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Original Article

# PREPARATION AND JUSTIFICATION OF NANOFIBRES-LOADED MAFENIDE USING ELECTROSPINNING TECHNIQUE TO CONTROL RELEASE

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**ABSTRACT**

**Objective:** The primary objective was to fabricate a novel drug delivery system capable of providing a controlled and prolonged release of antibiotics.

**Methods:** The experimental design was formulated using Design-Expert® software (version 13), enabling systematic and efficient fabrication process optimization. The study involved the preparation of various nanofiber formulations with different ratios of the three polymers to assess their impact on drug release behavior. Mafenide, a widely used antibiotic, was chosen as the model drug for this investigation. The electrospinning process allowed for producing uniform and fine nanofibers with a high surface area, ensuring a large drug-loading capacity. The synthesized nanofibers were characterized using scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FTIR) to evaluate their morphology, chemical interactions, and thermal properties. The drug release kinetics of the antibiotic-loaded nanofibers were studied under different physiological conditions to assess their sustained release behavior.

**Results:** The final nanofiber formula was successfully prepared using the electrospinning technique. The Fourier Transform Infrared Spectroscopy (FTIR) analysis was achieved to confirm the possibility of chemical interaction and bond formation between mafenide and the polymers. Present. The SEM picture of the optimized nanofiber formula showed the homogeneity and excellent entanglement of the electrospun nanofibers at a resolution of 5 µm. PVA/chitosan/HPMC and mafenide pure drug have been successfully fabricated with sufficient strength to resist swelling after absorbing wound exudate. The polymer network becomes more compact when chitosan and Hydroxypropyl Methyl Cellulose (HPMC) are combined with polyvinyl alcohol (PVA), enabling regulated swelling during solvent ingress. The polymer composite's three-dimensional network influenced how quickly the medication was released from the matrix. Sample 2's polymer network traps the medication, gradually releasing after controlled swelling, resulting in a sustained release profile compared to blank sample according to the cumulative release (%) study of mafenide loaded nanofiber and mafenide drug blank sample.

**Conclusion:** This research successfully demonstrated the fabrication of sustained-release antibiotic nanofibers using electrospinning and three biocompatible polymers. The systematic optimization approach using Design-Expert® software proved effective in tailoring the drug release behavior of nanofibers. The developed drug delivery system holds great promise for pharmaceutical applications, particularly in improving antibiotic therapies and patient care.

**Keywords:** Nanofibres, Mafenide, Electrospinning, PVA, HPMC, Chitosan


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## INTRODUCTION

In recent years, the emergence of antibiotic resistance has become a significant global health concern that challenges the efficacy of conventional antibiotic therapies and leads to increased treatment failures [1]. To address this pressing issue, researchers have been exploring innovative drug delivery systems capable of improving the therapeutic performance of antibiotics. One such approach is the development of sustained-release formulations that ensure a controlled and prolonged release of the drug, enhancing its effectiveness while reducing the dosing frequency and potential side effects [2, 3].

Electrospinning has emerged as a versatile and promising technique for fabricating nanofibers with high surface area and tuneable properties, making it an attractive method for drug delivery applications [4, 5]. Incorporating antibiotics into these nanofibers makes it possible to regulate the release kinetics and achieve sustained drug delivery, which can help maintain therapeutic drug concentrations within the therapeutic window for an extended duration [6, 7].

This research aims to prepare sustained-release antibiotic nanofibers using electrospinning technology and three biocompatible polymers: chitosan, polyvinyl alcohol (PVA), and hydroxypropyl methylcellulose (HPMC). These polymers were selected due to their biocompatibility, biodegradability, and ability to form nanofibers with excellent mechanical properties [8]. Incorporating these polymers in the nanofiber structure will enhance the overall drug delivery system, improving drug release characteristics and providing a controlled release profile for the encapsulated antibiotic [9].

This study chose mafenide as a model antibiotic drug, given its broad-spectrum activity against various bacterial infections. The sustained-release nanofibers loaded with mafenide have the potential to reduce dosing frequency further and reduce adverse effects associated with high peak concentrations observed in conventional drug delivery. The utilization of Design-Expert® software in the experimental design offers a systematic and efficient approach for optimizing the fabrication process, enabling the exploration of various combinations of polymer ratios and drug loading capacities to achieve the desired sustained release behaviour. By tailoring the nanofiber formulations, an optimized drug delivery system could be obtained that meets specific therapeutic requirements [10, 11].

This paper outlines the methodology, experimental design, and characterization techniques to prepare and evaluate the sustained-release antibiotic nanofibers. The findings of this research hold considerable promise for advancing antibiotic therapies and contributing to the development of effective and targeted drug delivery systems. As a result, these sustained-release nanofibers may address antibiotic resistance challenges, improve patient outcomes, and support the global fight against infectious diseases.

## MATERIALS AND METHODS

### Materials

Mafenide and Hydroxypropyl Methyl Cellulose (HPMC) were procured from ChemShuttle, China. Polyvinyl alcohol (PVA) (degree of hydrolysis 98-100%, average molecular weight 60000–125000 kDa) was procured from SD Fine Chemical, Mumbai, India, and Chitosan was purchased from Thomas Baker, India. Buffer solution pH 7 (phosphate) was procured from Fisher Scientific Loughborough, United Kingdom.

### Methods

#### Calibration curve of mafenide

The Mafenides calibration curve was carried out by preparing a stock solution (50 ml) in a concentration range of 0.02 µg. ml-1 to 0.25 µg. ml-1 of buffer solution. Then, eight concentrations were taken from the prepared stock solution; 2 ml of stock solution was withdrawn and diluted in 2 ml of deionized water, and the concentrations were measured at a 265 nm UV spectrophotometer (Shimazu, Japan). The same experiment was made with deionized water [12].

#### Preparation of PVA/Chitosan/HPMC/Mafenide for electrospinning

The solution had different amounts of three biopolymers: Polyvinyl Alcohol (PVA), Chitosan, and Hydroxypropyl Methyl Cellulose (HPMC). It also had the active pharmaceutical agent mafenide in it. The solution was made by dissolving each polymer in deionized water and stirring it with a magnetic stirrer overnight. According to preliminary studies conducted for this purpose, the three polymers (Polyvinyl Alcohol (PVA), Chitosan, and Hydroxypropyl Methyl Cellulose (HPMC)) were mixed in the following ratios: 8:1:1. The studies were conducted in triplicate to guarantee reproducibility. The Design-Expert® tool was utilized to input the minimum and maximum concentrations of polymers based on prior research findings [13]. To create a homogenous polyvinyl alcohol (PVA) solution, 1.0 g of polyvinyl alcohol (PVA) was shaken for 12 h in 50 ml of deionized water at 60 °C. 1% v/v acetic acid and deionized water were used to dissolve 0.25 g of chitosan, which was shaken for 6 h. The Hydroxypropyl Methyl Cellulose (HPMC) polymer was prepared by dissolving 0.5 g in 50 ml of deionized water and shaking it using a magnetic stirrer for 2 h at room temperature. Mafenide was precisely weighed and dissolved in deionized water with gentle stirring for 1 h to ensure complete dissolution. Next, it was added to the polymeric mixture in a ratio of 5%. Then, the final solution was stirred for 1 h until it became ready to be applied in the electrospinning process.

#### Fabrication of electrospun PVA/Chitosan/HPMC/Mafenide composite nanofibers

The concentration of the polymers used in solution preparation was proposed by Design-Expert® software using multi-factorial design, which sets eight runs with three blocks to study the effect of different factors on fiber formation with two responses, as listed in table 1. Responses included fiber diameter and entrapment efficiency. In order to detect possible hand errors and estimate a lack of fit, Design-Expert® software replicated some formulas at the same concentration of all polymers. The compositions of the eight formulae are illustrated in table 1.

#### Setting of electrospinning apparatus

Before starting the electrospinning process, the device had been set on several factors to control the whole process. Depending on preliminary studies, the flow rate of solution was set at 1 ml/h, the separate to collector distance was kept at 15 cm, the temperature of the device chamber was controlled at 20–25 °C, the relative humidity was adjusted at 30–35 °C, the electrical voltage applied by the power supply was reserved at 20 kV, and the ground collector was wrapped with aluminum foil [14].

**Table 1: Composition of formulas suggested by design-expert® software. The pure drug was used in a concentration 5% of the total polymers blended. The used units were gram**

| Run | Factor 1 (AVA) (g.100 ml$^{-1}$) | Factor (HPMC) (g.100 ml$^{-1}$) | Factor 3 (Chitosan) (g.100 ml$^{-1}$) |
|---|---|---|---|
| 1 | 1 | 0.5 | 0.1 |
| 2 | 4 | 0.5 | 0.25 |
| 3 | 4 | 0.25 | 0.25 |
| 4 | 1 | 0.25 | 0.1 |
| 5 | 4 | 0.25 | 0.1 |
| 6 | 1 | 0.5 | 0.25 |
| 7 | 1 | 0.25 | 0.25 |
| 8 | 4 | 0.1 | 0.1 |

#### Investigation of electrospun nanofibers

The nanofibers that are collected from aluminum foil after the electrospinning process undergo several investigations; scanning electron microscopy (SEM) for detection of fibre shape and diameter, entrapment efficiency to determine the ratio of drugs entrapped in the polymers and fourier transform infrared spectroscopy (FTIR) to determine the conjugation of drugs in the polymer [15].

#### Fourier transform infrared spectroscopy (FTIR) of mafenide

The Fourier Transform Infrared Spectroscopy (FTIR) spectrum was analyzed to determine the peaks at different bandwidth positions of mafenide nanofibers and the peaks of each molecule individually (mafenide, PVA, chitosan, HPMC). The Fourier Transform Infrared Spectroscopy (FTIR) analysis was achieved to confirm the possibility of chemical interaction and bond formation between mafenide and the polymers present in the formulation and to detect the compatibility between the drug and polymers. Therefore, when drugs and polymers are incompatible, each biomolecule shows its specific pure peaks in its Fourier Transform Infrared Spectroscopy (FTIR) bandwidth. However, the miscible polymers can shift the peak position due to possible interactions between the polymers themselves and the drug. The method was conducted by a Fourier Transform Infrared Spectroscopy (FTIR) (Shimadzu, Japan) at a band length ranging from 400 to 4000 cm [16].

#### Scanning electron microscopy (SEM)

By employing a concentrated high-energy electron beam, the scanning electron microscope (SEM) can reconstruct the picture of a sample. Micrographs make understanding the polymer's internal and external morphology easier [17]. The composite film samples were first gold-sputtered to increase surface conductivity before being scanned at 1000X and 2000X magnifications to evaluate the surface morphology [18]. The scanning electron microscope (SEM) showed that adding mafenide to the formula results in knots and changes in the uniformity of the final formula. The result was nanofiber with various sizes ranging from 29.43 nm to 33.03 nm. The final formula was loaded in a bag on valve spray dosage form; the final formula was mixed with sodium chloride solution as a preservative, resulting in a sustained release formula (fig. 4). Scanning electron microscopy (SEM) was used to measure the diameter of the electrospun nanofibers (Inspect F-150) [18].

#### The mechanical examination

Mechanical examination in order to support and aid in wound healing applications, biopolymeric films need to be extremely

strong; hence, the composite film's tensile property becomes a crucial criterion to be evaluated [19]. The universal testing machine (InstronTM 3366 universal testing equipment) was used to assess tensile strength and elongation according to the American Society for Testing and Materials (ASTM) standard procedures. Tensile strength indicates the material's capacity to withstand breaking under tensile stress, whereas elongation indicates the material's ductility [20].

**Drug diffusion behaviour**

The *in vitro* drug release was applied to the samples under conditions mirrored the skin's acidic composition. A diffusion cell and a semi-permeable membrane were used in the experiment. Using a pH 6.4 phosphate buffer solution as the release medium, 4 $cm^2$ drug-loaded film samples were tested at room temperature. The cumulative drug release (%) during three hours was recorded after release. Samples of five millilitres were taken at regular intervals and analysed using a UV spectrophotometer at 265 nm [21].

**Drug release kinetics**

It was used with kinetic models of zero order, first order, Higuchi, and Korsmeyer-Peppas to better understand how drugs spread and are released, as shown in the authors' previous research [22]. Subsequently, the highest coefficient of determination (R2 value) and release exponent (n) were observed to determine the best-fit model and release mechanism. Design expert software suggests that with the highest polyvinyl alcohol (PVA) and low Hydroxypropyl Methyl Cellulose (HPMC) polymers, the best formula [23].

**Statistical analysis**

The experiments were carried out in triplicates to ensure reproducibility; results were represented as arithmetic mean±standard deviation. Excel software was used to measure and analyse data and construct figures. ANOVA analysis was performed using Design-Expert® Software. Thus, P-values ≤0.05 were expressed as statically significant.

**RESULTS AND DISCUSSION**

**Calibration curve of mafenide**

The calibration curve was constructed as shown in fig. 1. The absorbance to concentration ratio of mafenide in buffer solution has been used and listed in table 2 [24]. The regression coefficient (R2) was 0.9996 and the linear equation generated was y = 2.2663x+0.0121. The calibration curve of mafenide solution in deionized water was constructed using a UV-spectrophotometer at λ max 265 nm. According to Beer law, a straight line was drowned between a series of mafenide solution concentrations versus obtained absorbance in nm. The result corresponded to the mafenide finding reported by Orachorn N. *et al.* (2021) [25], who reported standard solutions in a concentration range of 5–25 µg. ml, where the regression coefficient was R2 = 0.998 and drew the straight line, and Mahajan R. *et al.* (2022) [26] solubilize mafenide in deionized water and drew a straight line with 5 points and $R^2$ = 0.9995.

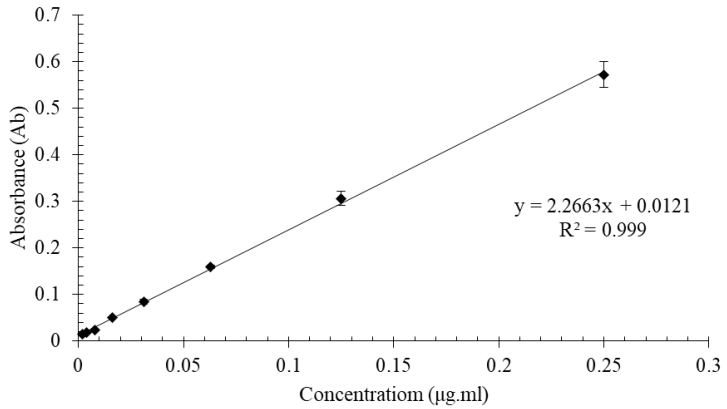



**Fig. 1: Calibration curve of mafenide. stuck solution 50 ml at the concentration range of 0.02 µg. ml to 0.25 µg. ml in deionized water. Then, serial of 8 concentrations were taken from prepared stuck solution; 2 ml of stuck solution withdrawn and diluted in 2 ml of deionized water and measured at 265 nm UV spectrophotometer (Shimazu, Japan)**

**Table 2: The concentration of mafenide in deionized water to absorbance of UV spectrophotometer**

| Concentration (µg. ml) | Absorbance* (a. u.) |
|---|---|
| 0.002 | 0.572±0.027±SD |
| 0.004 | 0.306±0.051±SD |
| 0.008 | 0.159±0.035±SD |
| 0.016 | 0.084±0.049±SD |
| 0.031 | 0.050±0.01±SD |
| 0.063 | 0.023±0.001±SD |
| 0.125 | 0.018±0.002±SD |
| 0.25 | 0.014±0.001±SD |

*data are mean±SD of three independent experiments.

**Fourier transform infrared spectroscopy analysis**

The Fourier Transform Infrared Spectroscopy (FTIR) spectrum was analysed to determine the peaks at different bandwidth positions of mafenide nanofibers and the peaks of each molecule individually (mafenide, PVA, chitosan, HPMC, and). The Fourier Transform Infrared Spectroscopy (FTIR) analysis was achieved to confirm the possibility of chemical interaction and bond formation between mafenide and the polymers present in the formulation and the detection of the compatibility between the drug and polymers [27]. Therefore, when drugs and polymers are incompatible, each biomolecule shows its specific pure peaks in its Fourier Transform Infrared Spectroscopy (FTIR) spectra bandwidth [28]. However, the miscible polymers can shift the peak position due to the possible interactions between the

polymers themselves and the drug [29]. The method was conducted by Fourier Transform Infrared Spectroscopy (FTIR) (Shimadzu, Japan) at a band length ranging from 400 to 4000 cm.

The pure mafenide spectrum showed the presence of (N-H) stretching, which appeared at wave number 3550-3000 cm-1, (N-H) bending at 1542 cm-1, CH2 appeared at 1413 cm-1, carbon-nitrogen group appeared at 1319 cm-1, and sulphonamide group appeared at 1090 cm-1 [30].

With wave number 3289.4 cm, the hydroxyl group (OH) showed polyvinyl alcohol (PVA) absorption bonds. The CH bonds were 2973.22-2935.7 cm, and the CO bonds were 1084 cm. Alishahi, M., Khorram, M., *et al.* (2020) presented comparable findings as shown in fig. 3D [31].

The Hydroxypropyl Methyl Cellulose (HPMC) polymer demonstrated absorption bands at 1117.01 cm-1, 2980.45 cm-1, and 3350 cm-1, which related to the stretching vibrations of the C-O, C-H, and O-H groups, respectively. That indicated stretching vibrations for each. Also, the $CH_3$ band appears at 1396.37 cm-1, and the $CH_2$ band appears at 1462 cm-1 as shown in fig. 3B [25].

Chitosan showed characteristic peaks of amide I at 1650 cm (C-O stretching), amide II at 1558 cm (N-H), (C-N stretching coupled with NH in-plane deformation) and $CH_2$ wagging coupled with OH in plane deformation at 1317 cm as shown in fig. 3C [32].

**Scanning electron microscopy (SEM)**

The average diameter was computed and compared to the expected value. The algorithms predicted a value of 50±20 nm for the electrospun nanofiber diameter, which greatly agrees with the result (fig. 4). The results demonstrated high accuracy.

The SEM picture of the optimized nanofiber formula showed the homogeneity and excellent entanglement of the electrospun nanofibers at a resolution of 5 µm [33].

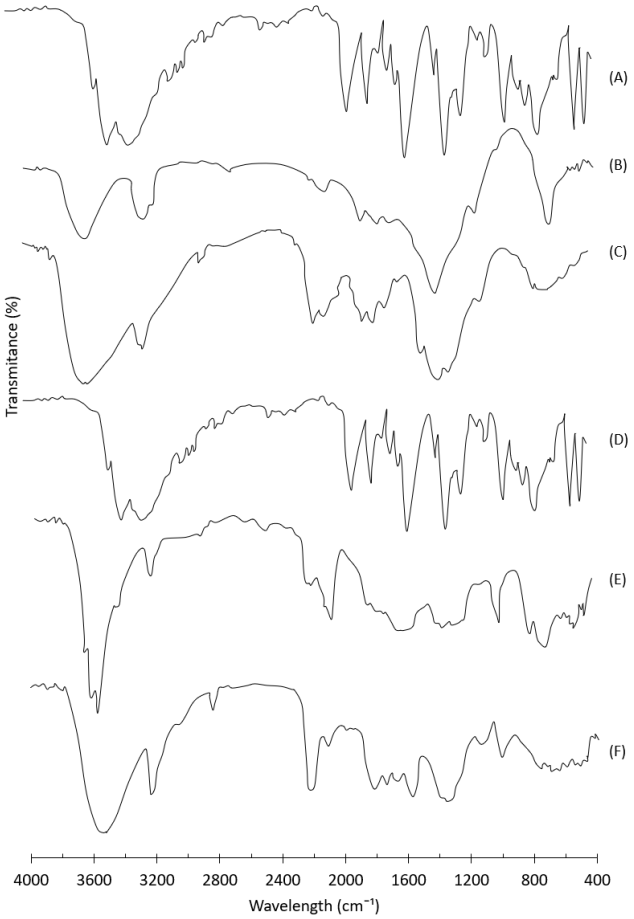
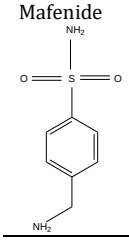



**Fig. 3: FTIR images (A) Pure mafenide; (B) HPMC polymer; (C) Chitosan polymer; (D) PVA polymer; (E) Nanofibre-free mafenide; and (F) Nanofibre-loaded mafenide. The FTIR spectrum of the compounds was diluted with 10 mg KBr and fitted on the lens. The chart was drawn with a resolution of 2 $cm^{-1}$. Measurements were taken in the range between 3500 and 500 $cm^{-1}$ using FTIR spectrophotometer.**

**Table 3: Characteristic FTIR absorption bands of mafenide**

| Compound | Band (ῡ. $cm^{-1}$) | Interpretation |
|---|---|---|
| Mafenide  | 3550 and 3000 | Stretching vibration of N-H of sulphonamide |
| | 1542, 1519 | N-H bending |
| | 1413 | C-H stretching vibration of amide |
| | 1319 | C-N stretching |
| | 1143 | Sulphonamide group |
| | 1090 | N-H bending |

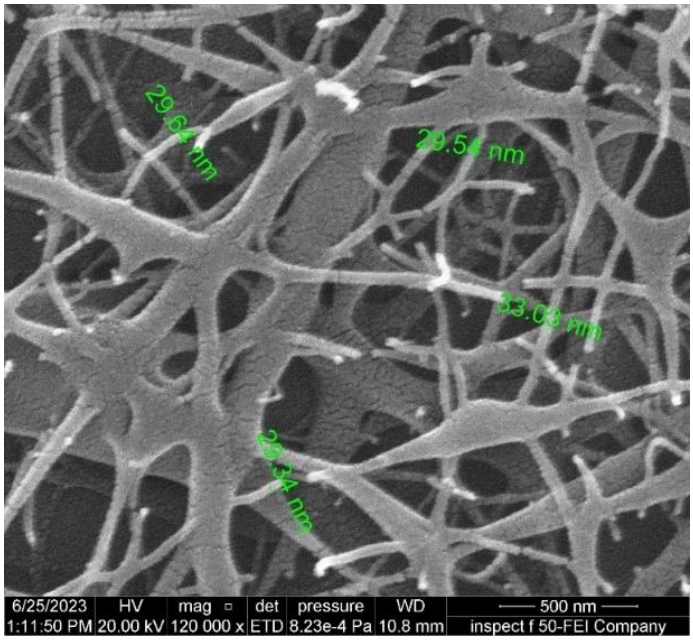



**Fig. 4: FESEM of the final formula of nanofiber on aluminium foil plait showing different nanofiber size. After cutting the sample (nanofiber containing PVA/HPMC/chitosan and mafenide on aluminium foil) into small pieces, the sample is fixed on the 13 mm radius aluminium stub using double-sided carbon adhesive tape. Then, the stub was placed in a sputter coater device for coating the samples with a thin layer of gold for 10 min to eliminate image artifacts that arise from the excess surface charge. The sample can be observed under field emission scanning electron microscopy**

**The mechanical examination**

The nanofiber was optimized, and only samples 2, 3, 5, and 8 mentioned in table 1 were considered for mechanical test as the others failed the swelling test. It was found that if the quantity of chitosan and HPMC increased, the nanofiber became more fragile, indicating reduced mechanical strength [34]. When polyvinyl alcohol (PVA) was added to the Hydroxypropyl Methyl Cellulose (HPMC) chitosan blend, the films became tougher and rigid, reflecting an increase in overall mechanical strength, a desired trait. Dathathri E. *et al.* (2017) [20] reported that incensed chitosan will reduce tensile strength and swelling properties. Abraham A. *et al.* [35] published that when polyvinyl alcohol (PVA) was added to the Hydroxypropyl Methyl Cellulose (HPMC) chitosan blend, the films got tougher and rigid, which was consistent with these results. Furthermore, increasing the polyvinyl alcohol (PVA) amount improved the tensile strength and elastic modulus. Hence, the mechanical strength confirms that the nanofiber formula containing PVA/chitosan/HPMC and mafenide pure drug have been successfully fabricated with sufficient strength to resist swelling after absorbing wound exudate.

**Drug diffusion behaviour**

Sample 2 was chosen for the drug release study because it had a uniform shape, good mechanical strength, and good swelling behavior, as shown by the tests used to characterize it. The film crumbled after a cumulative release lasting three hours, as shown in fig. 5 and listed in table 4. The polymer network becomes more compact when chitosan and Hydroxypropyl Methyl Cellulose (HPMC) are combined with polyvinyl alcohol (PVA), enabling regulated swelling during solvent ingress [36]. The polymer composite's three-dimensional network influenced how quickly the medication was released from the matrix [37, 38]. Sample 2's polymer network traps the medication, gradually releasing after controlled swelling, resulting in a sustained release profile.

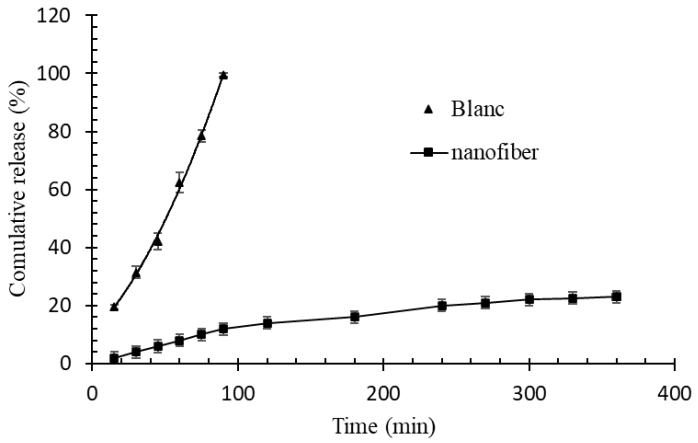



**Fig. 5: The cumulative release (%) study of mafenide-loaded nanofiber and mafenide drug (Blank). The nanofiber was kept in 150 ml phosphate buffer pH 5 at 37±0.5 °C and 5 ml of sample was withdrawn every 15 min for 360 minute and analysed spectrophotometrically at 265 nm. data are mean±SD of three independent experiments**

**Table 4: Cumulative drug release (%) of the nanofibre-loaded mafenide and free mafenide**

| Time (min) | Cumulative release (%) | |
|---|---|---|
| | Nanofibre-loaded mafenide | Free mafenide |
| 15 | 2 | 20 |
| 30 | 4 | 30 |
| 45 | 6 | 40 |
| 60 | 8 | 60 |
| 75 | 10 | 80 |
| 90 | 12 | 100 |
| 120 | 14 | |
| 180 | 16 | |
| 240 | 20 | |
| 270 | 21 | |
| 300 | 22 | |
| 330 | 22.5 | |
| 360 | 23 | |

Data is mean of three independent experiments.

## CONCLUSION

The final nanofiber formula was successfully prepared using the electrospinning technique. The three used polymers were biocompatible with the model drug mafenide. Nanofiber of Hydroxypropyl Methyl Cellulose (HPMC), chitosan, polyvinyl alcohol (PVA), and mafenide were developed in various ratios and characterized using FTIR analysis, mechanical studies, scanning electron microscope (SEM) analysis and swelling studies. Sample runs of 2, 3, 5, and 8 exhibited superior properties compared to the remaining blends. Scanning electron microscope (SEM) analysis revealed that the films were continuous and uniform, and the polymers had good miscibility. According to Design experts, software and tensile tests revealed that run 2 exhibited better mechanical stability than the 3, 5 and 8 runs. FTIR analysis revealed a physical interaction among the polymers, indicating that the formulations would have good release efficiency. Overall, sample 2 showed good potential as a nanofiber according to the Design-Expert® software analysis to aid and accelerate wound healing. In conclusion, a final formula of nanofibers containing mafenide exhibits sustained release properties.

## FUNDING

Nil

## AUTHORS CONTRIBUTIONS

All authors have contributed equally.

## CONFLICT OF INTERESTS

The author declares that there are no conflicts of interest regarding the publication of the paper.

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