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Monte Carlo simulations for the study of drug release from cylindrical matrix systems with an inert nucleus

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ABSTRACT

In this work, drug release from matrices with an inert nucleus using Monte Carlo simulation was studied. Drug-excipient systems were simulated, where the drug is a soluble material while the excipient is a non-soluble material. In the center of these devices, an inert nucleus was placed. The release of the drug was unidirectional and the results were fitted to the square root of time law (Higuchi law), the power law and the Weibull equation. The percolation threshold of the drug was found to be near 0.35 close to the expected value for the cubic lattice, the difference is due to the finite and rather small size of the systems in study as well as to the fact that the lattice in use is not exactly cubic. Near the percolation threshold, the parameters of the different release models presented a drastic change; this was due to a phase transition of the system. On the other hand, it was found that the size of the matrix system modifies the transport properties of the release platform. In general, the release kinetics was adequately described by the Weibull equation.

1. Introduction

The pharmaceutical industry has been highly interested in the development of new drug release systems that improve their performance in time and space. These devices have been widely used in humans and animals (Mathiowitz, 1999). Among these release systems, floating devices and high density devices "sinker" have been designed as retention systems. The development of these systems is possible modifying the device density. The difference in densities between the biological fluid and the release device dictates if the device remains on the surface or the bottom of the liquid (Rathbone et al., 1999; Takada and Yoshikawa, 1999). An alternative to modify the release platform density is inserting an inert nucleus in the matrix release platform. Drug release modeling and determination of the critical parameters of these systems is important to understand and elucidate the mechanical and transport properties. This way, process simulation has become an important and useful tool in the development of new pharmaceutical products since it allows the prediction of the drug release kinetics from chaotic media (Bunde et al., 1985; Kosmidis et al., 2003a; Villalobos et al., 2006a) or from homogeneous space (Kosmidis et al., 2003b; Villalobos et al., 2006b; Kosmidis and Macheras, 2007). In addition, the percolation theory has also been an important ally in the simulation by Monte Carlo methods, since it allows the calculation of critical parameters of the release system (Villalobos et al., 2005).

The percolation theory is a statistical theory that studies chaotic or disorganized media where the components are randomly distributed in a lattice. A cluster is defined as a group of neighboring sites occupied by the same substance; it is considered a percolating cluster when it extends from one extreme of the system to the other (Stauffer and Aharony, 1994). One of the most important parameters of the percolation theory is the percolation threshold, which is the maximum probability of finding an infinite or percolating cluster. At this point, the system properties suffer a drastic change, a disperse–continuous phase transition. However, the pharmaceutical devices are of finite size, and it has been demonstrated that finite-size effects will affect the value of the percolation threshold, particularly when it is partially exposed the surface of the device (Villalobos et al., 2006b). The concepts of the percolation theory have been widely used in explaining the drug release, considering diffusion as the main release mechanism from a matrix device (Bonny and Leuenberger, 1991; Leuenberger et al., 1992; Tongwen and Binglin, 1998; Melgoza et al., 2001; Soriano et al., 1998).

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Various mathematical models have been developed to describe drug release (Costa and Sousa, 2001); however, due to their simplicity and good adjustment, three models are commonly used:

Higuchi equation (1961, 1963) given by

$$\frac{M_t}{M_\infty} = k_H t^{1/2} \quad (1)$$

where M_t and M_∞ are the amounts of drug released at times t and infinity, respectively, and k_H is a constant given by the characteristics of the formulation.

The power law or Peppas model (1985) is given by:

$$\frac{M_t}{M_\infty} = kt^n \quad (2)$$

where k is an experimentally determined parameter, and n is an exponent that depends on the system geometry and the drug release mechanism (Costa and Sousa, 2001). It is evident that if the exponent n in Eq. (2) takes a value of 0.5 the release will be Fickian type, but if it takes a value of 1.0, the drug release rate is time independent; this case corresponds to release kinetics of zero order. In the case of a plane sheet the mechanism that corresponds to zero-order kinetics is known as Case II-transport (Peppas, 1985). The power law just like the Higuchi model only describes the drug release at the interval that corresponds to $M_t/M_\infty < 0.6$. The power law is considered as a generalization that encases two, apparently independent, drug transport mechanisms: Fickian diffusion and Case II-transport (Siepmann and Peppas, 2001).

The Weibull model can be used in almost all kinds of dissolution and release curves (Weibull, 1951; Costa and Sousa, 2001). When it is applied to drug release from a matrix system, the Weibull equation expresses the fraction of drug released, M_t/M_∞, as a function of time t:

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

where a and b are the constants, a is the scale parameter, while b is the shape parameter that characterizes the curve as exponential, sigmoid or parabolic (Costa and Sousa, 2001). This model has been used to study the drug release when the release mechanism is diffusion, fitting well along the whole release, both for Euclidean matrices as well as fractal systems (Kosmidis et al., 2003a). Recently, a physical meaning has been associated to the constants of this model, on one hand, it has been determined that the value of b is an indicator of the drug transport mechanism through the polymeric matrix (Papadopoulou et al., 2006), while the value of a is strongly related to the specific surface of the matrix device through which release is taking place (Kosmidis et al., 2003b).

Additionally, it has been showed that this stretched exponential function may be considered as the nearest approximate solution for the entire drug release process (Kosmidis et al., 2003a). In this work, the treatment of the release problem, applying fractal kinetics concepts, has been studied as follows. The drug release process is treated as the kinetic of reaction $A + B \rightarrow B$, where the A particles are traveling (diffusing) while the B particles are static. This scheme portrays the well-known trapping problem (Kopelman, 1989). In this scenario, the number of particles present in the matrix system at time t is N_t. It is expected that the particle escape rate will be proportional to the fraction $f(t)$ of drug particles that are able to reach an exit in a time interval dt. Initially all diffusing molecules are homogeneously distributed over the drug percolation cluster. Later, due to the release, a concentration gradient will appear. For this, $f(t)$ will be used to describe the segregation effects. Therefore, a differential equation is obtained:

$$\frac{dN_t}{dt} = -k' f(t) N_t \quad (4)$$

where k' is a proportionality constant, $f(t)N_t$ denotes the number of drug particles that are able to reach an exit in a time interval dt, and the negative sign denotes that N_t decreases with time. In this kinetic the number of B sites is constant and we have absorbed the constant trap concentration $[B]$, in the proportionality constant k'. The basic assumption of fractal kinetics is that $f(t)$ has a form approximately to t^{-m}. Therefore, when Eq. (4) is solved, the Weibull equation is obtained (Kosmidis et al., 2003a). The relation between the constants of Eqs. (3) and (4) are: $a = k'/m$ and $b = 1 - m$.

It is pertinent to mention that there are some important differences between the drug release problem and the classical trapping problem, they are: (i) in drug release, the traps are not randomly distributed inside the porous medium, but they are located only at the device boundaries. Actually, the boundary fraction that is part of the embedded drug clusters constitutes the trap sites; (ii) in the trapping problem the porosity of the system, ε, does not change broadly, whereas in drug release the porosity of the medium changes notably; and (iii) drug release devices are finite size, so the drug release from a matrix system is a finite-size problem (Kosmidis et al., 2003a). Then, finite-size effects are in this case essential. This means that the release processes will be affected by the size of the device. The infinite systems are not useful for release purposes because when the device size is increased till infinite, the drug release becomes null.

The objective of this research is to study, by means of Monte Carlo methods, the effect of the insertion of an inert nucleus in a cylindrical matrix platform on the structural properties of the matrix medium, the critical parameters of the system and the drug transport mechanism from this device.

2. Methods

The Monte Carlo method is a numerical simulation based on considering finite-size systems that uses a random number generator to mime the behavior of a system (Binder, 1997). In this study, it was simulated a binary drug-excipient matrix system to which an inert nucleus was inserted. First, this three-dimensional matrix system was given a cylindrical shape with a 1:1 relation between the diameter and height, h (see Fig. 1). The internal unitary conformation of the system is that of a simple cubic lattice. Once formed the cylindrical matrix an inert nucleus was inserted in the center of the structure. This nucleus also has a cylindrical geometry, where the diameter is the same as the height, l (see Fig. 1). The

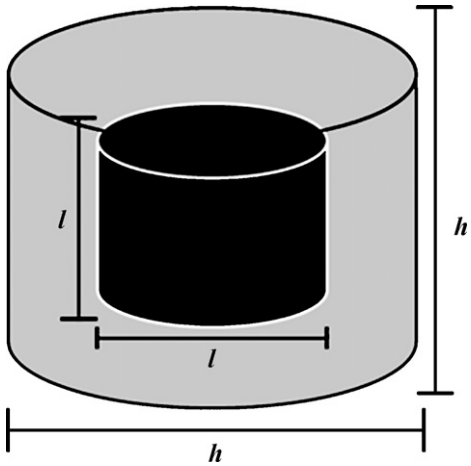

Fig. 1. Cylindrical device with an inert cylindrical nucleus. Each structure has a relation 1:1 between diameter and height. h is the height of the device, while l is the height of the inert nucleus.

Table 1
Distribution of the occupied space in the release device.

h (*l.u.*)	l (*l.u.*)	N_{total}	N_N	N_M
27	15	14,283	2,235	12,048
37	21	37,777	6,657	30,676
47	25	77,691	11,026	66,666

h, height of the device; l, height of the inert nucleus; *l.u.*, lattice units; N_{total}, total sites of the release device; N_N, number of sites occupied by the inert nucleus; N_M, number of sites occupied by drug-excipient matrix.

space occupied by the nucleus is a static volume, formed by sites occupied only by an inert, non-water-soluble material. This way, the material from this nucleus does not contribute with material to be released. The insertion of this type of nucleus is commonly used to modify the density of the release device. The conformation of the systems studied in the present research is described in Table 1. On this table N_{total} represents the total sites that form the release device, N_N the number of sites occupied by the inert-material cylindrical nucleus. This way, by subtracting N_N to N_{total}, the number of sites occupied by the drug-excipient matrix, N_M, is obtained.

Then, the filling of the matrix takes place by randomly placing a drug or excipient particle in each lattice site, according to an initial drug-excipient composition. Each site of the lattice has a probability that equals the initial drug load C_0 of being occupied by a drug particle; or a probability $1 - C_0$ of being occupied by an excipient particle. Matrix systems were generated at the following initial drug loads: 0.1, 0.2, 0.3, 0.35, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1. Obviously, at those loads, the remaining fraction of the matrix was occupied by excipient particles. In this research, excipient particles are considered to be the inert, insoluble and static part of the system, while the drug particles are soluble and move through the adjacent empty sites. It is assumed that the system hydrates instantly when placed in the dissolution medium. To begin the release simulation, the porosity is considered to be zero, meaning that no free sites are encountered, this is, all the sites of the matrix system will be taken by drug or excipient particles. As the release goes on, the system porosity becomes dynamic.

The release simulation is carried out considering a diffusive process which is described by a random walk. The simple cubic lattice has a connectivity of six and it is precisely through these neighboring sites where drug particles can move according to a random walk using the blind-ant algorithm (Stauffer and Aharony, 1994). In this algorithm the walker chooses randomly one of the six neighboring positions; if the site is taken by drug, excipient or inert material from the nucleus, the particle remains in place but if the site is empty, the particle moves to that position. With each attempt of moving, either accepted or not, the time increases in a value equal to $1/N_t$, where N_t is the number of drug particles within the matrix. So, when N_t particles have been chosen, it is considered an arbitrary time unit called Monte Carlo step (*MCS*). This is a standard method to consider time in a Monte Carlo process (Bunde et al., 1985; Sales et al., 1996; Kosmidis et al., 2003b). Under these rules, the drug particle keeps moving until it gets to a site on the exposed border of the matrix; once there, it is immediately removed from the system and it is counted as drug released. The time and the average of the amount of drug released were registered for 1000 realizations. The release of the drug particles from the cylinder was unidirectional; this is, the round surface and one flat face were blocked, allowing the drug release only through the remaining flat face, exposed to the dissolution medium. The release algorithm was carried out until the number of released drug particles was constant. From the number of released drug particles the fractional drug released, M_t/M_∞, is calculated; where M_t is the drug particles released at a time t and M_∞ represents the amount of drug released at a time equal to infinite. Then, the results of the drug released fraction were analyzed using the square root of time law, Peppas and Weibull models.

The calculation of the percolation threshold was made by the method suggested by Villalobos et al. (2005). In this method, the amount of drug trapped by the excipient carcass at an infinite time is plotted against the initial drug load, and it is considered that the inflection point of this curve represents the drug percolation threshold. The curve is described by:

$$Q_t = a' - a' Erf[b'(C_0 - C_{0c})] \quad (5)$$

where *Erf* is the function error, Q_t is the dose fraction trapped inside a matrix, a' and b' are the constants associated to the process, C_0 is the initial drug load in the matrix and C_{0c} is the drug percolation threshold.

3. Results and discussion

In Fig. 2 the results for the amount of drug trapped by the matrix carcass are shown as a function of the initial drug load inside the matrix, for three diameters of the cylindrical matrix, 27, 37 and 47 in lattice units, *l.u.* Each one of these devices contained a nucleus (see Fig. 1). A dependence with a sigmoid shape was observed, very similar to the behavior found by means of the Monte Carlo method (Villalobos et al., 2005), as well as the *in vitro* experiments (Leuenberger et al., 1995). In previous studies it has been shown that in these curves, the inflection point represents the geometrical phase transition; this is the drug percolation threshold of the system (Villalobos et al., 2005). The inflection point of the previous curves was evaluated by Eq. (5). The fitting was excellent, shown by the squared of the multiple correlation coefficient higher than 0.9975 for all the cases. According to this model the percolation thresholds were found at 0.366, 0.358 and 0.348 of initial drug load for the matrices with a diameter of 27, 37 and 47 *l.u.*, respectively. The standard error of the percolation thresholds was bounded by 0.002. In contrast, the reported percolation threshold for a cubic lattice exposing its total surface is 0.312 (Stauffer and Aharony, 1994). However, later studies showed that by reducing the

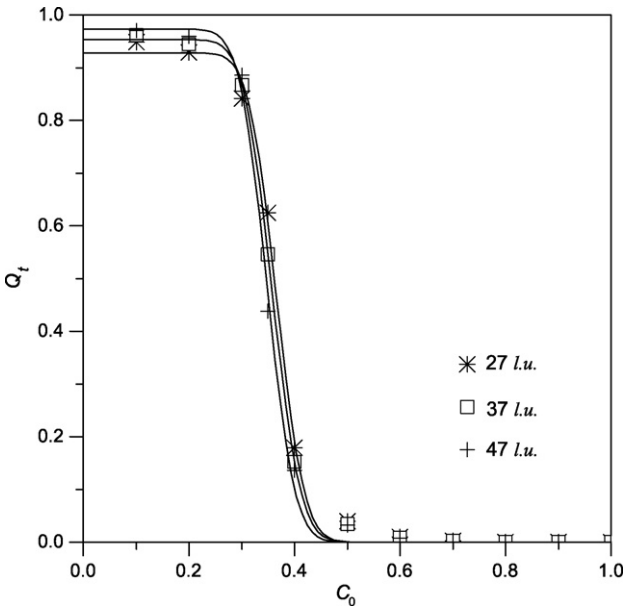

Fig. 2. Fraction of dose trapped in the matrix (Q_t) vs. the initial drug load (C_0), exposing one plane face of the cylindrical device, at various h values. Numerical results, dots, and their fitting by means of Eq. (5), solid line. The relative error of Q_t is bounded by 0.004.

exposed surface, the percolation threshold increases (Villalobos et al., 2005), finding a percolation threshold of 0.328 for cubic lattices exposing only two opposite faces. This value is lower than the one obtained for the matrices in the present research; this behavior can be explained by the insertion of the inert excipient nucleus. The presence of the inert nucleus inside the matrix medium interferes with the connectivity of the system; therefore, a higher amount of drug is needed to percolate the system. However, it is important to emphasize that in the present work as the matrix size increases, the percolation threshold decreases. This behavior is a result of the finite size of the system. In fact, we expected that when the size of the system tends to infinite, the percolation threshold goes to 0.3116. However, due to the fact that the pharmaceutical practice requires the use of finite-size devices, it is very important to know the influence of the system size on the transport properties of the medium.

In this research, the cylindrical matrices were allowed to release the drug only through one flat face, this means that the circular surface and one flat face were blocked. All this leads to one-directional release model, supposition assumed by square root time model. In Table 2 the regression analysis for the $\sqrt{t}$-kinetics is shown. The fitting to the model was performed considering the released drug fraction up to 0.6, in order to avoid errors due to depletion. According to the regression analysis it can be said that the matrix systems with C_0 of 0.5, 0.6, 0.7, 0.8, 0.9 and 1.0 show a lineal behavior for M_t/M_∞ vs. $\sqrt{t}$, which implies that the release is taking place from Euclidean space. The previous profiles are associated to two factors which are: The initial drug load in the matrix and the diffusion barrier generated by an increase in the excipient fraction. On the other hand, at initial drug loads of 0.30, 0.35 and 0.40, the determination coefficients for the amount of drug released vs. the square root of time, were found at an interval of 0.87–0.98, which shows a regular fitting to the $\sqrt{t}$ model. At initial drug loads of 0.35 and 0.40, values near the drug percolation threshold, a great amount of the drug is inserted inside the percolation cluster. It has been demonstrated that the percolation cluster presents a fractal structure, which makes the matrix space a macroscopic non-homogeneous media. Under these conditions, the diffusion coefficient does not get constant and in consequence, in these systems, the behavior of the released fraction vs. the square root of the time is non-linear. When the initial drug load is lower than 0.35 the system is below the drug percolation threshold. Under this condition the drug forms finite aggregates which are dispersed inside a continuous medium (excipient matrix); therefore, the only particles that are released are those connected to the surface of the tablet; leaving, as a consequence, a great amount of the initial drug load encapsulated inside the matrix carcass. Therefore, the released fraction of the drug is very small due to an incomplete release. In this case, the transport of drug by diffusion from the matrix carcass is minimum and as a consequence, there is not a good fitting to the $\sqrt{t}$ model.

Fig. 3 shows the value of the Higuchi constant as a function of the initial drug load inside the matrix. In this figure it is clearly shown that when the initial drug load starts from 0.10 and tends to the concentration corresponding to the percolation threshold, the value of the Higuchi constant decreases drastically. This is due to the fact that a change takes place in the matrix conformation, going from a non-connected or disperse system to a continuous one. Later, above the drug percolation threshold and increasing C_0, k_H also increases but in a gradual manner, because the change in the value of k_H is mainly associated to the diffusion barrier settled by the amount of excipient in the matrix space and since the matrix has a binary composition this barrier decreases when C_0 increases.

Table 3 shows the regression analysis for the power law. It is important to note that this model is valid up to a released fraction of 60%, so the release data used to obtain the coefficients for this

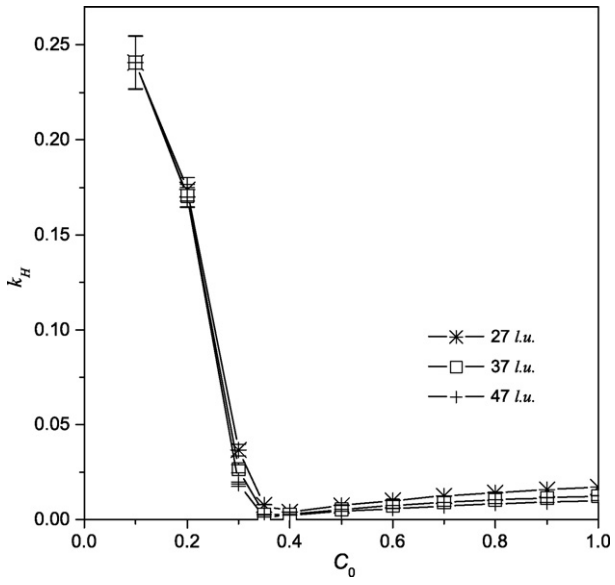

Fig. 3. Parameter k_H vs. the initial drug load for several h values. These results were obtained by exposing one plane face of the cylindrical device. Bars represent the SEM.

equation where those corresponding up to ≤60% of release fraction. In this table, while reviewing the exponent associated to the time, values between 0.440 and 0.594 were found for initial drug loads of 50–100%, which are associated to Fickian-type mass transport; this is, the drug transport is associated only to a diffusive process in a macroscopically homogeneous medium.

For initial drug loads of 35% and 40%, time exponents of 0.284 and 0.382 were found. Based onto the classical analysis of diffusion, the previous data correspond to an anomalous diffusion. Besides, according to the findings described by Bonny and Leuenberger (1991), at the percolation threshold the exponent n is close to 0.2. In our case, at the closest concentration to the percolation threshold $C_0 = 0.35$, the values found for n were 0.323, 0.288 and 0.284 for the matrices with diameters of 27, 37 and 47 *l.u.*, respectively. This anomalous behavior commonly occurs in the matrix type pharmaceutical forms where more than one transport mechanism is involved, such as erosion, swelling, etc. However, in our simulation the only transport mechanism involved is diffusion, so the deviation from 0.5 is due only to the heterogeneity of the system. In Fig. 4, a drastic change in the tendency of the value of n is observed around the drug percolation threshold. This must be associated to the phase transition that suffers the matrix system at this composition.

In the previous sections we performed the analysis of the release profiles until a drug released fraction of 60%, obtaining a good correspondence to the Higuchi model and the power law in systems with initial drug loads from 50% to 100%. However, the fitting of the release profiles to the mentioned two models differs significantly when M_t/M_∞ is above 60% and in matrices with an initial drug load equal to or under 40%. The Weibull equation has been successfully used to describe the release from fractal spaces as well as from Euclidean ones (Papadopoulou et al., 2006). So, in this research the Weibull equation was also used to study the profiles of drug released from the matrices created for this case. In Fig. 5 the release data obtained by simulation for the different matrix sizes and its fitting to the Weibull model are shown. In this figure it is observed that for systems with a high initial drug load there is a good fitting between the release results and the Weibull model. In Table 4, the results for the non-linear regression to the Weibull model are shown; to get such results, the release data up to 90% of M_t/M_∞ were used. From this data a good fitting ($r^2 > 0.99$) for the systems

Table 2
Evaluation of the dissolution data according to the square root time law.

C_0	Matrix diameter					
	27 *l.u.*		37 *l.u.*		47 *l.u.*	
	r^2	k_H	r^2	k_H	r^2	k_H
0.10	0.976	0.241*	0.977	0.241*	0.977	0.241*
0.20	0.986	0.174*	0.986	0.170*	0.987	0.170
0.30	0.880	0.037*	0.883	0.023*	0.906	0.019*
0.35	0.939	0.008*	0.898	0.003	0.959	0.001
0.40	0.965	0.004	0.976	0.003	0.989	0.002
0.50	0.992	0.007	0.991	0.005	0.995	0.004
0.60	0.996	0.010	0.994	0.007	0.995	0.006
0.70	0.997	0.012	0.996	0.009	0.997	0.007
0.80	0.998	0.014	0.997	0.010	0.999	0.008
0.90	0.998	0.016	0.997	0.012	1.000	0.009
1.00	0.998	0.017	0.998	0.013	1.000	0.010

C_0, initial drug load; *l.u.*, lattice units; r^2, squared correlation coefficient; k_H, constant defined in Eq. (1). The relative error of k_H is bounded by 0.03, except that data marked with *, in that case the relative error is bounded by 0.083.

Table 3
Evaluation of the dissolution data according to the power law.

C_0	Matrix diameter					
	27 *l.u.*		37 *l.u.*		47 *l.u.*	
	r^2	n	r^2	n	r^2	n
0.10	0.994	0.762*	0.993	0.760*	0.993	0.759*
0.20	0.980	0.696*	0.981	0.688*	0.982	0.686*
0.30	0.906	0.430*	0.902	0.390*	0.909	0.348*
0.35	0.961	0.323	0.967	0.288	0.992	0.284
0.40	0.984	0.351	0.989	0.358	0.994	0.382
0.50	0.990	0.440	0.992	0.441	0.995	0.449
0.60	0.990	0.486	0.992	0.480	0.995	0.492
0.70	0.990	0.518	0.992	0.511	0.996	0.523
0.80	0.989	0.544	0.992	0.536	0.997	0.553
0.90	0.989	0.563	0.992	0.554	0.998	0.576
1.00	0.989	0.578	0.992	0.565	0.998	0.594

C_0, initial drug load; *l.u.*, lattice units; r^2, squared correlation coefficient; n, constant defined in Eq. (2). The relative error of n is bounded by 0.03, except that data marked with *, in that case the relative error is bounded by 0.064.

with $C_0 \geq 0.60$ is observed; below this composition the fitting to the Weibull model is regular. The values of b for the matrices with initial drug load of 10% and 20% are found between 0.562 and 0.882 for the three different matrix sizes. These values of b are the highest of the studied systems. This behavior can be explained according to the following. In this case, the only particles that contribute to the release are those included in a drug cluster that is in direct contact with the external medium. At these drug loads, most of the drug particles are encapsulated in the matrix carcass, resulting in a small M_∞. This way, the drug clusters that are in contact with the dissolution medium are released quickly and independently of the internal morphology of the porous space, making this kinetics the fastest compared to the kinetics at higher concentrations. This way M_t/M_∞ quickly reaches its maximum value which is associated to higher b values.

The release results for the matrix with $C_0 = 0.35$ and diameter of 27 *l.u.* are adequately described by the Weibull model, which is confirmed by the determination coefficient of 0.992. However, for the matrices with diameters of 37 and 47 *l.u.*, at the same concentration of $C_0 = 0.35$, the determination coefficients were 0.986 and 0.977, respectively. These matrices are very close to the drug percolation threshold, forming a fractal media, morphologically similar to a percolation cluster. At this composition of the matrix system the values obtained for b are: 0.353, 0.364 and 0.434 for the matrices with diameters 27, 37 and 47 *l.u.*, respectively. According to Papadopoulou et al. (2006), when the release takes place from a medium at its percolation threshold, b takes values between 0.35 and 0.39. The values of b for the matrices of 27 and 37 *l.u.* fall within

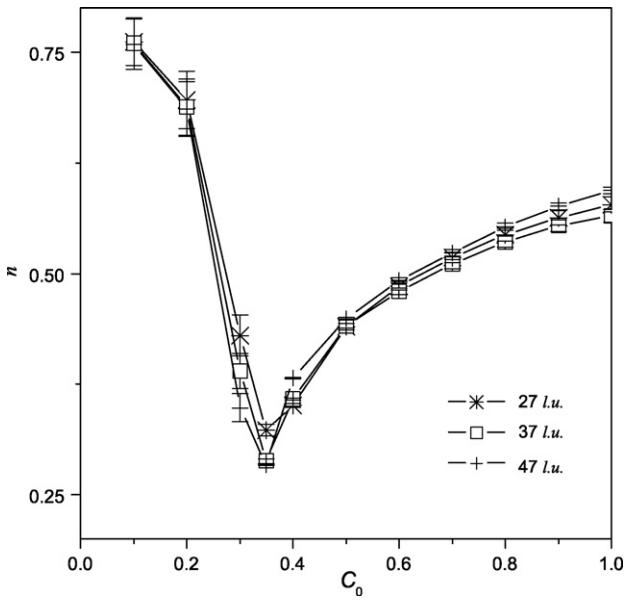

Fig. 4. Parameter n vs. the initial drug load for several h values. These results were obtained by exposing one plane face of the cylindrical device. Bars represent the SEM.

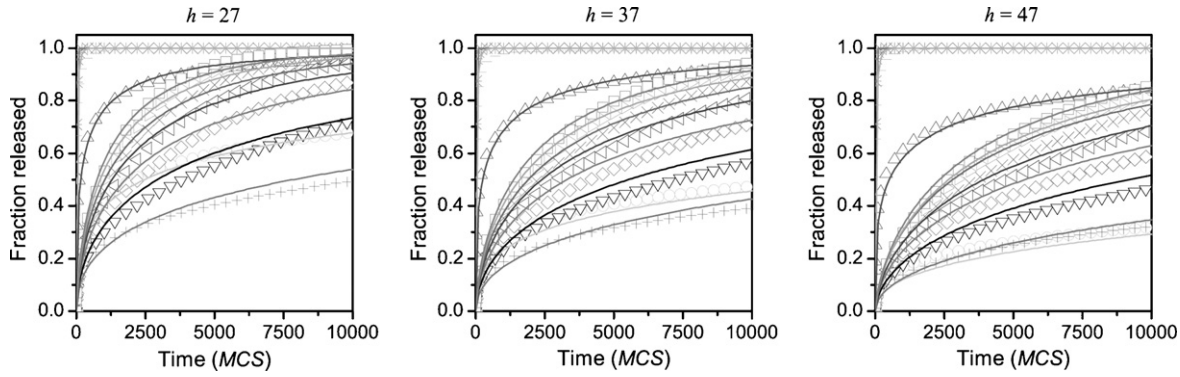

Fig. 5. Release profiles from one plane face of cylindrical device, at various h values, and different C_0. The symbols represent the Monte Carlo simulation data, while solid lines are the corresponding fitting by Weibull model. C_0 = 0.10 (*), C_0 = 0.20 (–), C_0 = 0.30 (Δ), C_0 = 0.35 (O), C_0 = 0.40 (+), C_0 = 0.50 (▽), C_0 = 0.60 (◊), C_0 = 0.70 (◁), C_0 = 0.80 (×), C_0 = 0.90 (▷), C_0 = 1.00 (□). The relative error of the fraction released was bounded by 0.01.

this interval; however, the value of b for the matrix of 47 *l.u.* differs from the proposed interval. The non-concordance of the simulated data with the b interval found by Papadopoulou, is explained by the fact that the interval determined by Papadopoulou was obtained for a release kinetics from a cluster at its percolation threshold in a square lattice, while in our case the lattice is three-dimensional. On the other hand, at an initial drug load of 40% the obtained values for b are: 0.454, 0.481 and 0.507 for the matrices of diameters 27, 37 and 47 *l.u.*, respectively. In this case, the porous media is found at a transition state from a fractal space (macroscopically non-homogeneous) to Euclidean space. For the initial drug concentrations from 50% to 100%, the values of b are found at an interval from 0.53 to 0.66; these values, according to Papadopoulou et al. (2006) indicate that the medium is disordered, macroscopically non-homogeneous, but different from that found at the percolation threshold. This implies that both, the transport properties of the system and the homogeneity of the medium, are affected by the inert nucleus inserted inside the matrix. This is, systems with initial drug loads equal or higher to 50% the medium should be Euclidean space; however, the insertion of the inert nucleus generates properties of non-homogeneity in the system. This last result differs with the findings of the square root of time model and power law model. This difference is due to the fact that the $\sqrt{t}$ model and the power law model use release data of up to 60% of M_t/M_∞, while the Weibull model analysis used data of up to 90% of M_t/M_∞. In this sense the $\sqrt{t}$ model and the power law model are affected by the inert nucleus in the final portion of the analyzed data; for which the effect of the inert nucleus, that affects the release data notoriously above 60% of M_t/M_∞, is not appreciated. In the case of the Weibull model, when using a wider portion of the release data, it is affected by the presence of the inert nucleus and the effect is reflected in a and b constants of this model.

In Table 4, it can be observed that in matrices of composition in the interval C_0 of 35–100% the value of b increases when the initial drug load in the matrix increases. As stated by Papadopoulou et al. (2006), this behavior is associated to the medium homogeneity. On the other hand, at the same interval of C_0, the constant a was found to decrease when the initial drug concentration in the matrix increases. The behavior of b found here agrees with the results from Kosmidis et al. (2003b); however, the behavior of a differs from the one found by the same author, which is explained as follows. In the case of Kosmidis et al. (2003b), they worked with Euclidean geometries, without the presence of excipient; this way, all the sites placed on the surface are exit sites. Then, since there is no excipient inside the matrix, the movement of the drug particles takes place easily. So, the drug release from this type of devices happens quickly, and the fitting to the Weibull model is good, both at the beginning of the experiment and at the end of the process. In our case, the exit sites are only those placed on the matrix device surface that are taken by the drug at the beginning of the experiment, and which are left empty once the drug is released to the external medium and they will form the porous space through which the drug that is inside the matrix will go out. The number of leak sites is represented by N_{leak}. In Fig. 6 the behavior of the proportion N_{leak}/N_{total} vs. C_0 is shown. Here, we can observe that by increasing C_0, N_{leak}/N_{total} increases proportionally, which is associated to more sites where the drug can be released generating, as a consequence, an increase in the release rate by the increase of C_0. On the other hand, the

Table 4
Evaluation of the dissolution data according to the Weibull function.

C_0	Matrix diameter								
	27 *l.u.*			37 *l.u.*			47 *l.u.*		
	r^2	a	b	r^2	a	b	r^2	a	b
0.10	0.994	0.155*	0.882	0.995	0.156*	0.882	0.995	0.156*	0.882
0.20	0.945	0.157*	0.597*	0.945	0.156*	0.587*	0.946	0.165*	0.562*
0.30	0.975	0.097*	0.392	0.980	0.090	0.370	0.982	0.086	0.336
0.35	0.992	0.044	0.353	0.986	0.021	0.364	0.977	0.006	0.434
0.40	0.980	0.012	0.454	0.973	0.007	0.481	0.974	0.004	0.507
0.50	0.990	0.011*	0.530	0.987	0.007*	0.536*	0.984	0.005*	0.554
0.60	0.994	0.010*	0.568	0.993	0.007*	0.565	0.992	0.005*	0.580
0.70	0.996	0.010*	0.596	0.995	0.007*	0.590	0.995	0.005*	0.605
0.80	0.997	0.010*	0.619	0.997	0.007*	0.610	0.997	0.004*	0.629
0.90	0.997	0.009*	0.637	0.997	0.007*	0.626	0.998	0.004*	0.650
1.00	0.998	0.009*	0.651	0.997	0.007*	0.636	0.998	0.004*	0.668

C_0, initial drug load; *l.u.*, lattice units; r^2, squared correlation coefficient; a and b, constants defined in Eq. (3). The relative error of a and b are bounded by 0.03, except that data marked with *, in that case the relative error is bounded by 0.085.

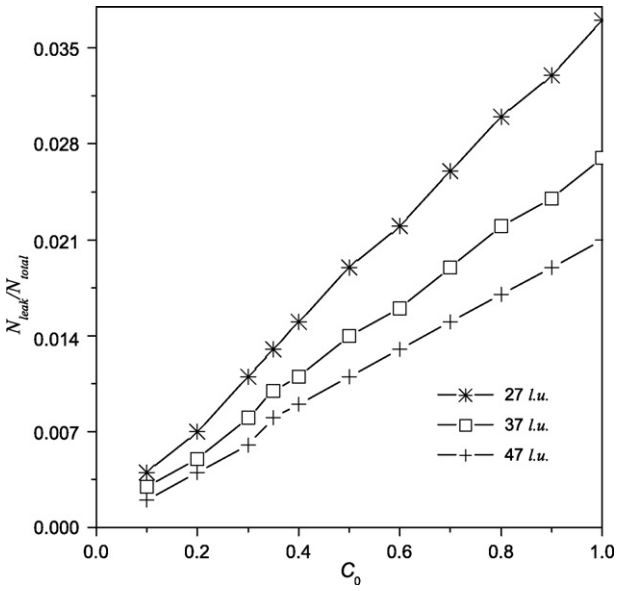

Fig. 6. Parameter N_{leak}/N_{total} vs. the initial drug load for several h values. These results were obtained by exposing one plane face of the cylindrical device. The relative error of N_{leak}/N_{total} was bounded by 0.0005.

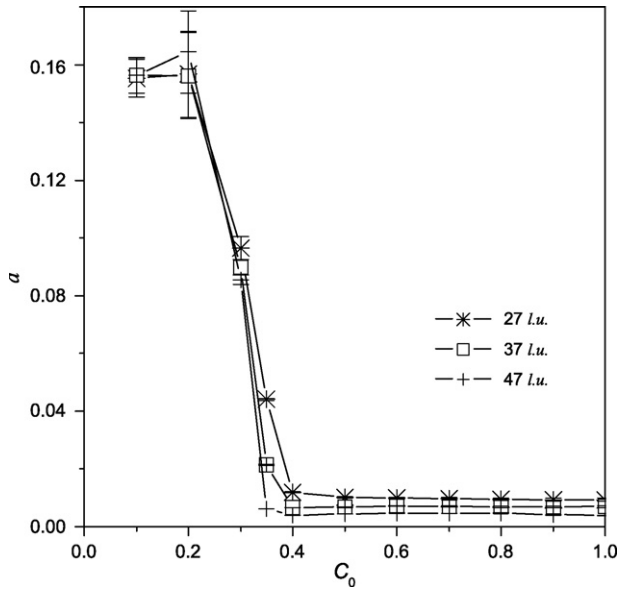

Fig. 7. Weibull exponent a vs. the initial drug load for several h values. These results were obtained by exposing one plane face of the cylindrical device. Bars represent the SEM.

presence of the inert nucleus inside the matrix slows the drug diffusion within the matrix. In this scenario, the release of the drug is governed greatly by the diffusion through a complex porous space, limited besides by the presence of the inert nucleus, which makes the release from the system slower compared to those studied by Kosmidis et al. (2003b). So, the b value determines the release profile throughout the release process. However, this fitting increases the value of a. This way, the Weibull model describes conveniently at long times, but at short times, there are differences between the data obtained by means of simulation and the fitting curve. These differences are minimal when the initial drug load is equal to or higher than 0.50, which agrees with the findings of Kosmidis et al. (2003b), because the matrices with C_0 equal to or higher than 0.50 tend to be Euclidean, proved by the value of the fractal dimension, which tends to three for these systems. On the other hand, the differences between the data obtained by simulation and the fitting curve are obvious around the drug percolation threshold due to the fractal structure presented by the porous space.

In general, it was found that when the size of the matrix increases, the drug release kinetics gets slower. This behavior is due to the relation N_{leak}/N_{total}, which is proportional to the specific surface of the cylinder (Kosmidis et al., 2003b), it decreases as the matrix size increases (see Fig. 6). In this case, there are less exit sites for more particles. Furthermore, when the size of the matrix increases, the drug particles have to go through a longer distance to be able to leave the matrix carcass. In addition, in our case, there are two more obstacles that complicate the particle trajectory even more. These obstacles are the inert nucleus that is located in the central zone of the matrix, and the blocked surface.

Figs. 7 and 8 show the behavior of the constants a and b for the fitting curves to the Weibull model. There, it can be observed that similarly to what happens with the constants corresponding to the square root of the time model and the power law model (see Figs. 3 and 4), when the initial drug load is close to the percolation threshold, the parameters a and b of the Weibull equation show a minimum value. This is further evidence that the drug at this concentration presents, within the matrix, a phase transition from disperse (discontinuous) to a continuous, highly connected medium.

Fig. 9 presents another way to investigate the validity of the fractal kinetics assumption. In this figure the results of $(dN_t/dt)N_t$ vs. time are shown. Due to the fact that a linear tendency is recovered we can say that $f(t)$ of Eq. (4) is described by a power relation of the form t^{-m}. This behavior has been found by other researchers (Kosmidis et al., 2003a; Villalobos et al., 2006a). From this relation it was possible to determine constants k' and m for each system of this work. For example, in systems with $C_0 = 0.35$ values of k' of 0.014, 0.009 and 0.003, and m 0.624, 0.649 and 0.575 were found for matrices of 27, 37 and 47 *l.u.*, respectively. The relative error of these data is bounded by 0.03. It has been proposed that these constants of Weibull differential equation are related with the constants of its integrated form, Eq. (3), as follows: $a = k'/m$ and $b = 1 - m$. With

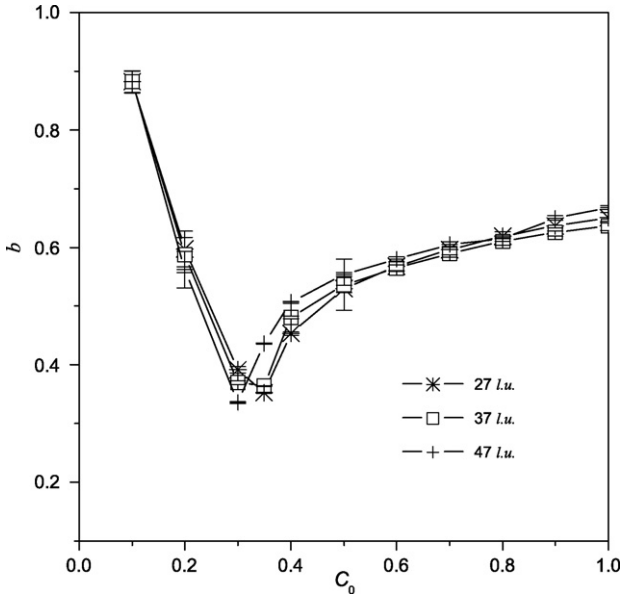

Fig. 8. Weibull exponent b vs. the initial drug load for several h values. These results were obtained by exposing one plane face of the cylindrical device. Bars represent the SEM.

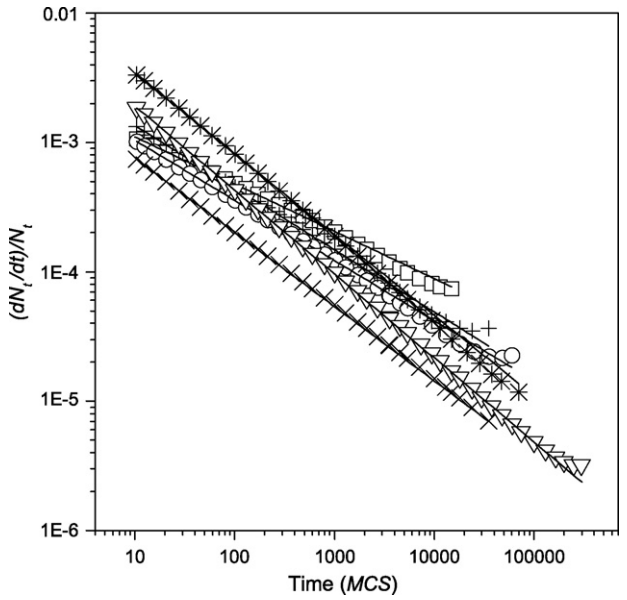

Fig. 9. Log–log plot of $(dN_t/dt)/N_t$, defined by Eq. (4), as a function of time. Symbols represent numerical results, $l = 27$ *l.u.*: $C_0 = 0.35$ (*), $C_0 = 0.50$ (□); $l = 37$ *l.u.*: $C_0 = 0.35$ (▽), $C_0 = 0.50$ (+); $l = 47$ *l.u.*: $C_0 = 0.35$ (×), $C_0 = 0.50$ (O). Their fitting by means of Eq. (4), solid lines. The relative error of $(dN_t/dt)/N_t$ is bounded by 0.03.

these relations and the found values of k' and m the correspondent values for a and b were calculated, finding a values of 0.023, 0.013 and 0.005, and for b of 0.376, 0.351 and 0.425 for systems of 27, 37 and 47 *l.u.*, respectively. These values are close to the ones found with Eq. (3) (see Table 4). This tendency was similar for the other systems studied here. Thus, it is shown that Weibull constants of Eqs. (3) and (4) are actually related. Another parameter that has been useful to describe fractal kinetics is the spectral dimension (Villalobos et al., 2006a). This parameter evaluates the heterogeneity present in a porous medium by relating the transit of a random walk and the fractal dimension of the media (Kopelman, 1989). It has been proposed that this value can be obtained directly from m. This is how, according to the previous discussion, the spectral dimension can be also estimated from the b value of the Weibull function. Therefore constant b must contain information about structural and transport properties of the matrix platform.

4. Conclusions

The simulation of drug release process from matrix media, by means of Monte Carlo methods, has a wide field of study. When it is used in conjunction with the percolation theory, it can explain and solve problems related to the design of matrix type pharmaceutical forms. Additionally, those concepts can be applied to perfect and facilitate the development of these pharmaceutical forms. Furthermore, partial dose lost could be avoided by understanding the fraction of the dose trapped by the matrix carcass vs. the initial drug load.

In the present research, by means of Monte Carlo methods, it was possible to simulate nucleated matrix systems in diverse scenarios and determine the transport properties of the drug in the corresponding media. It was found that the amount of drug trapped by the matrix carcass is a function of the initial drug load inside the matrix, as well as the specific surface of the matrix system that is in contact with the dissolution fluid. The insertion of an inert nucleus generated an increase in the drug percolation threshold in relation to the value reported by the bibliography, this difference is due to the finite and rather small size of the systems in study as well as to the fact that the lattice in use is not exactly cubic. It was also shown that during drug release from matrix platforms the insertion of an inert nucleus interfered with the drug exit, generating a decrease in the release kinetics. It was determined that the unidirectional release from a macroscopically homogeneous medium below 0.6 of M_t/M_∞ is adequately described by a Fickian transport. When the drug release took place from a macroscopically non-homogeneous medium, the transport mechanism was anomalous. The Weibull model was useful to describe the drug release profile up to 0.9 of M_t/M_∞. Besides, with the Weibull model it was possible to determine the heterogeneity of the medium due to the presence of the inert nucleus; this was not possible by using the square root of the time model or the power law model. It was found that release kinetics of the drug changes drastically in the concentrations near the percolation threshold. This change can be seen in the constants associated to the respective kinetics model. This presents another evidence of the phase transition that the matrix system undergoes at the percolation threshold. Finally, the Weibull equation shows consistency with the theoretical predictions under the framework of classical fractal kinetics.

Appendix A. Nomenclature

a	constant associated to the Weibull equation
a'	dimensionless real number
A	diffusing particles
b	constant associated to the Weibull equation
b'	dimensionless real number
B	static trapping sites
C_{0c}	initial drug load corresponding to drug percolation threshold
C_0	initial drug load, fraction of sites occupied by drug
ε	matrix porosity
Erf	function error
$f(t)$	fraction of drug particles that are able to reach an exit in a time interval
h	height of the cylindrical matrix
k	constant release of the power law
k'	constant release of the differential Weibull equation
k_H	constant release of the $\sqrt{t}$ law
l	height of the inserted cylindrical nucleus
l.u.	lattice units
m	exponent time of the differential Weibull equation
MCS	Monte Carlo step, time unit
M_t	drug released amount at time t
M_∞	drug released amount at infinite time
M_t/M_∞	fractional drug released
n	exponent release of the power law
N_{leak}	number of leak sites
N_M	number of sites occupied by the drug-excipient matrix
N_N	number of sites occupied by the inert-material cylindrical nucleus
N_t	number of sites occupied by drug at a time t
N_{total}	number of sites that form the release device
r^2	squared correlation coefficient
SEM	standard error of the mean
t	time
Q_t	dose fraction trapped inside a matrix

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