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FORMULATION, OPTIMIZATION AND EVALUATION OF TRANSDERMAL PATCH BY LOADING ELECTRO SPUN NANOFIBER OF GRISEOFULVIN

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Abstract

The potential of using the intact skin as port of drug Administration has been recognized for several decades. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. Griseofulvin (GSF) loaded polyvinylpyrrolidone (PVP k-90) composite electro spun nanofiber (NF) was developed, and hybridized as a transdermal patch. The Formulation was optimized by factorial design (design expert software). There are 8 batches are prepared and evaluated. The nanofiber was prepared by using 0.56% w/w PVP and loaded with 3 % wt. GSF. The prepared NF was characterized by scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FT-IR), ultraviolet–visible spectroscopy, differential scanning calorimetry (DSC), and X-ray diffraction (XRD). The NF mat was hybridized in to transdermal patches then its physical-chemical parameters and in vitro diffusion of GSF were also evaluated. The prepared formulation ideally followed the Zero-order kinetics (r2 = 0.973).) considered very high and fall under the accepted range. The Optimized formulation containing diameter of nanofiber 84.03 nm Cumulative drug release of NF is 88.3% for 5 hr.

Keywords: Nanofiber, Nanoscale, Life- threatening, Regression.

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1. INTRODUCTION

An effective drug delivery system is needed along with an ideal drug selection in order to attain the optimum therapeutic effects. In recent decades, the development of a controlled drug delivery system has become more crucial. As far as the pharmacological responses are concerned, both the therapeutic effect and the adverse effect depend on the drug concentration at the site of action. This concentration relies on the type of dosage form and the rate of absorption [1]. There are various types of dosage forms like parenteral and oral are being conventionally used. But these conventional dosage forms are having limitations such as; invasiveness, patient non-compliance, difficulty in maintaining steady state plasma concentration [2]. Transdermal drug delivery systems (TDDS) or patches have long been used to either treat tissues directly beneath the skin or for systemic application with advantages over the conventional dosage forms [3]. In general the TDDS can circumvent the first-pass degradation of the drug that occurs when it is given orally. Depending on the polymer chosen, the drug can be delivered in a controlled manner into the systemic circulation without any dose fluctuations [4]. General limitation for the conventional TDDS like patches is the stratum corneum of the skin, which acts as a barrier for the normal diffusion of the drug [5,6]. It is essential that a TDDS must effectively surpass this limitation [7].

Various nanoscale formulations, like liposomes, nanoparticles, nano emulsions, nanofibers, and recently lipid hybrid nanoparticles, are effectively been used for various skin ailments as TDDS due to their large drug loading and controlled drug delivering abilities [8]. Electrospinning nanofibers are one among them that play a pivotal role, by rendering greater adaptability in the selection of drugs or materials for the application of drug delivery. Nanofibers have many advantages such as high surface-to-volume ratio, greater drug loading ability, higher encapsulation efficiency, ease of fabrication and simultaneous delivery of various payloads [9,10]

Fungal infections pose a continuous and serious threat to human health and life.1 These fungal infections in humans can be classified into (a) allergic reactions to fungal proteins, (b) toxic reactions to toxins present in certain fungi and (c) infections (mycoses). Healthy individuals are susceptible to a host of superficial, cutaneous, subcutaneous and in certain instances, systemic infections that cause a variety of conditions ranging from Athletes foot and nail infections to severe life-threatening disseminated disease (e.g., histoplasmosis).[10] Many fungal infections are caused by opportunistic pathogens that may be endogenous (Candida infections) or acquired from the environment (Cryptococcus, Aspergillus infections). [11].

Griseofulvin is the Antifungal Class II drug. It is White to pale cream-colored crystalline powder. Griseofulvin is an antifungal agent used to treat a variety of superficial tinea infections and fungal infections of the fingernails and toes. Polyvinylpyrrolidone (PVP) MW111.1418, also known as K90 is a water-soluble polymer with good bio-stability. It is chemically stable, has low toxicity and is biocompatible. Hence, it is useful in a variety of applications such as cosmetics, tissue engineering, and biomedical engineering. Polyvinylpyrrolidone (PVP) is a water-soluble polymer obtained by polymerization of monomer N-vinylpyrrolidone. PVP is an inert, non-toxic, temperature-resistant, pH-stable, biocompatible, biodegradable polymer that helps to encapsulate and cater both hydrophilic and lipophilic drugs. It is a not thermo- or pH-sensitive under usual conditions. However, since this polymer is widely used, especially in medicine, several studies are dedicated to the problem of making this polymer stimuli-resposive, too.

By considering the advantages of GSF , in this work, the GSF-loaded PVP K90 nanofiber was prepared and hybridized as transdermal patch. PVP polymer was used to obtain porous nanofibers with good mechanical property and controlled biodegradability. Here, Ethanol was used as solvent to make solution of GSF loaded PVP, and make spun as fine and thin nanofiber. Scanning electron microscopy (SEM), along with other physical-chemical parameters, was evaluated in order to maintain the ideal morphology of the nanofibers. The usage of solvents, ideal concentrations of the polymers and drug were also examined, for better morphology of the nanofibers. The formulated nanofibers were characterized by Fourier-transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), and X-ray diffraction (XRD), along with evaluations of the TDDS and in vitro drug release studies.[12]

2. Materials and Methods

2.1 Materials

Polyvinylpyrrolidone (PVP K-90) was purchased from LOBA CHEM, Griseofulvin API (99.7%) pure was obtained from Nulife Pharmaceuticals. Double distilled water and ethanol as solvent (EtOH, 99%) were supplied by LOBA CHEM as chemical reagent.

2.2 Method

Preparation of electrospinning solution:

First, 560 mg of PVP were dissolved in EtOH to obtain 10 ml solutions. Then 30 mg of GSF were added into above prepared PVP solution, prepared with different concentrations, The solution was synthesized at 40 °C, stirred by a magnetic stirrer at ± 400 rpm for ± 60 min until a clear homogeneous solution was achieved while stirring for 4 h. Thus, the viscous sol-gel spinning solutions of GSF/PVP were obtained.[13]

Preparation of NFs by electrospinning processes:

The spinning solution was placed in a hypodermic syringe and was delivered to the blunt needle tip (nozzle diameter of approximately 0.8 mm) at a flow rate of 1 mL/h via a micro-syringe pump. at a fixed collecting distance (23 cm) between the tip of the syringe and rotating collector. The positive terminal of a high voltage power was applied to the needle of the syringe via an alligator clip delivering an applied voltage (25–40 kV). The GSF/PVP organic inorganic hybrid fibres were prepared by subjecting the solution to a high electrical potential of hot air and dried in a vacuum at 100 C for 24 h, and were then sintered in a muffle furnace at 450, 900 and 1100 C for 5 h in air to obtain GSF/PVP fibres. [14]

3. Optimization

Optimization of NF patch is carried out by using Design of Experiment Software (DOE). Optimization stud occurred by using Full factorial design 2^3 Factorial design is used for optimization batch. It means 2 level 3 factor. It obtains 8 batches.

4. Preformulation Study

Pre-Formulation study plays very important role in rational development of dosage forms. It is defined as evaluation and investigation of physical as well as chemical properties of drug and when mixed with other excipients. It is method to optimize the delivery of drug by determining physiochemical properties of the new compound that may affect on drug performance and development of the efficacious, stable and safe dosage form. In development of any drug delivery system the preformulation study is one of the important pre-requisites. The preformulation study provides the information required to defined the physicochemical properties of the drug substance and provide a structure for drug combination with pharmaceutical

excipients in the dosage form. Hence, the preformulation studies are carried out on the obtained sample of drug and polymer.

4.1 Physicochemical properties of drug:

4.1.1Organoleptic properties:

The physical appearance of drug was observed and compared with the pharmacopoeial specifications.

4.1.2 Solubility study: Solubility of drug were check by using different solvents

4.1.3 Drug confirmation

Identification of drug was done by using UV, DSC, IR, Melting point determination.

4.1.4 Calibration Curve of GSF:

GSF pure 100mg was weighed and transferred to 100 ml volumetric flask and dissolved in ethanol. It was dissolved properly and diluted up to the mark with diluent to obtain final concentration of 1000ug/ml. 5ug/ml solution was prepared from the stock solution was prepared using diluent which was used as working std. Absorbance check by using UV spectroscopy at 295nm. 100mg+100ml ethanol→ 1mg/ml [1000ug/ml] 100ml→ 1ml→ 10ml diluted with ethanol(100ug/ml)

4.1.5 Melting point determination by using Differential Scanning Calorimetry:

Differential scanning calorimetry (DSC) experiments were conducted using a (METTELER TOLEDO DSC-1USA). Samples were heated from 20 to 240 °C at 10 °C min−1 under a 50 mL min−1 flow of N2 gas. Modulated temperature DSC analysis was conducted on the same instrument from 100 to 190 °C or 90 to 240 °C using a temperature ramp of 3 °C min−1 and a modulation period of 60 s. Data analysis was carried out using the TA Universal Analysis software.

4.1.6 Identification by FTIR spectroscopy:

Drug was identified using FTIR spectroscopy. The FTIR spectrum of the obtained drug sample was compared with that of standard FTIR spectrum for functional group of the pure Griseofulvin. Infrared spectroscopy was carried out using a Spectrum 100 FTIR spectrometer (Schimadzu 1800) over the range 650−4000 cm−1 with resolution 1 cm−1.

5. Characterization:

The surface morphology of the prepared NFs was evaluated by using scanning electron microscopy (FEI Nova Nano SEM 450 EDS: Bruker X Flash 6I30). A square shaped portion of NF was fixed onto the stubs with double-sided adhesive carbon tape; then the samples were subjected to coating with gold plasma sputter (Chessington Sputter Coater-108 Auto, Korea). The structural changes were observed through Fourier transform infrared spectroscopy (FT-IR) using Schimadzu 1800) over the range 650−4000 cm−1 with resolution 1 cm−1.

The solid samples were made with KBr pellet and scanned between 4000 & 400 cm−1 wave numbers with 20 fixed scan cycles at 4 cm−1 resolution.

Powder X-ray diffraction (XRD) was used to evaluate the crystalline nature of the samples by using (Bruker D8 VENTURE) diffractometer with Cu / 40 kV / 40 Ma.

The crystallinity changes in the prepared NFs were compared with the raw components by differential scanning calorimetry (METTELER TOLEDO DSC-1USA). Samples were heated from 20 to 240 °C at 10 °C min−1 under a 50 mL min−1 flow of N2 gas.

5.1 Drug content estimation:

Nano fibre were cut into 4 × 4 cm and taken in a 100ml standard flask Dissolved the

contents in ethanol solution continuous shaking in a shaker for 3 hours. After proper Dilutions the absorbance was measured at 291, 295 nm using a UV visible spectrophotometer.[16]

$$\%\text{Drug content} = \frac{Practical\ yield}{Theoretical\ yield} \times 100$$

5.2 Degree of swelling:

The solvent diffusibility in the NF polymer is well determined by the swelling index. The swelling nature of the GSF containing PVP NF was evaluated for 24 h with specific time intervals (2, 4, 6, 8 h) in phosphate buffer (pH 6.8) with 20% v/v ethanol. The experiment proceeded by immersing the mat into the medium, and taking out from the medium at the above said time intervals, and wiping the solvent on the surface. The degree of swelling was then calculated by the following [17]

$$\text{Swelling Index} = \frac{Wt - Wo}{Wo}$$

Where 'Wt' is the weight of swollen nanofiber at time 't' 'W0 ' is the weight of dried nanofiber

6. Transdermal patch preparation:

A rectangular aluminium foil of 4 cm × 4 cm was used as a backing membrane, and a same-sized plastic sheet membrane of 1.00 mm thickness was attached to this by an adhesive. Again, a plastic sheet of the same size and thickness of the former plastic sheet was taken, and cut to 1.5 cm × 0.75 cm size, and fixed with adhesive. The formulated NF was placed over this area, wrapped with a nylon mesh, and an aluminium foil was fixed over it, to act as a peel strip. The homogeneous patch film was thus formed. This patch was stored in a desiccator between the wax sheets and used for the further studies.[18]

Table 1: Preparation of Optimized Nanofiber

Std	Run	Factor 1 A: Drug mg	Factor 2 B: Polymer mg	Factor 3 C: Ethanol ml
4	1	30	560	10
1	2	20	500	10
8	3	30	560	20
7	4	20	560	20
3	5	20	560	10
2	6	30	500	10
5	7	20	500	20
6	8	30	500	20

Figure: 1 Preparation of Nf patch F1 batch

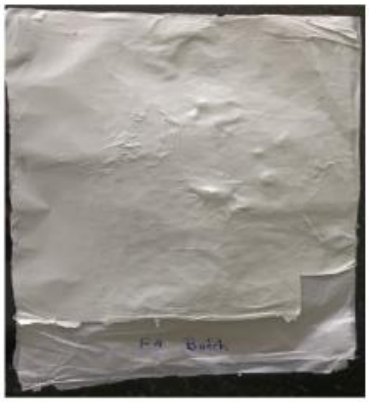

Figure: 2 Preparation of NF patch F2 batch

Figure: 3 preparation of NF patch F3 batch

Backing Membrane

NF loaded patch

Linear

Figure: 4 Formulation of Medicated NF

7. Evaluation methods for transdermal patch

7.1 Patch thickness:

The patch with nanofibers was measured for its thickness at three different spots using a digital micrometre (Mitutoyo Co., Japan). The least count of 0.001 mm was set in the digital micrometre prior to the each of the tests, and the average thickness was measured and the standard deviation calculated for the same, to ensure the thickness of the prepared patch.[19]

7.2 Weight uniformity:

Prior to the test, the above prepared patches were dried thoroughly at 60 °C for 4 h. The patch was then cut into different areas of equal size, and weighed in a digital balance. The average weight was calculated and the standard deviation was plotted from the individual weight. [20]

7.3 Folding endurance:

The folding endurance was measured manually for the prepared films. A strip of film (4 x 4 cm) was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance. [21,22]

7.4 Moisture content (%):

The moisture content of the prepared patches was determined by weighing

the patches individually, and placing in a desiccator containing the fused calcium chloride at room temperature. The desiccated patches were left undisturbed for 24 h, and then the patches were re-weighed for the presence of moisture. The following Eq. (3) was used to calculate the % moisture content.[23]

$$\% \text{ Moisture content} = \frac{patch\ wt\ initial - patch\ wt\ final}{patch\ wt\ final} \times 100$$

7.5 Tensile strength:

Tensile strength of the film was determined with Universal strength testing machine (Hounsfield, Slinfold, Horsham, U.K.). The sensitivity of the machine was 1 g. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (4 × 1 cm2) was fixed between these cell grips and force was gradually applied till the film broke 17, 24. The tensile strength of the film was taken directly from the dial reading in kg. Tensile strength is expressed as follows:[24]

$$\text{Tensile strength} = \frac{Tensile\ load\ at\ break}{Cross\ section\ area}$$

7.6 In vitro drug release studies:

In vitro skin permeation studies were performed by using a modified Franz diffusion cell with a receptor compartment capacity of 20 ml. The synthetic cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were cut into size of 4cmx 4cm and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH 6.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 37 ± 0.50C. The samples of 3 ml were withdrawn at time interval of 1, 2, 3, 4, and 5hr analysed for drug content spectrophotometrically at 295nm against blank. The receptor phase was replenished with an equal volume of phosphate buffer 6.4 at each time of sample withdrawal. The cumulative amounts of drug permeated per square centimetre of patches were plotted against time.[25]

8. Results and discussion

8.1 Preformulation Study

8.1.1 Physicochemical properties of drug:

8.1.2 Organoleptic Properties:

Griseofulvin was found to be White to pale cream-colored crystalline powder

8.1.3 Solubility study: Solubility of drug was observed in different solvents such as Ethanol, methanol.

8.1.4 Calibration Curve of GSF:

Regression ($R^{2)}$ of Pure API is Obtained 0.9991. It indicates that API (GSF) is 98% pure.

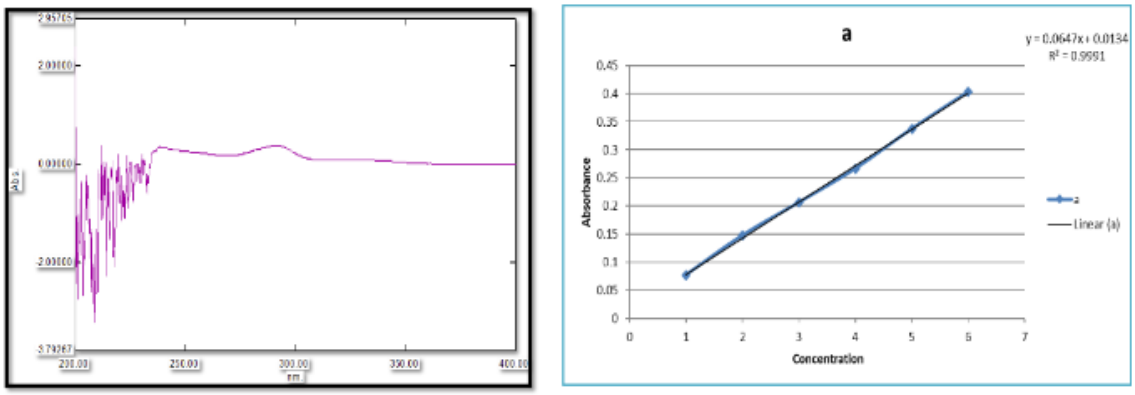

Figure: 5 Calibration curve of API by UV spectroscopy

8.1.5 Melting point determination by using Differential Scanning Calorimetry: Amorphous samples of the pure drugs were prepared for comparison purposes by loading a DSC pan with the drug and heating it above the API's melting point (at **221°C**). After DSC traces sharp peak is obtained It indicates that GSF has Crystalline in nature.

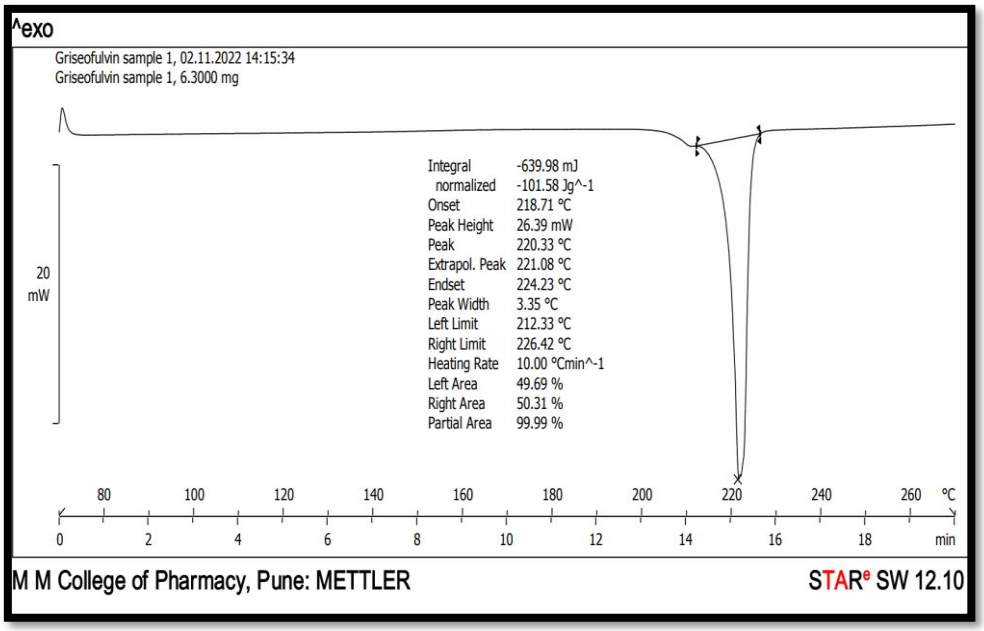

Figure: 6 DSC trace of API (GSF)

8.1.6 Identification by FTIR spectroscopy: Fig. GSF shows a number of bands in the carboxylate region, with particularly notable peaks at 1658.78, 1427.32, 887.26, 1344.30.

Table: 2 FTIR Stretches of API

Functional group	**Observed peak**
C=O stretch	1658.78
C-H stretch	1427.32
O-H bending	1344.30
C-Cl stretch	887.26

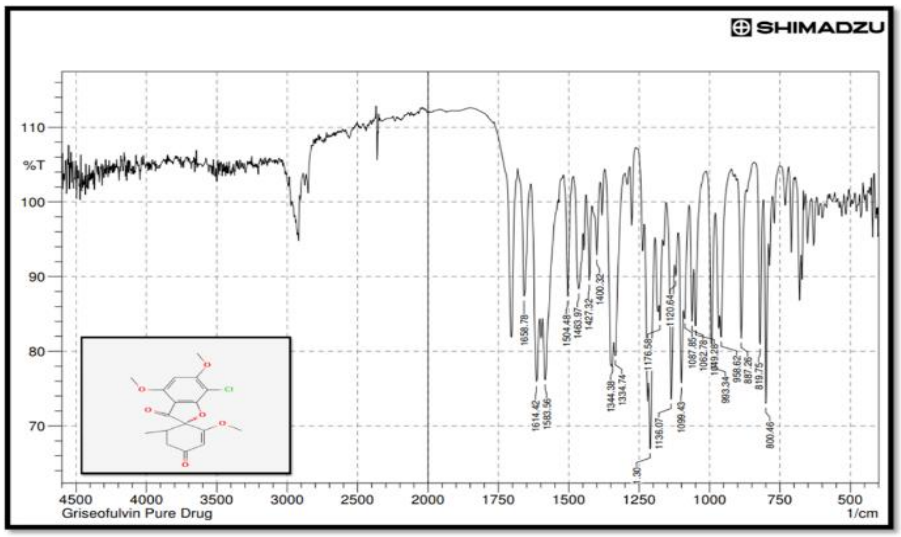

Figure: 7 FTIR Spectrum of API (GSF)

8.2 Preparation and morphology of nanofiber mats:

As per the previous works in the literatures, Ethanol as solvent have been used to successfully fabricate GSF loaded PVP k nanofibers, either individually, or in blends. The solvent composition used in the present work was a good solvent for both Drug and Polymer. After optimization of the process parameters, the final batch is obtained i.e. **F3.** And it leads to the thinner nanofiber [26,27].

As mentioned earlier, the PVP K (MW111.1418) is a water soluble polymer with good bio-stability. It is chemically stable, has low toxicity and is biocompatible. was added for the said purpose. In particular, the specific molecular weight was chosen to ideally moderate the release of GSF, because if the molecular weight or the concentration of the PVP increases, it will crystallize faster, along with insufficient interweaving during nanofiber formation. This leads to the faster erosion and dissolution of the PVP [28]. Generally, the polymer concentration plays a crucial role in the electrospinning process, because of the changes in the solution viscosity in different solvents [29]. The concentrations for PVP and GSF were empirically derived to obtain smoother and thinner nanofibers. Accordingly, the composite concentration was derived to fix at PVP K 5.6% with Ethanol 20%v/v solution and the GSF concentration was kept at 0.3% wt. towards the total polymers weight, since this concentration appeared to be morphologically ideal.

Fig. SEM Shows the characteristic morphological features of the prepared NFs with different composite compositions of PVPK with GSF.SEM of optimum batch obtained. As before, the fibres have uniform cylindrical morphologies, and there is no evidence for beading or the formation of API particles. GSF fibres are uniform in size. Although this solvent system permitted a higher GSF loading to be realised, the process was observed to be rather capricious with frequent needle clogging occurring, particularly with higher GSF concentrations. Details of these can be found in fig.2

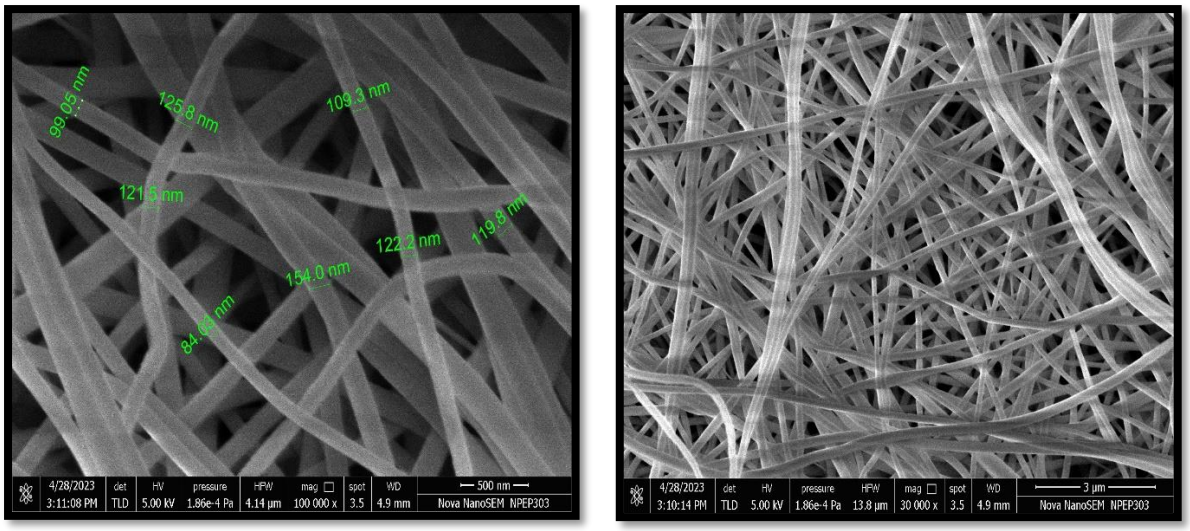

Figure 8: SEM images of prepared nanofibers with polymer composition with GSF.

As before, the fibres have uniform cylindrical morphologies, and there is no evidence for beading or the formation of API particles. All the fibre diameter was in the range of 80-200 nm. particularly with higher GSF concentrations. The flow rate was thus increased to 2 mL h-1 in the preparation of the final set of optimised fibres. SEM images are shown in Figure 7. [30]

8.3 FT-IR analysis:

GSF shows a number of bands in the carboxylate region, with particularly notable peaks at 1658.78, 1427.32, 887.26, 1344.30. the GSF bands are merged together with the PVP C=O peak in G5, with a main peak at 1658 – 1663 cm-1 and shoulders at 1614 and 1589 cm-1. In these Optimized NF patch Peaks are obtained as similar as GSF and PVP K-90 also. [31]

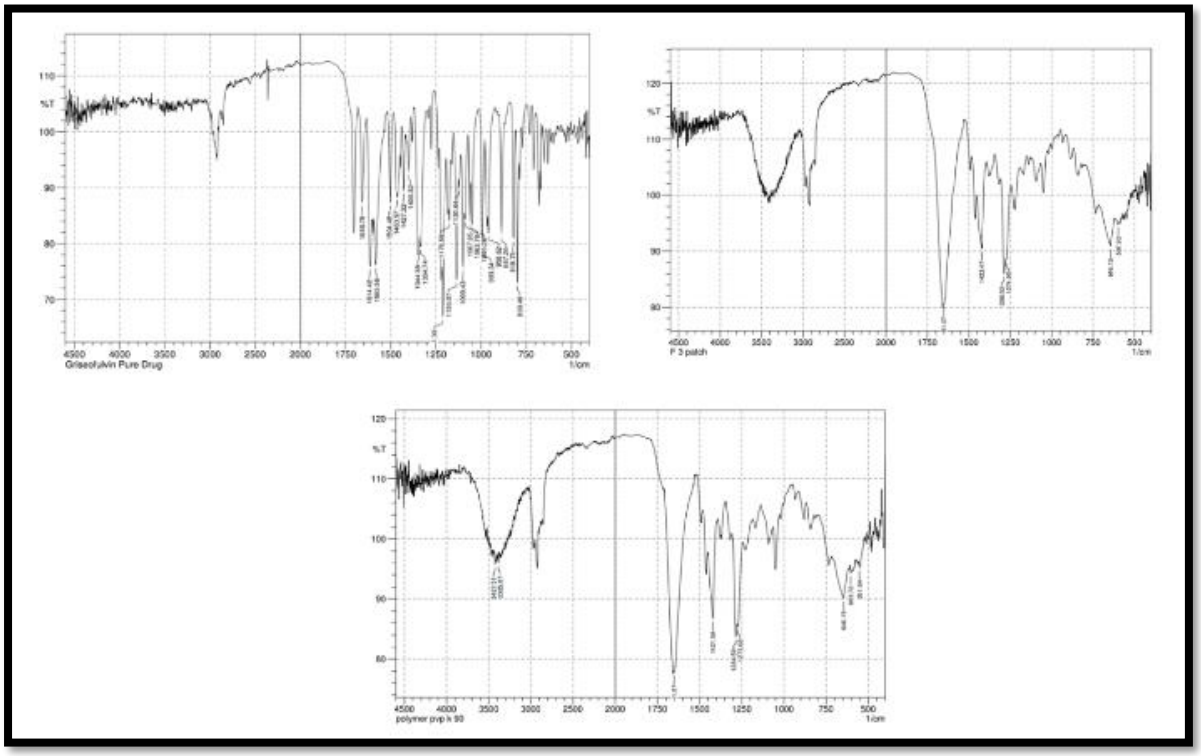

Figure: 9 IR spectrum of API (GSF), Polymer PVP K- 90 and NF formulation.

8.4 X-ray diffraction:

In the present study, essentially identical spectra were also obtained after they were melted, solidified, and pulverized. The presence of major griseofulvin diffraction peaks indicates that an crystalline form. Major X-ray diffraction peaks of griseofulvin, particularly at 10.76,13.22, 16.52,22.56 and 23.83. The API Griseofulvin shown peak at 2θ= 10.76˚c at the intensity of 3850, 2θ= 13.22˚c at the intensity of 3683, 2θ= 16.52˚c at the intensity of 7258.33, 2θ= 22.56˚c at the intensity of 5641.67, 2θ = 23.86˚c at the intensity of 3450. Formulation of nanofibrous patch shown peak at 2θ= 10.48˚c at the intensity of 483, 2θ= 13.26˚c at the intensity of 425, 2θ=16.32˚c at the intensity of 458, 2θ=22.94˚c at the intensity of 725, 2θ=26.68˚c at the intensity of 616.[32]

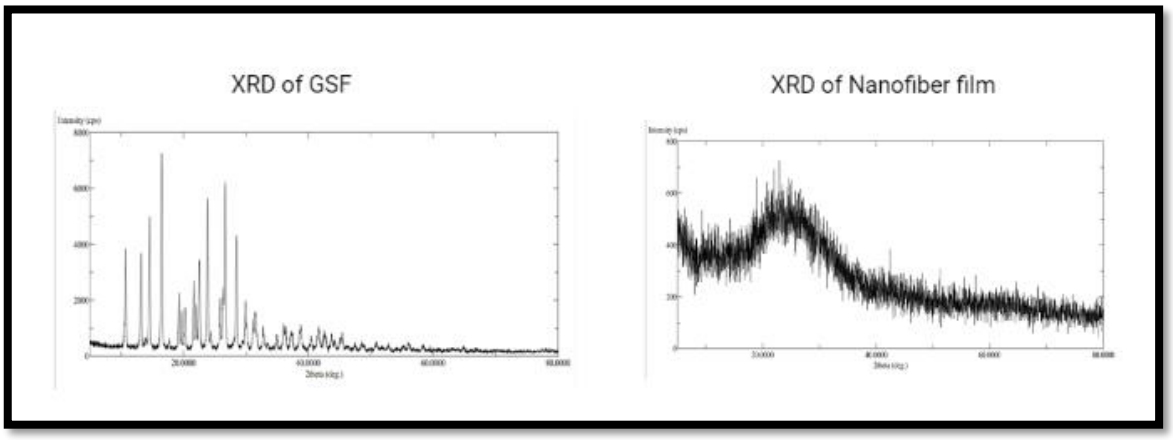

Figure: 10 XRD traces of GSF and PVP K -90 and GSF NF

8.5 Differential Scanning Colorimetry:

Fig. 7 shows the DSC traces of the polymer, GSF, Polymer API MIX, and NF. DSC data were also obtained after storage in a desiccator. Sharp Peak is obtained of API (GSF).The API obtained as crystalline in nature. DSC peak of Polymer + API obtained in amorphous nature It means there is change in both peaks.

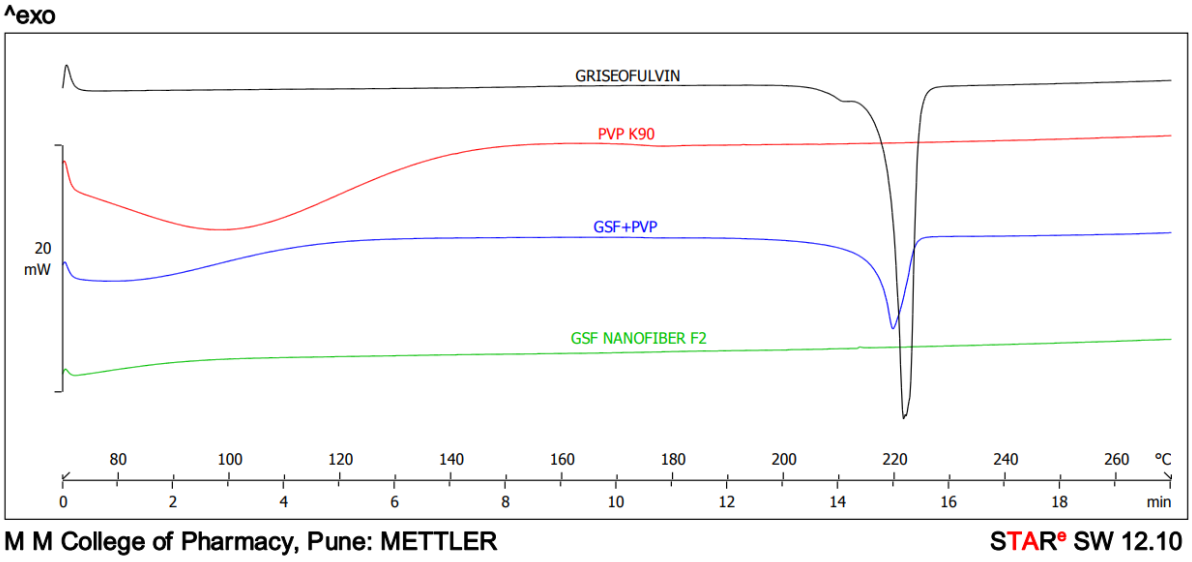

Figure:11 DSC traces of the polymer, GSF, Polymer API MIX, and NF.

8.6 Drug Content Estimation:

The percent drug content estimation of the prepared GSF loaded PVP K 90 NF was 92.2%. This higher drug content value was due to the passive drug loading onto the polymers, which was attributed to the high surface area, and consequently, the electrospinning process tightly solidifies the content, leading to drug entrapment within the fibre mat. This steep entrapment percentage contributes to the substantial flexibility and size reduction of the prepared NF mats.[16]

8.7 Degree of Swelling:

Table 2 shows the swelling pattern and its degree for prepared plain and drug-loaded NF. The release behaviour of the drug depends on the degree of swelling. The GSF-loaded PVP K 90 shows the maximum degree of swelling was obtained at 8 h. The weight gain was due to the engulfing of medium used within the pore generating PVP K 90.[17]

Table 3: A Degree of swelling with time and % weight change (Optimized batch)

Time (hr)	Swelling Index (%) F3
2	96.55%
4	109.28%
6	117.77%
8	141.37%

8.8 Evaluation of transdermal patch:

The optimized NFs were prepared as transdermal patches, and Table 2 shows its physical-chemical evaluation values. The minor difference in the patch thickness was due to the drug content in the NF, and the NF volume occupied in the patch. The folding endurance value was higher, which ensures higher mechanical stability and flexibility. The average weight uniformity of the patches was found to be 0.03 to 0.42gm with drug respectively. The mechanical stress resistance was ideal enough for the prepared patch, and was supported by the tensile strength The patches also showed greater bonding strength, which may provide ideal adhesion over the skin.

Table:4 Physical-chemical evaluation parameters and its obtained data for the prepared patches

S. No.	Evaluated Parameters	Obtained Results
1.	Patch thickness	0.06nm
2.	Weight uniformity	0.0321gm
3.	Folding endurance	262 ± 10a
4.	Tensile Strength	6.6kg/cm^2

8.9 In – Vitro Drug Release Study:

The profiling of in vitro diffusion studies is a vital tool for predicting the drug release in vivo in advance. Fig. 8 and 9 shows the release pattern of the in vitro skin permeation evaluations of GSF from the prepared transdermal patch of NF. The cumulative % release from the NF was **88.37%** for 5 h. The release kinetics observed in the drug permeation per square centimetre was found to be the Zero-order kinetics (r2 = 0.973). accorded with the in vitro diffusion profiles for the formulated patches. This indicates the diffusion mechanism was followed for the permeation of the drug from the patch and it **followed Zero- Order kinetics.**

Table: 5 Drug release kinetic study

Formulation	Mathematical Model R^2			
	Zero	First	Krosspeppas Model	Higuchi
F3	0.973	0.679	0.441	0.813

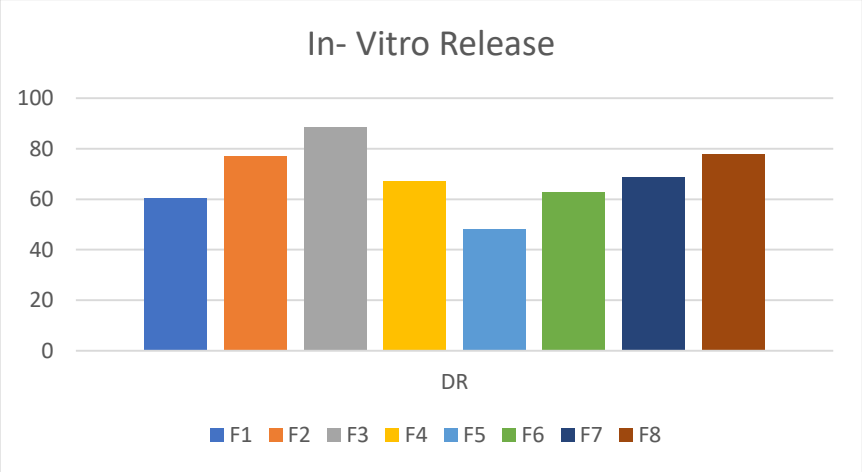

Figure: 12 In – Vitro release of F1-F8 batches

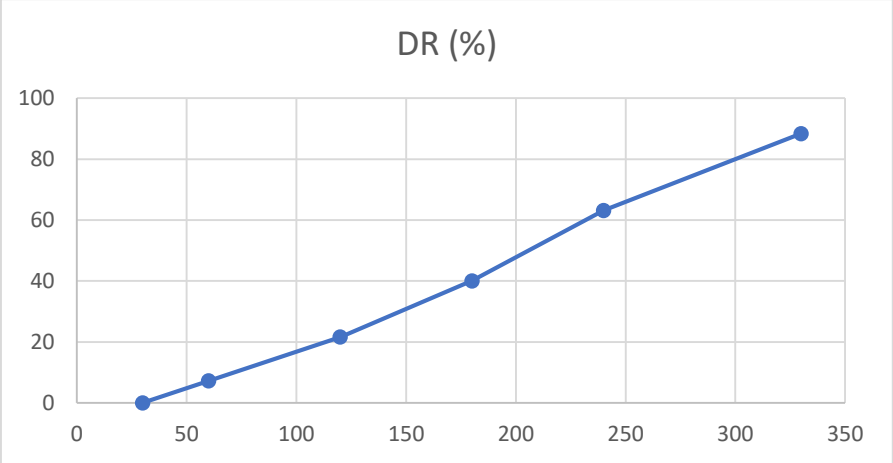

Figure: 13 In-vitro release of optimized batch F3.

9. Conclusion:

Electro spun fibres of poly(vinylpyrrolidone) and griseofulvin (GSF) were successfully prepared in this study. A GSF-loaded PVP K -90 polymeric composite NF patch was prepared and characterized in vitro for further suitability as once in a day transdermal drug delivery system for various types of wound applications. All the fibres prepared were smooth and cylindrical, The prepared GSF containing PVP K-90 composite NF mat showed an diameter of NF 84.03nm with 88.37% GSF drug release. FT-IR spectroscopy, differential scanning calorimetry, and Kinetic modelling showed that there were interactions between the drug and polymer with GSF. All the fibres were found to release the drug very rapidly, demonstrating accelerated dissolution over the pure drug. PVP K-90 showed good

morphology and narrow size distribution. The results of evaluation of the transdermal nanofiber patch also showed that the formulated nano fibre mats with the specific polymeric and drug ratios were sufficient to hybridize the prepared NFs as transdermal patches.

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Conflict of interest

This declaration is not applicable.

Financial support

This declaration is not applicable.

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