Modeling the diffusion-erosion crossover dynamics in drug release

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A computational model is proposed to investigate drug delivery systems in which erosion and diffusion mechanisms are participating in the drug release process. Our approach allowed us to analytically estimate the crossover point between those mechanisms through the value of the parameter b ($b_c = 1$) and the scaling behavior of parameter τ on the Weibull function, $\exp[-(t/\tau)^b]$, used to adjust drug release data in pharmaceutical literature. Numerical investigations on the size dependence of the characteristic release time τ found it to satisfy either linear or quadratic scaling relations on either erosive or diffusive regimes. Along the crossover, the characteristic time scales with the average coefficient observed on the extreme regimes (i.e., $\tau \sim L^{3/2}$), and we show that this result can be derived analytically by assuming an Arrhenius relation for the diffusion coefficient inside the capsule. Based on these relations, a phenomenological expression for the characteristic release in terms of size L and erosion rate κ is proposed, which can be useful for predicting the crossover erosion rate κ_c. We applied this relation to the experimental literature data for the release of acetaminophen immersed in a wax matrix and found them to be consistent with our numerical results.

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I. INTRODUCTION

Bioerodible polymers play an important role in the design of pharmaceutical devices in which the drug release mechanism is also determined by polymer erosion in addition to diffusion [1–8]. Biopolymers are commonly used to deliver many kinds of pharmaceutical compounds including as anticancer drugs, contraceptive steroids, antibiotics, and biomolecules such as proteins and DNA [6,7,9–12]. In addition, advances in biodegradable devices with applications for ocular drug delivery systems [8,13] and cancer therapies [2,4,5] have been reported in the literature. In these cases, bioerodible polymers are used for two main purposes: to control the drug release time and to improve biocompatibility. The latter requirement is of greater importance since in certain therapeutic treatments, as in the case of implantable systems, once the biopolymer has completely eroded and its fragments absorbed by the body, surgical removal of the implant can be avoided [9,10,13]. Thus, a better understanding of the characteristic release times as well as the erosion mechanism are essential for the development of more effective therapies.

Drug delivery systems based on polymeric materials can control the release rates by diffusion, erosion, and swelling and the prevalence of one of these processes depends on the interactions between polymer and the environmental fluid (water or biological fluid), in the sense that the polymeric device may have its physical structure unchanged during the release process or may be subject to a process of swelling or erosion. When the physical structure of the device remains unchanged, the release is basically controlled by simple diffusion and while erosion (or chemical reactions) of the polymer is taking place release rates can be controlled by the interaction between polymer and fluid molecules. For the case in which the release is controlled by the ability of the polymer to swell, that is, when a fluid penetrates the polymer, it promotes a volume variation in the polymeric matrix, thus generating a strain induced breaking [14–18]. In this latter case, drug release is controlled by the polymer chain relaxation rate (polymer swelling). In addition, release rates can be controlled by a combination of more than one mechanism and the predominance of one or other depends essentially on the characteristics of the polymer, fluid, and physicochemical properties of the drug [1,19]. Many other physical and chemical factors can also play an important role in this process, for example, microparticle size, device geometry, and drug dissolution (change of phase), among others [6,7,10,11,20–23].

In this scenario, the use of computational or mathematical models to describe the release kinetics plays a fundamental role in the development of new pharmaceutical devices. Among some of the benefits, modeling allows one to obtain physical insights into the release mechanism and to optimize an existing drug delivery system, eventually reducing the number of experimental tests and the average time and costs for the production of a new drug release device [24–30].

Erosion dynamics of polymeric materials and its effects on release kinetics have been the subject of many studies; for reviews, see [6,11,31]. Despite all the complexity involved in the release process, theories based on the classical diffusion equation give reasonable results when the main mechanism of

drug transport is diffusion. To include the effect of polymer erosion dynamics, it is common to consider the diffusion coefficient as a function of time, position, concentration, and, eventually, porosity, and in some cases it is possible to develop theoretical frameworks that are well in agreement with experimental results [20–22,32–36]. There are also sophisticated theoretical models that account for diffusion, erosion theories, and many other factors, based on partial differential equations or even coupled models between partial differential equations and Monte Carlo (MC) simulations [36,37]. In contrast, only a few microscopic models based on cellular automata or Monte Carlo approaches have been developed to investigate the effects of the polymer erosion and drug diffusion on the context of the drug release process [38–43].

In previous works from our group, a lattice gas model was used to simulate drug delivery devices and the effects of the membrane porosity on the drug release process were investigated using the MC approach for capsules in two and three dimensions with different sizes. Scaling relations between release parameters and porosity were obtained that could be used to fit up to 90% of the membrane content covering the capsule [44,45]. Considering the relevance of bioerodible membranes for the development of new pharmaceutical devices, in this work we generalize our previous model including the membrane erosion dynamics (or pore formation). For the purpose of implementing the erosion dynamics, we assume that on each MC step, there is a probability that a pore (leaking site) will be formed due to a possible reaction between the membrane and the fluid environment particles (e.g., water molecules).

The first step in achieving the description of any dynamical system is to understand its relaxation mechanism which, for many processes, is related to a nonexponential behavior [46–51]. In the case of drug release patterns, the nonexponential relaxation processes can be inferred by the fact that the Weibull distribution function is commonly used to adjust, both in experimental setups and Monte Carlo simulations, release data. Based on previous work, we adopt this distribution in the form [52–55]

$$\frac{N(t)}{N_0} = \exp\left[-\left(\frac{t}{\tau}\right)^b\right], \tag{1}$$

where $N(t)$ is the amount of drug particles inside the capsule as a function of time t, while $N_0 = N(0)$ is the initial number of particles; the characteristic release time τ is associated with the time in which ≈63% of the drug is delivered, whereas the release parameter b, in the pharmaceutical literature, is associated with the physical mechanisms that control the release process (for more details, see [44,45] and references therein), which has been successfully applied in different studies [56–58]. It is important to mention that Ignacio and Slater proposed a new semiempirical function based on diffusion theory that for a purely diffusive drug release problem, outperforms the Weibull function and, recently, they proposed an alternative way to obtain the diffusion constant from the drug release data [59,60].

In our simulations, the Weibull distribution function was found to reasonably adjust the release curve for different erosion rates and we were able to perform a scaling analysis on the parameters b and τ as a function of the erosion rate and the capsule size. By comparing the Weibull parameter b against the erosion rate it was possible to identify a crossover region where the effects of membrane erosion and drug diffusion were contributing with the same weight to the release mechanism. This crossover was identified to occur at $b = b_c \approx 1$, corroborating the discernment of the drug release mechanism proposed by Papadopoulou *et al.* [61]. A simple mathematical argument was presented to explain this behavior, favoring the usage of the Weibull parameter b to distinguish between the major drug release mechanisms [61].

In addition, the characteristic release time τ was found to satisfy a power law dependence in terms of the membrane erosion rate and this allowed us to build an analytical expression relating those two quantities. This relation was found to be consistent with experimental data for the release of acetaminophen immersed in a wax matrix [33].

The remainder of this paper is organized as follows: in Sec. II, we introduce our lattice model and the simulation methods used to investigate the influence of the membrane erosion dynamics on the drug release mechanism. Results and discussions are presented in Sec. III, while our conclusions are summarized in Sec. IV.

II. MODEL AND SIMULATION DETAILS

To investigate how the membrane erosion influences the release kinetics, we modified the two-dimensional (2D) lattice model of drug release [44,45]. Instead of presenting a rigid membrane with fixed porosity, with the random porous sites distributed along the membrane at the beginning of the simulation, we encapsulated the device with a bioerodible membrane, whose dynamics is defined along the simulation, as described below.

In our model, the drug device is represented by a lattice and each site can be occupied by a single drug particle or be empty. Drug dynamics occurs in a random way, but drug molecules are not allowed to jump into other sites occupied by either drug or membrane particles, i.e., the main effect of the membrane is to block drug molecules from leaking to the outside environment. Except for membrane dynamics, simulations are similar to our previous work and we refer to it for further details [45]. We start all simulations by considering 2D square lattices with size L, maximum initial drug concentration ($N_0 = L^2$), and membrane coverage ($M_0 = 4L$). A pictorial representation of our 2D device model is presented in Fig. 1 for a given time step.

The membrane erosion dynamics (or pore formation) is introduced in our lattice model as simply as possible with membrane and drug dynamics being independent of each other along a Monte Carlo step. Between MC steps, there is a constant probability that δM pore sites (leaking site) will be formed due to a possible reaction between a membrane site and an environment fluid particle (it is assumed that the system is immersed in an implicit aqueous medium).

Before proceeding, let us represent the erosion rate constant as $k = P\delta M l_0/\Delta t$, where P is the probability of erosion, l_0 is the pore length, Δt is the unit of time assumed for a MC step, and δM is the number of pores eroded along the Δt time

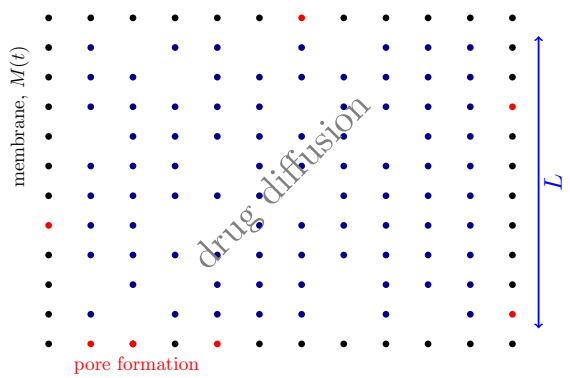

FIG. 1. Schematic representation of our two-dimensional device model with size $L = 10$, $N_0 = L^2$, and $M_0 = 4L$ for a given time step. The lattice is not represented, for more clarity. Nonetheless, each site has area of l_0^2 and can be occupied by a single particle or be empty. The erosion constant dictates the formation of pores, with six membrane sites (black) eroded (red) and some of the drug particles (blue) released.

interval. After each MC step, a random number x uniformly distributed between 0 and 1 is generated and, if $x \leqslant P$, δM new pores are created in random membrane sites.

For each configuration, i.e., different sizes L and erosion rates k, the final drug release profile and membrane coverage are obtained by averaging the particle number and membrane sites, as a function of the time, over 10^3 simulations. Each individual release curve is then adjusted to the Weibull distribution function using standard routines for nonlinear square fitting [62].

In Fig. 1, we show, for example, a possible obtained configuration for a given time step. As the final results are obtained as an average over different realizations, and the constant erosion probability is assumed, the average number of membrane sites decays linearly with time,

$$M(t) = M_0 - kt. \tag{2}$$

Generalizations of our microscopic probabilistic approach are straightforward to produce different decay profiles, $M(t)$, but here we are interesting in the process where the polymer membrane erosion follows a linear relation with time [28,33]. Furthermore, the erosion constant k is similar to the experimental erosion constants described in the cellular automaton model for the corrosion of a metal in an environment [63] and also in a model for swelling-controlled drug release [64]. Furthermore, it is important to mention that we are interested in the erosion of polymeric membranes, and other methods can be applied to investigate the erosion of polymeric matrices [38,65,66].

For simplicity, let us define the dimensionless erosion constant $\kappa = k\Delta t/l_0$ and consider $\delta M = 1$. As an illustration, for $\kappa = 1.0$, all attempts are accepted and 100 membrane sites will erode after 100 MC steps, for a large enough membrane, whereas for $\kappa = 0.01$, on average only one membrane site is converted into a pore site after 100 MC steps.

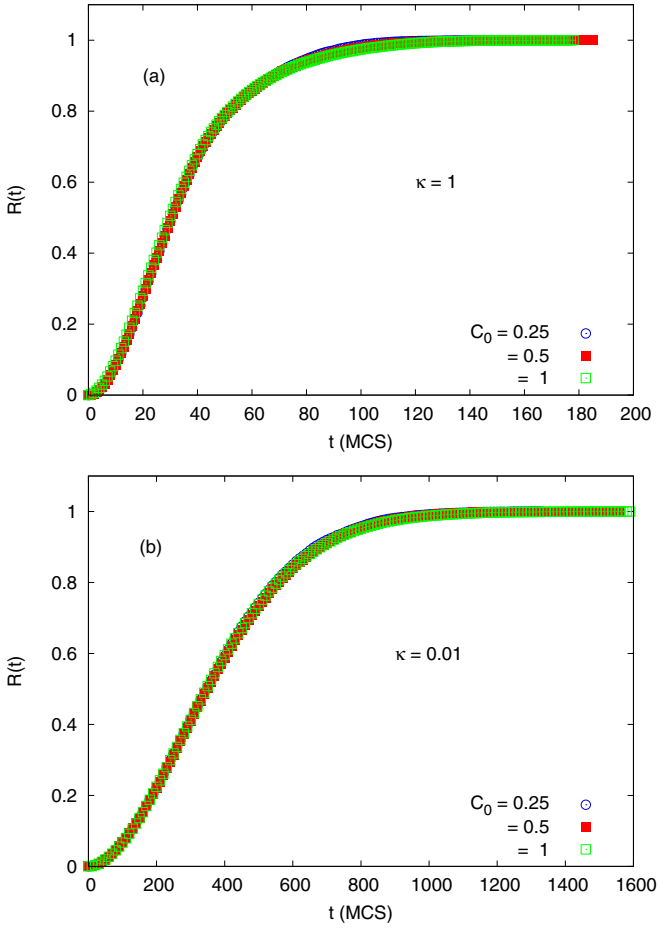

FIG. 2. Fraction of drug released, $R(t)$, as a function of the time t, in Monte Carlo steps, for different drug initial concentrations C_0 and for erosion constant (a) $\kappa = 1$ and (b) 0.01.

III. RESULTS AND DISCUSSION

We start presenting in Fig. 2 the release fraction $R(t) = 1 - N(t)/N_0$ resulting from the Monte Carlo simulation of drug device models with size $L = 200$ and the erosion constant, (a) $\kappa = 1.00$ and (b) 0.01, for different drug initial concentration, $C_0 = N_0/L^2$, where N_0 drug particles are initially placed randomly along the lattice. In this way, these figures indicate that the obtained results are universal since drug release data presents the same functional form dependent only on the erosion constant. On the other hand, this universality is expected to be broken for different devices geometries, for example, for rectangular lattices. Hereafter, we choose the initial concentration equal to one, as it seems to be closer to real cases in the sense that the drug device is completely filled with particles.

In Fig. 3, we show that the Weibull function provided accurate fits for release curves for different erosion constant values $\kappa = 0.01$ and 1.00, which illustrate the cases where either erosion or diffusion is the main mechanism dominating the drug release pattern. In both cases, the numerical data could be reasonably well adjusted to Weibull functions (continuous lines), as measured by $R^2 \approx 1$ and also through an analysis of its residuals [45].

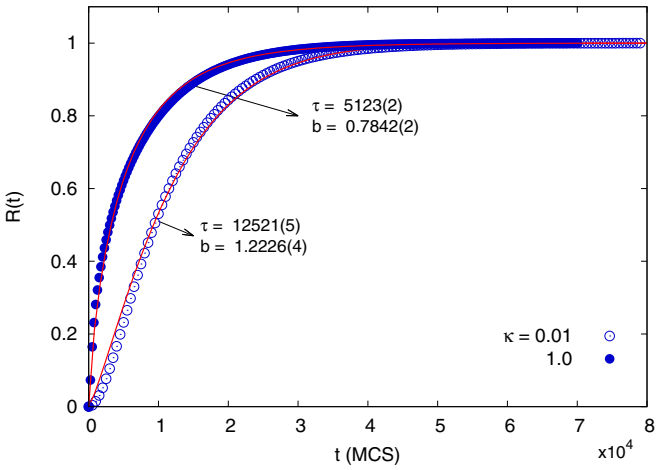

FIG. 3. Fraction of drug released as a function of the time t, in Monte Carlo steps, for device models with size $L = 200$ and different erosion rates κ. Simulation data points were adjusted to Weibull distribution functions (lines), with fitting parameters b and τ indicated along each curve.

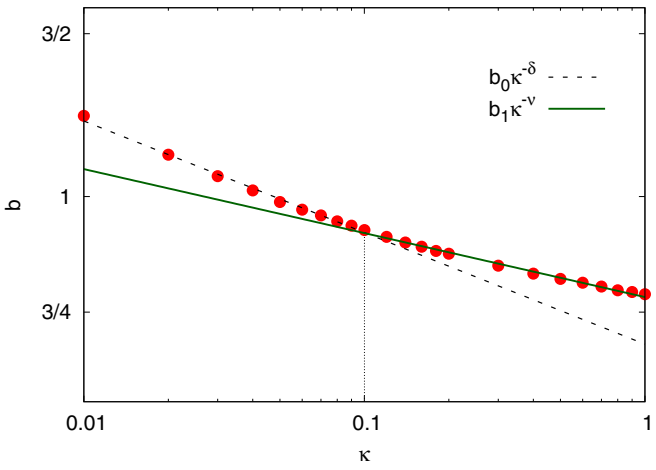

FIG. 4. Log-log plot of the release parameter b as a function of erosion rate κ for capsules with size $L = 200$. The lines are the fitted curves (see text). Note that there is a subtle deviation from the fitted curves when $\kappa \to 1$ and $\kappa \to 0$.

For $\kappa = 1.00$, the membrane erosion happens so fast that it is almost instantaneous in the time frame presented in Fig. 3. In this case, the Weibull adjusted parameters [67] were found as $\tau = 5123(2)$ MC steps and $b = 0.78$, with the latter being used in the literature [61] to associate the drug release mechanism with drug diffusion in a regular, Euclidean lattice, but with contributions from another mechanism which, in the case of current model, is immediately recognized as the membrane erosion. The presence of the membrane with a fast erosion dynamics also introduces numerically significant effects on the behavior of the characteristic release time τ, as will be discussed below.

For the slow erosion rate case [68], $\kappa = 0.01$, the membrane degradation takes about twice as much time as what is needed to release 99% of the initial drug load, and the drug release kinetics is mostly limited by the membrane erosion rate. For this case, Weibull adjusted parameters were found as $\tau = 12521(5)$ MC steps and $b = 1.22$, which could be used to classify this system as belonging to devices with a "complex release mechanism" [61], which evidently corresponds to a dominance of the membrane erosion dynamics on the drug release profile.

As discussed above, the presence of an erodible membrane covering the pharmaceutical device introduces an additional level of complexity on drug release patterns, presenting more important effects than would be presumed by simply noting that the membrane decreases the probability for drug molecules to escape the capsule. By comparing the cases of a simple device without a membrane to a series of systems covered with sequentially stiffer membranes, the characteristic times would increase but, also, the shape of the release curve would be radically changed, crossing drug release mechanisms from simple diffusion ($0.69 < b < 0.75$), normal diffusion with contribution from another mechanism ($0.75 < b < 1.0$), first order release ($b = 1$), and, finally, to complex release ($b > 1$). Since the Weibull distribution function provides a reasonably good approximation to release curves in the cases illustrated in Fig. 3, it should be interesting to perform a detailed scaling analysis on the dependence of release parameters b and τ with respect the capsule sizes L and the erosion rate κ within this interval. The following sections will be devoted to this task.

A. Relation between release parameter b and erosion rate κ

To investigate the interplay between membrane erosion and drug diffusion in the drug release, let us express the membrane fraction at short times ($t \ll \tau$) from Eq. (2) as

$$\lambda_M(t) = \frac{M(t)}{M_0} = \frac{M_0 - kt}{M_0} \approx \exp\left(-\frac{kt}{M_0}\right), \tag{3}$$

and compare it to the drug fraction inside the device *by assuming* that it can be approximated by the Weibull distribution function in Eq. (1),

$$\lambda_N(t) = \frac{N(t)}{N_0} = \exp\left[-\left(\frac{t}{\tau}\right)^b\right]. \tag{4}$$

Although the membrane kinetics is decoupled from the drug diffusion, both mechanisms are acting together in a nontrivial way to generate the final drug release profile. Under the condition that both mechanisms are contributing in a proportional way to the system dynamics (*crossover*), we shall have a very special case, such that the ratio $\frac{\lambda_M(t)}{\lambda_N(t)}$ is constant and equal to one, which holds true only if $b = 1$ and $\tau = M_0/k$, implying that in the crossover region, the drug release is described by an exponential decay. This is in accordance with the experimental classification scheme discussed above [61] and it is investigated with more numerical detail in Fig. 4, which presents the Weibull release parameter b for a capsule with size $L = 200$ by varying κ from 0.01 to 1.00. In this figure, presented in log-log scale, two different behaviors seem to occur for the data below and above $\kappa_c \approx 0.1$. In both cases, the data are well adjusted by power law scaling relations, but with different coefficients. For $\kappa < \kappa_c$, one can adjust the b data to $b = b_0\kappa^{-\delta}$, while in the other limit $\kappa > \kappa_c$, it can be

adjusted to $b = b_1\kappa^{-\nu}$, where b_0, b_1, ν, and δ are adjustable parameters [69]. It is important to mention that these scaling relations only allow us to find the crossover, when both are equal (see in Fig. 4), which means

$$b_c(\kappa_c) = \frac{b_1}{b_0}\kappa_c^{\delta-\nu}, \tag{5}$$

and, thus, when $\kappa_c = 0.1$, one obtains $b_c \approx 1.0$, which deviates by about 8% from the exact numerical value, $b_c = 0.92(1)$.

Therefore, it is possible to infer that the prevalence of the membrane erosion or diffusion mechanism on the release process determines the values observed on b. When the membrane erosion rate is fast (e.g., $\kappa = 1$), the drug diffusion is the dominant mechanism determining drug release.

As the erosion rate κ decreases towards the critical value, $\kappa \to \kappa_c$, there is a corresponding increase in the values of b, indicating a greater contribution from the erosion mechanism itself, and the two mechanisms occur in a proportional way at $\kappa = \kappa_c$, where we found $b = b_c \approx 1.0$, in accordance with the phenomenological description presented above. For κ values smaller than κ_c, the membrane erosion becomes a limiting step for the process of drug release and, in this regime, the membrane erosion dynamics becomes the dominant mechanism for controlled drug release.

In Fig. 5(a), the release parameter b is shown as a function of size L for different erosion rates κ. At fixed values of κ, the values of b decrease with increasing size L in a behavior which can be approximately described by a power law, $b = b_\kappa L^{-\alpha_\kappa}$, where the adjusted parameters b_κ and α_κ also depend on the erosion rate. Furthermore, the observed size dependence of b allows us to question what the crossover size L_c would be for each κ, as depicted in Fig. 5(b). From these two figures, it is evident that there is a threshold size L_c below which membrane erosion starts to be the dominant effect, for each κ, while above this size the drug diffusion becomes more relevant. These results reinforce the idea that the release parameter b could be used to discern the drug release mechanism, in the sense that for values $b > 1$, the system is controlled by the erosion mechanism.

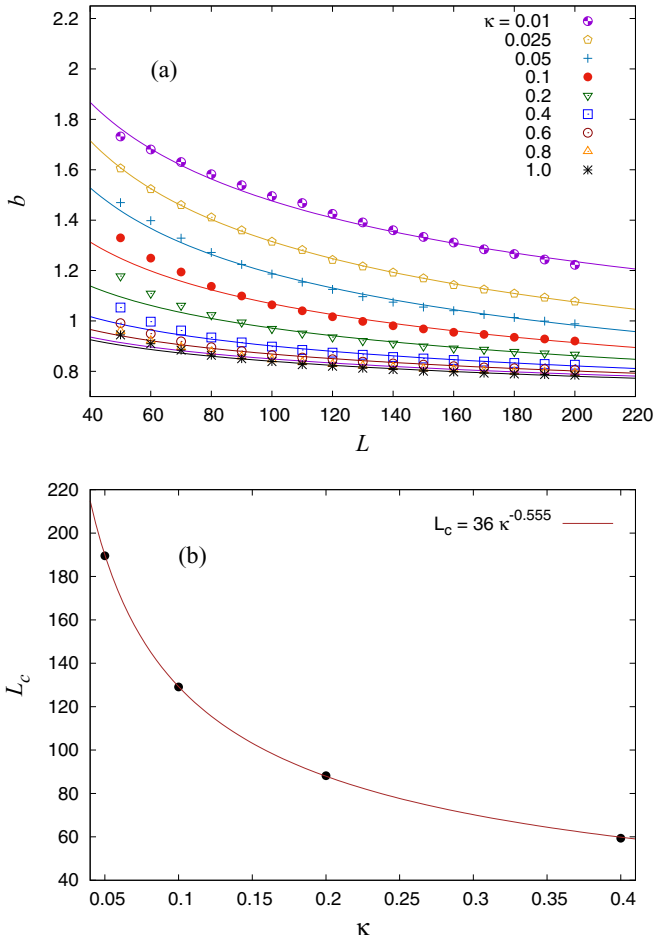

FIG. 5. (a) Release parameter b as a function of the capsule size L for different membrane erosion rates κ, with the points obtained from the simulation results whereas the lines represent the adjusted curves (see text). (b) The points represent the crossover size L_c against the erosion rate κ, whereas the line represents the fitted function.

B. Relation between characteristic time τ and erosion rate κ

Next we investigate the size contribution of the capsule to the release parameter τ for different erosion rates. In particular, this information is useful for understanding the interplay role of membrane erosion and drug diffusion on the drug release process, and its role in creating a crossover region. Before starting, it should be stressed that we are dealing with an out-of-equilibrium mesoscopic system and that, considering this, the observed crossover regions are not expected to occur concomitantly for the b and τ release parameters. Nevertheless, while increasing the system size, it should be reasonable to expect that the crossover signature in τ becomes closer to the those obtained for b.

Insights on the scaling behavior of τ with the capsule length can be obtained if one notes that the stochastic diffusion of the drug molecules inside the capsule satisfies

$$\langle r^2 \rangle \sim 2dD_0t \tag{6}$$

for long times, with $\langle r^2 \rangle$ the drug mean square displacement, d the system dimension, D_0 the diffusion coefficient of the drug inside the capsule, and t the time [48,70].

For a diffusion controlled devices, where erosion is faster than diffusion ($\kappa \gg \kappa_c$), the characteristic time τ will be mostly determined by the previous equation, scaling with the capsule size L as $\tau = aL^2$, with $a = 1/(2dD_0)$. On the other hand, for erosion controlled devices, where erosion is much slower than diffusion ($\kappa \ll \kappa_c$), becoming a limiting step for drug release, the characteristic time for drug release τ is expected to follow the trend presented by the membrane behavior and is expected to scale linearly with the size of the device $L(\tau \sim aL)$.

This pattern is verified numerically in Fig. 6, where τ values are shown for sizes between $L = 50$ and 200 and erosion rates κ between 0.01 and 1.00. It is possible to anticipate how the characteristic time will scale with L in the crossover region by making a simple average of the exponent μ in the expression $\tau \sim L^{2-\mu}$, considering the extreme cases, resulting in $\mu_c = (0 + 1)/2 = 1/2$, i.e., $\tau \sim L^{3/2}$. Appendix A shows that this scaling relation can be calculated with the assumption

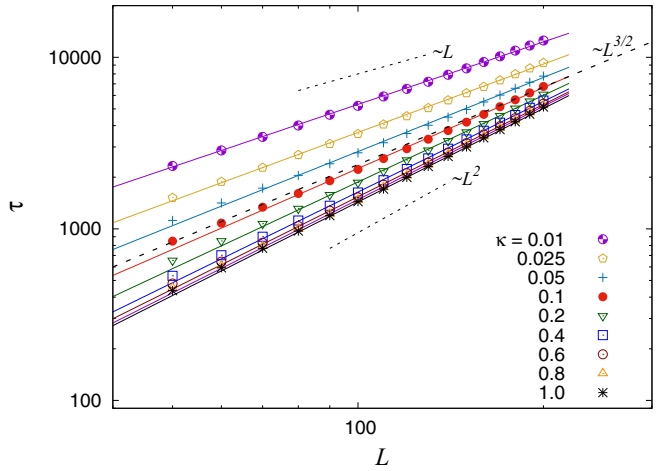

FIG. 6. Log-log plot of the characteristic release time τ as a function of the capsule size L for different membrane erosion rates κ with sizes L varying from 50 to 200; simulation data marked as points and adjusted curves with lines (see text).

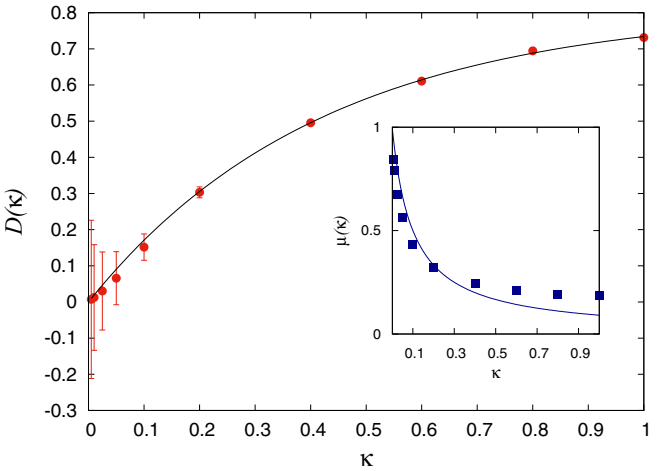

FIG. 7. The effective diffusion, $D(k) = D_0 F(\kappa)$, plotted against the erosion rate constant κ. Data points correspond to values adjusted from the simulations presented in Fig. 6 and a continuous line corresponds to the function adjusted from (9). Inset: Similar results for the exponent $\mu(\kappa)$ from (8).

that the generalized diffusion exponent for drug molecules inside the capsule satisfies an Arrhenius relation.

As shown in Fig. 6, our simulations do indicate that for large enough L, the crossover occurs at some critical erosion rate κ_c and its signature will be observed both through the scaling relation on $\tau_c \sim L^{3/2}$ and on the observed value of the Weibull parameter b, which will be $b_c \approx 1$. In other words, for large enough L, the crossover signatures in both b and τ happen for the same erosion rate κ_c. Also note that $\tau_c \sim L^z$ with $z = 3/2$ shows a possible connection with universal growth phenomena [71], which deserves further investigation. It also makes the electrochemical model [63] similar to the etching model [72], which belongs to the Kardar-Parisi-Zhang universality class.

C. An expression for $\tau(L, \kappa)$

Let us now introduce an expression for $\tau(L, \kappa)$ which adjusts our numerical data and could be useful for extrapolating experimental data and predicting crossover erosion rates κ_c. Despite being phenomenological by construction, the advantage of the current approach is that it is inspired by reasonable physical arguments regarding the crossover between the two mechanisms present in the current model, and also is consistent with current simulations. Later, we will apply it for the release of acetaminophen from the erosive wax matrix [33].

Considering that in a pure diffusive system $\tau \sim aL^2$, we choose to associate an effective diffusion coefficient of drug molecules inside the device by defining $a(\kappa) = \frac{1}{2dD(\kappa)}$. Further analysis of the characteristic time presented in Fig. 6 suggests a dependence on the erosion rate κ for both the size dependence exponent $\mu \equiv \mu(\kappa)$ and the effective diffusion $D \equiv D(\kappa)$. In this way, we choose to represent

$$\tau \equiv \tau(L, \kappa) \approx \frac{l_0^2 L^2}{2dD(\kappa)} L^{-\mu(\kappa)}. \tag{7}$$

Guided by the discussion in the previous section, we can approximate the numerical values for $\mu(\kappa)$ with reasonable precision by the function

$$\mu(\kappa) = \frac{1}{1 + \kappa/\kappa_c}, \tag{8}$$

which makes τ satisfy the expected linear (quadratic) behavior in the small (large) erosion limit, with κ_c being the size dependent crossover erosion rate, for which $\mu(\kappa_c) = 1/2$ (e.g., see Fig. 7). The effective diffusion $D(\kappa)$ is given by

$$D(\kappa) = D_0 F(\kappa), \tag{9}$$

with $F(\kappa)$ a function that switches off the diffusion coefficient D_0 as the membrane covering the device becomes stiffer. The limiting behavior of $F(\kappa)$ must satisfy

$$\lim_{\kappa \to 0} F(\kappa) = 0,$$

since drug molecules cannot escape from the device without erosion, and

$$\lim_{\kappa \to \infty} F(\kappa) = 1,$$

for recovering the limit of simple diffusion. With these definitions, we were able to use the simulations results presented in Fig. 6 to fit Eq. (9) with $F(\kappa)$ given by the function

$$F(\kappa) = 1 - \exp(-\gamma\kappa), \tag{10}$$

where $\gamma = 2.36(5)$ and $D_0 = 0.81(1)$ are model dependent constants, as shown in Fig. 7 for the numerical values from simulations and the best fitted functions for both $D(\kappa)$ and $\mu(\kappa)$ (inset). By using expressions (8)–(10) on definition (7), we obtain

$$\tau(L, \kappa) = \tau_D \frac{(l/l_0)^{-(1+\kappa/\kappa_c)^{-1}}}{1 - \exp(-\gamma\kappa)}, \tag{11}$$

where $l = Ll_0$ is the experimental capsule size and τ_D is a characteristic time that is independent of erosion or other

membrane properties, given by

$$\tau_D = \frac{l^2}{2dD_0}. \tag{12}$$

It should be noted that the product $\gamma\kappa$ is dimensionless and the physical dimension of the diffusion coefficient, D_0, is $[\text{length}]^2/[\text{time}]$, which imposes the correct unit of time in the expression (11).

While expression (11) was devised in a phenomenological approach to resemble the behavior observed in our model, we note that the main assumptions used in deriving it were related to the comprehension that there is an interplay between two release mechanisms: the erosive mechanism whose dynamics introduces a linear relation between characteristic time and characteristic length, and the random diffusion that drug particles perform *inside* the capsule device, which connects characteristic times and length in a quadratic way. In this way, we expect that expression (11) could be useful in situations that despite being different from the statistical model used to deduce it, also present those two release mechanisms. This is done in the following section, where we discuss the possibility of applying our approach to the release of acetaminophen (paracetamol) immersed in a wax matrix [33].

A low erosion rate limit expression for (11) can be easily calculated, which in turn allows the major physical quantities to be obtained from a simple linear fit. This could be useful for determining both κ_c and γ, but demands data about devices with small erosion rate κ, as compared to the yet unknown κ_c, and also small variations in the characteristic time τ while changing κ. Due to this requirement, this approach cannot be used with the experimental data discussed in the next section, but we keep the low-κ limit calculation in Appendix B as it can be useful in other contexts.

D. Acetaminophen release from a wax matrix

Agata *et al.* [33] developed a theoretical model based on the solution of the diffusion equation for three-dimensional capsules, in which the capsule radius changed with time, $a(t) = a_0 - kt$, with a_0 being the initial value of the capsule radius and κ the erosion rate of the eroding front. The model was successfully applied to adjust the release of acetaminophen in a wax matrix in which the erosion was increased with the addition of a pH-dependent functional polymer aminoalkyl methacrylate copolymer E (AMCE) and, besides accurately adjusting release curves, they also obtained values of erosion and drug diffusion rates for 30 experimental batches with different concentrations of acetaminophen and AMCE, as well as different capsule sizes and pH values. The fact that in this work both erosion and diffusion rates can be calculated makes it possible to use those data as input in Eq. (11) in order to calculate the main feature pointed by our model: the crossover erosion rate κ_c. Nevertheless, predicting k_c from the data available on [33] is challenging because, even after using k and D_0 from this paper, Eq. (11) is still left with three quantities to be determined: k_c, γ, and l_0, but for this work, at most, two batches were prepared with equivalent sizes and fraction of acetaminophen.

To overcome this difficultly, we first estimate the pore size l_0 using the diameter of the acetaminophen molecule in a spherical molecular approximation, $l_0 \sim V^{1/3}$, which can be calculated as $l_0 = 5.7805 \times 10^{-4}$ μm ($C_8H_9NO_2$) by using its molecular weight and density values, which are 151.16 g/mol and 1.3 g/cm^3, respectively [73]. With this value, Eq. (11) is undetermined by two parameters, κ_c and γ, but it is still necessary to investigate the meaning of characteristic time τ in the experimental setup [74].

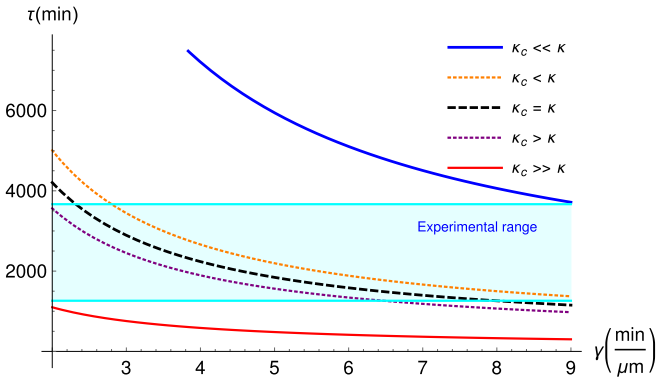

FIG. 8. Characteristic release time of acetaminophen from the erosive wax matrix as a function of the (undetermined) parameter γ, obtained from Eq. (11), with experimental values of capsule size, erosion rate, and diffusion constant from [33].

Within this context, we devised two criteria for selecting a batch: (i) the capsules should be big enough in order to reduce small size effects and, particularly, considering that we observed that different signatures for the crossover between the erosive and diffusive regimes converge to the same values of erosion for bigger systems, and (ii) the capsule should be eroding as slowly as possible in order to distinguish it properly from the diffusive regime, which is well described by the diffusion equation without erosion. In this way, we choose to apply Eq. (11) to batch 5 at pH 6.5, as indicated in Table 2 of Ref. [33], and we use their estimates for the erosion rate, $k = 6.37 \times 10^{-2}$ μm/min, diffusion coefficient, 8.07×10^{-2} $(\mu\text{m})^2$/min, and mean particle radius size, $l = 234.1 \pm 6.9$ μm. We extracted the drug release data for this batch from Fig. 1 of Ref. [33] and adjusted it to the Weibull distribution function, having found $b = 1.12(4)$ and $\tau = 1149(23)$ minutes which, in our proposition, indicates that the erosion mechanism controls the release dynamics.

Next, we show that by choosing some k_c (values around the experimental erosion constant) as a function of γ, we are able to find the drug release time which, for some $\{k_c, \gamma\}$, falls in the experimental range. Although this process seems naive, it can be used by an experimental researcher to make some predictions about the drug release mechanism and/or improve a particular drug device in order to obtain a desired drug delivery (weeks, months, etc.), which is extremely difficult to achieve by knowing only the type of the polymer matrix and the diffusion coefficient of the pharmaceutical component.

In this way, in Fig. 8, the characteristic release time τ is shown as a function of γ (μm/min), using five different values of k_c. The filled area between the vertical lines corresponds to the reasonable experimental range values expected for τ, ranging from around 63% to 100% of the release of acetaminophen from the wax matrix in batch 5 [33]. Five values

of k_c were chosen, $\{4.5, 6.05, 6.37, 8.8, 9.5\} \times 10^{-2}$ μm/min, corresponding to the cases where the erosion rate is slightly lower, slightly higher, and equal to the crossover erosion rate, as well as much lower and much higher than the erosion rate of the setup (6.37×10^{-2} μm/min).

For $k_c = k$ (dashed line in Fig. 8), the values of τ obtained from Eq. (11) are within the experimental range and its value is close to 63% of release when $\gamma \approx 8$ μm/min. In order to compare this value of γ to our computational model, we consider the product γk_c which was found to be $\gamma k_c \approx 0.24$ in our model and approximately 0.5 for the experimental batch considered here.

The same figure also shows curves of τ in terms of γ for $k_c < k$ and $k_c > k$, where we choose κ_c as being displaced 5% below or above κ in each case. These curves behave similarly, showing that within the current approach, batch 5 is close to the crossover erosion rate. In the cases where either $k_c \ll k$ (diffusion dominant, $k_c = 4.5 \times 10^{-2}$ μm/min) or $k_c \gg k$ (erosion dominant, $k_c = 9.5 \times 10^{-2}$ μm/min), τ is out of the experimental range, as shown in Fig. 8. This is another evidence indicating that the release process is not determined by only one mechanism (either erosion or diffusion), and that even without the AMCE compound, erosion is relevant to the drug release mechanism.

IV. CONCLUSION

In this work, we have extended the stochastic lattice model implemented in previous work from our group [44,45] to investigate the effects of membrane polymer erosion on the drug release mechanism. The Weibull function was found to describe with good approximation the entire release curve in our model, for different erosion rates. By comparing the time evolution of the membrane content and the amount of drug within the capsule, we found that at $b_c \approx 1$, there is crossover between the dominant mechanisms: for b values bigger than b_c, erosion is the predominant mechanism controlling the drug release, while for $b < 1$, diffusion is governing the release. As shown in Fig. 4, within each of this two regions, the values of b can be approximated by scaling laws of erosion rates with different exponents.

We have also identified that within the crossover, the characteristic time satisfies $\tau_c \approx L^{3/2}$, which can be justified through the Arrhenius relation for diffusion (see Appendix A). The arguments used to demonstrate the size dependence on the characteristic time τ allowed us to propose the phenomenological function in (11), which nicely adjusted the drug release from the Monte Carlo simulations of the model proposed in this work. Experimental data for the release of acetaminophen from the wax matrix were investigated using the expression for $\tau \equiv \tau(L, \kappa)$ and it was shown that erosion rates of the investigated devices (batch 5 of paper [33]) were close to the crossover erosion rate, with the parameter γ compatible with those obtained in our simulations.

The computational results and the analysis of the experimental data for acetaminophen release with Eq. (11) suggest that it should be possible to use scaling laws to improve our comprehension of the competition between different mechanisms governing the drug release dynamics. In particular, for the case of acetaminophen in a wax matrix, in which the erosion can be controlled with the addition of AMCE, our work indicates that through controlled increase of erosive agents, it should be possible to test the hypothesis in our models as well as the usage of Eq. (11), or the small-κ expression in (B5), to obtain the crossover erosion rate κ_c.

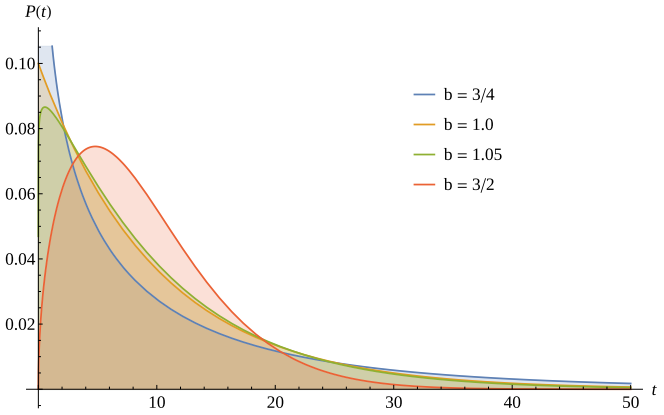

FIG. 9. Plots of the Weibull probability density distribution $P(t)$ against time t for different values of b (y-axis values in Fig. 4). The time t and $\tau = 10$ are in arbitrary units.

Although the results presented in the current work started assuming linearly decaying membranes, it could also be generalized to exponentially decaying membranes with distribution probabilities satisfying a Poisson process [3]. Even though it is outside the scope of the current work, these modifications should be straightforward to be performed, and we expect it should be compatible with most of our results, as can be readily inferred from Eq. (3).

It is important to stress that our model does not address the issue of indicating what drives the molecular relation between erosion and capsule size, geometry, drug load, and concentration of erosive compounds. Further theoretical or experimental data are needed for determining κ and other parameters needed to calculate κ_c. Nevertheless, the proposition in our work is that in regimes where different mechanisms are controlling the drug release, different scaling laws should be used to describe the relevant parameters describing the release process and that by knowing the release behavior in those extreme regimes, it should be possible to predict scaling behavior in the crossover. We expect that these ideas could be useful in providing some guidance to select the most useful properties and characteristics of capsules and devices for testing drug delivery systems.

Last remarks. Finally, we would like to provide some arguments for why the Weibull distribution seems to correctly describe the drug release process. First, let us consider the drug release fraction $R(t)$ (e.g., see Fig. 3), which can be recognized as the cumulative probability distribution (CPD), while $P(t) = \frac{dR(t)}{dt}$ corresponds to the Weibull probability density distribution function (PDF) with $t > 0$, $b \geqslant 0$, and $\tau > 0$, which is also called "failure density" and gives the chance that a unit (drug particle) will fail (release) at time t [57,75]. For example, in Fig. 9, we show $P(t)$ against t for different values of b. As we can see, small deviations in b, such as those presented in Fig. 4, change the shape of the PDF, essentially altering the characteristic release times, e.g., the

first moment of $P(t)$ (average time), $\langle t\rangle = \int_0^\infty tP(t)dt$, with $P(t)$ normalized.

There is also a microscopic time associated with the particle trajectories [the time which the drug particle takes to be released (fail)], which can be shorter or longer due to many factors, for example, excluded volume interactions and initial position of the particles (whether or not it is closer to a leaking site; see Fig. 1). For different realizations and particles, we must have different trajectories; for a capsule with mesoscopic size, we expect that the particle takes a very long time to reach a pore and be released. In other words, the microscopic release time is a rare event and should satisfy the principles of the extreme value distribution [76], being directed related to the mean-first-passage time of a Brownian particle [77], which may be the reasons for the Weibull distribution to describe the drug release processes correctly, and it will be investigated further in our future works.

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APPENDIX A: DERIVATION OF CROSSOVER EXPONENT μ_c

Let us start by assuming that drug particles are leaving the capsule through an Arrhenius process in which the diffusion coefficient satisfies

$$D \propto \exp(-\beta\Delta E), \tag{A1}$$

where $\beta = 1/k_BT$, with k_B being the Boltzmann constant and ΔE the activation energy for the process of a drug particle to leave the capsule. For a purely diffusive system, dimensional analysis can be used to express the D as

$$D = \text{const} \times \frac{l^2}{\tau}, \tag{A2}$$

where l is the capsule size, τ is the characteristic release time defined above, and const is a constant which is possibly dependent on the system dimension and geometry. With these definitions, τ can be written as

$$\tau = Ae^{\beta\Delta E}, \tag{A3}$$

where A is a constant dependent on the system details. In order to consider the effect of erosion, we will introduce a dependence on the erosion constant on all major functions, redefining (A3) as

$$\tau_\kappa = A_\kappa e^{\beta\Delta E_\kappa}. \tag{A4}$$

In addition, we use the fact that $\tau_\kappa \equiv \tau(\kappa)$ depends on κ through the scaling law given by Eq. (7), and by using (A4) back in this expression, one obtains the *activation free energy* for the drug release process for a certain erosion rate κ as

$$\beta\Delta E_k = [2-\mu_\kappa]\ln L - \ln\left[\frac{2dD_\kappa A_\kappa}{l_0^2}\right], \tag{A5}$$

where $D_\kappa = D(\kappa)$ and $\mu_\kappa = \mu(\kappa)$.

From this latter expression, the simplest assumption about the value of crossover activation energy is that it could be the average between the two independent processes, $\Delta E_c = (\Delta E_D + \Delta E_E)/2$, where subindexes c, E, and D denote the erosion constant values corresponding to *crossover*, erosion control, and diffusion controlled systems. Through this latter assumption, it is possible to calculate

$$\beta\Delta E_c = [2-\mu_c]\ln L - \ln\left(\frac{2dD_cA_c}{l_0^2}\right), \tag{A6}$$

where

$$\mu_c = \mu(\kappa_c) = \frac{\mu_E+\mu_D}{2} = \frac{1}{2}, \tag{A7}$$

$$D_c = \sqrt{D_E D_D}, \tag{A8}$$

$$A_c = \sqrt{A_E A_D}, \tag{A9}$$

which provides a stronger derivation for the phenomenological value of the crossover scaling exponent μ_c, as discussed on more phenomenological grounds in Sec. III B. It is also interesting to note that the diffusion (A8) and the coefficient A_c (A9) at the crossover satisfy a combination rule similar to that of Lorentz and Berthelot [78,79] for the Lennard-Jones interaction coefficients between atoms of different species.

APPENDIX B: LOW-κ EXPRESSION FOR τ

Before proceeding, let us define $x = \kappa/\kappa_c$, which will be used to express the characteristic time in Eq. (11), as

$$\frac{\tau(L,x)}{\tau_D} = \frac{(l/l_0)^{-(1+x)^{-1}}}{1-\exp(-\gamma\kappa_c x)}. \tag{B1}$$

If the erosion mechanism is dominant, the system will be far from the *crossover*, i.e., $x \ll 1$. Within this limit, Taylor expansions can be used to write

$$\left(\frac{l}{l_0}\right)^{-\frac{1}{1+x}} \approx \left(\frac{l}{l_0}\right)^{-1}\left(\frac{l}{l_0}\right)^{x} \tag{B2}$$

and

$$1-\exp(-\gamma\kappa_c x) \approx \gamma\kappa_c x, \tag{B3}$$

where it was implicit that $\gamma\kappa_c$ is a small number, as in our simulations. By using (B2) and (B3) in (B1), one gets

$$\frac{\tau(L,x)}{\tau_D} \approx \left(\frac{l}{l_0}\right)^{-1}\frac{L^x}{\gamma\kappa_c x} = \left(\frac{l}{l_0}\right)^{-1}\frac{\exp(x\ln L)}{\gamma\kappa_c x}. \tag{B4}$$

If one assumes that the capsule is small, in the sense that $x < x\ln L \ll 1$, it is possible to simplify this equation even further

by writing it as

$$\tau(L,x) \approx \left(\frac{\tau_D}{\gamma\kappa_c}\right)\left(\frac{l}{l_0}\right)^{-1}\left(\frac{1}{x}+\ln\frac{l}{l_0}\right). \tag{B5}$$

Note that the right-hand side of this expression was rearranged to emphasize that the contributions to τ are coming from three different terms. The characteristic release time τ_D is modulated by $\gamma\kappa_c$ because this is the low limit of function $F(\kappa)$ defined in (10) to reduce the diffusion constant inside the capsule as an effect of the presence of the erosive membrane covering it. The term $(l/l_0)^{-1}$ appears due to the choice made in Eq. (7), which is associated to the linear scaling linear law dependence of τ with size in the slow erosive regime, while the last term expresses that τ increases with $1/x$ and that there is a logarithmic correction with the capsule size, which is independent of κ.

It is interesting to rewrite Eq. (B5) as

$$L\frac{\tau}{\tau_D} = A\frac{1}{\kappa} + B, \tag{B6}$$

where $A = 1/\gamma$ and $B = \ln L/(\gamma\kappa_c)$, which is amenable to simple linear interpolation in terms of $1/\kappa$. In this way, experimental values of γ and κ_c could be obtained through $\gamma = A^{-1}$ and $\kappa_c = \ln LA/B$.

[1] R. Langer, New methods of drug delivery, Science **249**, 1527 (1990).

[2] H. Brem, Polymers to treat brain tumours, Biomaterials **11**, 699 (1990).

[3] A. Göpferich and R. Langer, Modeling of polymer erosion, Macromolecules **26**, 4105 (1993).

[4] H. Brem and P. Gabikian, Biodegradable polymer implants to treat brain tumors, J. Control. Release **74**, 63 (2001).

[5] H. He *et al.*, Use of a nanoporous biodegradable miniature device to regulate cytokine release for cancer treatment, J. Control. Release **151**, 239 (2011).

[6] N. Kamaly, B. Yameen, J. Wu, and O. C. Farokhzad, Degradable controlled-release polymers and polymeric nanoparticles: Mechanisms of controlling drug release, Chem. Rev. **116**, 2602 (2016).

[7] S. Talebian *et al.*, Biopolymers for antitumor implantable drug delivery systems: Recent advances and future outlook, Adv. Mater. **30**, 1706665 (2018).

[8] C. Lynch *et al.*, Advances in biodegradable nano-sized polymer-based ocular drug delivery, Polymers **11**, 1371 (2019).

[9] A. Santos *et al.*, Drug-releasing implants: Current progress, challenges and perspectives, J. Mater. Chem. B **2**, 6157 (2014).

[10] J. Siepmann, R. A. Siegel, and M. J. Rathbone, *Fundamentals and Applications of Controlled Release Drug Delivery*, Advances in Delivery Science and Technology (Springer, New York, Dordrecht, Heidelberg, London, 2012).

[11] Y. Xu, C.-S. Kim, D. M. Saylor, and D. Koo, Polymer degradation and drug delivery in plga-based drug-polymer applications: A review of experiments and theories, J. Biomed. Mater. Res., Part B **105**, 1692 (2017).

[12] S. Zhang *et al.*, Release mechanisms and practical percolation threshold for long-acting biodegradable implants: An image to simulation study, J. Pharm. Sci. (2021).

[13] H. Kimura and Y. Ogura, Biodegradable polymers for ocular drug delivery, Ophthalmologica **215**, 143 (2001).

[14] F. A. Oliveira, B. A. Mello, and I. M. Xavier Jr, Scaling transformation of random walk distributions in a lattice, Phys. Rev. E **61**, 7200 (2000).

[15] A. M. Maroja, F. A. Oliveira, M. Cieśla, and L. Longa, Polymer fragmentation in extensional flow, Phys. Rev. E **63**, 061801 (2001).

[16] C. L. Dias, M. Dubé, F. A. Oliveira, and M. Grant, Scaling in force spectroscopy of macromolecules, Phys. Rev. E **72**, 011918 (2005).

[17] M. Engelsberg and W. Barros, Free-evolution kinetics in a high-swelling polymeric hydrogel, Phys. Rev. E **88**, 062602 (2013).

[18] W. Barros, Solvent self-diffusion dependence on the swelling degree of a hydrogel, Phys. Rev. E **99**, 052501 (2019).

[19] L. T. Fan and S. K. Singh, *Controlled Release: A Quantitative Treatment* (Springer-Verlag, Berlin, 1989).

[20] J. Siepmann, N. Faisant, J. Akiki, J. Richard, and J. Benoit, Effect of the size of biodegradable microparticles on drug release: Experiment and theory, J. Control. Release **96**, 123 (2004).

[21] D. Klose, F. Siepmann, K. Elkharraz, and J. Siepmann, Plga-based drug delivery systems: Importance of the type of drug and device geometry, Intl. J. Pharm. **354**, 95 (2008).

[22] J. Siepmann and A. Göpferich, Mathematical modeling of bioerodible, polymeric drug delivery systems, Adv. Drug Delivery Rev. **48**, 229 (2001).

[23] S. Fredenberg, M. Wahlgren, M. Reslow, and A. Axelsson, The mechanisms of drug release in poly (lactic-co-glycolic acid)-based drug delivery systems—A review, Intl. J. Pharm. **415**, 34 (2011).

[24] N. A. Licata and A. V. Tkachenko, Kinetic Limitations of Cooperativity-Based Drug Delivery Systems, Phys. Rev. Lett. **100**, 158102 (2008).

[25] J. Siepmann and F. Siepmann, Mathematical modeling of drug delivery, Intl. J. Pharm. **364**, 328 (2008).

[26] J. Siepmann and F. Siepmann, Modeling of diffusion controlled drug delivery, J. Control. Release **161**, 351 (2012).

[27] A. Rahman, S. Ghosh, and R. Pal, Modeling of drug diffusion in a solid tumor leading to tumor cell death, Phys. Rev. E **98**, 062408 (2018).

[28] D. Caccavo, An overview on the mathematical modeling of hydrogels' behavior for drug delivery systems, Intl. J. Pharm. **560**, 175 (2019).

[29] G. Pontrelli, E. J. Carr, A. Tiribocchi, and S. Succi, Modeling drug delivery from multiple emulsions, Phys. Rev. E **102**, 023114 (2020).

[30] E. Kara, A. Rahman, E. Aulisa, and S. Ghosh, Tumor ablation due to inhomogeneous anisotropic diffusion in generic three-dimensional topologies, Phys. Rev. E **102**, 062425 (2020).

[31] C. Mircioiu *et al.*, Mathematical modeling of release kinetics from supramolecular drug delivery systems, Pharmaceutics **11**, 140 (2019).

[32] A. Charlier, B. Leclerc, and G. Couarraze, Release of mifepristone from biodegradable matrices: Experimental and theoretical evaluations, Intl. J. Pharm. **200**, 115 (2000).

[33] Y. Agata, Y. Iwao, K. Shiino, A. Miyagishima, and S. Itai, A theoretical approach to evaluate the release rate of acetaminophen from erosive wax matrix dosage forms, Intl. J. Pharm. **414**, 63 (2011).

[34] Y. Nitanai, Y. Agata, Y. Iwao, and S. Itai, A novel mathematical model considering change of diffusion coefficient for predicting dissolution behavior of acetaminophen from wax matrix dosage form, Intl. J. Pharm. **428**, 82 (2012).

[35] L. L. Lao, N. A. Peppas, F. Y. C. Boey, and S. S. Venkatraman, Modeling of drug release from bulk-degrading polymers, Intl. J. Pharm. **418**, 28 (2011).

[36] J. Siepmann, N. Faisant, and J.-P. Benoit, A new mathematical model quantifying drug release from bioerodible microparticles using monte carlo simulations, Pharm. Res. **19**, 1885 (2002).

[37] A. Göpferich and R. Langer, Modeling monomer release from bioerodible polymers, J. Control. Release **33**, 55 (1995).

[38] A. Göpferich, Erosion of composite polymer matrices, Biomaterials **18**, 397 (1997).

[39] K. Zygourakis, Development and temporal evolution of erosion fronts in bioerodible controlled release devices, Chem. Eng. Sci. **45**, 2359 (1990).

[40] K. Zygourakis, and P. A. Markenscoff, Computer-aided design of bioerodible devices with optimal release characteristics: A cellular automata approach, Biomaterials **17**, 125 (1996).

[41] N. Bertrand, G. Leclair, and P. Hildgen, Modeling drug release from bioerodible microspheres using a cellular automaton, Intl. J. Pharm. **343**, 196 (2007).

[42] A. Barat, H. J. Ruskin, and M. Crane, Probabilistic models for drug dissolution. Part 1. Review of Monte Carlo and stochastic cellular automata approaches, Simul. Model. Prac. Theor. **14**, 843 (2006).

[43] M. Bezbradica, M. Crane, and H. J. Ruskin, Release modelling of nanoencapsulated food ingredients by probabilistic models: Cellular automata and Monte Carlo methods, in *Release and Bioavailability of Nanoencapsulated Food Ingredients*, edited by S. M. Jafari (Elsevier, New York, 2020), pp. 273–309.

[44] M. S. Gomes-Filho, F. A. Oliveira, and M. A. A. Barbosa, A statistical mechanical model for drug release: Investigations on size and porosity dependence, Physica A **460**, 29 (2016).

[45] M. S. Gomes-Filho, M. A. A. Barbosa, and F. A. Oliveira, A statistical mechanical model for drug release: Relations between release parameters and porosity, Physica A **540**, 123165 (2020).

[46] M. H. Lee, Can the Velocity Autocorrelation Function Decay Exponentially? Phys. Rev. Lett. **51**, 1227 (1983).

[47] R. Morgado, F. A. Oliveira, G. G. Batrouni, and A. Hansen, Relation Between Anomalous and Normal Diffusion in Systems with Memory, Phys. Rev. Lett. **89**, 100601 (2002).

[48] F. A. Oliveira, R. M. S. Ferreira, L. C. Lapas, and M. H. Vainstein, Anomalous diffusion: A basic mechanism for the evolution of inhomogeneous systems, Front. Phys. **7**, 18 (2019).

[49] M. H. Vainstein, I. V. L. Costa, R. Morgado, and F. A. Oliveira, Non-exponential relaxation for anomalous diffusion, Europhys. Lett. **73**, 726 (2006).

[50] M. H. Vainstein, I. V. Costa, and F. Oliveira, Mixing, ergodicity and the fluctuation-dissipation theorem in complex systems, in *Jamming, Yielding, and Irreversible Deformation in Condensed Matter*, edited by M. C. Miguel and M. Rubi (Springer, New York, 2006), pp. 159–188.

[51] I. Costa, M. Vainstein, L. Lapas, A. Batista, and F. Oliveira, Mixing, ergodicity and slow relaxation phenomena, Physica A **371**, 130 (2006).

[52] W. Weibull, A statistical distribution function of wide applicability, J. Appl. Mech. **18**, 293 (1951).

[53] T. C. Tsu, Discussion: A statistical distribution function of wide applicability, J. Appl. Mech. **19**, 233 (1952).

[54] F. Langenbucher, Letters to the editor: Linearization of dissolution rate curves by the Weibull distribution, J. Pharm. Pharmacol. **24**, 979 (1972).

[55] S. Casault and G. W. Slater, Comments concerning: Monte Carlo simulations for the study of drug release from matrices with high and low diffusivity areas, Intl. J. Pharm. **365**, 214 (2009).

[56] F. Mohammadpour *et al.*, The PLGA microspheres synthesized by a thermosensitive hydrogel emulsifier for sustained release of risperidone, J. Pharm. Innovat. 1 (2021).

[57] C. Corsaro, G. Neri, A. M. Mezzasalma, and E. Fazio, Weibull modeling of controlled drug release from ag-pma nanosystems, Polymers **13**, 2897 (2021).

[58] M. Berthault, J. Santos-Peña, D. Lemordant, and E. D. Vito, Dynamics of the 6li/7li exchange at a graphite–solid electrolyte interphase: A time of flight–secondary ion mass spectrometry study, J. Phys. Chem. C **125**, 6026 (2021).

[59] M. Ignacio, M. V. Chubynsky, and G. W. Slater, Interpreting the Weibull fitting parameters for diffusion-controlled release data, Physica A **486**, 486 (2017).

[60] M. Ignacio and G. Slater, Using fitting functions to estimate the diffusion coefficient of drug molecules in diffusion-controlled release systems, Physica A **567**, 125681 (2021).

[61] V. Papadopoulou, K. Kosmidis, M. Vlachou, and P. Macheras, On the use of the Weibull function for the discernment of drug release mechanisms, Intl. J. Pharm. **309**, 44 (2006).

[62] P. K. Janert, *Gnuplot in Action: Understanding Data with Graphs* (Manning Publications, Greenwich, CT, 2009).

[63] J. Saunier, A. Chaussé, J. Stafiej, and J. Badiali, Simulations of diffusion limited corrosion at the metal-environment interface, J. Electroanal. Chem. **563**, 239 (2004).

[64] H. Laaksonen, J. Hirvonen, and T. Laaksonen, Cellular automata model for swelling-controlled drug release, Intl. J. Pharm. **380**, 25 (2009).

[65] T. D. Reynolds, S. H. Gehrke, A. S. Hussain, and L. S. Shenouda, Polymer erosion and drug release characterization of hydroxypropyl hethylcellulose matrices, J. Pharm. Sci. **87**, 1115 (1998).

[66] S. N. Rothstein, W. J. Federspiel, and S. R. Little, A simple model framework for the prediction of controlled release from bulk eroding polymer matrices, J. Mater. Chem. **18**, 1873 (2008).

[67] Weibull parameter b is shown with three significant digits and the error on its value, as obtained from the

precision of the adjustment, is smaller than the last significant digit.

[68] In our model, for a system with $4L = 800$ membrane sites and an erosion rate equal to $\kappa = 0.01$, it would take 8×10^4 MC steps for the membrane to disappear.

[69] Adjusted parameters are equal to $b_0 = 0.6924 \pm 0.0006$, $\delta = 0.120 \pm 0.003$, $b_1 = 0.778 \pm 0.002$, and $\nu = 0.069 \pm 0.001$.

[70] Silvio R. A. Salinas, *Introduction to Statistical Physics* (Springer Verlag, New York, 2001).

[71] M. S. Gomes-Filho, A. L. Penna, and F. A. Oliveira, The Kardar-Parisi-Zhang exponents for the 2+1 dimensions, Results Phys. **26**, 104435 (2021).

[72] W. P. Gomes, A. L. A. Penna, and F. A. Oliveira, From cellular automata to growth dynamics: The Kardar-Parisi-Zhang universality class, Phys. Rev. E **100**, 020101(R) (2019).

[73] National center for biotechnology information. "pubchem compound summary for cid 1983, acetaminophen" PubChem https://pubchem.ncbi.nlm.nih.gov/compound/Acetaminophen (unpublished).

[74] We choose to be careful on the interpretation of τ in relation to the experimental data since we are working with a phenomenological theory and, considering this, it should be important not to input biases (e.g., toward the usage of the Weibull function) in our assumptions.

[75] H. Rinne, *The Weibull Distribution: A Handbook* (CRC Press, New York, 2008).

[76] A. Hansen, The three extreme value distributions: An introductory review, Front. Phys. **8**, 604053 (2020).

[77] S. Redner, *A Guide to First-Passage Processes* (Cambridge University Press, Cambridge, UK, 2001).

[78] H. A. Lorentz, Ueber die Anwendung des Satzes vom Virial in der kinetischen Theorie der Gase, Ann. Phys. **248**, 127 (1881).

[79] D. Berthelot, Comptes rendus hebdomadaires des sances de l'Académie des Sciences, Acad. Sci. Bach. Paris **126**, 1703 (1898).