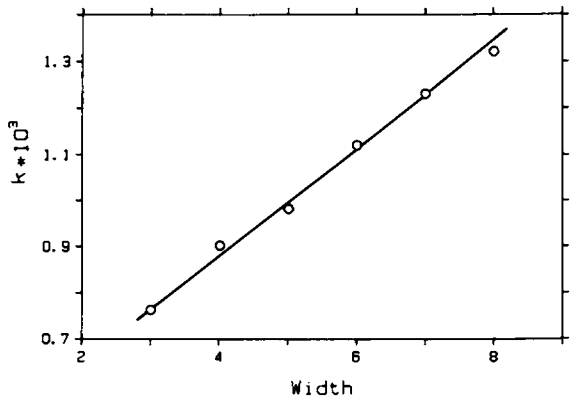

FIGURE 9 The magnitude of the release rate, k, vs. the width of the interconnecting tunnel for $d_1 = d_2$ is shown.

If we consider the case where $d_1 \neq d_2$, it is evident that if $d_1 > d_2$ (the exit aperture is greater than the tunnel width), the flow rate from the second pore is still the rate-limiting step and, as above, the release rate will scale linearly with the width of the tunnel, d_2. If, on the other hand, $d_1 < d_2$ (the exit aperture is less than the tunnel width), there is a bottleneck effect. Type 2 species flow into the first chamber, which still contains a significant number of type 1 species. Thus, release from the first chamber is the rate-limiting step and hence, the overall release rate no longer scales with the width of the interconnecting tunnel.

We note that as the width of the tunnel is increased beyond 8 units (⅘ of the available hole space), the structure can no longer be considered as two pores interconnected by a constricted channel. In fact, when the tunnel width becomes comparable to the diameter of the pore, the results converge on the value obtained for flow from one large pore. In the next simulation, the channel length was increased to 7 lattice units, whereas $d_1 = d_2$ were varied from 1 to 8 lattice spacings. All the results obtained from the tunnel of unit length persist in this configuration as well.

The dependence of the release rate (k) on the length of the constricted tunnel between the pores is of particular interest. Here again, one finds that the chambers act sequentially; the long-time behavior of the system is dominated by flow from the second pore. Though k always decreases with increasing tunnel length, distinctly different results are observed for the following two cases. (*a*) The length of the connecting tunnel is less than the length of the pore, and (*b*) the length of this tunnel is greater than or equal to the length of the pore. For tunnel lengths of 1 to 9 lattice units (case *a* above), Fig. 10 shows a linear relationship between the square root of time (the inverse of the release rate) and L, the length of the tunnel. More specifically, one can deduce from this graph that the inverse of the release rate, t, is proportional to the factor $(L + 18)$.[2] (The actual equation obtained from the graph is $t = [L + 17.8]^2/138.4$). Since each pore is 10 lattice units long, this result indicates that the time (or $1/k$) is

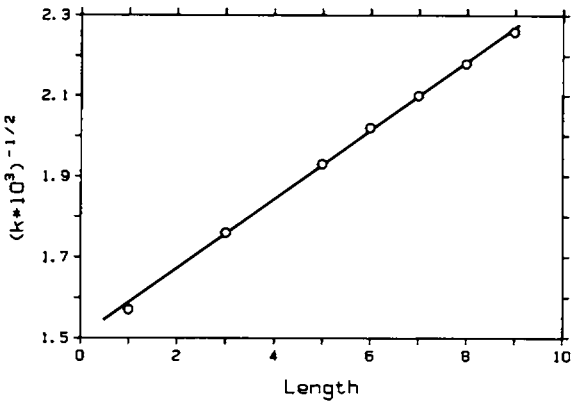

FIGURE 10 The square root of $1/k$ (the inverse of the release rate) vs. L, the length of the tunnel is shown. The length was varied from 1 to 9 units.

approximately proportional to the square of the length of the entire system (two pores and the interconnecting tunnel). On the other hand, Fig. 11 shows a linear relationship between the release rate and the inverse of the tunnel length ($1/L$), for tunnels ≥ 10 units long. (For both the above cases, d_1 and d_2 are fixed at 1 lattice spacing).

Though the initial choice of 10×10 arrays for the pore sizes was arbitrary, the above indicates how the results would scale with variations in the length of either the pores or channel. Furthermore, changing the ratio of the width of the pores to the width of the channel will not make a qualitative difference to our results in those cases where transport through the narrow channel is rate limiting.

DISCUSSION

These simulations have yielded several noteworthy results. First, it has been shown that the specific interactions between the diffusing particles play little role in the overall release rates (at least for repulsive interactions). Second, the calculation on the single pore demonstrates the population of particles remaining in the chamber decays exponentially with time. Third, we see that when two pores are interconnected by a constricted tunnel, whose width is equal to or less than the diameter of the exit hole, the chambers act almost independently and sequentially. When the exit aperture is greater than or equal to the width of the interconnecting tunnel, the overall release rate is proportional to the width of the channel (d_2). Fourth, for the case where the length of the interconnecting tunnel is less than the length of the pore, the release rate, k, is proportional to the factor $1/(L + 18)^2$, where L equals the tunnel length. (From the previous section, we see that $k = 138.4/[L + 17.8]^2$). However, when the tunnel length is greater than or equal to the length of the pore, the rate of release is found to be inversely proportional to the length of the tunnel.

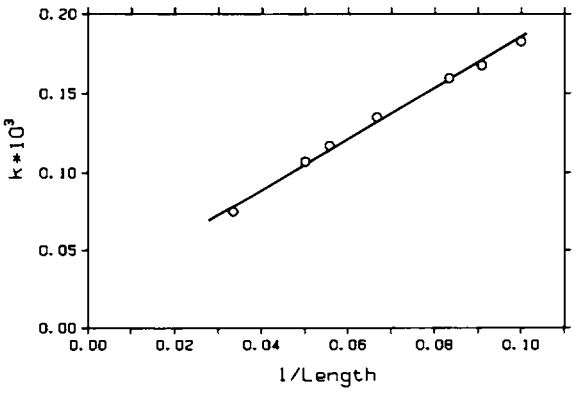

FIGURE 11 The magnitude of the release rate, k, vs. $1/L$ of the interconnecting tunnel is shown. Here, the length was varied from 10 to 30 lattice units.

All of these results seem intuitively correct. For the case where the length of the tunnel is less than the length of the pore, $1/k$ or the time is found to be approximately proportional to l^2, the square of the length of the entire system. This result is consistent with non–steady-state diffusion from a rectangular slab of length l (Crank, 1975). However, this is not the situation when the length of the tunnel equals or exceeds the length of the pore. A flux proportional to $1/L$ is obtained for one-dimensional diffusion along a length L, subject to steady-state conditions (Crank and Park, 1968). Since the particles in the constricted tunnel can move only backwards or forwards and since the number of particles in chamber 2 is greater than the number of particles in the tunnel, at all but long times, the one-dimensional analogy is plausible for determining the rate-limiting behavior. In summary, when the ratio of the length of the tunnel to the length of the pore is <1, the system displays approximately the characteristics of non–steady-state diffusion from a rectangular slab, whose length is equal to the sum of the lengths of the pores and the interconnecting tunnel. However, when the ratio of the length of the tunnel to the length of the pore is ≥ 1, flow through the tunnel becomes the rate-limiting step. The system displays the characteristics of steady-state one-dimensional diffusion along a length equal to the length of the interconnecting tunnel. It is also reasonable that the rate should vary linearly with the tunnel width if we think of the tunnel as a set of W-independent narrow tunnels. We note this result is consistent with a characteristic first passage time proportional to W, the result found by R. Siegel and R. S. Langer (unpublished results). Thus, for the case where the length of the tunnel is greater than or equal to the length of the pore, we arrive at the simple relation for the first-order release rate k: $k \propto w/L$.

From the equation above, it is easy to see that the release rate can be significantly reduced (and consequently the time for release significantly increased) by increasing the length and decreasing the width of the connecting channel. The intuitive validity of our results gives us confidence in applying the two-dimensional simulation results to the three-dimensional world. The argument given in the

Appendix explaining the lack of importance of repulsive interactions is independent of dimension. Because we see steady-state (first-order) behavior in the population decay and not any complicated time dependence typical of two dimensions, the mathematically more well-behaved three-dimensional cases can be expected to be similar.

The first-order behavior we have observed, in addition to similarity between interacting and noninteracting walkers, suggests that to simulate the entire network of pores, one can combine rates from detailed calculations such as this one, with percolation models of randomly connected nodes.

We have shown that our lattice random-walk model yields a simple way to incorporate various structural features of a porous polymer and provides a good way to evaluate how these features affect the release rates of the diffusing drug molecules. From a practical standpoint, the model will be useful for providing guidance in the development of delivery systems with desired release rates. Since some drugs are very potent and need to be released daily in microgram or nanogram quantities, whereas others need to be administered daily in milligram dosages (Langer and Peppas, 1981), it would be useful to be able to design systems to accommodate these different regimens, a process that is now done solely by trial and error. The model can tell us, however, the effect of the number of pores and the size of the constrictions on release rates. Since these parameters can be experimentally controlled by varying drug particle numbers, size, and shape (Rhine et al., 1980), guidance could now be provided and predictions made on how to control the above experimental parameters to achieve desired release rates.

APPENDIX

In the text, it was stated that there was little observed difference between models that include the excluded volume effect of multiple random walkers and those that do not. Here we show why, at the master equation (ME) level of description, this seems to be so.

For noninteracting random walks on a simple lattice, the probability of being at site **i** after n steps, $P_i(n)$ obeys a ME

$$P_i(n) = P_i(n-1) + \sum_j W_{ij}P_j(n-1) - \sum_j W_{ji}P_i(n-1), \quad \text{(A1)}$$

where W_{ij} is the probability of hopping from site **j** to site **i**. This equation simply states that the probability of being at site **i** is the probability the particle was there the previous time step, plus the probability of hopping onto the site from elsewhere, minus the probability of hopping away. The vector **i** designates the location on the hypercubic lattice. As discussed in the text, the inclusion of excluded volume modified the hopping rules in two ways; this requires the addition of two terms to the right-hand side of Eq. A1. First, walkers cannot hop onto a site that was already occupied. This is reflected in ME by modifying the hopping terms

$$P_i(n) = P_i(n-1) + \sum_j W_{ij}[1 - P_i(n-1)]P_j(n-1) - \sum_j W_{ji}[1 - P_j(n-1)]P_i(n-1). \quad \text{(A2)}$$

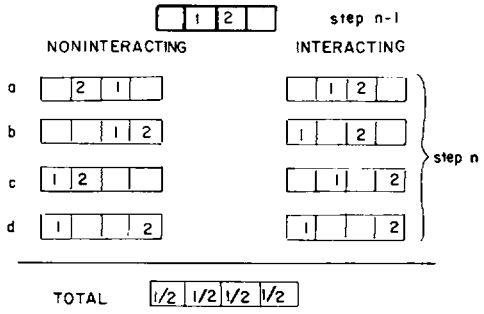

FIGURE 12 Two walkers, labeled *1* and *2*, are at adjacent sites at step n (*top* line). The four possible moves for noninteracting and interacting walkers are shown on lines *a*, *b*, *c* and *d*. The average occupation probability for both cases is the same, as shown on the *bottom* line. We note that when two walkers are separated by an empty site, the simulation includes the possibility of multiple occupancy for the noninteracting case and does not permit multiple occupancy for the interacting cases.

The probability of hopping from site **i** to **j** is now proportional to the probability that site **j** is empty, $1 - P_j[n-1]$, one minus the probability it is occupied. Eq. A2, is, however, the same as Eq. A1 (when the hopping rate is symmetric, $W_{ij} = W_{ji}$), since the quadratic terms cancel. Physically this result arises because the probability that appears in the ME refers to the probability of occupancy of a given lattice site irrespective of the identity of the walker. Fig. 12 demonstrates the type of motion that these terms describe, in this example, for the two walkers adjacent to each other on a one-dimensional lattice. The four equally probable moves for the interacting and for the noninteracting walkers are shown. The total probability that a given site is occupied is ½ regardless of the rule. The same figure illustrates that there will clearly be a difference for tagged particle diffusion.

The second modification due to excluded volume is the bounce rule, where two or more particles attempting to move to an open site bounce back and are not moved. This introduces higher order (such as cubic) terms in the ME, which do not cancel; the corresponding occupation probabilities after the move are not the same for interacting and noninteracting walkers (as the interested reader can easily see by constructing a figure similar to Fig. 12). However, a simple numerical examination of the importance of these terms for a one-dimensional chain showed them to be of little significance. This is in keeping with our simulation results where these events are relatively infrequent and seem to have little effect on the results. This problem will be discussed in more mathematical detail in a forthcoming note.

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REFERENCES

Baker, R. W., and H. K. Lonsdale. 1974. Controlled release: mechanisms and rates. *In* Controlled Release of Active Agents. A. C. Tanquarry and R. E. Lacey, editors. Plenum Publishing Corp., New York. 15–71.

Barber, M. N., and B. W. Ninham. 1970. Random and Restricted Walks, Theory and Applications. Gordon & Breach, Science Publishing Inc., New York.

Brown, L., C. Wei, and R. Langer. 1983. *In vitro* and *in vivo* release of macromolecules from polymeric drug delivery. *J. Pharm. Sci.* 72:1181–1185.

Crank, J. 1975. The Mathematics of Diffusion. Clarendon Press, Oxford.

Crank, J., and G. S. Park. 1968. Diffusion in Polymers. Academic Press, Inc., London. 5.

De Gennes, P. G. 1971. Reptation of a polymer chain in the presence of fixed obstacles. *J. Chem. Phys.* 55:572–579.

Langer, R. 1982. Controlled release of macromolecules. *Chemtech.* 12:98–105.

Langer, R., and J. Folkman. 1976. Polymers for the sustained release of proteins and other macromolecules. *Nature (Lond.).* 263:797–800.

Langer, R., and N. Peppas. 1981. Present and future applications of biomaterials in controlled drug delivery systems. *Biomaterials.* 2:195–210.

Peppas, N. A. 1983. Mathematical modeling of diffusion processes in drug delivery polymeric systems. *In* Controlled Drug Bioavailability, Vol. 1. Drug Product Design and Performance. V. Smolen, editor. John Wiley & Sons, Inc., New York. 274–329.

Pollard, H. B., C. J. Pazoles, C. E. Creutz, and O. Zinder. 1979. The chromaffin granule and possible mechanisms of exocytosis. *Int. Rev. Cytol.* 58:160–198.

Rhine, W. D., D. S. T. Hsieh, and R. Langer. 1980. Polymers for sustained macromolecule release: procedures to fabricate reproducible delivery systems and control release kinetics. *J. Pharm. Sci.* 69:265–270.

Samson, R., and J. M. Deutch. 1977. Exact solutions for the diffusion controlled rate into a pair of reacting sinks. *J. Chem. Phys.* 67:847.

Siegel, R., and R. Langer. 1984. Controlled release of polypeptides and other macromolecules. *Pharmaceutical Research.* 1:1–10.