Coarse-Grained Simulations of Diffusion Controlled Release of Drugs from Neutral Nanogels: Effect of Excluded Volume Interactions.

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Abstract.

The primary goal of this work is to assess the effect of excluded volume interactions on the diffusion controlled release of drug molecules from a spherical, neutral, inert and cross-linked device of nanometric size. To this end, coarse-grained simulations of the release process were performed. In this way, the inner structure and topology of the polymer network can be explicitly taken into account as well. Our *in silico* experiments reveal that the boundary condition of constant surface concentration is not appropriate for nanogels. In particular, the predictions based on the perfect sink condition clearly overestimate the fraction of drug released. In addition, these simulations provide values for the release exponent that depends on both the diameter of drug molecules and the number of drug molecules loaded in the matrix, which clearly contrasts with the classical prediction of a constant release exponent. Consequently, the widely used classification of drug release mechanisms based on this kinetic exponent must be extended to include new situations.

KEY WORDS: drug release; coarse-grained simulations; Fickian diffusion; diffusion controlled release.

INTRODUCTION.

Nanogels are nanometer-sized particles consisting of a cross-linked polymer network with the ability to swell in thermodynamically good solvents.[1] Their low size and their capability to swell or shrink depending on many external stimuli such as temperature, pH, salt concentration or solvent nature, make them very attractive for biomedical applications and, in particular, for controlled release of drugs.[2–11] With regards to the nature of the release mechanism, it can be distinguished three main categories: diffusion-controlled, swelling-controlled and chemically-controlled release.[12] In diffusion-controlled release, the polymeric chains of the crosslinked network provide a steric obstacle to the drug molecules to be delivered, which reduces its diffusion coefficient. In swelling-controlled release, drug molecules are initially immobilized in the shrunken network and their rapid diffusion occurs in the swollen nanogel. Finally, in chemically-controlled release, drug molecules are released from the nanogel network because of chemical reactions in the matrix. Nevertheless, this is only an ideal classification because, in practice, it is usual to find a combination of the above mentioned release mechanisms.

In this work, we restrict ourselves to diffusion-controlled release, whose evolution in time can be mathematically computed from solutions of Fick's law of diffusion provided that the diffusion coefficient of the solute inside the gel is known.[13,14] In practice, however, different empirical equations have been commonly employed in the development of new pharmaceutical products to fit release curves and obtain parameters that characterized the mechanisms involved. Predominant among these are the Peppas law and the Weibull function[15]. The first one provides the value of an exponent *n* that depends on both the geometry of the systems and the release mechanism[16,17]. Unfortunately, the values of

these parameters are unknown a priori and they can change from case to case, which does not contribute to improve our capability of prediction.

In this framework, computer simulations have been proposed as a useful tool to understand and predict release profiles of drugs due to its capacity to carry out a systematic and independent analysis of each type of release mechanism. Therefore, computer simulations (also known in this field as *in silico* experiments) are configured as a valuable and promising alternative to *in vitro* studies, which require expensive materials and can be excessively time consuming.[18] Nevertheless, there are only a few papers in which diffusion-controlled release profiles are explicitly simulated,[15,18,19] and some aspects of these pioneering works can be improved. First, they are based on lattice simulations in which the inner structure of the polymer network is not explicitly considered. Moreover, the authors of these surveys assume that particles are removed as soon as they reach the border of the matrix. Thus the concentration of the drug outside the polymer network remains null. In other words, the perfect sink condition (PSC) is usually assumed. Finally, it should be also stressed that those simulations were performed within the conventional Monte Carlo (MC) algorithm, in which time does not take part explicitly. For that reason, the number of executed steps was employed to monitor the changes in the release profile. But this trick cannot give us an idea of the time that the release takes and is not very rigorous.

In this work, we use off-lattice computer simulations for a systematic study of the diffusion-controlled release of drug molecules from a spherical, neutral, inert and cross-linked nanogel using a coarse-grained model of reality,[20–22] which had not been previously applied to obtain release profiles. In this way, the inner structure and topology of the nanogel is explicitly considered. A Brownian dynamics algorithm for simulation of the dynamics of hard sphere suspensions was employed instead of the conventional

MC scheme.[23] Thus time is explicit and rigorously implemented in our simulations. Our first goal is to find out to what extent the widely used power law proposed by Ritger and Peppas are valid for nanometric matrices in the absence of perfect sink conditions. After confirming its validity, it is worth exploring the effect of the drug size on the release exponent *n* since the coarse-grained model used here considers excluded volume interactions.

METHODS.

Model.

In the coarse-grained picture employed in this work, monomer units and drug molecules were modeled as spheres, whereas the solvent was considered a continuum. Similar coarse-grained models have extensively employed in the study of the collapse and adsorption of polyelectrolytes.[24–31] Monomers with a diameter of 0.65 nm were employed in all the cases. However, the diameter of the drug molecule (*d*) varied from 0.25 to 3 nm. The nanogel was made of 368 polymer chains of 10 monomers connected by 220 crosslinkers. Many of these crosslinkers, the inner ones (124), connected four polymer chains. But the most external crosslinkers connected only three or two polymer chains. The nanogel with this structure and topology was generated from simulations described elsewhere.[20,32] Similar nanogels have been employed by other authors to study different single-particle properties.[33–39] Coarse-grained simulations have also proved that hollow nanogels can be employed as drug containers.[40] Figure 1 shows the nanogel of this study loaded with drug molecules of 2 nm of diameter. The geometrical radius (*a*) of this nanogel considered as a sphere turned out to be 17.31 nm. It should be mentioned, however, that nanogels do not have a well-defined surface and there is a fraction of

monomers outside the hypothetical sphere employed as imaginary border of these nanoparticles. From the geometrical radius and the monomer distribution, a polymer volume fraction (φ) of 0.02325 was estimated in the core of the nanogel. On average, the distance between nodes of the polymer network (also known as mesh size, ξ) was 4.34 nm.

The parameters employed in these simulations can be found in real systems. For instance, many monomers have diameters close to 0.65 nm.[41] The length of the chain (10 monomers per chain) is representative of highly crosslinked gels, microgels and nanogels. In a previous work, a poly(*N*-isopropylacrylamide)-based microgel with 8 monomers per chain was synthesized.[42] The polymer volume fraction (0.02325) can also correspond to highly crosslinked polymer/polyelectrolyte networks. However, it might also be representative of nanogels with larger chains that are moderately collapsed.[42] The mesh size is consistent with the number of monomers per chain and the polymer volume fraction. Regarding the drug size, the diameter of doxorubicin (a common anti-tumor drug) is about 1.2 nm.[43]

It should be also stressed that this preliminary survey is restricted to rigid nanogels. In other words, the fluctuations of polymer chains are neglected. There are weighty reasons for the use of this restriction in a preliminary study like this. First, it is usual in physics: i) to go from simple models to sophisticated approaches; ii) to analyze the effect of a given variable while the others remain fixed. Since nanogels could modify their size during the release process due to changes in osmotic pressure, it seems appropriate to start with rigid nanogels. In addition, restricting ourselves to neutral nanogels allows us to focus on the effect of excluded volume interactions on the release process.

Simulations.

Given that polymer chains do not fluctuate in our model, only the movements of the drug molecules must be considered. In this work, a Brownian dynamics algorithm was employed to move drug molecules instead of the conventional Monte Carlo scheme based on the Metropolis algorithm. In this way, time explicitly takes part. In addition, diffusion processes can be modeled as a Brownian random walk in continuous space. In this context, Cichocki and Hinsen[23] modified the Brownian dynamics algorithm proposed by Ermak and McCammon to consider the case of suspensions of hard spheres in the absence of hydrodynamic interactions. This kind of stochastic procedures has been commonly used to simulate Brownian diffusion of spherical particles in physical chemistry and cell biology.[44–47] Despite its relative simplicity, the algorithm of Cichocki and Hinsen agrees perfectly with more sophisticated procedures that incorporate particle velocities. According to the idea of Cichocki and Hinsen, the movement of drug particles was implemented as follows. In the initial state, these beads were randomly distributed in the empty space between polymer chains avoiding overlaps (see Figure 1). For each particle, a random displacement in each spatial direction is generated from a Gaussian distribution of mean 0 and standard deviation $\sqrt{2D_0\Delta t}$, where D_0 is the free-particle diffusion coefficient in water and Δt is the simulation time step. The free-particle diffusion coefficient was estimated from the radius of the drug molecule, the viscosity of the solvent and the absolute temperature applying the Einstein-Stokes relationship. Let particle *i* be the drug molecule that the algorithm intends to move. If the resulting position causes an intersection between particle *i* and any other particle (monomer, crosslinker or drug molecule), this displacement is rejected and particle *i* stays in its original position. If not, particle *i* is moved to the new position.

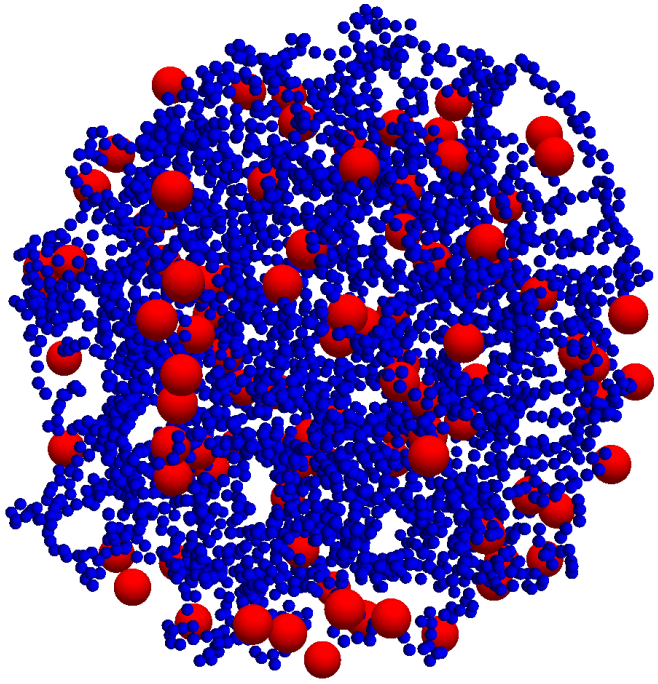

Figure 1. Snapshot of the nanogel loaded with drug molecules. Blue beads stand for monomers and crosslinkers forming the nanogel. Red beads represent drug molecules of 2 nm of diameter.

It should be mentioned that the Cichocki and Hinsen algorithm produces valid results in the limit $\Delta t \to 0$, but this would lead to extremely time-consuming simulations. In practice, Δt was taken small enough to guarantee that results are insensitive to Δt ($5 \cdot 10^{-11}$ s in our case). The released drug profiles included in this work were obtained averaging six independent runs. *In silico* experiments were performed at 293 K. A cubic simulation box with a side of 1000 nm was employed in all the cases. Periodic boundary conditions were applied. The mass fraction of drug released was computed dividing the number of drug molecules outside the nanogel by the total number of drug molecules.

THEORY.

Theory of diffusion-controlled release from spherical gels.

As mentioned in the introduction, Fick's second law has been employed to describe the diffusion process of drug particles through polymeric matrices (like gels). In the case of a spherical matrix, this differential equation takes the form:

$$\frac{\partial C}{\partial t} = D_g \left(\frac{\partial^2 C}{\partial r^2} + \frac{2}{r} \frac{\partial C}{\partial r} \right) \quad (1)$$

Here C is the concentration of drug particles, r is the radial coordinate, t is the time and D_g is the effective drug diffusion coefficient inside the gel (which is constant). It is also assumed that drug molecules are completely dissolved (monolithic solution).

Different boundary conditions can be imposed to solve Eq. 1. If the initial concentration of drug inside the gel is C_1 and the concentration of drug at the surface and the surrounding medium is maintained constant at C_0 the solution is:[48]

$$\frac{C(r,t) - C_1}{C_0 - C_1} = 1 + \frac{2a}{\pi r} \sum_{n=1}^{\infty} \frac{(-1)^n}{n} \sin \frac{n\pi r}{a} \exp(-D_g n^2 \pi^2 \, t/a^2) \quad (2)$$

Again a stands for the radius of the spherical gel. The amount of drug that stays inside the gel at time t, $M_{in}(t)$, can be computed from this solution as:

$$M_{in}(t) \equiv \int_0^a C(r,t) 4\pi r^2 dr \quad (3)$$

On the other hand, the amount of drug released at time t, M_t , is given by:

$$M_t \equiv M_1 - M_{in}(t) \quad (4)$$

Here M_1denotes the initial mass of drug contained inside the polymeric matrix. It can be shown that the mass fraction of drug released is:

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp(-D_g n^2 \pi^2 \, t/a^2) \quad (5)$$

Here M_∞ is the cumulative amount of drug released at infinity, which is identical to M_1 only if the drug concentration in the surrounding bulk fluid can be considered negligible

during the whole process of release (i.e., $C_0 = 0$). This particular case is known as perfect sink condition by some authors.[49] However, the reader should keep in mind that Eq. 5 is valid for any value of C_0. Under this assumption, Eq.5 might be employed to predict the release kinetic if D_g is known. Lustig and Peppas proposed the following expression for this diffusion coefficient:[50]

$$D_g = D_0 \left(1 - \frac{d}{2\xi}\right) exp\left(\frac{-\varphi}{1-\varphi}\right) \quad (6)$$

Here *d* is the diameter of drug molecules. At this point, we should however mention that the polymer chains of the gel are not the only obstacles that a drug molecule encounters in its way. The presence of other drug molecules also constitutes a steric hindrance. In fact, the self-diffusion coefficient of drug molecules in suspension at a given concentration differs from the diffusion coefficient of an isolated drug molecule, D_0. Different authors have paid considerable attention to the problem of self-diffusion in suspensions of hard spheres. The case of dilute suspensions was theoretically addressed by Batchelor,[51] who considered hydrodynamic interactions in his calculations, and by Ackerson and Fleishman,[52] who solved the generalized Smoluchowski equation without hydrodynamic interactions. Beenakker and Mazur[53] extended Batchelor's work to concentrated suspensions and Brady[54] focused on long-time self-diffusivity. In the case of dilute suspensions, the self-diffusion coefficient is given by $D_s = D_0(1 - \alpha\varphi_{dm})$, where φ_{dm} is the drug molecule volume fraction and α a constant. Ackerson and Fleishman[52] showed that $\alpha = 2$ in the absence of hydrodynamic interactions. On the other hand, Beenakker and Mazur[5] found that $\alpha \approx 1.73$ if hydrodynamic interactions are considered. In any case, it should be kept in mind that D_g or D_s are not required as input parameters in the coarse-grained simulations performed here because the steric hindrance due to their respective excluded-volume interactions are explicitly considered in the

algorithm when displacements yielding overlaps are rejected. In fact, Cichocki and Hinsen proved with their algorithm that $\alpha = 2$ in the absence of hydrodynamic interactions.[23]

Eq. 5 contains an infinite series that is slowly converging for short times. Thus some solutions were obtained for small times.[49] Similarly, Ritger and Peppas proposed a power law for the first 60% of the release curve:[16]

$$\frac{M_t}{M_\infty} = kt^n \tag{7}$$

Where *k* is a structural constant for a particular system and *n* is a release exponent. Peppas and coworkers performed a characterization of some release mechanisms by using Eq. 7 and more specifically the release exponent. Table 1 shows the results obtained for spherical matrices. Anomalous transport refers to a competing release mechanism between diffusion-controlled and swelling-controlled mechanisms.

Table 1. Release exponent and release mechanism

Exponent *n*	Drug release mechanism
0.43	Diffusion-controlled
$0.43 < n < 0.85$	Anomalous transport
0.85	Swelling-controlled

Regarding the structural parameter, *k*, its value for spheres was estimated in this work plotting the mass fraction of drug released (computed from Eq. 5) as a function of $(D_g t/a^2)^{0.43}$. It can be easily shown that the first 60% of the release curve exhibits a

linear behavior whose slope turned out to be 2.246. Thus the structural parameter is given by:

$$k \cong 2.246 \left(\frac{D_g}{a^2}\right)^{0.43} \quad (8)$$

The power law given by Eq. 7 is commonly used as the starting point of many release studies. In particular, it has been applied to identify the release mechanism in macroscopic hydrogels.[13,55] Recently, it has also been employed to analyze the release kinetics of nanogels.[56–58] But we should recall that Eq. 7 was derived under the assumption of constant surface concentration. In the case of macroscopic gels and in-vitro experiments, the concentration of the surrounding medium can be maintained constant by stirring. But this is not a realistic hypothesis in the case of nanogels. A macroscopic gel can remain at rest while the surrounding fluid is stirred. However, nanogels will be dragged by the current (together with drug molecules) when the suspension is stirred. Consequently, the removal of drug molecules leaking out of nanogels will not be efficient. Furthermore, stirring is not possible when *in vivo* experiments are performed. Here we assume that the drug molecules leaving the nanogel can freely diffuse in the surrounding medium. Under this assumption, the PSC could be valid if these particles diffuse away so fast that their concentration in the vicinity of the polymer network is negligible. This implies that $D_g \ll D_0$. The estimate obtained for D_g from Eq. 6 for d= 3 nm (the largest particle size) is 0.64. Consequently, D_g is not much smaller than D_0 and the breakdown of the PSC is expected. In a similar context, a few recent works focused on multilayer capsules have developed mathematical models that consider the diffusivity of the drug molecules in the external medium.[59–61]

RESULTS AND DISCUSSION.

Figure 2 shows the mass fraction of drug released versus the dimensionless time $\tau = D_0 t/a^2$ in a typical computer experiment. In this case, the nanogel was loaded with 500 drug molecules of 2 nm of diameter. Many of the simulations performed here were carried out with 500 drug particles. If we assume that the molecular weights of monomers and drug molecules are similar, the quotient between the mass of drug encapsulated and the mass of the nanogel will be of the order of 0.1. This could be the case of 5-fluorouracil encapsulated in poly(*N*-isopropylacrylamide)-based microgels.[58]

In Figure 2 we have also plotted the prediction of Eq. 5 and 6 assuming that the concentration of drug is negligible in the surrounding medium ($C_0 = 0$). As mentioned previously, M_∞ and M_1 are identical under this assumption. As can be concluded from Figure 2, the release obtained from simulation is considerably slower than the release predicted by Eq. 5 and 6. We should recall that the drug molecules that cross the imaginary border of the nanogel do not disappear. Instead, they diffuse freely. Thus the drug particles that have just crossed the border might return to the nanogel.

In order to find out if the significant deviations between simulation and theoretical prediction can be attributed to the PSC, it is quite enlightening to compare the prediction of Eq. 5 under PSC and the results obtained in *in silico* experiments also under PSC. This condition can be simulated removing drug particles as soon as they cross the imaginary border of the nanogel. Ina any case, we should bear in mind that the PSC is imposed here just as a mere reference for comparison. As can be seen, the discrepancies between theory and simulation are now much smaller. This suggests that the PSC is responsible to a great extent for the overestimation of the prediction of Eq. 5 and 6 as compared to the results obtained from simulations (in the absence of PSC).

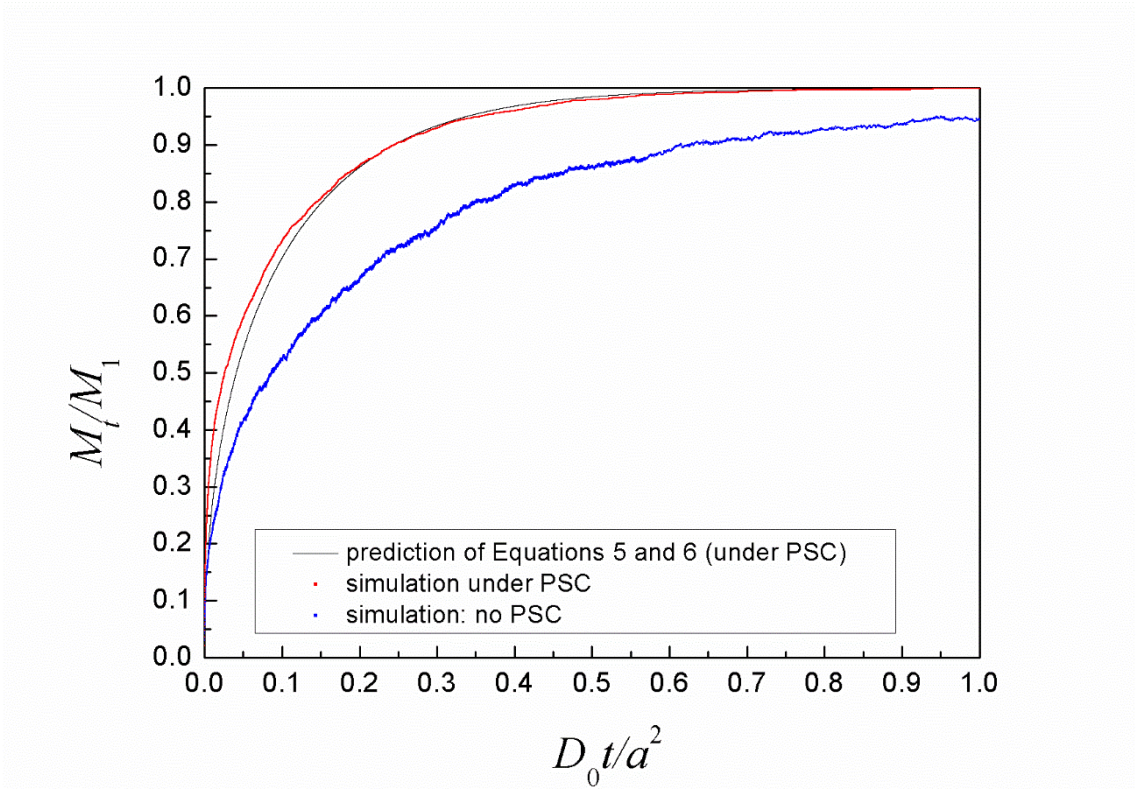

Figure 2. Fraction of drug released versus the dimensionless time $\tau = D_0 t/a^2$ for a nanogel loaded with 500 drug molecules of 2 nm of diameter. Red and blue symbols denote the results obtained from simulations under PSC and in the absence of PSC. The black solid line represents the prediction provided by Equations 5 and 6.

The minor discrepancies between theory and simulation observed when PSC are employed for both can be attributed to some aspects of the structure of the nanogel, which are not explicitly incorporated in Fick´s second law. At short times, the drug molecules located in cavities near the imaginary border of the nanogel do not find opposition to diffuse outwards due to the absence of polymer chains and other drug molecules in this way (see Figure 1). On the contrary, the drug molecules located in such voids do find such obstacles when they try to move inwards, so these molecules preferentially diffuse outwards. This explains why at small times ($\tau < 0.15$) the drug is released more rapidly in the PSC simulation than what Eq. 5 predicts.

Figure 2 also shows that the fraction of drug released tends to 1 much more slowly when the drug leaving the nanogel can freely diffuse and the PSC is not imposed. It should be

stressed, however, that the drug will be completely released only if the simulation cell is infinite, which is equivalent to considering an isolated nanogel. If the simulation cell is finite, a fraction of the drug will remain inside the polymer network. The distribution of drug inside and outside the nanogel when the equilibrium is reached depends on the volume of the nanogel and the available outer space per nanogel particle as well as the so-called partition coefficient. The simulations of this work were performed in a cell whose length (1000 nm) was much larger than the nanogel radius to minimize this partitioning and achieve a complete release.

As pointed out above, Figure 2 reveals that the prediction of Eq. 5 and 6 (under PSC) clearly overestimates the mass fraction obtained from simulation if drug molecules can freely diffuse after leaving the nanogel. Figure 3 displays the surface concentration of drug molecules, $C(a,t)$ obtained from simulation for the system analyzed in Figure 2. As can be seen, this function is far from zero at short times and does not vanishes even at long times. In addition, it must be stressed that $C(a,t)$ is not constant. In other words, Figure 3 corroborates that the PSC is not an appropriate boundary condition for the nanogel of this study. Consequently, the validity of Eq. 5 can be questioned in this case since it was derived under the assumption of constant surface concentration.

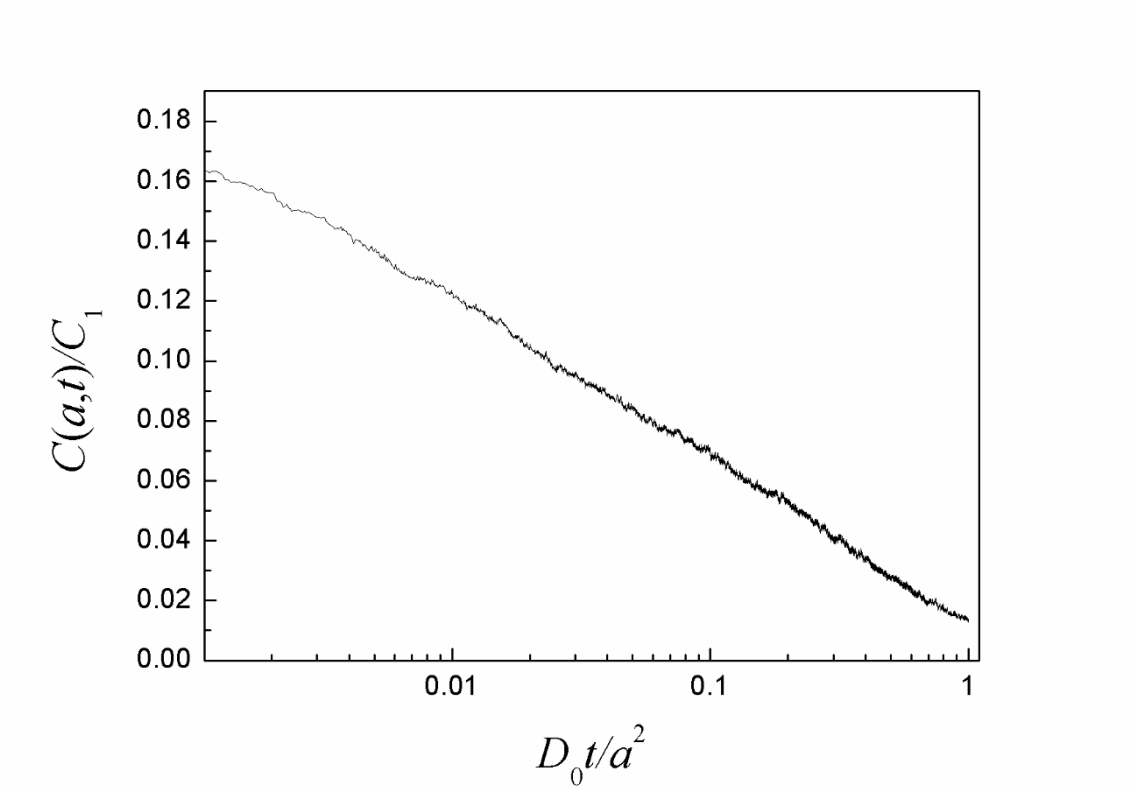

Figure 3. Surface drug concentration normalized by the initial concentration, $C(a,t)/C_1$, as function of the dimensionless time, $\tau = D_0 t/a^2$, for a nanogel loaded with 500 drug molecules of 2 nm of diameter. To reduce the statistical noise, this function was computed averaging over 60 independent runs.

Nonetheless, it is worth finding out whether the first 60% of the release profile obeys a power law like Eq. 7 since, as mentioned before, this expression is the starting point of a many release studies. Figure 4 shows the release profiles obtained from simulations (in the absence of the PSC) for a load of 500 drug molecules with diameters 0.25, 1 and 2 nm is again drawn in a log-log plot. As can be seen, these curves exhibit a reasonable linearity up to the 60% (horizontal line) and the slope of these curves can be interpreted as a release exponent, n.

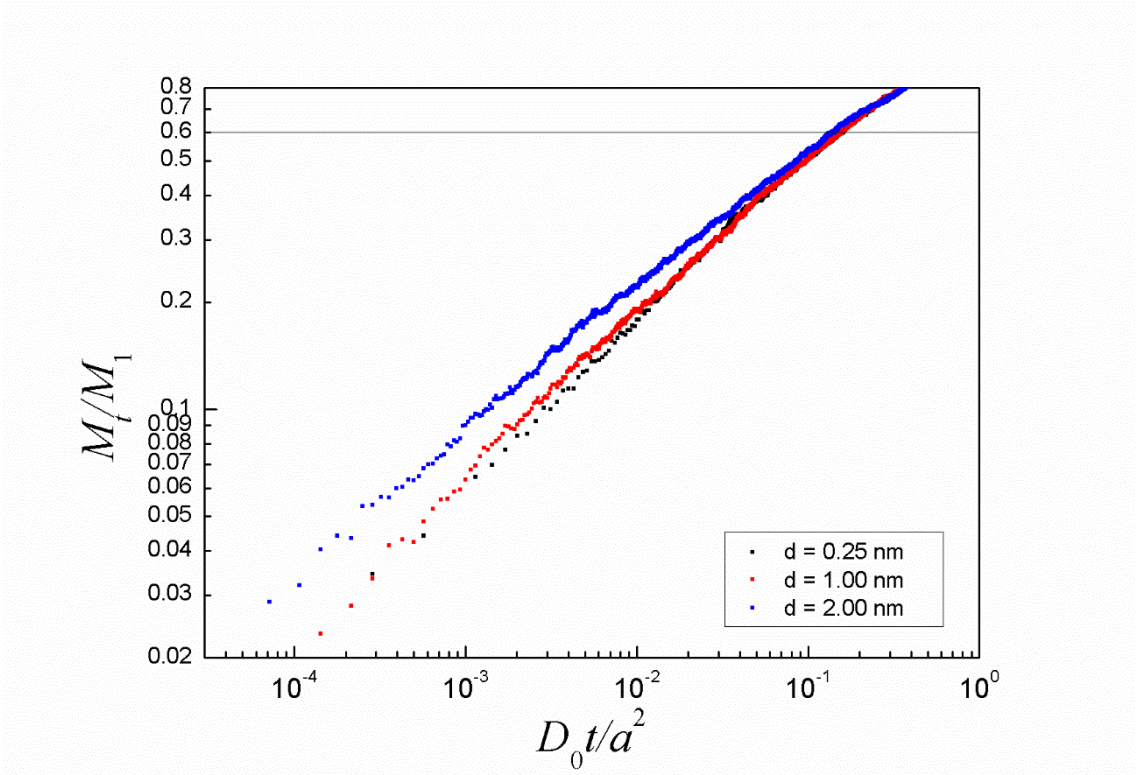

Figure 4. Fraction of drug released obtained from simulations versus the dimensionless time $\tau = D_0 t/a^2$ for a nanogel loaded with 500 drug molecules of diameter 0.25 nm (black), 1.00 nm (red) and 2.00 nm (blue). The horizontal line indicates the first 60%.

Following this procedure, the effect of the drug size on the release exponent was investigated. Figure 5 displays the release exponent *n* versus the diameter of the drug molecules. These *n*-values were obtained from *in silico* experiments averaging the results obtained from three different profiles. The total number of loaded drug molecules was the same in all the simulations (500 molecules). Two regimes can be distinguished in this figure On the one hand, there is a plateau with *n*-values slightly higher than 0.43, the value predicted by Peppas for this mechanism of drug release. This plateau includes drug molecule diameters from 0.5 to 1.5 nm.

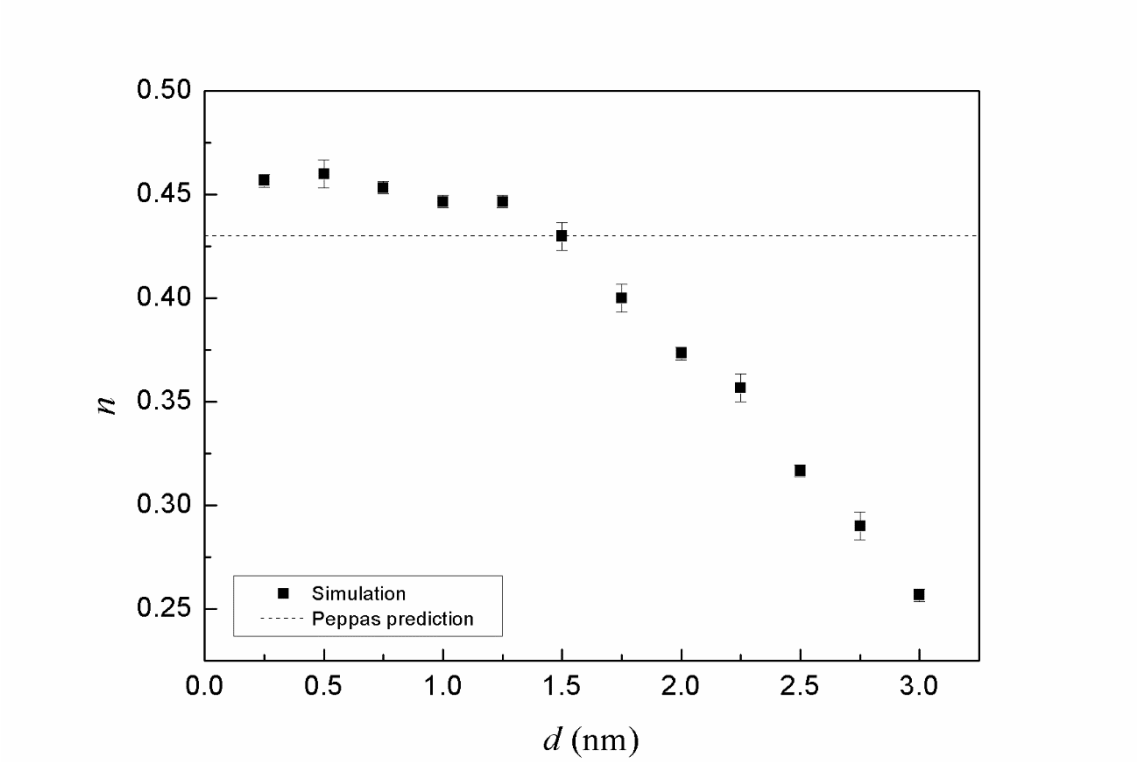

Figure 5. Release exponent (*n*) as a function of the diameter (*d*) of the drug molecules for a nanogel loaded with 500 drug molecules.

On the other hand, there is a linear decrease of the release exponent with the molecule diameter for diameters greater than 1.5 nm. This decrease in *n* implies a slowdown of the drug release when the volume fraction occupied by drug molecules (φ_{dm}) grows above 0.04 ($\varphi_{dm} > 0.04$ when $d > 1.5$ nm). Given that the only interactions involved in these simulations are excluded volume interactions and their effects increase with the volume fraction, the decrease in *n* observed in Figure 5 can be attributed to an increase of the steric hindrance.

It should be also stressed that this figure reveals that a purely diffusive release is not unambiguously characterized by *n*=0.43, as the classical theory previously sketched predicts. Smaller exponents can be found for large particles according to our simulations and even in experiments. For instance, some authors have recently reported *n*-values smaller than 0.43 for nanogels loaded with different anti-tumor drugs[57,58]. Release

exponents smaller than 0.43 were also reported for macroscopic gels[62] and spheres of a few hundreds of nanometers.[63] Such release exponents are interpreted as diffusion-controlled release processes by some of these authors. Our results confirm that excluded volume interactions can be responsible for this deviation from the classical prediction for diffusion-controlled release.

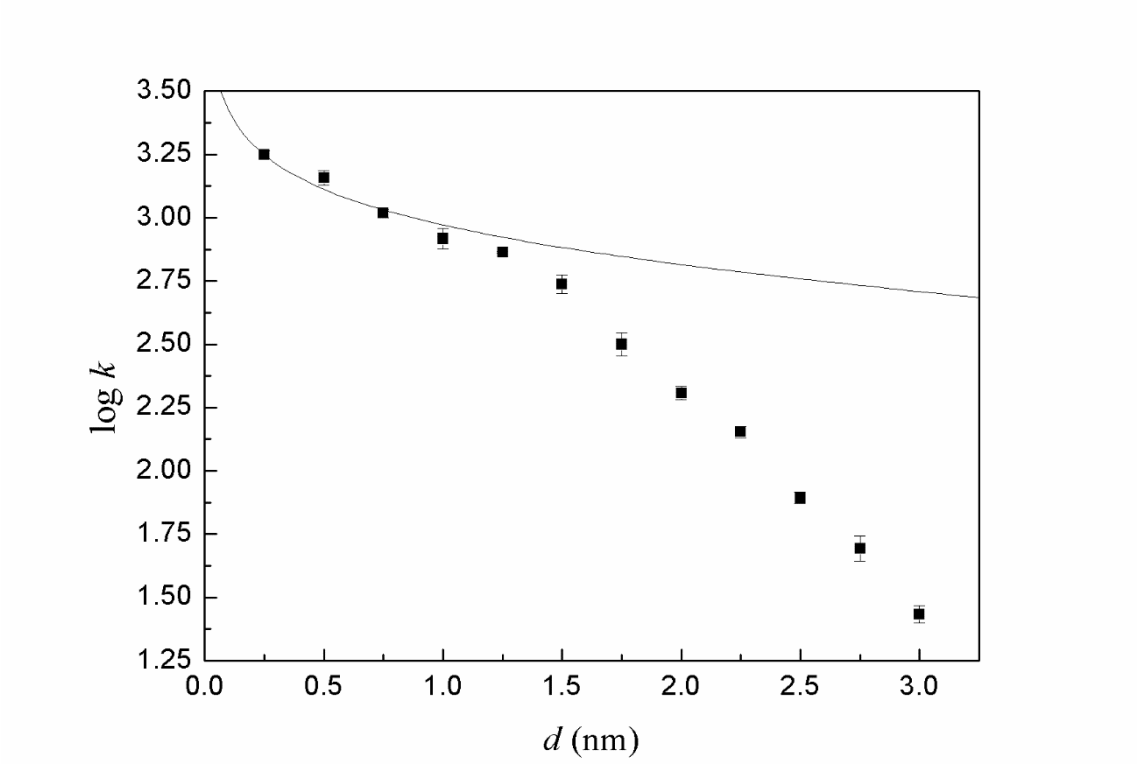

Figure 6. Logarithm of the structural constant k as a function of the diameter (d) of the drug molecules for a nanogel loaded with 500 drug molecules. The line represents the prediction obtained from Eq. 8 and 6.

The fitting procedure performed to obtain n-values from the release profiles obtained from *in-silico* experiments also provides the logarithm of the structural constant k. Figure 6 displays *log* k-values as a function of the diameter of drug molecules. As can be seen, the structural constant decreases with the molecule diameter. The prediction for k obtained from Eq. 8 and 6 is also plotted in Figure 6. As can be seen, there is agreement between theory and simulation for drug diameters smaller than 1 nm. For greater sizes,

the theoretical prediction overestimates the *k*-value. In any case, the combination of *n*- and *log k*-values reported by Figures 5 and 6 allows us to predict the first 60% of the release curve by means of the use of Eq. 7.

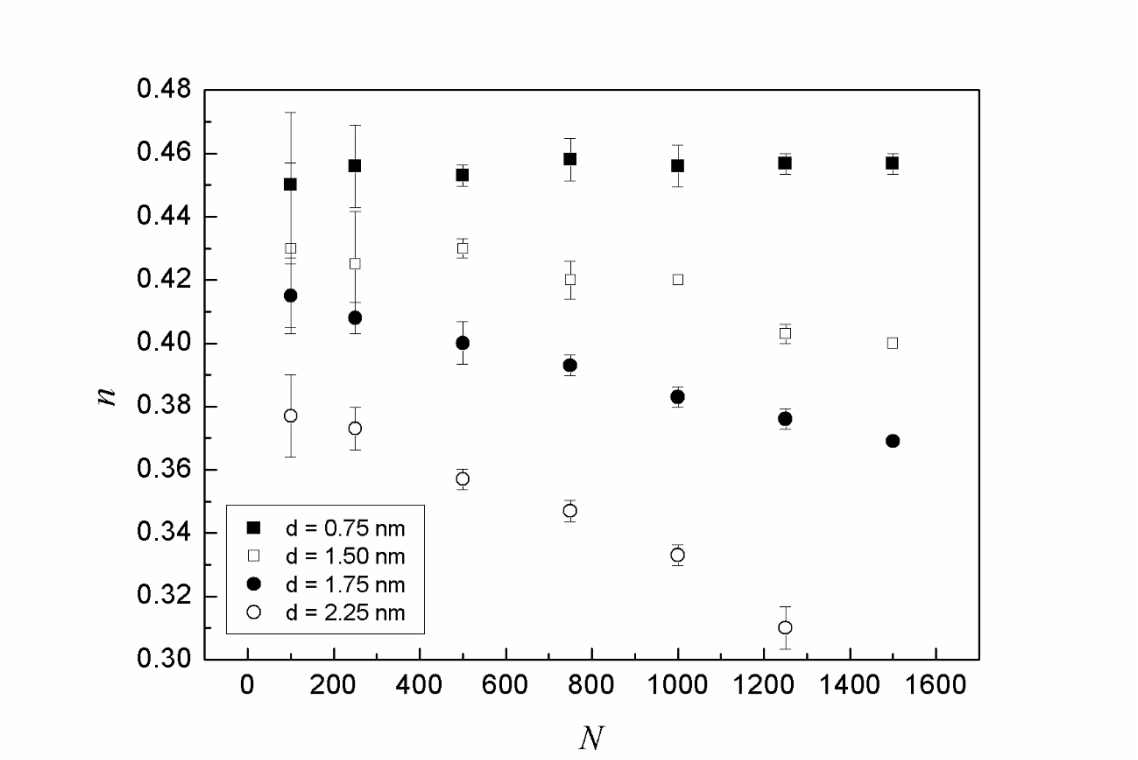

Figure 7. Release exponent (*n*) as a function of the number of drug particles loaded in the nanogel (*N*) for different particle diameters: 0.75 nm (solid square), 1.50 nm (open square), 1.75 nm (solid circle), 2.25 nm (open circle).

The steric hindrance that modifies the values of *n* and *k* could not only depend on the polymer network but also on the drug concentration (inside the nanogel). Figure 7 shows the release exponent *n* versus the number of drug molecules for different diameters of drug molecules. This figure again reveals that diffusion-controlled *in silico* experiments with nanogels do not provide an only and constant value for the release exponent. In fact, the *n*-values obtained here depend on both the diameter and the number of drug molecules. More specifically, *n* decreases with the number of drug molecules loaded in the matrix for diameters greater than 1.50 nm, which once again suggests the emergence of steric obstacles that delay the drug release.

It is quite instructive to represent the *n*-values of Figure 7 as a function of the initial volume fraction of the drug molecules inside the nanogel (see Figure 8). This plot suggests the existence a common asymptotic behavior of the release exponent at high values of the volume fraction.

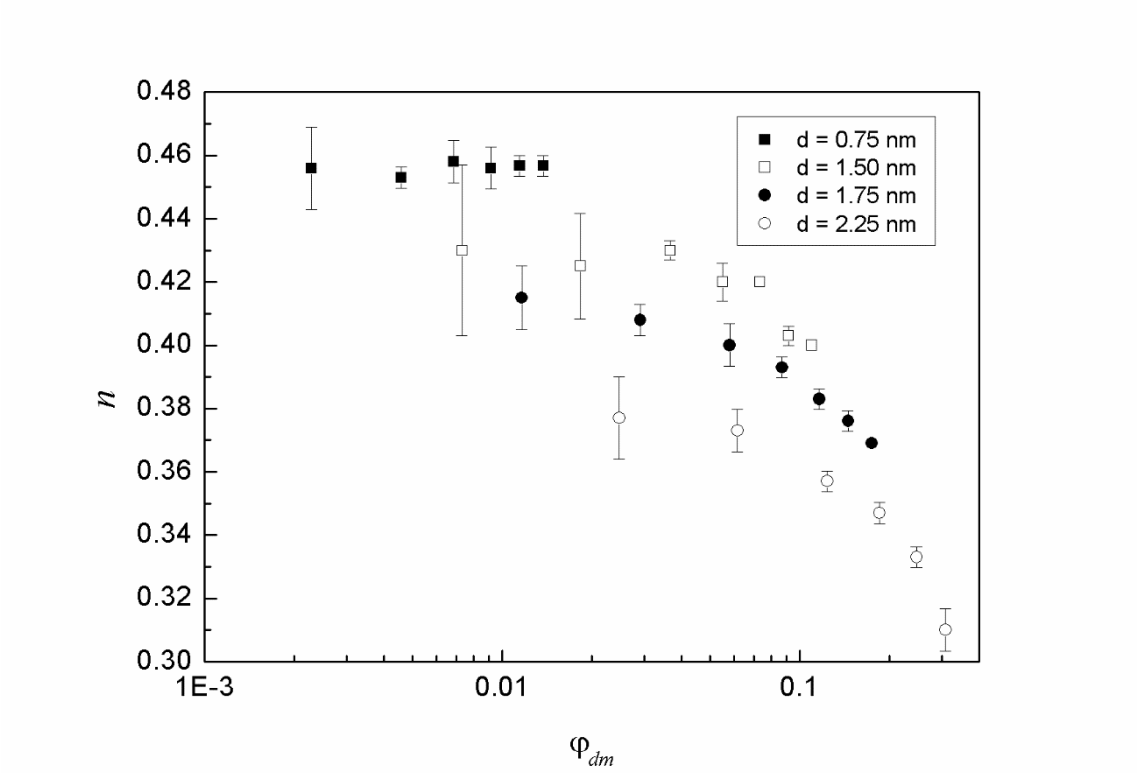

Figure 8. Release exponent (*n*) as a function of the volume fraction of drug molecules (φ_{dm}) loaded in the nanogel for different particle diameters: 0.75 nm (solid square), 1.50 nm (open square), 1.75 nm (solid circle), 2.25 nm (open circle).

Before ending this section, it should be mentioned that the algorithm proposed by Cichocki and Hinsen does not include hydrodynamic interactions. It is worth figuring out if these interactions would have a considerable effect on the results obtained here. Just as an example, let us consider the self-diffusion coefficient, which is affected by excluded volume forces among drug molecules. Figure 8 clearly illustrates that most of the simulations performed here were carried out with drug molecule volume fractions less

than 0.1. As pointed out above, the self-diffusion coefficient is given by $D_s = D_0(1 - \alpha\varphi_{dm})$ in the dilute regime, with $\alpha \approx 1.73$ if hydrodynamic interactions are considered and $\alpha = 2$ in the absence of them.[52,53] Computing D_s for $\varphi_{dm} = 0.1$ in both cases it can be inferred that hydrodynamic interactions yield a relative increase in the diffusion coefficient of the order of 3%. Recent Brownian Dynamics simulations have reported somewhat larger discrepancies but smaller than 10% in any case.[64]

CONCLUSIONS.

In this study, we have simulated the diffusion-controlled release of drug molecules from neutral nanogels employing a coarse-grained model that explicitly considers excluded volume interactions and the inner structure of the polymer network. Our results suggest that the assumption of constant surface concentration and particularly the perfect sink condition could not be appropriate to mathematically model diffusion-controlled drug release processes from gels of a few tens of nanometers. In these systems, the drug molecules that diffuse near the surface of the nanogel after being released can be responsible for considerable deviations from PSC-based predictions.

Our *in silico* experiments also reveal that excluded volume interactions can induce important changes in the classical Peppas law. The first 60% of the release kinetics simulated here can be fitted using this power law, but the release exponent depend on both the diameter and the initial concentration of drug molecules, which constitutes a novelty itself. More specifically, the *n*-values obtained here are considerably smaller than the classical value of 0.43 for diffusion-controlled conditions if the drug diameter and the drug concentration are large enough. Some experiments performed with nanogels, microspheres and gels have also reported *n*-values significantly smaller than 0.43. In

addition, the classical theory also overestimates the structural constant if the drug size is big enough.

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