Scientific paper

Ibuprofen Loaded Electrospun Polymeric Nanofibers: A Strategy to Improve Oral Absorption

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Abstract

The poor aqueous solubility of candidate drugs has presented a great challenge to formulation scientists for their effective oral delivery. Poor solubility is often associated with poor dissolution behavior and, subsequently, poor bioavailability for those drugs when intestinal absorption is dissolution rate limited. In the present study electrospun polymeric nanofibers were developed to address the poor aqueous solubility of ibuprofen, a Biopharmaceutic Classification System (BCS) class-II drug. Hydrophilic spinnable polymers like polyvinyl pyrrolidone were deployed as a carrier system for the fabrication of nanofibers. The electrospinning parameters like flow rate, voltage, and spinneret to collector distance were optimized. The fabricated ibuprofen-loaded nanofibers were characterized using scanning electron microscopy and differential scanning calorimetry. Drug release studies and ex vivo intestinal absorption studies were also carried out. The nanofiber-based platform significantly improved in vitro absorption of ibuprofen compared to pure ibuprofen crystals.

Keywords: Electrospinning; Nanomedicine; Bioavailability; Absorption; Ibuprofen.

1. Introduction

Effective delivery of active ingredients (APIs) to the target site at the desired concentration and rate is of paramount importance in systemic drug therapy. Poorly soluble drug candidates continue to pose challenges to their optimal administration and have therefore drawn the attention of researchers around the world.[1–5] Poor water solubility of drug molecules often limits gastrointestinal absorption and hence oral bioavailability, leading to therapeutic failure. The aggressive research efforts to provide solutions to drug insolubility problems are evident from the abundance of literature available.

Based primarily on the physicochemical properties of the active ingredients, a diverse strategy for active ingredient delivery has been proposed to increase the solubility and/or the rate of dissolution of such molecules.[6] These fascinating techniques include chemical modification,[7] co-crystals,[8] micro- / nanonization,[3,5,6] polymorphic improvements,[9] lipid-based systems,[6,10] micellar solubilization including self-emulsifying drug delivery systems,[11] inclusion complexes,[12–15] amorphous solid dispersion/solution[16–18] etc. In addition, nanotechnology has provided solutions for improving the solubility and/or bioavailability of active ingredients.[19–23] Among all of these available techniques, strategies involving the development of amorphous solid drug products have received much attention in the recent past due to the tremendous improvement in the solubility of drug candidates under this approach.[3,19] Electrospinning is widely used by pharmaceutical researchers to deliver a wide variety of active ingredients to treat various disease states. The very efficient amorphization effect of electrospinning is based on the immediate evaporation of the solvent, which leads to a solid solution of the active ingredient in the polymer matrix.[24] Amorphous solid dispersions based on electrospun fibers can retain an incorporated active substance in the amorphous physical form for longer periods due to their homogeneous distribution of active substances within the matrix and the possibility of inhibiting molecular mobility, which leads to impaired devitrifica-

tion. In an attempt to improve the dissolution of ibuprofen, a co-axial solid core spinneret-based electrospinning method was adopted and the dissolution was reportedly improved drastically.[25] The objective of the study was mostly to characterize the fast dissolution of the cargo molecule.

In the present study, attempts were made to explore a convenient and efficient electrospinning approach to amorphizing ibuprofen (a poorly soluble drug candidate) to improve its oral absorption.

2. Materials and Methods

2. 1. Materials

Ibuprofen was obtained as a gift sample from Cipla Ltd (Mumbai, India). Polyvinylpyrrolidone K30 (CAS Number-9003-39-8; PVP K30, MW= about 40,000 g/mol), and ethanol (analytical grade) were obtained from Sigma-Aldrich Corp (India). All other chemicals used were of analytical grade and procured locally.

2. 2. Fabrication of Nanofibers

The ibuprofen loaded PVP-based nanofibers and only PVP nanofibers were prepared by electrospinning equipment (Super ES 2; E-Spin Nanotech, India). The nanofibers were electrospun from 8% (w/v) PVP solution with or without 2% (w/v) ibuprofen at an applied DC voltage of 12 kV. The working solution was initially stirred magnetically for 2–3 h to completely dissolve PVP in ethanol. Subsequently, ibuprofen was added to the polymer solution and stirred for another 1 h to completely dissolve the drug. This solution was then electrospun at a flow rate of 2.0 ml/h using a syringe pump. The spinneret-to-collector distance was fixed at 15 cm and a plate collector was used for the collection of the nanofibers. The spinning parameters were optimized after the trial batches.

2. 3. Scanning Electron Microscopy

The fiber morphology and diameter were analyzed using a scanning electron microscope (SEM). Samples were coated with 20 nm of gold under a vacuum using a sputter coater. All micrographs were taken at an acceleration voltage of 5 kV. The secondary electrons were detected using an Everhart-Thornley detector.

2. 4. X-ray Diffraction Studies

The samples of nanofibers and raw ibuprofen were assessed for crystallinity using an X-ray diffractometer (Model: SEIFERT, C-3000, Germany) using Nickel-filtered CuKa radiation (k = 1.54 A˚). The voltage and current were 35 kV and 30 mA, respectively, and smoothed 95. Measurements were carried out in the angular range from 5° to 40° (2θ) using step sizes 0.05 and 0.25 s per step.

2. 5. Differential Scanning Calorimetry

The solid-state properties of the raw ibuprofen and fabricated nanofiber samples were studied using differential scanning calorimetry (DSC 822, Mettler Toledo). Each powdered sample (5 mg) was placed in an aluminum pan, sealed, and heated to 200 ° C at a heating ramp rate of 10 ° C / min under nitrogen gas (50 L/min). Before each measurement, the sample was allowed to equilibrate for 5 min at 30 ° C. Transition temperatures and enthalpy readings were automatically calculated using Mettler Toledo software for each peak.

2. 6. Drug Entrapment Efficiency (DEE)

The drug loading efficiency was calculated using the following equation (Eq 1).

$$DEE\ (\%) = (W_m/W_a) \times \boldsymbol{100\%} \quad (1)$$

where W_m is the ibuprofen content measured in the electrospun nanofibers, and W_a is the ibuprofen added to the working fluid during the preparation. All tests were repeated in triplicate and the mean is reported. The ibuprofen content in the generated fibers was determined by dissolving the fibers in ethanol. The solutions were then analyzed spectrophotometrically at 220 nm to assess the amounts of ibuprofen in each sample.

2. 7. In Vitro Dissolution and Solubility Studies

Samples of pure ibuprofen drug (10 mg) and nanofiber sample equivalent to 10 mg ibuprofen were subjected to dissolution studies in 900 ml of distilled water under sink conditions (USP paddle method: Thermonic, Campbell Electronics, Mumbai, India, at 100 rpm and 37 °C).[19] At predetermined intervals, a sample of the solution was removed and filtered through a 0.45 μm filter, and the same amount of medium was replaced at the same temperature. The drug content in the withdrawn aliquots was spectrophotometrically analyzed at 220 nm (UV-160, Shimadzu, Japan). The experimental points were the average of at least three repetitions. To assess the solubility of ibuprofen in studied dissolution media, an excess of ibuprofen was added to distilled water and stirred for 24 hours. Later the suspension was centrifuged and the supernatant was filtered using Whatman filter paper. Further, the drug concentration was measured spectrophotometrically at 220 nm.

2. 8. Ex Vivo Intestinal Permeation Studies

The ex vivo intestinal permeation studies were performed as per a previously reported method by the author.[19] The goat's small intestine was collected from a local slaughterhouse for the study, kept in buffer fluid (Krebs-

Ringer solution), and used immediately without storage for a prolonged period. The tissue sample was properly cleaned to separate the mesentery, rinsed with the buffer, and then cut into different sections. Each section was everted on a Teflon rod and fixed on its location using a thread. The setup consisted of an intestinal holder which was a cylindrical glass vessel connected to a "U" glass tube whose one portion was represented by the intestine. Intestine holders (four in one set) filled with buffer fluid represented the receiver environment (4 × 12 mL) and the holder was placed in the donor environment. Both the receiver and donor phases were continuously aerated to keep the intestine cells alive during experimentation. At regular intervals of time, after the beginning of the permeation test, 4 mL of the receiver phase were sampled from each intestine holder and replaced with pure buffer, for a time duration of 120 min. The concentration of ibuprofen in each of the four liquid phases sampled was estimated using a UV spectrophotometer (UV-160, Shimadzu, Japan).

2. 9. Statistical Analysis

The performance of raw ibuprofen and ibuprofen-loaded nanofibers in the in vitro dissolution studies and the ex vivo intestinal permeation studies were analyzed following a t-test at an overall significance level of 0.05 using Sigma Stat software (Sigma Stat 3.5, SPSS Inc, Chicago, IL).

3. Results and Discussions

Hydrophilic and water-soluble polymers have been widely exploited by formulation scientists to enhance the solubility of poorly soluble drugs.[19, 23–26] It is supposed that these polymers act as antinucleating agents and stabilizers inhibiting the devitrification of amorphized drugs.[6] Moreover, nanotechnology-based drug delivery approaches have gained a lot of momentum providing viable solutions for optimal therapeutic delivery of poorly soluble drug candidates.[27, 28] In the present work, PVP was used for the preparation of nanofibers due to its inherent properties such as outstanding physiological compatibility, and satisfactory solubility in water along with other organic solvents. The solvent plays a vital role in the successful preparation of electrospun nanofibers. The solvent should dissolve the drug conveniently while keeping the electrospinnability of polymer solutions intact. Amongst several solvents screened for solubilization of ibuprofen and PVP, ethanol was found to be suitable.

3. 1. Scanning Electron microscopic Investigation

The formation of nanoscopic fibers was confirmed using SEM (Fig. 1). The nanofiber diameter, as revealed by SEM, fell in the approximate range of 450–500 nm. The SEM images revealed no visible surface deposition of drug crystals indicating molecular dispersion of the loaded ibuprofen in the PVP matrices. On the other hand, SEM images of pure ibuprofen revealed distinct needle-shaped crystals.

3. 2. X-ray Diffraction Studies

X-ray diffraction studies of the prepared samples were carried out to assess the polymorphic transitions (if any) that might have been taken place in ibuprofen when

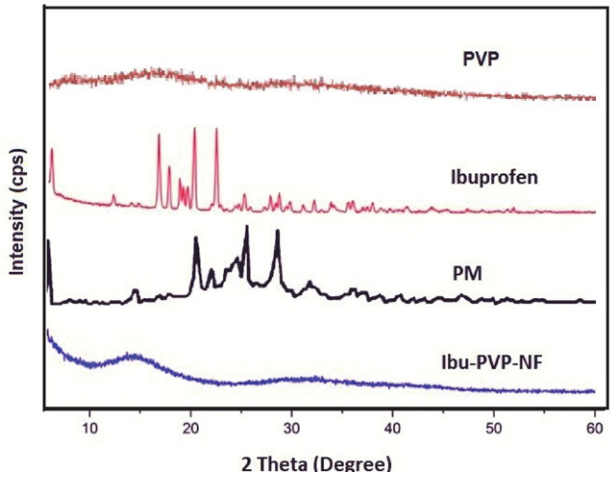

Fig 2. X-ray diffraction patterns of the studied samples indicated negligible or no crystallinity in the ibuprofen-loaded nanofiber sample (Ibu-PVP-NF). The raw ibuprofen (Ibuprofen) and physical mixture (PM) samples retained the crystalline peaks. PVP nanofibers (PVP) exhibited no crystalline peak indicating their amorphous nature.

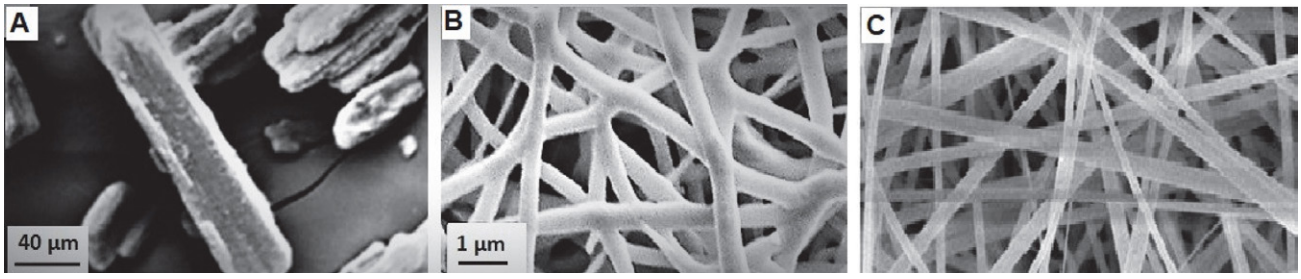

Fig 1. Scanning electron microscopy of (A) raw ibuprofen, (B) ibuprofen loaded PVP nanofibers, and, (C) PVP nanofibers.

formulated as nanofibers. The X-ray diffraction patterns of ibuprofen alone, as a physical mixture with the matrix-forming polymer and ibuprofen, loaded nanofibers are depicted in Fig. 2. The XRD pattern of ibuprofen alone exhibited intense peaks of high-intensity reflections to the interplanar distances 13.5, 7.2, 5.3, 4.7, and 4.0 Å at 6.3°, 12.4°, 15.9°, 18.2°, and 22.5° (2θ), respectively which reveal its crystalline nature. However, the pattern of ibuprofen-loaded nanofibers showed broad and diffuse maxima peaks which may be attributed to the amorphization of ibuprofen in the nanofiber samples. Furthermore, the physical mixture (PM) samples prepared by physically mixing ibuprofen and PVP, exhibited the retained crystalline properties of ibuprofen. It has been well documented that the amorphous state of drug substances possesses many advantages including enhanced solubility, improved wettability, and increased dissolution rate when compared to its crystalline counterpart.[29–30]

3. 3. Differential Scanning Calorimetry (DSC)

The DSC thermograms of samples are in agreement with the results of XRD studies (Fig. 3). Ibuprofen alone showed a sharp endothermic peak at 79.8 °C corresponding to its melting point confirming its crystalline nature. The physical mixture sample retained the melting endotherm of ibuprofen in the DSC studies. However, the peak associated with ibuprofen melting was significantly affected (small peak) in the nanofiber samples indicating its significant amorphization. Thus, the results of DSC studies were in agreement with the XRD analysis.

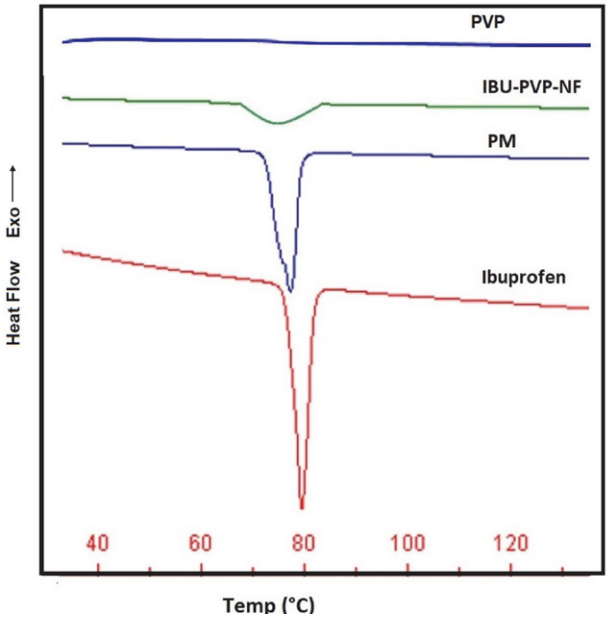

Fig 3. DSC thermograms of the studied samples indicate sharp melting endotherms at the melting point of ibuprofen in raw ibuprofen (Ibuprofen) and physical mixture (PM) samples. Ibuprofen-loaded nanofiber sample (IBU-PVP-NF) lacks a sharp endothermic peak. PVP nanofiber sample (PVP) exhibited no endothermic peak indicating its amorphous nature.

3.4. Drug Loading Efficiency

Drug loading in drug delivery systems is considered an important parameter when assessing the suitability of the drug carrier systems. The methods of drug loading in polymeric nanofibers are diverse and include blending (the drug is dissolved/dispersed in polymer solution), surface modification (drugs are conjugated to the nanofiber surfaces), coaxial process (co-electrospinning of drug solution as core and polymer solution as a sheath), etc. The present study adopted the blending method for loading ibuprofen. The ibuprofen loading efficiency in the fabricated electrospun nanofibers was found to be as high as 93.42 ± 4.21%w/w.

3. 5. In Vitro Dissolution Studies

For BCS II drug candidates like ibuprofen, dissolution is the rate-limiting step for oral absorption. In such, a scenario, improving the dissolution of the drug has been an ideal strategy for its effective oral delivery. The raw ibuprofen (Ibu) dissolution in distilled water was found slow and incomplete (55.72± 4.82%). Moreover, the solubility of raw ibuprofen in distilled water was also found very poor (10.23 ±1.44 mcg/ml). The dissolution profile of the studied samples (Fig. 4) revealed a significant improvement ($p < 0.05$; t-test) in drug release from the nanofiber samples (Ibu-PVP-NF) when compared to native raw ibuprofen (Ibu). The improved dissolution of ibuprofen (88.96±3.22%) from the nanofiber samples may be due to the amorphous state of the drug.[31,32] In our previous report, a similar improvement in dissolution was observed while attempting co-processing with hydrophilic polymers like hydroxypropyl methylcellulose.[19]

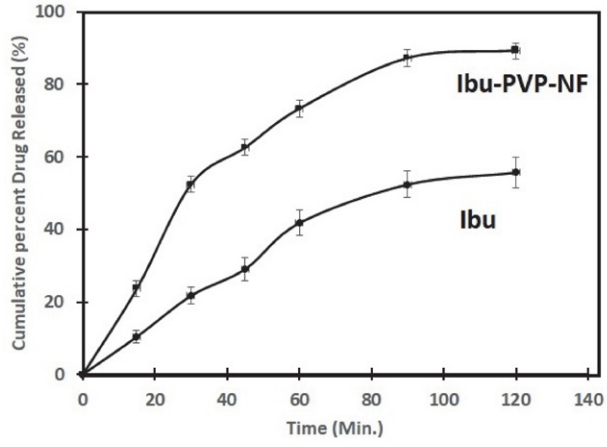

Fig 4. The dissolution profile of the raw ibuprofen (Ibu) and nanofiber (Ibu-PVP-NF) samples.

3. 6. Ex vivo intestinal permeation studies

As a surrogate for in vivo bioavailability studies, we have carried out ex vivo intestinal permeation studies to confirm dissolution data. The study conducted for two

hours revealed a significant ($p < 0.05$) improvement in the rate and extent of permeation of ibuprofen from nanofiber samples (equivalent weight of nanofiber containing 50 mg of ibuprofen) when compared to raw ibuprofen samples (50 mg) (Fig. 5). Raw ibuprofen (Ibu) exhibited a lower percentage of permeation (34.66 ± 5.27 %). However, the nanofiber samples exhibited significantly ($p > 0.05$) higher intestinal permeation (79.83± 7.29 %). Since, intestinal permeation of ibuprofen is dissolution rate limited, the present approach to enhance the dissolution of ibuprofen using nanofiber technology successfully improved the ex vivo intestinal permeation of the cargo.

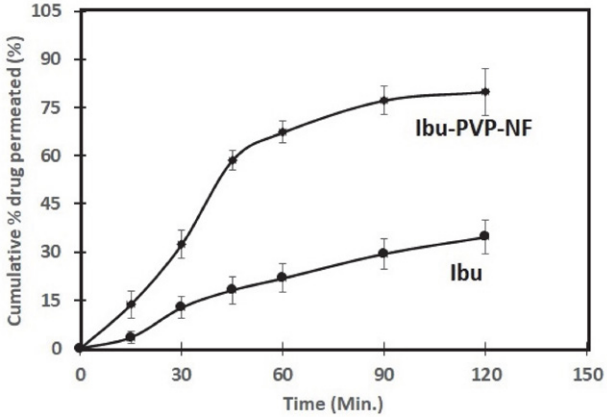

Fig 5. Ex vivo intestinal permeation pattern of raw ibuprofen (Ibu) and nanofiber (Ibu-PVP-NF) samples.

4. Conclusion

Hydrophilic polymer electrospun nanofibers for oral delivery of ibuprofen are reported with enhanced dissolution and ex vivo permeation. The results are very promising with the existence of ibuprofen in an amorphous state in the nanofiber matrix evident from the DSC and XRD investigations. The apparent absence of crystalline traces of ibuprofen in the nanofiber samples may be due to the antinucleating properties of PVP. The study has provided enough supporting data for further preclinical investigations.

Conflict of Interest

The authors declare no conflict of interest. The authors alone are responsible for the content and writing of the article.

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Povzetek

Slaba topnost zdravilnih učinkovin v vodi predstavlja velik izziv za farmacevtske tehnologe, ki pripravljajo formulacije za učinkovito peroralno dostavo. Slaba topnost je pogosto povezana z oteženim raztapljanjem in posledično nizko biološko uporabnostjo tistih učinkovin, pri katerih je črevesna absorpcija omejena s hitrostjo raztapljanja. V tej študiji so z elektrostatskim sukanjem razvili polimerna nanovlakna s ciljem izboljšanja vodotopnosti ibuprofena, zdravila II. razreda po biofarmacevtskem klasifikacijskem sistemu. Hidrofilne polimere, kot je polivinil pirolidon, ki se lahko sukajo, so uporabili kot nosilni sistem za izdelavo nanovlaken. Optimizirali so parametre elektrostatskega sukanja, kot so pretok, napetost in razdalja med šobo in zbiralnikom. Izdelana nanovlakna z vključenim ibuprofenom so ovrednotili z vrstično elektronsko mikroskopijo in diferenčno dinamično kalorimetrijo. Izvedli so tudi raziskave sproščanja učinkovine in absorpcije v ex vivo pogojih. Platforma na osnovi nanovlaken je bistveno izboljšala in vitro absorpcijo ibuprofena v primerjavi s čistimi kristali ibuprofena.