RELEASE CHARACTERISTICS OF NAPROXEN LOADED ELECTROSPUN THERMOPLASTIC POLYURETHANE NANOFIBERS

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ABSTRACT

Combination of biocompatibility, non-toxicity, toughness and functionality of thermoplastic polyurethanes (TPU) has led their widespread use in medical applications [1-3]. Electrospinning of thermoplastic polyurethane nanofibers have been reported to have a potential use for the preparation of drug loaded non-biodegradable membranes for topical drug administration [4]. In the present study, ultra-fine fiber mats of TPU containing naproxen was successfully prepared by electrospinning from 8% (w/w) TPU solutions in dimethylformamid (DMF). The amount of naproxen in the solutions was 10 and 20 % based on the weight of TPU granules. The drug-loaded electrospun TPU fibers collection period was changed to 5, 10 and 20 h. The morphology of the 10 and 20% naproxen loaded electrospun TPU fiber mats was smooth and the average diameters of these fibers were 527 and 537 nm respectively. The release characteristics of the naproxen loaded TPU fiber mats were carried out by the total immersion method in the phosphate buffer solution at 37 ^{o}C. Collection period played a major role on the release rate of naproxen from electrospun TPU mats.

Key Words: Nanofibers, Electrospinning, Thermoplastic polyurethane, Naproxen, Release rate

1. INTRODUCTION

Electrospinning process has attracted a great deal of attention due to vast possibilities for surface functionalization [5] with high surface area to volume or mass ratio, small inter-fibrous pore size and high porosity of electrospun mats. Due to the high surface area and porous structure of the electrospun fiber mats, they find applications in many fields such as medicine [3-8], biosensors [9], tissue engineering [2,10], antimicrobial materials, membranes [4,9] and so on.

The application of electrospinning technology to drug-based delivery systems has been examined by many researchers [3,5-7, 10-15]. To develop drug delivery systems based on this approach, a drug is incorporated along with the polymer in the solution to be electrospun. Verreck et al. [7] evaluated two model drug, itraconazole and ketanserin, using a polyurethane carrier. Kenawy at al.[6] used ketoprofen as non-steroidal anti-inflammatory drug in partially and fully hydrolyzed poly(vinyl alcohol) (PVA). Taepaiboon et al. [14] selected sodium salicylate (freely soluble in water), diclofenac sodium (sparingly soluble in water), naproxen (NAP), and indomethacin (IND) (both insoluble in water), as model drugs. Zong et al [15] also used PLA as the matrix and used mefoxin (an antibiotic drug) as the model drug. They found a similar result that nanofibrous drug carriers show better release characteristics than films, that observed by Kenawy et al. Naproxen 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 [16-17]. Thermoplastic polyurethanes (TPU) are water-insoluble, non-biodegradable polymers specifically show good biocompatibility, non-toxicity, toughness

properties which led them widespread use in medical applications [1, 18-20] and can be easily electrospun. The main objective of the present study is to develop and characterize novel electrospun nanofibrous TPU materials containing naproxen and determine in vitro release properties of them. Further, effect of drug concentration added to the bulk polymer solution prior to electrospinning on the morphology and release properties were investigated.

2. EXPERIMENTAL

2.1 Materials

Thermoplastic polyurethane used in this study was the commercial Pellethane 2103-80AE, based on 4,4-methylene bis (phenylene isocyanate) (MDI), polytetramethylene oxide (PTMO) and 1,4 butanediol was provided from Velox (Lubrizol Advanced Materials). Naproxen and N,N,Dimethylformamid (DMF) were purchased from Sigma Aldrich. The chemical structure for the model drug, Naproxen is shown in Figure 1.

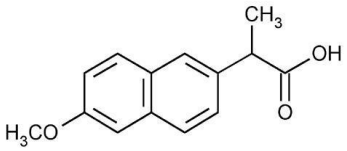

Figure 1 Chemical Structure Naproxen

2.2. Electrospinning of naproxen loaded TPU fibers

TPU granules were dissolved in DMF at room temperature for 24 h to prepare TPU solutions at 8% (w/w). After the solution was prepared, Naproxen was added into the TPU solution under constant stirring rate for 4 h. The amounts of the naproxen in the solutions were 10 and 20% based on the weight of TPU granules. Electrospinning of the prepared solutions was carried out by connecting the emitting electrode of positive polarity from a high-voltage DC power supply (Simco, MP Series CM5 30 P, Charging Generator Output 30 kV DC) to the solutions contained in a standard 10 ml syringe, the open end of which was attached with 2.5 cm long 22 gauge flat-tipped stainless steel needle used as a nozzle, and the grounding electrode to a stationary rectangular metal collector covered by a piece of aluminum foil used as the fiber collecting area. The electrostatic field strength was fixed at 13 kV/20 cm. The feed rate of the solutions was controlled to about 1 ml h^{-1} using a syringe pump for stable electrospinning jet. The drug-loaded electrospun TPU fibers collection period was changed to 5, 10 and 20 h. The complete electrospinning apparatus was enclosed in a glass box and the electrospinning of the nanofibers was carried out at room temperature.

2.3 Characterization of naproxen loaded electrospun TPU mats

The morphological appearance of drug-loaded electrospun mats was observed by a scanning electron microscope (SEM; FEI Quanta250 FEG scanning electron microscope). The electrospun mats were sputtered by EMITECH K550X ion sputtering device with a thin layer of gold prior to SEM observation. The mean diameter of the resultant fibers was calculated from measurements on SEM images of 10000× magnification by using Image J program. Approximately 40 measurements were carried out from the different parts of each sample.

The thickness of the nanofibrous membranes were measured by Mitutoyo digital micrometer at 0,001 mm accuracy. Each sample was measured at eight points of nanofibrous membranes (Figure 2(a)). In Figure 2b, it was shown the thicker regions with darker and thinner regions with paler colour.

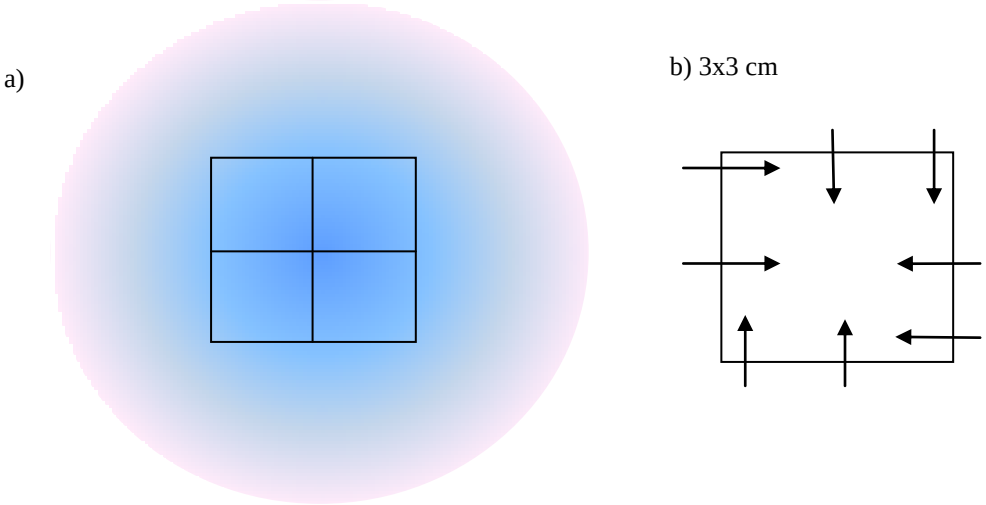

Figure 2. Location of the samples taken from the collection area (a) thickness measurement points of the samples (b)

2.4 Release Characteristics of naproxen loaded electrospun TPU mats

Total immersion method was used to study the release characteristics of the drug from the drug-loaded electrospun TPU fiber mats. The samples (in dimension of 3x3 cm) were accurately weighed and immersed in a glass bottle containing phosphate buffer pH 7.4 USP and the bottles were incubated in a horizontal incubation shaker (LAB-LINE MaxQ6000) at of 37± 0.5°C, 75 rpm. At a specified immersion period ranging between 0 and 5 h (300 min), 0.5 ml of the sample was taken out at selected times and an equal volume of medium was returned to the system after withdrawal. The samples were then assayed spectrophotometrically at 263 nm. The experiments were carried out in triplicate. The release of the drug from the samples was reported as the cumulative release of the drug as a function of the immersion period.

3. RESULTS AND DISCUSSION

To determine the morphology of the electrospun fibers, an analysis of the scanning electron micrographs (SEM) images was performed. Figure 3 illustrates SEM images of 20 hours collected elctrospun TPU mats containing 10 and 20% naproxen and their diameter distribution histograms. Based on these SEM images, the average diameter of 10% and 20% naproxen loaded electrospun TPU fibers were 527 and 537 nm respectively. Mean difference was analyzed by Students't-test and significance was tested at the 0.05 of probability but no significant difference was observed between average mean diameters. This result indicates

that changing the naproxen concentration 10 to 20 have no effect on the average fiber diameter.

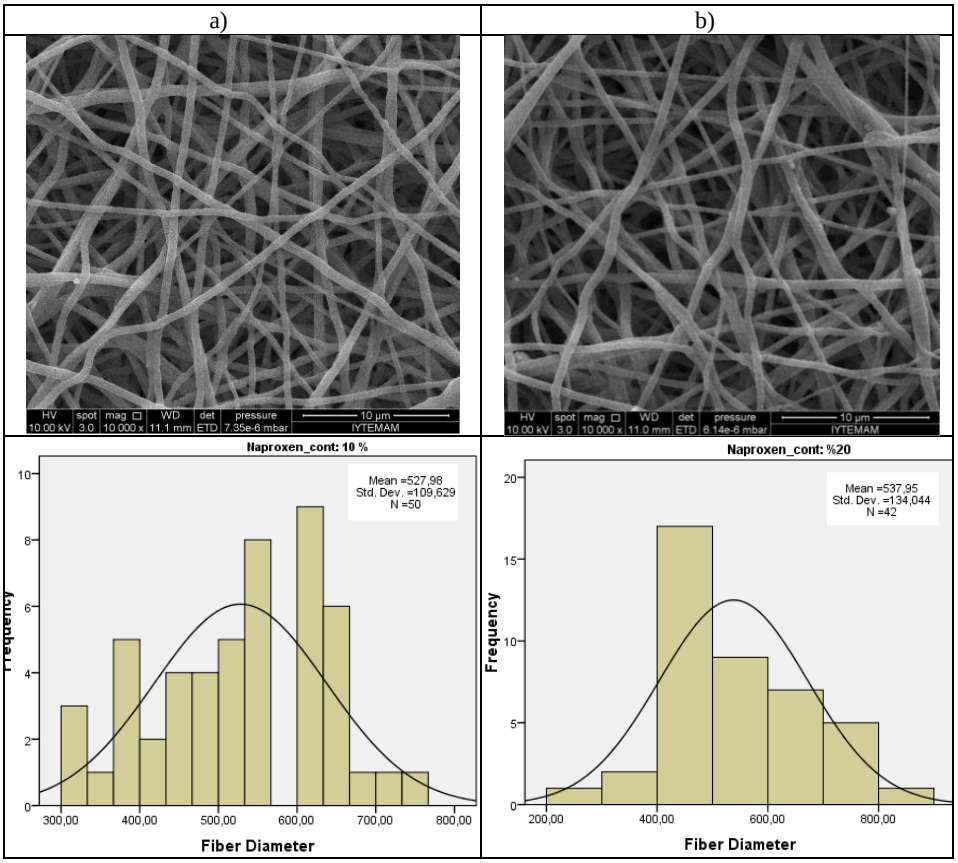

Figure 3. SEM images of 20 hours collected naproxen loaded TPU mats, 10% (a), 20% (b) and their fiber diameter distribution histograms

Since our current electrospinning system is using single needle, collection area is circular as shown in Figure 2(b). The thickness of the collection area decreases radially. Diameter of the collection area was large and approximately 30 cm because of the low viscosity of the 8% TPU solution (Figure 4). The increase of the collection area decreases the thickness uniformity of the mat. Average thickness, average weight and theoretical naproxen content of the 10 and 20% naproxen loaded 8% TPU mats were given in Table 1.

Figure 4 Collection area of naproxen loaded 8% TPU mat

Table 1. The thickness, average weights and theoretical naproxen contents of naproxen loaded 8% TPU mats according to collection period

	Average thickness (mm) ±SE	*Average weight (mg) ±SE*	*Theoretical naproxen weight (mg) ±SE*
8% TPU/10% Nap 5 hours collection	0.03 ±*0.028*	29.40 ±*2,54*	2.67 ±*0,23*
8% TPU/10% Nap 10 hours collection	0.09 ±*0.038*	57.70 ±*2,54*	5.25 ±*0,23*
8% TPU/10% Nap 20 hours collection	0.30 ±*0.015*	169.87 ±*11,90*	15.44 ±*1,08*
8% TPU/20% Nap 5 hours collection	0.02 ±*0.026*	21.90 ±*1,76*	3.65 ±*0,29*
8% TPU/20% Nap 10 hours collection	0.07 ±*0.004*	46.40 ±*3,52*	7.73 ±*0,59*
8% TPU/20% Nap 20 hours collection	0.22 ±*0.011*	127.37 ±*9,09*	21.23 ±*1,51*

The release characteristics of naproxen from the drug-loaded electrospun TPU fiber mats are shown in Figure 5. Evidently, naproxen release from 5 and 10 hours collected TPU mats showed burst effect during 15-30 min. It was thought that the reason of burst effect is very low thickness of the mats. Thus, diffusion path of the drug would be shorter. On the other hand, naproxen release of 20 hours collected TPU mats continued up 5 hours. It can be seen from Table 1 that thicknesses of 20 hours collected mats are approximately 3 times more than 10 hours and 10 times more than 5 hours collected mats. Comparing the release rates of 10 and 20% naproxen loaded TPU mats, it was seen that release percentage of 20%naproxen loaded was greater than 10% naproxen loaded mats. High release of 20% naproxen loaded electrospun TPU mats could be related to the amount of drug.

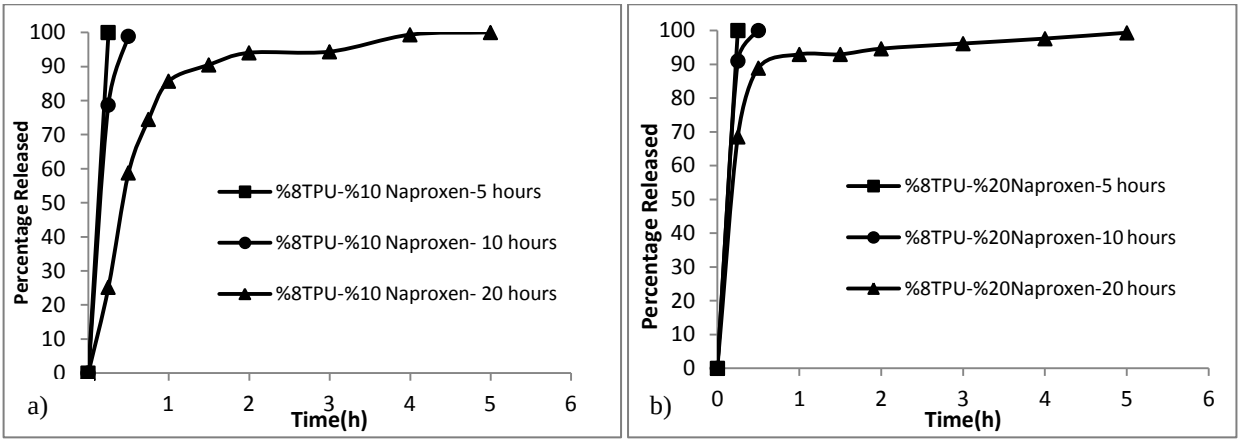

Figure 5. Percentage release of 8%TPU mats; (a)10% naproxen loaded, (b) 20% naproxen loaded

4. CONCLUSIONS

Electrospun polyurethane nanofibers containing naproxen was developed and their release characteristics were investigated. It was seen that, the thickness of the mats, the collection time and drug content played an important role on release rate.

5. ACKNOWLEDGEMENT

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