Effect of polyvinylpyrrolidone and ethyl cellulose in polyurethane electrospun nanofibers on morphology and drug release characteristics

Elektro-eğirme yöntemi ile üretilen poliüretan nanoliflerin morfolojileri ve ilaç salım özellikleri üzerinde polivinilpirolidon ve etil selülozun etkisi

ASLI GENÇTÜRK¹, Emine Kahraman², SEVGİ GUNGÖR², YILDIZ OZSOY², A.Sezai Sarac³

¹Polymer Science and Technology, Istanbul Technical University, Istanbul, Turkey

²Department of Pharmaceutical Technology, Faculty of Pharmacy, Istanbul University, Istanbul, Turkey

³Nanoscience and Nanoengineering, Istanbul Technical University, Istanbul, Turkey

Abstract

Objectives: Polyurethanes are widely opted for composing nanofibers due to their ability of spinnability, biocompatibility, high chemical stability, good mechanical and elasticity properties. The desired release behaviours are also achieved by using combination of polyurethanes and various polymers. In the present study, we aimed to investigate effects of polyvinylpyrrolidone and ethyl cellulose in polyurethane electrospun nanofibers in terms of the morphological structures and drug release characteristics.

Materials and Methods: The nanofibers were prepared with the blends of polyurethane with either ethyl cellulose or polyvinylpyrrolidone at different ratios by electrospinning method. The effect of polyvinylpyrrolidone or ethyl cellulose on morphology and nanofiber diameter of the prepared nanofibers was examined with scanning electron microscopy. Compatibility of components used in the formulations of nanofibers was determined by Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy. Donepezil hydrochloride, a water soluble compound, was selected as a model drug to examine its release characteristics from both polyurethane/polyvinylpyrrolidone and polyurethane/ethyl cellulose electrospun nanofibers. *In vitro* drug release studies from electrospun nanofibers were performed according to method defined in the monograph as "paddle over disk method" of United State Pharmacopeia 38.

Results: The electron microscopy images showed that addition of ethyl cellulose or polyvinylpyrrolidone into polyurethane solutions affected generation of the nanofibers with smooth surface, non-beads in nanoscale. Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy spectra disclosed that ethyl cellulose and

polyvinylpyrrolidone were separately incorporated to polyurethane matrix. *In vitro* release data indicated that presence of ethyl cellulose or polyvinylpyrrolidone in polyurethane nanofibers dramatically changed release behaviour of Donepezil hydrochloride. Polyurethane/ethyl cellulose nanofibers (F4) provided a sustained drug release with Korsmeyer-Peppas drug release kinetic mechanism, in which the release rate was controlled by the diffusion of drug, while all of polyurethane/polyvinylpyrrolidone nanofibers exhibited fastly drug release.

Conclusion: Overall, this ability of polyurethane/ethyl cellulose (10/8) electrospun nanofibers has suggested the potential use of it as a drug carrier from which a water-soluble drug release may be in a sustained release fashion.

Keywords: Electrospun nanofibers, drug release, polyurethane, polyvinylpyrrolidone, ethyl cellulose

Özet

Amaç: Elektro-eğirme yöntemi sırasında işlem kolaylığı sağlamaları, biyoyumlu olmaları, yüksek kimyasal stabiliteye, istenilen mekanik ve elastik özelliklere sahip olmaları nedeniyle nanoliflerin oluşumunda çoğunlukla poliüretanlar tercih edilmektedir. Hedeflenen salım davranışları da poliüretanların çeşitli polimerlerle bileşimi kullanılarak elde edilmektedir. Sunulan çalışmada ise elektro-eğirme yöntemi ile üretilen poliüretan nanoliflerin morfolojileri ve ilaç salım özellikleri üzerinde polivinilpirolidon ve etil selülozun etkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Nanolifler farklı oranlarda etil selüloz veya polivinilpirolidonun poliüretan ile karışımları kullanılarak elektro-eğirme yöntemiyle hazırlandılar. Hazırlanan nanoliflerin morfolojisi ve çapı üzerinde polivinilpirolidon veya etil selülozun etkisi taramalı elektron mikroskobu ile incelendi. Nanolif formülasyonlarında kullanılan maddelerin geçimliliği Zayıflatılmış Toplam Yansıma üniteli Fourier Dönüşümlü Kızılötesi Spektroskopisi ile belirlendi. Hem poliüretan/polivinilpirolidon hem de poliüretan/etil selüloz nanoliflerin salım davranışlarını incelemek için suda çözünen bir ilaç olan donepezil hidroklorür model ilaç olarak seçildi. Nanoliflerden ilaç salım çalışmaları Amerikan Farmakopesi 38'de tanımlanan *"disk üzerinde palet yöntemi"*ne göre yapıldı.

Bulgular: Elektron mikroskobu görüntüleri etil selülozun veya polivinilpirolidonun poliüretan çözeltisine eklenmesinin nanolif oluşumunu etkilemediğini, oluşan nanoliflerin pürüzsüz yüzeye sahip olduğunu ve boncuk şeklinde yapılar içermediğini göstermiştir. Zayıflatılmış Toplam Yansıma üniteli Fourier Dönüşümlü Kızılötesi spektrumları ise etil selüloz ve polivinilpirolidonun poliüretan matrikse yüklendiğini ortaya koymaktadır. *In vitro* salım verileri ise poliüretan nanoliflerde etil selüloz veya polivinilpirolidon varlığının donepezil hidroklorürün salım davranışını önemli ölçüde değiştirdiğini göstermiştir. Ayrıca poliüretan/polivinilpirolidon nanolifleri hızlı bir şekilde ilaç salımı sergiliyorken poliüretan/etil selüloz nanolifleri (F4) ise salım hızının ilacın difüzyonuyla kontrol edildiği Korsmeyer-Peppas kinetik mekanizması ile uyumlu uzatılmış ilaç salımı göstermiştir.

Sonuç: Suda çözünen bir ilacın uzatılmış salımının yapılabilmesi için ilaç taşıyıcı bir sistem olarak poliüretan/etil selüloz (10/8) nanoliflerin olası kullanımı önerilmektedir.

Anahtar kelimeler: Elektro-eğirme yöntemi ile üretilen nanolifler, ilaç salımı, poliüretan, polivinilpirolidon, etil selüloz

1. Introduction: Electrospun nanofibers has attracted a great attention due to their potential applications for biomedical devices, tissue engineering, biosensors, filtration, wound dressing, enzyme immobilization, and drug delivery in recent years.¹ They have received a great attention in drug delivery especially due to their high surface area to volume ratio that could allow drug molecules to diffuse out of matrix readily because of their highly porous structure.^{2,3} In addition, the electrospun nanofibers have other superiorities such as high drug loading capacity, cost-effectiveness, and ease of fabrication process.⁴

Polyurethanes (PUs) are widely opted for composing nanofibers due to their ability of spinnability, biocompatibility, chemical stability, good mechanical and elasticity properties. They could generally adapt for many applications such as filters, wound dressing materials, protective textiles, biosensors, biomedical devices, and tissue engineering, owing to their various structures.⁵ The addition of the second component such as cellulose derivatives, polyethylene glycol (PEG), polycaprolactone, poly (vinyl alcohol) (PVA), poly (acrylic acid) (PAA) to PUs could give rise to fabrication of a new nanofiber with different morphological and physical structures for special applications.^{6,7}

The desired release behaviours are also achieved by using various polymer combinations.⁸

Ethyl cellulose (EC) is a non-ionic and physiologically inert cellulose derivative. This polymer which is insoluble in the water due to its hydrophobic nature has a relatively small swelling degree.⁹ Therefore; it is a suitable compound for preparation of sustained drug release matrix¹⁰ and does not require addition of release modifiers.¹¹

Polyvinylpyrrolidone (PVP) is a non-ionic, biodegradable and biocompatible polymer made from the monomer N-vinylpyrrolidone.^{12,13} It features an outstanding spinnability in various solvents such as ethanol, methanol, or chloroform.^{12,14} PVP has a hygroscopic property, so that absorbs water up to 40 % of its weight in atmospheric conditions and could result in unstable nanofibers. But besides these properties, PVP is a hydrophilic polymer which leads to fast dissolution and immediate release of drugs.¹⁵ PVP has already been used to modulate release of drugs from the nanofibers.¹⁶ The release behaviour of drug loaded PVP, EC or PVP/EC electrospun nanofibers have been studied by some researchers.¹⁷⁻²⁰ However, morphology and drug release characteristics of the electrospun fibers composed of the blends of PU with either EC or PVP have not yet been available in the literature.

In this study, we aimed to investigate effect of EC and PVP in polyurethane electrospun nanofibers on morphology and drug release characteristics. At the second stage, the fibers were prepared from PU and either hydrophobic polymer EC or hydrophilic polymer PVP blends in different combinations. PU/EC and PU/PVP fibers were evaluated as a drug carrier material to modulate the release profile. The developed PU/EC and PU/PVP fibers in different combination were characterized morphologically and structurally. At the second stage, the effect of EC or PVP content on the release rates of donepezil hydrochloride (DNP), which is a water-soluble drug, are discussed and their kinetic mechanisms were estimated following *in vitro* release data.

2. Materials and Methods

2.1. Materials: Polyurethane (PU; Mw~93,000 g/mol) was supplied from Flokser Corporation (Turkey). Ethyl cellulose (EC) and polyvinylpyrrolidone K30 (PVP,

Mw=360,000 g/mol) were purchased from Dow (United States) and Hangzhou Sunflower Technology (China) respectively. N, N-dimethylformamide (DMF) was obtained from Labkim (Turkey). Donepezil hydrochloride (DNP) was kindly donated by Santa Farma Pharmaceutical Company (Turkey). All the chemical materials were of analytical grade.

2.2. Preparation of Electrospun Nanofibers: Homogeneous PU solutions were prepared by dissolving PU (12.5%, w/v) in dimethylformamide. DNP was added to these clear polymer solutions, and it was dissolved. Following addition of either EC or PVP at different ratio into PU solutions (Table 1), the mixtures were stirred for an hour to provide a homogenous solution for electrospinning procedure.

The conductivity of these solutions was measured by a conductivity meter (Eutech Instruments, PC2700, Landsmeer, Netherlands) at room temperature. Each of measurements was performed in triplicate.

“INSERT FIGURE 1”

“INSERT TABLE 1”

In the electrospinning process (Fig. 1), each of the mixed polymer solutions were loaded into 10 mL syringes equipped with the metallic needle of an outer diameter of 0.8x38 mm. A syringe was mounted horizontally on syringe pump (NE-500 Model, New Era Pump Systems, Inc. USA) and aluminium collector. A positive electrode of high voltage power supply (ES 30 Model, Gamma High Voltage Inc., USA) was attached onto a syringe needle. The polymer solution was fixed at rate of 1 mL/h. The high electric voltage was set to 15 kV, the distance between needle tip and aluminium collector distance was 15 cm. All solution preparations and electrospinning were carried out at ambient temperature.

2.3. Morphology of Electrospun Nanofibers: The surface morphology of drug loaded PU/EC and PU/PVP electrospun nanofibers were examined with scanning electron microscope (SEM) (Philips-XL30 SFEG, Tokyo, Japan) after each of the samples were coated with a thin layer of gold/palladium (Au/Pd) alloy to render them electrically conductive. The SEM images were recorded at an accelerating voltage of 20 kV and

average fiber diameters (AFD) were calculated using Image J by randomly measuring the diameters of 20 different fibers in the images for each sample.

2.4. Compatibility of Components on Electrospun Nanofibers: Compatibility of components used in the formulations of nanofibers is crucial for fabrication of stable nanofibers. For this reason, FTIR spectroscopic analysis of prepared electrospun nanofibers were carried out using an Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy (ATR-FTIR) (Perkin Elmer, Spectrum One; with a universal ATR attachment with a diamond and ZnSe crystal C70951, Massachusetts, USA).

2.5. *In vitro* Drug Release from Electrospun Nanofibers: *In vitro* drug release studies were carried out according to method defined in the monograph as "*paddle over disk method*" of United State Pharmacopeia (USP 38).²¹ The nanofiber sections with 2.5 cm diameter were immobilized between a glass container and a sieve of stainless steel. The samples were immersed into 500 mL of phosphate buffer (PBS, pH: 6.5) to maintain sink conditions for DNP. At the specified time points (from 30th minute up to 6th hour), 2 mL aliquots of the samples were withdrawn periodically from the release medium and, equal volumes of the release medium were immediately replaced to maintain a constant volume. Concentrations of DNP in the samples were analyzed by a UV-visible spectrophotometer (Shimadzu, UV-1601, Tokyo, Japan) at the wavelength of 229 nm. The cumulative amount of released DNP per cm² from electrospun nanofibers was plotted versus time. Each experiment was conducted in triplicate. The UV visible spectrophotometry method was validated for selectivity, linearity, accuracy, and precision. It was determined to be linear over concentration range 2.5-20 µg/mL with a high correlation coefficient ($r^2 > 0.999$) and accurate, (recovery > 98%). There were no interfering absorbances with DNP confirming selectivity of the method.

2.6. Analysis of Drug Release Kinetics and Modelling: In order to understand the mechanism and kinetics of DNP release from electrospun nanofibers, the release data were fitted to kinetic models via free open source software DDSolver^{® 22} as described below (1-5):

The zero order kinetic model;

$$C = k_0 t + C_0 \quad (1)$$

The first order kinetic model;

$$\ln C = \ln C_0 + k_1 t \quad (2)$$

The Higuchi square root kinetic model;

$$C = k_2 t^{1/2} \quad (3)$$

where, C is drug concentration released at time t , C_0 is drug concentration at the beginning, k_0 , k_1 and k_2 are zero, first order and Higuchi release rate constants, respectively.

The Hixson–Crowell kinetic model;

$$W_0^{1/3} - W_t^{1/3} = k_H t \quad (4)$$

where, W_0 is initial amount of drug in the formulation, W_t is remaining amount of drug in the nanofiber at time t and k_H is release rate constant for Hixson-Crowell model.

The Korsmeyer-Peppas kinetic model;

$$M_t / M_\infty = k_{KP} t^n \quad (5)$$

where, M_t is drug concentration released at time t , M_∞ is equilibrium concentration of drug that must be released at infinite time in the release medium, M_t / M_∞ is the fraction of drug in the release medium at time t , k_{KP} is release rate constant, n is diffusional exponent indicating type of drug release mechanism. If n equals 1, the release mechanism is zero order; on the other hand, if $0.5 < n < 1$, non-Fickian transport is the case. Also, the first 60% drug release data were fitted in this model.²³

The coefficient of correlation (r^2) values were determined for the linear curves obtained by regression analysis of drug release profile. The highest r^2 value was selected as the most appropriate model.

3. Results and Discussion

3.1. Preparation of Electrospun Nanofibers: The solution properties such as type of polymer and its concentration as well as electrospinning process parameters include the flow rate, applied voltage, tip-to-collector distance are crucial to obtain the bead-free electrospun fibers in nanometric scale.²⁴ Therefore, the preliminary electrospun nanofiber fabrication studies were conducted using pure PU solutions at different concentrations and the electrospinning process parameters such as flow rates, applied voltages, tip-to-collector distance were tested to find the optimum electrospinning process parameters and, polymer concentration as described our previous study.²⁵ The

results had showed that the bead-free electrospun fibers could be merely obtained with 12.5% (w/v) concentration of PU solution²⁵. In the present study, DNP, either EC or PVP at different ratios (Table 1) were added to the optimized PU solution and, then conductivity of the solutions was measured to observe effect on morphology of electrospun nanofibers. The conductivity of the solutions and average fiber diameter of electrospun fibers are presented in Table 2. Interestingly, there has been a correlated increase in conductivity with increasing average fiber diameter of the PU/EC/DNP and PU/PVP/DNP nanofibers. However, this case did not show a linear increase between conductivity of the polymer solutions and average fiber diameter of the nanofibers, as expected.

“INSERT TABLE 2”

3.2. Morphology of Electrospun Nanofibers: To investigate the effects of EC or PVP amounts on the morphology of PU/DNP electrospun nanofiber and, to verify fabrication of the nanofibers with smooth surface, non-beads in nanoscale; the morphological features of PU/EC/DNP and PU/PVP/DNP electrospun fibers were examined using SEM analysis. Fig. 2(a-b) and Fig. 3(a-b) present the morphological features and the diameter histograms of PU/EC/DNP and PU/PVP/DNP electrospun fibers containing different ratios of EC and PVP. Most of electrospun fibers (except of PU/PVP/DNP nanofiber at ratio of 10/8/1) had smooth surfaces and uniform structures without any "beads-on-a-string" morphology. Also, no drug particles were observed on the surface of the fibers and outside the nanofibers, indicating good compatibility between the polymers and drug and, encapsulation of drug in the nanofiber. SEM images of PU/EC/DNP nanofibers are given in Fig. 2a. The diameter of the PU/EC/DNP electrospun fibers depends on the presence of EC in the nanofiber composition. PU/DNP (10:1) electrospun fibers without EC had mean diameter of $775 \pm 16 \text{ nm}$ ²³, while mean diameter of the nanofibers with addition of EC decreased in range of 410 ± 47 and 603 ± 42 (Table 2). Also, the shape and uniformity of PU/EC/DNP electrospun fibers were kept even when increasing of the EC content in the nanofibers.

“INSERT FIGURE 2a”

“INSERT FIGURE 2b”

SEM images of PU/PVP/DNP nanofibers are given in Fig. 3a. The PU/PVP/DNP electrospun nanofibers containing different ratios of PVP had mean diameters from 279±57 nm to 340±56 nm. Also, the mean diameter of nanofibers decreased with addition to PVP to electrospun fiber formulations, such as observed by PU/EC/DNP electrospun fibers. However, some clumps were observed in PU/PVP/DNP electrospun nanofiber at ratio of 10/8/1, due to low solubility of PVP in electrospinning solution (Fig. 3a), as reported earlier.¹⁷ Overall, these results verified that PU/PVP/DNP and PU/EC/DNP electrospun fibers with smooth surface, non-beads in nanoscale were fabricated almost in all of ratios.

“INSERT FIGURE 3a”

“INSERT FIGURE 3b”

3.3. Compatibility of Components on Electrospun Fibers: ATR-FTIR spectra of PU/EC/DNP and PU/PVP/DNP (10/2/1, 10/4/1, 10/8/1) are seen in Fig. 4 and 5 recorded in the wave number range of 4000-800 cm⁻¹, spectra of 10/1/1 was not given because there was no differences between 10/1/1 and 10/2/1. Both the spectrum of drug loaded PU/EC and PU/PVP nanofibers have nearly similar characteristic FTIR bands, but the spectra of fibers show some small difference also. Characteristic absorption bands of PU described in detail in our previous study²⁵ such as: the 1727 cm⁻¹ band, due to the carbonyl groups in urethane bonds (C=O); the 1550 cm⁻¹ band, usually assigned to secondary amide (RCONHR'); the 1630 cm⁻¹ band, assigned to carbonyl groups in urea bond; the 1170 cm⁻¹ band due to C-O stretch and C-N stretch; the 3350 cm⁻¹ and 2944 cm⁻¹ bands from N-H and C-H groups.

Decreasing of characteristic absorption bands of PU at 1727 cm⁻¹ band from 10/2/1 to 10/8/1 (PU/EC/DNP) and also amendments at the 1062 cm⁻¹ and 2952 cm⁻¹ clarifies that EC incorporate to the PU matrix in Fig. 4. Because of the lower rate of the drug according to PU/EC and PU/PVP mixture, characteristic absorption bands of drug molecule may not be observed. Hence, the interactions could not be determined between the drug and polymers.

“INSERT FIGURE 4”

With the addition of PVP in PU, a new broad peak located at 3434 cm^{-1} and 1658 cm^{-1} are observed in Fig. 5. The new bands at 3434 cm^{-1} is due to the stretching vibration of the hydroxyl group (OH) and 1658 cm^{-1} is stretching vibration of the C=O. Increasing at 2949 cm^{-1} belongs to C-H asymmetric stretching vibration from PVP.

“INSERT FIGURE 5”

3.4. *In vitro* Drug Release Studies: In order to investigate the effect of EC and PVP amount added to PU solutions on the release of model drug; PU/EC/DNP and PU/PVP/DNP (at ratios of 10/1/1, 10/2/1 10/4/1 and 10/8/1, respectively) electrospun nanofibers were utilized. The release profiles of DNP from PU/EC electrospun nanofibers are shown in Fig. 6.

All of the electrospun nanofibers fabricated showed biphasic drug release profiles with relatively fast release in 30 min. Higher amount of drug release was observed by PU/PVP/DNP (10/8/1) nanofibers consisted of the highest ratio of PVP than those of other electrospun nanofibers comprised of PVP (*data not given*). However, the increment of the EC amount added to PU solution was resulted in decrease of drug release (Fig. 6). While about 350 mcg/cm^2 of DNP from that PU/PVP/DNP (10/8/1) nanofiber was released in an hour (*data not given*), the concentration of released DNP from nanofibers PU/EC/DNP (10/8/1) was about 100 mcg/cm^2 (approximately 20 %) at the end of an hour. This case was attributed to the hydrophilic character of PVP, which might accelerate the release rate of drug from PU nanofibers when its ratio was increased. The observed slow drug release effect of EC may be explained by its hydrophobic property when its ratio was increased in the composition of PU nanofibers. Besides, the clumps on the nanofibers consisted of PVP (Fig. 3a) might contribute to that higher immediate drug release. Interestingly, among the other PU/DNP nanofibers composed of either PVP or EC, no linear correlation between the released amount of drug and their ratios in the nanofiber composition were observed. The results revealed that EC may lead to retention of the water soluble drug in the polymer, which was resulted in inhibiting drug release and presenting a sustained drug release, as reported

earlier.²⁶ On the other hand, PVP could also accelerate the release of a water soluble drug, as also reported for poorly water-soluble drug (ibuprofen).¹⁷ Moreover, it is well known that the water-soluble drugs are released fast; this case is a crucial point for the controlled release of these types of drugs.²⁷ Based on that data, the sustained release behaviour of a water soluble drug from PU/EC electrospun fibers can be possible when the ratio of EC was increased (Fig. 6), which would be an advantage for providing a sustained release manner for water-soluble compounds.

“INSERT FIGURE 6”

3.5. Analysis of Drug Release Kinetics and Modeling: The *in vitro* release data of nanofibers were analyzed using to kinetic models mentioned in the method section to understand the release mechanism and kinetics of model drug from PU/EC electrospun nanofibers. The drug release mechanism and kinetics were determined based on the coefficient of correlation (r^2) values, which signifies the goodness of the fit. Table 3 present coefficient of correlation (r^2) values estimated for linear curves of PU/EC/DNP electrospun fibers. Also, the coefficient of correlation (r^2) values were not been estimated for kinetic models as the drug release from PU/PVP/DNP electrospun fibers were resulted in the immediate release. The regressed results for PU/EC/DNP electrospun fiber at ratio of 10/8/1 exhibited the highest coefficient of correlation ($r^2=0.999$) (Table 3) for Korsmeyer-Peppas model. This result indicated that the release of drug from PU/EC/DNP electrospun fiber in ratio of 10/8/1 was controlled by Fickian diffusion mechanism with a value of the release exponent (n) 0.31 (<0.5). Namely, the drug was released by molecular diffusion based on the chemical potential gradient. The similar release kinetic for PVP/EC nanofibers loaded with ketoprofen, which is a poorly soluble drug, has also been reported by Yu *et al.*²⁸ However, the other nanofibers consisting of EC (at ratios of 10/1/1, 10/2/1 and 10/4/1) also did not exhibit Korsmeyer-Peppas model (Table 3). In this case, an increase of EC ratio in the composition of PU based nanofiber can affect release kinetics and mechanisms of a water-soluble drug, which was resulted in a sustained-drug release fashion. This improvement in

PU/EC/DNP electrospun fiber (10/8/1) might be attributed to the hydrophobic nature of EC.

“INSERT TABLE 3”

4. Conclusion: Electrospun nanofibers composed of different blends of either PU/EC or PU/PVP have been utilized with electrospinning procedure. DNP was loaded into these nanofibers as a water-soluble model drug. All electrospun nanofibers fabricated had smooth surfaces and uniform structures without any beads-on-a-string morphology. The PU/EC electrospun nanofibers exhibited Korsmeyer–Peppas drug release kinetic mechanism in which the release rate was controlled by the diffusion of drug, when the EC ratios were increased in the nanofiber composition. The results also suggest that the types and ratios of the polymer blends need to be judiciously adjusted so as to optimise the release rate of the drug. Overall, this ability of PU/EC (10/8) electrospun nanofibers has suggested the potential use of it as a drug carrier from which a water-soluble drug release may be in a sustained release fashion.

Acknowledgements:

Conflicts of Interest: The authors declare no conflict of interest.

References:

1. Bhardwaj N, Kundu SC. Electrospinning: A fascinating fiber fabrication technique. *Biotechnol Adv.* 2010;28:325–347.
2. Luong-Van E, Grøndahl L, Chua KN, Leong KW, Nurcombe V, Cool SM. Controlled release of heparin from poly(epsilon-caprolactone) electrospun fibers. *Biomaterials.* 2006;27:2042-2050.
3. Vrbata P, Berka P, Stránská D, Doležal P, Lázníček M. Electrospinning of diosmin from aqueous solutions for improved dissolution and oral absorption. *Int J Pharm.* 2014;473:407-413.

4. Hu X, Liu S, Zhou G, Huang Y, Xie Z, Jing X. Electrospinning of polymeric nanofibers for drug delivery applications. *J Control Release*. 2014;185:12–21.
5. Akduman Ç, Akçakoca Kumbasar EP. Electrospun Polyurethane Nanofibers. In: Yilmaz F. Ed. *Aspects of Polyurethanes*. London, IntechOpen; 2017: Chapter 2.
6. Raschip IE, Vasile C, Macocinschi D. Compatibility and biocompatibility study of new HPC/PU blends. *Polym Int*. 2009;58:4–16.
7. Aytimur A, Serincay H. Preparation of PVA/PAA/PEG/PVP Nanofibers with HPMC and Aloe Vera. *Curr Nanosci*. 2013;9:489-493.
8. Wilmington DE. Polymer blend matrix for oral sustained drug delivery. *Pharmaceutical Technology Report 016*. Hercules Incorporated, Aqualon Division. 2002.
9. Callahan JC, Cleary GW, Elefant M, Kaplan G, Kensler T, Nash RA. Equilibrium moisture content of pharmaceutical excipients. *Drug Dev Ind Pharm*. 1982;8:355-369.
10. Huang LY, Branford-White C, Shen XX, Yu DG, Zhu LM. Time-engineered biphasic drug release by electrospun nanofiber meshes. *Int J Pharm*. 2012;436:88–96.
11. Emeje MO, Kunle OO, Ofoefule SI. Compaction characteristics of ethylcellulose in the presence of some channeling agents: technical note. *AAPS PharmSciTech*. 2006;7:E18-E21.
12. Yang GZ, Li HP, Yang JH, Wan J, Yu DG. Influence of working temperature on the formation of electrospun polymer. *Nanoscale Res Lett*. 2017;12:55-65.
13. Illangakoon UE, Gill H, Shearman GC, Parhizkar M, Mahalingam S, Chatterton NP, Williams GR. Fast dissolving paracetamol/caffeine nanofibers prepared by electrospinning. *Int J Pharm*. 2014;477:369–379.
14. Li CC, Wang ZH, Yu DG, Williams GR. Tunable biphasic drug release from ethyl cellulose nanofibers fabricated using a modified coaxial electrospinning process. *Nanoscale Res Lett*. 2014;9:258-268.
15. Samprasit W, Akkaramongkolporn P, Ngawhirunpat T, Rojanarata T, Kaomongkolgit R, Opanasopit P. Fast releasing oral electrospun PVP/CD nanofiber mats of taste-masked meloxicam. *Int J Pharm*. 2015;487:213–222.

16. Xu J, Jiao Y, Shao X, Zhou C. Controlled dual release of hydrophobic and hydrophilic drugs from electrospun poly (l-lactic acid) fiber mats loaded with chitosan microspheres. *Mater Lett*. 2011;65:2800–2803.
17. Yu DG, Shen XX, Branford-White C, White K, Zhu LM, Bligh SA. Oral fast-dissolving drug delivery membranes prepared from electrospun polyvinylpyrrolidone ultrafine fibers. *Nanotechnology*. 2009;20:055104(9pp).
18. Yu DG, Branford-White C, Williams GR, Bligh SA, White K, Zhu LM, Chatterton NP. Self-assembled liposomes from amphiphilic electrospun nanofibers. *Soft Matter*. 2011;7:8239–8247.
19. Park JY, Kim JI, Lee IH. Fabrication and characterization of antimicrobial ethyl cellulose nanofibers using electrospinning techniques. *J Nanosci Nanotechnol*. 2015;15:5672-5675.
20. Yu DG, Wang X, Li XY, Chian W, Li Y, Liao YZ. Electrospun biphasic drug release polyvinylpyrrolidone/ethyl cellulose core/sheath nanofibers. *Acta Biomater*. 2013;9:5665–5672.
21. United State Pharmacopeia (USP) 38-NF33 Chapter Topical and transdermal drug products- Product Performance Tests for TDS. 750:764.
22. Zhang Y, Huo M, Zhou J, Zou A, Li W, Yao C, Xie S. DDSolver: an add-in program for modelling and comparison of drug dissolution profile. *APPS J* 2010;12: 263-272.
23. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. *Acta Pol Pharm-Drug Res*. 2010;67:217-223.
24. Zamani M, Prabhakaran MP, Ramakrishna S. Advances in drug delivery via electrospun and electrosprayed nanomaterials. *Int J Nanomed*. 2013;8:2997–2917.
25. Gencurk A, Kahraman E, Güngör S, Özhan G, Özsoy Y, Sarac AS. Polyurethane/hydroxypropyl cellulose electrospun nanofiber mats as potential transdermal drug delivery system: characterization studies and in vitro assays. *Artif Cells Nanomed Biotechnol*. 2017;45:655-664.
26. Rowe RC, Sheskey PC, Quinn ME. Handbook of pharmaceutical excipients. London: Pharmaceutical Press. 2009.

27. Enayatifard R, Saeedi M, Akbari J, Tabatabaee YH. Effect of hydroxypropyl methylcellulose and ethyl cellulose content on release profile and kinetics of diltiazem HCl from matrices. *Trop J Pharm Res.* 2009;8:425-432.
28. Yu DG, Wang X, Li XY, Chian W, Li Y, Liao YZ. Electrospun biphasic drug release polyvinylpyrrolidone/ ethyl cellulose core/sheath nanofibers. *Acta Biomater.* 2013;9:5665–5672.