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Effect of the Drug–Excipient Ratio in Matrix-Type-Controlled Release Systems: Computer Simulation Study

Rafael Villalobos
UAM-Iztapalapa, Departamento de Química, Mexico City, Mexico
and
División de Estudios de Posgrado (Tecnología Farmacéutica), Facultad de Estudios Superiores Cuautitlán/UNAM, Cuautitlán Izcalli, Estado de México, Mexico

Adriana Ganem
División de Estudios de Posgrado (Tecnología Farmacéutica), Facultad de Estudios Superiores Cuautitlán/UNAM, Cuautitlán Izcalli, Estado de México, Mexico

Salomón Cordero
UAM-Iztapalapa, Departamento de Química, Mexico City, Mexico

Ana Maria Vidales
Departamento de Física, CONICET, Universidad Nacional de San Luis, San Luis, Argentina

Armando Domínguez
UAM-Iztapalapa, Departamento de Química, Mexico City, Mexico

ABSTRACT The main objective of this work is to study the drug release behavior from inert matrix systems by using computer simulation. This study allowed us to propose a new statistical method to evaluate the drug percolation threshold as a function of the exposed surface area of the device. The matrix system was simulated as a simple cubic lattice. The sites of the lattice were randomly occupied at various drug–excipient ratios. By simulating a diffusive process, the drug was delivered from the matrix system. The obtained release profiles were fitted to two different models: near the excipient percolation threshold, the square root of the time was well fitted, whereas close to (but above) the drug percolation threshold, the power law described accurately the release data. A relationship between the initial drug load and the amount of drug trapped inside the matrix system at infinite time was found. This relationship was conveniently described by an error function. Percolation thresholds in the matrix systems were determined from the latter relationship by using a nonlinear regression method. The assessment of percolation thresholds depends on the exposed surface area of the matrix systems. Moreover, estimated percolation thresholds were in agreement with the predicted values stated in the percolation theory.

KEYWORDS Percolation theory, Drug release, Matrix systems, Monte Carlo simulation, Anomalous diffusion

INTRODUCTION

A drug release profile from a delivery system has great impact over therapeutic effect. Matrix platforms are commonly used to manufacture sustained release dosage forms (Takada & Yoshikawa, 1999). The correct assessment of the mechanisms involved in the drug delivery from matrix systems becomes crucial in order to accurately predict release profiles, which help in the correct technological and biological design of the pharmaceutical devices. Different models were proposed to describe drug delivery from matrix systems. Among them, there are the diffusion equation (Crank, 1975), the

Address correspondence to Rafael Villalobos, UAM-Iztapalapa, Departamento de Química, Av. San Rafael Atlixco 186, Col. Vicentina, Mexico City 09340, Mexico; E-mail: yeccanv@yahoo.com

square root of the time law (Higuchi, 1963), and the power law (Peppas, 1985). The last two models are the most commonly used due to their simplicity (Costa & Sousa, 2001).

On the other hand, it was found that the percolation phenomenon greatly influences the release profile from matrix systems (Bonny & Leuenberger, 1993; Caraballo et al., 1994; Ehtezazi & Washington, 2000; Leuenberger et al., 1992; Yamane et al., 1998). A percolating system inherently forms a fractal structure, which exerts a strong effect over the release profile near the drug percolation threshold (pc1). The excipient percolation threshold (pc2) is useful to correctly design the mechanical properties of the dosage form. Leuenberger et al. (1992) have established that the concentration of a granular drug inside the matrix can be expressed as a site percolation probability, p. They found that the amount of drug released as a function of time Q(t) from one face of the tablet is proportional to t^k, where the exponent k directly depends on the percolation probability. When the values of pc1, pc2, and p are expressed as a function of the initial drug load, Q(t) follows one of the next behaviors: 1) p<pc1—in this scenario, only a few groups of particles are in direct contact with the tablet surface, thus, Q(t) reaches a constant value; 2) p≈pc1±0.1pc1—anomalous diffusion in three dimensions with $k \approx 0.2$; 3) pc1<p<pc2—normal matrix diffusion with k=0.5; and 4) pc2<p—zero-order release kinetics with k=1.

The latter shows the importance of the experimental assessment of the percolation threshold. Several methods were used to accomplish this task, among them, the most outstanding are based on electrical conductivity (Fernandez-Hervas et al., 1995; Siegmund & Leuenberger, 1999), mechanical properties (Leu & Leuenberger, 1993), and dissolution studies (Bonny & Leuenberger, 1991). Percolation threshold determined from drug release data is the standard method proposed by Bonny and Leuenberger (1991); this method uses the property β, which is obtained from the Higuchi equation. When β is related to the diffusion coefficient obtained from the scaling law, they found that

$$\beta = -c\varepsilon_c + c\varepsilon \qquad (1)$$

where ε is the porosity of the carcass, ε_c is the drug percolation threshold, and c is a constant. In this way, Eq. 1 allows for the assessment of ε_c. This last method was compared with experimental data and is consistent with the expected values from the percolation theory. However, this technique is restricted to drug release from only one face of the tablet and cannot be used if the release kinetic does not fit the Higuchi equation. Leuenberger et al. (1995) developed another method using the fraction of drug trapped in the matrix and relating it to the Bethe lattice equations. Nevertheless, this last technique can only be applied to this kind of lattice.

So far, computer simulation has successfully been used to study the drug release from two kinds of matrix systems: 1) systems near the drug percolation threshold (Bunde et al., 1985; Kosmidis et al., 2003a), and 2) systems with Euclidean structure (Kosmidis et al., 2003b). In this work, we study the drug release profiles from cubic lattices using different drug-excipient ratios. The main contribution of this work is the development of a new method derived from normal distribution elements, which makes possible the determination of the drug percolation threshold as a function of the exposed surface area of the device. Finally, we examine whether there is a transition zone going from typical Fickian release to an anomalous transport.

THEORY

According to percolation theory, if, in a lattice, a certain fraction of sites is occupied, in a random way, several aggregates of different sizes are formed (Sahimi, 1994; Stauffer & Aharony, 1994). Some of these aggregates will be connected to the external medium, while others will be trapped inside the lattice. In a drug–excipient matrix system, where the excipient is inert, let us designate Q_c as the fraction of drug connected to the external medium and Q_t as the fraction of drug trapped inside the insoluble carcass. Thus, the normalized amount of drug is

$$Q_t + Q_c = 1 \qquad (2)$$

Now, every drug particle connected to the exterior can be quantified by the amount of drug released at time equal to infinity (M_∞). If this last quantity is divided by the number of drug particles in the matrix at the

beginning of the experiment (N_0), then the fraction of drug connected to the exterior is obtained by

$$\underline{Q}_c = M_\infty / N_0 \tag{3}$$

and the fraction of drug trapped in the insoluble carcass is given by

$$\underline{Q}_t = 1 - \frac{M_\infty}{N_0} = 1 - \underline{Q}_c \tag{4}$$

Both $\underline{Q}_c$ and $\underline{Q}_t$ can be described as a cumulative probability. Then, $\underline{Q}_c$ represents the cumulative probability that a drug particle is connected to the exterior:

$$\underline{Q}_c = \int_0^\infty n_{sc} s ds \tag{5}$$

and $\underline{Q}_t$ represents the cumulative probability that one drug particle has no connection with the exterior medium:

$$\underline{Q}_t = \int_0^\infty n_{snc} s ds \tag{6}$$

where n_{sc} is the number of drug clusters of size s connected to the exterior, and n_{snc} is the number of drug clusters of size s not connected to the exterior. When the above cumulative probabilities are approximated to the cumulative probability of a normal distribution, the function describing $\underline{Q}_t$ has the following form

$$\underline{Q}_t = a + a\ \mathrm{Erf}[b(-\varepsilon_c + \varepsilon)] \tag{7}$$

where Erf is the function error, a and b are constant values associated with the process, ε represents the initial drug load, and ε_c represents the drug percolation threshold. On the other hand, the change in the connected amount of drug with respect to the initial amount of drug ($d\underline{Q}_c/d\varepsilon$) is obtained by deriving Eq. 7:

$$\frac{d\underline{Q}_t}{d\varepsilon} = -\frac{2ab}{\sqrt{\pi}} e^{[-b^2(-\varepsilon_c+\varepsilon)^2]} \tag{8}$$

This last Gaussian distribution has a point at which $d\underline{Q}_t/d\varepsilon$ is a maximum. At this point, the percolating cluster is formed, i.e., the drug percolation threshold. This maximum of $d\underline{Q}_t/d\varepsilon$ corresponds to the inflection point of Eq. 7, that is, $-\varepsilon_c+\varepsilon=0$. So, the percolation threshold can be easily determined by plotting the amount of drug trapped at time equal to infinity versus the initial amount of drug inside the matrix. The correct analysis of the latter data by a nonlinear regression of Eq. 7 also makes it possible to assess the values a, b, and ε_c.

METHODS

The matrix system is represented as a cubic lattice with 27^3 sites. Thus, the idealized tablet is a conglomerate of sites of the same size. The matrix is simulated as a binary system composed by a drug (water soluble) and excipient (inert, nonsoluble material). The sites are randomly occupied either by isometric spherical particles of drug or excipient, according to given proportions of drug and excipient. The initial porosity is considered equal to zero, and double occupation is excluded. The excipient is considered as an inert material, so the carcass does not change as a function of time. The diffusive process is simulated by a random walk algorithm (Bunde et al., 1985; Stauffer & Aharony, 1994). In this way, a site occupied by drug is randomly chosen, then, one of its nearest neighbor sites is chosen at random. If the chosen neighboring site is empty, then the drug particle moves to this new site; if it is not empty, then the movement is rejected. This sequence of steps is repeated until the drug particle reaches a site at the exposed surface, where it becomes part of the dissolution medium. At this point, we assumed sink conditions, so the drug release is not limited by solubility. After each trial, the time is increased by a value equal to $1/N_t$, where N_t is the number of drug particles remaining inside the matrix when the time is equal to t. Every N_t trials constitute an elapsed time equal to one Monte Carlo step (MCS), the unit of time. This is a standard method to consider time in a Monte Carlo process (Bunde et al., 1985; Kosmidis et al., 2003b; Sales et al., 1996), which may eventually correspond to a real time unit (Kosmidis et al., 2003b). In this source, they tried to relate the mean free path with the drug diffusion coefficient to get the mean free time, a concept close to one MCS. The time and the amount of drug released are recorded at every moment. Different ratios of drug–excipient were studied. The release kinetics through two opposite faces (one-dimensional) and through the total exposed surface area of the lattice are also studied. Finally, the simulations of the cubic lattices and the diffusive processes taking place therein were

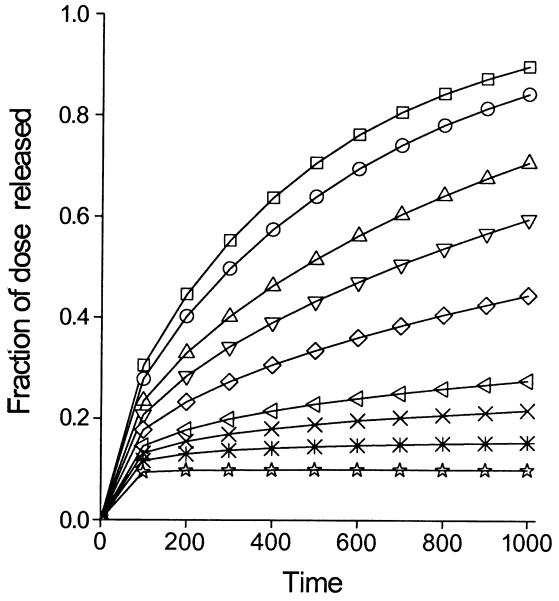

FIGURE 1 **Release Profiles from Cubic Lattices Through Two Opposite Faces, with Different Initial Drug Load (C_0). (□) $C_0=1.00$; (○) $C_0=0.85$; (△) $C_0=0.65$; (▽); $C_0=0.55$; (◇) $C_0=0.45$; (◁) $C_0=0.35$; (×) $C_0=0.31$; (*) $C_0=0.25$; (☆) $C_0=0.15$.**

implemented with a program written in ANSI C++ code, and simulations were performed in a PC with an AMD athlon processor and 512 MB RAM. The program simulation was run in the compiler Borland C++ version 5.0A.

RESULTS AND DISCUSSION

The drug release profile from a cubic network (exposing only two opposite faces) as a function of initial drug load is shown in Fig. 1. This profile is associated with two factors: 1) initial drug load in the network and 2) the barrier generated by increasing the fraction of excipient. When the fraction of dose released was related to the square root of the time, a slightly sigmoid behavior was observed; however, when a linear regression was made, we found a good fit to this model for systems with initial drug load from 0.45 to 1.0 (see Table 1). However, we observe that the fit is not good as the initial drug load is diminished. When the initial drug load was 0.35, the squared correlation coefficient of $\sqrt{t}$-evaluation was 0.9617, so it is no longer in agreement with the $\sqrt{t}$-model. At this concentration, the system is close to the drug percolation threshold, ε_c=0.3116 (Stauffer & Aharony, 1994), it means that a great extent of the initial drug load belongs to the percolation cluster. This cluster has a fractal structure, which means that the system is macroscopically nonhomogeneous, so the relation of the square root of the time is not suitable at this point.

The computed power law exponents are shown in Table 1: a linear behavior was observed for all systems with initial drug load greater than the drug percolation threshold. Below the drug percolation threshold, the behavior is not linear. The above mentioned is associated with the fact that only a fraction of the initial drug load is able to leave the system through the ramifications created by the drug itself. Drug particles without communication with the exterior cannot come out, in such a way that the entire connected drug is gradually released, and finally, the fraction of dose released becomes constant. Values for the exponent n close to 0.5 were found in systems with initial drug loads between 0.55 and 1—this implies that the release of these systems is Fickian. In the systems with initial drug loads less than 0.55, the exponent associated with the time moves away from 0.5, and it corresponds to an anomalous diffusion according to the classic analysis of diffusion (Peppas, 1985). The

TABLE 1 **Evaluation of Dissolution Data (Two Opposite Faces)**

	$\frac{M_t}{N_0}=a_H+K_H\sqrt{t}$		$\frac{M_t}{N_0}=a'+b't^n$	
Drug content	K_H	r^2	n	r^2
1	0.033	0.9991	0.57	0.9983
0.85	0.029	0.9999	0.52	0.9997
0.65	0.023	0.9997	0.49	0.9999
0.55	0.019	0.9986	0.46	0.9999
0.45	0.012	0.9977	0.40	0.9997
0.35	0.008	0.9617	0.29	0.9967
0.31	0.005	0.8613	0.20	0.9970
0.25	0.004	0.8336	0.09	0.9652
0.15	0.002	0.8059	0.04	0.9536

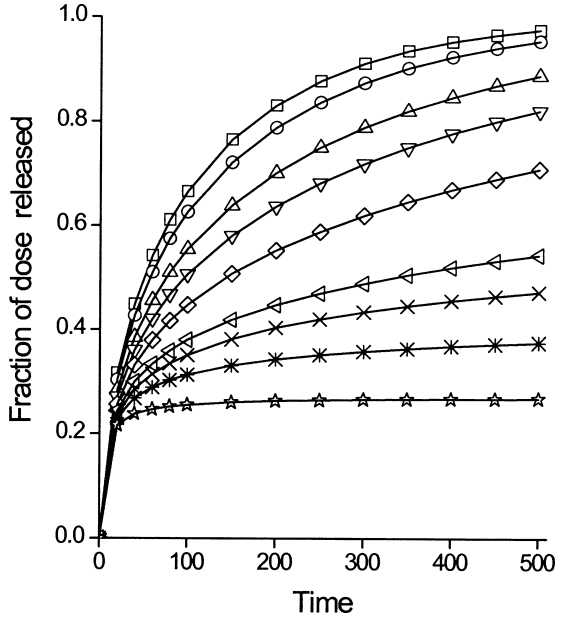

FIGURE 2 **Release Profiles from Cubic Lattices Through Their Total Area, with Different Initial Drug Load (C_0). (□) C_0=1.00; (○) C_0=0.85; (△) C_0=0.65; (▽); C_0=0.55; (◇) C_0=0.45; (◁) C_0=0.35; (×) C_0=0.31; (*) C_0=0.25; (☆) C_0=0.15.**

previous results can be explained as a function of the formed structures. For concentrations between 0.55 and 1, a diffusive behavior is followed, although clusters of excipient begin to appear. As these systems are well above the drug percolation threshold, the size of the network is greater than the size of these clusters of excipient, so the matrix structure as a whole behaves as a macroscopically homogeneous system (Sahimi, 1994), and the presence of the excipient only drags the diffusion. Nevertheless, as the drug–excipient ratio comes closer to the drug percolation threshold, clusters of excipient with a size similar to the total size of the network are formed. Therefore, the drug molecules diffuse in a structure macroscopically nonhomogeneous, generating in this way an anomalous diffusion.

The release profiles from cubic lattices through their total surface area are shown in Fig. 2. As expected, when the total area of the matrix is exposed, the release is faster than when the release occurs through only two opposite faces. Data were analyzed by means of the equation of the square root of the time. A good fit to this model was observed when the initial drug load was greater than or equal to 0.65. However, at lower concentrations, the square root of the time model does not successfully describe the drug release profile (see Table 2). Applying the power law model, a better fit to the release profile was observed, although, it is necessary to emphasize that the model was applied fitting data up to the point when 60% of the release was completed. Beyond this percentage, the model overestimates the fraction of dose released. The exponents associated with the time in the power law model for the initial drug loads between 0.65 and 1.0 were close to 0.5. These results confirm what we previously mentioned in the sense that the square root of the time describes successfully the release profile from these matrix systems at these initial drug loads. On the other hand, it was found that systems with initial drug load less than or equal to 0.55 present release exponents associated with an anomalous transport. The value of the exponent decreases as the drug load falls (see Table 2). As the initial drug load decreases, the fraction occupied by the insoluble carcass (excipient) is increased, making the drug diffusion through the matrix system more difficult, with the consequent decrease in the release rate, which is reflected in the decrease of the exponent associated with the time in the power law. Finally, when the

TABLE 2 **Evaluation of Dissolution Data (Total Area)**

	$\frac{M_t}{N_0} = a_H + K_H\sqrt{t}$		$\frac{M_t}{N_0} = a' + b' t^n$	
Drug content	K_H	r^2	n	r^2
1	0.070	0.9979	0.48	0.9987
0.85	0.064	0.9973	0.48	0.9965
0.65	0.049	0.9912	0.43	0.9993
0.55	0.044	0.9809	0.39	0.9955
0.45	0.032	0.9617	0.32	0.9983
0.35	0.014	0.9085	0.23	0.9952
0.31	0.007	0.7751	0.17	0.9900
0.25	0.005	0.5636	0.11	0.9693
0.15	0.004	0.3674	0.07	0.7811

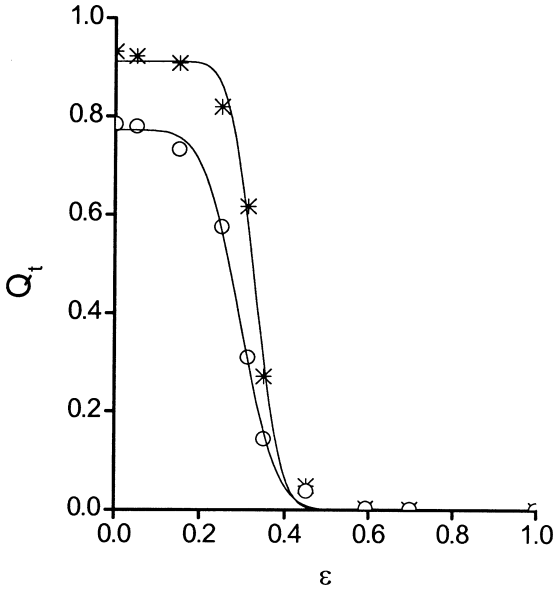

FIGURE 3 **Fraction of Dose Trapped in the Matrix (Q_t) vs. the Initial Drug Load, Exposing Different Area. Numerical Results, Dots, and Their Fitting by Means of Eq. 7, Solid Line. Two Opposite Exposed Faces (*), and Total Area Exposed (○).**

initial drug load is low (less than 0.3), only a small fraction of the dose is connected with the external medium, and thus, the release profile reaches a constant value.

A pharmaceutical system fitting the assumptions of our model was studied by Bonny and Leuenberger (1991). They performed experiments on the release of caffeine (as a water-soluble drug) from a matrix of ethyl cellulose (nonswelling water-insoluble excipient). In this study, the release exponent n ranges from 0.17 to 1.09 for matrices with initial drug load from 10 to 100% w/w, respectively. Around the drug percolation threshold, an anomalous transport was found, evidenced by an exponent, n, close to 0.3. Furthermore, a Fickian release was observed when the drug–excipient ratio formed a bicoherent system, i.e., between 40 and 60% w/w. Our results agree with these findings. Nevertheless, Bonny and Leuenberger (1991) found a zero-order release kinetics (i.e., n tends to 1) for high initial drug loadings (above the excipient percolation threshold). This behavior corresponds to the release of a drug from a solid, decreasing its volume, but with a constant exposed surface area, generating in this way a constant drug release as a function of time. In our case, we did not find values of n close to 1 when ε tends to 1, because an erosion process was not considered, i.e., in our work, when ε is close to a unit, drug release was simulated from a homogeneous matrix system without volume change.

By means of computer simulations, the amount of drug released at infinite time (M_∞) was also calculated. We consider M_∞ as the amount of drug released to the environment when MCS=100,000. From these results, the amounts of drug trapped in the matrix when exposing a fraction of area and when exposing the total area of the matrix were determined (Fig. 3). In Fig. 3, it is observed that in both cases, the amount of trapped drug moves from zero to a maximum value as the initial drug load inside the matrix goes down to zero. The amount of drug trapped as a function of the initial drug load was subjected to a nonlinear regression according to the model represented by Eq. 7. A square of the multiple correlation coefficient of 0.9982 was obtained (exposing the total area), and 0.9958 was obtained when only two faces were exposed. These values indicate that the model reproduces our results quite well (see Fig. 3). When the total area of the device is exposed, the fitted equation has the following form:

$$Q_t = 0.386 + 0.386\ \mathrm{Erf}[-10.269(-0.293 + \varepsilon)] \quad (9)$$

In this way, the estimated value of the percolation threshold was 0.293 (standard error=0.003). The difference between this value and the reported value of 0.3116 (Stauffer & Aharony, 1994) is due to the

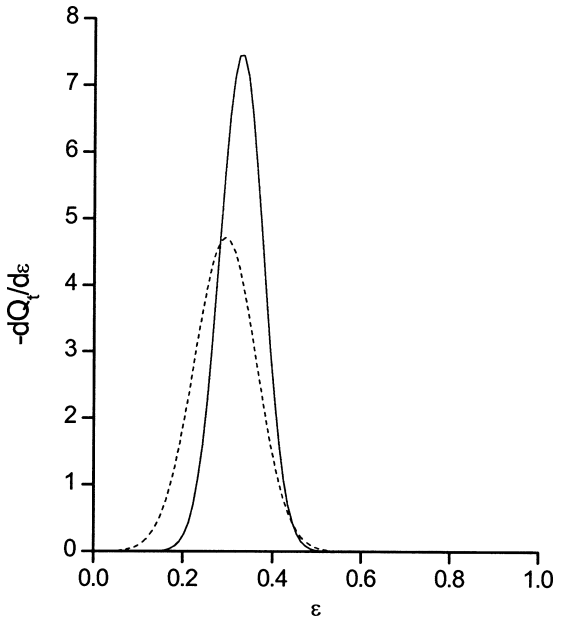

FIGURE 4 **Rate of Dose Trapped with Respect to the Initial Drug Load in the Matrix ($dQ_t/d\varepsilon$). Exposing Two Opposite Faces, Solid Line. Exposing the Total Area, Dotted Line.**

finite matrix employed here. By deriving the previous equation, we find that the change of the trapped amount with respect to the initial drug load is given by

$$\frac{dQ_t}{d\varepsilon} = -4.518e^{[-105.457(-0.293+\varepsilon)^2]} \qquad (10)$$

The curve described by this equation is presented in Fig. 4. For high initial drug content (above 60%), practically all the drug molecules are connected among them, so the trapped amount and its variation are almost zero. Subsequently, as the initial drug load inside the matrix decreases, the fraction of excipient increases, and finite clusters of drug begin to be trapped by the insoluble carcass. For an even lower drug load (but greater than the drug percolation threshold), the amount of trapped drug continues to increase, as well as its reason for change ($dQ_t/d\varepsilon$). In the vicinity of the drug percolation threshold, the maximum variation of the trapped amount versus the initial drug load was observed. This behavior must be associated with the geometric transition of the matrix at that point. Before the drug percolation threshold is achieved, finite clusters of drug are dispersed, but when the network is just percolated, the dispersed clusters get together, i.e., a continuous cluster between the ends of the matrix is formed, generating in this way an abrupt change in the value of Q_t. This transition is better observed in the curve of $dQ_t/d\varepsilon$, because the last one becomes a maximum at this point of geometric change (see Fig. 4). At low initial drug concentrations ($\varepsilon < 0.3$), the amount of trapped drug presents a plateau (c.f., Fig. 3), which finally reaches a maximum value as the drug load moves to zero. This limit of trapped amount can be determined theoretically as follows: when there exists only one drug particle inside the network, the trapped amount is the probability that this drug particle is connected with the exterior. In our network, the total number of sites is 27^3, and among these sites, 4058 are located on the surface. Therefore, if only one drug particle exists inside the network, the probability that this drug particle is in some superficial place is equal to 4058/19683. This means that the fraction of drug connected to the external medium is equal to 0.206, then Q_t=0.794. The value 0.794 is close to 0.784, i.e., the value that we obtained by means of simulation. Similar behavior is observed for the case of the release through two opposite faces: the expected value of Q_t is 0.926, which is very close to 0.931, the value obtained by computer simulation.

When only two opposite faces of the matrix were exposed, and using the previous methodology, a value of 0.328 was found for the percolation threshold with respect to the initial drug load (standard error=0.003). From the case mentioned above, it comes out that the trapped amount is a function of the exposed surface area of the matrix system. This is due to the fact that the number of cavities connected with the exterior is in a direct relationship with the exposed surface. On the other hand, the increase of the percolation threshold when only two faces are exposed can be explained by a decrease of the percolation probability, because the system has only one direction in which to form a continuous cluster. On the contrary, when the total surface area of the matrix is exposed, the network system has three directions (x,y,z) to form the percolating cluster. Therefore, more initial drug load is required to compensate for the decrease in the percolation probability in one direction.

In Fig. 4, it is shown that $dQ_t/d\varepsilon$ suffers a greater change around the percolation threshold when only a fraction of the total surface area of the matrix is exposed than when the total area of the system is exposed. This is because, below the drug percolation threshold, the clusters of drug have a higher probability of being on the surface when exposing the total surface area of the system than when only one fraction is exposed. In this way, Q_t increases gradually when exposing the total surface area of the matrix; therefore, $dQ_t/d\varepsilon$ presents a less abrupt change around the percolation threshold. When only a fraction of the total surface area of the matrix is exposed, the probability that isolated clusters are located on the surface is low. However, around the percolation threshold, when these isolated clusters begin to be connected, Q_t diminishes quickly. This generates higher values of $dQ_t/d\varepsilon$ than the analogous values found when only a fraction of the matrix surface area is exposed.

In spite of our matrix system being an idealized model, some reported drug percolation thresholds determined experimentally agree with our results. For example, in Bonny and Leuenberger (1991, 1993) and Caraballo et al. (1999), determined drug percolation thresholds were close to the theoretical value of

random site percolation in a simple cubic lattice. On the other hand, there are some works that demonstrated that the size ratio of drug–excipient modifies the percolation threshold (Caraballo et al., 1996; Millan et al., 1998). However, for matrix systems corresponding to a drug–excipient size ratio equal to one, i.e., matrices formed with drug particles and excipient particles with similar size, drug percolation thresholds very near to the threshold value predicted by random percolation in a simple cubic lattice were found. These findings are in agreement with our numerical results. Besides, these authors (Caraballo et al., 1996; Millan et al., 1998) reported that the higher the drug–excipient size ratio is, the higher the drug percolation threshold. They also claimed that this could be explained by a correlated percolation process, where the lattice sites are no longer occupied at random. Therefore, now these are occupied in a preferential way according to certain parameters (e.g., particle size), producing spatial correlations between the elements that conform to the matrix system.

CONCLUSIONS

A Monte Carlo method allowed us to mimic drug release from an inert matrix-type-controlled release system for initial drug dose in the range from 0.15 to 1.0 fraction v/v. This simulation can generate useful results independent of the shape of the matrix, as well as of the exposed surface area. The obtained results showed how device structure changes can affect both kinetics and final yield of the drug release from these kind of systems. The observed behavior can be explained by the concepts of percolation theory, i.e., it was found that the drug spatial distribution in these systems is associated with the random percolation phenomenon. The drug–excipient ratio determines the matrix structural properties and controls the drug release profile. Close to the excipient percolation threshold, the drug release process is carried through a macroscopically homogeneous matrix (nonfractal), and in this zone, the square root of the time can be used to describe the release profile. Later, diminishing the initial drug load, the matrix enters a transition zone (prefractal) until arriving at the drug percolation threshold (fractal structure, the matrix is macroscopically nonhomogeneous), and in this case, the power law fit the found release profiles well.

Furthermore, a new method to estimate the drug percolation threshold is presented. This method has no assumption about drug release kinetics and is capable of estimating the drug percolation threshold as a function of the exposed surface area of the matrix device. It was found that the amount of drug trapped by the matrix (carcass) is a function of both the initial drug load in the matrix as well as the exposed surface area of the matrix. The amount of drug trapped in the matrix was well described by the error function, making it possible to establish the drug percolation threshold. This function can be very useful to describe the bioavailability of a matrix-type-controlled release system with a certain initial drug dose. Special care should be taken when a percolation threshold is reported, given that the drug percolation threshold is a function of the exposed surface area of the device. If in a release experiment only a fraction of the total area of the device is exposed, the obtained percolation threshold will not correspond to the value obtained when the total surface area of the matrix is exposed. Attention should be paid to this point, especially when in vitro studies are carried out with controlled area versus in vivo performance, where the total area of the matrix device is commonly exposed.

These findings can be valuable in the rational design of matrix-type-controlled release dosage forms. In fact, the modeling of drug release from delivery systems is important in understanding and elucidating the transport mechanisms, and it allows us to predict the effect of the device design parameters on the drug release rate and final yield.

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