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A fiber distribution model for predicting drug release rates

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ABSTRACT

Sustained drug release can be achieved by loading a drug into polymer material. The drug release can then be controlled for potential use in various biomedical applications. A model for drug release from a polymeric fibrous scaffold, which takes into account the distribution of fiber diameters within its structure, is developed here. It is demonstrated that the fiber diameter distribution significantly affects the drug release profile from electrospun scaffolds. The developed model indicates that altering the fiber distribution can be used as an additional tool to achieve an appropriate drug release profile. Using published data, it was demonstrated that an application of the model allows a more precise calculation of the drug diffusion coefficient within the polymer, which is important for predicting drug release rates from fabricated materials.

1. Introduction

Polymeric materials are often used as drug delivery vehicles which are capable of controlling the rate of drug release, as well as targeting the effect of the drug to a specific location [1,2]. Mathematical modeling is required to adequately describe the main mechanisms responsible for drug release from various polymeric materials. The modeling should be able to predict the drug release kinetics for different external conditions as well as variations in material structure. Furthermore, it is potentially possible to define the optimal design of drug delivery devices in each therapeutic field.

The variation in the polymer composition of a targeted drug delivery device and the type of drug loading, as well as its size and shape, lead to differing drug release kinetics. When a polymeric material is designed for drug release purposes, there are many mass transport and chemical reaction processes to be considered such as [3]: drug dissolution, diffusion of the drug inside the polymer matrix, polymer degradation, crystallization of polymer degradation products and/or drugs within the system, pH changes inside the polymer matrix pores caused by degradation products, osmotic effects, polymer swelling, and convection processes. All of the effects cannot be taken into account simultaneously, as the mathematical modeling would be overcomplicated. Thus, it is crucial to identify the most influential processes, and use only them in developing a mathematical model.

Mathematical models used for describing drug release kinetics, in general, can be divided into two categories: empirical/semi-empirical and mechanistic. Empirical/semi-empirical models are merely mathematical descriptions, which are not based on any real physical, biological or chemical processes [1,4]. These models do not allow the formation of a deeper insight into the factors and mechanisms responsible for the release of drugs; thus, the model prediction level remains low. On the other hand, mechanistic models are based on real phenomena and, therefore, can serve as an efficient tool for the understanding of the processes underlying drug release.

Most mechanistic models which describe drug release are based on the diffusion equation derived from Fick's second law [4]. The solution to a diffusion equation for many real physical systems can be obtained in the form of an infinite sum using the Fourier method (separation of variables) [5]. The major difficulty in this case is the choice of the necessary number of terms in the series and the need to solve transcendental equations to determine these terms. For the precise modeling of experimental data in the early stages of drug release, a large number of terms is crucial, since this series converges slowly. Moreover, the solution to a diffusion equation in cylindrical coordinates using infinite sums contains zeros of Bessel function ($I_0(q_n) = 0$), and the necessity to define them makes the calculation process of series sums even more complicated.

Consequently, the preferred mathematical approach is the Laplace transform, which is a more simple and practical alternative to the use of a Fourier series for the numerical solution of a diffusion equation in cylindrical coordinates [6–8]. Such software as MULTI FILT, MINIM and SCIENTIST is capable of using nonlinear regression for the analysis of experimental data by directly implementing the Laplace transform in the calculation process [9]. Therefore, by using the Laplace transform it

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is possible to avoid the difficulties of solving the diffusion equation with infinite sums.

Electrospinning is a widely used technology for the fabrication of fibers ranging from nanometres to microns in diameter [10]. Manufactured fibers possess a high surface area-to-volume ratio exhibiting extremely high porosity [11–14]. Their structure mimics the extracellular matrix; thus resulting in the high level of proliferation and cell differentiation, which is essential for various biomedical purposes [11]. Moreover, the great adjustability of electrospinning parameters makes it possible to produce polymeric scaffolds which are suitable for a broad spectrum of applications including wound dressing [15–18], drug delivery [12,19–32], tissue engineering [33–35], and enzyme immobilization [36,37].

The structure of polymeric scaffolds produced by electrospinning is complicated, as it consists of randomly entangled cylindrical fibers of various diameters. Therefore, the model should be developed with consideration given to the cylindrical shape of the fibers which form the structure of these scaffolds. A classic homogeneous model in cylindrical coordinates can be considered as a tool for predicting drug release kinetics from an electrospun system [5]. However, it is uncertain whether or not a homogeneous model is able to precisely define the diffusion coefficient of a drug from release data.

It is known from multiple experimental results that the fibers in electrospun structures are distributed by diameter [30,32,38]. In this study, the new model, which takes into account the observed fiber radius distribution within the structure of an electrospun polymeric scaffold, is introduced. The distribution can be determined by quantitatively measuring the scaffold fiber diameters within the obtained scanning electron microscopy (SEM) images (Fig. 1). It is hypothesised in this work that taking into account this distribution will significantly impact the drug release profile and will influence the determination of the diffusion coefficient.

Polymers which are usually used for the fabrication of such scaffolds are biodegradable. However, mass loss through degradation of the polymer can be, in many cases, assumed to be negligible for early stages of drug release. Therefore, in our work, diffusion is considered as the main drug release mechanism, which allows for the calculation of the intrinsic diffusion coefficient from drug release data. This approach allows for further use of the obtained values of diffusion coefficients in other similar polymer-drug systems. This not only makes any additional experiments potentially more cost effective and less time consuming, but also provides a significantly increased prediction accuracy. The obtained diffusion coefficient values can be applied for drugs which are similar in terms of their molecular weight and/or other physicochemical properties such as octanol-water partition coefficient and melting point.

2. Methods and numerical analysis

2.1. Fiber distribution measurement

In order to obtain the fiber radius distribution for further use in the mathematical model for this study, the topography of already experimentally fabricated electrospun materials can be investigated. By measuring the size of a statistically significant number of fibers on SEM images, an approximate shape of the fiber radius distribution can be obtained. Fibers can be measured by using ImageJ software (National Institutes of Health, MD, USA). The measurement is performed in three steps. Firstly, the scale bar on a chosen SEM image is measured in order to be able to determine the actual diameter of fibers. Then, each clearly visible fiber, which is observed on the SEM image, is measured. In the end, when the array of fiber diameters is obtained, the diameters are sorted out by value and then grouped depending on how many columns in the final fiber distribution histogram are desired to be observed. To illustrate this point, the topography of the produced polymeric fibrous scaffold was studied [39], and the fiber diameter distribution histogram was built (as shown in Fig. 1). It is noteworthy that although the measurements are presented as diameters, the model is designed for fiber radii.

2.2. Drug release data extraction

The extracted experimental data was obtained by using Web Plot Digitizer [40]. The chosen plots, which represented drug release profiles in the papers, were imported into the software in order to manually acquire data points using 2D (X-Y) Plot orientation in the software.

2.3. Model development

Fick's second law in a differential form for one-dimensional diffusion in cylindrical coordinates, assuming axial symmetry, is:

$$\frac{\partial C}{\partial t} = D\left(\frac{\partial^2 C}{\partial r^2} + \frac{1}{r}\frac{\partial C}{\partial r}\right), 0 \le r \le R, \tag{1}$$

where r is the distance from the axes, R is the fiber radius, D is the diffusion coefficient which does not depend on concentration changes. The following derivation is similar to the one given in [41] for the purpose of calculating of heat transfer. For the functionality of the model, fibers within the structure of the produced electrospun scaffold are considered to be ideal infinite cylinders. This assumption is appropriate providing that the lengths of the fibers are significantly greater than the fiber radii. It is also assumed that at $t = 0$, the concentration of the drug in the fiber is uniform and is equal to C_0 for

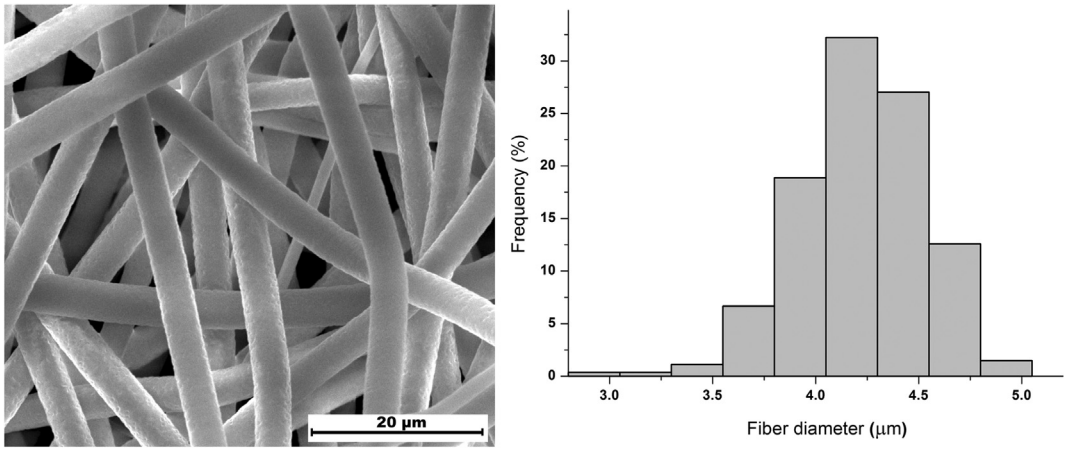

Fig. 1. SEM image of the polymeric electrospun fibrous scaffold (adapted from [39]) and the respective fiber diameter distribution histogram.

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