BJPS

Brazilian Journal of
Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902019000318440

Article

Preparation and characterization of naftifine-loaded poly(vinyl alcohol)/sodium alginate electrospun nanofibers

İmren Esentürk[1,3], Timuçin Balkan[2,4], Sevgi Güngör[1], Sezai Saraç[2], Meryem Sedef Erdal[1*]

[1]Department of Pharmaceutical Technology, Faculty of Pharmacy, Istanbul University, Istanbul, Turkey, [2]Polymer Science and Technology, Istanbul Technical University, Istanbul, Turkey, Nanoscience and Nanoengineering, Istanbul Technical University, Istanbul, Turkey, [3]Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Health Sciences Turkey, Istanbul, Turkey, [4]TUPRAS Energy Center (KUTEM), Koc University, Istanbul, Turkey

In this study, naftifine (a topical antifungal drug) loaded poly(vinyl) alcohol (PVA)/sodium alginate (SA) nanofibrous mats were prepared using the single-needle electrospinning technique. The produced nanofibers were crosslinked with glutaraldehyde (GTA) vapor. The morphology and diameter of the electrospun nanofibers were studied by scanning electron microscopy (SEM). SEM images showed the smoothness of the nanofibers and indicated that the fiber diameter increased with crosslinking and drug loading. Atomic force microscopy (AFM) images confirmed the uniform production of the scaffolds, and elemental mapping via energy dispersive X-ray spectroscopy (EDS) showed the uniform distribution of the drug within the nanofibers. An attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy study demonstrated that naftifine has sufficient secondary interactions with the polymer blend. The crosslinking treatment decreased the burst drug release effectively and the release mechanism followed Korsmeyer-Peppas Super Case-II transport. Overall, these findings suggest the potential use of naftifine-loaded PVA/SA nanofibers as a topical antifungal drug delivery system.

Keywords: Naftifine. Nanofibers. Electrospinning. Topical drug delivery.

INTRODUCTION

In recent years, electrospun nanofibers have gained great interest as drug delivery vehicles due to their ultrafine structure, large surface area to volume ratio, and high porosity with a small pore size. In addition to use in several applications such as tissue engineering, wound healing, burn therapy and haemostatic devices, drug delivery is one of the most promising uses of nanofibers (Hu *et al*., 2014; Huang *et al*., 2003). A wide range of natural and synthetic polymers can be electrospun into nanofiber matrices. Natural polymers are mostly preferred for biomedical applications due to their biocompatibility and low immunogenicity. Sodium alginate (SA) is the sodium salt of alginic acid which is a naturally occurring polysaccharide from marine brown algae and composed of 1,4-linked β-D-mannuronic (M) and α-L-guluronic acid (G) units. SA is biodegradable and biocompatible, and exhibits bacteriostatic properties (Arthanari *et al*., 2016; Bogun *et al*., 2013; Li *et al*., 2013; Lu *et al*., 2006). However, electrospinning SA is difficult and can only be achieved with blends of synthetic polymers such as poly(vinyl alcohol) (PVA) (Li *et al*., 2013; Shalumon *et al*., 2011). PVA is a hydrophilic, biocompatible and biodegradable semi-crystalline synthetic polymer with excellent electrospinnability (Yang *et al*., 2016). PVA/SA blend nanofibers have been studied as drug

***Correspondence:** M. Sedef Erdal, Department of Pharmaceutical Technology, Faculty of Pharmacy, Istanbul University, 34116 Istanbul, Turkey. Phone: 0902124400000. E-mail: serdal@istanbul.edu.tr

delivery vehicles for hydrophilic drugs and promising results have been obtained (Arthanari *et al*., 2016; Fu *et al*., 2016; Kataria *et al*., 2014).

Naftifine HCl (naftifine) is a broad-spectrum allylamine derivative fungicide that is mainly effective against superficial dermatophytes. The molecular mechanism of the drug is the inhibition of the enzyme squalene epoxidase in fungal ergosterol biosynthesis at an early stage. Topical cream, gel and solution formulations of naftifine are commercially available. Taking the highly lipophilic nature (logP: 5.4) and low aqueous solubility of naftifine into account, new topical formulation approaches became necessary to improve the solubility and to enhance the topical delivery of the drug. So far, complexation of naftifine with cyclodextrins has been investigated in order to enhance its solubility (Uzqueda *et al*., 2009; Uzqueda *et al*., 2006) and β-cyclodextrin hydrogels of naftifine have been studied as drug delivery systems (Machín, Isasi, Vélaz, 2012). Barakat *et al*. (2009) developed a topical alcohol-free niosome gel containing naftifine to achieve entrapment efficiency and stability (Barakat *et al*., 2009). Erdal *et al*. (2016) formulated microemulsions of naftifine as nanosized colloidal carriers for an effective and safe topical delivery system. To our knowledge, naftifine-loaded nanofibers have not been reported in research literature.

In this study, naftifine-loaded PVA/SA electrospun nanofibers have been developed. The nanofiber mats were crosslinked by glutaraldehyde (GTA) vapor to suppress the burst release behavior. The physicochemical properties of blank and drug-loaded nanofibers were characterized by scanning electron microscopy (SEM), atomic force microscopy (AFM), elemental mapping via energy dispersive X-ray spectroscopy (EDS) and attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy studies. *In vitro* drug release from nanofibers was investigated and the release kinetics were determined.

MATERIAL AND METHODS

Material

Naftifine HCl (naftifine) was kindly provided by Zentiva (Istanbul, Turkey). Polyvinyl alcohol (PVA, Mw 89000-98000, 99% hydrolyzed), sodium alginate (SA) from brown algae (medium viscosity), and glutaraldehyde solution (25% aqueous solution) (GTA) was obtained from Sigma Chem Co. (St. Louis, MO, USA). Deionized water was supplied from Merck Millipore Milli-Q ultrapure water system (Merck Millipore, Molsheim, France). All other chemicals were of analytical grade and used without further purification.

Preparation of the electrospinning solution

Initially, PVA (16%, w/v) and SA (2%, w/v) solutions were prepared by dissolving the polymers separately in deionized water for 3 h at 85 ºC and 25 ºC, respectively. Then, the plain PVA/SA blend (ratio 8:2) was stirred at 400 rpm for 1 h at 25 ºC.

Characterization of the polymer solution

The viscosity of the polymer mixture and drug containing polymer mixture solutions was determined with a viscometer (Brookfield Engineering, Spindle No:52, Middleboro, MA, USA) at 50 rpm. Ionic conductivity measurements of the polymer solutions (three different samples) were carried out using a conductivity meter (Eutech Instruments, PC2700, Landsmeer, The Netherlands). A pH meter (InoLab 7310, WTW, Weilheim, Germany) was used to measure the pH of the polymer solutions. All the samples were measured at 25 ºC.

Electrospinning process

Electrospinning was carried out according to the following conditions. A horizontal electrospinning setup comprising a high-voltage power supply (ES 30 Model, Gamma High Voltage, Inc., FL, USA), a syringe pump (NE-500 Model, New Era Pump Systems, Inc., Farmingdale, NY, USA), a 2-mL syringe connected to a flat-end metal needle with an inner diameter of 0.7 mm, and an aluminum plate as a collector, which was placed vertically at a fixed distance of 15 cm from the needle tip, were used in nanofiber preparation. The solution feed rate was set at 1 mL/h and the applied voltage was 15 kV. Nanofiber mats were dried in a vacuum desiccator for 24 h to remove any solvent residue. Crosslinking of plain and drug-loaded fiber mats was achieved with GTA (25%, w/v, aqueous solution) vapor in a sealed vessel (Gomes *et al*., 2015). The system was placed in an oven at 37 ºC for 24 h. Then, the crosslinked PVA/SA scaffolds were placed in a vacuum desiccator for 72 h to remove any residual GTA. Naftifine-loaded nanofibers

were prepared by primarily dissolving the drug in methanol (v/v, 20% of the polymer blend) and then, this drug solution was added into the polymer blend at a concentration of 2.1% (w/w, naftifine to the total PVA/SA percentage) (Fu *et al*., 2016).

Characterization of nanofibers

Scanning Electron Microscopy (SEM)

The surface morphologies of PVA/SA (blank nanofibers), GTA/PVA/SA (crosslinked blank nanofibers), NFT/PVA/SA (naftifine-loaded nanofibers) and GTA/NFT/PVA/SA (naftifine-loaded crosslinked nanofibers) nanofiber mats were carried out using SEM (FEI-QUANTA FEG 450, Oregon, USA) at an acceleration voltage of 15 kV. All samples were dried at room temperature, and then coated with ultra-thin gold film to prevent electrostatic charge on the surface. The matrix morphology and fibrous diameter characterization were carried out using Image J analysis software.

Elemental Mapping via Energy Dispersive X-Ray Spectroscopy (EDS)

The elemental distribution of the nanofibers was investigated via EDS (FEI-QUANTA FEG 450, Oregon, USA). Before the experiment, samples were coated with ultra-thin gold film to prevent electrostatic charge on the surface. The images of the samples and the mapping images were obtained by scanning 16 frames.

Atomic Force Microscopy (AFM)

The topographic and 3D images of the nanofibers were determined by AFM (Nanosurf EasyScan2, STM model, Liestal, Switzerland) in non-contact mode using Al-coated high resonance frequency silicon tips (Nanosensors NCRL tips, 40 µm width, 225 µm length). Easy Scan 2 SoftwareTM (Version 3.0.2.4) was used for imaging functions.

Attenuated Total Reflectance Fourier Transform Infrared (ATR-FTIR) Spectroscopy

In order to investigate the effects of the processing parameters on the drug-polymer interactions, naftifine, a physical mixture of naftifine-polymer blend (PVA/SA), and plain or drug-loaded PVA/SA and GTA/PVA/SA nanofibers were analyzed using an ATR-FTIR spectrophotometer (Perkin Elmer Spectrum 100 FT-IR Spectrometer, PerkinElmer Inc., Waltham, MA, USA).

Drug content

Naftifine-loaded nanofibers (r = 0.75 cm) were dissolved in 3 mL of water/acetonitrile mixture (1:1, v:v) and an HPLC analysis was performed. The drug content was calculated using the following equation:

Drug content (%) = (Mass of maximum drug released/Mass of total drug added) x 100 (Kataria *et al*., 2014).

In vitro drug release study

The *in vitro* release of naftifine from nanofiber formulations was performed using a dialysis tubing cellulose membrane (avg. flat width 25 mm, 14,000 MWCO, Sigma Aldrich, USA) with Franz diffusion cells (Permegear, V6A Stirrer, PA, USA). The receptor compartment (effective diffusion area: 1.77 cm^2) was filled with a 12 mL phosphate buffered saline (PBS, pH 5.0): EtOH (70:30, v:v) mixture in order to maintain sink conditions. The receptor phase remained at 37 ± 1 ºC under constant stirring at 250 rpm with a magnetic bar. Nanofiber-containing naftifine (r = 1.5 cm) was applied onto the membrane and the sample holder was covered with Parafilm M® (Bemis, Oshkosh, WI, USA). The release of naftifine from nanofibers was followed up to 24 hours. Samples (1 mL) were taken periodically from the receptor phase and replenished with the same volume of fresh buffer. The permeant concentrations were determined by HPLC (Shimadzu Model LC 20AT; Shimadzu Corporation, Kyoto, Japan). The cumulative percent release of naftifine from nanofibers was plotted against time. The *in vitro* release data were fitted to different kinetic models (Table I) to determine the mechanism controlling the naftifine release kinetics from the synthesized nanofibers.

TABLE I - Kinetic models used to assess drug release from the nanofiber mats

Kinetic Model	Equation	
Zero order	$C = k_o t + C_o$	C: Drug concentration at time t C_o: Initial drug concentration k_o: Zero order rate constant
First order	$\ln C = \ln C_o + k_1 t$	C: Drug concentration released at time t C_o: Initial drug concentration k_1: First order rate constant
Higuchi square root	$C = k_3 t^{1/2}$	C: Drug concentration at time t k_3: Higuchi release rate constant
Hixson–Crowell	$W_0^{1/3} - Wt^{1/3} = k_H$	W_0: Initial drug amount Wt: Drug amount at time t k_H: Hixson–Crowell rate constant
Korsmeyer-Peppas	$Mt/M\infty = k_{KP} t^n$	Mt: Drug concentration at time t M∞: Equilibrium drug concentration in the release medium Mt/M∞: Drug fraction in the release medium at time t k_{KP}: Release rate constant *n*: Diffusional exponent

HPLC analysis

For the HPLC (Shimadzu Model LC 20AT; Shimadzu Corporation, Kyoto, Japan) analysis of naftifine, a reversed phase C18 column (4.6 x150 mm, 5 m; EMD Millipore, Billerica, MA, USA) preceded by a guard column (44 mm, 5 m, Merck) was used as the stationary phase. The mobile phase consisted of a acetonitrile:tetrahydrofuran:tetramethylammonium hydroxide buffer (pH 7.8) (62:10:28). The flow rate and detection wavelength were set at 1.2 mL/min and 280 nm, respectively. The temperature was adjusted to 30 ºC. The HPLC method was validated for selectivity, linearity, accuracy and precision. It was found to be linear between the concentration range 0.025-100 µg/mL with a high correlation coefficient ($r^2 > 0.999$), precise (intra- and inter-day variation < 2%) and accurate (mean recovery > 99%). All experiments were carried out in triplicate.

Statistical analysis

The statistical analysis was performed using the one-way ANOVA with $P < 0.05$ as the level of significance (GraphPad Software, Inc., version 7.0a, La Jolla, CA, USA).

RESULTS AND DISCUSSION

Preparation and characterization of the polymer solution

The electrospinning process has been recognized as an established technique for nanofiber formation and involves the application of a strong electric field across a conductive capillary, attached to a polymer solution reservoir, and a screen collector (Supaphol *et al*., 2012). Although it is a simple process, there are a number of different parameters effecting electrospinnability (Esenturk, Erdal, Gungor, 2016). Particularly, the properties of the polymer solution could influence the formation and structure of the obtained fibers. SA is a water-soluble, biocompatible and biodegradable natural polymer. It cannot be electrospun from its aqueous solutions, but the processability of SA may be enhanced by blending with PVA; then smooth electrospun fibers can be obtained (Tort, Acartürk,

2016). In our preformulation studies, the optimum ratio of the PVA/SA mixture solution was found to be 8:2 in terms of electrospinnability and having the most uniform fibrous morphology.

The solutions of the PVA/SA polymer mixture (8:2) were characterized to evaluate the effects of the polymer solution properties on the resultant nanofibers. The viscosity, conductivity and pH values of the PVA, SA, PVA/SA, and drug-loaded NFT/PVA/SA solutions are given in Table II. A polymer solution should have a certain viscosity for a successful electrospinning process (Tort, Acartürk, 2016). After blending with PVA, the viscosity of the SA solution is increased to an appropriate value, making electrospinning successful. This finding is in accordance with the literature (Sangnim *et al*., 2018).

The very high conductivity of the SA solution led to a depleted tangential electric field along the surface of the fluid droplet, preventing Taylor cone formation (Pelipenko, Kocbek, Kristl, 2015). The addition of PVA decreased the conductivity to a moderate value. There was an increase in conductivity after adding the drug into the blend solution due to the hydrochloride salt form of naftifine. Sangnim *et al*. reported that the electrospinning solution conductivity increased significantly with increasing drug (clindamycin) content as the hydrochloride form of clindamycin was protonated in the aqueous solution, resulting in higher conductivity (Sangnim *et al*., 2018).

TABLE II - The viscosity, conductivity and pH values of the polymer solutions alone [PVA (16%, w/v) and SA (2%, w/v)], the polymer blend solution (PVA/SA, 8:2), and naftifine containing polymer blend solution (NFT/PVA/SA)

	Viscosity (cP)	Conductivity (µS/cm)	pH
PVA	1369	530.8	5.98
SA	234.2	4158	7.17
PVA/SA	575.5	870.6	6.04
NFT/PVA/SA	404.8	890.2	5.28

Electrospinning process

The electrospinning of a PVA (16%, w/v) and SA (2%, w/v) solution blend at a ratio of 8:2 resulted in completely homogenous and uniform nanofibers. The obtained blank or naftifine-loaded nanofiber mats were then crosslinked through 25% GTA (w/v) vapor at 37 ºC for 24 h.

Crosslinking is an effective technique to improve the stability and mechanical properties of polymers. GTA has been used to crosslink hydroxyl containing polymers such as PVA through a vapor phase crosslinking reaction with high efficiency, short reaction time and low cost. In comparison with other crosslinking agents, GTA has lower cytotoxicity and the crosslinked materials are biocompatible and have good mechanical properties (Wang *et al*., 2016). The concurrent crosslinking of nanofibers by electrospinning is a very difficult process and post-crosslinking by GTA vapor is often preferred to enhance nanofiber stability, to control drug release and avoid burst release and to improve the mechanical performance (Cheng *et al*., 2015; Wang *et al*., 2016).

After GTA vapor crosslinking, the nanofiber membrane shrank dimensionally (Figure 1). After immersing in water for 24 h, the crosslinked nanofiber membrane showed no significant change (Figure 2) and our results indicated that the crosslinking process improved the hydrophilicity and mechanical properties of PVA/SA nanofibers without altering the fiber morphology.

FIGURE 1 - Naftifine-loaded PVA/SA nanofiber mats before and after the crosslinking procedure.

FIGURE 2 - Naftifine-loaded NFT/PVA/SA and GTA/NFT/PVA/SA nanofiber mats after immersing in water for 24 h.

Characterization of nanofibers

SEM, EDS and AFM

The SEM images of plain (PVA/SA and GTA/PVA/SA) and naftifine-loaded (NFT/PVA/SA and GTA/NFT/PVA/SA) nanofibers are shown in Figures 3a-3d. SEM imaging indicated that the blank PVA/SA fibers were continuous in length with an average diameter of 242.46 ± 63.74 nm (Figure 3 a). After GTA vapor crosslinking, the fiber membrane shrank dimensionally but the fibers still maintained the fibrous morphology, with the diameter having changed to 441.85 ± 127.68 nm (Figure 3b). The addition of the drug increased the thickness of the nanofibers to 457.71 ± 134.88 nm and 527.74 ± 251.12 nm for NFT/PVA/SA and GTA/NFT/PVA/SA nanofibers, respectively (Figures 3c and 3d). This finding could be due to the inability of naftifine to fully settle into the nanofiber structure. The results obtained in this study are consistent with the results of other studies, which reported that the addition of the drug can increase the diameter size of electrospun nanofibers (Tort, Acartürk, 2016).

The elemental mapping of NFT/PVA/SA nanofibers is represented in Figure 4. The red dots represent sodium (Na) in sodium alginate (Figure 4a) whereas the green dots indicate chlorine (Cl) in naftifine hydrochloride (Figure 4b). A uniform dispersion of naftifine in the PVA/SA blend of nanofibers is observed according to the EDS analysis (Figure 4c).

High resolution AFM images of the studied nanofiber formulations are represented in Figure 5. The obtained 2D and 3D images confirmed the uniform production of the fibers and showed the topographic structure of plain (Figure 5a and Figure 5b) and drug-loaded nanofibers (Figure 5c and Figure 5d).

ATR-FTIR Spectroscopy

It has been reported in the literature that secondary interactions such as hydrogen bonds, and electrostatic or hydrophobic interactions between the components of a drug delivery platform could increase the compatibility between the components of the formulation which in turn enhances the features of the delivery system (Karthikeyan *et al*., 2015). The secondary interactions between the individual components of nanofibers were studied by ATR-FTIR spectroscopy and the spectra of naftifine, the physical mixture of the polymer blend (PVA/SA) and naftifine, and plain (PVA/SA and GTA/PVA/SA) and drug-loaded nanofibers (NFT/PVA/SA and GTA/NFT/PVA/SA) are given in Figure 6. The FTIR spectra of naftifine-loaded nanofibers showed prominent peaks of the PVA/SA polymer blend and the characteristic peaks of the drug were not present. This indicated that naftifine has sufficient secondary interactions with the polymer and hence, the PVA/SA nanofiber offers a compatible delivery system for naftifine. The spectral results demonstrated hydrogen bonding interactions due to the hydroxyl groups of PVA and the hydroxyl groups of SA. Moreover, the absorption peak at 1142 cm^{-1} indicated the success of chemical crosslinking for both GTA/PVA/SA and GTA/NFT/PVA/SA nanofibers (Wang *et al*., 2016).

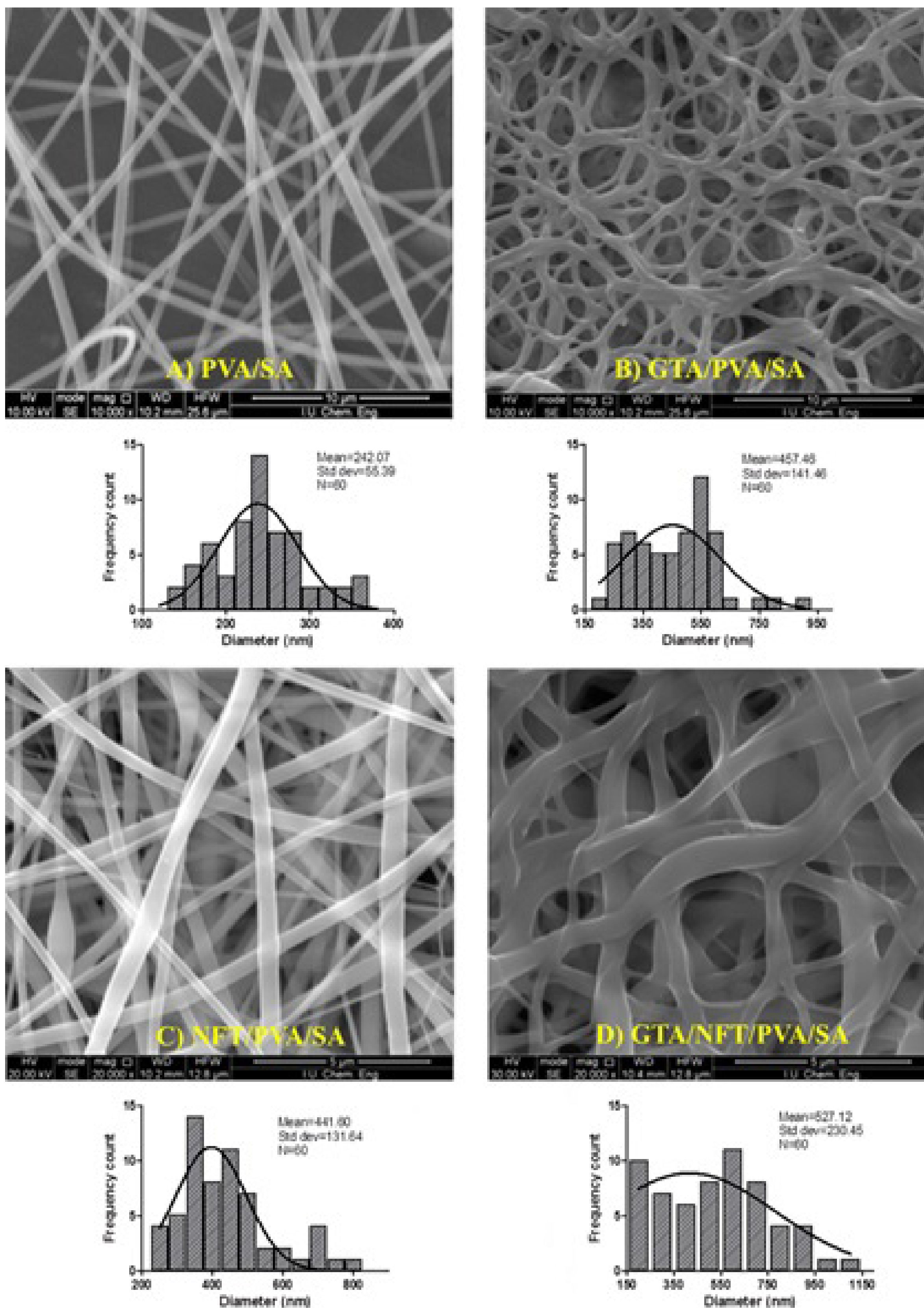

FIGURE 3 - SEM images and fiber size distributions of a) PVA/SA, b) GTA/PVA/SA nanofibers at 10.000x magnification and c) NFT/PVA/SA, d) GTA/NFT/PVA/SA nanofibers at 20.000x magnification.

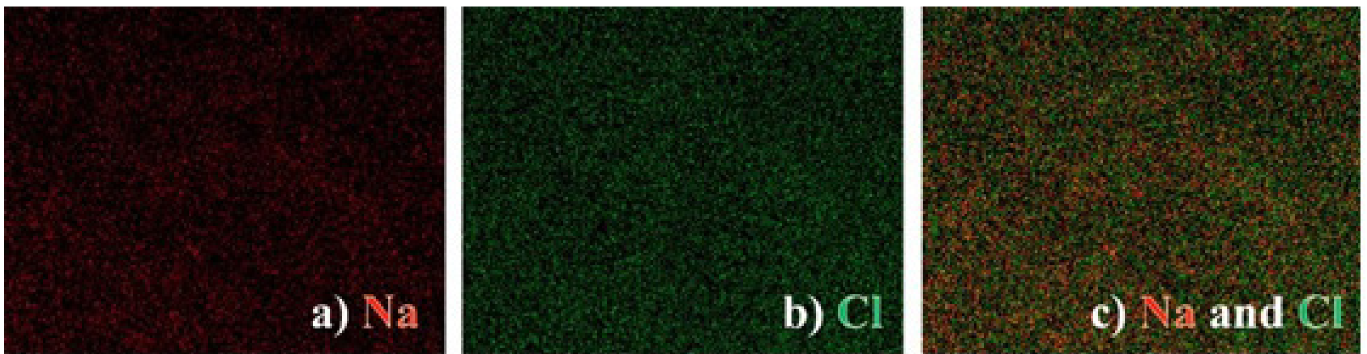

FIGURE 4 - Elemental mapping of NFT/PVA/SA nanofibers (red and green dots represent sodium and chlorine, respectively).

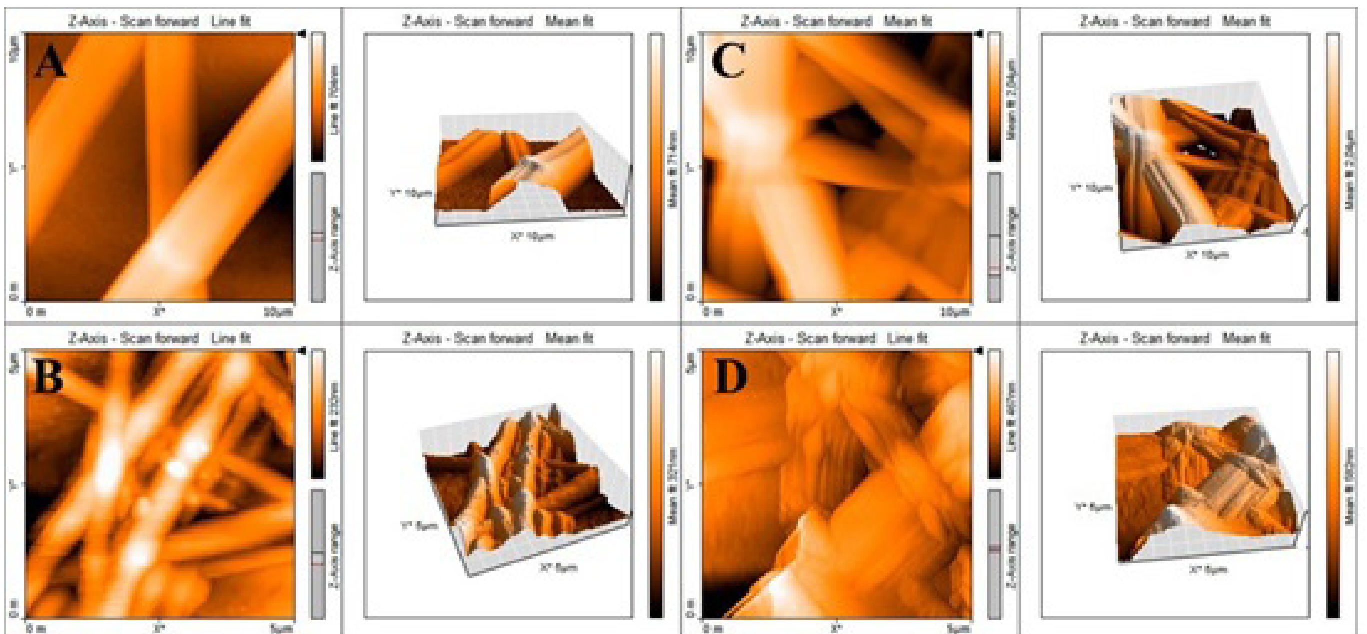

FIGURE 5 - 2D and 3D AFM images of a) PVA/SA b) GTA/PVA/SA c) NFT/PVA/SA and d) GTA/NFT/PVA/SA nanofibers.

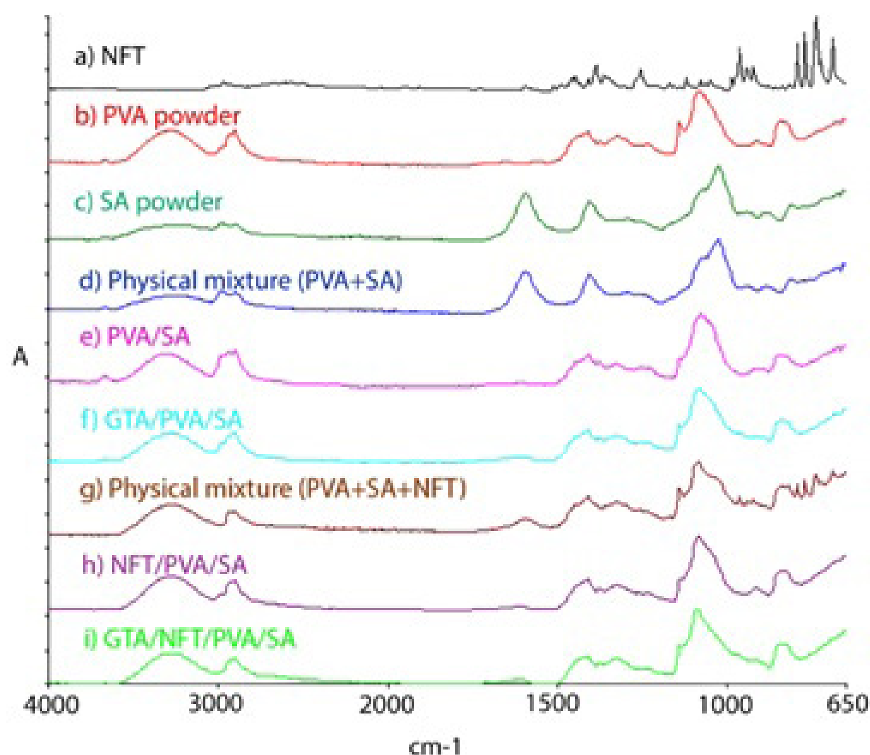

FIGURE 6 - ATR-FTIR spectra of a) naftifine (NFT) b) PVA c) SA d) physical mixture of PVA and SA e) PVA/SA nanofiber f) GTA/PVA/SA nanofiber g) physical mixture of PVA, SA and NFT h) NFT/PVA/SA nanofiber i) GTA/NFT/PVA/SA nanofiber.

Drug content

The solubility of the drug in the polymer solution has been reported to affect the drug entrapment efficiency in nanofibers (Arthanari *et al*., 2016). When the drug and polymer are not soluble in the same solvent, the drug can be solubilized in a small amount of another solvent before being added to the polymer solution (Pillay *et al*., 2013). Naftifine is poorly soluble in basic aqueous solutions. Therefore, it was dissolved in methanol (v/v, 20% of the polymer blend) prior to the electrospinning process. The drug content of NFT/PVA/SA and GTA/NFT/PVA/SA nanofibers was found to be 88.81 ± 0.75% and 88.35 ± 1.11%, respectively. The low standard deviation of the naftifine assay revealed that the drug was homogenously distributed in the nanofibers (Tort, Acartürk, 2016).

In vitro drug release

The cumulative percent release of naftifine from the NFT/PVA/SA and crosslinked GTA/NFT/PVA/SA nanofibers is shown in Figure 7. A release of about 64% of naftifine from NFT/PVA/SA nanofibers is detected throughout 8 h, with an initial burst release of 19% in the first 30 min. The initial burst release could be the result of a rapid release of surface associated with drug molecules (Abdul Khodir *et al*., 2018). GTA/NFT/PVA/SA nanofiber mats released only 4% of naftifine in the first 30 min, indicating that the crosslinking with GTA depressed the initial burst release of naftifine effectively ($P < 0.001$, compared to the release in the first 30 min from NFT/PVA/SA nanofibers). At the end of 8 h, the total percentage of drug release from GTA/NFT/PVA/SA nanofiber mats was 59%.

It is known that the drug release kinetics is mainly controlled by the composition of polymer blends. Drug diffusion and polymer relaxation/dissolution have been considered as the basic mechanisms for drug release from a polymeric matrix (Meera Moydeen *et al*., 2018). In this study, the mechanism of drug release for all prepared nanofibers was examined on the basis of zero-order, first-order, Hixson-Crowell cube root, Higuchi, and Korsmeyer-Peppas kinetic models. The release profile

of the NFT/PVA/SA nanofiber formulation correlated best with zero order kinetic models and the drug release rate was independent of time (Table III) (Maderuelo, Zarzuelo, Lanao, 2011). The release profile of the GTA/NFT/PVA/SA nanofiber formulation correlated best with the Korsmeyer-Peppas model, and the exponential factor "n" was > 1 for GTA/NFT/PVA/SA nanofibers. For n > 1, the mechanism of drug release is regarded as super Case-II transport showing that the release mechanism is controlled by the erosion and swelling of the synthesized nanofibers (Stastna, 1995; Shi, 2004; Lee, Yeo, 2015; Wen *et al*., 2015).

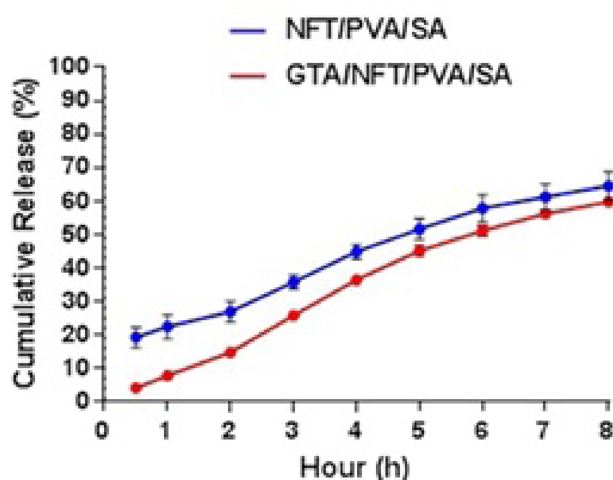

FIGURE 7 - Release profiles of NFT from NFT/PVA/SA and GTA/NFT/PVA/SA nanofibers.

TABLE III - Mathematical models used to explain naftifine release kinetics from the NFT/PVA/SA and GTA/NFT/PVA/SA nanofibers

	NFT/PVA/SA	GTA/NFT/PVA/SA
Zero order kinetic model	0.983	0.981
First-order kinetic model	0.945	0.858
Hixson-Crowell kinetic model	0.962	0.918
Higuchi square root kinetic model	0.977	0.982
Korsmeyer-Peppas kinetic model	0.940	0.994

CONCLUSION

Naftifine-loaded PVA/SA electrospun nanofibers were prepared using the single-needle electrospinning method. The produced nanofibers were treated with a post-cross-linking method with GTA. SEM images showed the smoothness of the nanofibers and indicated that the fiber diameter increased with crosslinking and drug loading. An EDS analysis showed the uniform distribution of the drug within the nanofibers and AFM images confirmed the uniform production of the nanofiber mats. An ATR-FTIR study revealed that naftifine has sufficient secondary interactions with the polymer blend and hence, the PVA/SA nanofiber offers a compatible delivery system for naftifine. Crosslinking treatment effectively decreased the burst release and the release mechanism followed Korsmeyer-Peppas-super Case-II transport. Overall, these findings suggest the potential use of naftifine-loaded PVA/SA nanofibers as a topical antifungal drug delivery system.

ACKNOWLEDGMENTS

This research was supported by TUBITAK (The Scientific and Technological Research Council of Turkey) Research Fellowship Programme for PhD Students (2211-A) and financially supported by Istanbul University Scientific Research Projects (BAP) under the number 58473.

DISCLOSURE

The authors report no conflicts of interest in this work.

REFERENCES

Abdul Khodir WKW, Abdul Razak AH, Ng MH, Guarino V, Susanti D. Encapsulation and characterization of gentamicin sulfate in the collagen added electrospun nanofibers for skin regeneration. J Funct Biomater. 2018;9(2):E36.

Arthanari S, Mani G, Jang JH, Choi JO, Cho YH, Lee JH, et al. Preparation and characterization of gatifloxacin-loaded alginate/poly (vinyl alcohol) electrospun nanofibers. Artif Cells Nanomed Biotechnol. 2016;44(3):847-852.

Barakat HS, Darwish IA, El-Khordagui LK, Khalafallah NM. Development of naftifine hydrochloride alcohol-free niosome gel. Drug Dev Ind Pharm. 2009;35(5):631-637.

Bogun M, Krucinska I, Kommisarczyk A, Mikolajczyk T, Blazewicz M, Stodolak-Zych E, et al. Fibrous polymeric composites based on alginate fibres and fibres made of poly-epsilon-caprolactone and dibutyryl chitin for use in regenerative medicine. Molecules. 2013;18(3):3118-3136.

Cheng F, Gao J, Wang L, Hu XY. Composite chitosan/poly(ethylene oxide) electrospun nanofibrous mats as novel wound dressing matrixes for the controlled release of drugs. J Appl Pol Sci. 2015;132(24):42060.

Erdal MS, Özhan G, Mat MC, Özsoy Y, Güngör S. Colloidal nanocarriers for the enhanced cutaneous delivery of naftifine: characterization studies and *in vitro* and *in vivo* evaluations. Int J Nanomedicine. 2016;11:1027-1037.

Fu R, Li C, Yu C, Xie H, Shi S, Li Z, et al. A novel electrospun membrane based on moxifloxacin hydrochloride/poly(vinyl alcohol)/sodium alginate for antibacterial wound dressings in practical application. Drug Deliv. 2016;23(3):828-839.

Gomes SR, Rodrigues G, Martins GG, Roberto MA, Mafra M, Henriques CM, et al. *In vitro* and *in vivo* evaluation of electrospun nanofibers of PCL, chitosan and gelatin: a comparative study. Mater Sci Eng C Mater Biol Appl. 2015;46:348-358.

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.

Huang ZM, Zhang YZ, Kotaki M, Ramakrishna S. A review on polymer nanofibers by electrospinning and their applications in nanocomposites. Comp Sci Technol. 2003;63(15):2223-2253.

Esentürk I, Erdal MS, Güngör S. Electrospinning method to produce drug-loaded nanofibers for topical/transdermal drug delivery applications. J Fac Pharm Istanbul. 2016;46(1):49-69.

Karthikeyan K, Sowjanya RS, Yugandhar ADV, Gopinath S, Korrapati PS. Design and development of a topical dosage form for the convenient delivery of electrospun drug loaded nanofibers. Rsc Advances. 2015;5(65):52420-52426.

Kataria K, Gupta A, Rath G, Mathur RB, Dhakate SR. *In vivo* wound healing performance of drug loaded electrospun composite nanofibers transdermal patch. Int J Pharm. 2014;469(1):102-110.

Lee JH, Yeo Y. Controlled drug release from pharmaceutical nanocarriers. Chem Eng Sci. 2015;125:75-84.

Li W, Li X, Chen Y, Li X, Deng H, Wang T, et al. Poly(vinyl alcohol)/sodium alginate/layered silicate based nanofibrous mats for bacterial inhibition. Carbohydr Polym. 2013;92(2):2232-2238.

Lu JW, Zhu YL, Guo ZX, Hu P, Yu J. Electrospinning of sodium alginate with poly(ethylene oxide). Polymer. 2006;47(23):8026-8031.

Machín R, Isasi JR, Vélaz I. β-Cyclodextrin hydrogels as potential drug delivery systems. Carbohydr Polym. 2012;87(3):2024-2030.

Maderuelo C, Zarzuelo A, Lanao JM. Critical factors in the release of drugs from sustained release hydrophilic matrices. J Control Release. 2011;154(1):2-19.

Meera Moydeen A, Syed Ali Padusha M, Aboelfetoh E F, Al-Deyab SS, El-Newehy MH. Fabrication of electrospun poly(vinyl alcohol)/Dextran nanofibers via emulsion process as drug delivery system: Kinetics and *in vitro* release study. Int J Biol Macromolec. 2018;116:1250-1259.

Pelipenko J, Kocbek P, Kristl J. Critical attributes of nanofibers: Preparation, drug loading, and tissue regeneration. Int J Pharm. 2015;484(1-2):57-74.

Pillay V, Dott C, Choonara YE, Tyagi C, Tomar L, Kumar P, Du Toit LC, NdesendO VMK. A review of the effect of processing variables on the fabrication of electrospun nanofibers for drug delivery applications. J Nanomater. 2013;2013:789289.

Sangnim T, LimmatvapiraT S, Nunthanid J, Sriamornsak P, Sittikijyothin W, Wannachaiyasit S, et al. Design and characterization of clindamycin-loaded nanofiber patches composed of polyvinyl alcohol and tamarind seed gum and fabricated by electrohydrodynamic atomization. Asian J Pharm Sci. 2018;13(5):450-458.

Shalumon KT, Anulekha KH, Nair SV, Nair SV, Chennazhi KP, Jayakumar R. Sodium alginate/poly(vinyl alcohol)/nano ZnO composite nanofibers for antibacterial wound dressings. Int J Biol Macromol. 2011;49(3):247-254.

Shi D. Biomedical devices and their applications. Heidelberg: Springer; 2004.

Stastna J. Transport properties in polymers. Taylor & Francis; 1995.

Supaphol P, Neamnark A, Taepaiboon P, Pavasant P. Effect of degree of acetylation on *in vitro* biocompatibility of electrospun cellulose acetate-based fibrous matrices. Cellulose. 2012;11:13.

Tort S, Acartürk F. Preparation and characterization of electrospun nanofibers containing glutamine. Carbohydr Polym. 2016;152:802-814.

cc BY This is an open-access article distributed under the terms of the Creative Commons Attribution License.

Uzqueda M, González Gaitano G, Wouessidjewe D, Zornoza A, Sánchez M, Martín C, Et Al. Spectroscopic characterisation of the inclusion complexes between the antifungal drugs naftifine and terbinafine and cyclodextrins. Supramolec Chem. 2009;21(8):759-769.

Uzqueda M, Martin C, Zornoza A, Sanchez M, Martinez-Oharriz MC, Velaz I. Characterization of complexes between naftifine and cyclodextrins in solution and in the solid state. Pharm Res. 2006;23(5):980-988.

Wang W, Jin X, Zhu Y, Zhu C, Yang J, Wang H, et al. Effect of vapor-phase glutaraldehyde crosslinking on electrospun starch fibers. Carbohydr Polym. 2016;140:356-361.

Wen X, Zheng Y, Wu J, Wang LN, Yuan Z, Peng J, Meng H. Immobilization of collagen peptide on dialdehyde bacterial cellulose nanofibers via covalent bonds for tissue engineering and regeneration. Int J Nanomedicine. 2015;10:4623-4637.

Yang JM, Yang JH, Tsou SC, Ding CH, Hsu CC, Yang KC, Et Al. Cell proliferation on PVA/sodium alginate and PVA/poly(gamma-glutamic acid) electrospun fiber. Mater Sci Eng C Mater Biol Appl. 2016;66:170-177.

Received for publication on 08th June 2018
Accepted for publication on 01st October 2018