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Preparation and characterization of naproxen-loaded electrospun thermoplastic polyurethane nanofibers as a drug delivery system

Cigdem Akduman [a], Işık Özgüney [b,*], E. Perrin Akcakoca Kumbasar [c]

[a] Pamukkale University, Denizli Vocational School of Technical Sciences, Department of Textile Technology, Denizli 20100, Turkey
[b] Ege University, Faculty of Pharmacy, Department of Pharmaceutical Technology, 35100 Izmir, Turkey
[c] Ege University, Faculty of Engineering, Department of Textile Engineering, 35100 Izmir, Turkey

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ABSTRACT

The design and production of drug-loaded nanofiber based materials produced by electrospinning is of interest for use in innovative drug delivery systems. In the present study, ultra-fine fiber mats of thermoplastic polyurethane (TPU) containing naproxen (NAP) were successfully prepared by electrospinning from 8 and 10% (w/w) TPU solutions. The amount of NAP in the solutions was 10 and 20% based on the weight of TPU. The collection period of the drug-loaded electrospun TPU fibers was 5, 10 and 20 h, and they were characterized by FTIR, DSC and TGA analysis. The morphology of the NAP-loaded electrospun TPU fiber mats was smooth, and the average diameters of these fibers varied between 523.66 and 723.50 nm. The release characteristics of these fiber mats were determined by the total immersion method in the phosphate buffer solution at 37 °C. It was observed that the collection period in terms of the mat thickness played a major role in the release rate of NAP from the electrospun TPU mats.

1. Introduction

Drug delivery systems (DDS) are defined as formulations or devices that enable the introduction of a therapeutic substance into the body improving its efficiency and safety [1]. Transdermal drug delivery is an approach used to deliver drugs through the skin for therapeutic use and includes: local application formulations, e.g., transdermal gels and penetration enhancers; drug carriers, e.g., liposomes and nanoparticles; transdermal patches; and so on [1–2]. While local application formulations such as ointments and creams are usually used for topical delivery to the skin, patches have been developed for controlled systemic delivery [3]. Topical patches deliver drugs to a local site of action [4]. One of the significant achievements of nanotechnology today is drug-containing electrospun fiber mats that can be used as drug release systems [5–9], especially in transdermal and topical drug deliveries.

The electrospinning process simply uses a high voltage power source, a nozzle and a collector covered with aluminum foil. The potential difference between nozzle and collector leads to stretch of the solution and creates a thin jet from polymeric solution towards to the collector. During the stretch of the solution to the collector, the solvent evaporates and ultrafine nanofibers are collected [10,11]. The electrospinning process has attracted a great deal of attention due to its relative ease of use, adaptability, the ability to fabricate fibers with diameters on the nanometre scale [12,13], vast possibilities for surface functionalization [14,15] with high surface area to volume or mass ratio, small inter-fibrous pore size and high porosity [12,16–17]. The design and production of drug-loaded nanofiber-based materials generated by electrospinning is of interest in terms of innovative drug delivery systems. Since electrospun fiber mats exhibit a much greater surface area than those from the conventional film-casting technique, they could potentially allow drug molecules to diffuse out from the matrix much more conveniently [18,19]. The main advantages of the fibrous carriers are that they can be used as a topical drug delivery system, they offer site-specific delivery of drugs to the body, and they may reduce the total drug dose thereby minimizing nontargeted site toxicities [20].

To generate drug delivery systems based on electrospinning, a drug is incorporated along with the polymer in the solution to be electrospun [5,8,21]. The large surface area associated with electrospun mats allows for fast and efficient solvent evaporation, which gives the incorporated drug limited time to recrystallize favouring the formation of amorphous dispersions or solid solutions [20]. Then the mat releases the drug to the dissolution medium via diffusion. In the matrix type of diffusion-control system, the drug is uniformly distributed throughout the polymer matrix [22,23]. The release of the drug from the matrix is governed by the diffusion of the dissolution medium within the matrix phase [23]. Drug-release rates will be dependent upon the diffusion coefficient of the drug within the polymer matrix and the initial drug load. In addition to the material and system parameters, the membrane thickness may also affect the rate of drug release [24].

* Corresponding author.
E-mail address: isik.ozguney@ege.edu.tr (I. Özgüney).

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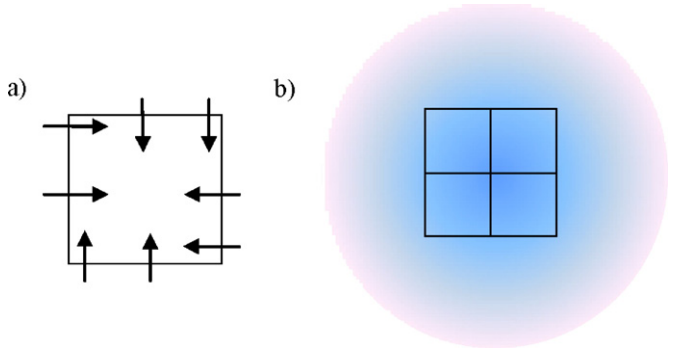

Fig. 1. Thickness measurement points of the mat (a) location of the mat taken from the collection area (b).

A wide variety of polymeric materials either biodegradable [5–6,8, 19,25–28] or non-biodegradable [7,20] but biocompatible, can be used as the matrix material. The choice of polymer and therapeutic substance are determined by the requirements of the specific application. Many types of therapeutic substances that have been incorporated into the nanofibrous mats are successfully released without a significant loss of their activity [29]. Some low molecular drugs, antibiotics [6,21], non-steroidal anti-inflammatory drugs (NSAID) [8,19,25], vitamins [27,30], chemotherapeutics [31] and many others have already been studied [29]. Mostly protein-based higher molecular compounds have also been shown to be effectively released from nanofibers [28,32].

However, in many studies immediately upon placement of the produced drug-loaded electrospun membrane in the release medium, an initial large bolus of the drug is released before the release reaches a stable profile [6,7,21,25,33]. This phenomenon is typically referred to as "burst release." Despite the fact that the fast release of the drug in the burst stage is utilized in certain drug administration strategies, the negative effects brought about by the burst can be pharmacologically dangerous and economically inefficient [22]. One suggested explanation for the burst effect in monolithic systems is that some drug becomes trapped on the surface of the polymer matrix during the production process especially in the case of high drug loading and is released immediately upon activation in a release medium [34]. Another explanation is that the migration of drugs during drying and storage steps may result in a heterogeneous distribution of the drug in the polymer matrix and lead to burst release [35,36]. In cases where the drug is uniformly dissolved or dispersed in the polymer matrix, the release rates continuously diminish with time due to the increasing diffusion distance that hinders drug transfer [22]. In this scope membrane thickness can be increased to extend the drug release period [24], as well as reduce the drug loading. Thus, drug utilization will be improved, burst release could be eliminated, and fewer adverse effects could be achieved.

To the best of our knowledge, the electrospinning of naproxen (NAP)-loaded thermoplastic polyurethane (TPU) for a topical drug delivery system and the effect of the mat thicknesses on release profile have not yet been thoroughly investigated. Thermoplastic polyurethanes (TPU) are a widely used class of polymer, which have good biocompatibility and high mechanical properties and can be easily electrospun. Therefore electrospun TPU membranes are of interest in terms of biomedical applications [37,38]. Their biocompatibility, non-toxicity, toughness and functionality have led to the widespread use of TPUs in implantable devices (vascular grafts, pacemaker leads, blood bags, bladders and artificial heart valves) and medical applications [39–41]. There are studies which describe the production of polyurethane nanofibers [42–44]. NAP is one of the most efficient nonsteroidal anti-inflammatory drugs (NSAIDs), with analgesic and antipyretic properties and is widely used for the treatment of osteoarthritis, rheumatoid arthritis and acute pain in musculoskeletal disorders [45–48]. Lipophilicity is essential for topical delivery because the stratum corneum, the major barrier to drug permeation, is lipophilic and, in general, favours permeation by lipophilic drugs. In this scope NAP possesses an appropriate lipophilicity for skin permeation [47]. Cellulose acetate [7] poly

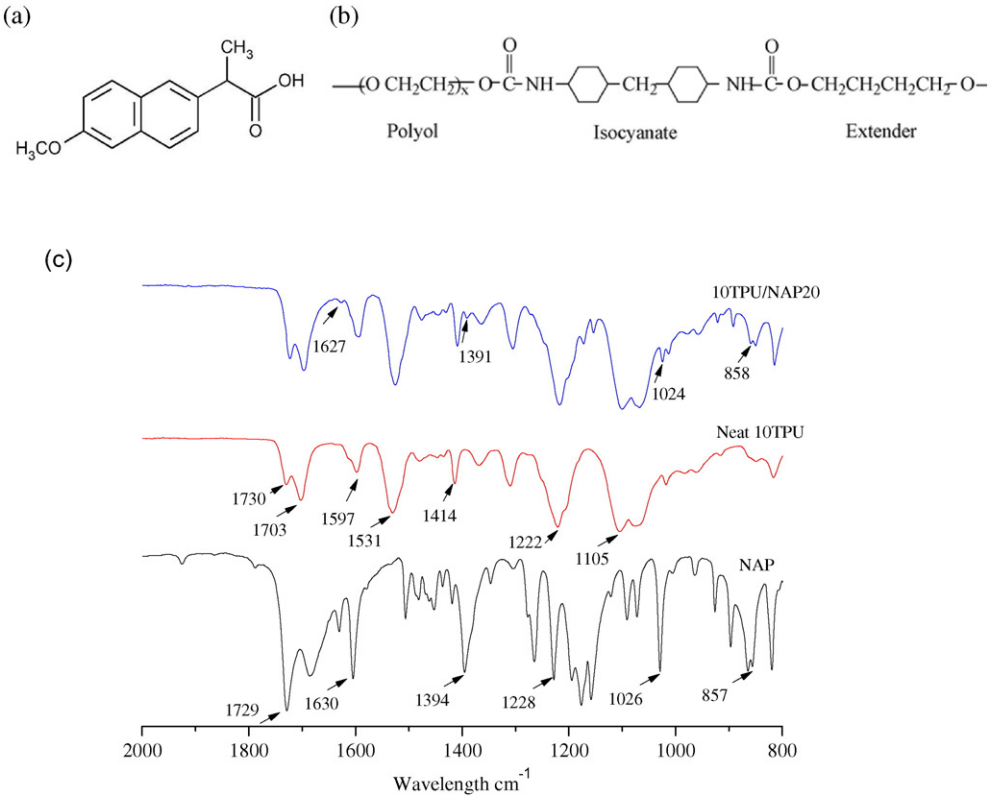

Fig. 2. (a) NAP, (b) TPU general formula, (c) FTIR spectra of 10TPU/NAP20, neat 10TPU nanofibers, and pure NAP powder.