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A statistical mechanical model for drug release: Investigations on size and porosity dependence

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ABSTRACT

A lattice gas model is proposed for investigating the release of drug molecules in capsules covered with semi-permeable membranes. Release patterns in one and two dimensional systems are obtained with Monte Carlo simulations and adjusted to the semi-empirical Weibull distribution function. An analytical solution to the diffusion equation is used to complement and guide simulations in one dimension. Size and porosity dependence analysis was made on the two semi-empirical parameters of the Weibull function, which are related to characteristic time and release mechanism, and our results indicate that a simple scaling law occurs only for systems with almost impermeable membranes, represented in our model by capsules with a single leaking site.

1. Introduction

Many pharmaceutical components, such as tablets, micro/nanoparticles, and others based on natural/synthetic encapsulants and drugs, were developed with assisted computational design. Besides, mathematical modeling and computer simulations can be useful for predicting release profiles, to assist the design process of drug delivery systems [1–6].

Despite the emergence of numerical models and computer simulations as a standard tool for investigating drug release systems, it is also common to analyze release data using empirical and semi-empirical functions whose parameters are useful for empirically estimating the release mechanisms of the system [7,8]. For this purpose a power law time dependence [9–11] and the Weibull function [12,8] are among the most used empirical expressions (other propositions are discussed in Refs. [1,5]). It is also common to fit drug release data using the semi-empirical Higuchi equation [13,14], which was derived by assuming diffusion in devices with slab geometry and states that the amount of drug released is proportional to the square root of time.

The main advantage of using empirical and semi-empirical functions stands on its easy use and the possibility of gaining physical insights on the mechanisms governing drug release profiles. Nevertheless, as discussed by Siepmann and Peppas [1], the main limitation on using these functions is that an apparent power law behavior cannot be used to infer the physical mechanism for drug release on a certain device since similar patterns could also appear from a superposition of different mechanisms.

Although this criticism is focused on the application of power-law and Higuchi functions to HPMC devices [1], it is general enough and should be applied to any release system. Thus, it would be desired to justify the use of empirical and semi-empirical functions through statistically consistent and physically based models for drug release. Although the Higuchi

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equation is based on a simple physical model it is valid as a short time approximation for the whole release process and cannot be normalized. While the same problem happens with a power-law function, the Weibull distribution function does not present this issue and can be used to consistently describe the whole release period.

In this work, simple lattice models for drug release were investigated through Monte Carlo simulations and their release profiles were adjusted to the empirical parameters of the Weibull function to understand the effect of system dimensionality, capsule size and membrane porosity on the empirically adjusted parameters of the Weibull function.

An appropriate answer to this question deserves a scaling analysis of the release profiles of different systems (varying dimensionality, size, and porosity) and regimes (short/long time, single pore/empty membrane). Such analysis was present in early works [15,16] but these studies are complemented by considering the use of the Weibull distribution function, a broader range of system sizes, and the use of a random distribution of pores (that we believe to be physically more plausible on drug capsules with nanoscopic/microscopic size).

To achieve this goal, the lattice gas model is modified with the inclusion of a membrane and pore (or leaking) sites to represent individual drug capsules (or devices). While a single pore was used in the one dimensional model the membrane porosity is investigated in detail in two dimensional systems. This is the new feature of the proposed model. Although being unrealistic, one dimensional models are important test cases since more detailed, analytical calculations can be obtained. We worked on an analytical solution of the one dimensional diffusion equation with sink boundary conditions and found it to be in good agreement with computer simulations. Besides, the one dimensional analytical solution presented features which are common to two dimensional systems.

This paper is organized as follows: in Section 2, semi-empirical functions used for fitting drug release data are discussed and the lattice models are introduced in Section 3. Our results and discussions are presented in Section 4 while our conclusions are made in Section 5. The analytical solution of the diffusion equation on a continuous system similar to our 1D model is left for Appendix.

2. Empirical functions for drug release

The use of power law expressions to evaluate the drug release mechanisms was first proposed by Peppas and co-authors [17,9–11] based on time analysis of dissolution data and also on solutions of the diffusion equation for different device geometries. In their proposition, the amount of drug released at a time t (for times corresponding to releases smaller than 60% of the total drug on the device, M_∞) can be approximately adjusted by:

$$\frac{M(t)}{M_\infty} = kt^n, \tag{1}$$

where k and n are fitting parameters, n being related to the release mechanism. Ritger and Peppas investigated the exponent n for non-swellable [9] and swellable [10] devices in the form of slabs, spheres, and cylinders, and numerically quantified n values corresponding to different release mechanisms. As an example, on systems constrained to homogeneous thin films with $n = 0.5$ the release mechanism is found to correspond to simple Fickian diffusion, while for $0.5 < n < 1.0$ release mechanism is due to non-Fickian processes [9]. As discussed before, the main disadvantage of Eq. (1) is the unbounded increase of drug release that limits its use to short times. An alternative is to use the Weibull statistical distribution function [12] which, in the drug release literature, is commonly written as

$$\frac{M(t)}{M_\infty} = 1 - \exp\left[-at^b\right], \tag{2}$$

where a and b are fitting parameters, which b is related to the release mechanism. Note that for short times, Eq. (1) is a first order expansion of (2), with $b = n$. As suggested by Casault and Slater [18], a better the physical interpretation of data is obtained by changing Eq. (2) to:

$$\frac{M(t)}{M_\infty} = 1 - \exp\left[-\left(\frac{t}{\tau}\right)^b\right], \tag{3}$$

so that the τ becomes a characteristic time, corresponding to $M(\tau)/M_\infty = 1 - 1/e \approx 63.2\%$ of drug release. When the Weibull function is expressed as in (2) the units of a are δt^{-b} (with δt defining time units). Although being a possibility, it complicates the analysis of the empirical parameters without adding new value to the function. Besides, in the original paper from Weibull, there was a misprint in a parenthesis (related to this parameter), as noted by T.C. Tsu in Ref. [19]. The use of a or τ is not really a problem in limiting cases where exponential behavior takes place, but in other cases the use of τ facilitates a scaling analysis on the empirical parameters of the Weibull function, as will be performed here. Besides, Weibull distribution with parameter τ (instead of a) has also been used to adjust experimental data in pharmaceutical literature [20].

Moreover, it will be convenient to investigate the amount of drug inside the device, $N(t) = M_\infty - M(t)$, by changing Eq. (3) to

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

where $N_0 = M_\infty$.