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ORIGINAL ARTICLE

Fabrication of electrospun nanofibres of BCS II drug for enhanced dissolution and permeation across skin

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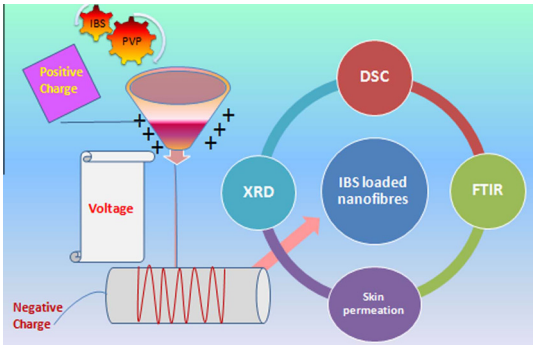
GRAPHICAL ABSTRACT



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ABSTRACT

The present work reports preparation of irbesartan (IBS) loaded nanofibre mats using electrospinning technique. The prepared nanofibres were characterized by scanning electron microscopy, Fourier transform infrared spectroscopy, differential scanning calorimetry, X-ray diffraction analysis, *in vitro* diffusion and *ex vivo* skin permeation studies. FTIR studies revealed chemical compatibility of IBS and polyvinyl pyrrolidine (PVP K-30). SEM images confirmed formation of nanofibres wherein IBS existed in amorphous form as revealed by DSC and

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XRD analyses. The prepared nanofibre mats of IBS were found to be superior to IBS loaded as cast films when analysed for *in vitro* IBS release and *ex vivo* skin permeation studies since the flux of IBS loaded nanofibres was 17 times greater than as cast film. The improvement in drug delivery kinetics of IBS loaded nanofibres could be attributed to amorphization with reduction in particle size of IBS, dispersion of IBS at molecular level in PVP matrix and enormous increase in the surface area for IBS release due to nanonization. Thus transdermal patch of IBS loaded nanofibres can be considered as an alternative dosage form in order to improve its biopharmaceutical properties and enhance therapeutic efficacy in hypertension.
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Introduction

One of the commonest disorders responsible for cardiovascular mortality and morbidity in large population is hypertension [1]. Various routes including oral and parenteral are reported for delivery of drugs to the patients suffering from hypertension. In most of the cases, oral route is preferred over any other routes of drug delivery owing to its advantages such as ease of administration and patient compliance. However, the oral drug delivery system also proposes drawbacks such as uneven biodistribution of drug, lack of drug targeting and specificity, requirement of large doses in order to achieve therapeutic plasma drug levels and adverse side effects associated with such high dose. The transdermal route of drug administration can deliver drugs locally as well as into the systemic circulation. Thus it is recognized as one of the potential routes of drug delivery. Owing to the advantages such as bypassing first pass effect, sustained drug release, reduced side effects with frequency of drug administration and patient compliance, transdermal drug delivery systems have attracted most of the researchers [2].

Irbesartan (IBS) is BCS II drug with low solubility and high permeability. It is primarily used for the treatment of cardiovascular diseases including hypertension, cardiac insufficiency and cardiac arrhythmia [3,4]. It is an angiotensin II receptor type 1 antagonist and also reported to delay progression of diabetic nephropathy. Moreover, it is also indicated for the reduction of renal disease progression in patients with type II diabetes. However, its low solubility and in turn bioavailability act as a hurdle in development of dosage form. Additionally, it shows side effects such as the gastric irritation, stomach upset when administered orally. Thus various approaches for solubility enhancement of irbesartan have been reported which include formulation of nanocomposites [5], solid dispersions [6], self emulsifying systems [7] and β, γ-cyclodextrin complexes [8,9]. There is lacuna in the literature on the preparation of IBS-loaded transdermal nanofibre mats to enhance its dissolution and permeation across the skin.

Formulation scientists have been working on development of drug loaded nanofibres since they offer advantages such as high ratio of surface area to mass or volume, high porosity and extremely small pore size within fibres. Further, nanofibres can be useful in targeting drug molecules to specific sites since they present large possibilities for surface functionalization. Electrospinning has been used most commonly to produce drug loaded nanofibres owing to their advantages such as simple and continuous technique having ability to produce nanofibres from a large variety of polymers with an ability of industrial scale-up [10]. In the electrospinning process, a sufficiently high voltage is applied to a liquid droplet containing polymer inducing the charge (positive or negative) in the same. The droplet is stretched due to attraction by the oppositely charged collector thus forming a stream of liquid from the surface at a critical point which is known as the Taylor cone. The charged liquid jet dries in flight leading to formation of fibres which are collected on the rotating drum (collector) [11].

Considering the drawbacks associated with irbesartan and the superiority of transdermal drug delivery, formulation of irbesartan loaded nanofibre mat having an ability to provide optimum amount of drug to control the disease condition with minimum side effects is the need of hour. Further, it is believed that such system can also lead to cost effectiveness of healthcare treatment for long-term management of hypertension [12,13]. In current work, irbesartan loaded nanofibres of polyvinyl pyrrolidone (PVP) were prepared using electrospinning technique and characterized for drug content, FTIR, DSC, morphology, XRD, *in vitro* diffusion and *ex vivo* permeation studies using Franz diffusion cell.

Material and methods

Materials

Irbesartan was generously gifted by Lupin Research Park, Pune, India. Polyvinyl pyrrolidone (PVP K-30) was purchased from Loba chemi, Mumbai, India. Methanol and N, N-dimethylacetamide (DMAc) were purchased from S.D. Lab and Labscan (Asia), Mumbai, India, respectively.

Methods

Preparation of spinning solutions

An accurately weighed PVP powder was dissolved in methanol/DMAc (3:1 v/v) mixture to obtain a PVP solution (15% w/v). Irbesartan (20% by weight of dry PVP) was added into the base PVP solution under constant stirring for 4 h at 200 rpm (Heidolph mixer RZR 2051 control, Heidolph India, Hyderabad, India).

Preparation of nanofibres

The prepared solutions were loaded in 5 mL syringe with 18 gauge needle (Resource Pharmaceuticals, Vadodara, India). The feeding rate (0.5 mL/h) was controlled by a syringe pump. A high voltage supply fixed at 12 kV was applied to the metallic needle. A piece of aluminium foil kept at horizontal

distance of 15 cm from the needle tip was used to collect the ultrafine fibres. The electrospinning process was carried out under ambient conditions using an instrument E-Spin Nano (PECO-Chennai, India). IBS loaded PVP films were also prepared for comparison using solutions of similar composition by solvent casting technique.

Characterization

Drug content and encapsulation efficiency (EE)

UV spectrophotometric method was used for quantification of IBS loaded into PVP nanofibres and solvent cast films. To describe in brief, the IBS loaded e-spun PVP fibre mats and as cast IBS loaded films (cut into circular discs of 2.8 cm in diameter) were dissolved in 5 mL of methanol separately. The volume of each of the solution was made up to 10 mL with 7.4 pH phosphate buffer. Absorbance of each solution was recorded at 224 nm using a UV spectrophotometer (Shimadzu UV-1601, Kyoto, Japan) in order to obtain exact IBS content. The results of drug content were used for determination of EE using Eq. (1) [14]

$$\%\mathrm{EE} = \frac{\text{Weight of irbesartan in the nanofibre mat or film}}{\text{Total weight of irbesartan feeded}} \times 100 \tag{1}$$

Scanning electron microscopy (SEM)

Scanning electron microscope (JEOL JSM-6360A, Tokyo, Japan) was used to characterize morphology of both neat and IBS loaded e-spun PVP fibre mats along with solvent cast film separately. The fibre mat or film was mounted on aluminium stud separately and sputtered with a thin layer of platinum using auto fine coater (Joel, JFC, Tokyo, Japan) prior to observation. The average diameter of IBS loaded e-spun mats was measured.

Differential scanning calorimetry (DSC)

Thermal behaviour of IBS, neat e-spun PVP mats and IBS loaded nanofibre mats was analysed using a differential scanning calorimeter (Mettler Toledo DSC 821e, Mettler-Toledo, Greifensee, Switzerland). The samples (10–20 mg) were hermetically sealed in aluminium crucibles separately and heated at a constant rate of 10 °C/min over a temperature range of 25–300 °C [15]. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 mL/min.

X-ray diffraction (XRD) analysis

Wide-angle X-ray diffraction analyses (XRD) of IBS alone, IBS loaded nanofibre mats and IBS loaded as cast films were carried out separately using a D/Max-BR X-ray diffractometer (RigaKu, Tokyo, Japan). The samples were irradiated with Cu Kα radiation and analysed in the 2θ range of 5–60°.

Fourier transform infrared spectroscopy (FTIR)

IBS alone, blank PVP nanofibres, IBS loaded nanofibre mats and IBS loaded as cast films were analysed by Fourier transform infrared spectroscopy (FT/IR4100, JASCO International Co., Ltd., Tokyo, Japan). The samples were mixed with dry potassium bromide (2 mg sample in 200 mg KBr) and placed in the mould. The IR spectra for the samples were recorded in region from 4000 to 400 cm^{-1}.

In vitro drug diffusion studies

In vitro drug diffusion studies for dry IBS loaded nanofibre mat and as cast film samples were performed using Franz diffusion cell (Dolphin Instruments, Mumbai, India) with a reservoir capacity of 32 mL. Each of the samples was cut into circular discs of ~1.5 cm in diameter containing 50 mg of IBS. The disc was placed in a donor compartment over the cellophane membrane and covered with parafilm. The temperature of the receptor compartment containing phosphate buffer pH 7.4 was maintained at 37 ± 2 °C throughout the experiment. The amount of IBS diffused through the membrane was determined by withdrawing 1 mL of buffer from the receptor compartment at a predetermined time interval and replacing an equal volume of buffer thus ensuring sink condition throughout the experiment. The samples were filtered through Whatman filter paper and analysed spectrophotometrically at 224 nm for IBS content.

Ex vivo skin permeation studies

Ex vivo skin permeation studies were performed for IBS loaded nanofibre mat and as cast film samples using Franz diffusion cells fitted with excised rat skin [16]. Hairs on the abdominal area of Wistar rat were shaved after its sacrification by chloroform inhalation method. The subcutaneous tissue was surgically removed from the skin upon excision from the abdomen of the rat. Further, isopropyl alcohol was used for wiping the dermis side of the skin so as to remove the residual fat on its surface. Distilled water was then used for washing the skin followed by treatment with 2 M sodium bromide solution for 7 h. Finally, a cotton swab moistened with distilled water was used for separating epidermis which was cleaned by washing with distilled water. The skin thus obtained was used for permeation studies. *The experimental protocol was approved by the Animal Ethics Committee of Bharati Vidyapeeth University, Poona College of Pharmacy, Pune (Approval no.: CPCSEA/13P/2014)*. A vertical Franz diffusion cell having a surface area of 2.54 cm^2 and a reservoir capacity of 32 mL was used. The receptor compartment was filled with phosphate buffer pH 7.4 which was constantly stirred using magnetic stirrer throughout the experiment. The temperature of the buffer was maintained at 37 ± 1 °C. IBS loaded nanofibre mats, as cast films (IBS equivalent to 50 mg) and irbesartan alone (50 mg) were applied on the epidermal surface of the skin separately. A media sample (2.5 mL) was withdrawn at a fixed time intervals. Sink condition was maintained throughout the experiment. The samples were filtered through Whatman filter paper and analysed for IBS content using HPLC method upon appropriate dilution. HPLC was used for quantification of IBS because some of the skin components show absorbance at 224 nm which may interfere with the results.

The HPLC system consisted of a chromatographic pump (LC-20AT, Shimadzu, Kyoto, Japan) fitted with a UV detector. For HPLC separation, a reversed-phase C18 column (4.6 × 150 mm, micelle size 5 µm, Thermo Scientific, Massachusetts, United States) was used. The mobile phase was composed of acetonitrile: ammonium acetate buffer (pH 5.5) in a ratio of 30:70 with a flow rate of 1.5 mL/min. The run time for analysis was 10 min and the detection wavelength was

set at 235 nm. The mobile phase was filtered through 0.45 μm millipore membrane filter and degassed by sonication (Bransonic, CT, USA) before use. The sample injection volume was 20 μL. The retention time of IBS was found to be 7.2 min [17].

The cumulative amount of IBS permeated across skin (μg/cm^2) was plotted against time (min). The steady state flux "J" (mcg cm^{-2} h^{-1}) was determined from the slope of the linear portion of the graph. Permeability Coefficient "Kp" (cm h^{-1}) was calculated using Eq. (2),

$$Kp = J/C_0 \quad (2)$$

where C_0 = concentration of drug in donor phase and J = flux.

Results and discussion

The utility of water soluble polymers in enhancing solubility of water insoluble drugs has been well documented in the literature. It is believed that these polymers act as stabilizers and modify the surface of precipitated particles by hindering their growth and preventing agglomeration. Various water soluble polymers including HPMC, polyethylene glycols, cyclodextrins and polyvinyl pyrrolidone (PVP) have been used for solubility enhancement of poorly water soluble drugs [18]. In the present work, PVP was used for preparation of nanofibres owing to its inherent properties such as excellent physiological compatibility, and reasonable solubility in water along with other organic solvents. Further, in the preliminary studies, PVP was found to be effective in controlling the particle size and particle size distribution of IBS.

The solvent plays a key role in the successful preparation of electrospun nanofibres. The solvent should dissolve the drug easily while keeping electrospinnability of polymer solutions intact. Amongst several individual and combinations of organic solvents screened for solubilization of IBS and PVP, a mixture of methanol and DMAc was found to be suitable. Moreover, it was observed that the electrospinning process always proceeded uninterrupted when using this mixture which could be attributed to the high boiling point of DMAc favouring formation of a stable Taylor cone and preventing spinneret clogging through prevention of gel-formation at the jet surface [19]. Thus the current work involved preparation of IBS loaded PVP nanofibres using electrospinning method. The prepared fibres were investigated for morphology and dimensions.

SEM of IBS loaded PVP fibre mats

SEM was used in order to confirm formation of nanofibres (Fig. 1). SEM images revealed formation of discrete IBS loaded PVP nanofibres having size in the range of 60–80 nm. Since the images did not show the presence of the drug crystals and/or aggregates it is postulated that the drug was encapsulated and molecularly dispersed within the electrospun fibres. This is in contrast to the IBS loaded solvent cast film which showed the presence of drug crystals on its surface. The non-existence or the existence of the drug aggregates on the surface of the fibres or films could also be due to the difference in the evaporation rate of the solvents (methanol and DMAc) during fabrication. The evaporation of the solvents from the fibres occurred in an extremely short time (i.e. during their flight to the collecting device). On the other hand, the evaporation of the solvent from the films occurred slowly. The longer time for evaporation of the solvent from the drug-loaded as cast films could be responsible for the observation of the drug aggregates on their surface [20].

X-ray diffraction studies

X-ray diffraction analysis of the prepared samples was performed in order to assess the polymorphic transitions (if any) that might have been taken place in IBS when formulated as nanofibres. Further, XRD patterns can also be used to evaluate the degree of crystallinity of sample using the relative integrated intensity of reflection peaks in the given range of reflecting angle 2θ.

XRD patterns of IBS alone, as cast film and IBS loaded nanofibres are shown in Fig. 2. The XRD pattern of IBS alone exhibits intense peaks at 2θ angles of 4.97°, 9.35°, 12.41°, 16.92°, 19.30°, and 23.05° which reveal its crystalline nature [21]. However, diffractogram of IBS loaded nanofibres showed broad and diffuse maxima peaks which may be attributed to the amorphization of IBS when formulated as nanofibres. It has been well reported that the amorphous solid state of a compound possesses several advantages including enhanced solubility, improved wettability and increased dissolution rate to its crystalline counterpart. IBS loaded as cast films retained the peaks which were attributed to the crystalline IBS indicating existence of IBS in crystalline form.

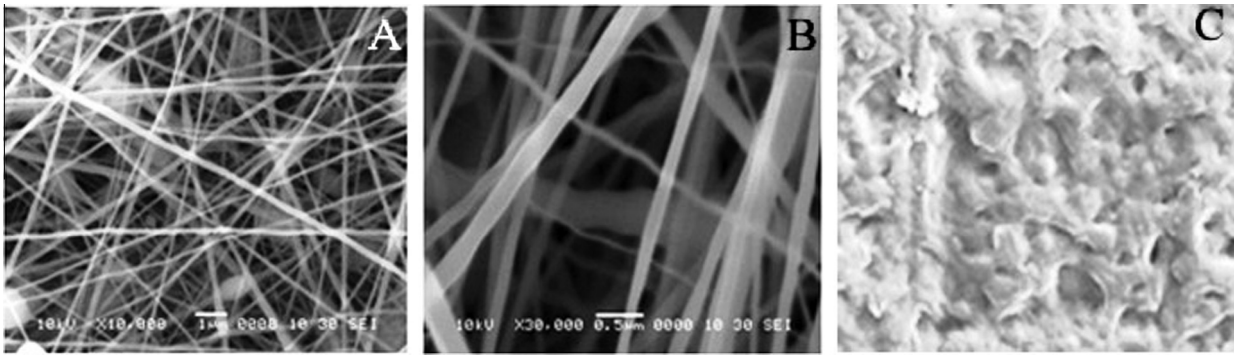

Fig. 1 SEM images of (A) IBS loaded nanofibres at 10,000×, (B) IBS loaded nanofibres at 30,000× and (C) IBS loaded solvent-cast films at 10,000×.

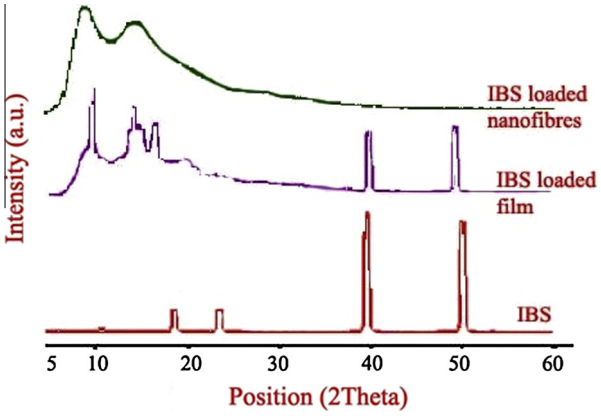

Fig. 2 XRD analysis of irbesartan, irbesartan loaded nanofibres and as cast films.

Differential scanning calorimetry (DSC)

DSC thermograms of prepared samples supported the results of XRD studies (Fig. 3). DSC is a tool used to measure the temperature and energy variation involved in the phase transitions of the compound which in turn helps to reveal degree of crystallinity associated with it. IBS alone showed sharp endothermic peak at 188.9 °C (with an enthalpy of 97.3 J/g) corresponding to its melting point confirming its crystalline nature. The DSC thermogram of PVP K-30 showed a broad endotherm at 92.62 °C which is indicative of loss of water by extremely hygroscopic PVP polymer chains.

IBS loaded as cast film showed melting endotherms at 90.13 °C and 184.7 °C which is self indicative of existence of IBS in crystalline form and the result was in accordance with XRD analysis. However, IBS loaded nanofibre mat showed a single endothermic peak at 91.52 °C. Additionally, peak associated with IBS melting point was absent indicating its complete amorphization when formulated as nanofibres [22]. Thus results of DSC studies were in accordance with the XRD analysis.

Fourier transformed infrared spectroscopy (FTIR)

FTIR spectra were recorded for IBS alone, IBS loaded as cast films and IBS loaded nanofibres (Fig. 4). IBS alone showed

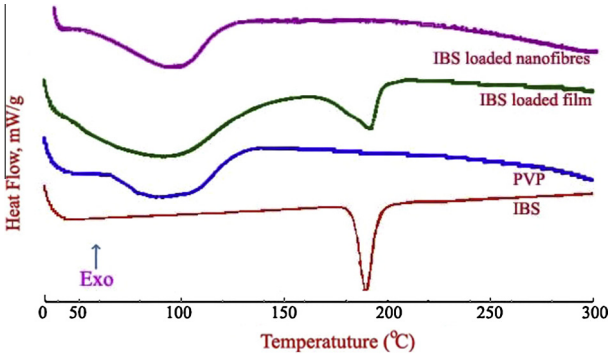

Fig. 3 Differential scanning calorimetric thermograms of irbesartan, PVP-K30, IBS-loaded as cast film and nanofibres.

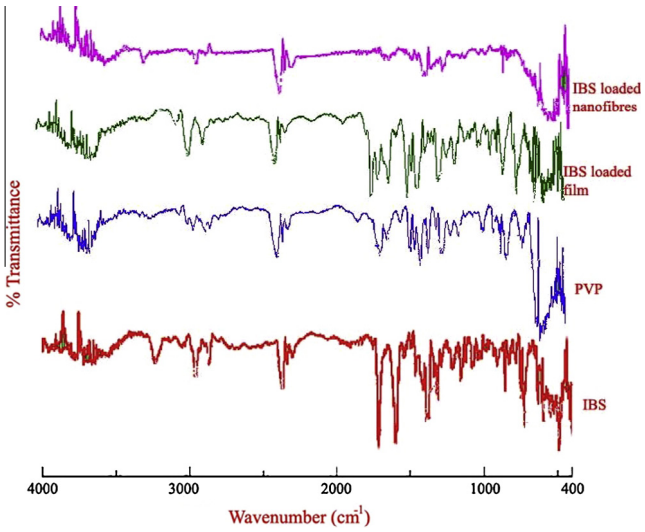

Fig. 4 FTIR spectra of (A) irbesartan, (B) PVP, (C) IBS-loaded nanofibre mats and (D) IBS-loaded as-cast films.

sharp characteristic bands at 3436.51 cm^{-1} (N—H stretching), 2960.52 cm^{-1} (C—H stretching), 1733.30 cm^{-1} (C═O stretching), 1485.77 cm^{-1} (C═C stretching) and 1614.83 cm^{-1} (N—H bending). The IR spectrum of PVP K-30 showed characteristic bands at 3435 cm^{-1} (O—H), 2955 cm^{-1} (C—H stretch) and 1654 cm^{-1} (C═O) [23,24].

The spectra of IBS loaded nanofibres and as cast film showed retention of all the characteristics bands of IBS and PVP. Further, there was no predominant shifting of existing bands or appearance of new bands suggesting compatibility of IBS with PVP due to the absence of any chemical interaction.

Drug content and encapsulation efficiency

IBS content in the prepared e-spun PVP nanofibres was found to be 82.62 ± 2.1%w/w whereas solvent cast films showed IBS loading of about 64.8 ± 1.21%w/w. Additionally, the EE of e-spun PVP nanofibres was found to be 97.13 ± 1.38%w/w whereas solvent cast films showed EE of about 78.8 ± 2.13%w/w. The films were casted at higher temperature (70 ± 1 °C) so as to remove the solvent completely. It is well reported in the literature that IBS degrades at high temperature. Such thermal degradation of IBS might have been responsible for reduction in the drug content of solvent cast films [17].

In vitro IBS diffusion studies

The IBS release from the nanofibre mats and as cast film was performed in phosphate buffer pH 7.4 and compared to release curve of IBS powder (Fig. 5). IBS loaded e-spun nanofibre mat showed 89.91 ± 1.87% release after 4 h whereas the as cast film showed IBS release of about 71 ± 1.6% after 8 h. Diffusion of IBS alone was found to be 32 ± 1.24% after 8 h confirming its low solubility in phosphate buffer pH 7.4.

The slower rates and the lower maximum amount of IBS released from IBS loaded as cast films in comparison with those from the nanofibre counterparts could be attributed to

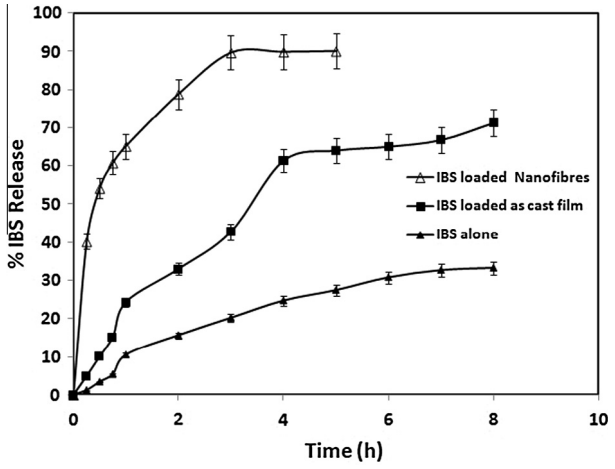

Fig. 5 *In vitro* diffusion study of IBS loaded nanofibres and as-cast films.

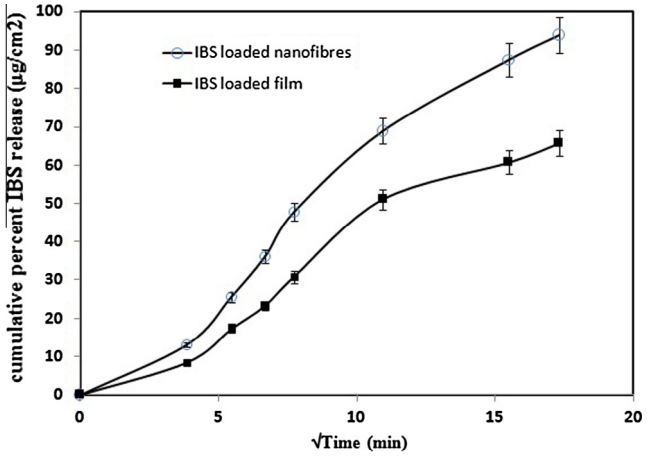

Fig. 6 Skin permeation profile of IBS-loaded nanofibres and as-cast films.

the crystalline nature of IBS and slow swelling of the PVP films. The slow swelling of film resulted in slow diffusion of IBS from the polymer matrix. Additionally, IBS aggregates were formed on the film surface which might have dissolved to a lesser extent. On the contrary, nanofibres contained non-aggregated IBS in amorphous state which has been reported to have high solubility than crystalline form. The enormously increased surface area for dissolution, amorphization of IBS and the absence of IBS aggregates might be responsible for the improvement in the diffusion of IBS when formulated as nanofibres. The analogy of drug diffusion through swollen polymer matrix was confirmed from the IBS release curves of nanofibres mats and as cast films. The curves were subjected to model fitting consisting of various models such as zero order, first order, Higuchi, Hixson–Crowell and Korsmeyer–Peppas model [25]. Both the release curves followed Kormeyer–Peppas model ($R^2 = 0.998$) which express diffusion controlled release of drug as expressed by Eq. (3) confirming diffusion of IBS through swollen polymer matrix as suggested previously [26].

$$Q = kt^n \quad (3)$$

Table 1 Skin permeation kinetics of irbesartan from IBS loaded nanofibre mats and as cast PVP film.

Formulation	IBS loaded nanofibres	IBS loaded solvent cast films
Flux	5.01 ± 0.38	0.301 ± 0.23
Permeability	0.00482	0.000588

Mean ± SD.

where Q is the percentage of drug released at time t, k is a kinetic constant and n is the diffusional exponent indicative of the release mechanism. When the value of $n = 0.5$ indicates Fickian diffusion, values below 0.5 suggest non-Fickian transport of drug.

The diffusion exponent 'n' was 0.5003 and 0.3237 for IBS loaded nanofibres and as cast film respectively. The 'n' value for IBS loaded nanofibre mats indicates that the IBS release follows Fick's law of diffusion. Drug release from as cast film was likely to be controlled by a combination of diffusion and erosion mechanisms [26]. Permeation of the drug from a transdermal drug delivery system mainly involves the factor of diffusion.

Ex vivo skin permeation

The *ex vivo* skin permeation data revealed superiority of IBS loaded nanofibres mats over as cast films (Fig. 6, Table 1) since the flux of nanofibres mats was 17 times greater than that of as cast film. Further, the permeability coefficient was also found to be greater for nanofibres as compared to the films. The superiority of nanofibre mats over as cast films may be attributed to the solubility improvement of IBS due to molecular dispersion within PVP, fast swelling of porous nanofibres mats due to small size and enormous increase in the area ultimately leading to leaching out of IBS molecules at a faster rate when compared to as cast films. Additionally, linear increment in the permeation flux with increase of IBS in both IBS loaded nanofibre mats and as cast PVP films was observed. This may be attributed to the reduction in the relative amount of polymer which acts as a diffusion barrier for IBS resulting in increased IBS release. Thus the higher concentration gradient provided the greater permeation of IBS from the nanofibre mats.

Conclusions

In the present work, IBS loaded nanofibre mats were successfully prepared using electrospinning technique. The prepared nanofibre mats of IBS were found to be superior to IBS loaded as cast films when analysed for *in vitro* IBS release and *ex vivo* skin permeation studies. The improvement in drug delivery kinetics of IBS loaded nanofibre mats could be attributed to amorphization with reduction in particle size of IBS, dispersion of IBS at molecular level in PVP matrix and enormous increase in the area for IBS dissolution due to nanonization as revealed by SEM, XRD and DSC studies. Hence, transdermal patch of IBS loaded nanofibres can be considered as an alternative dosage form in order to improve its biopharmaceutical properties and enhance therapeutic efficacy in hypertension.

Conflict of Interest

The authors have declared no conflict of interest.

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