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Drug delivery systems using sandwich configurations of electrospun poly(lactic acid) nanofiber membranes and ibuprofen

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ABSTRACT

The primary advantages of electrospun membranes include the ability to obtain very thin fibers that are on the order of magnitude of several nanometers with a considerable superficial area and the possibility for these membranes to be manipulated and processed for many different applications. The purpose of this study is to evaluate and quantify the transport mechanisms that control the release of drugs from polymer-based sandwich membranes produced using the electrospinning processes. These electrospun membranes were composed of poly(lactic acid) (PLA) because it is one of the most promising biodegradable polymers due to its mechanical properties, thermoplastic processability and biological properties, such as its biocompatibility and biodegradability. The transport mechanism that controls the drug delivery was evaluated via the release kinetics of a bioactive agent in physiological serum, which was used as a corporal fluid simulation. To describe the delivery process, mathematical models, such as the Power Law, the classical Higuchi equation and an approach to Fick's Second Law were used. Using the applied mathematical models, it is possible to conclude that control over the release of the drug is significantly dependent on the thickness of the membrane rather than the concentration of the drug.

1. Introduction

Over the past 20 years, the interactions of the fields of polymer and materials science with the pharmaceutical industry have resulted in the development of what are known as drug delivery systems (DDSs), or controlled-release systems [1–4].

Drug delivery systems can be classified according to the mechanism that controls the release of the drug [5], such as diffusion-controlled systems, chemically controlled systems, solvent-activated systems, modulated-release systems and bioerodible-release systems [4–9].

One of the most promising biodegradable polymers for use in bioerodible-release systems is poly(lactic acid) (PLA) because of its mechanical and biological properties.

PLA is a thermoplastic polyester derived from renewable resources, such as corn starch. PLA has a hydrolytic degradation mechanism, and it is capable of degrading into innocuous lactic acid and then into CO_2 and water, which are absorbed by the body. PLA is used in medical implants in the form of screws, pins, rods and as a mesh [10,11]. Depending on the exact type used, PLA degrades in the body within 6 months to 2 years [12]. This gradual degradation is desirable for a support structure because it gradually transfers the load to the body as the organ heals.

In this study, the properties of a different drug-delivery system, which consists of different nanofiber membrane configurations, were examined. The membrane configuration was based on sandwiching the drug between two adjacent layers of electrospun PLA membranes to determine the mass transport behavior of the drug through different polymeric membrane configurations.

Similar studies have been conducted by Fied et al. [13] with the purpose of developing ultrafiltration membranes. Tiemessen et al. [14] have also described a so-called occlusion simulation model based on sandwiching the stratum corneum between sticky silicone membranes to provide a means for simulating skin penetration under occlusion.

The electrospun PLA membranes were shown to provide a useful mechanical support for the drug. The initial studies on the sandwich model also revealed that this model provides an elegant means to kinetically control the water uptake by the drug. Although the PLA membrane is biodegradable or erodible (i.e., a system that disintegrates over time), this phenomenon can be irrelevant when the entire drug is released before the dissolution of the polymer becomes important. Therefore, the membranes could be considered non-erodible.

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Drug release from a non-erodible system can occur in several ways. Fig. 1 presents four theoretical curves (A, B, C and D) that describe four types of release behavior. The curves are all plotted as a percentage of the drug released versus time [15].

Curve A represents the release behavior of a perfect non-erodible system that delivers the drug by steady-state diffusion through a coating or membrane with a uniform thickness. If some of the material migrates through the membrane during storage, a burst effect occurs, which is represented by curve B. If the membrane functions as an inert matrix from which the drug is dispersed, the Higuchi model is valid for up to 60% release of the drug. In this case, a plot of the percentage of drug released versus the square root of time is linear, as shown by curve C. The first-order release of the drug is represented by Curve D.

In this study, an analogy was made between the theoretical curves presented in Fig. 1 and the experimental curves obtained after kinetics tests. A comparison based on the similarities of both curves, theoretical and experimental, was performed to identify the behavior of the releasing process and consequently, the mass transport behavior.

The objective of this study is to evaluate the mass transport of ibuprofen through various sandwich configurations of electrospun poly(lactic acid) nanofiber membranes designed to be used in medical applications, such as patches or implants in places where human serum can act as a swelling agent, as a carrier of the active compound. Therefore, this new system can be directly used in the prophylactic period of patients who recently underwent an operation, when in situ application is required. In some cases, this particular membrane can act not only as a carrier but also as cavity filler with therapeutic agents.

2. Materials and methods

2.1. Materials

The materials used to prepare the polymeric solution included poly(lactic acid) (PLA, GMO free, supplied by VELOX GmbH) and extra pure dichloromethane, which was supplied by Scharlau (CH_2Cl_2, M = 84.93 g/mol). The active compound was powdered ibuprofen ($C_{13}H_{18}O_2$, M = 206.28 g/mol) supplied by Sigma-Aldrich.

The glass transition temperature of PLA ranges between 60 and 65 °C, and its melting temperature ranges between 173 and 178 °C. The general structure of the PLA molecule is presented in Fig. 2.

2.2. Methods

2.2.1. Preparation of polymeric solution

The polymeric solution used to produce the polymeric nanofibers was obtained by dissolving 10% of the solution weight of poly(lactic acid) in dichloromethane under constant magnetic agitation and at a constant

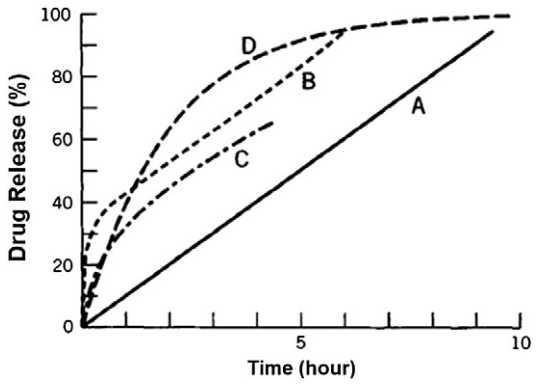

Fig. 1. Theoretical release curves expected for different types of non-erodible delivery systems. A: Membrane reservoir-type free of lag time and burst effects; B: same as A, with burst effects, C: matrix or monolithic sphere with square root time-release, and D: system with first-order release.

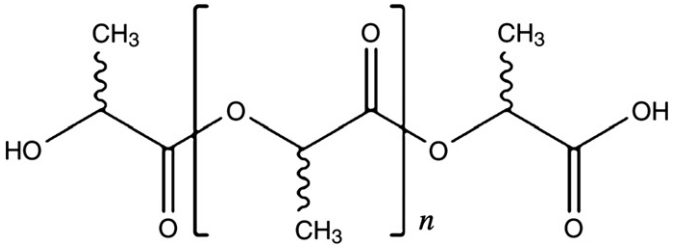

Fig. 2. Structure of the PLA molecule.

room temperature of 23–25 °C. The magnetic agitation remained constant until the PLA was completely dissolved, which was indicated by the solution becoming translucent and when no solid particles were detected. Complete dissolution was achieved after 1 h of agitation.

2.2.2. Preparation of polymeric membrane

The preparation of the polymeric membrane was conducted in a prototypical electrospinning device developed by INTEXTER; the intellectual property rights belong to the Polytechnic University of Catalonia.

To conduct the experiment, a high voltage power supply, a spinneret (a capillary tube with very small diameter) and a grounded collector plate (a plate usually composed of metal) were required.

During the electrospinning process, a strong electrostatic field is applied to a polymer solution held in a syringe with a capillary outlet. A pendent-shaped droplet of the polymer solution from the capillary outlet is deformed into a Taylor cone [16] by the electrostatic field. When the voltage surpasses a threshold value, the electric force overcomes the surface tension of the droplet and a charged jet of the solution is ejected from the tip of the Taylor cone. As the jet moves toward a collecting metal screen (counter electrode), the solvent evaporates and a non-woven fabric mat is formed on the screen [17].

The operation conditions used in this study were:

- Applied voltage: 10 kV;
- Polymeric solution flow rate: 2 mm/h;
- Distance between the spinneret and collector: 8.5 cm;
- Spinneret opening diameter: 0.4 mm
- Metallic tambour diameter: 4 cm.

2.2.3. Introduction of ibuprofen into the sandwich membrane configuration

Ibuprofen was placed between two adjacent layers of the polymeric membranes. When the first layer of the electrospun membrane was dried and solidified, the drug, which was in a dried medium, was evenly dispersed on the membrane surface. The amount of drug was controlled using a Mettler Toledo AG204 analytical balance. After placing the drug on the membrane surface, a second membrane layer was electrospun over the first layer to cover the drug [18]. The sandwich membrane configuration is illustrated in Fig. 3.

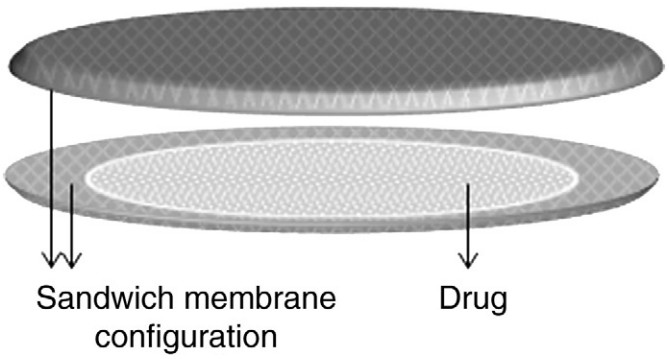

Fig. 3. Schematic illustration of a sandwich membrane configuration.