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Monte Carlo simulations for the study of drug release from matrices with high and low diffusivity areas

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Abstract

We use Monte Carlo simulations in order to study diffusion controlled drug release from matrices consisting of random mixtures of high and low diffusivity areas (random mixing), and from matrices covered by a thin film of low diffusivity (ordered mixing). We compared our results with the Weibull model for drug release and found that it provides an adequate description of the release process in all cases of random mixing and most cases of ordered mixing. We have studied the dependence of the Weibull parameters on the diffusion coefficient and, in most cases, found a rather simple linear dependence. Moreover, our results indicate that a device covered by a thin film with diffusion coefficient three orders of magnitude lower that the coefficient of the rest of the device, will release drug at constant rate for most of the release process. This last result may have considerable practical applications.

Keywords: Controlled release; Diffusion; Monte Carlo simulations; Weibull model

1. Introduction

Understanding and controlling the drug release rate from a release device is a subject of significant practical importance. The release of a drug from such a device must take place at appropriate rates, in order to ensure the desired therapeutic effect. Theoretical modeling of the processes involved in controlled drug release is essential (Macheras and Iliadis, 2005), since the development of new pharmaceutical products is highly facilitated from the possibility to predict the desirable release kinetics in advance. Several models have been proposed for the description of drug release (Higuchi, 1961; Peppas, 1985; Ritger and Peppas, 1987a,b; Peppas et al., 1980; Gao et al., 1995; Siepmann et al., 1999; Siepmann and Peppas, 2000, 2001; Costa and Lobo, 2001; Weibull, 1951; Bonferoni et al., 1998; Sathe et al., 1996) but, in practice, the mathematical models most commonly used to describe the release kinetics from a large variety of devices are

(a) The Higuchi law (Higuchi, 1961), which is valid for systems where the drug concentration c_o is much higher than the drug solubility c_s and has the form:

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

where M_t is the cumulative amount of drug released at time t, A the surface area of the controlled release device exposed to the release medium, D the drug diffusion coefficient, c_o the initial drug concentration and c_s is the drug solubility.

(b) The power law (or Peppas model) (Peppas, 1985). This law has the simple form:

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

where M_t and M_∞ are the amounts of drug released at times t and ∞, respectively, k is an experimentally determined parameter, and s is an exponent that depends on the geometry of the system. It also depends on boundary conditions such as the presence of stagnant layers surrounding the matrix, or non-uniform initial drug distribution. The exponent s can be related to the drug release mechanisms and it is extensively used because of this property.

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(c) The Weibull model (Weibull, 1951; Bonferoni et al., 1998; Sathe et al., 1996):

$$\frac{M_t}{M_\infty} = 1 - \exp(-at^b) \quad (3)$$

where a and b are constants. This model describes experimental dissolution data (Gao et al., 1995) quite well and a physical meaning of the constants a and b is provided in Kosmidis et al. (2003a) and Papadopoulou et al. (2006). The exponent b originates from the fact that a depletion zone is created gradually near the boundaries of the release device, and thus, the drug concentration in the device is not uniform.

Here, we will focus exclusively on diffusion controlled drug release, which we will study using Monte Carlo simulations (Landau and Binder, 2000). This method provides a useful and intuitively plausible way of following the time evolution of a system. Monte Carlo simulations have recently been used to study drug release from Euclidean and fractal geometries, yielding interesting results (Kosmidis et al., 2003a,b; Bunde et al., 1985; Villalobos et al., 2006, 2005; Haddish-Berhane et al., 2006). See also Barat et al. (2006a,b) for a detailed comparative review.

In this paper, we are interested in the way the release rate is changed, when the release device is not uniform, but consists of a mixture of areas with high D_h and low D_l diffusion coefficients. We use Monte Carlo simulations and study drug release from random mixtures of high and low diffusivity areas (random mixing). In this case we are mostly interested in whether there is an observable effect when the density of low diffusivity approaches the percolation threshold (Bunde and Havlin, 1995). We also examine the case where the release device consists of a uniform high diffusivity area covered by a very thin layer with low diffusivity (ordered mixing). We find that in all cases of random mixing, the Weibull function (Eq. (3)) provides an adequate description of the release kinetics and that only the exponent a depends on the diffusion coefficient, while the exponent b is constant. Moreover, no effects were observed at the percolation threshold for the simulated range of D_l and D_h. This is in marked difference with the case of ionic transport in two-component systems, for example, where percolation effects are of outmost importance (Bunde and Havlin, 1995). In the case of ordered mixing, the Weibull approximation continues to be valid for a large range of the ratio D_l/D_h. In the case, however, where D_h is about three orders of magnitude higher than D_l (i.e. when $D_l/D_h = 0.001$) the Weibull approximation fails. In this case the release rate is constant for more than 90% of the release process, i.e. we observe a constant release rate when $M_t/M_\infty < 0.90$. This fact, is of considerable practical importance, as it is always desired to construct release devices that deliver the drug at a constant rate.

Our results are valid in several cases of practical interest where the design of the system controls the molecular diffusion of drug molecules in and/or surrounding the delivery system. The following rate-preprogrammed systems fall within this category: (i) polymer membrane permeation-controlled drug delivery systems, (ii) polymer matrix diffusion controlled drug delivery systems, (iii) polymer (membrane/matrix) hybrid-type drug delivery systems and (iv) microreservoir partition controlled drug delivery systems (Boylan and Swarbrick, 2002).

2. Methods

The Monte Carlo method (Landau and Binder, 2000) 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. Initially, we consider either a two-dimensional square lattice of size $L \times L$ or a three-dimensional cubic lattice of size $L \times L \times L$. Then, we place a number of particles randomly on the sites of the lattice, according to the initial particle concentration c, avoiding double occupancy. Unless explicitly stated otherwise, we assume an initial particle concentration $c = 0.5$, meaning that 50% of the sites are initially occupied by particles, and the rest are empty. The boundaries of the lattice are leak areas. If a particle attempts to cross the boundaries, then it is immediately removed from the system. In the case of random mixing, each site of the lattice has a probability p to be a site of low diffusivity or a probability $1 - p$ to be a site of high diffusivity, see Fig. 1 for a schematic.

In the case of ordered mixing, only the lattice sites that are neighboring to the boundary are sites of low diffusivity, see Fig. 2.

Particles are moving inside the lattice performing random walks (Weiss, 1994). To be specific, a particle is selected at ran-

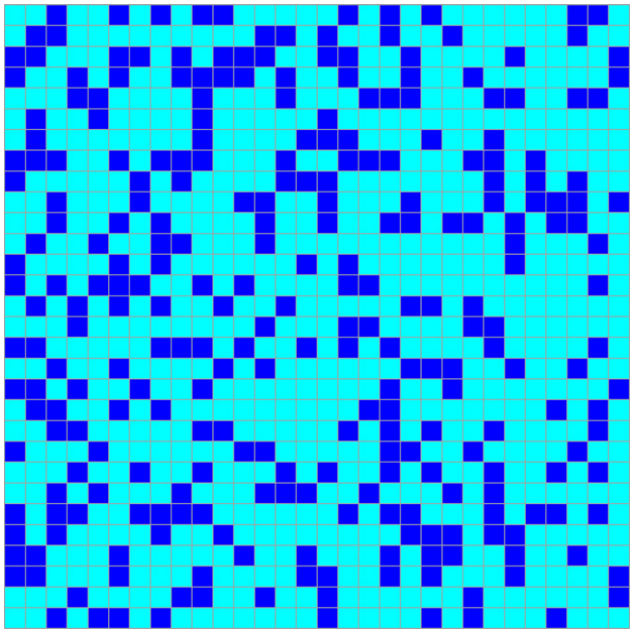

Fig. 1. An illustration of a matrix comprised of 70% high (light) and 30% low (dark) diffusivity areas randomly mixed (random mixing).

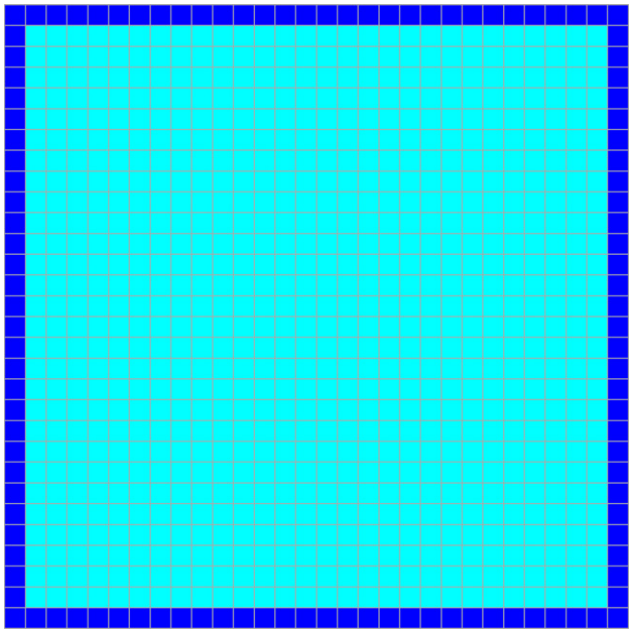

Fig. 2. An illustration of a matrix comprised of a high diffusivity interior (light) and a low diffusivity (dark) thin layer around the border (ordered mixing).

dom. The particle may stay immobile with a probability q, or move at a new randomly chosen neighboring site with probability $1-q$. The case where $q=0$, is identical to the classical random walk algorithm that is used to simulate diffusive motion (Kosmidis et al., 2003a; Landau and Binder, 2000; Kosmidis et al., 2003b; Bunde et al., 1985). The case $q \neq 0$ allow us to simulate diffusion processes with different diffusion coefficients. If the site where the particle is located is marked as a high diffusivity area, then $q=0$, otherwise q has a predefined non-zero value. The parameter q can be directly related to the diffusivity ratios and, thus, is of central importance in the following analysis. 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 (the boundary). After each particle selection, 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 (Bunde et al., 1985). 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.

A well known result in random walks (Landau and Binder, 2000; Weiss, 1994) is that the mean square displacement of a random walker is equal to the number of steps the walker does, and this result holds in all Euclidean dimensions. For simplicity let us consider an one-dimensional random walk. If x denotes the displacement from the start, then, for a walk of n steps:

$$\langle x^2 \rangle = n \tag{4}$$

If, however, there is a probability q that the walker remains at his position, instead of jumping at one of his closest neighboring sites, then the actual number of steps that the walker will do, on average, is $(1-q)n$. Thus, the above equation is to be modified to

$$\langle x^2 \rangle = (1-q)n \tag{5}$$

From the classical theory of diffusion (Weiss, 1994), we know that the mean square displacement for unbounded diffusive motion in one dimension is

$$\langle x^2 \rangle = 2Dt \tag{6}$$

Let us consider a particle moving at a high diffusivity area. Then $q=0$ and the diffusion coefficient is D_h. For a low diffusivity area there is a non-zero q and the diffusion coefficient is D_l. From the above equations and taken that the time needed for a step is a constant we find that

$$\frac{D_\mathrm{l}}{D_\mathrm{h}} = 1-q \tag{7}$$

The above equation (Eq. (7)) connects a quantity that is easily controlled in a Monte Carlo simulation with the ratio of the diffusion coefficients of the different areas.

3. Results and discussion

The Weibull model, Eq. (3), implies that the number of particles inside the lattice in time t is equal to

$$N(t) = N_0 \exp(-at^b) \tag{8}$$

Fig. 3 shows the number of particles inside a square lattice with $L=100$ as a function of time for three different values of q, $q=0, 0.5, 0.8$, i.e. for three different diffusion coefficients. Points are Monte Carlo simulation results and the lines are fits of the Weibull model, Eq. (8), to the data. We notice that the Weibull model fits the simulation data rather well. The fit is very good at the initial part of the release but not equally good towards

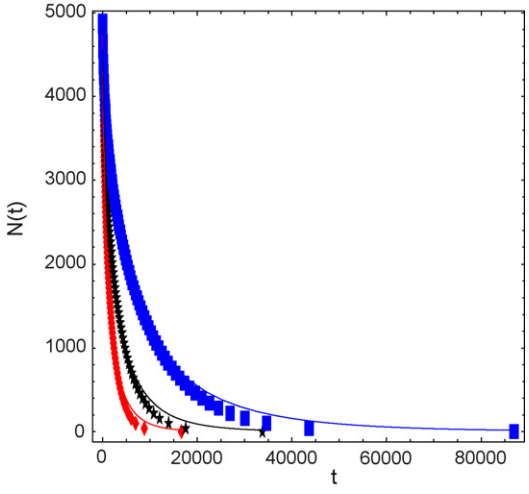

Fig. 3. Number of particles inside a uniform ($p=0$) matrix vs. time for $q=0$ (diamonds), $q=0.5$ (stars), $q=0.8$ (squares). The lines are fits of the Weibull model, Eq. (8).

the end of the release where the Weibull function overestimates the number of particles inside the lattice. This is to be expected as the assumption used to derive the Weibull approximation in Kosmidis et al. (2003a) is that a depletion zone is created around the boundary and that the effect of this depletion zone may be modeled by a power law. When the vast majority of particles are released, it is not still plausible to speak of a depletion zone since there are only a few particles and they are almost randomly scattered inside the system. We can still, however, use the Weibull model to describe the 100% of the release process, knowing that the model is an approximation and not an exact solution.

In order to study how the Weibull coefficients a and b depend on the diffusion coefficient, we have simulated the release process from lattices with $L = 100$ and 200, when the lattice consists of a uniform area where, at each site, the particles have the same probability $1 - q$ to move. We repeated our simulations for several q values and fitted Eq. (8) to our results to determine the values of the exponents a and b. In all cases, we found that the exponent b was equal to 0.64, independent of q and thus, independent of the diffusion coefficient. This is in close proximity with the value $b = 0.69$ that has been observed in Kosmidis et al. (2003a) for release from cylindrical and spherical geometries. This, lower, value of the exponent is in agreement with the known facts that the lattice geometry is more "restricted" than the three-dimensional geometries (Weiss, 1994) and that the Weibull exponent assumes lower values in restricted geometries (Papadopoulou et al., 2006; Kosmidis et al., 2003b). In Fig. 4, we show the dependence of a on q, for the two above mentioned square lattice sites. As expected, the exponent a is a decreasing function of q. This is not surprising, since the higher the q value, the lower the diffusion coefficient that is simulated. When the diffusion coefficient is low, then the particle mobility is low and the particles need more time to escape from the release device. Thus, the exponent a in Eq. (8) is expected to be smaller for low diffusion coefficients and this is confirmed by the simulation. The relation between a and q is quasi-linear in the most part of the [0, 1] regime. Only for $q > 0.9$ the deviation

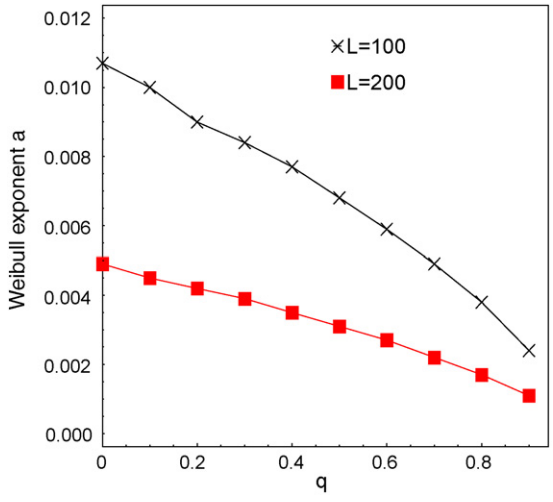

Fig. 4. Dependence of the Weibull exponent a on the parameter q. The exponents were calculated from fitting of a Weibull function to Monte Carlo simulation data of uniform ($p = 0$) lattices with $L = 100$ and 200.

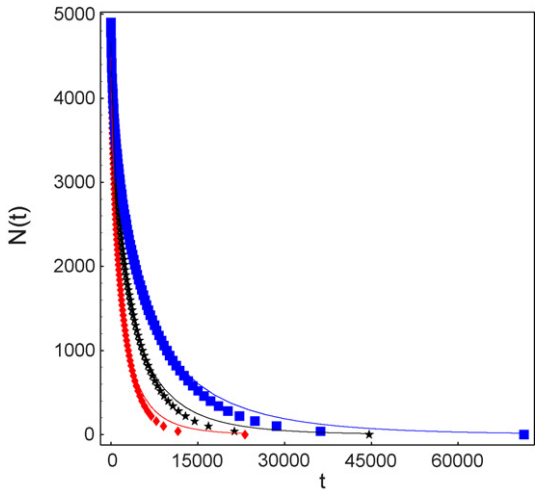

Fig. 5. Number of particles inside a matrix (random mixing) vs. time for $q = 0.8$ and $p = 0.1$ (diamonds), $p = 0.4$ (stars), $p = 0.8$ (squares). Lines are fitting to a Weibull function Eq. (8) with $b = 0.64$ and $a = 0.0096$, 0.0068, 0.0044, respectively.

from linearity is more evident. The exponent a is also a decreasing function of the system size. This dependence was studied and explained in Kosmidis et al. (2003a).

Fig. 5 shows the number of particles inside a square lattice with $L = 100$ versus time. The lattice is a random mixture of low and high diffusivity areas (see Fig. 1 for a schematic). The diamond symbols are simulation results for $p = 0.1$, i.e. when 10% of the lattice consists of low diffusivity material. The star symbols are simulation results for $p = 0.4$ and the square symbols for $p = 0.8$. In all cases we have used the value $q = 0.8$. So in the low diffusivity areas the diffusion coefficient is considerably lower than that of the high diffusivity areas. The solid lines are fits to the Weibull model. Again, we see that the Weibull approximation is valid also in the case of random mixtures, with the same restriction that the number of particles is overestimated towards the end of the release curve. In order to study the dependence of the Weibull parameters a and b to the proportion of low diffusivity areas we have simulated the release procedure from a square lattice with $L = 100$ for two fixed values of q, $q = 0.3$, 0.8 and varying concentration of low diffusivity areas p. In all cases we have found that the exponent b does not depend on the value of p and for a square lattice we have always found a constant value for b, $b = 0.64$. In Fig. 6, we plot the Weibull exponent a as a function of p. The dependency may be approximately considered as linear, for practical purposes. Moreover, if we compare this figure with Fig. 4 we can see that if we know (experimentally) the value of $a = a_1$ for a system with known diffusivity D_l and the value of $a = a_2$ for a system with the same dimensions and different diffusivity D_h, then we may estimate quite well the value of the parameter $a = a_m$ for a random mixture by a linear equation $a_m = pa_1 + (1 - p)a_2$, where p is the fraction of the system with diffusivity D_l.

Next, we study the release from a square lattice with ordered mixing (see Fig. 2 for a schematic). In Fig. 7, we plot the number of particles inside the matrix as a function of time for three values of q, $q = 0.8$, 0.99, 0.999. Results are presented with dia-

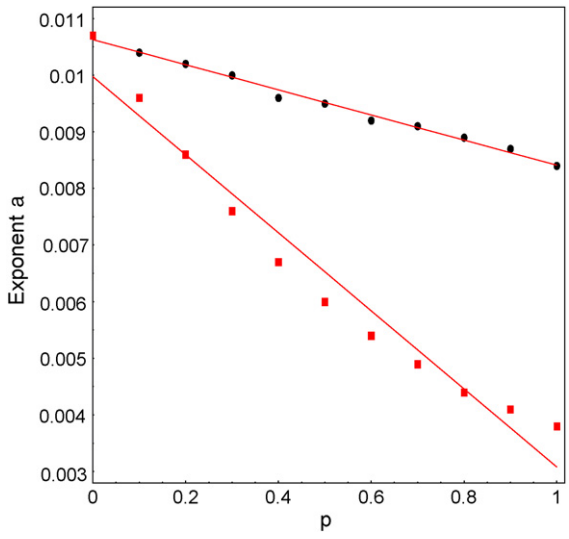

Fig. 6. Weibull exponent a vs. the probability p of low diffusivity areas for $q=0.3$ (circles) and $q=0.8$ (squares). Straight lines are linear fits. The exponents were calculated from fitting of the Weibull function to Monte Carlo simulation data of square lattices with $L=100$.

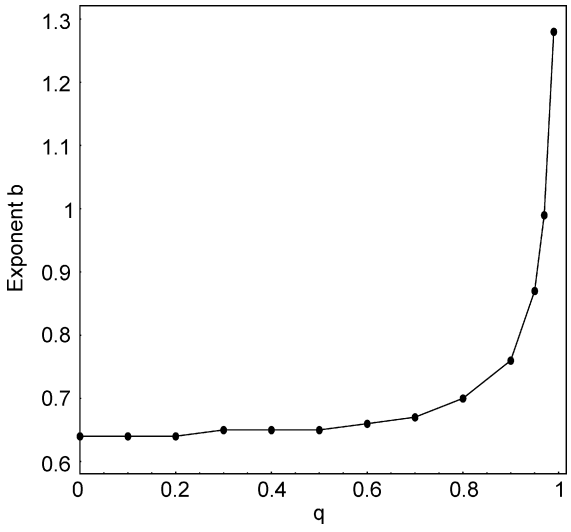

Fig. 8. Weibull exponent b vs. the parameter q. The exponent was calculated from fitting of the Weibull function to Monte Carlo simulation data of a square lattice with $L=100$.

monds, stars and square points, respectively. The solid lines are fits of a Weibull function to release simulation data for $q=0.8$, 0.99 and a fit of a straight line to simulation data for $q=0.999$. The Weibull model describes well the simulation data in the case $q=0.8$, 0.99, but it is not adequate in the case $q=0.999$. In order to understand the reason for this difference, we studied systematically the dependence of the exponents a and b on the parameter q. The behavior of the exponent a (data not shown) is similar to the case of random mixing. The exponent b, however, shows a different behavior, as shown in Fig. 8, where we plot the Weibull exponent b as a function of the parameter q in the case of "ordered" mixing, i.e. in the case where a matrix (two dimensional in this example) with high diffusion coefficient is covered with a thin film with low diffusion coefficient.

For a large regime of q, the Weibull exponent has roughly the same value $b\approx 0.64$ as in the case of random mixing. There is, however, a sharp increase of the b value for $q>0.9$. The reason for the sharpness is that q depends on the ratio of the diffusivities of the two areas. Thus, $q=0.9$ corresponds to diffusivities that are different by one order of magnitude, while $q=0.99$ corresponds to diffusivities different by two orders of magnitude. Thus, although the numerical values of q in both cases are very close to each other, they correspond to diffusion coefficients that have considerable difference. The reason for the increase in the Weibull exponent is that when the diffusivity in the surrounding area is sufficiently low, then a depletion zone around the boundary is not created, since the quickly moving drug molecules inside the matrix have enough time to occupy this space. As it was shown in Kosmidis et al. (2003a), the reason for the appearance of a Weibull exponent $b\neq 1$ is the creation of the depletion zone near the leak boundaries. Thus, it is normal to expect that when this zone is absent, we will have an increase of the Weibull exponent towards $b=1$ which corresponds to the simple fact that the number of molecules that exit from the matrix in a time interval dt is proportional to the number of molecules in the matrix.

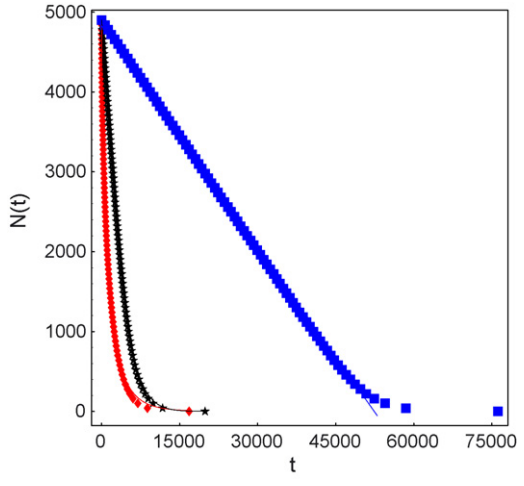

Fig. 7. Number of particles inside a matrix with ordered mixing vs. time for $q=0.8$ (diamonds), $q=0.99$ (stars) and $q=0.999$ (squares).

It is not correct, however, to conclude that the release profile will be sigmoidal ($b>1$) for even larger q values. The fitting of the release simulation data to a Weibull function gives b values higher than 1, but in these cases the Weibull approximation is no longer a correct description of the release. The Monte Carlo Simulation results do not show a sigmoid profile but a very large linear regime, as seen in Fig. 7. When the parameter q takes the value $q=0.999$, i.e. when the low diffusion coefficient is approximately three orders of magnitude different from the high diffusion coefficient, then the Weibull model is no more an adequate description of the release. In fact, the majority of the release is done at constant rate, as is evident from the straight line part of the curve in Fig. 7 for $q=0.999$ (square symbols). For sufficiently large values of q, when a drug molecule exits from the matrix there is always enough time for another molecule to replace it near the boundary. Thus, the aver-

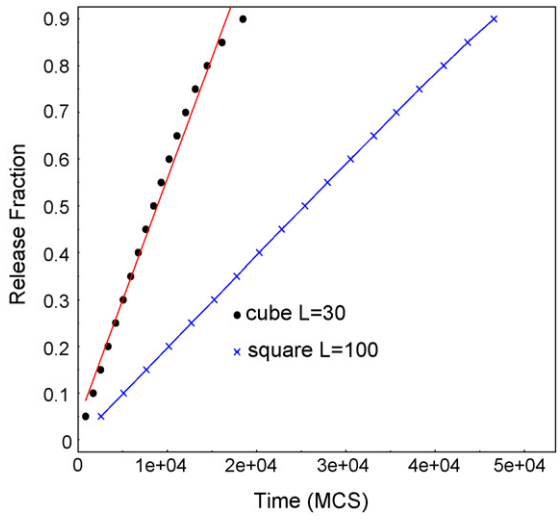

Fig. 9. Release fraction vs. time for a cubic matrix with $L=30$ and $q=0.999$ (circles) and for a square lattice with $L=100$ and $q=0.999$ (x-symbol). The straight lines are a guide to the eye.

age number of molecules that are "ready" to exit the matrix is practically constant for the major part of the release and so is the rate of release.

Since this last effect may be of considerable importance for practical applications we have verified it for higher dimensions. In Fig. 9, we plot the release fraction M_t/M_∞ versus time, as is commonly done in pharmaceutic applications. Here, M_t is the number of particles that have been removed from the system at time t and M_∞ is the number of particles that will be released at infinite time (i.e. the initial number of drug particles inside the release device). We present results for a square lattice with $L=100$ and a three-dimensional cubic lattice with $L=30$. We have checked also other size systems with qualitatively the same results. We monitor the system until 90% of the release is completed and as shown in the figure the release curves can be safely considered straight lines, indicating a constant release rate. To the best of our knowledge, this last finding has not been observed in other simulations or experimental studies. It is, however, very well known in kinetics that the lower of two processes in series controls the overall rate, acting as a rate limiting step. Thus, a rule of thumb is used whenever the rate constants of two processes in series are remarkably different. We would, hence, expect that in the case of ordered mixing the release system would behave as a device with a low diffusion coefficient. Thus, the release profile would still be described by a Weibull function with a very low a value. Instead, we find that the functional form changes completely. Thus, in our study we are able to provide a specific cutoff limit for this rule of thumb, associated with the ratio of the diffusivities.

4. Conclusions

We studied drug release from random mixtures of high and low diffusivity areas (random mixing) and from uniform release devices covered by a very thin layer with low diffusivity (ordered mixing). We find that in all cases of random mixing the Weibull function (Eq. (3)) provides an adequate description of the release and that only the exponent a depends on the diffusion coefficient, while the exponent b is constant. Furthermore, we do not observe any important effect near the percolation threshold. In the case of ordered mixing, the Weibull approximation continues to be valid for a large range of the ratio D_l/D_h. In the case, however, where D_h is about three orders of magnitude higher than D_l (i.e. when $D_l/D_h=0.999$) the Weibull approximation fails. In this case the release rate is constant for more than 90% of the release. This fact, is of considerable practical importance, as it provides a means to construct release devices which deliver the drug at a constant rate.

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