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A statistical mechanical model for drug release: Relations between release parameters and porosity

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ABSTRACT

A lattice gas model is proposed for investigating the release of drug molecules on devices with semi-permeable, porous membranes in two and three dimensions. The kinetic of this model was obtained through the analytical solution of the three-dimension diffusion equation for systems without membrane and with Monte Carlo simulations. Pharmaceutical data from drug release is usually adjusted to the Weibull function, $\exp[-(t/\tau)^b]$, and the dependence of adjusted parameters b and τ is usually associated, in the pharmaceutical literature, with physical mechanisms dominating the drug dynamics inside the capsule. The relation of parameters τ and b with porosity λ are found to satisfy, a simple linear relation for between τ and λ^{-1}, which can be explained through simple physically based arguments, and a scaling relation between b and λ, with the scaling coefficient proportional to the system dimension.

1. Introduction

The advances in the synthesis technology of porous materials allowed the development of new matrices (monolithic) and membrane pharmaceutical devices where size, shape and pore distribution can be fine controlled during the fabrication process [1–4]. Understanding the connection between drug release rates and the characteristics of the device has an enormous potential for improving the treatment of various diseases.

Mathematical modeling of drug release usually involves finding the proper form of a diffusion equation considering the essential physical phenomena occurring as particles diffuse through the capsule device [5–7]. In the pharmaceutical literature it is also a common procedure to fit drug release data to semi-empirical functions and use this information to obtain insights onto the processes through which the drug is released. Since many factors can contribute to determine the final drug release, this procedure can be subject to ambiguous interpretations that could make the data analysis even more confusing [8]. Thus, a more systematic approach for understanding the relation between release data and physical processes occurring inside the capsule is desired. We work in this direction by simulating minimalist lattice models devised to describe both drug and physical device (or capsule) and investigate the relation between drug release patterns and the system porosity through the semi-empirical parameters of the Weibull function.

In this work a lattice gas model is proposed for investigating the release of drug molecules encapsulated on devices with semi-permeable, porous membranes in two and three dimensions, following a previous work on 1D and 2D systems [9].

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Release patterns were obtained through analytical solution of the three-dimension diffusion equation, for systems without membrane, and Monte Carlo simulations (MC), for systems with porous membrane, and adjusted to the Weibull function, $\exp[-(t/\tau)^b]$. The dependence of the characteristic time τ with the membrane content, defined as the inverse power of porosity, $\zeta = \lambda^{-1}$, was found to satisfy linear relation, that is justified using reasonable physical arguments. The parameter b was found to satisfy a scaling relation with ζ from a regime without membrane for up to 90% of membrane coverage.

This article is organized as follows, in the next section we present the Weibull distribution and discuss previous investigations about its semi-empirical parameters using statistical mechanical models, the current model and the simulations protocol are introduced in Section 2, while our results and discussions are presented in Section 3. An analytical solution for the diffusion equation of a continuous system similar to our 3D lattice model is presented in Appendix.

1.1. Weibull distribution

The Weibull distribution function was originally proposed by Waloddi Weibull in 1951 as an empirical function used to adjust non-linear experimental data from complex systems [10]. Distributions on systems as diverse as electric bulb duration, life expectancy in human populations, and yield strength of steel where investigated in the original work, but its range of application is much broader since the Weibull function is one of possible distributions of extreme statistics, along with Fréchet and Gumbel distributions [11,12]. For further details on the Weibull distribution see the Ref. [13], which discusses the history, the statistical properties, and other topics related to this distribution. On the pharmaceutical research it was first used to adjust data from drug release on 1972 by Langenbucher [14] and, since then, it became common to use the Weibull function to obtain phenomenological insights into the intrinsic mechanisms governing the drug release. As discussed by Slater [15], it is appropriate to write this as:

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

where $N(t)$ is the amount of drug molecules inside the device as a function of time t and $N_0 \equiv N(0)$ is the initial number of drug molecules inside the device. The parameter τ is associated with the time where approximately 63% of the drug has been released and b with the physical mechanisms leading to drug release within the device [14,16,17]. Expression (1) is found as a distribution function in out of equilibrium systems and $b \neq 1$ in diffusive models is usually associated to process with colored noises and/or memory effects [18,19].

Lattice models have been used to investigate the relation between the release and capsule parameters [20,21]. While early works were devoted to finding scaling properties of regular, fractal and multi-channel matrices [22,23], more recent work using lattice models (usually on the pharmaceutical literature) was focused on validating the usage of semi-empirical functions, as well as understanding the relation between various physical aspects of the capsule, such as shape, system dimension, drug concentration on drug release [24,16,25–28,17,29–35,9,36,37]. In the current work we investigate the relation between porosity and drug release by using the Weibull function as an interpolating function, as in the previously mentioned work, assuming that the semi-empirical parameters b and τ retains relevant physical information about the nature of the capsule. We present physical arguments which result in a linear relation between characteristic release times and membrane content (which will be defined in terms of porosity, in the following) and, besides that, results from Monte Carlo Simulations indicate that the parameter b is related to porosity through simple scaling relations.

2. Model and Monte Carlo simulation

The model investigated here is based on a previous work on 1D and 2D system inspired on the lattice gas model to represent a system of device capsule plus drug, and simulate the non-equilibrium drug release process [9]. The current modeling includes 2D square and 3D simple cubic lattice, both with size L, for representing the devices delivering drugs. Drug molecules are represented as single particles occupying lattice sites and kinetics is obtained by allowing particles to move randomly to unoccupied nearest neighbor sites. Excluded volume interaction precludes two drug molecules to share the same site. A membrane with edge size $L+1$ covers the device and acts by blocking drug molecules from leaking to the outside environment. There are n randomly positioned leaking sites on this membrane "surface", and the porosity parameter λ can be define as $\lambda_d = n/n_{S,d}$, where $n_{S,d}$, the number of surface sites on a capsule with dimension d, is identical to $4L$ ($n/6L^2$) for 2D (3D) system. A single 3D model device with $L = 10$ ($L^3 = 10^3$ sites) and porosity $\lambda = 1/6$ (100 leaking sites) is represented on Fig. 1(a). It is important to mention that the current implementation of our simulation protocol fixes the code of our previous 2D simulations [9].[1]

Drug release kinetics is obtained through Monte Carlo simulations, as discussed in the literature [38–40], with the difference that both the average and standard deviation of particle numbers are collected on each time step. On this work, standard deviations will be used to weight data while adjusting the entire release curve to the Weibull function. The

[1] The code used for generating the MC simulations in our previous work [9] was written in C and presented a bias in the procedure for sampling membrane pores, towards one of the edges. This error introduced an artifact in the behavior of b as a function of λ, thus hiding the scaling relations that we observed here for both 2D and 3D systems.

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