Research Article

Design, Optimization and Evaluation of Nanofibers Containing NSAID for Controlled Drug Delivery System

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ABSTRACT

In the present research work, an attempt was made to develop nanofiber patches for piroxicam by using the polymers such as Ethycellulose, PVP. The advantages of nanofibers include the production of nanofibers layers from various polymers, and the incorporation of medications or growth factors into different nanofibers layers for wound care management. Piroxicam is a water-insoluble drug, its shows high first-pass metabolism and hence an attempt was made to enhance solubility, to improve bioavailability and reduce toxicity. The physicochemical characterization for a pure drug such as organoleptic properties, spectral analysis UV spectroscopic studies, ATR-FTIR and DSC, was investigated and confirmed. Preparation of drug-loaded nanofibers patch (NFs) by Electrospinning process coupled layer-by-layer assembly method. The prepared nanofibers were analyzed for surface morphology by Scanning electron microscopy at different magnifications and evaluated the entrapment efficiency of drug-loaded nanofiber showing that the fibre formed with a smooth surface morphology and was spherical at 300nm. The prepared patches were subjected to evaluate the percentage of moisture content, tensile strength, swelling index, and in vitro diffusion studies for up to 12 hr. The stability study for the optimized nanofiber patch formulation was conducted for three months. Electrospun drug-loaded fibre patches could be a potential strategy in the lookout for a new platform with high drug and transdermal enhancer compatibility.

Keywords: Nanofibers, Electrospinning, Magnification, Diffusion studies, Transdermal patches.

INTRODUCTION

Piroxicam, a first-line choice of NSAID for the analgesic and anti-inflammatory action, on a chronic regimen are more likely to cause cardiac attack or stroke and these effects may occur without notice and result in death. Oral administration of Piroxicam may cause muscular weakness, edoema and fluid retention thus rendering the oral dosage form of this drug unsuitable for long-term usage. Also the oral route of administration doesn't allow the choice of control on the administration of the drug into the system, as possible in the TDD system.Thus, in order to avoid dose-related ADR, the necessity to overcome these limitations associated with piroxicam medicine led to the development of a Piroxicam loaded Nanofibers dosage form to improvise patient compliance and minimize dose frequency to reduce Piroxicam related chronic toxicity. The phrase "nanofibers" may be divided into 2 parts, namely "Nano" and "fibres." Fibres are defined in the textile business as a filament that can be spun into yarn and is either natural or synthetic, such as cotton or nylon. A "fibre" is a thin, elongated, threadlike item or structure from a geometrical aspect. Nanofibers have a diameter

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of less than 50-500 nanometers, and the term "Nano" refers to the size of a billionth of a unit. Nanofibers are defined by the National Science Foundation (NSF) as having at least one dimension of 100 nanometers (nm) or less. Nanofibers have recently been employed in healthcare systems as a drug delivery technology for several ailments. The advantages of nanofibers include the production of nanofibers layers from various polymers, the incorporation of medications or growth factors into different nanofibers layers for wound care management, and the development of nanofibers layers from various polymers. The relevance and convenience of nanofibers as medication carriers are demonstrated by their utilization. Their reduced size improves in the delivery of the drug to the correct sites in the body. Electrospinning is by far the most popular and widely utilised technology for producing nanofibers. Electrospinning is the most widely utilised industrial manufacturing process so far. Electro-spinning processes are used to manufacture more than half of the nanofiber. Loading active pharmaceutical components using the electrospinning technology, which creates ultra-fine fibres (diameters ranging from micro to nanometers) with a controlled surface, the shape is an alternate option for various forms of release. These fibres are made by applying a high electrical field to a desirable polymer solution, or by melting the polymer and exposing it to the electrical field if the polymer does not have a good solvent. Predictable and reproducible kinetics of medicines delivered by orally continuous for a set the amount of time throughout the GIT. Drug-encapsulating devices are used in controlled release drug delivery, which allows therapeutic substances to be released at a controlled rate for long periods, ranging from days to months.[1-5]

Controlled-release (CR) formulations were brought into drug therapy with two major purposes in mind: to minimise the number of single doses per day, increase patient compliance and to limit plasma level fluctuations, resulting in higher therapeutic efficacy and reduced toxicity. There are a variety of controlled-release pharmaceutical systems available today, ranging from monolithic matrices, membrane reservoirs, and highly permeable polymers to more technically advanced in pH-independent formulations, ion exchange resins, and osmotically and geometrically modified systems. Many of these systems aren't made in a way that allows for large-scale production, and they may not have the desired zero-order release kinetics. However, the cost of formulation research, raw materials, and manufacturing technology are all important variables in the formulation of Controlled Release delivery systems for oral dosage.[6]

Preformulation studies[7-9]

Organoleptic Properties

The Organoleptic Properties of drug samples were studied for appearance, color and odor.

UV spectroscopy (Determination of λ_{max})

The standard solution of piroxicam was scanned between 200-400 nm using a UV spectrophotometer in a solution of 0.1M methanolic HCl.

Standard Calibration Graph of Piroxicam

In a volumetric flask (100 ml), a weighed amount of drug (20 mg) was dissolved in a small amount of methanol. Finally, 0.1M methanolic HCL was used to bring the volume up to the required level, resulting in a final concentration of 100 g/mL. From this, the secondary stock was created by combining 1 mL of primary stock with 10 mL of volumetric flask and diluting to the desired volume. (20 g/ml Stock II). Different concentrations of 1 – 20 g/ml solutions were generated from the above stock solutions and evaluated using a UV-visible spectrophotometer at 336 nm. The result is shown in Figures 1 and 2.

Drug excipients interaction studies by ATR-FTIR

ATR-FTIR spectrum was used to identify and validate the drug. The average absorption peak of Piroxicam

UV-Visible Spectrophotometer

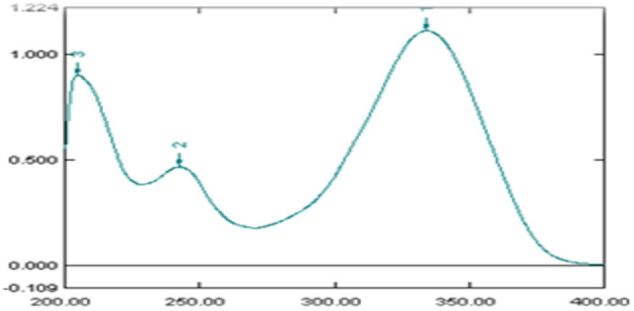

Figure 1: Maximum absorbance of piroxicam.

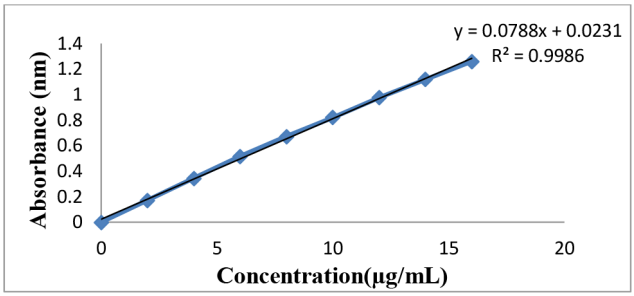

Figure 2: Standard graph of piroxicam in 0.1N methanolic HCL at 336 nm.

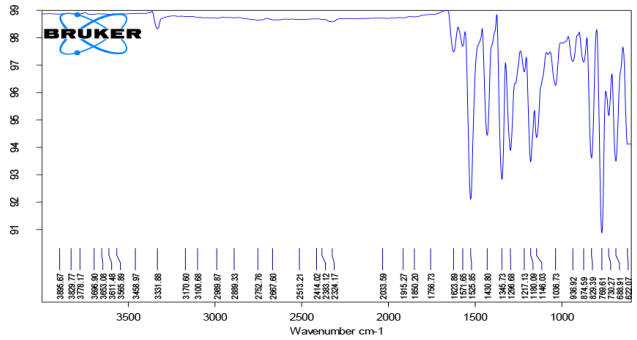

Figure 3: ATR- FTIR Spectrum of pure piroxicam.

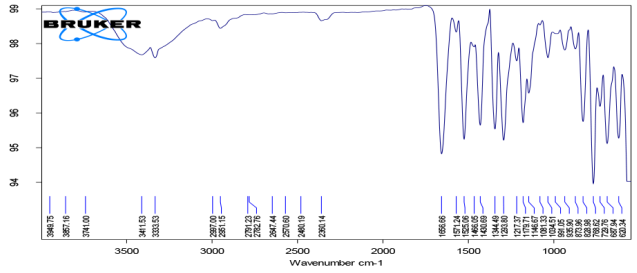

Figure 4: ATR- FTIR Spectrum of the optimized formulation.

and its excipients was within pharmacopeial limitations. According to the functional category, these excipients were mixed in different ratio with piroxicam. The peaks obtained in the spectra in the optimized formulation are correlated with the peaks of Piroxicam spectrum. The result is shown in Figure 2,3,4.

Solid State Characterization by Differential Scanning Calorimetry

This approach was used to deposit a weighed amount of drug and excipient into a crucible. The crucible was covered and then pressed by using a pressing machine. Then it was placed into the instrument. For DSC analysis, a sample (3–5 g) was heated at 0–25°C in a nitrogen atmosphere at a scanning speed of 100 C/min. The DSC thermogram was used to analyse the drug's solid state chemistry in composite polymeric nanofiber. The result is shown in Figure 5.

Preparation of Drug-loaded Nanofiber Patches[10-13]

Using an electrospinning process combined with a layer-by-layer assembly method, drug-loaded nanofiber patches were made. PVP powder was weighed and dissolved in ethanol for 3 hr at 80°C to make a PVP solution with a concentration of 10% w/v. The prepared solutions were electrospun by connecting the positive polarity emitting electrode from a Gamma High-Voltage Research ES30PN/M692 high voltage DC power supply to the solutions contained in a standard 50-mL syringe, the open end of which was joined to a blunt 20 gauge

Differential Scanning Calorimetry (DSC)

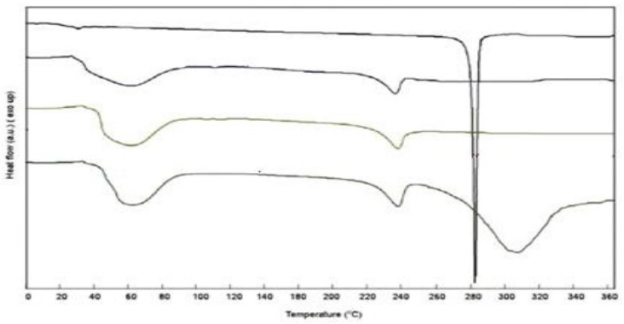

Figure 5: Differential Scanning Calorimetry (DSC) of piroxicam, PVP, EC and physical mixtures.

stainless steel needle with an outer diameter of 0.91 mm, used as the nozzle, and the grounding electrode to a home-made rotating metal drum (outer diameter of 0.91 The spindle revolution rate was set to 20 cycles per minute, The shear rate was set at 10 sec per second. A fixed electrical potential of 15 kV was delivered across a predetermined distance of 15 cm between the tip of the nozzle and the outer surface of the drum. The spinning drum revolved at a rate of 50-60 revolutions per minute. The liquids were given at a rate of about 1 ml h-1 using a syringe pump. The nanofiber sheets were cut into 1cm to 2cm patches for further characterisation.

Layer-by-layer assembly procedures were used to make the patches based on medicated fibre patches. Drug-in-fiber was used to describe the comprehensive preparation steps. To continue, prepared fibre was placed with a wet film applicator over a silicone-coated release liner to produce a film. The fibre film was obtained and coated with a layer of medicated fibre mat containing piroxicam and PVP after drying for about 24 hr at room temperature. After that, an ethylcellulose backing membrane adhered to the aforesaid system. Finally, the Drug-in-Fiber patch was obtained and trimmed to the appropriate sizes. For further research, the patches were wrapped in tin foil and preserved in desiccators. The formulation is shown in Table 1.

Evaluation Studies for Prepared Nanofiber Patches[14-18]

Morphology Analysis (Scanning Electron Microscope Study)

The morphology for plain and prepared nanofiber patches was analyses by using a Hitachi S-4700 SEM (scanning electron microscope in Hitachi Company, Japan). Before being considered, samples were placed on metal ends using double-sided adhesive tape and vacuum-coated with a gold sputter layer. The diameters

Table 1: Preparation of drug-loaded nanofiber patches.

Ingredients	PRX1	PRX2	PRX3	PRX4	PRX5
Piroxicam (mg)	20	20	20	20	20
Polyvinyl pyrrolidone (mg)	50	100	150	200	250
Ethycellulose (mg)	50	100	150	200	250
Ethanol (mg)	100ml	100ml	100ml	100ml	100ml

Surface morphology (Scanning electron microscopy)

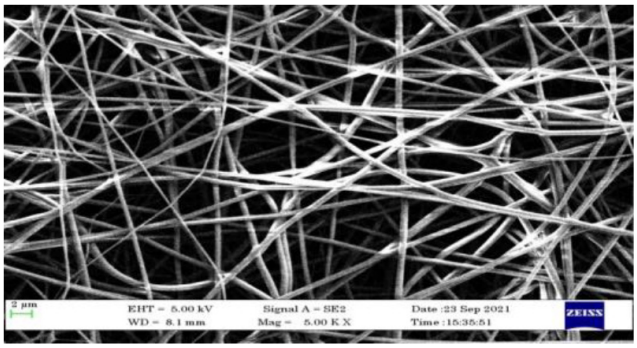

Figure 6: The Nanofibers view under X 5.00 K magnification.

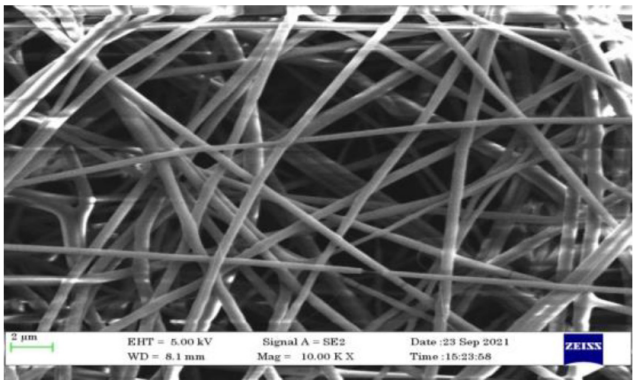

Figure 7: The Nanofibers view under X 10.00 K magnification.

and distributions of the electrospun fibres were examined from the SEM images using Image analysis software. The result is shown in Figure 6,7,8,9.

Entrapment Efficiency

Due to their large surface area, electrospun nanofibers are projected to have a high drug entrapment efficiency (EE). The efficiency of the preparation process for incorporating the medication into the carrier system is described by EE. Weighing and dissolving the drug-loaded nano-fibre patch in phosphate buffer pH 7.4 A UV spectrophotometer set to 330 nm was used to test the solution for entrapped drug concentration in triplicate. The result is shown in Table 2. The following formula was used to calculate the percentage of drug EE:

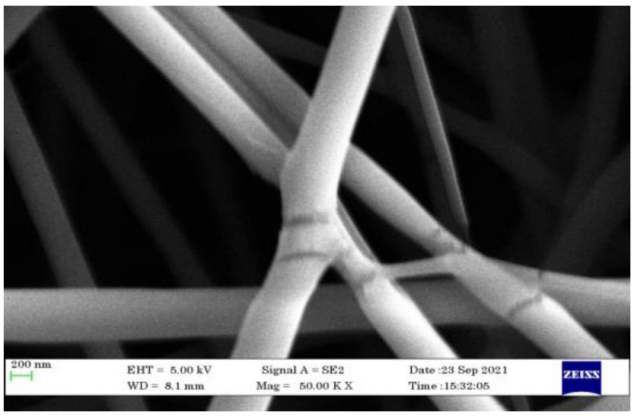

Figure 8: The Nanofibers view under X 50.00 K magnification.

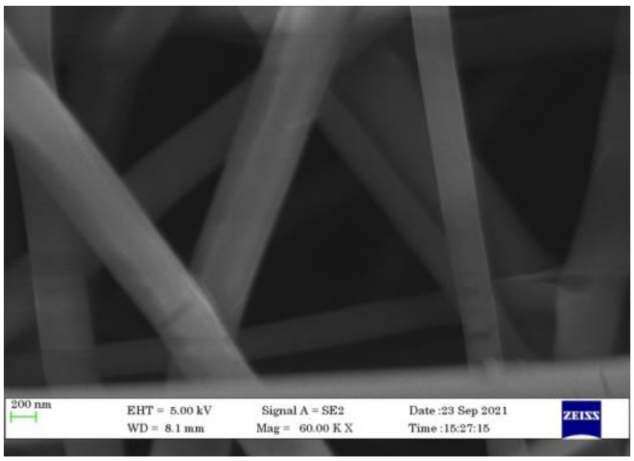

Figure 9: The Nanofibers view under X 60.00 K magnification.

$$EE\ \% = \frac{\text{Entrapped drug}}{\text{The total amount of drug}} \times 100$$

Percentage of Moisture Content

The produced transdermal films were weighed separately and maintained at room temperature for 24 hr in desiccators with fused calcium chloride. The films were re-weighed after 24 hr. The result is shown in Table 2.

$$\text{Percentage moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Tensile Strength of Patches

Tensile strength is a mechanical property that determines a formulation's capacity to withstand wear and tear during transit and handling. With the use of clamps, nanofibers measuring 8 cm in length and 4 cm in width were arranged vertically along the axis of the Brookfield texture analyzer. After base localization, the instrument was permitted to operate with a minimum sensitivity

force of 3 gm/cm2. The result is shown in Table 3. It was established how much power was necessary to break the mat into two parts.

$$\text{Tensile strength} = \frac{\text{Force at break (Kg)}}{\text{Cross n sectional area of the sample (cmsq)}}$$

Swelling Index

The piroxicam transdermal patches were equilibrated in 250 ml of phosphate buffer (pH 7.4) at 25°C after being thoroughly dry and pre-weighed. After 24 hr, the water absorption of the films is assessed using an analytical balance. The result is shown in Table 2. The following equation is used to calculate the swelling ratio (Q) of the films:

$$Q = W_s/W_d$$

In this, Ws shows the weight of the swelling film at various time intervals, whereas W_d shows the weight of the dry film.

In vitro Drug Release

The Franz diffusion cell was used for the *in vitro* diffusion study. The receptor compartment was filled with 20 mL Acetate buffer pH 5.5 and kept at 37°C. Over a dialysis membrane, an optimized nanofiber sample was retained in the donor compartment. A reasonable interval of time was used to remove the aliquot of 1ml and replace it with a new buffer solution kept at the same temperature. A UV spectrophotometer was used to evaluate the material in triplicate at 336 nm. The result is shown in Table 4, Figure 10.

Stability Studies

The optimized formulation of piroxicam loaded Nanofiber patch was tested for stability according to ICH guidelines in a short-term condition at room temperature and refrigerated temperature (25°C and 4°C) for three months. After 3 months, the entrapment efficiency, swelling index and *in-vitro* release of piroxicam were evaluated. The result is shown in Table 5.

RESULTS AND DISCUSSION

The present study was carried out to develop an Electrospun Nanofiber formulation of Piroxicam with the aim of enhancing absorption and bioavailability. In concern to this approach, the necessity of formulating stable drug-loaded Nanoparticle-based fibres and 3studying the pre and post-evaluation parameters were studied, for which the results are discussed below.

Evaluation of prepared Nanofiber patches

Entrapment Efficiency and Percentage of moisture content

Table 2: Evaluation studies for formulation (PRX1-PRX5) Entrapment Efficiency and Percentage of moisture content.

Formulation code	Entrapment efficiency (%)	%moisture content
PRX 1	93.15	1.89
PRX 2	93.95	2.16
PRX 3	95.80	2.21
PRX 4	96.45	2.41
PRX 5	94.05	3.16

Tensile strength and Swelling index

Table 3: Evaluation studies for formulation (PRX1-PRX5) Tensile strength and % of the swelling index.

Formulation code	Tensile strength	% of the swelling index
PRX 1	5.38	12.13
PRX 2	5.42	14.35
PRX 3	5.50	15.51
PRX 4	5.54	16.67
PRX 5	5.48	13.56

Organoleptic Properties

The organoleptic characteristics of the drug sample were investigated since they are one of the initial criteria for compound identification and show conclusions that are comparable with literature review standards. The description of piroxicam is white powder and odourless in nature

DISCUSSION[19-21]

Organoleptic Properties

The sample received for its organoleptic properties such as white colour, odourless and appearance in powder shows results which comply with reported literature standards.

UV-Visible Spectrophotometer

Using a UV spectrophotometer to scan the maximum absorbance of the obtained drug helps in detecting and validating the API's reliability. The resulting spectrum was compared to a standard API of 336 nm, confirming that the medication has a maximum absorbance of 336 nm and is in good agreement with the working standard.

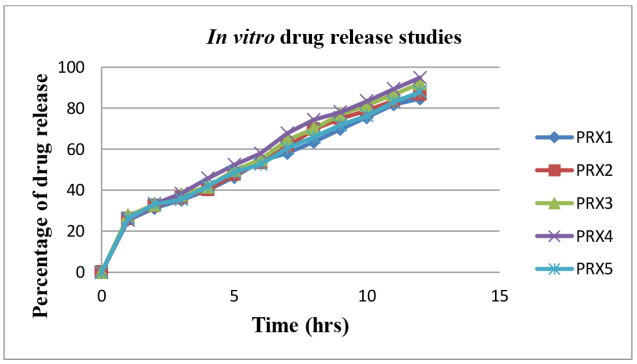

Figure 10: *In vitro* drug release studies for all formulations (PRX1-PRX5).

In vitro Drug Release Studies

Cumulative Drug Release Data of ES-NF

Table 4: *In vitro* drug release studies for all formulations (PRX1-PRX5).

In vitro drug release studies					
Time (hr)	PRX1	PRX2	PRX3	PRX4	PRX5
0	0	0	0	0	0
1	25.53	26.15	27.70	25.41	26.20
2	31.32	32.35	32.91	33.36	33.34
3	35.18	36.26	37.78	38.37	35.45
4	40.16	40.25	41.72	45.73	41.87
5	46.34	47.67	49.81	52.31	48.72
6	54.11	53.41	55.00	57.95	52.63
7	58.09	61.34	64.43	67.79	60.53
8	63.58	69.64	70.01	74.37	65.89
9	69.81	74.92	76.92	78.01	71.75
10	75.57	78.93	81.44	83.46	76.33
11	81.81	83.59	86.65	89.31	82.90
12	84.66	86.78	91.97	94.86	87.88

The medication obeys the beer-lamberts rule in the concentration range of 2, 4, 6, 8, 10, 12, 14, and 16 g/mL for 0.1N methanolic HCL in the medium, according to the standard calibration curve of piroxicamin 0.1N methanolic HCL. UV spectral studies authenticate the spectra obtained standard pure drug gave the maximum absorption peak at 336nm and good linearity with R^2 value of 0.998, which suggests that it obeys the Beer-Lamberts law.

Drug and excipients interaction studies by ATR-FTIR

The comparison of ATR-FTIR spectra of piroxicam and a mixture of drug and polymer confirms that there is no appearance of additional new peaks and the disappearance of existing peaks from that of the drug. This indicates that there is no interaction between the drug and the polymer used in the study.

Stability Studies

Table 5: Stability studies of Optimized piroxicam nanofiber patches (PRX4) formulation at refrigerated temperature (4°C) and Room temperature (25°C) for three months.

Time	[Swelling index (nm)		Tensile strength		*In vitro* drug release	
	At 4°C	At 25°C	At 4°C	At 25°C	At 4°C	At 25°C
Initial	16.3	16.6	5.52	5.54	94.85	94.86
15 days	16.7	16.6	5.37	5.51	94.83	94.82
30 days	16.9	16.6	5.23	5.46	94.75	94.76
45 days	17.2	16.7	5.16	5.45	94.62	94.63
60 days	17.8	16.7	4.89	5.43	94.53	94.51
90 days	18.2	16.7	4.85	5.42	93.98	94.11

Differential Scanning Calorimetry (DSC)

The solid characterization of piroxicam and mixture of drug and polymer were studied by using DSC this indicates that there is no interaction between the drug and polymer used in the study. The DSC thermogram of piroxicam and mixture of drug and polymer exhibited a sharp endothermic peak at 280-300°C.

Surface morphology (Scanning electron microscopy)

Scanning electron microscopy of the prepared nanofibers at different magnifications such as X5 K, X10 K, X50 K and X60 K showed that the fibre formed with a smooth surface morphology and was spherical in shape at 300nm. Based on the results of the surface morphological study, it was confirmed that the prepared nanofiber was formed well as conformed under various magnifications in scanning electron microscopy.

Entrapment Efficiency and Percentage of Moisture Content

Formulations containing selected polymer entrapment efficiency and percentage of moisture content ranged from 93.15 to 96.45% and 1.89 to 3.16% respectively. Among this study's formulations PRX1 - PRX5 the formulation PRX4 showed entrapment efficiency and percentage of moisture content value of 96.45% and 2.41% respectively which was an optimal range for the rest of these formulations.

Tensile Strength and Swelling Index

Formulations of prepared patches indicate the study result of tensile strength and swelling index ranging

from 5.38 to 5.54 and 12.13 to 16.67% respectively. Among this studied formulation PRX1 - PRX5 the formulation PRX4 showed tensile strength and swelling index values of 5.54 and 2.41% respectively which was the optimal range compared to other formulations.

In vitro Drug Release Studies

The *in-vitro* release drug release studies of piroxicam-loaded nanofiber patches were carried out using the diffusion technique and a pH 5.5 acetic buffer. the I *in vitro* drug release was found to be regulated using a pH 5.5 acetic buffer based on the findings. In a pH 5.5 acetic buffer, drug release from PRX1, PRX2, PRX3, PRX4, and PRX5 formulations was 84.65 %, 86.78 %, 91.96 %, 94.86 %, and 87.88 %, respectively, from formulations incorporating polyvinyl pyrrolidone and ethylcellulose. In a pH 5.5 acetic buffer, researchers studied the release of piroxicam from nanofiber patches over 12 hr. Among the PRX1-PRX5 formulations studied, PRX4 had a higher release rate than the others.

Stability Studies

For three months, stability investigations were done at room temperature (25°C) and refrigerated temperature (4°C) for the final optimized formulation (PRX4). Mild variations were noticed in tensile strength, swelling index and *in vitro* drug release. As a consequence, the formulation (PRX4) was discovered, and all of the reports at refrigerated stability experiments were found to be within specification limits.

SUMMARY AND CONCLUSION

In the current study, an attempt was made to develop nanofiber patches for piroxicam by using the polymers such as Ethylcellulose, and PVP. Piroxicam is a poorly water-soluble drug, its shows high first-pass metabolism, hence an attempt was made to formulate as drug-loaded Nanofibers to enhance solubility and to improve the patient complaints. In this work, efforts were made to prepare stable nanofibers for reducing the toxicity of piroxicam. It was concluded from these results that the medicated membrane played significant functions in the controlled transdermal drug delivery system, while also having a direct impact on the therapeutic effectiveness of patches. A drug-loaded fibre patch made by electrospinning might be a viable way to start looking for a new platform that is optimized for drug and transdermal enhancer compatibility. It also shows enhanced diffusion, reduces the dosing frequency and increases patient compliance, as well as effective controlled release patches when administered topically.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ADR: Adverse Effect; **ATR-FTIR:** Attenated Total Reflectance- Fourier Transform Infrared; **DSC:** Differential Scanning Calorimetry; **EE:** Entrapment Efficiency; **GIT:** Gastro intestinal track; **PVP:** Polyvinyl Pyrrolidone; **NFs:** Nanofibers; **NSAID's:** Non Steroidal Anti Inflamatory's; **Rpm:** Rotations Per Minute; **TDD:** Targeted Drug Delivery; **UV:** Ultra Violet.

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