RESEARCH ARTICLE

Centrifugal Melt Spun Microfibrous Solid Dispersion of Diclofenac Sodium with Enhanced Solubility

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ABSTRACT

A lower dissolution rate of poorly soluble drugs is the prime factor affecting their bioavailability. The centrifugal melt spinning method is a simple, affordable and scalable technique to prepare microfibers with enhanced solubility and dissolution rate. This study aimed to enhance the solubility and dissolution rate of poorly soluble drug diclofenac sodium by centrifugal melt spinning technique. Microfibrous solid dispersion of diclofenac sodium 10% w/w with sucrose were prepared to utilize a cotton candy device. The dissolution studies revealed that the drug-loaded microfibers released 98.10 ± 0.52% of drug within 5 minutes as compared with pure drug and physical mixture. The drug-loaded microfibers were bead-free with uniform morphology and diameter of 13.25 ± 4.4 µm. The centrifugal melt-spinning process converted the drug and carrier to amorphous state, which was further confirmed from the calorimetric and crystallographic study results. The results indicated that the centrifugal melt spinning process rapidly produced microfibers with improved solubility and dissolution rate. The results of this study have shown that the centrifugal melt spinning technique may provide an easy, highly scalable, and adaptable fabrication technique to increase the solubility and rate of dissolution of poorly soluble drugs.

Keywords: Poorly soluble drug, Microfibers, Centrifugal melt spinning, Enhanced solubility

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INTRODUCTION

Enhancing a poorly soluble drug's solubility and dissolution rate remains an important challenge in pharmaceutical industry. Poor solubility in water is expected to affect the likelihood of drug absorption after oral administration in up to 75% of the drugs being developed right now.[1] Majority of these drugs belong to BCS class II. For poorly soluble drugs, methods that increase the drug's surface area and hence speed up its solublization can be considered a feasible alternative.[2] A variety of formulation techniques have been used to address these drugs solubility and/or dissolution issues.[3] One such effective strategy for poorly soluble drugs is to prepare micro or nanofibrous amorphous solid dispersions (ASD) in a hydrophilic carrier.[4]

Poorly water-soluble medicines' solubility and rate of dissolution can be successfully increased by formulating ASD. Solid dispersions enhance the dissolution rate by reducing particle size, hydrophilic properties of carrier material, enhanced wetting ability of drug, improving dispersion ability, and transformation of drug to the amorphous form.[5] Solid dispersions have a lot of potential, but their usage is now "under-realized" mostly because of their structural stability issues, high-cost production, and up-scaling of the finished product.[6] Nowadays, solid dispersion technology combined with nanotechnology has attracted more attention than before, particularly with regard to the creation of solid dispersions in nano/micro fibers forms employing methods like electrospinning.[7] Nano and microfibers based solid dispersions exhibit better drug dissolution enhancement in comparison to conventional solid dispersion techniques which has resulted in significant utilization of these novel solid dispersions in drug delivery applications.[8,12-15] Studies utilizing electrospinning have demonstrated that due to presence of extensive porous structure and larger surface area of the nanofibers it may be helpful in resolving the problems related to poor drug solubility of many drugs. Despite of the advancement of scale-up strategies such as multi-nozzle,[9] nozzle-free,[10] and high speed electrospinning,[11] rational utilization of the electrospinning technique in commercial market has been restricted owing to its complexity, poor yield, low production rates and high cost.

In this study a novel fiber preparation technique namely centrifugal melt spinning (CMS) was utilized to prepare microfibers for solubility enhancement of poorly soluble drug diclofenac sodium.[12-15] The centrifugal melt spinning

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technique has been investigated recently as a versatile method to synthesize large quantities of micro and nanofibers. The technology is based on the well-known technique of 19th century, cotton candy production, where a solution of the material or its melt contained in a vessel/spinneret is rapidly rotated, ejecting the material through orifices around the boundary, producing near-continuous fibers that are deposited on a fixed collector.[16] This technology aims at mass-scale nano/microfibre production. The method provides the increased output and ease of equipment setup without the difficulty of high voltage in upscaled processing. The most extraordinary benefit of the centrifugal melt spinning technique is its exceptional output.[17] According to a recent study, the productivity of the centrifugal melt spinning process is about 500 times higher than that of traditional electrospinning when it comes to creating multilevel organized silica micro and nanofibers.[18] The technique can process various polymers, including melts, solutions, and emulsions.

Diclofenac sodium (DIC) is a strong NSAID having analgesic and antipyretic characteristics. DIC sustained release formulations commonly treat rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and sport injuries. DIC has limited solubility, especially in gastric environments, and oral treatment might result in low or unfavorable bioavailability and variable analgesic efficacy.[19] Many solid dispersion controlled release DS delivery systems have been studied over the past decade. There are limited studies on DS quick or immediate-release formulations. Considering these issues and the rising use of oral DS in anti-inflammatory and analgesic therapy, a new formulation in the form of fast-dissolving microfibers with sucrose as carrier were developed. Thus, our study developed microfibrous solid dispersion of diclofenac sodium in sucrose with improved solubility and dissolution characteristics.

MATERIALS AND METHODS

Materials

DIC was obtained from Aarti Drugs ltd, Mumbai, Sucrose was obtained from Sigma Aldrich, All other material used in this study were of analytical grade.

Method

Preparation of Diclofenac Sodium-loaded Sucrose Fibers by Centrifugal Melt Spinning

DIC-loaded sucrose microfibers 10% (w/w) were formulated using a tabletop model of candy floss machine as the centrifugal melt spinning device (Figure 1). Sucrose (90% w/w) and drug (10% w/w) were mixed in a mortar for about 5 minutes. An amount equivalent to 10 g of mixture was accurately weighed and placed into a preheated spinneret. Spinning operations were carried out at a speed of 5300 rpm and spinneret temperature of 140–200°C.

Characterization of DIC Loaded Sucrose Microfibers

Yield and Drug Loading Efficiency (DLE)

The % yield of DIC incorporated sucrose microfibers obtained from 5 gm of mixture was computed using following equation.

Figure 1: Centrifugal melt spinning machine

$$\text{Yield } \%\left(\frac{W}{W}\right)_{x100} = \frac{\text{weight of prepared solid dispersion}}{\text{weight of drug + carrier}}$$

10 mg of fibers were dissolved in 5 mL of DMSO and the required volume was made up using phosphate buffer (pH 6.8). The amount of drug was calculated by UV spectrophotometry at 276 nm.

Drug loading efficiency (DLE) was computed by using the given equation:

$$\text{DLE}\left(\%\ \frac{W}{W}\right) = \frac{\text{amount of drug measured}}{\text{theoretical amount of drug}} \times 100$$

W theoretical amount of drug

Microscopic Analysis of DIC Loaded Sucrose Fibers

Metzer Trinocular research microscope analyzed the freshly prepared DIC loaded sucrose fibers using Metzer-M Bio wizard image analysis software. The diameter of fine fibers was measured at 5X resolution. The images were captured by 5.0 megapixel camera. The average diameter was determined from 10 individual measurements.

Scanning Electron Microscope (SEM)

The morphologic characteristics of freshly prepared DIC loaded sucrose microfibers were examined using SEM scanning electron microscope (JEOL JSM 6360 A).

Saturation Solubility of DIC and DIC Loaded Sucrose Microfibers

A 10 mL of phosphate buffer pH 6.8 was taken in a conical flask, and excess pure DIC drug and DIC loaded sucrose microfibers were added to the flask. The flasks were shaked on a rotary shaker maintained at temperature of 37°C for 72 hours. A membrane filter filtered the samples. The amount of drug dissolved in both flasks was detected by UV spectroscopy at 276 nm. The saturation solubilities of DIC loaded sucrose microfibers and pure DIC were calculated and compared.

Powder X-ray Diffraction (PXRD)

X ray scattering measurements of pure drug DIC, physical mixture and DIC-loaded sucrose microfibers were recorded to assess if the substance was crystalline or amorphous in nature. A wide-angle X-ray diffractometer (Rigaku Ultima IV,Japan) was utilized for the study. Samples were scanned over a two-theta range of 10–80°.

Differential Scanning Calorimetry (DSC) Analysis

DSC study of pure DIC and DIC loaded sucrose microfibers was performed using Mettler Toledo DSC equipment. 1–3 mg

of each samples were filled in a heated aluminium pan at a nitrogen flow rate of 50 mL/min at a heating temperature of 10°C/min.

ATR-FTIR Spectroscopy

FTIR study aims to identify the molecular composition and physical state of microfibers and study potential drug-carrier molecular interactions resulting from centrifugal melt spinning processing at high temperature conditions. ATR-FTIR spectra of DIC and DIC incorporated sucrose microfibers were recorded using ATR-FTIR spectrophotometer (ATR-FTIR Shimadzu).

Dissolution Studies (*In-vitro*)

Drug release from prepared DIC loaded sucrose microfibers, Pure DIC and physical mixtures were studied. *In-vitro* dissolution tests were carried out using a USP type II paddle apparatus. The dissolution medium comprised of 900 mL of phosphate buffer (pH 6.8). The study was carried out at a temperature of 37 ± 0.2°C, 50 rpm speed. Fibers corresponding to 50 mg of drug were dispersed in the dissolution medium and the time was recorded. To maintain a constant total dissolution volume, 5 mL of the samples were removed at 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, and 60 minutes and replaced with fresh medium. The amount of drug released was measured by UV spectrophotometer at 276 nm.

RESULT AND DISCUSSION

The percentage yield of DIC-loaded microfibers was found to be 83.73 ± 1.4% and drug loading efficiency was found to be 97.29 ± 1.9%.

Microscopic Analysis of DIC Loaded Sucrose Fibers

The results are as shown in Figure 2 a and b. The fiber diameters ranged from 7–25 µ. The average particle diameter was found to be 13.25 ± 4.4 µ. The results are summarized in Table 1.

Scanning Electron Microscopy

The DIC loaded sucrose microfibers (Figure 3) exhibited consistent morphology, smooth surface and random orientation, suggesting that the drug is molecularly distributed within sucrose microfibers.

Table 1: Average diameter of DIC loaded sucrose fibers

Sr. No.	*Diameter(µ)*
D1	7.89
D2	13.41
D3	7.89
D4	13.41
D5	14.17
D6	21.21
D7	18.60
D8	13.41
D9	8.32
D10	14.17
Average Diameter	**13.25 ± 4.4µ**

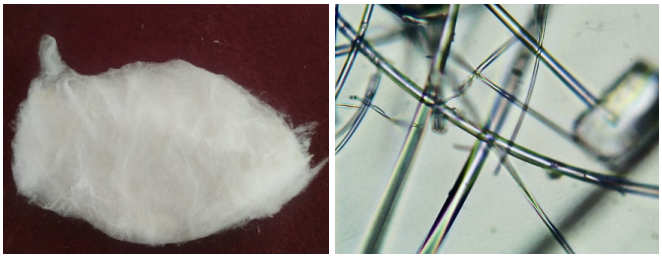

Figure 2: a)DIC loaded sucrose microfibers 2b) DIC microfibers under trinocular microscope

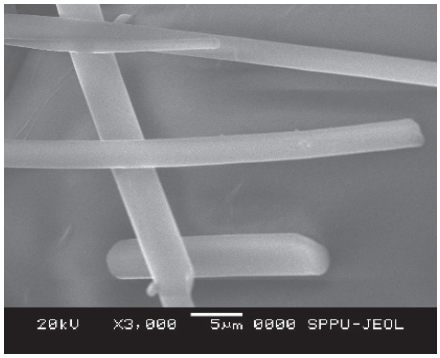

Figure 3: SEM of DIC loaded sucrose microfibers

Saturation Solubility of DIC and DIC-loaded Sucrose Microfibers

The comparative saturation solubility of DIC and DIC-loaded sucrose microfibers in phosphate buffer pH 6.8 is represented in Figure 4. The solubility of pure Diclofenac was found to be 0.0160 ± 0.17 mg/mL, while DIC-loaded sucrose microfibers showed a solubility of 0.056 ± 0.24 mg/mL. The DIC-loaded sucrose microfibers exhibited 3.5 folds and increased solubility as compared to pure DIC. This increased solubility in DIC-incorporated sucrose microfibers is due to the amorphization of DIC in sucrose during the centrifugal melt spinning process, which is confirmed by XRD data and DSC thermogram (Figure 5A).

Powder X-ray Diffraction (PXRD)

The X ray diffractogram for the drug DIC (Figure 5B) exhibited numerous distinctive peaks at 20.38, 21.31,26.25, and 27.323° 2θ indicating its crystalline nature. Distinct peaks of DIC disappeared in the diffractogram of DIC loaded sucrose microfibers (Figure 5C) and remaining detectable characteristic DIC peaks were of reduced intensity, indicating that DIC is present in an amorphous state in the fibers.

Differential Scanning Calorimetry (DSC) Analysis

The primary objective of DSC is to evaluate the thermal melting characteristics of DIC and DIC loaded sucrose microfibers formulated by centrifugal melt spinning technique. The DSC thermogram of Sucrose (Figure 6) depicted melting endotherm at 188°C; the DIC thermogram (Figure 7) depicted melting endotherm at 289.9°C. The thermogram of DIC loaded sucrose microfibers (Figure 8) showed only one sharp melting peak around 178.92–185.05°C corresponding to melting of sucrose and disappearance of DIC endothermic peak inferring

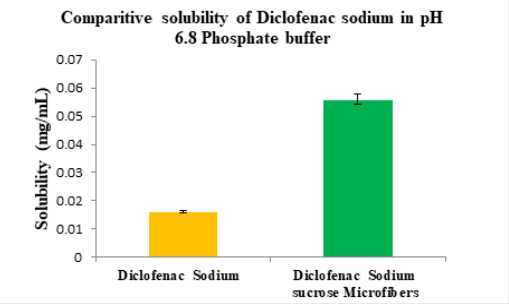

Figure 4: Comparative solubility of diclofenac sodium in pH 6.8 phosphate buffer

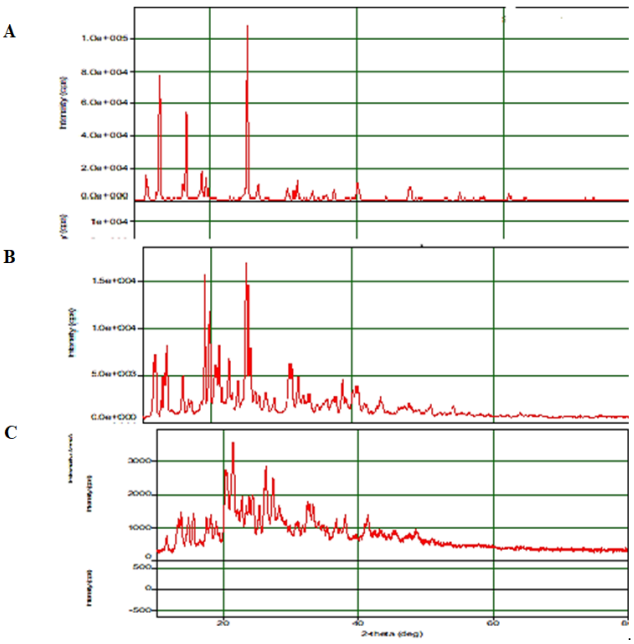

Figure 5: XRD diffractogram of sucrose (A), Diclofenac sodium (B), DIC loaded sucrose microfibers (C)

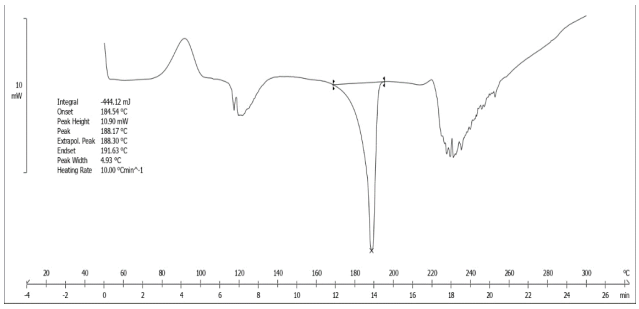

Figure 6: Sucrose DSC thermogram

the conversion of crystalline diclofenac sodium into amorphous phase during the centrifugal melt spinning process.

ATR-FTIR Spectroscopy

The principal peaks of DIC were observed at wavenumbers 1285 cm^{-1}(C-N stretching), 1508 cm^{1} (C-C stretching) and 1573 m^{-1} (C-O stretching) in the IR spectra of DIC (Figure 9). IR spectra of sucrose (Figure 10) depicted multiple O-H and C-O stretching peaks. The ATR-FTIR spectra of DIC-loaded

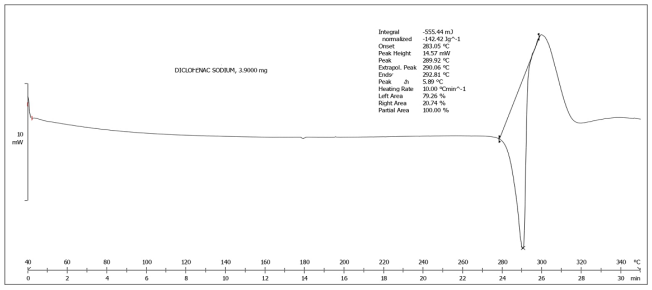

Figure 7: Diclofenac sodium DSC thermogram

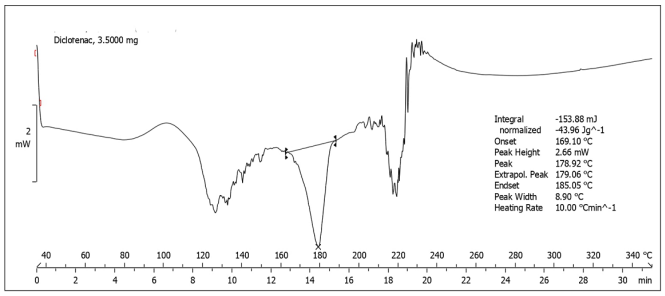

Figure 8: Diclofenac sodium loaded sucrose microfibers DSC thermogram

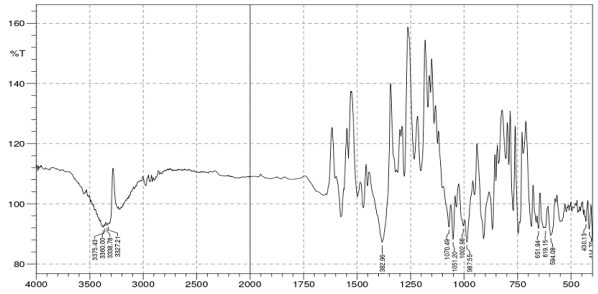

Figure 9: Diclofenac sodium ATR FTIR Spectra

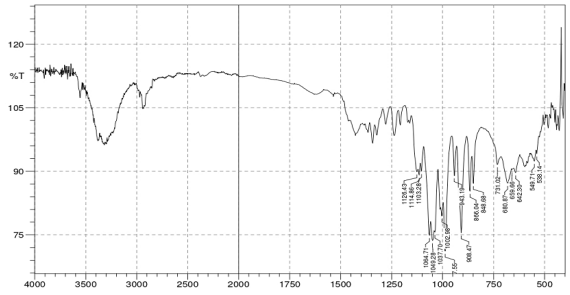

Figure 10: Sucrose ATR FTIR Spectra

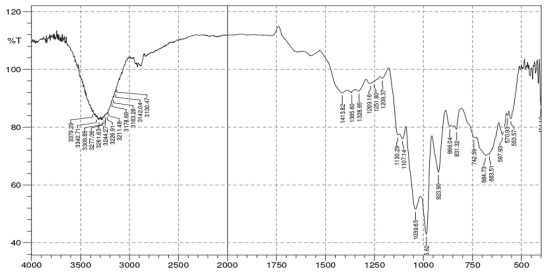

Figure 11: DIC loaded sucrose microfibers ATR FTIR Spectra.

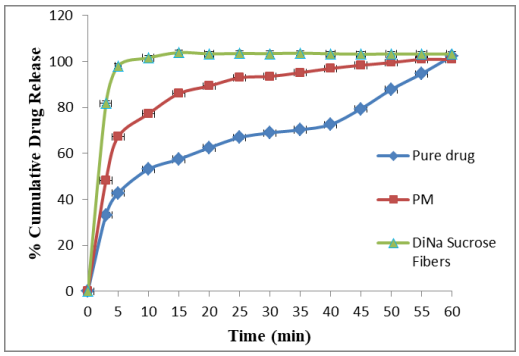

Figure 12: Dissolution profile of DIC, Pysical mixture and DIC loaded sucrose microfibers

sucrose fibers (Figure 11) exhibited fewer characteristic peaks of the drug and were broader than in the spectra of the pure DIC, thus confirming the conversion of drug to an amorphous state.

Dissolution Studies (*In-vitro*)

The comparative dissolution profile of DIC, Physical mixture and DIC-loaded sucrose microfibers is shown in Figure 12. The cumulative drug release of Pure drug shows lowest dissolution of about 42.72 ± 1.1% within 5 minutes, whereas the physical mixture and DIC-loaded sucrose fibers exhibited significant enhancement in dissolution rate about 67.25 ± 0.37% and 98.10 ± 0.52% within 5 minutes respectively. Thus the DIC loaded sucrose fibers exhibited excellent drug release as compared to the pure drug and physical mixture. As per the results shown in DSC and XRD investigations the conversion of drug in amorphous form and resultant higher surface area of the microfibers prepared by centrifugal melt spinning technique are responsible for the extensively fast and higher drug dissolution rate compared to the pure drug. Other reason for enhanced solubility can also be attributed to close proximity of sucrose to diclofenac during dissolution which may promote wetting and minimize agglomeration.

CONCLUSION

The study demonstrated the utilization of a centrifugal melt spinning process for rapid production of poorly soluble drug-loaded microfibrous solid dispersions with higher dissolution characteristics. The prepared fibers appear smooth and consistent in morphology. Findings indicated that sucrose microfibers containing 10% w/w diclofenac sodium were effectively synthesized with a high yield value and loading efficiency. SEM images revealed the homogeneous appearance of the microfibers, suggesting the successful incorporation of diclofenac sodium into sucrose carrier. The DSC, FTIR and XRD results confirm the amorphization of Diclofenac sodium in the microfibers. The drug-loaded fibers released 98.10 ± 0.52% of drug within 5 minutes. The solubility and dissolution rate of DIC loaded 3.5 folds increased sucrose microfibers compared to PMs and the pure drug. This suggests that the produced microfibers may have the ability to increase the rate and improve the amount of drug released at the site of absorption, enhancing oral bioavailability. Thus, sucrose-based drug-loaded microfibers with excellent dissolution performance can be successfully prepared using the centrifugal melt spinning technique. This technique can be utilized as a novel, efficient, scalable, environment-friendly alternative method to prepare nano and microfibers for various drug delivery applications.

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