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Monte carlo simulation of diffusion-limited drug release from finite fractal matrices

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Abstract How fast can drug molecules escape from a controlled matrix-type release system? This important question is of both scientific and practical importance, as increasing emphasis is placed on design considerations that can be addressed only if the physical chemistry of drug release is better understood. In this work, this problem is studied via Monte Carlo computer simulations. The drug release is simulated as a diffusion-controlled process. Six types of Menger sponges (all having the same fractal dimension, $d_f = 2.727$, but with different values of random walk dimension, $d_w \in [2.028, 2.998]$) are employed as models of drug delivery devices with the aim of studying the consequences of matrix structural properties (characterized by d_f and d_w) on drug release performance. The results obtained show that, in all cases, drug release from Menger sponges follows an anomalous behavior. Finally, the influence of the matrix structural properties on the drug release profile is quantified.

Keywords Menger sponge · Drug release · Fractal dimension · Random walk dimension · Monte Carlo simulation · Anomalous diffusion.

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Introduction

An ideal drug release system provides a controlled amount of medication over an adequate period of time without any adverse interaction with healthy tissue. This definition applies to drug release devices that are implanted or inserted in the vicinity of the target tissue [1]. The modeling of drug release from delivery systems is important to understand and elucidate the transport mechanisms that are taking place, and allows the effect of the device design parameters on the drug release rate to be predicted, which determines the effect on the target tissue [2]. Hence, the development of new biomedical and pharmaceutical products is greatly facilitated because the desired release kinetics can be predicted in advance and thus can be more readily achieved [3]. This may provide a valuable decision making tool in pharmaceutics and other related fields, when facing the dilemma of whether one should invest in expensive micro or nano sol-gel technology, in order to achieve controlled release. Sol-gel devices are important when trying to decrease the size of drug release devices. Frequently, real delivery systems are matrix platforms with fractal geometry, as revealed [4] by techniques such as mercury porosimetry where experimental data are interpreted to determine the fractal dimension of a porous body. A tablet consisting of both a soluble and brittle drug (caffeine) and a non-swelling water insoluble polymer (ethyl cellulose), becomes porous during drug release. A leached and subsequently dried tablet represents, in a narrow range of resolution, a sponge-like structure. The distribution of pores corresponding to the original sites occupied by caffeine particles has been related to the fractal dimension of monolithic devices. Furthermore, it has been found that the fractal dimension of the porous tablet resulting from a fixed mixing ratio depends on the particle size of the soluble substance and, in all cases, the value of d_f was in the range

(2.733−2.838). Therefore, fractal structures are helpful models of drug delivery devices such as the Menger sponge, which is characterized by $d_f = 2.727$ (which is very near to the experimental d_f values).

The Menger sponge has been used as a model of matrix dosing system (see for example [4, 5]). In this work, drug release is simulated by a diffusion-controlled process (random walk). Six different types of Menger sponges, *i.e.* six fractal porous structures having the same fractal dimension, $d_f = 2.727$, but different values of the random walk dimension, $d_w \in [2.028, 2.998]$ ([6] and references therein) are used as models of porous solid dosing systems, with the aim of elucidating the effect of the structural properties of the porous matrix (d_w) on drug release behavior.

Some drug release kinetic equations

In spite of the complexity of the phenomena involved in drug release mechanisms, three equations have been proposed and are currently employed for describing experimental drug dissolution profiles, *i.e.* the amount of drug released as a function of time [7]. These equations are:

(i) The Higuchi equation,

$$\frac{M_t}{M_\infty} = k\sqrt{t} \tag{1}$$

where M_t and M_∞ are the amounts of drug released at times t and infinity, respectively, and k is the Higuchi dissolution constant;

(ii) The Peppas equation or the so-called power law,

$$\frac{M_t}{M_\infty} = Kt^n \tag{2}$$

where K is an experimentally determined parameter, and n is a real number related to the structure of the drug releasing system;

(iii) The Weibull equation,

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

where a and b are real numbers; a defines the time scale of the process and b characterizes the shape of the kinetic curve. 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 drug release. Furthermore, this equation is consistent with the theoretical predictions obtained under the framework of classical fractal kinetics.

A drug release problem can be seen as a study of the kinetics of the reaction $A + B \rightarrow C$ [8], where A represents traveling particles while B and C are regarded as static particles; the above scheme portrays the well known trapping problem [6]. In this approach, there exist three key dimensions: d_f, d_w, and the *fracton dimension*, d_s. The last parameter takes into account the way by which a diffusing molecule "sees" the heterogeneities present in the porous medium during its random walking transit, and is related to d_w and d_f by:

$$d_s = 2d_f / d_w \tag{4}$$

It is pertinent to note that there are two important differences between the drug release problem and the classical trapping problem:

I. During drug release, the traps are not randomly distributed throughout the porous medium. Instead, they are mainly located at the device boundaries. In fact, the boundary fraction, which is part of the embedded drug clusters, constitutes the trap sites.

II. During trapping, the porosity of the system, ε, is not changing greatly, whereas in drug release the porosity of the tablet changes notably. It is then expected that $d_s > d_s^*$, where d_s^* is the *fracton dimension* of the drug release problem.

In this work, Monte Carlo simulations, based on the random walk model for Fickian diffusion with excluded volume interactions, are used to study the consequences of these fractal dimension differences on the drug delivery profile and to reexamine the release problem from the point of view of a fractal kinetics framework.

Methodology

Menger sponges are a special class of three-dimensional fractals ($d_f = 2.727$) [5]. Figure 1 demonstrates the generation procedure of Menger sponges. The construction of these substrates begins with a solid cube and involves an iterative process involving the removal of different parts of this initial cube. Let us label as CMS_0 our initial cube. Then, CMS_1 will be generated by partitioning CMS_0 into 27 identical cubes and taking out the central cube as well as the 6 cubes that are located at the middle of each face of CMS_0 (*c.f.* Fig. 1). Next, CMS_2 will be constructed by repeating the same process for each of the cubes constituting CMS_1. In this way, a nested sequence of configurations, CMS_i, can be produced, whose intersection should become the limiting sponge, CMS_∞. CMS_∞ is then a self-similar fractal known as the classical Menger sponge. Each of the particular Menger sponges built in this work are generated after performing three of these partitioning iterations ($i = 3$). To build the diverse sponges, the seven sub-cubes removed in each iteration are (the position vectors (x, y, z) correspond to
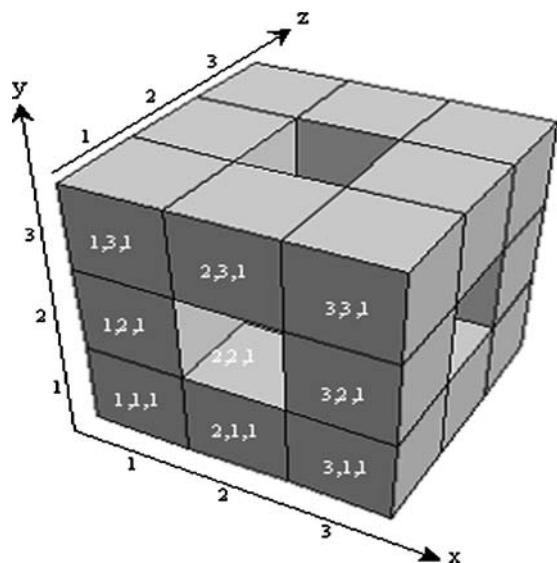
Fig. 1 Illustration of the classical Menger sponge generator, and the axes of the vectors position.

the axes shown in Fig. 1): (i) (1,3,2), (1,3,3), (2,1,3), (2,2,1), (2,2,2), (2,3,1), (3,2,2) for substrate *AMS*, (ii) (1,1,3), (1,2,2), (1,3,1), (1,3,2), (1,3,3), (2,3,1), (3,2,3) for substrate *BMS*, (iii) (1,2,2), (2,1,2), (2,2,1), (2,2,2), (2,2,3), (2,3,2), (3,2,2) for substrate *CMS*, (iv) (1,2,2), (1,3,1), (1,3,2), (2,3,3), (3,1,2), (3,1,3), (3,3,2) for substrate *DMS*, (v) (1,1,1), (1,2,2), (2,1,2), (2,2,1), (2,2,3), (2,3,2), (3,2,2) for substrate *EMS*, and (vi) (1,2,2), (2,1,1), (2,1,2), (2,2,1), (2,2,3), (2,3,2), (3,2,2) for substrate *FMS*.

The drug dissolution algorithm can be summarized as follows:

I. The sponge is generated from a lattice consisting of $27 \times 27 \times 27$ sites, and after the third iteration, each site is either saturated with drug (if this site is forming part of the porous volume) or excipient (if the site forms part of the solid body). If drug is held in a site, this site is called a *drug particle*,

II. The drug particles are allowed to move throughout the porous space according to the random walk model (*i.e.* according to a "blind ant" routine [10]), and

III. Excluded volume interactions between the drug particles are assumed.

The release process attempts to mimic the leaking of drug particles from a tablet, when this substrate (which is constituted by both drug and excipient particles [11]) is placed in contact with a solvent phase. The diffusion of drug molecules from the substrate is simulated by selecting a drug particle at random and attempting to move it randomly to any one of its adjacent sites. If the chosen site is already occupied (by either another drug or excipient particle) the movement is rejected, but if the neighboring site is empty the movement is accepted. The drug particles can finally exit the tablet when

they reach a site located at the border of the sponge. After each drug movement (either successful or not) the time is incremented by a value equal to $1/N$, where N is the number of total drug particles remaining into the matrix [2, 9]. The number of particles remaining in the matrix is monitored as a function of time until only 10% of the drug particles remain inside the matrix. The release rate, dQ/dt, is monitored by counting the number of particles that diffuse from the escaping area (i.e. from the six faces of the sponge) in the interval between t and $t + 1$.

Diffusion can be studied by means of a random walk routine [10, 12]. Our particular routine considers a drug particle undergoing nearest-neighbor random site displacements [11] in each one of the previously described Menger sponges. The porous space of the Menger sponges is considered empty (there are no drug particles) and the sponge structure is repeated in all directions to render a homogeneous structure of a sufficiently large length. Then, a walking drug element is released at a randomly chosen site and the distance traveled is measured at time intervals corresponding to $t = 10k$, $k \in \{1, 2, 3, \dots\}$. The mean square distance $\langle r^2 \rangle$ traveled by the walking drug element is averaged over 1000 different walks. In this case, the time unit corresponds to one Monte Carlo step (i.e. a number of walking attempts equal to the total number of sites). In fractal bodies, diffusion becomes anomalous (i.e. non-Fickian) and is consistent with the law $\langle r^2 \rangle \propto t^{2/d_w}$, where $d_w > 2$, thus implying a sub-diffusive behavior. Initially, the walking drug element "sees" a fractal structure as long as it is confined within a distance close to the size of the sponge (27 in our case); therefore diffusion is anomalous since $d_w \neq 2$. For longer times, however, the walking drug element traverses the entire sponge and diffusion becomes normal. The d_w value is determined in this work from the linear fit of $\log \langle r^2 \rangle$ against $\log t$ for $\langle r^2 \rangle \in (0.00, 182.225)$.

Results and discussion

In Table 1 the calculated d_w values are presented. Their relative error, *r.e.*, is bounded by 0.005. In this way, we have achieved 3D fractal structures with $d_f = 2.727$, which is a plausible drug dosing value. Additionally, d_w values cover the range $d_w \in (2.02, 3.00)$. Another useful parameter is $\frac{N_{leak}}{N_{total}}$, where N_{leak} denotes the number of drug escaping sites and N_{total} is the total number of sites. The M_t/M_0 (drug release fraction) values corresponding to the various Menger sponges are shown in Fig. 2 as function of time. Note that porous structures, having the same fractal dimension but endowed with different topological properties, render different release profiles. In addition, this figure shows fitted lines (according to Eq. (3)) for each data set.

Table 1 Drug release parameters corresponding to Menger sponges, $d_f = 2.727$ Delivery occurs through the six cube faces

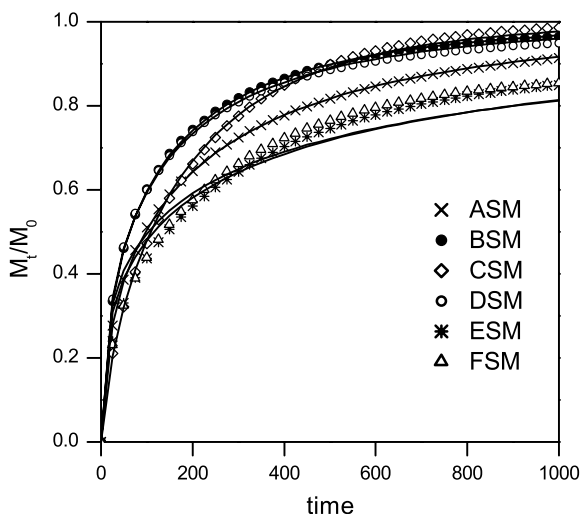| Sponge	$\frac{M_\infty}{M_0}$	d_w	$\frac{N_{leak}}{N_{total}}$	a	b	d_s^*	d_s
ASM	0.962	2.455	0.107	0.056	0.548	0.938	2.222
BSM	0.985	2.194	0.132	0.064	0.575	0.878	2.486
CSM	1.000	2.028	0.066	0.020	0.759	0.398	2.689
DSM	0.971	2.366	0.133	0.071	0.552	0.974	2.305
ESM	0.896	2.761	0.092	0.048	0.540	0.985	1.975
FSM	0.866	2.998	0.083	0.041	0.572	0.979	1.819

Fig. 2 Drug release from Menger sponges. Symbols represent numerical results, while solid lines show the fitting of these data through the Weibull equation.

Table 1 lists the estimated a, and b Weibull values. The relative errors, *r.e.*, are 0.02 for a, and 0.005 for b. Overall, there exists a very good agreement between the plotted data and the predicted behavior advanced by Eq. (3). This means that drug release from finite Menger sponges can be well represented by the Weibull equation. Also note the differences among the diverse M_∞/M_0 values, Table 1. Here $\infty = 10^5$ Monte Carlo steps. The dissimilar amounts of drug entrapped inside the blind porosity (i.e. pores which are not connected to the exterior) of each sponge is responsible for these differences.

The a and b parameters are related to the structural properties of the matrix platform. As mentioned elsewhere ([9]), the values of a and $\frac{N_{leak}}{N_{total}}$ obey a linear relationship. In our case, this expression has the following form:

$$a = -0.017 + 0.651\, N_{leak}/N_{total} \tag{5}$$

Notice that the independent term (-0.017) is quite small with respect to the dependent term (0.651), and thus the value of a is mostly determined by the $\frac{N_{leak}}{N_{total}}$ ratio; therefore we may conclude that $a \propto N_{leak}$ since $\frac{N_{leak}}{N_{total}} \propto N_{leak}$ [9]. In contrast,
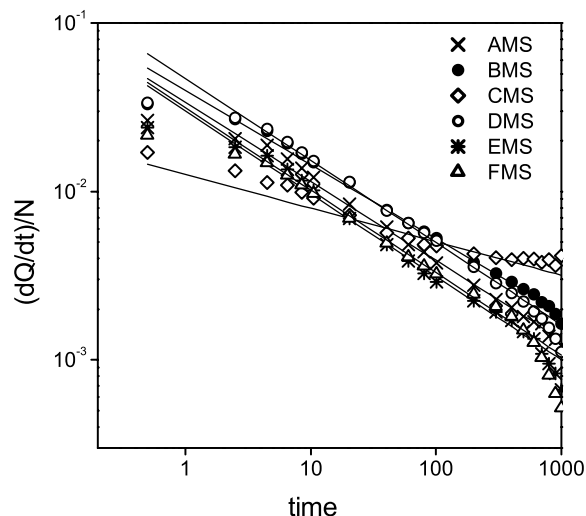

Fig. 3 Determination of d_s^* values. Symbols represent numerical results, while solid lines show the fitting of these data.

our results show no linear relationship between b and $\frac{N_{leak}}{N_{total}}$. The b values can have two contributions: (i) b should be proportional to the specific surface area of the matrix, since a high value for this parameter means that there are many exits for drug escape; and (ii) b should be a function of the ability of the drug particles to travel inside the matrix platform.

The values of d_s^* are calculated [6] from the slopes of the $\log((dQ/dt)/N(t))$ vs. $\log t$ curves plotted in Fig. 3 [8]. The d_s^* values are presented in Table 1, and are very different to those computed from Eq. (4). As mentioned earlier, the reasons for this difference are the spatial segregation of the leaking sites and the dynamic behavior of the porosity value. It is found that b has a linear dependency on d_s^*:

$$b = 0.907 - 0.374 d_s^* \tag{6}$$

Equation (6) clearly shows that b is truly related to the transport properties of the drug delivery system.

Conclusion

Drug release from Menger sponges is characterized by a non-Fickian behavior. Nevertheless, this abnormal process can be described in terms of a Weibull equation, in which the device surface is defined by Weibull's a value while the device transport properties are defined by Weibull's b value.

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