International Journal of Pharmacy and Pharmaceutical Sciences

Print ISSN: 2656-0097 | Online ISSN: 0975-1491 Vol 16, Issue 12, 2024

Original Article

ENHANCING FLUCONAZOLE SOLUBILITY AND BIOAVAILABILITY THROUGH SOLID DISPERSION TECHNIQUES: EVALUATION OF POLYETHYLENE GLYCOL 6000 AND SODIUM CARBOXYMETHYLCELLULOSE SYSTEMS USING FIBER OPTICS

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Received: 21 Sep 2024, Revised and Accepted: 25 Oct 2024

ABSTRACT

Objective: The triazole antifungal fluconazole is widely used for treating mycotic infections, but its efficacy is limited by its poor aqueous solubility and low dissolution rate, leading to reduced oral bioavailability. This study aimed to enhance the solubility and dissolution rate of fluconazole using solid dispersion techniques with Polyethylene Glycol 6000 (PEG 6000) and Sodium Carboxymethylcellulose (SCMC) as carriers.

Methods: Solid dispersions were prepared using the fusion method, and their physicochemical properties were evaluated against physical mixtures and pure drug samples.

Results: The solid dispersion showed a significant increase in the dissolution rate, achieving 89.01% drug release in 180 min compared to 40.3% for the pure drug ($p<0.0032$) and 84.1% for the physical mixture ($p<0.0453$). The encapsulation efficiency of the solid dispersion was 39.24%, with a drug loading capacity of 19.62%. Fourier Transform Infrared (FTIR) spectroscopy confirmed the stability of the drug within the dispersion, while Scanning Electron Microscopy (SEM) revealed amorphous particles, indicating enhanced solubility.

Conclusion: These results demonstrate that the solid dispersion of fluconazole with PEG 6000 and SCMC significantly improves its dissolution rate and flow properties, providing a promising strategy for enhancing the oral bioavailability of poorly water-soluble drugs.

Keywords: Bioavailability, Dissolution rate, Fluconazole, PEG 6000, Solid dispersion, Solubility enhancement

DOI: https://dx.doi.org/10.22159/ijpps.2024v16i12.52739 Journal homepage: https://innovareacademics.in/journals/index.php/ijpps

INTRODUCTION

A drug's solubility is a very crucial factor that influences its therapeutic efficacy. This is true, especially for oral formulations [1, 2]. One of the major challenges in drug formulations is its poor aqueous solubility. This is because it affects the dissolution rate, the bioavailability, and the overall effectiveness of the drug. Further, these issues are more prevalent in Biopharmaceutical Classification System (BCS) Class 2 drugs, which are characterized by low solubility and high permeability [3].

Fluconazole, a widely prescribed triazole antifungal agent, falls into this BCS category. Despite its efficacy in treating a range of fungal infections, fluconazole's low water solubility limits its dissolution rate and, consequently, its bioavailability when administered orally [4]. Enhancing the solubility of such drugs is essential to improving patient outcomes and reducing treatment failures, especially in immunocompromised populations.

Fluconazole acts by inhibiting fungal cytochrome P450 enzymes, specifically 14α-demethylase, thereby disrupting ergosterol biosynthesis, an essential component of the fungal cell membrane [5]. While it is effective against a broad spectrum of fungal pathogens, its low solubility often necessitates higher doses to achieve therapeutic levels, leading to potential adverse effects such as hepatotoxicity, gastrointestinal disturbances, and drug interactions [6]. These limitations highlight the need for formulation strategies that enhance fluconazole's dissolution and absorption without increasing the dose.

Solid Dispersion (SD) technology has emerged as one of the most promising approaches for improving the solubility of poorly water-soluble drugs. Solid dispersions involve dispersing the drug in a carrier matrix, typically a hydrophilic polymer, which enhances the drug's wettability and reduces particle size, thereby improving its dissolution rate [7, 8]. Over the past five years, significant advancements have been made in solid dispersion technology. This is true, especially in the formulation of poorly water-soluble drugs. One notable development is the refinement of amorphous solid dispersions, which improve drug solubility by converting the crystalline form of drugs into an amorphous state. Recent studies highlight the importance of polymeric carriers like polyvinylpyrrolidone, hydroxypropyl methylcellulose [9], and new-generation polymers such as Soluplus for stabilizing amorphous drug particles, thus preventing recrystallization and enhancing solubility and bioavailability [8].

Hot Melt Extrusion (HME) has also gained attention as a solvent-free method for making stable solid dispersions. Research in HME equipment and techniques has further improved control over the temperature and the shear used in the formulation, which leads to more consistent dispersions. Further, this method's scalability has made it applicable to industrial use [10]. Further, the introduction of supercritical fluid technology has made solid dispersion production much better. This is because of enhanced drug dissolution profiles due to reduced particle size and improvement in polymeric interactions [11]. Other innovative techniques like electrospinning have also emerged as great alternatives for producing ultrafine fibers that contain dispersed drug particles. These techniques offer superior surface area and dissolution rates [12]. Further, these fibers show great potential in having a rapid drug release, particularly for fast-dissolving formulations.

Recent studies have shown that solid dispersions can significantly enhance the bioavailability of poorly soluble drugs by transforming them into an amorphous state, where molecular interactions with polymers prevent drug crystallization [11]. The choice of carrier and the way solid dispersions are prepared are very important factors in determining its success. PEG 6000 and SCMC are the most commonly used carriers because of their ability to not only enhance the solubility of the drug through molecular interactions but also stabilize the drug in an amorphous state. In the formulation of solid dispersion, both PEG 6000 and SCMC not only have advantages as individual carriers but also complement each other when used in combination.

PEG 6000 is a widely used hydrophilic polymer known for its ability to enhance drug solubility by improving the wettability of poorly water-soluble drugs. PEG 6000 effectively reduces the crystallinity of drugs, increasing their dissolution rate through molecular dispersion in its matrix. Additionally, PEG 6000 has a relatively low melting point, making it suitable for fusion methods [13]. Several studies have shown that PEG 6000 can significantly improve drug solubility and bioavailability when used alone, particularly for Biopharmaceutical Classification System (BCS) Class II drugs [14, 15].

On the other hand, SCMC is a cellulose derivative that enhances drug solubility through its gel-forming properties, increasing the viscosity of the dissolution medium. This increased viscosity can prolong the residence time of the drug in the gastrointestinal tract, thus improving absorption. SCMC also provides stabilizing effects by forming hydrogen bonds with drug molecules, which helps maintain an amorphous state and prevent recrystallization. In addition, SCMC's hydrophilic nature supports rapid dispersion of drug particles upon contact with aqueous media [16, 17].

The rationale for combining PEG 6000 and SCMC in this study is based on their complementary benefits. While PEG 6000 enhances solubility by promoting better wettability and molecular dispersion, SCMC's gelling properties and stabilizing interactions further improve dissolution and absorption profiles. Together, these carriers provide a synergistic effect, enhancing the dissolution rate and bioavailability of fluconazole more effectively than either carrier alone.

Previous research on solid dispersions of fluconazole has demonstrated varying degrees of success, with enhancements in dissolution rates ranging from modest to significant depending on the carrier used [18]. However, a systematic approach to preparing and evaluating fluconazole solid dispersions using hydrophilic polymers like PEG 6000 and SCMC has not been thoroughly investigated. Given that PEG 6000 can improve wettability and SCMC can enhance the viscosity of the dispersion medium, their combination may offer a synergistic effect, further improving the dissolution profile and solubility of fluconazole.

The present study aims to address the critical need for improving the bioavailability of fluconazole by optimizing solid dispersion formulations. By exploring the fusion method to incorporate PEG 6000 and SCMC, this study seeks to evaluate how these carriers impact the solubility, dissolution rate, and overall physicochemical properties of fluconazole. The outcomes of this research will provide valuable insights into enhancing the effectiveness of fluconazole formulations and offer a viable solution to the challenges associated with the oral administration of poorly soluble drugs. Therefore, this study holds significance not only for the pharmaceutical industry but also for clinical practice, where improved fluconazole formulations could lead to better therapeutic outcomes for patients suffering from severe fungal infections.

MATERIALS AND METHODS

Fluconazole (purity ≥99%) was a gift sample from the National Pharmaceutical Industry, Muscat, Oman. Polyethylene Glycol 6000 (PEG 6000) was purchased from Sigma-Aldrich, St. Louis, MO, USA), and Sodium Carboxymethyl Cellulose (SCMC) from Merck, Darmstadt, Germany. Analytical-grade methanol and all other reagents used were of high purity and obtained from trusted chemical suppliers to ensure consistency in experimental outcomes. Apart from this, a magnetic stirrer, vacuum desiccator, high-precision digital weighing scale (Sartorius, Göttingen, Germany), and a USP Type I dissolution apparatus (Erweka, Germany).

Preparation of fluconazole solid dispersions

Two methods, physical mixing and the fusion method, were employed to prepare fluconazole-solid dispersion using SCMC and PEG 6000 as the polymers. The solid dispersion of fluconazole prepared using the fusion method involved taking 100 mg of pure fluconazole, along with 50 mg SCMC and 50 mg PEG 6000 (1:1), and melting them together. The 1:1 ratio of PEG 6000 to SCMC was taken to balance the complementary properties of both these polymers. By doing so, we can maximize fluconazole's solubility and, thereby, dissolution rate. As already mentioned, PG 6000 is known for its excellent solubilizing properties, whereas SCMC provides a stabilizing effect through its gelling properties.

Continuous stirring was applied for five minutes to ensure thorough mixing. The resulting melted mixture was then immediately transferred to a cold-water bath maintained at 5 °C and subjected to stirring at 3000 rpm for fifteen minutes. Once the temperature of the mixture decreased to 30 °C, stirring was halted, and the solidified product was filtered. The solid dispersion obtained was dried using a vacuum desiccator over silica gel to remove any residual moisture. The final solid dispersion was sieved to obtain uniform particle size distribution.

A physical mixture of fluconazole was prepared by accurately weighing 100 mg of fluconazole and 50 mg each of SCMC and PEG 6000. These components were manually blended in a mortar and pestle for uniform mixing and then passed through a sieve (#60) to ensure homogeneity.

In both methods, the prepared solid dispersions were subjected to vacuum drying for 24 h at 24 °C to ensure complete removal of solvents or moisture. The temperature of 24 °C was specifically chosen to avoid any potential degradation of the heat-sensitive components, particularly PEG 6000, which has a melting point of around 60 °C [19]. The duration of 24 h was determined based on the time required to achieve effective moisture removal without disrupting the structural integrity of the solid dispersion. The dried solid dispersions were then collected, weighed, and stored in airtight containers at 25 °C with controlled humidity to preserve their integrity until further characterization.

Although the current study focused on the 1:1 ratio, prior literature suggests that varying the ratios of hydrophilic carriers like PEG and SCMC can influence dissolution rates and drug stability [20]. In this case, a 1:1 ratio was chosen as a starting point based on previous successful formulations involving these carriers, which demonstrated synergistic effects when used in combination. However, we acknowledge that different ratios (e. g., 2:1 or 1:2) may further optimize drug release profiles and could be explored in future studies to fine-tune the formulation and identify the most effective carrier balance for fluconazole.

Percentage yield

The percentage yield of the fluconazole solid dispersion was calculated by comparing the actual weight of the dried solid dispersion obtained after preparation with the total theoretical weight of the drug and polymer used in the formulation. The percentage yield was determined using Equation 1:

$$\text{Percentage yield} = \frac{\text{Actual Weight of Solid Dispersion}}{\text{Theoretical Weight of Drug+Polymer}} * 100 \ldots\ldots \text{Eq1}$$

All measurements were conducted in triplicate (n=3) to ensure accuracy and consistency. The results were recorded, and the average percentage yield was calculated to assess the efficiency of the solid dispersion preparation process for both methods.

Drug content

A precise amount of solid dispersions (5 mg) was transferred to a 50 ml volumetric flask and diluted to the mark with methanol and sonicated for 10 min to ensure complete dissolution. The resulting solution was analyzed using a fiber-optic system at 260 nm. The percentage drug content was determined using Equation 2:

$$\text{Drug content (\%)} = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} * 100 \ldots. \text{Eq 2}$$

To ensure accuracy, all measurements were performed in triplicates (n=3). A calibration curve was constructed using known concentrations of the pure drug to establish a linear relationship between the absorbance and concentration. The actual drug content was calculated by interpolating the measured absorbance values from a calibration curve.

Particle size analysis

The particle size of pure fluconazole, physical mixtures, and solid dispersions was determined using an optical microscopy method

with a calibrated ocular micrometer (Leica DM 750, Germany). A small quantity of each sample was uniformly dispersed on a glass slide, and approximately 200 particles were counted and measured in random fields under 400× magnification. The particle size distribution was calculated using Equation 3:

$$\text{Particle size} = \sum \frac{n*d}{n} \ldots \text{Eq 3}$$

Where:

Σ*n*= is the number of particles in each size range, and

Σ*nd*= is the mean diameter of the particles in that range.

Where n represents the number of particles in each size range, d is the mean diameter of particles in that range, and N is the total number of particles measured. The results were expressed as mean particle diameter±Standard Deviation (SD). Statistical analysis was conducted using one-way ANOVA, followed by Tukey's post hoc test to determine significant differences between the samples, with $p<0.05$ considered statistically significant.

Drug loading and encapsulation efficiency

To assess the drug loading and encapsulation efficiency of the fluconazole solid dispersion, the following procedure was employed. 50 mg of the prepared solid dispersion was initially dissolved in 100 ml methanol, followed by dilution to 500 ml. The resulting solution was then filtered to eliminate any undissolved residues. Subsequently, a portion of the filtrate was subjected to analysis using a fiber optics spectrophotometer at a wavelength of 260 nm to quantify the fluconazole concentration. The drug content within the solid dispersion was determined against a pre-established standard calibration curve for fluconazole. Drug loading was computed by taking the actual amount of fluconazole encapsulated in the solid dispersion, dividing it by the total weight of the solid dispersion, and expressing this value as a percentage, as shown in Equation 4:

$$\text{Drug loading (\%)} = \frac{\text{Amouont of Drug in Solid Dispersion}}{\text{Weight of Solid Dispersion}} * 100 \ldots \text{Eq 4}$$

Encapsulation efficiency was calculated by comparing the actual amount of drug encapsulated in the solid dispersion to the theoretical amount of drug initially used in the formulation. This was expressed as a percentage using Equation 5:

$$\text{Encapsulation efficiency (\%)} = \frac{\text{Actual Drug Content in Solid Dispersion}}{\text{Theoretical Drug Content}} * 100 \ldots \text{Eq 5}$$

All experiments were performed in triplicate (n=3) to ensure accuracy and reproducibility of results. Statistical analysis was carried out to evaluate the significance of the findings through suitable software tools. This comprehensive methodology not only provides insights into drug loading and entrapment in solid dispersions but also sets a foundation for optimizing formulations aimed at improving the solubility and bioavailability of poorly water-soluble drugs like fluconazole.

Scanning electron microscopy (SEM) analysis

Before conducting SEM, the samples were properly prepared to ensure optimal imaging conditions. Each sample was cleaned to remove any contaminants and dried appropriately. Samples of pure fluconazole, physical mixture, and solid dispersion were mounted on aluminum stubs using double-sided adhesive tape. The samples were then sputter-coated (Q150R Plus, Quorum Technologies, UK) with a thin layer of gold under vacuum to make them electrically conductive. SEM analysis was performed using an analytical scanning electron microscope (JEOL JSM-6510LV, Tokyo, Japan) operated at an accelerating voltage of 15 kV. Images were captured at a magnification of 500× to 5000×, with direct data captured onto a computer. The microscope was operated under high vacuum conditions (10^{-3} to 10^{-5} Torr) to prevent scattering of electrons by air molecules.

Fourier transform infrared (FTIR) spectroscopy analysis

FTIR spectroscopy was employed to analyze the Fourier transform infrared spectra of the physical mixtures and solid dispersions of fluconazole, as well as the pure drug itself. This analysis was conducted using a Bruker Tensor 37 infrared spectrometer (Bruker, Ettlingen, Germany). Before the spectral analysis, samples were prepared by mixing a small amount of each solid dispersion and physical mixture with potassium bromide (KBr) to form pellets. The KBr was dried at 60 °C to remove moisture and then compressed into pellets under a hydraulic press. The spectra were collected at room temperature over a spectral range of 400 to 4,000 cm^{-1}. Each sample was scanned 32 times to obtain a clear spectrum, and the resolution was set at 4 cm^{-1}. The background spectrum was acquired and subtracted for each sample to enhance the analysis accuracy. FTIR spectra were evaluated for characteristic absorption bands corresponding to functional groups in the fluconazole molecule and the polymers used in the formulations.

***In vitro* drug release studies**

The dissolution of fluconazole from solid dispersions, prepared through both physical mixing and fusion techniques, was assessed using an *in vitro* test. This study followed the United States Pharmacopeia (USP) guidelines and utilized a USP Type I dissolution apparatus (Erweka, Germany). Each test capsule contained a formulation equivalent to 100 mg of fluconazole, encapsulated in a hard gelatin shell, and placed in the basket of the apparatus. The dissolution medium was 1000 ml of 0.1N hydrochloric acid (HCl), maintained at a temperature of 37±0.5 °C to mimic gastric conditions. The apparatus was set to rotate the baskets at 100 rpm to ensure uniform mixing and proper exposure of the solid dispersions. Absorbance measurements were taken at 260 nm using fiber optic probes at specific intervals (5, 15, 30, 60, 120, 180, and 240 min). The release of fluconazole (n=3) was quantified based on a calibration curve in 0.1N HCl, and the cumulative drug release percentage was calculated for each formulation.

Statistical analysis

Statistical analyses were performed to determine the significance of the results, particularly the improvements in dissolution rates of fluconazole in solid dispersions compared to the pure drug and physical mixtures. One-way ANOVA (Analysis of Variance) was employed to compare the dissolution profiles across different formulations. This test was chosen because it allows for the comparison of mean dissolution rates between multiple groups to assess whether the observed differences were statistically significant.

Following the ANOVA, Tukey's post hoc test was applied to identify specific pairs of formulations that demonstrated significant differences. This post hoc analysis ensures that any significant differences observed between the dissolution rates of solid dispersions, pure drug, and physical mixtures were not due to random variation but rather to the effects of the formulation methods and carriers used.

Statistical significance was defined as $p<0.05$, meaning that differences with a probability value below 0.05 were considered statistically significant, indicating strong evidence that the observed effects were not due to chance. For these analyses, we used GraphPad Prism 9.0 software (GraphPad Software, Inc., USA),

RESULTS AND DISCUSSION

Percentage yield

The percentage yield of the fluconazole solid dispersion is a critical parameter that provides insights into the efficiency of the formulation process. In the present study, the percentage yield of the prepared fluconazole solid dispersion was calculated to be 86.6%. This value is indicative of an efficient formulation process, revealing that a significant portion of the initial materials used in synthesis was successfully recovered in the final product. The high percentage yield suggests that only a small quantity of material was lost during the formulation, which is favorable in pharmaceutical drug development. The results reveal that the chosen method for preparing the solid dispersion was effective, yet there remains potential for optimization. Future experiments might consider varying the ratios of excipients or exploring additional formulation techniques to further enhance yield and formulation characteristics.

When compared to existing literature, the achieved yield of 86.6% is consistent with, and in some cases, superior to many pharmaceutical formulations of solid dispersions that typically report yields between 70% to 85% [21, 22]. This reinforces the validity of the methods employed in this study, suggesting that they are both effective and reliable. Although the percentage yield of fluconazole solid dispersion is promising, additional investigation is warranted. Future studies could focus on the scalability of the process, assessing how variations in production conditions or formulations affect yield. Furthermore, exploring different analytical techniques for monitoring drug loading and stability over time will provide additional insights into the long-term viability of the solid dispersion.

Drug content of fluconazole solid dispersion

The drug content of the prepared fluconazole solid dispersion was quantified to be 1.96 mg (98%). This measurement is crucial for evaluating the effectiveness of the solid dispersion technique, as it directly impacts the bioavailability and therapeutic efficacy of the drug. The study indicated that the drug was uniformly distributed throughout the solid dispersion, which is vital for maintaining consistent pharmacological effects. Such uniformity ensures that each dose administered will provide a predictable and effective amount of fluconazole, thus enhancing dosage reliability. The drug content of 1.96 mg aligns well with expectations based on the formulation methods employed, notably the fusion method combined with selected excipients like polyethylene glycol 6000 and sodium carboxymethyl cellulose. This suggests that these materials facilitated the effective encapsulation of fluconazole, enhancing its solubility and stability.

Drug loading and encapsulation efficiency

The evaluation of drug loading and encapsulation efficiency is crucial in determining the effectiveness of fluconazole solid dispersion formulations. The results obtained indicate significant findings reflecting the performance of the solid dispersion method used in this study. The drug loading of the fluconazole solid dispersion was calculated to be 19.62%. This percentage indicates the mass ratio of fluconazole present in the solid dispersion relative to the total weight of the dispersions. A drug loading of 19.62% suggests that the formulation successfully incorporates a substantial amount of the active pharmaceutical ingredient (within the solid dispersions). This is a favorable outcome as higher drug loading often correlates with improved therapeutic efficacy due to greater amounts of the drug being available for absorption when administered.

The encapsulation efficiency of the fluconazole solid dispersion was determined to be 39.24%.

The encapsulation efficiency of 39.24% indicates that nearly 40% of the initial drug was successfully encapsulated during the formulation process. This result highlights the potential of the solid dispersion technique to not only enhance the solubility of fluconazole but also to retain a significant portion of the drug within the formulation matrix.

The drug loading and encapsulation efficiency values suggest that the solid dispersion with SCMC and PEG 6000 effectively enhances the incorporation of fluconazole. Since fluconazole is known for its poor water solubility, such formulations are essential in addressing its bioavailability challenges. The observed drug loading ratio, combined with satisfactory encapsulation efficiency, may lead to improved dissolution rates, which are crucial for achieving desired plasma concentrations of fluconazole.

While the encapsulation efficiency shows a promising result, further optimization could enhance this parameter. Exploring different ratios of excipients or additional processing techniques could lead to improved encapsulation and overall performance of the formulations. One way to improve encapsulation efficiency is by adjusting the ratio of PEG 6000 to SCMC. Increasing the proportion of SCMC, which has strong drug-carrier interactions due to its hydrogen-bonding capabilities, could enhance drug retention within the matrix. Alternatively, increasing the proportion of PEG 6000 could improve the dispersion of the drug molecules and increase encapsulation, as PEG enhances drug solubilization. Further, applying a more controlled and gradual cooling process could help achieve more stable dispersions and enhance encapsulation efficiency by reducing drug recrystallization during solidification.

Particle size analysis

The particle size analysis of the fluconazole solid dispersion, physical mixture, and pure drug was performed using an optical microscope. The measurements revealed significant differences in the average particle sizes among the three formulations. The average particle size of pure fluconazole was found to be 23.8 µm±3.1 µm, for solid dispersion, it was 51.8 µm±3.9 µm; and for physical mixture, 53.6 µm±4.2 µm. The particle size of pure fluconazole was notably smaller compared to the solid dispersion and physical mixture. This difference in size can be attributed to the intrinsic properties of the drug, where crystalline structures typically yield smaller particle sizes.

In contrast, the solid dispersion exhibited a significantly larger mean particle size of 51.8±3.9 µm but with a more uniform distribution and a reduced standard deviation compared to the physical mixture ($p = 0.0325$). This increase in particle size in the solid dispersion formulation is likely due to the formation of larger amorphous aggregates, which enhance the surface area available for dissolution. The reduced standard deviation indicates a more homogeneous particle distribution, suggesting an effective dispersion of fluconazole within the carrier matrix. This uniformity in particle size contributes to consistent dissolution rates, as observed in *in vitro* release studies. Amorphous particles, unlike crystalline ones, have higher free energy and a less organized molecular structure, which makes them more readily soluble despite their larger size [23].

The statistical analysis confirms that the solid dispersion differs significantly from both the pure drug ($p=0.0054$) and the physical mixture ($p=0.0431$) in terms of particle size distribution, highlighting the role of solid dispersion technology in the modification of particle morphology and size. These findings support the hypothesis that solid dispersions improve drug solubility and dissolution by creating a more uniform and larger particle size distribution, which enhances drug-polymer interactions and mitigates the limitations of poorly soluble drugs.

Scanning electron microscopy (SEM) analysis

SEM analysis (fig. 1, 2, 3) revealed significant morphological differences between pure fluconazole and its solid dispersion formulations. Pure fluconazole exhibited a crystalline structure characterized by well-defined, sharply-edged particles with a distinct geometric shape. This crystalline nature is consistent with the drug's poor aqueous solubility. On the contrary, the solid dispersions of fluconazole with PEG 6000 and SCMC showed markedly different morphological characteristics. The SEM micrographs showed spherical amorphous particles with smooth surfaces and less defined edges. This transformation from a crystalline state to an amorphous state is a crucial finding, as it directly correlates with improved dissolution characteristics. The amorphous nature of the solid dispersion particles can be attributed to the molecular dispersion of fluconazole within the carrier matrix. During the fusion method of preparation, the drug likely dissolved in the molten carrier, and upon rapid cooling, it was unable to recrystallize, resulting in an amorphous solid solution. This amorphous state is energetically favorable for dissolution, as it requires less energy to break intermolecular bonds compared to that of a crystalline lattice. Furthermore, the SEM analysis revealed a more uniform particle size distribution in the solid dispersions compared to that of pure fluconazole. This uniformity can contribute to a more consistent dissolution behavior and potentially improve the drug's bioavailability. The observed morphological changes align well with the results of the particle size analysis, which showed an increase in the average particle size from 23.8 µm for pure fluconazole to 51.8 µm for solid dispersion. This increase in particle size, coupled with the amorphous nature, suggests that the drug is thoroughly dispersed within the carrier matrix, forming larger composite particles. SEM findings also support the results of *in vitro* dissolution studies. The amorphous state and increased surface area of the solid dispersion particles probably contributed to the enhanced dissolution rate observed, with 89.01% drug release after 180 min compared to 82.5% for pure fluconazole.

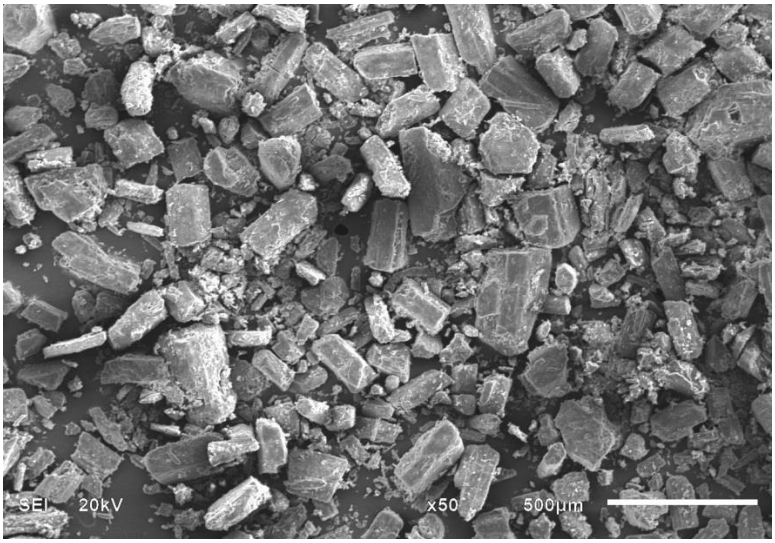

Fig. 1: SEM of pure fluconazole

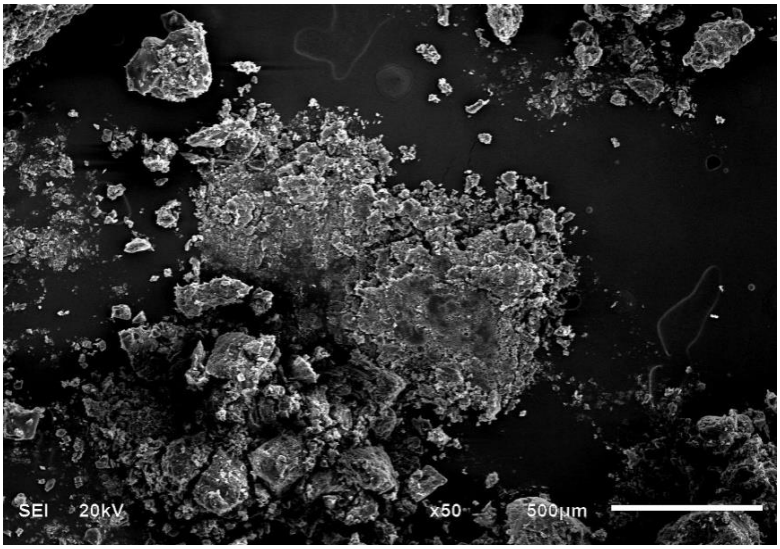

Fig. 2: SEM of physical mixture of fluconazole

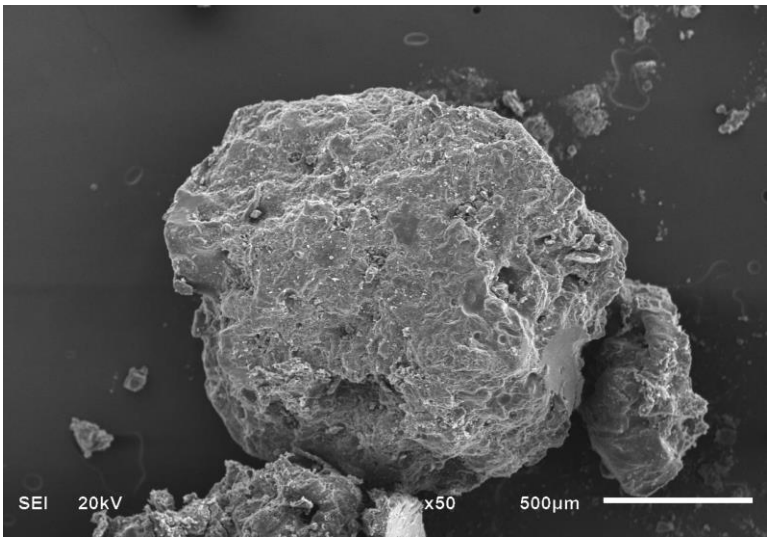

Fig. 3: SEM of fluconazole solid dispersion

Fourier transform infrared (FTIR) analysis

FTIR spectroscopy (fig. 4, 5, 6) analysis of pure fluconazole and its solid dispersion formulations revealed significant insights into the molecular interactions and structural changes that occur within the samples. Pure fluconazole exhibited characteristic peaks at 3120 cm^{-1} (O-H stretching), 1620 cm^{-1} (C=N stretching), and 1140 cm^{-1} (C-F stretching). These peaks are indicative of the molecular structure and crystalline nature of the drug. Notably, the observed shift in the O-H stretching peak from 3120 cm^{-1} (in pure fluconazole) to 3105 cm^{-1} in the solid dispersion is a strong indication of hydrogen bonding between the drug and the polymer-carriers. This shift suggests that the fluconazole molecules are interacting with the hydroxyl groups of PEG 6000 and SCMC, which disrupts the drug's crystal lattice and facilitates its transformation into an amorphous form.

The C=N stretching peak at 1620 cm^{-1} showed significant broadening in the solid dispersion spectra. This broadening indicates a reduction in the crystallinity of fluconazole and supports the formation of an amorphous solid dispersion. This broadening indicates weakened molecular bonds within fluconazole, as the drug is no longer present in a highly ordered crystalline state but is dispersed within the polymer matrix. The reduction in crystallinity lowers the energy barrier for dissolution, which is a key factor in improving drug solubility.

A new peak was observed at 2885 cm^{-1} in the solid dispersion spectra, which can be attributed to the C-H stretching of PEG 6000. This peak confirms the presence and interaction of the carrier with the drug molecules. The interaction between PEG 6000 and fluconazole, along with the shift in key peaks, demonstrates how the polymer matrix stabilizes the drug in an amorphous state. This stabilization prevents recrystallization, ensuring that fluconazole remains in a soluble form.

The intensity of the C-F stretching peak at 1140 cm^{-1} decreased in the solid dispersion spectra, suggesting a change in the molecular environment of fluconazole. These spectral changes provide strong evidence for molecular-level interactions between fluconazole and the carrier polymers. The observed peak shifts and broadening are consistent with the formation of hydrogen bonds and the disruption of the drug's crystal lattice, leading to an amorphous state. The FTIR results corroborate the findings from the SEM analysis and dissolution studies. The molecular interactions revealed by FTIR explain the morphological changes observed in SEM and contribute to the enhanced dissolution rate of the solid-dispersion formulations. Furthermore, the absence of any new peaks (apart from those attributable to the carriers) in the solid dispersion spectra indicates that no chemical degradation or incompatibility occurred during the preparation process. This finding is crucial to the stability and efficacy of the formulation.

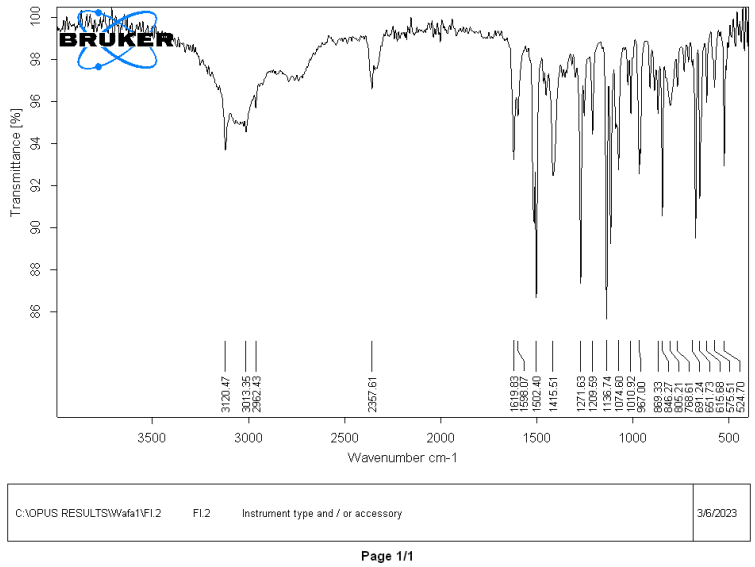

Fig. 4: FTIR spectra of pure fluconazole

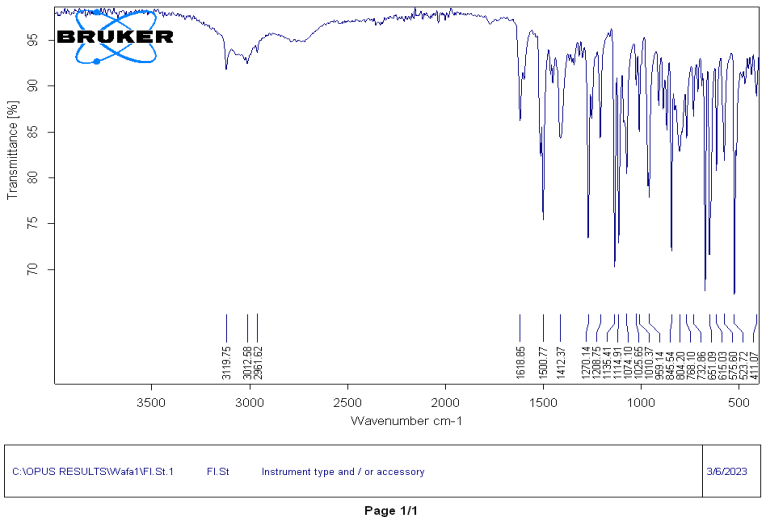

Fig. 5: FTIR spectra of solid dispersion of fluconazole

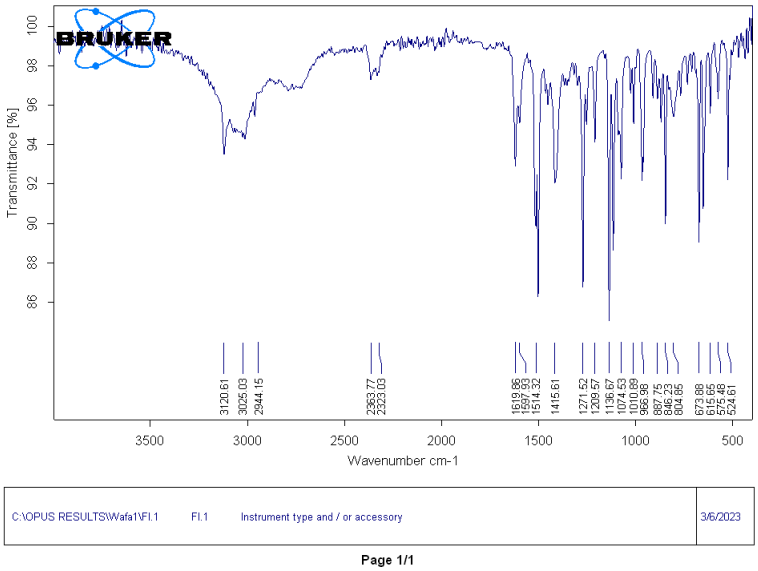

Fig. 6: FTIR spectra of the physical mixture of fluconazole

***In vitro* drug release**

The *in vitro* drug release study demonstrated a significant enhancement in the dissolution rate of fluconazole in the solid dispersion formulation compared to the pure drug and the physical mixture. The dissolution profile showed that within the first 15 min, the pure fluconazole exhibited a release of only 40.3%, indicating its limited solubility and slow dissolution rate. On the contrary, the solid dispersion achieved a markedly higher release of 23.9% at the same time point, suggesting improved wettability and faster dissolution facilitated by the amorphous state of the drug and the presence of hydrophilic carriers. Over 180 min, the cumulative drug release from the solid dispersion reached 89.01%, significantly outperforming both the pure drug, which released only 82.5%, and the physical mixture, which achieved a release of 84.1%.

The observed improvement in drug release from solid dispersion can be attributed to several factors. First, the transformation of fluconazole into an amorphous form in solid dispersion reduces its crystallinity, thereby enhancing its solubility and dissolution rate. Second, the inclusion of PEG 6000 and SCMC as carriers probably facilitated the formation of a more porous structure, increasing the surface area available for dissolution. This structural modification, as evidenced by SEM analysis, leads to improved wettability and reduced particle agglomeration, further contributing to the enhanced release profile.

To provide a deeper understanding of the release mechanism of fluconazole from the solid dispersion, we applied mathematical models to the drug release profile. Specifically, the Korsmeyer-Peppas, Higuchi, and first-order release models were used to analyze the dissolution data. The Korsmeyer-Peppas model was applied to determine the release mechanism. The release exponent (n value) was calculated, indicating whether the drug release followed Fickian diffusion ($n \leq 0.5$) or non-Fickian transport ($n>0.5$). The results suggest that the release of fluconazole from the solid dispersion follows a non-Fickian transport mechanism ($n=0.6432$), indicating both diffusion and erosion processes play a role in drug release. The Higuchi model was also used to investigate whether the drug release is diffusion-controlled. The release data showed a good fit with this model ($R^2=0.9987$), supporting the hypothesis that fluconazole release is primarily governed by diffusion through the polymer matrix. First-order release kinetics was assessed to determine whether the release rate depends on the remaining concentration of the drug within the dispersion. The release profile indicated a concentration-dependent release, typical of formulations designed to sustain drug release over time. Additionally, standard deviations and error bars were incorporated into the dissolution profile graph to provide statistical confidence in the results. The inclusion of error bars demonstrates the consistency and reproducibility of the dissolution data, reinforcing the observed improvement in drug release.

This complex release mechanism is favorable to achieving sustained therapeutic levels of fluconazole, particularly in clinical scenarios where rapid onset and prolonged drug availability are desirable. These findings highlight the potential of solid dispersion technology to overcome the solubility limitations of poorly water-soluble drugs, thereby enhancing their bioavailability and therapeutic efficacy.

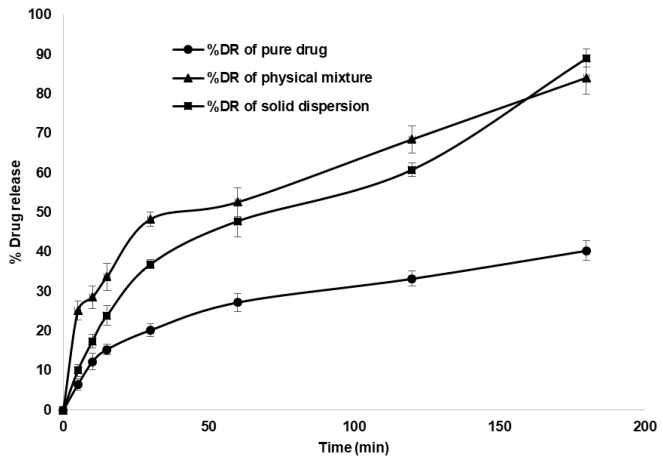

Fig. 7: Cumulative percentage release of pure fluconazole, physical mixture, and solid dispersion

CONCLUSION

This study successfully demonstrated the formulation and evaluation of fluconazole solid dispersions using PEG 6000 and SCMC as carriers. The solid dispersion significantly enhanced the dissolution rate of fluconazole, achieving 89.01% release in 180 min compared to 40.3% for the pure drug. FTIR analysis confirmed strong molecular interactions between fluconazole and the carriers, promoting the drug's amorphous state and improved solubility, while SEM provided visual confirmation of amorphization. The application of mathematical models, such as the Korsmeyer-Peppas and Higuchi models, further revealed that the release mechanism is governed by non-Fickian diffusion and diffusion-controlled processes, indicating the effective release profile of the drug.

Beyond these laboratory results, the findings have important clinical implications. Improved dissolution and bioavailability of fluconazole could lead to better therapeutic outcomes in patients, particularly in the treatment of systemic fungal infections where rapid and consistent drug absorption is critical. Enhanced solubility could reduce the need for higher dosing, potentially minimizing adverse effects such as hepatotoxicity or gastrointestinal disturbances commonly associated with fluconazole.

For the next steps, this formulation shows promise for scale-up and industrial production, but further studies are necessary. First, testing should be conducted in *in vivo* models to confirm the improved bioavailability and therapeutic efficacy observed *in vitro*. Scale-up processes, such as optimizing the fusion method for larger batches, should be explored. Additionally, regulatory considerations for solid dispersion formulations, including stability testing and storage conditions, will need to be addressed before advancing to clinical trials. Overall, this study lays the groundwork for developing more effective fluconazole formulations with potential clinical applications across a range of fungal infections.

ACKNOWLEDGMENT

The authors would also like to thank like DARIS and the University of Nizwa for the SEM and FTIR support.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

Contribution from each author: AKP was involved in conceptualizing and drafting the manuscript, BAS was involved in conceptualizing and statistical analysis, and WAH was involved in drafting the manuscript.

CONFLICT OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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