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Fractional derivatives in the diffusion process in heterogeneous systems: The case of transdermal patches

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ABSTRACT

In this note, we present a simple mathematical model of drug delivery through transdermal patches by introducing a memory formalism in the classical Fick diffusion equation based on the fractional derivative. This approach is developed in the case of a medicated adhesive patch placed on the skin to deliver a time released dose of medication through the skin towards the bloodstream.

The main resistance to drug transport across the skin resides in the diffusion through its outermost layer (the stratum corneum). Due to the complicated architecture of this region, a model based on a constant diffusivity in a steady-state condition results in too simplistic assumptions and more refined models are required.

The introduction of a memory formalism in the diffusion process, where diffusion parameters depend at a certain time or position on what happens at preceeding times, meets this requirement and allows a significantly better description of the experimental results.

The present model may be useful not only for analyzing the rate of skin permeation but also for predicting the drug concentration after transdermal drug delivery depending on the diffusion characteristics of the patch (its thickness and pseudo-diffusion coefficient).

1. Introduction

Transdermal patches are pharmaceutical devices of varying sizes, containing, one or more active drugs, intended to be applied to the unbroken skin in order to deliver the active ingredient to the systemic circulation after passing through the skin barriers. In this way, through a simple diffusion process, the drug enters the bloodstream directly through the skin.

In principle, the transdermal penetration of drugs, or more generally of hydrophilic (or even hydrophobic) solutes, trough intact human skin can be modeled, from a theoretical point of view, as a process of molecular diffusion through a composite multilayer membrane whose main barrier to transport is localized within the stratum corneum [SC]. This layer is composed by flattened dead cells (corneocytes) embedded in a matrix of staked lipid lamellae composed by free fatty acids, ceramides and cholesterol. Because of its very complex structure, the mechanism by which solutes crosses human skin is not completely well characterized.

In the classical diffusion problems, when the mean squared displacement of the diffusing objects is proportional to time (random walk process), the overall diffusion mechanism is described by Fick's law. Recently, Jepps at al. [1] have reviewed the status-of-art of skin transport modeling, taking into account the different structures involved, and different more or less sophisticated approaches have been proposed, all of them based on the *classical* diffusion equations with *classical* diffusion coefficients.

However, this is not always appropriate and in many highly heterogeneous media, as for example biological systems are, there is strong experimental evidence that deviations from the classical behavior have been observed, and diffusion processes are governed by a *memory effect*.

For example, in many biological systems, the *state* of whichever drug during the diffusion process in the tissue, due to the complex architectural structure of the medium it crosses, depends on its *state* at a previous time. Since fractional derivatives take into account all values of a function in a time interval in which a process that is analyzed takes place (fractional derivatives take history of a process into account), it may be convenient the use of derivatives of positive *real* order which allow to take history of a process into account.

Recently, many contributions appeared concerning the diffusion of different substances, mainly drugs, across differently structured

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porous materials using fractional calculus with the attempt to give a better description of the phenomenon in different fields [2].

Typical examples of the use of fractal derivatives can be found in physics and mathematics [3–7], in pharmaco-kinetics [8,9], in bioengineering [10,11], in geophysics [12–14] and in relaxation in filled polymers [15]. In particular, various aspects of transdermal delivery have been recently reviewed in the light of classical models of drug diffusion in the skin [16–18] and different models of skin permeability have been proposed [19–21].

On the other side, memory formalism has been successfully applied to the diffusion processes of a model compound (4-cyanophenol in saturated aqueous solution) and to a nonsteroidal anti-inflammatory drug (piroxicam) through the skin [22], where it has heen shown that the introduction of the fractional derivative offers a better description of the diffusion processes in the stratum corneum in comparison to other classical models.

In this note, we deal with a simple mathematical model based on diffusion with memory to take into account the process where a specific dose of medication is delivered from a medicated adhesive patch placed on the skin through the stratum corneum into the bloodstream. The present approach differs from analogous ones we have already proposed [23–26]. In fact, in this note, we discuss the diffusion of a generic drug through two contiguous layers, i.e., from a saturated layer of a finite thickness to an adjacent half-space region initially free of drug, making use of continuity conditions which imply the continuity of the flux at the patch-skin interface. This approach allows a rather realistic description from a macroscopic point of view of the transport of drug through the model system employed and furnishes suggestions on the patch architecture in order to gain the desired effects.

2. The diffusion model: extension of the classical Fickian model

We write the diffusion equations, as today is usually done, by substituting the gradient of concentration $p_x(x, t)$ with its fractional derivative $D^{(\nu)}p_x(x, t)$ of order ν in order to represent the inherent delay of the diffusion mechanisms in highly heterogeneous media.

The fractional derivative $D^{\nu}f(x, t)$ of order ν, known as the Caputo fractional derivative, is defined as [6,27]

$$D^{\nu}f(x,t) = \frac{1}{\Gamma(1-\nu)}\int_0^t \frac{1}{(t-\tau)^{\nu}}\left[\frac{\partial f(x,t)}{\partial t}\right]_{t=\tau} d\tau \tag{1}$$

with $0 < \nu < 1$ and $\Gamma(x)$ the Euler Gamma function.

The physical meaning of the fractional derivative in this context resides in the fact that the memory function captures the past. What the fractional derivative memory function is remembering is the past values of the function, which implies that the function is constructed by adding to the initial value the successive weighted increments over time. The increments per unit time are represented by the first order derivative under the integral sign and the weights are represented by the factor of the first order derivative in Eq. (1) which are decreasing with increasing time separation from the time t. Thus, a variable's value is a weighted mean of its past values.

The equations involved in the study of diffusion are the constitutive diffusion equations with memory formalism. They read

$$q(x,t) = -dD^{\nu}\left(\frac{\partial}{\partial x}[p(x,t)]\right) \tag{2}$$

$$\frac{\partial}{\partial x}[q(x,t)] + \frac{\partial}{\partial t}[p(x,t)] = 0 \tag{3}$$

where $q(x, t)$ is the flux, $p(x, t)$ the concentration at position x and time t within the medium and d is the pseudo-diffusion coefficient (with memory). Eqs. (2) and (3) represent a generalization of the Fick's laws with the introduction of the memory formalism, working through the fractional derivative.

Solution of Eqs. (2) and (3) can be found, in this context, in the Laplace domain taking advantage of the property of the Laplace transform that converts time derivatives into algebraic functions of position and a variable s, thereby reducing the partial differential diffusion equation into an ordinary differential equation that is much easier to solve.

Taking the Laplace Transform [LT] of Eqs. (2) and (3) and using capital letters to define the LT of the corresponding lower case letter, i.e., $Q(x, s) = LT[q(x, t)]$ and $P(x, s) = LT[p(x, t)]$, we obtain the following equation

$$P_{xx}(x,s) = GP(x,s) - \frac{s^{-\nu}}{d}p(x,0) \tag{4}$$

with

$$G = \frac{s^{1-\nu}}{d} \tag{5}$$

Here, the subscript x indicates the order of the derivative with respect to the variable x.

The formal solution of Eq. (4) is given by

$$P(x,s) = \frac{p(x,0)}{s} + A(s)\exp(\sqrt{G}x) + B(s)\exp(-\sqrt{G}x) \tag{6}$$

where $A(s)$ and $B(s)$ are arbitrary functions depending on the variable s to be used to satisfy the boundary conditions of the particular problem under investigation.

The flux $Q(x, s)$ is given, according to Eq. (2) by

$$\begin{aligned} Q(x,s) &= -ds^{\nu}P_x(x,s) \\ &= -\sqrt{d}s^{\frac{1+\nu}{2}}\left(A(s)\exp(\sqrt{G}x) - B(s)\exp(-\sqrt{G}x)\right) \end{aligned} \tag{7}$$

with the condition

$$\frac{d}{dx}(p(x,0)) = 0 \tag{8}$$

3. Equations governing the diffusion with memory formalism

We model the diffusion of drugs from a transdermal patch (a plaster) to the body considering a porous layer saturated with the drug at a given initial concentration C_0 in contact with a particular region of the body where the diffusion process is expected. We will model this region as a permeable half space.

Initially, the layer is saturated with the drug, while the half space medium is assumed free of drug. With this initial condition, the drug will flow from the layer into the half-space and the problem is to find the concentration and the flux of drug at any point within both media (layer and half space) as a function of time. We will also require that at $t > 0$ there will be continuity in the concentration and flux across the plane x=0 separating the two media. A sketch of the model under consideration is shown in Fig. 1.

3.1. Diffusion in the layer and the appropriate boundary conditions

We will apply the above stated diffusion mechanism in the region $-h \le x \le 0$ which characterizes the layer of thickness h (see Fig. 1). In order to specify that we will consider here the layer, we will add the suffix "0" to each symbol. A list of the symbols employed is given in Table 1.

In the Laplace domain, the boundary condition $q_0(-h, t)$=0, i.e., the absence of flux at the outer boundary of the layer, reads $Q_0(-h, s)$=0, yielding

$$Q_0(-h,s) = -\sqrt{d}s^{\frac{1+\nu}{2}}\left(A_0(s)\exp(-\sqrt{G_0}h) - B_0(s)\exp(\sqrt{G_0}h)\right) = 0 \tag{9}$$