RESEARCH ARTICLE

Solubility Enhancement of Itraconazole by Centrifugal Melt Spinning Technique

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ABSTRACT

Itraconazole is an antifungal drug with poor water solubility and limited bioavailability, presenting difficulties in achieving effective therapeutic applications. This study aimed to employ centrifugal melt spinning, an innovative method, to improve the solubility of itraconazole. In this process, itraconazole was subjected to centrifugal forces while melting, forming amorphous solid dispersions. Microfibers loaded with 10% w/w itraconazole were prepared through centrifugal melt spinning, employing sucrose as a carrier. ITZ-sucrose microfibers with uniform morphology and an average diameter of 14.27 ± 2.90 µm were successfully fabricated, as evidenced by the scanning electron microscopy results. XRD and DSC measurements confirmed the amorphous nature of the spun microfibers. The solubility of Itraconazole sucrose microfibers was significantly enhanced by 12-fold compared to plain Itraconazole. The dissolution experiments demonstrated that sucrose microfibers loaded with ITZ achieved a significant release of 94.96 ± 1.47% within 10 minutes, representing a substantial enhancement compared to plain drugs. The study indicated that utilizing the centrifugal melt spinning technique successfully generated amorphous solid dispersions of itraconazole, leading to a considerable improvement in the drug's solubility.

Keywords: Poorly soluble drugs, Solubility, Centrifugal melt spinning, Microfibers, Amorphous solid dispersion.

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INTRODUCTION

A drug's solubility is critical to its formulation, absorption, and therapeutic efficacy. However, many drugs developed in the pharmaceutical industry exhibit poor solubility in water or biological fluids, presenting a significant challenge in their effective delivery and utilization. Poorly soluble drugs often suffer from low bioavailability, erratic absorption, and reduced therapeutic outcomes, making it imperative to enhance their solubility to overcome the above limitations.[1-4] Improving the solubility of pharmaceuticals with low solubility is a vital area of research within the field of pharmaceutical sciences. Enhancing a drug's solubility can directly impact its dissolution characteristics, resulting in higher drug concentrations within the systemic circulation. This, in turn, can result in improved therapeutic outcomes, reduced dosage requirements, and potentially reduced side effects.[5] Various approaches have been devised to address the challenges related to the solubility of poorly soluble medications. These methods involve altering the drug physically through processes like particle size reduction, amorphous solid dispersions, and complexation with cyclodextrins. Chemical modifications, such as prodrug formation, can also be employed to enhance solubility.[6-10] Additionally, the use of novel drug delivery systems, including lipid-based formulations,[11] nanoparticles (NP), and self-emulsifying systems,[12] has shown promise in improving the solubility of the drug and its bioavailability.[13]

The formation of fibrous solid dispersions is indeed an effective approach in the field of solubility enhancement. This approach involves dispersing a hydrophobic drug within a hydrophilic carrier in the form of fibers. The hydrophilic carrier acts as a matrix or scaffold, facilitating the dispersion of the hydrophobic drug throughout the system. This technique results in the formation of microfibers with significantly increased surface area, which consequently leads to higher dissolution rates. The pharmaceutical industry is witnessing an emerging trend wherein solid dispersions are being fabricated into microfibers, resulting in increased surface areas. This approach shows significant potential for enhancing the solubility profile and dissolution characteristics of medications with low solubility.[14]

The literature discusses several fiber generation techniques, including melt blowing,[15] phase separation,[16] bicomponent fiber spinning,[17] template synthesis,[18] self-assembly,[19] and electrospinning.[20] However, these techniques often suffer from limitations such as low production rates, complex manufacturing equipment, difficulties in separation and collection, limited material choices, and safety concerns associated with the application of current and gas pressure.

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These drawbacks highlight the advantages of centrifugal melt spinning (CMS) as a superior alternative for microfiber formulation.

CMS is an innovative and highly promising technique aimed at enhancing the solubility of drugs with low solubility. This method encompasses rapid solidification of a molten blend of medicine and carrier through high-speed spinning. As a result, it produces ultrafine drug fibers characterized by an augmented surface area and enhanced dissolution characteristics. The process of centrifugal melt spinning begins by melting the drug and any desired excipients or additives to form a homogenous melt. The molten drug is then ejected through small orifices at the periphery of the rotating disc. The centrifugal force generated due to the spinning motion forces the molten material to expand outward along the spinning wheel's surface, where it rapidly solidifies due to contact with a cooled surface or a temperature gradient. The utilization of CMS offers numerous advantages over other techniques. It is a continuous and scalable process that can be easily integrated into existing manufacturing setups. One notable advantage of this technique is its avoidance of the need for organic solvents, rendering it environmentally friendly. By eliminating the reliance on organic solvents, potential issues associated with residual solvents in the final product are circumvented. This aspect contributes to the overall safety and sustainability of the CMS method. Additionally, it allows for the inclusion of diverse excipients or additives during the spinning process, enabling further optimization of drug solubility and stability.[21]

Several factors contribute to the observed enhancement in solubility achieved through the application of CMS. First, particle size reduction improves the surface area readily available for dissolving, allowing for faster drug release and improved bioavailability.[22] Additionally, the amorphous or partially amorphous nature of the solidified particles produced by this technique can further enhance solubility. Amorphous drugs display higher energy states and greater molecular mobility, resulting in elevated dissolution rates.[23] The CMS approach has garnered significant attention in recent studies, as it enables the production of drug-loaded microfibers with improved solubility and fast release profile.[24-26]

Itraconazole is a potent antifungal drug widely used to treat various fungal infections. Nevertheless, the drug's therapeutic effectiveness is frequently hindered by its low solubility in water, resulting in reduced bioavailability and insufficient delivery of the medication. To overcome this challenge, scientists have extensively investigated diverse strategies aimed at augmenting the solubility and dissolution rate of Itraconazole.[27-29]

This study investigates the solubility enhancement of Itraconazole (ITZ) through CMS, a solid-state processing technique. The objective is to improve ITZ's solubility and dissolution rate by transforming its crystalline structure to an amorphous state.

MATERIALS AND METHODS

Itraconazole was gifted by Nulife Pharmaceuticals Pune. Sucrose was purchased from Sigma Aldrich Mumbai.

Preparation of Centrifugal Melt Spun ITZ-sucrose Microfibers

Sucrose microfibers containing 10% (w/w) ITZ, were produced using a sugar spinning machine. In 5 g of the initial material was weighed and placed in a warmed spinneret for 5 minutes. The spinning operation was conducted at 5000 rpm and a temperature of 180 to 200°C. Within 24 hours of processing, the freshly prepared microfibers were collected and characterized.

Yield and Drug Loading Efficiency

The percentage yield of sucrose microfibers incorporated with ITZ, obtained from a 5 g mixture, was calculated using the following equation.

$$\text{Yield}\left(\frac{\%\,W}{W}\right) = \frac{\text{weight of prepared solid dispersion}}{\text{weight of drug + carrier}} \times 100$$

In 10 mg of fibers were added in 5 mL of dimethyl sulfoxide (DMSO). Hydrochloric acid (HCl), 0.1 N, was then added to the mixture to make up the volume. The quantity of the drug was determined using the calibration curve.

Drug loading efficiency (DLE) was calculated by using the provided equation.

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

Study of Surface Morphology of Microfibers

The morphological description of the ITZ-sucrose fibers was studied utilizing both an optical microscope and a scanning electron microscope (SEM). These instruments were utilized to examine and analyze the morphological features of the fibers at different magnifications, providing valuable insights into their structure and surface properties.

Optical Microscopy

Metzer trinocular research microscope, equipped with Bio wizard image analysis software, was employed to thoroughly examine freshly prepared ITZ sucrose microfibers. The diameter of the tiny fibers was measured at a resolution of 5X. Ten different measurements were used to calculate the average diameter.

Scanning Electron Microscope

For a more comprehensive understanding of the morphological characteristics of the freshly prepared ITZ sucrose microfibers, SEM (JEOL JSM 6360 A) was employed.

Saturation Solubility Studies

In a conical flask, 10 mL of 0.1 N hydrochloric acid (HCl) was added. Subsequently, an excess amount of plain ITZ and ITZ-sucrose microfibers were introduced into the flask. The mixture was then placed on a rotary shaker and agitated at 37°C for a duration of 72 hours. The samples were then subjected to filtration by using a membrane filter. The amount of the dissolved drug in both flasks was quantified using UV spectroscopy at a wavelength of 255 nm. The obtained results were analyzed to calculate and compare the saturation solubilities of ITZ-sucrose microfibers and plain ITZ.

Powder X-ray Diffraction

The X-ray diffraction patterns of the samples were studied using Rigaku Ultima IV X-ray diffractometer. The measurements were conducted within the range of 20–80°, utilizing Cu-kα radiation (λ = 1.5406 Å). This analysis enabled the evaluation of the crystalline properties of the plain ITZ drug, physical mixture, and ITZ-sucrose microfibers.

Differential Scanning Calorimetric Analysis

A Mettler Toledo DSC instrument performed DSC on plain ITZ, sucrose, and ITZ-sucrose microfibers. The measurements were conducted with a heating rate of 10°C/min while maintaining a nitrogen flow rate of 50 mL/min. Each sample, weighing approximately 1 to 3 mg, was carefully positioned in a heated aluminum pan.

ATR-FTIR Spectroscopic Examinations

ATR-FTIR spectra of ITZ, ITZ-sucrose physical mixture, and ITZ-incorporated sucrose microfibers were obtained from Bruker Alpha-E spectrophotometer, equipped with ATR accessory. The samples were scanned between 1000 and 4000 cm^{-1}.

Dissolution Studies of Itraconazole Sucrose Fibers

The *in-vitro* dissolution tests were conducted using paddle type apparatus II rotating at 75 rpm. Freshly prepared 900 mL of 0.1 N HCl medium was maintained at a temperature of 37 ± 0.2°C. A volume of 5 mL of the test samples was collected at 5-minute intervals and then replenished with fresh medium. The amount of drug in the dissolution medium was quantified at a wavelength of 255 nm using a UV spectrophotometer.

RESULT

The Itraconazole sucrose microfibers displayed a high percentage yield of 87.5 ± 0.17%, signifying the substantial amount of desired product obtained from the initial starting material. Furthermore, the drug loading efficiency was determined to be 89 ± 0.4%, reflecting the effectiveness of incorporating Itraconazole into the sucrose microfibers.

Study of Surface Morphology of Microfibers

Optical microscopy

The optical microscopic images of the microfibers reveal that they exhibit a transparent appearance and do not exhibit any observable beads. The results obtained from the optical microscopic analysis are presented in Figure 1a and b. The fiber diameters varied between 8 and 19 µm, with an average diameter of 14.27 ± 2.90 µm. A comprehensive summary of the findings is available in Table 1.

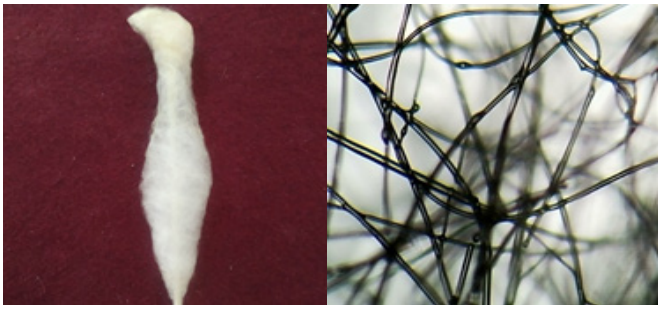

Figure 1: a) ITZ-Sucrose microfibers b) ITZ-sucrose microfibers under optical microscope

Table 1: Average diameter of ITZ-sucrose microfibers

Sr. No.	*Diameter (µ)*
ITZF1	19.15
ITZF2	13.15
ITZF3	15.34
ITZF4	13.15
ITZF5	14.17
ITZF6	13.15
ITZF7	18.60
ITZF8	8.32
ITZF9	14.60
ITZF10	13.15
Average Diameter	**14.27 ± 2.90 µm**

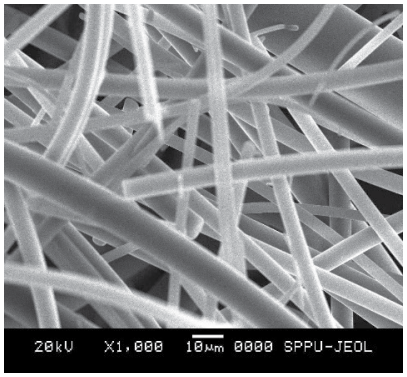

Figure 2: SEM of ITZ-Sucrose microfibers

Scanning electron microscopy

Figure 2 depicts sucrose microfibers that have been loaded with ITZ. The microfibers exhibit a consistent morphology, characterized by a uniform structure throughout. Their surface appears smooth, lacking any apparent irregularities or roughness. Furthermore, the microfibers show random orientation. The image visually demonstrates that the drug is evenly distributed at a molecular level within the sucrose microfibers.

Saturation solubility studies

Figure 3 compares the saturation solubility of ITZ and ITZ-sucrose microfibers in 0.1N HCl. The solubility of pure ITZ in 0.1N HCl was determined to be 16.29 ± 0.07 µg/mL. In contrast, the solubility of ITZ-sucrose microfibers was measured to be 190.6 ± 0.7 µg/mL. These results indicate a significant 12-fold increase in solubility for the ITZ-sucrose microfibers compared to pure ITZ.

XRD studies of itraconazole sucrose fibers

The XRD analysis of itraconazole (Figure 4) revealed distinct peaks within the 20º to 30º range, indicating the presence of crystalline structures. However, a significant reduction in intensity in the prominent peak of ITZ sucrose microfibers at a 2θ value of 20.32 was observed. The distinct crystalline peaks of ITZ were absent in the ITZ sucrose microfibers.

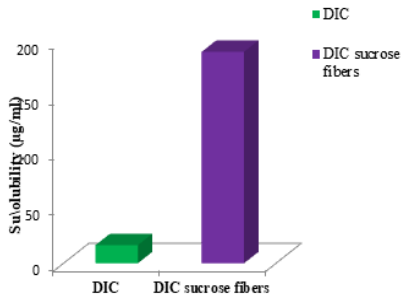

Figure 3: Comparative Solubility study of Itraconazole and Itraconazole fibers in 0.1 N HCl

ATR-FTIR spectroscopy

The plain ITZ exhibits notable spectral features: a prominent peak at 1699 cm^{-1}, indicating the C=O stretching of a ketone group; a sharp peak at 1510 cm^{-1}, associated with an aromatic C-C stretching band; and a distinctive peak at 1228 cm^{-1}, resulting from the in-plane bending of aromatic C-H bonds. Moreover, the sucrose molecule displays O–H stretching mode bands at 3566, 3391, and 3339 cm^{-1}. Analysis of the main characteristic region indicates changes in the absorption bands' intensity. Notably, a chemical shift of the (C=O) peak towards a lower wavenumber may suggest the occurrence of hydrogen bonding between sucrose and itraconazole. (Figure 5)

Upon analyzing the spectra of ITZ-sucrose microfibers, it was observed that the distinct peaks corresponding to ITZ were fewer in number and exhibited broader profiles when compared to the spectra of plain ITZ. This observation implies the transformation from a crystalline to an amorphous state.

Differential scanning calorimetric analysis

The pure ITZ sample exhibited a notable endothermic peak at 170ºC, aligning with its well-established melting point. Similarly, the thermogram of sucrose demonstrated a sharp endothermic peak at 188ºC, indicating the melting point of sucrose. Interestingly, no ITZ melting peak was detected when the microfibers containing ITZ were subjected to heating. This finding suggests that ITZ was homogeneously dispersed at a molecular level within the sucrose microfibers. Figure 6 displays the DSC thermograms.

Dissolution studies of ITZ sucrose fibers

The dissolution studies data (Figure 7) revealed ITZ-sucrose microfibers released 94.96 ± 1.4 % of the drug within 10 minutes, whereas the pure ITZ released 10.24 ± 0.25% of the drug after 60 minutes.

The findings demonstrate a significant enhancement in the dissolution rate of ITZ-sucrose fibers when compared to plain ITZ.

DISCUSSION

This research focused on investigating the application of the centrifugal melt spinning method to produce drug-loaded microfibers with improved solubility rapidly. The primary objective was to enhance solubility and dissolution performance. The study's findings highlighted the effectiveness of the centrifugal melt spinning technique in producing 10%

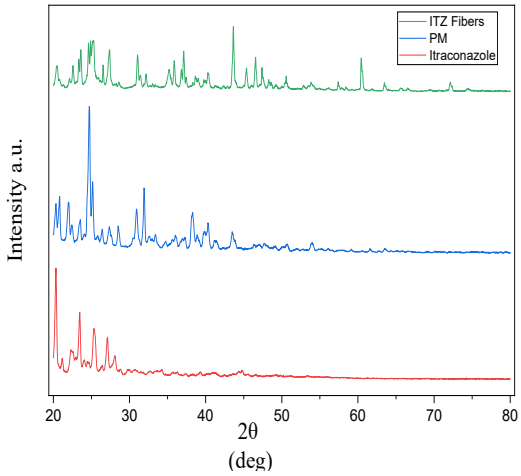

Figure 4: XRD plots of Itraconazole, physical mixture and Itraconazole- sucrose fibers

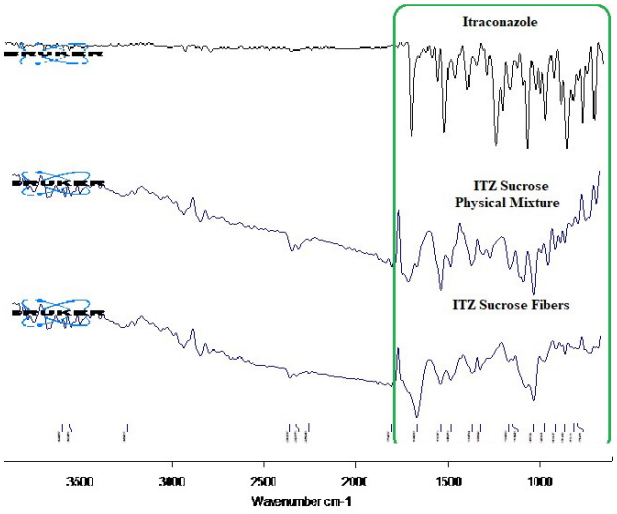

Figure 5: ATR FTIR spectra of Itraconazole, Itraconazole sucrose PM and Itraconazole sucrose microfibers

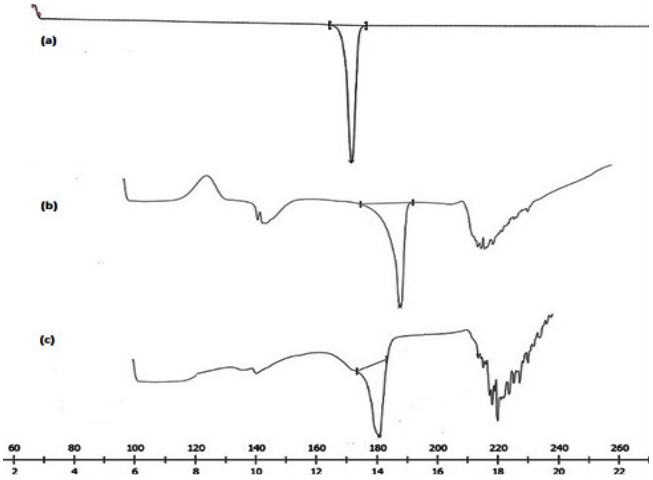

Figure 6: DSC thermogram of (a) ITZ, (b) Sucrose, and (c) ITZ sucrose microfibers

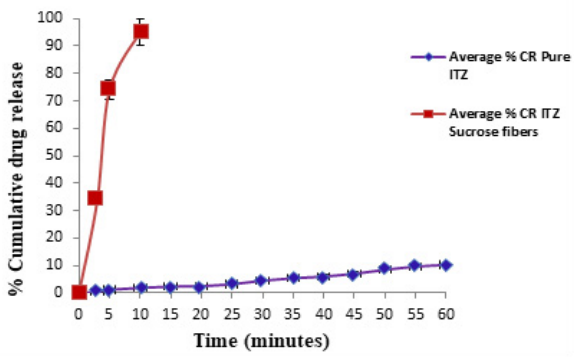

Figure 7: Dissolution profile of Itraconazole and Itraconazole sucrose microfibers

ITZ-sucrose microfibers with notable achievements in terms of high production yield, loading efficiency, and substantially improved solubility. Various solid-state characterization techniques were used to assess the microfibers' quality. Notably, SEM pictures showed microfibers without phase separation and with a consistent shape, demonstrating effective integration of ITZ into the carrier substance. The solubility studies results demonstrated about 12-folds increase in the solubility of ITZ-sucrose microfibers as compared to pure ITZ. The dissolution rate of prepared ITZ sucrose microfibers was significantly enhanced with more than 95% of the drug release in 10 minutes. In summary, this study's centrifugal melt spinning technique successfully yielded ITZ-sucrose microfibers with increased surface area and improved solubility. The transformation to an amorphous state contributed to the enhanced dissolution rate.

CONCLUSION

The study's findings demonstrate that ITZ-sucrose microfibers prepared by the centrifugal melt spinning method have the potential to enhance the solubility and dissolution rate of itraconazole. The centrifugal melt spinning technique shows promise as an effective approach to address the limited aqueous solubility of itraconazole by improving its solubility and dissolution characteristics. The production of drug-loaded microfibers using sucrose as the base material through centrifugal melt spinning represents a remarkable advancement in the formulation approach, especially in the context of solid dispersions. The application of microfiber-based solid dispersions holds exciting prospects for drug delivery applications, thus garnering considerable interest for research and development in the pharmaceutical industry.

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