Development of nanofibers based neuropathic patch loaded with Lidocaine to deal with nerve pain in burn patients

S Abid1, T Hussain1, A Nazir1, N Khenoussi2, A Zahir1 and S Riaz1

1National Textile Research Center, National Textile University, Pakistan
2Université de Haute-Alsace, Laboratoire de Physique et Mecanique Textiles, France
E-mail: m.sharjeel.abid@gmail.com

Abstract. Burns wounds are difficult and different to treat when compared with other wounds. The management of burn wounds is divided into three main categories; pain management, infection management and healing. Various commercial products are available to treat and prevent infection in burn patients but, for the management of pain, intravenous (IV) route is preferred which is associated with different side-effects. The local release of analgesic agent for nerve pain can reduce the IV related side effects and can provide quick and effective nerve pain management in burn patients. In this study, electrospun nanofibers of sodium alginate/PEO were loaded with lidocaine to reduce nerve pain and the effect of parameters were studied to get optimized bead free nanofibers. The drug release was tunable (from minutes to hours) and other properties like liquid absorption were studied against distilled, saline and solution A. The combination of moist environment and strong nerve pain inhibitor could be salient features to be used as contact layer for burn wound as well as the use of antidepressant drugs could be skipped.

1. Introduction

To deal with burn wounds is critical and tricky as compared with other wounds [1]. They are broadly categorized as first, second and third-degree wounds depending on the depth of damage [2]. The major problem is the destruction of the obstacle “skin” which is a protective barrier for pathogens, therefore, the burn patients are much more favorable to different microbes [3]. Thus, major focus of medical practitioners and researchers is to develop different tools that may aid in infection prevention. Whereas, first approach is to reduce the pain associated with burns which in turn depends on the degree of burns. For example, first degree burns are superficial and less painful, while, the second and third-degree burns require proper analgesic and pain killers to reduce the pain due to the damaged nerves ends reside in dermis and subcutis. The changing pattern of pain as well as the patient’s response to pain requires adequate monitoring for proper analgesic dosages [4].

Lidocaine, also known as lignocaine or xylocaine, is known as an effective analgesic drug; being used for over half century [5]. It has been used extensively either by IV route or as topical gel [6]. A patch loaded with 5% lidocaine has been reported in literature to provide peripheral analgesic action with improved pain relief as per clinical study [7]. Commercial available lidocaine patch is known as Lidoderm which uses 5% active drug attached with polyester felt as backing materials and polyethylene terephthalate as release liner. On the other hand, nanofibers are getting diverse attention in almost every field of life due to the exceptional properties they offer [8]. They are being used in medical and other industries as an effective tool for various applications [9]. Polyethylene oxide (PEO) is a synthetic hydrophilic but biocompatible polymer approved by FDA to be used for various medical applications including the drug delivery [10]. Sodium alginate (SAIg) is a natural biopolymer known to provide favorable environment for wound healing and a good drug delivery tool [11-13].

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Thus, the purpose of present study is to fabricate lidocaine loaded nanocomposite nanofibers of PEO-SAAlg that can provide localized analgesic effect, appropriate environment for healing and avoid the other IV related side effects.

2. Materials and Methods

2.1 Materials
Sodium alginate, Triton X-100 and PEO were purchased from Sigma-Aldrich. Lidocaine was kindly donated by Saffron Pharmacy Private Ltd.

2.2 Solution Parameters
Sodium alginate and PEO solutions were made in double distilled water in separate container at 400 rpm and 80 °C for 24 hours to get homogenous solutions. The electrospinning solution was made by adding 20 parts of SAlg (2% w/v) and 80 parts of PEO (5% w/v). To reduce the surface tension of the final solution, 1% Triton X-100 was added and stirred for 4 hours at room temperature. Then, lidocaine (5% OWF) was added in the above solution and stirred for further 5-6 hours at 400 rpm for complete blending of drug. The final viscosity of the solution was about 5200 cP.

2.3 Electrospinning
Electrospinning was done in needle electrospinning machine Fluidnatek LE-100 Bioinica, Spain. Flow rate of 200-300 µl, voltage range from 6 to 12 kV. The syringe was connected with a positive voltage and collector was grounded. The voltage range mentioned earlier was used to get stabilized Taylor cone so that smooth and bead free fibers could be collected. The fibers were collected on an aluminum sheet and separated (peeled) for further testing.

2.4 Surface Morphology of Nanofibers
The resultant nanofibers were sputter coated with gold and then analyzed using SEM-FEI Quanta 250 series machine equipped with EDX. The diameter of the nanofibers was measured by built in scale at various points on fibers and the mean diameter was reported.

2.5 Fourier Transform Infra-Red Spectroscopy and XRD
The drug loaded and without drug nanofibers were characterized by FTIR (Spectrum two-Perkin Elmer, USA) within scanning range of 600-4000 cm⁻¹. Samples were placed in a desiccator prior to analysis to remove moisture from the sample. The nanofibers were characterized using XRD (PANalytical X’pert Pro, Netherland) analysis for the change in crystallinity of the nanofibers after the incorporation of drug.

2.6 Liquid Absorption and Drug Release
The liquid absorption of nanofibers was tested against solution A, saline and distilled water. Drug release of produced nanofibers was analyzed at specific wavelength which was determined earlier by preliminary experiments using UV-VIS-NIR (Perkin Elmer, Lambda 950, UK). Then, fibers were immersed in phosphate buffer solution at 7.4 pH and after specific interval 2ml of solution was taken and analyzed in UV-VIS-NIR.

3. Results and Discussions
3.1 Morphology of produced Nanofibers
The selected blended of polymer produced smooth fibers at all selected electrospinning process parameters. The average size of nanofibers produced without drug was around $271 \pm 51$ nm.

![Figure 1: Nanofibers without Drug](image1.png)  ![Figure 2: Nanofibers with Drug](image2.png)

When the drug was incorporated, the average diameter of resultant nanofibers was $242 \pm 55$ nm. The SEM images of the produced nanofibers with and without drug loading can be seen in figure 1 and 2, respectively. The reduction in average diameter could be attributed to the changed solution properties after the addition of drug in dope solution. It was observed that the viscosity of the final solution after the addition of drug was reduced slightly. This reduction in viscosity is known to be one of the factors for diameter reduction in nanofibers.

3.2 XRD and FTIR Analysis

X-ray Diffraction is an effective technique to evaluate the crystal size as well as crystallinity of the polymer material. XRD patterns of drug and without drug loaded nanofibers are shown in figure 3. Characteristic peaks at $19.6^\circ$ and $23.5^\circ$ exhibits PEO/Alginate within the nanofibers. However, additional sharp peaks at $28.8^\circ$ and $41^\circ$ represent Lidocaine drug within the nanoweb [14]. Crystal size of the nanofiber web was determined by Deby-Scherrer formula described in eq. 1 [15].

$$D = \frac{c\lambda}{\beta\cos\theta}$$  \hspace{1cm} (1)

Where C is the Deby-Scherrer constant, $\lambda$ is wavelength of the x-ray (K-Alpha = 1.504 Å), $\beta$ is the full width of half maximum and $\theta$ is the Braggs diffraction angel. With the loading of Lidocaine drug, the crystal size of the Nanofiber web is reduced to 64 Å and 58 Å from 140 Å and 90 Å respectively. Loading of drug within the core of the nanofiber web removes free spaces between the polymeric chains of the PEO/Alginate thus, reduces the crystal size of the nanofiber web and increases its crystallinity [16].
IR spectra of PEO/Alginate nanoweb with and without Lidocaine are shown in figure. For PEO/sodium Alginate, broad shallow characteristic peak at 3355 corresponds to -OH, peak at 2880 represents -CH stretching within the pyranose ring. Sharp transmittance peaks at 1636 and 1469 is attributed to asymmetric and symmetric C=O stretching vibrations respectively [16, 17]. Loading of Lidocaine drug within the nanofiber web showed prominent changes in IR spectra as can be seen in figure. Transmittance peak 1470 cm\(^{-1}\) is due to joint bend vibration of O-H and C-H, shifting of peak from 1636 to 1598 is due to the C-N stretching.

3.3 Liquid Absorption and Drug Release of Nanofibers

The nanofibers with and without drug were tested against solution A, saline and distilled water and showed changed liquid absorption capacity. Both fibers showed high liquid absorption for saline solution, followed solution A and then the distilled water. Without drug nanofibers showed better liquid absorption capacity than drug loaded nanofibers as shown in figure 4.

Figure 4: Liquid Absorption and Drug release of Nanofibers

Though, the liquid absorption was lowered a bit, but still, these fibers could hold a high amount of liquid and thus, are suitable to be used for wounds with exudate. The produced nanofibers showed less absorption as compared to our previously reported results in the case of alginate/PVA nanofibers, but, this could be attributed to the composition of co-polymer [18]. The produced nanofibers showed burst release of drug within first hour and this could be beneficial for effective analgesic effect as per requirement for pain management. It was
observed that around 60% drug was release within 10 hours which was due to the solubility of PEO in water.

4 Conclusion

Lidocaine loaded defect free nanofibers of about 242 nm were successfully developed by electrospinning technique. The produced fibers showed good liquid absorption as well as desirable drug release for effective swear nerve pain management in burn wounds. FTIR analysis of nanofibers confirmed the incorporation of lidocaine drug in the produced nanofibers. The XRD analysis showed increased crystallinity of drug loaded fibers. The overall results confirmed that the promising results of produced nanofibers can make them a choice to deal with burn wounds for pain relief.

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