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In silico study on the effects of matrix structure in controlled drug release

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Abstract

Purpose: To study the effects of drug concentration and spatial distribution of the medicament, in porous solid dosage forms, on the kinetics and total yield of drug release.

Methods: Cubic networks are used as models of drug release systems. They were constructed by means of the dual site–bond model framework, which allows a substrate to have adequate geometrical and topological distribution of its pore elements. Drug particles can move inside the networks by following a random walk model with excluded volume interactions between the particles. The drug release time evolution for different drug concentration and different initial drug spatial distribution has been monitored.

Results: The numerical results show that in all the studied cases, drug release presents an anomalous behavior, and the consequences of the matrix structural properties, i.e., drug spatial distribution and drug concentration, on the drug release profile have been quantified.

Conclusions: The Weibull function provides a simple connection between the model parameters and the microstructure of the drug release device. A critical modeling of drug release from matrix-type delivery systems is important in order to understand the transport mechanisms that are implicated, and to predict the effect of the device design parameters on the release rate.

Keywords: Drug release; Dual site–bond model; Inert matrix; Monte Carlo simulation; Weibull equation

1. Introduction

This manuscript is related to the problem of drug delivery from inert porous matrices. This kind of delivery plays an important role in pharmaceutics when a drug-controlled release is required [1]. It is commonly accepted that the structure of the dosage form influences the drug release kinetics and the final amount of

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Nomenclature

a	dimensionless real number
b	dimensionless real number
b_i	element of F_b
C_0	initial drug concentration, fraction of sites occupied by drug
$C^{xy}(u)$	correlation coefficient
D	drug
DSBM	dual site–bond model
$\mathrm{d}Q/\mathrm{d}t$	release rate
E	excipient
ε_t	matrix porosity at time t
F_s	uniform real numbers distribution for sites
F_b	uniform real numbers distribution for bonds
L	characteristic lattice length, lattice units
LDS	low dimensional system
l_0	correlation length, lattice units
MCS	Monte Carlo step
M_∞	dimensionless mass of drug released at time infinity
M_t	dimensionless mass of drug released at time t
N_{border}	number of sites on the network boundary
N_{leak}	number of trapping sites
N_{total}	number of sites in the network
N_t	number of drug particles remaining in the cubic lattice at time t
R	dimensionless real number
R_i	numeric label of the element i
s_i	element of F_s
t	dimensionless time
u	distance in lattice units
Ω	overlapping between F_b and F_s

released drug [2], but little is known concerning how these events occur. This work focuses on the case of drug release from inert matrices, i.e., a water-soluble drug is embedded in a finely dispersed state in an insoluble carrier material (excipient) and released by diffusion. The excipient is considered as an inert material, so the carcass does not change as a function of time, i.e., carcass degradation, disintegration, swelling, etc. are excluded. The model could also correlate when the drug is dispersed molecularly. The amounts of both constituents are crucial for the proper design of pharmaceutical dosage forms since drug release from these devices is a percolating process in itself [3,4]. If an initial drug concentration, C_0, is below the drug percolation threshold (for a cubic network this is equal to 0.3116 [5]) then a significant amount of drug can be trapped inside the excipient matrix and never released. On the contrary, if the excipient concentration is below the excipient percolation threshold, then the tablet can break up, then leading to uncontrolled dissolution. Following Refs. [2,3], a drug delivery device can be depicted as a network of drug particles spanned through an excipient matrix. This network structure is what makes difficult to understand the delivery dynamics and mechanism since the drug diffusion process is occurring inside a relatively low-dimensional space rather than in a Euclidean one. This work pursues to quantify the influence that the device structure properties, notably those that can be controlled by means of the initial drug spatial distribution and the initial drug concentration, have on the drug release profile and on the final quantity of released drug. The physical idea concerning the design of the drug-releasing device is that of a three-dimensional space in which drug and excipient grains of diverse sizes are randomly distributed throughout the available volume. The novel aspects of this investigation deal with the following issues: (i) to assess the influence of the structural properties of the porous medium on

the distribution and extent of drug grains and on the transport (diffusion) properties of the delivery device, (ii) to consider the porosity of the drug delivery form as a dynamic property that can be changing during the drug dissolution process; (iii) to have the idea of employing a lattice model to represent a correlated porous substrate by means of the Dual Site Model.

This manuscript is planned as follows. First, the pertinent antecedents are briefly presented, screening the generic nature of the Weibull equation. Second, the particular program conceived to build the solid porous models, to characterize their structure and the corresponding transport properties, as well as to simulate the drug release as a diffusion-controlled process is introduced. Finally, some selected numeric results related to drug release kinetics as a function of the porous substrate topology are presented and discussed.

2. Drug-release from a tablet

Our main goal is to describe the escaping of particles from an inert release device (e.g., a tablet). For simplicity, the D-particles (i.e drug particles, primary clusters of water-soluble drugs), and the E-particles (i.e., excipient particles or primary clusters of an inert material) are assumed to form binary powder mixtures, which can be compressed to form cubic tablets of volume L^3 with null porosity. During the compression process, different types of bonds (D–D, E–E, and D–E) between the particles are formed. Thus, the tablet can be imagined as a L^3 volume spanned in the form of a cubic lattice, where all lattice sites are occupied, thus forming clusters of substances D or E (2). It is evident that if C_0 is varied, percolation phenomena can take place [3]. During the drug-release process, medicine should be first dissolved and then transported through the liquid phase. It is assumed here that the dissolution step is instantaneous, thus the release should be controlled by the specific surface area of the dosage body and by the mass diffusion occurring in a low-dimensional system (LDS). In fact, when the release device is immersed in water, drug particles located at the device borders are quickly transported to the liquid phase and released to the surroundings; nevertheless, this material is quickly exhausted and more soluble matter has to be transported from far distances inside the releasing device. Evidently, this transport process becomes slow and inefficient at an early stage due to intricate diffusion mechanism within the matrix porous space, as this involves drug permeable (void volume) and drug impermeable (volume occupied by substances D or E) zones. Consequently, drug release kinetics can present anomalous characteristics [2,6]. The problem of the release rate from LDS (as fractal clusters and porous networks) was first studied by Bunde et al. [6]. They specifically reported that the release rate follows a power-law (Peppas law). This has the form:

$$\frac{M_t}{M_\infty} = kt^n, \tag{1}$$

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 depends on the system geometry and drug release mechanism. Eq. (1) has been extensively used because of these properties [7]. Kosmidis et al. [8,9] have shown that the Weibull function is the most appropriate one to describe the entire duration of the drug release process, and the power-law can be considered as an approximation for short times. Furthermore, the Weibull function is consistent with the theoretical predictions that have been made under the frame of fractal kinetics [8,9]. This Weibull equation has the form:

$$\frac{M_t}{M_\infty} = 1 - \exp(-at^b), \tag{2}$$

where a and b are real numbers, a is related to the specific surface of the dosage matrix form, and b is mainly related to the mass transport characteristics of the device [9]. The present work aims to quantify these quantities for the case of LDS by means of simulation methods, which are able to reproduce drug-release experiments and allow the virtual study of scenarios which are difficult, time consuming, or expensive to examine by means of direct experimental work. In this way, simulation methods are valuable tools to understand and to predict release profiles of drugs from pharmaceutical dosage forms, and offer the possibility of relating release profiles to the structural parameters of the delivery device. Because of that, a lot of work needs to be done in drug-release simulation and only a few works have been devoted to this purpose. So far,

Monte Carlo methods have been used to study the release problem in one type of two-dimensional fractal structures [6,8], as well as in three-dimensional Euclidean ones. In the latter ones, cylindrical and spherical three-dimensional lattices have been simulated with leak sites located at the boundaries of the lattice arrangement, and particles have been allowed to move inside the porous network by using a random walk model. This work also studies the drug release kinetics from matrix platforms by means of Monte Carlo simulations, which are based on the random walk model of Fickian diffusion with excluded volume interaction, i.e., it is assumed that moving particles act as hard spheres that collide with each other and with no possibility for a sphere to penetrate into another [10]. This seeks to clarify the influence that the device structural properties have on the drug release profile, and on the final amount of drug to be released. The main contributions are: (i) in Refs. [6–9] the porosity was kept at a constant value, whereas here this porosity follows a dynamical behavior, then allowing the study of the initial release step, which has been overlooked in previous works; and (ii) this work considers the initial drug concentration and the drug spatial distribution as variables, both of them which have not been analyzed in previous works. The particular program conceived to construct our solid porous structures, to characterize their structure and transport properties, and to simulate the drug release as a diffusion-controlled process is described next.

3. Methods

Cubic lattices of sizes, $L \in \{10, 15, 20, 27, 35, 81\}$, and of various topologies are used as suitable models of drug release porous devices. In these models, the sites are occupied by one D-particle or one E-particle, according to a given C_0 value. C_0 values range between the drug and excipient percolation thresholds. In all the simulations the initial porosity is taken as zero and the possibility of double occupancy is excluded. In this way, we can handle three-dimensional structures resembling real and plausible drug dosage forms. In the next part, the network construction, the establishment of the initial conditions (drug concentration and drug spatial distribution), and the algorithm to simulate the drug release process are described.

3.1. Networks construction

Cubic lattices were built by means of the dual site–bond model (DSBM). This is a Monte Carlo method already published and which so far has been applied to generate porous substrates and heterogeneous surfaces, at this respect please c.f. Refs. [11,12] and references therein. This method is intended to mimic heterogeneous porous structures, i.e., pores of different sizes interconnected in the way of a simple cubic network, c.f. Fig. 1, and can be summarized as follows. First, two real number distributions with a shared

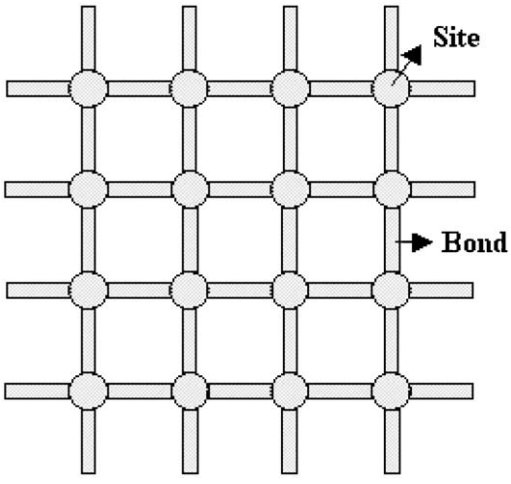

Fig. 1. Schematic representation of the porous space in terms of sites and bonds. In this work, a cubic lattice represents the porous medium where sites are located at the nodes while each bond connection is located in between two adjacent sites.

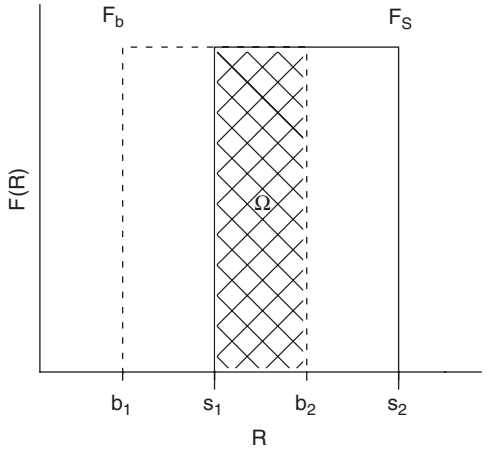

Fig. 2. Uniform probability densities F_s and F_b as a function of R, for sites and bonds respectively, showing the overlap Ω between them.

overlapping area, $\Omega \in [0, 1]$, are set: one of them, F_b, comprises smaller numbers than the other, F_s. Fig. 2 shows the uniform number distributions used in this work. The numbers are assigned to the sites (nodes) of the network by picking up randomly a real number, R, from the F_s distribution. Likewise, numbers are assigned to the bonds of the network by selecting a number at random from the F_b distribution function. Thus, at the end of the assignation process every site and bond in the network has an associated number identifying it. Afterwards, a spatial correlation among the sites of the network is disseminated by imposing the following condition: the associated number of every site should be greater or at least equal to anyone of its delimiting bonds. If $\Omega > 0$, consequently some sites could not satisfy the preceding condition; therefore, the spatial distribution of numbers over the elements of the network needs to be changed. To do this, the numbers of either two sites or two bonds selected at random are exchanged; the movement is accepted if after it the two selected elements fulfill the imposed correlation condition, if not the move is rejected. The movements continue until all the network sites satisfy the previous requirement. Thus the value of Ω determines the degree of correlation among the sites of the network. An empirical equation relating the value of the correlation length, l_0 (the average extent of sites patches having similar numbers), among the sites of a two-dimensional network to the overlapping Ω has already been established [13]:

$$l_0 = \frac{2\Omega^2}{(1-\Omega)^2}. \tag{3}$$

So, the parameter Ω is the predominant one that determines the topology of the porous space, i.e., the precise sequence, statistically expressed, in which the numerical labels of the void-elements distribute throughout the porous network. To clarify ideas, let us analyze the two limiting situations: (i) if $\Omega = 0$, then $l_0 = 0$, sites and bonds are not correlated at all and their associated numbers can be distributed completely at random, and (ii) if $\Omega = 1$ then $l_0 = \infty$, a size segregation takes place in such a way that the network results into a collection of homogeneous regions of different labels; however, on each homogeneous region, sites and bonds have virtually the same numeric label. Here, it is considered that during tablet fabrication, the network self-organizes in such a way that drug grains of mean size l_0 are formed.

Eq. (3) is only valid for square networks, and no relationship between l_0 and Ω has been established for cubic networks. That is why, to look into the way by which network elements are interlinked inside a simulated three-dimensional site–bond lattice, a correlation length is calculated as expounded in Ref. [12]. For that, it is assumed that the numeric label correlation coefficient, $C^{xy}(u)$, for two net elements x and y separated by a distance u (in lattice units), is given by the following expression:

$$C^{xy}(u) = \frac{\langle (R_x - \bar{R}_x)(R_y - \bar{R}_y)\rangle}{[\langle (R_x - \bar{R}_x)^2\rangle \langle (R_y - \bar{R}_y)^2\rangle]^{1/2}}, \tag{4}$$

where R_i represents an element numerical label, and x, y being either S (a site) or B (a bond). This correlation function can be measured through Monte Carlo simulation by using a network of a finite size L. In this work the spatial correlation of the system is characterized via the site–site correlation length, ξ_{SS}, which is calculated by means of the expression proposed in Ref. [14]:

$$C^{SS}(u) = \exp\left(-\frac{u}{\xi_{SS}}\right), \tag{5}$$

where $C^{SS}(u)$ is the numeric correlation coefficient between two sites separated by a distance u.

3.2. Initial conditions

As mentioned before, Ω makes possible to impose a spatial correlation among the sites forming the network. When a correlated network with the requested value of l_0 is constructed, the spatial distributions of D-particles and E-particles inside the network proceed as following, c.f. Fig. 3. The normalized area below F_s has two real limits, s_1 and s_2, i.e., the minimum and the supreme of the F_s set, respectively (c.f. Fig. 2):

$$\int_{s_1}^{s_2} F_s \, \mathrm{d}R = 1. \tag{6}$$

23.68	16.80	21.66	22.75	15.08	16.08
17.39	21.18	17.39	19.01	20.77	18.17
15.90	19.93	23.58	17.83	18.66	19.51
18.96	14.98	16.74	16.50	14.95	14.22
17.02	15.61	23.48	22.94	17.07	23.81

E	D	E	E	D	D
D	E	D	E	E	E
D	E	E	D	E	E
E	D	D	D	D	D
D	D	E	E	D	E

Fig. 3. Schematic representation of the initial conditions. For instance, when $\Omega = 0.6$, the sites of the lattice are labeled with numbers in the interval (14, 24), in the numeric experiences these figures are float. To get a $C_0 = 0.4$, it is necessary to choose a threshold equal to 18, i.e., the sites labeled with a number smaller or equal to 18 are considered drug sites (D-sites), else they are considered sites occupied by excipient (E-sites).

There is an equivalent relationship among b_1, b_2 and F_b. Then, it is possible to match a portion from the F_s normalized area with a value equal to the desired drug concentration C_0:

$$C_0 = \int_{s_1}^{s_i} F_s \, \mathrm{d}R, \tag{7}$$

where $s_i \in [s_1, s_2]$. As, at this stage, all the sites of the network are labeled with numbers coming from F_s, then, as illustrated in Fig. 3, the allotment of drug and excipient particles to the sites of the network is achieved straightforwardly; those with an assigned number smaller or equal to a threshold value are considered D-sites and those with an assigned number larger than the threshold are considered E-sites. It is pertinent to mention that: (i) after correlating the D-site or E-site assignations, the number R given to each site does not have any more relevance during the simulation, (ii) D-particles are considered indistinguishable, and (iii) we interpret the l_0 value as the characteristic size of the drug grains in the device. Finally, the number of leaking sites, N_{leak}, the number of sites in the network, N_{total}, and the number of sites at the lattice border, N_{border}, are counted up and registered.

3.3. Drug-release algorithm

The drug release process is described as a diffusive escape of D-particles, equivalent to the ant in the labyrinth problem [2,6]. In this case the labyrinth consists of a simple cubic network of sites, where the empty sites are accessible to D-particles, whilst the sites occupied by drug or excipient are inaccessible to them. We assume excluded volume interactions among D-particles, meaning that two D-particles cannot occupy the same site simultaneously. The release process tries to mimic the leaking of the drug particles from the tablet because of the contact made between the drug and a solvent phase. At this point, we assumed sink conditions, i.e., the drug is considered freely soluble in aqueous phase, so the medicine release is not limited by drug solubility. Of course, the first contact begins in the drug particles placed at the tablet borders. The later diffusional drug escaping is simulated by selecting a D-particle at random, and moving it haphazardly towards any one of its six closest sites. If the chosen site is already occupied (either by another D-particle or excipient) the movement is discarded, but if that site is empty, then the movement is accepted. The D-particles can finally leak from the tablet when they reach a site on the border of the cubic lattice. After each move (either accepted or not), the time is increased by a value equal to $1/N_t$, where N_t is the number of D-particles remaining inside the cubic lattice; this is a standard method to consider time in a Monte Carlo process [6,8]. When a total of N_t D-particles have been chosen, this corresponds to a time step (Monte Carlo step, [MCS]). The monitored variables are N_t, t, and the drug-release rate $\mathrm{d}Q/\mathrm{d}t$. We average our results over 1000 realizations with different initial random configurations, and monitor the release rate $\mathrm{d}Q/\mathrm{d}t$ by counting the number of particles that diffuse into the leaking surface area in the interval between t and $t+1$. Also, from the obtained results, the values of a and b in Eq. (2) can be computed. Kosmidis et al. [8,9] have shown that this stretched exponential function may be considered as the soundest approximate solution for the entire duration of the drug release; besides this equation is consistent with the theoretical predictions under the frame of classical fractal kinetics [8,15].

4. Results and discussion

Fig. 4 shows simulation results of the rate of D-particles release as a function of time, in the case of release through only one face of the cubic lattice and from a matrix containing 20^3 sites with $C_0 = 0.5$ and $l_0 = 0.0$. In the same figure, we include the data obtained from Ref. [6], under similar thermodynamic conditions, but resting on a shorter time interval, $t \in [0, 2000]$. Time interval in Fig. 4 is $t \in [0, 3000]$ in order to show details, however our simulation halts when more than 90% of the D-particles have been released from the matrix, i.e., about 20,000 MCS. Notice the qualitative similarity between both sets of data, for $t < 200$ there is a very fast decrease of $\mathrm{d}Q/\mathrm{d}t$ value as t goes up, and when $t > 200$ this trend is gradually mitigated until a linear drop correlation between $\mathrm{d}Q/\mathrm{d}t$ and time is established, this last behavior agrees well with the observations done in Ref. [8]. However, note also the quantitative difference between these two sets of data. Initially, $t < 50$, D-particles placed on the lattice border are released fast, hence this early step is mainly controlled by the value

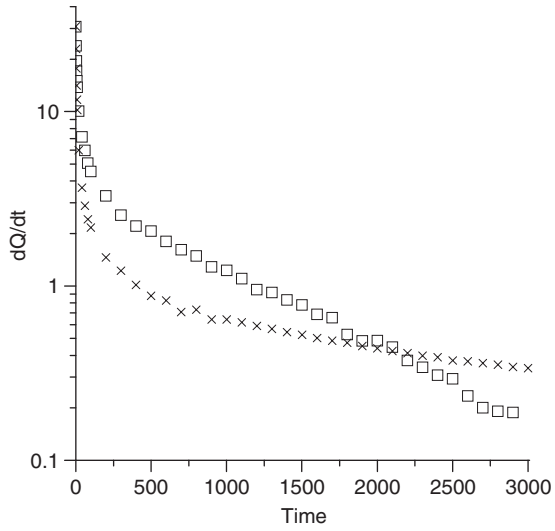

Fig. 4. Plot of the release rate dQ/dt vs. time. The lattice size is 20^3 and the initial concentration of drug particles is $C_0 = 0.5$. Dotted line is the result given by Bunde et al. [6], while the solid line is the result of the current simulation averaged over 10^3 simulation experiments.

of the specific area, N_{leak}/N_{border}; here both models have very similar behaviors. When the soluble material placed near the lattice border is exhausted, drug must be transported from the interior of the release device, and so, gradually mass transport inside the porous matrix becomes the most relevant transport mechanism. In Ref. [6] the matrix porosity is practically invariable and all the matrix sites are accessible to D-particles, whereas in this work the matrix porosity starts from cero, and has a monotonous increase as release occurs, moreover only half of the network sites are potentially opened to D-particles, and the rest are totally closed to them. Thus, our simulations present a more difficult diffusion (sub-diffusive behavior) of D-particles inside the matrix core, and then a less efficient release than that occurring from an all-open network. In brief, within this time interval, $t \in [200,2000]$, our simulation presents a lower reduction of dQ/dt as t increases than the simulation results given in Ref. [6]. Finally, when $t > 2000$, the all open porous media is almost empty, the escape probability drops to zero, and a crossing between the two sets of data is produced, i.e., for $t > 2000$, the dQ/dt value from our simulation is higher than the akin value given by Ref. [6].

Fig. 5 shows the effect of L on the release profile occurring through two opposite faces of the lattice platform, and when $C_0 = 0.594$. In agreement with Ref. [9], Fig. 5 shows that the release profile is a function of L. In all the cases shown here, there is first a time interval showing fast release kinetics, second there is a transition zone where the release rate goes down, and finally, there is a zone characterized by slow release kinetics. This behavior can be explained as follows. During the release process, drug should be first dissolved and after that transported in the liquid phase. At first, the drug placed at the device's border is quickly transferred into the liquid phase and released to the surroundings, so this step is characterized by a quick release and mainly controlled by the specific surface area of the device. Nevertheless, when this material is exhausted, drug has to be transported from the core of the device; hence the release is more and more controlled by mass diffusion. This gradual change on the control mechanism produces both, first the transition zone, and second the slow release zone wholly controlled by drug diffusion. In brief, the combined effects of these two mechanisms determine the release profile. These observations are confirmed by data in Table 1, where N_{leak}/N_{total} values are given by the release through two opposite faces of simple cubic networks for $L \in \{27, 40, 45, 50, 60, 81\}$ in lattice units, with $C_0 = 0.594$. Notice that $(N_{leak}/N_{total}) \to 0$ when $L \to \infty$, i.e., the portion of drug initially placed close to the network boundary decreases as L increases, so the meaning of the release controlled by drug mass diffusion increases as L increases, then the slow kinetics step takes place relatively earlier as L increases. Note also that in all the presented cases, it is possible to achieve a quite accurate fitting of the simulation results using Eq. (2). Table 1 gives the estimated values of a, and b. The relative errors of a and b are bounded by 0.05 and 0.02, respectively. It turns out that: (i) the a factor takes

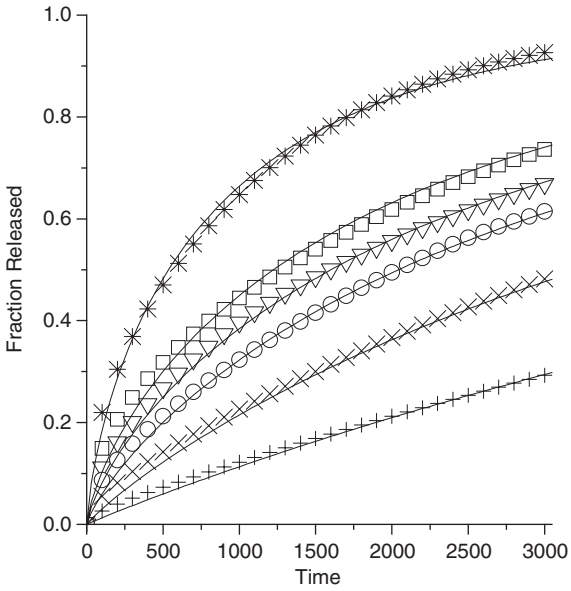

Fig. 5. Release profiles from two opposite faces of cubic matrices, at various L values, and $C_0 = 0.594$. The symbols represent the Monte Carlo simulation data, while solid lines are the corresponding fitting by Weibull model. $L = 27$ (*), $L = 40$ (□), $L = 45$ (∇), $L = 50$ (○), $L = 60$ (×), and $L = 81$ (+).

Table 1
Simple cubic networks

L	$\frac{N_{leak}}{N_{total}}$	a	b
27	0.044	0.0102	0.678
40	0.030	0.0035	0.743
45	0.026	0.0026	0.757
50	0.024	0.0015	0.805
60	0.020	0.0005	0.895
81	0.015	0.0002	0.967

Release through two opposite faces. The values of N_{leak} correspond to the exposed area, i.e., two faces. $C_0 = 0.594$. a and b are the amounts defined in Eq. (2). The relative error of a and b are bounded by 0.05 and 0.02, respectively.

values from 0.0070 to 0.0002 as L goes up from 27 to 81, i.e., the numbers in this table follow the same behavior as N_{leak}/N_{total}, and it mainly represents the influence of the device's specific surface area on the release [8,9], and (ii) the stretching exponent b takes values in the range 0.678–0.967, i.e., larger values than those given in Refs. [8,9] for systems with higher dimensionality, and then easier mass transfer. It is pertinent to bring up that in Ref. [16] the authors explicitly study release from coated theophylline particles and present results from an experimental drug release study for different values of coating and plasticizer added to the coating polymer. The values of b exponent are in all cases in the range of 0.54–1.18, depending on the amount of coating and plasticizer, notice that all the results of our simulations fall inside this last range.

On the other hand, it has been already mentioned, the power-law model, Eq. (1), is believed to describe accurately the release at short times. Fig. 6 shows our simulation results and fittings with the Weibull and the power-law model. As signaled in Ref. [9], the Weibull equation describes quite well all drug release data, whereas the power-law diverges after a certain point in time, and its utility is limited by the initial part of the release curve.

Fig. 7 shows the drug release profiles obtained from systems characterized by various correlation lengths, $l_0 \in \{0.17, 0.68, 1.07, 1.35, 1.88, 2.99, 4.01\}$, in lattice units, for $L = 27$. Remember that the higher is the correlation length, the higher is the mean extent of the original drug grains (drug clusters). In general, the

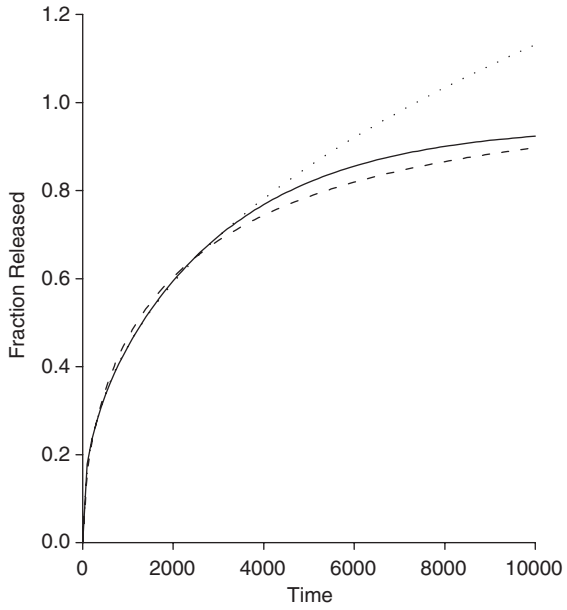

Fig. 6. Plot of cumulative amounts of drug released from cubic matrices with $L = 27$ and through two opposite faces as a function of time. Solid line, Monte Carlo simulation; dotted line, power-law fitting; dashed line, Weibull model fitting.

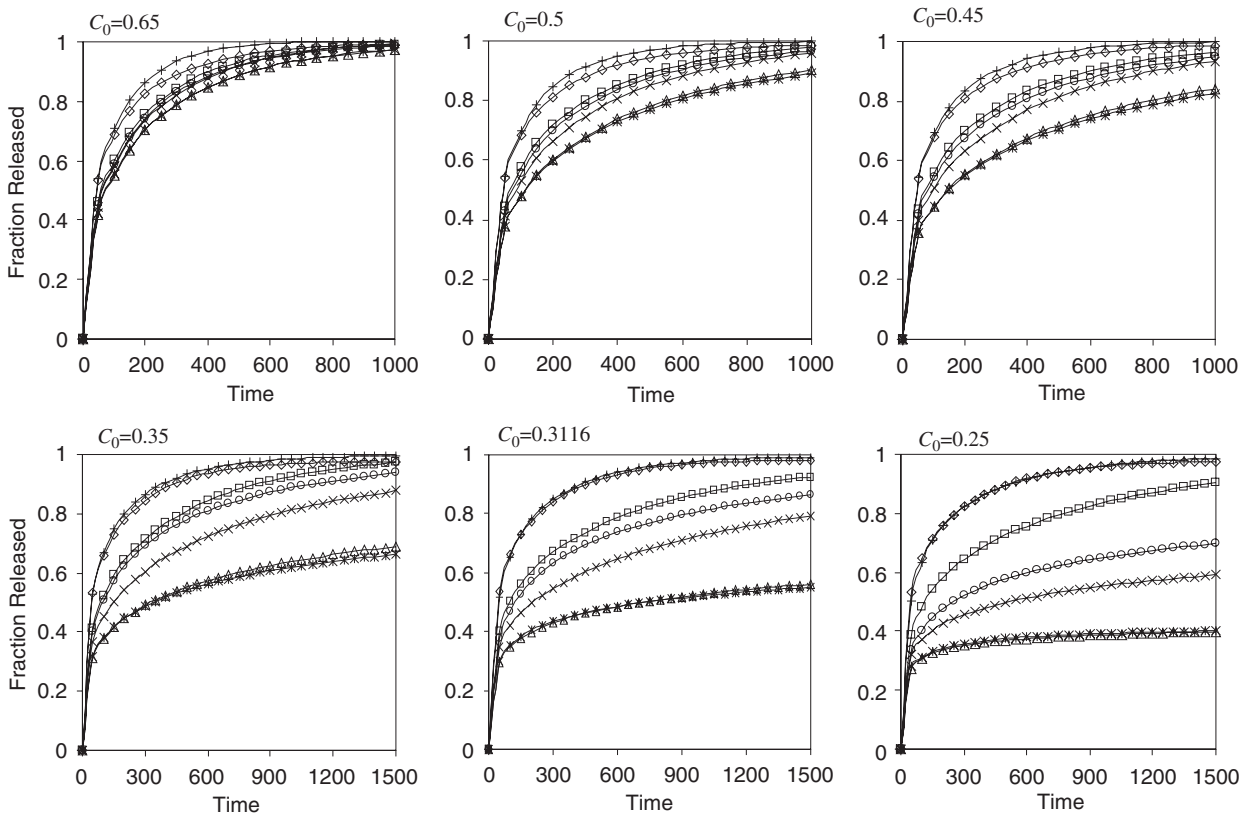

Fig. 7. Results from Monte Carlo simulation. Fraction of dose released from cubic matrices by their total surface area with diverse initial drug load (C_0) and several correlation lengths, l_0. (+) $l_0 = 4.01$, (◇) $l_0 = 2.99$, (□) $l_0 = 1.88$, (○) $l_0 = 1.35$, (x) $l_0 = 1.07$, (Δ) $l_0 = 0.68$, (*) $l_0 = 0.17$.

higher the l_0 value is, the faster the release is, because a higher l_0 value means stronger interactions among D-particles, so the release of a D-particle promotes the transfer of other D-particle, making their release easier as l_0 grows. Furthermore, when C_0 goes down, the effect of l_0 is more significant. First, when $C_0 = 0.65$, practically all D-particles in all the networks are connected to the environment, i.e., there is no drug trapping. However, when C_0 value decreases the dose fraction that is trapped increases. This effect is more evident as the value of l_0 is smaller because the percolation threshold is a function of l_0 [11,17], and decreases as l_0 value increases; in fact, the percolation threshold was roughly calculated as 0.251, 0.244, 0.146, 0.083, 0.016, 0.012 and 0.007 [18] for l_0 values equal to 0.17, 0.68, 1.07, 1.35, 1.88, 2.99, and 4.01, respectively. Observe that the profile corresponding to $l_0 = 4.01$ and $l_0 = 2.99$, the highest l_0 values, are little affected by the C_0 value; on the contrary, the other drug outlines change a lot.

As a whole, there is a very good agreement between our Monte Carlo simulation data and Eq. (2). The parameters a and b of this equation are somehow connected to the properties of the matrix platform. Fig. 8 presents the obtained a values as a function of the N_{leak}/N_{total} values, and also the best fitted straight line for each l_0 value, the equations of these fitted lines are given in Table 2, they are computed by considering only the figures corresponding to C_0 values higher than the respective percolation threshold. For drug concentration values smaller than the network percolation threshold, the behavior is very different, i.e., there is not a linear relationship between a and N_{leak}/N_{total}. In Ref. [9] a values and N_{leak}/N_{total} values get a positive linear relationship, whilst our results have negative linear relationships. This difference could be explained as follows, in Ref. [9] the used matrices are Euclidean (all the sites are accessible) while our drug-excipient systems are LDS. In Euclidean networks, all the release sites have the same relevance, while in a LDS, the significance of a release site is a function of the mean extent of the cluster where it belongs, hence if C_0 grows, the number of important release sites does not grow in the same proportion than N_{leak}/N_{total} value, producing a linear and negative relationship between a value and N_{leak}/N_{total} value. Notice that, in general, the slope of this trend goes down as l_0 grows, for instance when $l_0 = 0.17$ we find $a = 0.094 - 0.311N_{leak}/N_{total}$, and when $l_0 = 4.01$ we find $a = 0.129 - 0.542N_{leak}/N_{total}$. Notice also that for the same C_0 value, a decreases as l_0 increases. In brief, we may conclude that in LDS, the parameter a is determined by both, the specific surface area of the device and its l_0 value. Finally, Fig. 9 shows, for each l_0 value, a linear and positive relationship between b values and N_{leak}/N_{total} values, the equations of these relationships are given in Table 2, as before the

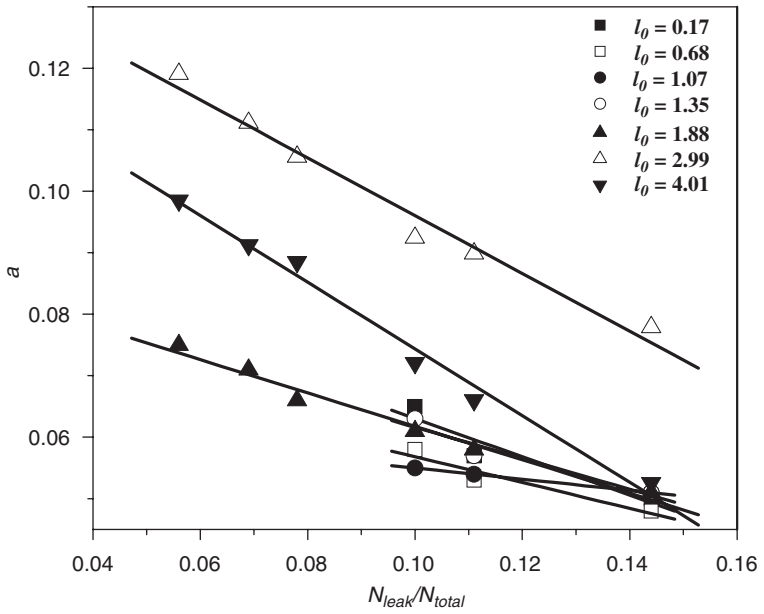

Fig. 8. Parameter a vs. N_{leak}/N_{total} for several correlation lengths. These results were obtained by exposing the total surface area of the device.

Table 2
The equations of lines fitted to data presented in Figs. 8 and 9, for various l_0 values

l_0	$a = a\left(\frac{N_{leak}}{N_{total}}\right)$	$b = b\left(\frac{N_{leak}}{N_{total}}\right)$
0.17	$a = 0.094 - 0.311\frac{N_{leak}}{N_{total}}$	$b = 0.207 + 2.773\frac{N_{leak}}{N_{total}}$
0.68	$a = 0.078 - 0.210\frac{N_{leak}}{N_{total}}$	$b = 0.226 + 2.430\frac{N_{leak}}{N_{total}}$
1.07	$a = 0.064 - 0.091\frac{N_{leak}}{N_{total}}$	$b = 0.401 + 1.528\frac{N_{leak}}{N_{total}}$
1.35	$a = 0.088 - 0.252\frac{N_{leak}}{N_{total}}$	$b = 0.392 + 1.619\frac{N_{leak}}{N_{total}}$
1.88	$a = 0.089 - 0.272\frac{N_{leak}}{N_{total}}$	$b = 0.398 + 1.640\frac{N_{leak}}{N_{total}}$
2.99	$a = 0.143 - 0.470\frac{N_{leak}}{N_{total}}$	$b = 0.379 + 1.948\frac{N_{leak}}{N_{total}}$
4.01	$a = 0.129 - 0.542\frac{N_{leak}}{N_{total}}$	$b = 0.385 + 2.146\frac{N_{leak}}{N_{total}}$

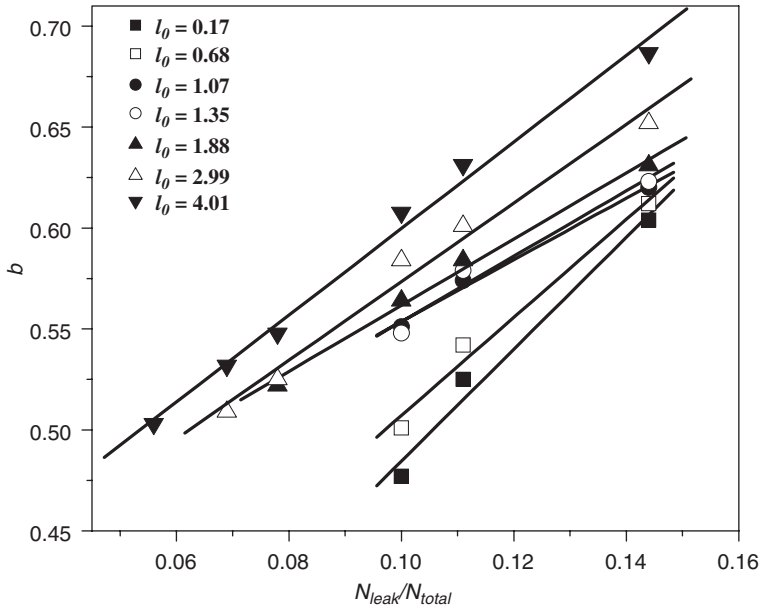

Fig. 9. Parameter b vs. N_{leak}/N_{total} for different correlation lengths. These results were obtained by exposing the total surface area of the device.

lines are computed considering only the data that correspond to a C_0 value higher than the respective drug percolation threshold. Under this threshold, there is not a well-established tendency between b and N_{leak}/N_{total}. From data in Fig. 9, we find that, for a given l_0 value, b seems to be essentially a function of N_{leak}/N_{total} value. For instance, we find $b = 0.207 + 2.722N_{leak}/N_{total}$ and $b = 0.385 + 2.146N_{leak}/N_{total}$, for $l_0 = 0.17$ and $l_0 = 4.01$, respectively. Observe that in these equations, the slope is larger than the independent term. This tendency is more evident as the value of l_0 decreases. Indeed, the value of b should include two contributions: (i) it should be proportional to the specific surface area since a high specific surface means that there are many exits, so it is easier to find an escaping route, and (ii) it should be a function of the ability of the drug particles to move inside the matrix platform. This last point is confirmed by the effect of the correlation length over b (see Fig. 9), i.e., at the same C_0 value, the higher l_0 value is, the higher the b value is, because a higher l_0 means an easier mass transfer inside the matrix. Also notice that the slope of the fitted line goes down as l_0 grows. Therefore we may conclude that b is also determined by both the specific surface area and the internal topology of the matrix, i.e., the l_0 value.

5. Conclusions

From the simulation results it was found that the drug-excipient ratio is a factor that determines the release mechanism from a matrix system. A sub-diffusive behavior of the drug inside the matrix was due to the presence of the excipient. Another factor that modified the release profile was the N_{leak}/N_{total} value. It was found that the N_{leak}/N_{total} value is directly related to the surface/volume ratio of a matrix device. Since this last value is a function of the matrix size, the size of the matrix system affected the drug release profile too.

On the other hand, the DSBM is a simple model (in fact the simplest, to our knowledge) capable of describing random media with different topological structures. These are generated by varying a single parameter, Ω, the overlapping between the site and bond probability densities, while the details of the porous medium will depend, of course, on the shape of these distributions. The parameter Ω can be associated to a correlation length l_0, in such a way that $l_0 \to 0$ as $\Omega \to 0$ and $l_0 \to \infty$ as $\Omega \to 1$. From this concepts, it has been possible to simulate drug release from porous networks topologically equivalent to a granular structure, where l_0 was the mean granule size. We found an excellent fitting between our drug release results and the Weibull function. The values of parameters a and b of this equation were strongly dependent on: (i) the specific surface area, and (ii) the internal topology of the matrix. How does topology affect the percolation properties of the medium? In a similar way as for the Cayley tree, in this work, we found that percolation probabilities increase and percolation thresholds decrease as Ω increases.

It was demonstrated that the clarity of the concepts involved in the DSBM could be easily applied or associated with percolation theory, which helps us to understand solid matrix systems as drug-controlled release platforms. Finally, the critical modeling of drug-release from matrix-type delivery systems is important in order to understand the implicated transport mechanisms, and to predict the effect of the device design parameters on the release rate.

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