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...
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 °C and 25 °C, respectively. Then, the plain PVA/SA blend (ratio 8:2) was stirred at 400 rpm for 1 h at 25 °C.

**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 °C.

**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 °C 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:

\[
\text{Drug content} \% = \frac{\text{Mass of maximum drug released}}{\text{Mass of total drug added}} \times 100 
\]

(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 cm²) 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   | \( C = k_j t^{1/2} \)                                                   |
|                        | \( C \): Drug concentration at time \( t \)                              |
|                        | \( k_j \): Higuchi release rate constant                                  |
| Hixson–Crowell        | \( W_0^{1/3} - W_t^{1/3} = k_{Ht} \)                                    |
|                        | \( W_0 \): Initial drug amount                                           |
|                        | \( W_t \): Drug amount at time \( t \)                                   |
|                        | \( k_H \): Hixson–Crowell rate constant                                   |
| Korsmeyer–Peppas      | \( M_t / M_{\infty} = k_{kr} t^n \)                                     |
|                        | \( M_t \): Drug concentration at time \( t \)                            |
|                        | \( M_{\infty} \): Equilibrium drug concentration in the release medium   |
|                        | \( M_t / M_{\infty} \): Drug fraction in the release medium at time \( t \) |
|                        | \( k_{kr} \): 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 °C. 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,
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.
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 3a). 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 chloride (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.
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

| Model                              | 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 electrosprinning 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.

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