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Monte Carlo simulations and fractional kinetics considerations for the Higuchi equation

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ABSTRACT

We highlight some physical and mathematical aspects relevant to the derivation and use of the Higuchi equation. More specifically, the application of the Higuchi equation to different geometries is discussed and Monte Carlo simulations to verify the validity of Higuchi law in one and two dimensions, as well as the derivation of the Higuchi equation under alternative boundary conditions making use of fractional calculus, are presented.

1. Introduction

This year we celebrate the 50th anniversary since the publication of the Higuchi's law article (Higuchi, 1961). We do not use this historical milestone to reflect on the progress that has been made in the field of controlled release based on the Higuchi equation in the last five decades. In addition, we do not feel that the several hundred citations of the Higuchi's paper reflect its real impact on the evolution of the field. Rather, we would like to emphasize T. Higuchi's fundamental contribution towards the introduction of rigorous physicochemical and mathematical approaches in the pharmaceutical sciences. To this end, this work highlights some physicomathematical aspects relevant to the derivation and use of the Higuchi equation. More specifically, this article deals with the use of Monte Carlo simulations to verify the validity of Higuchi law in one and two dimensions as well as the derivation of the Higuchi equation under alternative boundary conditions making use of fractional calculus. The latter is a tool which has been recently introduced in the pharmaceutical sciences.

2. Application of the Higuchi law to different geometries

Drug release can be defined roughly as the mass transfer of drug molecules from the dosage form to the surrounding fluid. This process is usually driven by the concentration gradient between a high concentration region (dosage form) and a region of low concentration (surrounding fluid). (Higuchi, 1961) considered a homogeneous matrix in which drug is dispersed with an initial concentration C_0 while drug's solubility in the matrix is C_s which is lower than C_0 ($C_0 > C_s$). He also assumed that the matrix is placed in a perfect sink at $t = 0$ and a region with depleted drug is penetrating into the matrix. He derived his equation (Eq. (1)) for the total mass, $M(t)$ released up to time t using the additional assumption that the mass flux throughout the depleted region is independent of the position on the surface

$$M(t) = A[DC_S(2C_0 - C_S)t]^{1/2} \quad (1)$$

where A is the total area and D is the diffusion coefficient of the drug in the matrix. A few years later, Eq. (1) was extended and modified to consider different matrix systems including porous structures (Higuchi, 1961, 1963; Desai et al., 1965, 1966; Lapidus and Lordi, 1966, 1968).

Although the derivation of Eq. (1) applies to slab geometry, Roseman and Higuchi (1970), Brophy and Deasy (1987) have shown that a similar relationship keeping the $t^{0.5}$ proportionality for $M(t)$ can be also derived for homogeneous cylindrical and spherical matrix systems, respectively under the pseudo steady-state assumption $C_0 \gg C_s$

$$M(t) = A[2DC_SC_0t]^{1/2} \quad (2)$$

where A in Eq. (2) is either the area of a cylinder (Higuchi, 1963) or the area of a sphere (Desai et al., 1965). In addition, Brophy and Deasy (1987) have shown that under the assumptions delineated above any particle with a regular boundary will follow for a short

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time the release given by Eq. (2), where A represents the total area of the particle.

Overall, the routine use of the Higuchi law for the release of drug from delivery systems of varying geometry is extended to 60% of the release data and is usually called "a short time approximation". In this context, a linear plot of the cumulative amount of drug released $M(t)$ vs the square root of time is routinely used in the literature as an indicator for a classical diffusion controlled release (Siepmann and Peppas, 2001).

3. Monte Carlo simulations of the Higuchi law

One of Higuchi's basic assumptions in order to derive his famous release law is that a sharp moving depletion layer is created near the release device surface and realized that this layer is important in the shaping of the release profile. Using a simplified one dimensional geometry, the simplest possible linear form for the depletion layer and the assumption that the system's "drug concentration" is much higher than its "solubility", he derived the well known $t^{0.5}$ time dependence of the profile.

Here, we describe a Monte Carlo algorithm that can be used to simulate the conditions of the Higuchi law.

(i) We start from either a one-dimensional matrix of L sites or from a two-dimensional matrix of $L \times L$ sites.
(ii) Each site is labeled with the number of particles it currently hosts. Initially, all sites have n particles.
(iii) The right side of the matrix is considered to be the exit of the release device and sites belonging to it are labeled as leak sites.
(iv) We assume that drug molecules move inside the matrix by the mechanism of Fickian diffusion. Diffusion is simulated using the random walk model.
(v) Particles cannot move to a site unless this site is empty. Thus, the system is expected to behave as if its "drug concentration" (n particles per site) is much higher than its "solubility" (1 particle per site).
(vi) We select a particle at random and try to move it to a randomly selected nearest neighbor site.
(vii) If the new site is an empty site then the move is allowed, and the particle is moved to this new site.
(viii) If the new site is already occupied, the move is rejected.
(ix) A particle is removed from the lattice as soon as it migrates to the leak site; see Figs. 1 and 2 for a schematic of the one and two-dimensional case, respectively.
(x) After each particle move, time is incremented. The increment is chosen to be $1/N$, where N is the number of particles remaining in the system. This implies that the unit time characterizing the system is the mean time required for every one of the N particles to be offered the possibility of moving one step. This is a typical approach in Monte Carlo simulations.

We monitor the number of particles that are present inside the cylinder as a function of time until the cylinder is completely empty of particles (Kosmidis et al., 2003). In the simulations presented in this paper we have used $L = 200$ for the one-dimensional case and $L = 50$ for the two-dimensional case. The initial number of particles per site was $n = 10$.

Fig. 3 shows the function $(1 - N/N_0)$ vs. time for the one-dimensional (left) and the two-dimensional (right) case, where N_0 is the total initial number of particles and $N(t)$ is the number of particles in the system at time t. One can immediately see that $N_0 = nL$ for the one dimensional case and $N_0 = nL^2$ for the two-dimensional case. Points represent Monte Carlo simulation data whilst the slope of the lines is equal to 0.50, equal to the value 0.50 expected from theory. The results for the one-dimensional configuration are in full

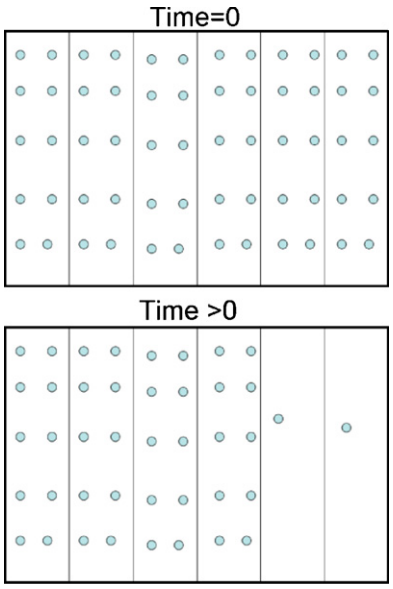

Fig. 1. Schematic representation of the system used to simulate the Higuchi law. (Top) Initial configuration of the one-dimensional system. (Bottom) evolution after time t. Particles are allowed to leak only from the right side of the system.

agreement with our previous study (Kosmidis et al., 2003). We can see that the Higuchi law can be derived from our simulation model as a "short" time case (60% of the release data) of such a system. This conclusion is valid for both the one and the two-dimensional case and is in good agreement with the analysis of Siepmann and Peppas (2001).

4. Fractional calculus and the Higuchi law

The square root law of Higuchi was derived under certain conditions as mentioned in Section 2. However, its wide applicability extends beyond these conditions. Here we give an alternative

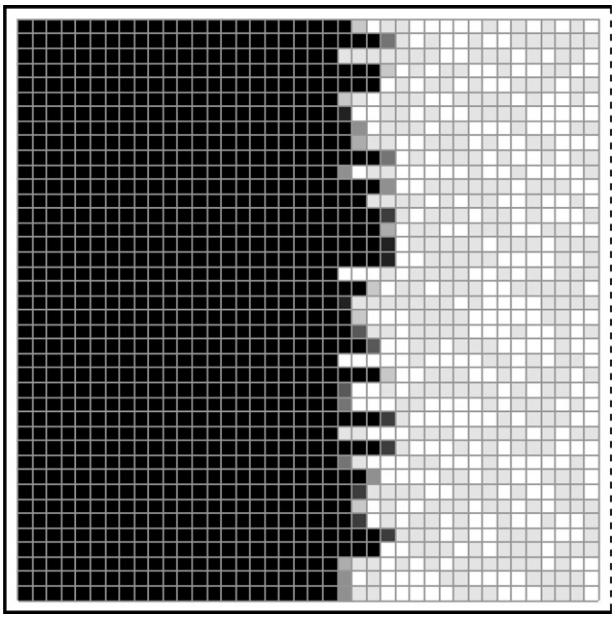

Fig. 2. Density plot of a snapshot of the 2D system with $L = 40$. Black sites are fully occupied with 10 particles. White sites are empty. Gray sites are occupied with particles whose number varies between 1 and 9. Darker shading indicates higher number of particles. The dashed line marks the exit side. At $t = 0$ all sites would be black.

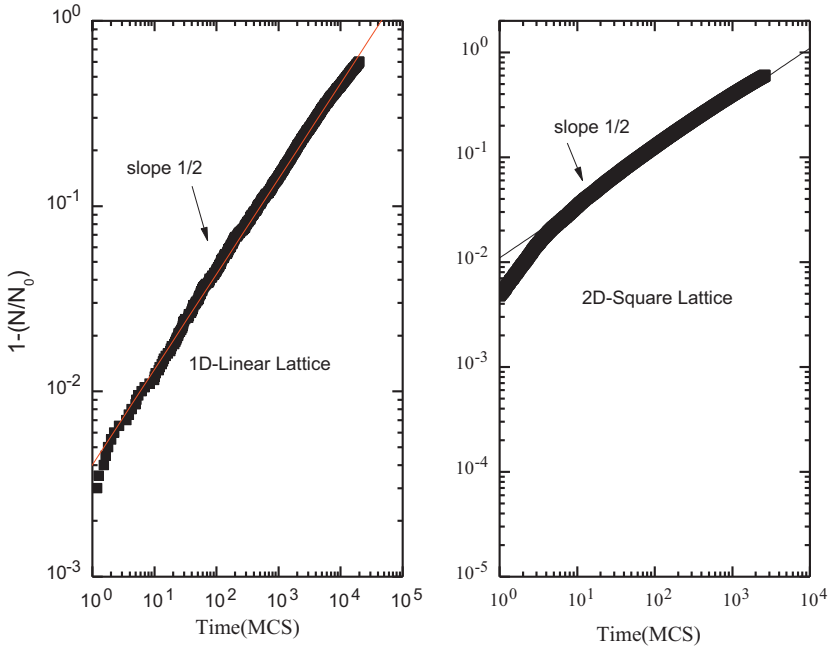

Fig. 3. Log-log plot of $1 - N/N0$ vs. time (Monte Carlo steps-units) for the one-dimensional (left) and the two-dimensional (right) case. Points are Monte Carlo Simulation results. The slope of the straight lines in both figures is equal to 0.50 and corresponds to the exponent of the Higuchi law. We plot the initial 60% of the release data.

derivation of the Higuchi square root equation starting from the one-dimensional diffusion equation, a derivation borrowed from the problem of heat transfer as it is treated in (Podlubny, 1999). Within this derivation a derivative of order one half appears. Fractional derivatives and integrals are extensions of ordinary derivatives and integrals, respectively, but of non-integer order. The so called Riemann–Liouville fractional integral of order $\alpha < 1$, of a function $f(t)$ is defined as follows

$$ {}_0D_t^{-\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-\tau)^{\alpha-1} f(\tau) d\tau \tag{3} $$

where Γ is the gamma function. Although Eq. (3) is the only definition of the fractional integral, there are more than one definition for a fractional derivative. The Riemann–Liouville fractional derivative of order $\alpha < 1$, of a function $f(t)$ is one of them and is defined as the ordinary derivative of the fractional integral of order $1 - \alpha$, as follows:

$$ {}_0D_t^{\alpha} f(t) = \frac{d}{dt}({}_0D_t^{-(1-\alpha)} f(t)) \tag{4} $$

We consider a device carrying drug which is in contact with a medium (Fig. 4). We study the concentration of drug in the medium in time and in a one-dimensional spatial coordinate. The one dimensional diffusion equation describing the concentration

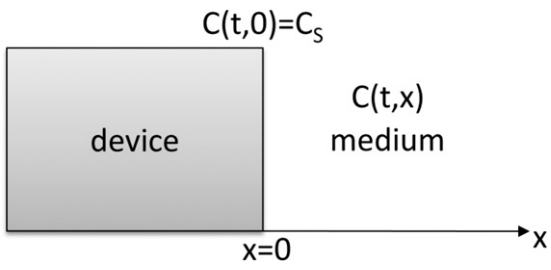

Fig. 4. Schematic representation of a system of a drug carrying device which is in contact with a medium.

of drug in the medium is

$$ \frac{\partial C(t,x)}{\partial t} = \kappa \frac{\partial^2 C(t,x)}{\partial x^2} \tag{5} $$

where x is the spatial coordinate and κ the diffusion coefficient. The border between the medium and the device is at $x = 0$, while the medium is large enough and considered to extent to infinity, $x \to \infty$.

The initial condition at $t = 0$ is $C(0,x) = 0$, i.e. initially there is no drug in the medium. The boundary conditions are: at the boundary between the device and medium, $x = 0$, the concentration is fixed at $C(t,0) = C_s$, the saturation solubility, while away from the boundary at $x \to \infty$, concentration is considered to be finite, i.e. $|\lim_{x\to\infty} C(t,x)| < \infty$.

By taking the Laplace transform of Eq. (5) with respect to time, we end up with the following equation

$$ s \cdot c(s,x) = \kappa \frac{d^2 c(s,x)}{dx^2} \tag{6} $$

Eq. (6) is an ordinary differential equation of second order with respect to x, which has the following solution

$$ c(s,x) = c(s,0) \exp\left(-x\sqrt{\frac{s}{\kappa}}\right) \tag{7} $$

Differentiating Eq. (7), we obtain

$$ \frac{dc}{dx}(s,x) = -c(s,0)\sqrt{\frac{s}{\kappa}} \exp\left(-x\sqrt{\frac{s}{\kappa}}\right) \tag{8} $$

From Eq. (8), for $x = 0$ we obtain

$$ \frac{1}{\sqrt{s}} \frac{dc}{dx}(s,0) = -\sqrt{\frac{1}{\kappa}} c(s,0) \tag{9} $$

Since the Laplace transform of a fractional integral of a function $f(x)$ is (Podlubny, 1999)

$$ L({}_0D_t^{-\alpha} f(t), s) = s^{-\alpha} F(s), \tag{10} $$

Eq. (9) can be written in terms of a fractional integral of order 1/2.

$$ {}_0D_t^{-1/2}\frac{\partial C}{\partial x}(t,0) = -\sqrt{\frac{1}{\kappa}}C(t,0) \tag{11} $$

Eq. (11) can be written as follows in terms of a fractional derivative of order 1/2

$$ \frac{\partial C}{\partial x}(t,0) = -\sqrt{\frac{1}{\kappa}}\,{}_0D_t^{1/2}C(t,0) \tag{12} $$

The flux J across the interface $x = 0$ is

$$ J(t) = -\kappa\frac{\partial C}{\partial x}(t,0) = \sqrt{\kappa}\,{}_0D_t^{1/2}C(t,0) \tag{13} $$

Given the fact that $C(t,0) = C_S$, a constant, and the derivative of order 1/2 with respect to t of a constant C_S is $C_S/\sqrt{\pi t}$, the flux J becomes

$$ J(t) = \sqrt{\kappa}\,{}_0D_t^{1/2}C_S = \sqrt{\frac{\kappa}{\pi t}}C_S \tag{14} $$

The total amount that has been released to the medium up to time t is

$$ Q(t) = A\int_0^t J(t)dt = A\int_0^t \sqrt{\frac{\kappa}{\pi t}}C_S dt = 2A\sqrt{\frac{\kappa}{\pi}}C_S\sqrt{t} \tag{15} $$

where A is the area of contact between device and medium.

Eq. (15) is another form of Higuchi's square root law but derived in different boundary conditions than the usual ones.

5. Conclusion

Higuchi's square root law has been proven to have wide applicability in drug release devices. In this short article we demonstrate the validity of Higuchi's law in Monte Carlo experiments in 1 and 2 dimensional systems and we also offer an alternative derivation of the Higuchi's equation under different boundary conditions, using fractional calculus, which offers insights for the wide applicability of this equation. In pharmaceutical sciences fractional calculus is considered to be a promising new tool and the relevant applications are growing rapidly (Dokoumetzidis et al., 2010a,b; Verotta, 2010; Kytariolos et al., 2010).

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