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Release characteristics of Naproxen loaded poly (vinyl alcohol) nanofibers

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Abstract. The use of electrospun fibers as drug carriers is promising especially for pain-related topical administrations. Non-steroidal anti-inflammatory drugs (NSAIDs) are used for controlling pain and inflammation. The present contribution reports the use of electrospun poly (vinyl alcohol) (PVA) nanofibers as carriers for delivery of the model drug, naproxen (NAP). The release mechanisms of drug-loaded electrospun PVA nanofibers are based on the diffusion of the drugs through the swollen PVA fibrous matrix and the release due to partial dissolution of the matrix . Control over the release characteristics of the drugs can be provided through partial crosslinking of the PVA fibrous matrix. In this study polycarboxylic acids; 1,2,3,4 butanetetracarboxylic acid (BTCA) and citric acid (CA) were used to crosslink the PVA nanofibers. Produced nanofibers ranged between 228.8 and 291.6 nm. Crosslinking enhanced the protection of mat structure against dissolution in PBS and slowed down the release of NAP from the drug-loaded nanofibers. The total amount of the drug released from the NAP/PVA-BTCA and NAP/PVA-CA nanofibers were 93% and 78% respectively within 60 min whereas non-crosslinked NAP/PVA nanofibers released all of its drug content within 45 min for 10 h collected fibers. In case of 20 h collected fibers NAP/PVA-BTCA and NAP/PVA-CA nanofibers released 50% of the NAP content in ~3 h and released 74% and 70% of NAP content, respectively, after 8 h. NAP release reached 77% for NAP/PVA-BTCA nanofibers and 76% for NAP/PVA-CA nanofibers after 24 h.

1. Introduction

The development and production of drug-loaded nanofiber-based materials produced by electrospinning is of interest in terms of innovative drug delivery systems. One of the main advantages of the drug loaded nanofiber systems is the highly porous structure of electrospun fiber mats which exhibit greater surface area that assumingly could allow drug molecules to diffuse out from the matrix much more conveniently. PVA can be prepared by partial or complete hydrolysis of poly vinyl acetate (PVAc). It is synthetic, neutral, biodegradable and hydrophilic polymer which is commercial and widely used in paper

industry [1,2]. Electrospun PVA nanofibers have been one of the most extensively studied topics due to its biocompatibility, nontoxicity, hydrophilicity and ease of processability [3,4].

Reactive hydroxyl groups present in PVA can be conveniently chemically modified [1] and control of the release characteristics of the drugs can be provided through partial crosslinking of the PVA fibrous matrix [5]. The release mechanisms of drug-loaded electrospun PVA nanofibers are based on the diffusion of the drugs through the swollen PVA fibrous matrix and the release due to partial dissolution of the matrix [2,5,6]. PVA cross-linked hydrogels exhibit much better swelling behavior in water or biological fluids [1]. BTCA and citric acid are low cost alternatives that have been reported to easily crosslink electrospun PVA hydrogels [7,8]. Another important advantage is the miscibility of them with PVA solutions, thus they can directly be added into the electrospinning solutions [9].

The use of electrospun fibers as drug carriers will be promising in the future of drug delivery applications especially, pain related topical administrations. NSAIDs are used for controlling pain and inflammation in rheumatic diseases. NAP which is one of the most efficient NSAIDs [10] was selected as a model drug for this study and release characteristics were investigated in means of total immersion method.

2. Experimental

2.1. Materials

For the preparation of NAP loaded PVA nanofibers, PVA with average molecular weight of ~125,000 g/mol, NAP, BTCA, CA, cyanamide were purchased from Sigma Aldrich Chemical Company. Distilled water was used as solvent.

2.2. The preparation of electrospinning solutions

A weighed amount of PVA was was added slowly into hot water and stirred it until clear solution obtained. A fixed concentration of 10% w/w was used. After allowing the solution to cool down to room temperature, BTCA or CA, as crosslinking agents, was directly added into the spinning solution with cyanamide as a catalyst in ratio of 2:1 (w/w) followed by stirring for 15 min. The concentration of the BTCA and CA were fixed at 20% ($w/w_{polymer}$) based on preliminary studies. 10% ($w/w_{polymer}$) NAP was dispersed in the PVA solution followed by stirring for 4 h prior to electrospinning.

2.3. Electrospinning

Electrospinning of the polymer solutions was carried out by a set-up consisting of a syringe (10 mL) and a stainless steel needle (1.5-cm long, 22 gauges, and flat tip), a ground electrode and a high voltage supply (Simco, MP Series CM5 30 P, Charging Generator Output 30 kV DC). A grounded stationary rectangular metal collector covered by a piece of aluminum foil was used for the nanofiber deposition. Polymer solutions were electrospun at a voltage of 18 kV, a tip-to-collector distance of 15 cm with a feeding rate of 0.5 and 0.7 ml/h. Electrospinning of each sample were carried out for 10 h and 20 h.

After electrospinning, to enhance the esterification reaction.PVA/BTCA and PVA/CA nanofibers were heat set at 110ºC for 20 min in an oven.

2.4. SEM analysis

The morphology of PVA nanofibers were observed by a scanning electron microscope (SEM; FEI Quanta250 FEG scanning electron microscope). The electrospun nanofibers 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 50 measurements were carried out from the different parts of each sample.

2.5. In vitro drug release studies

Total immersion method was used to study the release characteristics of the drug from the NAP loaded electrospun PVA nanofiber mats. The samples (in dimension of 3x3 cm) were accurately weighed and immersed in a glass bottle containing 40 mL PBS, and the bottles were incubated in a horizontal incubation shaker (Thermo-Scientific MaxQ6000) at of 37± 0.5°C, 60 rpm. At a specified immersion period ranging between 0 and 24 h, 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 and released drug amounts were calculated from the calibration curve of NAP.

3. Results and Discussion

The composition of the spinning solution is directly related to the resultant fiber morphology. Table 1 displays changes in some of the most important solution parameters after the addition of BTCA and CA. The conductivity of the solutions showed an increase with the BTCA and CA additions. Solutions with BTCA and CA had same viscosity values compared to pure PVA solution. There was a slight decrease in the surface tension with the addition of the BTCA and CA. It was also seen that NAP addition didn't significantly affect neither the surface tension nor the viscosity of the PVA solutions. Electrospinning of the PVA/NAP-BTCA and PVA/NAP-CA solutions were easier to electrospin according to the higher conductivity and surface tension of the solutions which also decreased the diameter of the produced nanofibers [9].

Table 1. Surface tension, conductivity and viscosity measurements of neat and NAP loaded PVA and BTCA and CA added PVA solutions.

Solution Concentrations *(w/w)*	Surface Tension *(m/Nm)*	Conductivity *(µS/cm)*	Viscosity *(cp)*
%10 PVA	58.7	356	200
%10 PVA/NAP	58.5	229	266.7
%10 PVA/NAP-BTCA	49.6	1040	266.7
%10 PVA/NAP-CA	54.3	1729	266.7

The SEM images and mean diameter of the nanofibers and the mean thickness of the membranes are given in Fig. 1 and Table 2, respectively. It was seen that smooth NAP/PVA-BTCA and NAP/PVA-CA nanofibers were successfully produced. No NAP crystals were detected by SEM either on the surface of the fibers or outside the fibers as shown in Fig. 1.

Table.2 Mean diameter of 10h produced electrospun neat PVA, NAP/PVA, NAP/PVA-BTCA and NAP/PVA-CA nanofibers, and their mean thickness

	Mean Diameter ± SD (nm)	**Mean Thickness ± SD (cm)**	**Diameter of the deposition area**
Neat PVA	291.60 ±38.70	0.1271 ± 0.03[a]	~20 cm
NAP/PVA	274.26 ±47.88	0.1829 ± 0.03[a]	~20 cm
NAP/PVA-BTCA	228.80 ±46.66**	0.3271 ± 0.07[b]	~17 cm
NAP/PVA-CA	246.99± 66.09**	0.2417 ± 0.12[c]	~17 cm

*[a,b,c,] ** p<0.05 One Way ANOVA, Tukey HSD post hoc test*

Differences in fiber diameters and thickness were analyzed by one-way analysis of variance (ANOVA) followed by a Tukey test for pairwise comparison. It was observed that, there is no significant effect of NAP addition on the fiber diameter. The resultant fiber diameters decreased by the addition of BTCA and CA compared to non-crosslinked samples due to the increase of the solution conductivity. This difference at $p<0.05$ was considered statistically significant, but there is no significant difference between NAP/PVA-BTCA and NAP/PVA-CA nanofibers.

The release of the drug from the samples was reported as the cumulative release of the drug as a function of the immersion period. When neat and NAP/PVA nanofiber mats were immersed in PBS, they shrunk immediately and became almost transparent. On the other hand, BTCA and CA crosslinked mats became bulky and stayed opaque due to the crosslinking of the polymer matrix. The nanofibrous structure of non-crosslinked PVA nanofibers was almost destroyed due to high solubility. BTCA crosslinked mat preserved its nanofibrous structure, however CA crosslinked mat almost lost their fibrous structure with a swollen and conjoint appearance due to the highest swelling capacity of the NAP/PVA-CA nanofibers and lower crosslinking. The results showed that BTCA crosslinked mats preserve its fibrous structure in an aqueous environment.

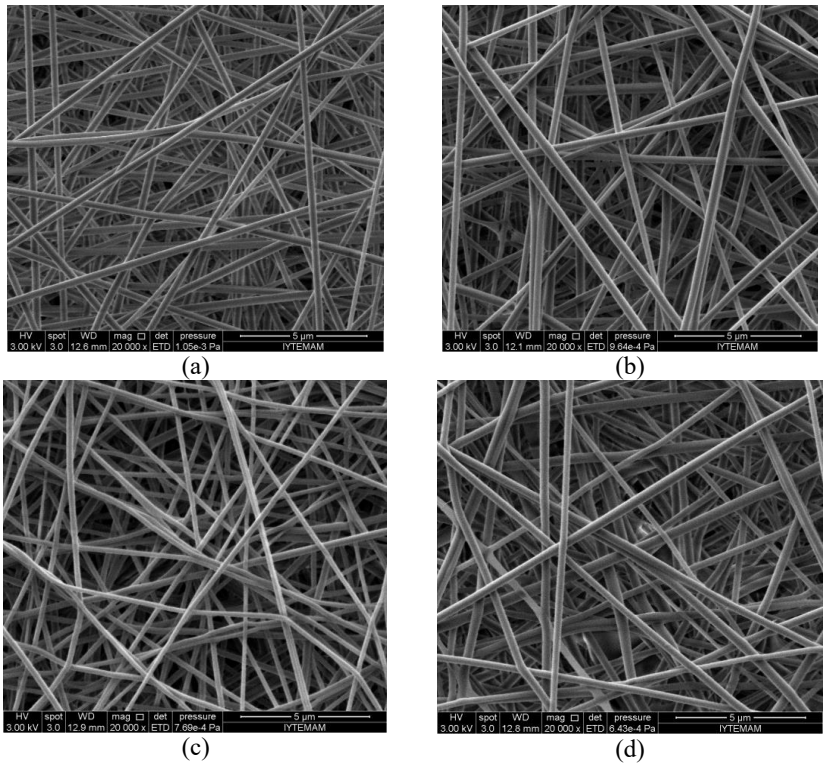

Figure 1. SEM Images of 10h produced (a) neat PVA, (b) NAP/PVA, (c) NAP/PVA-BTCA and (d) NAP/PVA-CA nanofibers

3.1. Drug Release from NAP loaded neat and crosslinked electrospun PVA nanofibers

The release characteristics of NAP from the NAP loaded electrospun nanofibers for 10h and 20h production period are shown in Fig. 2 and Fig. 3, respectively. The release mechanisms of drug-loaded electrospun PVA nanofibers are based on the diffusion of the drugs through the swollen PVA fibrous matrix. NAP release from NAP/PVA nanofibers showed burst release during 15-30 min due to the

solubility of PVA. It lost its all drug content immediately. Especially for a hydrogel drug carrier, key factor that controls the release of a drug from a drug delivery system, is its swelling behavior [1,9]. As soon as the PVA matrix began to swell; NAP molecules were leached out from the matrix very rapidly. Another contributing factor was the dissolution of the PVA matrix within the release medium. These indicated that the mechanism for the burst release of NAP included the swelling and the partial dissolution of the PVA matrix.

Obviously, crosslinking enhances the protection of mat structure against dissolution in PBS and slowed down the release of NAP from the drug-loaded nanofibers. The release of drugs from hydrogels involves the absorption of water into polymer matrix and release of the drug via diffusion. Crosslinked NAP/PVA nanofibers resulted lower drug release rates compared to the non-crosslinked NAP/PVA mats. The total amount of the drug released from the NAP/PVA-BTCA and NAP/PVA-CA nanofibers were 93% and 78% respectively within 60 min whereas non-crosslinked NAP/PVA nanofibers released all of its drug content within 45 min. Crosslinking did not decrease the total released drug amount.

Generally, drug release rate reduces due to the increase in the thickness of the nanofiber mats which makes the drug diffusion path more compact, and it takes longer for the drug to be released out of the matrix [9]. Therefore, NAP/PVA and NAP/PVA-BTCA, NAP/PVA-CA nanofibers were produced for 20h to produce thicker mats and to see whether it is possible to extent the release time by increasing the diffusion path.

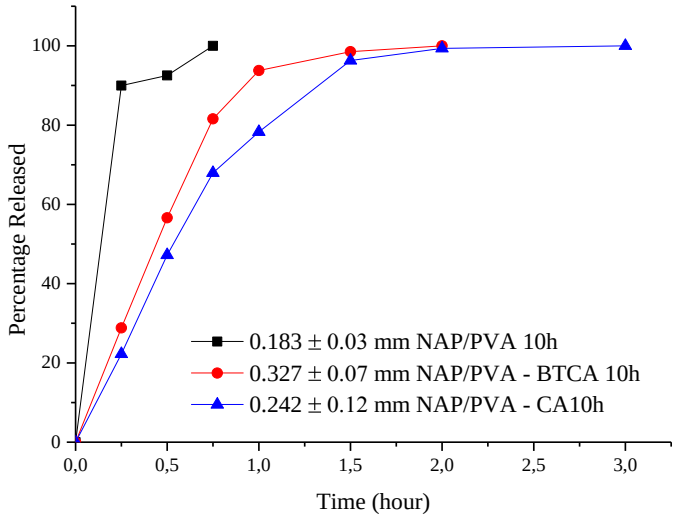

Figure 2. Percentage release of 10h produced (■) NAP/PVA, (●) NAP/PVA-BTCA, (▲) NAP/PVA-CA nanofibers

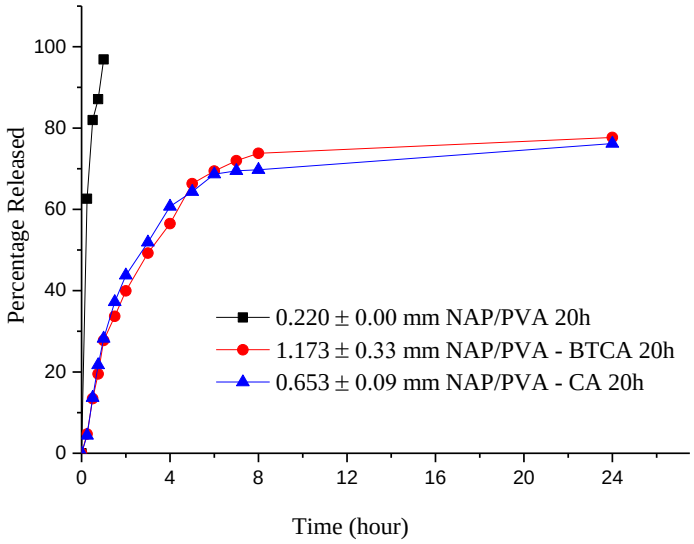

Figure 3. Percentage release of 20h produced (■) NAP/PVA, (●) NAP/PVA-BTCA, (▲) NAP/PVA-CA nanofibers

Neat PVA solution has a lower conductivity values when compared to the BTCA and CA added solutions. While NAP/PVA nanofibers were producing due to the charge accumulation of the collected fibers, collected fibers pushed further collection which resulted a larger deposition area than crosslinked nanofibers. Thus higher production period did not increase the thickness of the NAP/PVA nanofibers (0.220 ± 0.004 mm). Another reason is that, since NAP did not dissolve in the PVA solutions, polymer jet breaks down occasionally during the electrospinning and this lead to lower productivity of the thicker PVA mats. Conductivity of the solutions increased with BTCA and CA addition to the spinning solutions, and for both 10h and 20h collected samples, collection areas were smaller than non-crosslinked NAP/PVA samples. NAP/PVA nanofibers released 81% of NAP content in 30 min, NAP release reached to 97% at the end of the 60 min. In the CA added solution productivity was also low and produced mat thickness was thinner than BTCA added mats (BTCA;1.17± 0.33mm, CA; 0.653 ± 0.09mm). Despite this CA crosslinked nanofibers showed similar drug release values to the BTCA crosslinked nanofibers, possibly related to the higher swelling ratio. NAP/PVA-BTCA and NAP/PVA-CA nanofibers released 50% of NAP content approximately 3 hours and at the end of the 8 hours they released 74% and 70% of NAP content, respectively. NAP release reached to 77% for NAP/PVA-BTCA nanofibers and 76% for NAP/PVA-CA nanofibers after 24 hours (Fig. 3). Increase of the mats thicknesses slow down the NAP release however it was unable to release all its drug content. This was possibly the result of the compact structure of the thicker nanofiber mats and the rest of the unreleased drug may be retained in the nanofibers mats.

4. Conclusions

Crosslinked NAP/PVA nanofibers were developed by adding two different polycarboxylic acids; 1,2,3,4 butanetetracarboxylic acid (BTCA) and citric acid (CA) to PVA solutions. Conductivity of the solutions increased with BTCA and CA addition to the spinning solutions Developed NAP loaded nanofiber mats exhibited an enhanced impact on NAP release behavior by crosslinking. It was also observed that it is

possible to produce thicker nanofiber mats especially with BTCA than non-crosslinked NAP/PVA nanofiber mats.

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