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FABRICATION AND CHARACTERIZATION OF DRUG-LOADED BIONANOFIBERS AS A PLATFORM FOR DRUG DELIVERY

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Keywords:

Bionanofibers, PVP, Macitentan, Electrospining Method

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ABSTRACT: The Bionanofibers drug delivery systems can reduce toxicity, improve therapeutic efficacy and increase patient compliance by delivering drugs at a controlled rate to the site of action. The major aim in designing nanostructures as delivery systems is to deliver pharmacologically active molecules with accurate doses at targeted sites. The present research work developed Bionanofibers as a carrier for drug delivery. Because of the very small nanoscale diameter and high surface area, significantly higher drug content can be loaded in a very small volume. Bionanofibers were manufactured from Macitentan drug using PVP and Soybean PC by electrospinning. The obtained bionanofibers were characterized based on morphology, entrapment efficiency, and drug release behavior. FE-SEM images showed that the length of obtained bionanofibers is about 580nm to 1250nm in diameter. FTIR analysis shows no significant interaction between the drug and the polymer. The *in-vitro* release study demonstrated that there is a controlled release pattern of drugs from bionanofibers.

INTRODUCTION: Nanofibers are known as fibers having diameters lower than 50-500 nanometers range. Nanofibers composed of bio-based polymers potentially discover applications in the delivery of drugs, in medicine, in the protection of the environment, in agriculture, production, and processing of food, as well as other areas. It's having rare properties like high tensile strength, high surface area-to-volume ratio, high Young's modulus and lower coefficient of thermal expansion [1]. By releasing drugs to the local site at a controlled rate over time to achieve therapeutic effects, bionanofibers drug delivery systems are able to improve therapeutic efficacy, overcome toxicity and boost patient compliance.

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Bionanofibers are an innovative new class of material with a wide range of uses, including medical, consumer, and industrial products as well as more complex ones like drug delivery systems, including colonic drug delivery, wound dressing, air and liquid filtration, composites for aerospace, battery separators and optical and chemical sensors [2]. The use of natural gum for pharmaceutical applications because of its properties such as biodegradable, biocompatible, easily available, nontoxic, economic and capable of chemical modifications mainly used in drug delivery as suspending agent, disintegrants, emulsifying agent, binder and release retardant [3, 4].

The major aim in designing nanostructures as delivery systems are to deliver pharmacologically active molecules with accurate doses at targeted sites. Several studies have been conducted on the use of nanostructured biopolymers from renewable resources. Among that, the polysaccharides are the most abundant and renewable natural polymers. Cellulose is used as raw material in the production

of bio-based nanofibers due to their ability to form transparent and strong fibers [5, 6].

MATERIALS AND METHODS:

Material: PVP with a mean molecular weight of 111.14 kD, Macitentan and all the solvents used for the electrospining were obtained from Sigma Aldrich. The solvents consisting of Methanol.

Methods: Prepare a polymer 1, 2, 3, 5 and 7% w/v solution of PVP and Soybean PC in Methanol (Solution A) by prespinning technique and In addition, a 3% (w/v) pre solution of the drug was prepared by dissolving the appropriate amount of pure Macitentan in methanol aqueous solutions before the electrospinning process at the same conditions. (Solution B) with stirring at ambient temperature and ambient humidity. The final spinning solution was obtained by mixing solutions A and B. In this study, electrospinning process was performed under ambient conditions. In order to provide the final spinning solution for the various formulations, a certain concentration of the PVP solution was added to the drug solution **Table 1**. The final spinning solution was mixed and stirred by a magnetic stirrer with a fixed speed of 50 RPM for 30 min at room temperature and ambient humidity to obtain a homogeneous spinning solution. The solutions were degassed using an Ultra-Sonicator for 10 min. The spinning solutions were carefully loaded into a 10 ml syringe to avoid any air bubbles. The single-syringe infusion pump was used for injecting the spinning solution. The feed rate was fixed at 1.5 ml/ h. A high-voltage power DC supply was used as the positive electrode at a voltage of 14 kV. A metal collector was covered with aluminum foil and was applied as the grounded electrode. The Electrospun nanofibers were collected. The metal needle tip has 0.25 mm inner diameter. All samples were placed in silica gel beads in desiccators to facilitate the removal of moisture and residual organic solvents.

TABLE 1: SOLUBILITY STUDIES OF PURE MACITENTAN, ELECTROSPUN NANOFIBER-BASED SOLID DISPERSIONS, AND THE PHYSICAL MIXTURE CONTAINING PVP

			Theoretical drug content	
Batch	**Process**	**Drug (w/v): Polymer (w/v) (%: %)**	**Amount(mg)**	**Expressed (%)**
Macitentan	-	3:0	100	100
M1	Electrospinning	3:1	75	100
M2	Electrospinning	3:2	60	100
M3	Electrospinning	3:3	50	100
M4	Electrospinning	3:5	37.5	100
M5	Electrospinning	3:7	30	100
PM	Physical mixture	3:7	30	100

In the next step, samples were collected for doing different tests. All samples were kept in plates with closed lids, out of sun radiation and at room temperature up to the next tests.

Preparation of Physical Mixtures as Controls: For the purpose of comparison, the drug and the polymer (%, w/w) was simply triturated to produce solid dispersions with the same content. In a porcelain mortar (drug and carrier were homogenized in a glass mortar by a spatula for 5 min). The mixtures were then sieved and stored in amber glass capped containers.

Evaluation of Macitentan Nanofibers:

Drug Entrapment Study: Samples were centrifuged, the amount of drug contained in the clear supernatant was measured (w) using a UV spectrophotometer set to a wavelength of 280 nm. For this, a drug calibration curve that is considered to be standard was plotted. The total amount of drug added during preparation was then deducted from the amount of drug in the supernatant (W). Effectively, (W-w) will give the amount of drug entrapped in the particles.

Then percentage entrapment of a drug was calculated according to Equation,

$$\% \text{ Drug Entrapment} = (W\text{-}w/W) \times 100$$

The efficiency study was determined by free drug content in the supernatant, which is obtained after centrifuging the solid lipid suspension at (15,000rpm for 20 min at 0°C using ultracentrifuge). The absorbance was measured at 280 nm by UV spectrophotometrically.

Characterization of Macitentan Nanofibers:

Optical Microscopy: For assessing the spontaneous formation of self-assembled, 1.0 ml of distilled water was added to the pre-weighted sample (100 mg) of Macitentan -loaded NFs. The mixture was then gently and manually shaken for about 1–2 min at an ambient room temperature (22 ± 2 °C) to obtain a homogenous dispersion. The dispersion was equilibrated for at least 10 min to form the self-deposition. The sample dilution was required for acquiring proper images. Then, the formation of the self-assembled imaged with an optical microscope.

Fourier Transform Infrared Spectroscopy: For verifying drug-polymer interactions of NFs, a Fourier transform infrared (FTIR) spectroscope and Single Reflection ATR crystal were used for the Macitentan, PC and PVP powders, as well as for the electrospun NFs. The analytical range was from 550 cm^{-1} to 4000 cm^{-1} and spectra (n = 3) were normalized and scaled.

Scanning Electron Microscopy: Different types of interactions, including secondary electrons, backscattered electrons, and distinctive X-rays, are produced when a precisely focused electron beam is traversed across the surface of the sample in scanning electron microscopy (SEM). Images of the sample are developed from these signals by detectors and projected onto a cathode ray tube screen. The elements present in the features can then be promptly determined using WDS. SEM is typically used to observe morphological, structural and surface properties of the nanofibers.

***In-vitro* Drug Release:** Drug release from the electrospun nanofibers was carried out by placing a pre-defined size of nanofibers (1×1 cm^2) in 100 ml of Phosphate Buffer pH 6.8. The release investigations were performed in a thermostatic shaking incubator at 37 °C and 100 rpm. The amount of drug present in the aliquots was determined at pre-defined intervals using a UV–visible spectrophotometer (Lab India UV-3000) at a λ_{max} of 280 nm, followed by the addition of fresh media to maintain sink conditions.

RESULT AND DISCUSSION:

Evaluation of Macitentan Nanofibers:

Drug Entrapment Efficiency: The Entrapment efficiency of Macitentan Nanofiber was analyzed by dialysis method. Increase the concentration of polymer, the entrapment efficiency Increases. From the above result **Table 2**, formulation M5 shows the highest percentage of entrapment efficiency of 95%, so formulation M5 was selected for further studies.

TABLE 2: ENTRAPMENT EFFICIENCY OF MACITENTAN NANOFIBER

Formulation code	Entrapment Efficiency (%)
M1	60±0.12
M2	69±0.17
M3	78±0.12
M4	82±0.11
M5	95±0.04
PM	66±0.09

Characterization of Macitentan Nanofibers:

Optical Microscopy: The optical microscope (OP) magnifies an image by sending a beam of light through the object. The condenser lens focuses the light on the sample, and the objective lenses(10X, 40X, 2000X) magnify the beam, which contains the image; to the project or lens so the observer can view the image. Not many optical micrographs of nanofibers have been encountered in the open literature; however, this technique can give information about the overview of the nanofibers. An example is shown in **Fig. 1**.

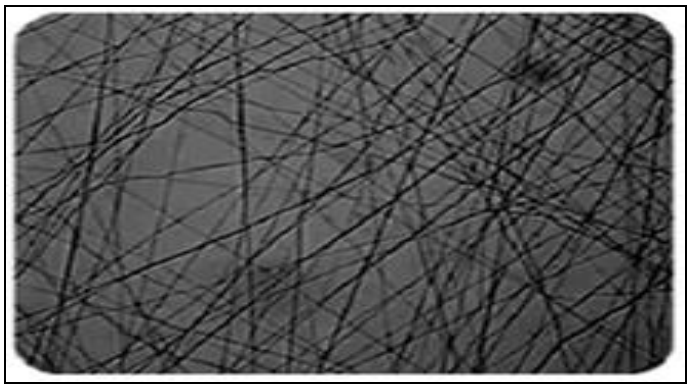

FIG. 1: OPTICALMICROGRAPH: MACITENTANNANOFIBERS100X

FTIR Studies:

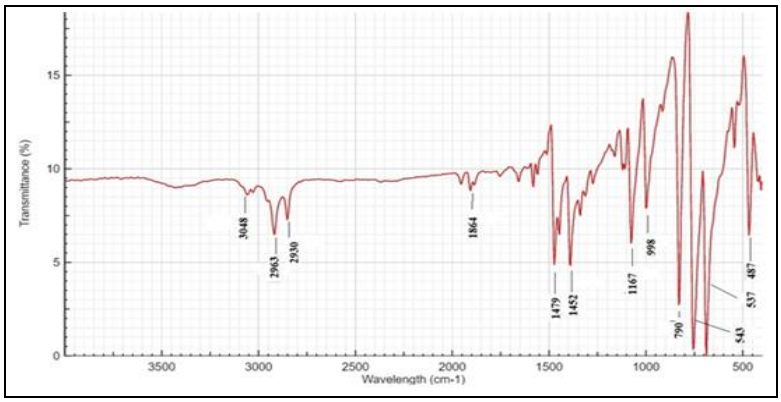

FIG. 2: FTIR SPECTRA OF MACITENTAN

Sr. no.	Functional group	Wave no.(cm^{-1})
1	-OHstretch	3389
2	-C=O Stretch	1661
3	-C=Cstretch	1621
4	-CN Stretch	1076, 1026

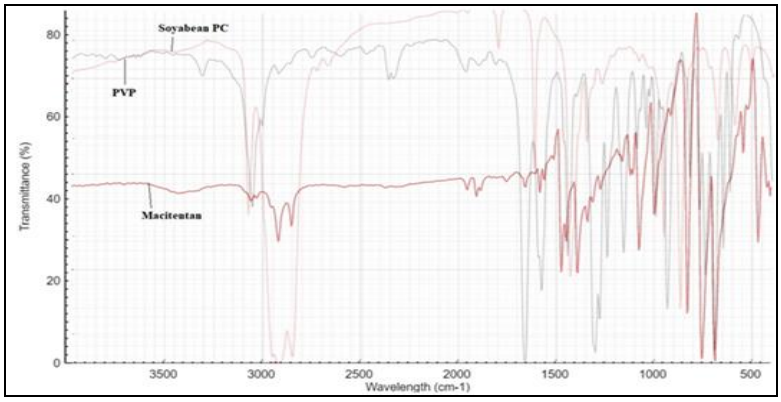

FIG. 3: FTIR SPECTRA OF MACITENTAN WITH PVP, SOYBEAN PC POLYMER COMPATIBILITY

SEM Analysis of Amphiphilic NFs and Templates: Fig. 4 shows the representative SEM images. The isolated and milled Macitentan powder consisted of large irregular particles with a particle size ranging from some tenths of micrometers to several hundred micrometers **Fig. 4A**. We discovered that the addition of Macitentan and soybean PC to the ES carrier polymer PVP had no impact on the efficiency of an ES process or the generation of NFs. The ES solutions containing Macitentan, soybean PC and PVP generated continuous elongated NFs with a smooth surface and uniform diameter **Fig. 4B**. The topography of the nanofibrous solid templates exhibited a non-woven and loosely packed platform with randomly oriented individual NFs. The existing amphiphilic nanofibrous templates had exterior pores with sizes ranging from a few micrometers to ten micrometers.

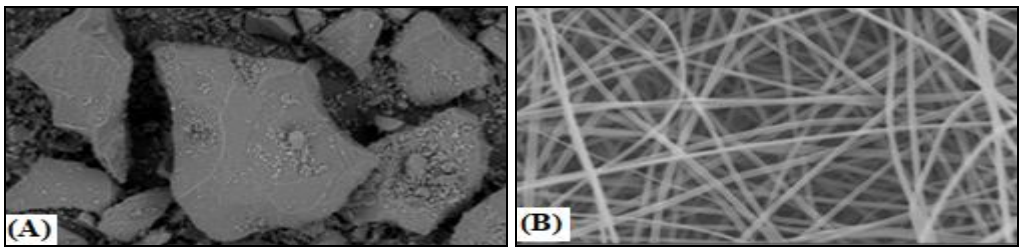

FIG. 4: SEM MICROGRAPHS OF THE AMPHIPHILIC ELECTROSPUN NFS, WHICH CONSTITUTED AS A SOLID TEMPLATE FOR THE SELF-ASSEMBLED LIPOSOMES (B), AND AN ISOLATED AND MILLED MACITENTAN POWDER (A) 200 M (A) AND 2.0 M SCALE BARS (B)

The amphiphilic NFs in our investigation had a figure diameter of 392 66 nm (n = 100) as assessed on the SEM micrographs **Fig. 4**. Individual NFs had diameters ranging from 197 nm to 534 nm. The average fiber diameter of the corresponding amphiphilic NFs (without Macitentan) ranged from 580nm to 1250nm. The size of the NFs can be tailored by varying the content of PC in the NFs, The average diameter of NFs made entirely from PVP was 910 110 nm, and as the NFs' PC content increased, the average particle diameter significantly reduced to 580 90 nm at 33.3% w/w PC. However, as the PC content was increased to 50% (*w*/*w*), the average diameter of NFs was significantly increased to 1010±110nm. The presence of PC, as a zwitterionic surfactant, changes the surface tension and viscosity of the PVP solution, thus affecting the morphology and diameter of the NFs. It is well known that PVP is a good carrier polymer for ES to generate NFs. PC generates electrostatic, hydrophobic interactions with PVP when administered to PVP solutions. The shape of a PVP chain and PVP-PVP molecular interactions are modified by these molecular-level interactions, which reduce entanglements and viscosity.

***In-vitro* Drug Release:** The cumulative dissolution profiles of Macitentan loaded in the amphiphilic Electrospun NFs formulation M5 are shown in **Table 3** and **Fig. 5**.

TABLE 3: *IN-VITRO* DRUG RELEASE OF MACITENTAN NANOFIBERS

Time in (Hr)	% Drug Release of M5
0	0
1	8.74 ± 1.23
2	15.17± 1.45
3	20.24± 1.12
4	39.17± 1.20
5	58.14± 1.53
6	78.19± 1.60
12	82.19± 1.13
18	90.20± 1.08
24	95.17± 1.90
48	98.58± 1.65

More than 50% of Macitentan released within the first 2 h, approximately 80% released within the next 2 h, and the rest of the active agent (100%) released within 30 h. The initial burst release of the drug-loaded amphiphilic nanofibers could be attributed to the surface or near-surface distribution of Macitentan in the nanofibers. This results in swelling of the nanofibrous template. Only evaluating the dissolve assessment of the current amphiphilic nanofibrous templates loaded with the active ingredient is the purpose of our dissolution investigation.

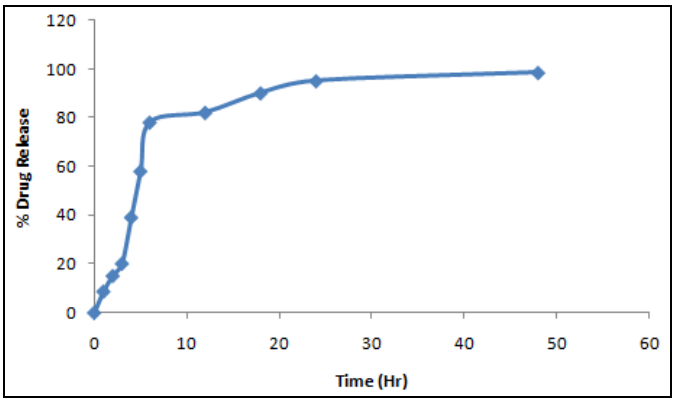

FIG. 5: THE *IN-VITRO* DISSOLUTION PROFILES OF MACITENTAN -LOADED AMPHIPHILIC ELECTRO-SPUN NFS FORMULATION M5

CONCLUSION: In the present research work bionanofibers were successfully developed by using the electros pining Method. SEM and FTIR etc investigated chemical structure, morphology, thermal stability of bio-nano-fibers. FTIR measurements show no interaction in between drug and polymers. In SEM study concluded that PVP is a good carrier polymer for ES to generate NFs. After drug loading, the surface area and roughness of nanofibers were decreased. The *in-vitro* activity showed a controlled release pattern of the drug from bionanofibers. Thus, the present investigation directs the delivery of drug through nanofibers at the targeted site.

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CONFLICTS OF INTEREST: The authors declare that there is not any conflict of interest.

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