Synthesis and Spectroscopic Characterization of Co-Crystals of Fluconazole with Succinic Acid and Urea as Coformer

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| ABSTRACT |
| *Co-crystal engineering is an important aspect of pharmaceutical development as it enables the obtainment of structural varieties of drug forms of same active pharmaceutical compounds while maintaining or improving physico-chemical and therapeutic activities of the active pharmaceutical compounds. In this work, we report the green synthesis of two co-crystals of fluconazole with succinic acid and urea. White block single crystals were obtained after slow evaporation of ethanolic solution of fluconazole (FLU) with the coformers (succinic acid and urea) in 1:1 molar ratio and were characterized using UV and Fourier Transform Infrared (FTIR) spectroscopy. FTIR spectra of the co-crystals confirms the formation of the co-crystals in solid state with the appearance of diagnostic FTIR bands of both fluconazole functional groups and those of the coformers (succinic acid and urea) in succinic acid-fluconazole (SFLU) and urea-fluconazole (UFU) respectively. UV-Vis spectra also features the π-π\* absorption maxima of fluconazole in the co-crystals, providing additional evidence for the formation of the co-crystals.*  ***Keywords:*** *Fluconazole, Succinic acid, Urea, Co-crystals, Co-former, FTIR spectroscopy.* |

**1. Introduction**

The increasing epidemic in different parts of the world and the current COVID-19 pandemic [1] coupled with the global menace of drug-resistance by microbes [2] have increased the demand and continuous search for potent drugs and alternative therapies for combatting diseases that affect the populace. Since it will not necessarily require the laborious, time-consuming and costly clinical trials, one way to meeting this expanding need for pharmaceuticals is through improvement of the potencies and properties of existing pharmaceuticals and repurposing them for other disease conditions that they are not primarily indicated for [3].

Vast research on modifications of properties of drug compounds such as solubility, dissolution rate, bioavailability and stability have been achieved through derivatization of existing pharmaceuticals by means of salt and co-crystal formation [4],[5] as well as co-amorphous solid dispersions [6]. Often times, the resulting new compounds from afore-mentioned schemes have made possible new compounds with improved physico-chemical properties and therapeutic potentials [7]. These new compounds also have added advantage of acting through different mechanisms and/or overcoming common multidrug resistance (MDR) through synergistic effects of the individual components [8]. Co-crystal engineering affords the generation of a variety of solid forms of a drug that have physicochemical properties distinct from the solid co-crystal components. Such properties include but are not limited to solubility, dissolution, bioavailability, hygroscopicity, hydrate/solvate formation, crystal morphology, fusion properties, chemical and thermal stability, and mechanical properties. These properties can directly or indirectly affect the suitability and effectiveness of a particular API as a pharmaceutical product [9].

Co-crystal engineering has become of such great importance in the field of pharmaceuticals that a particular subdivision of multicomponent co-crystals has been given the term pharmaceutical co-crystals to refer to a solid co-crystal former component and a molecular or ionic API. The objective for pharmaceutical co-crystals is to have therapeutic agents with better properties, fewer side effects and that could overcome the problem of multidrug resistance more than the pure API [10]. Co-crystallization is a viable option and promising alternatives to expanding the structural and physico-chemical characteristics of existing organic compounds [11].

In this work, we report the green synthesis and spectroscopc characterization of two co-crystals of fluconazole, a broad-spectrum triazole antifungal drug with two pharmaceutically acceptable coformers, succinic acid and urea.

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| --- | --- | --- |
|  |  |  |
| (a) | (b) | (c) |

**Fig.1.** Structure of (a) fluconazole, (b) succinic acid, and (c) urea

**2. Materials and Methods**

***2.1. Materials***

All reagents (fluconazole, succinic acid and urea) and solvents (methanol ethanol, used in this research were of analytical reagents grade and were procured from VWR International and used without further purifications. UV-Visible absorption spectra of the co-crystal and respective API were recorded in the range of 200-400 nm on a JascoV-730 UV-Visible spectrophotometer and Infrared Spectra were recorded in the range 4000-400 cm-1 on Shimadzu FT-IR-8400 on samples pressed in KBr pellet at Redeemer University of Nigeria, Osun State.

***2.2. Synthesis***

***2.2.1. Fluconazole-Succinic acid Co-crystal (1:1, SFLZ)***

This co-crystal was obtained by solution-based co-crystallization method from 1:1 molar ratio of fluconazole and succinic acid. 0.06 g, 1 mmole of succinic acid and 0.153 g, 1 mmole of FLZ were accurately measured and both dissolved in 2 ml of ethanol and left for slow evaporation. Fine white block crystals were obtained after 9 days, which were collected into a tight container and stored for further analysis. UV-Visible (EtOH): 255.8 nm and 261.4 nm.

***2.2.2. Fluconazole - Urea Co-crystal (1:1, UFLZ)***

This co-crystal was obtained by solution-based co-crystallization method from 1:1 molar ratio of fluconazole and urea. 0.03 g, 1 mmole of urea and 0.153 g, 1 mmole of FLZ were accurately measured and both dissolved in 2 ml of ethanol and left for slow evaporation of the solvent. Fine white block crystals were obtained after 9 days, which were collected into a tight container and stored for further analysis. UV Visible (EtOH): 259 nm and 265 nm.



**Fig.2.** Synthetic scheme for synthesis of fluconazole-urea (UFLU), fluconazole-succinic acid (SFLU) co-crystals

**3. Results and Discussion**

***3.1. UV spectra***

The absorption spectra of the co-crystal and fluconazole were recorded in the range of 200-400 nm in the solvent used for the synthesis (ethanol). The electronic spectra of fluconazole (FLU) and the co-crystals (UFLU and SFLU) were illustrated in Fig.3. The peaks between 250 and 265 nm which fall in the ultraviolet region indicate π-π\* transition of the fluconazole moeity. In the synthesized co-crystal, peaks obtained were compared to the peaks of the respective APIs. The new co-crystals essentially have same UV spectra with the parent API (fluconazole) except for slight shift in absorption peaks. This confirms the formation of the co-crystals between fluconazole and the coformers (succinic acid and urea).



**Fig.3.** Electronic absorption spectra of fluconazole (FLU) and fluconazole - urea (UFLU) co-crystal

**Table 1.** Summary of physico-chemical parameters and UV-Vis absorption bands of fluconazole & its co-crystals

|  |  |  |  |
| --- | --- | --- | --- |
| **Compound** | **Appearance** | **Colour** | **API transition (nm), π-π\*** |
| **FLU** | Powdery | white | 258.3, 263.8 |
| **SFLU** | crystalline | white | 255.8, 261.4 |
| **UFLU** | crystalline | white | 259, 265 |

***3.2. FTIR spectra***

The FTIR spectra of the newly synthesized co-crystals have been taken on Shimadzu 8400-S FTIR spectrophotometer in the region of 400-4000 cm-1. The comparison of FTIR spectra of fluconazole with that of its co-crystals revealed certain characteristic differences and is consistent with the FTIR spectra of fluconazole and its previously determined co-crystals [12],[13].

One of the significant differences to be expected between the FTIR spectra of the parent API and its co-crystal is the absorption band at 3381 cm-1 in the spectrum of fluconazole attributed to O-H stretchingof fluconazole. This band is absent in the FTIR spectra of the co-crystals as it is involved in hydrogen bonding with the coformers (succinic acid and urea). The O-H bending at 1371 cm-1 in fluconazole is also absent in the FTIR spectrum of SFLU co-crystal. This further confirms the formation of co-crystal between fluconazole and succinic acid by the O-H group of fluconazole. C-O stretch of urea and succinic appeared at 1226 and 1307 cm-1 in UFLU and SFLU respectively. C-F stretching remained unchanged at 1421 and 1139 cm-1 in fluconazole and its co-crystals. The C-N and C-F stretching of fluconazole remained unchanged in the spectra of fluconazole and its co-crystals indicating that these groups are not involved directly in bonding interactions. This confirms the presence of urea and succinic acid in UFLU and SFLU co-crystals respectively. The FTIR spectra of the APIs (fluconazole) and its co-crystal are summarized in Table 2 below.

**Table 2.** Diagnostic FTIR bands of fluconazole and its co-crystals

|  |  |  |  |
| --- | --- | --- | --- |
| Fluconazole, cm-1 | UFLU, cm-1 | SFLU, cm-1 | Assignment |
| 3381 sh | - | - | O-H stretch |
| 3020, 2956 | 2956 | 3020, 2956 | =C-H stretch |
| - | 1666 | 1693 | C==O stretching of urea and succinic |
| 1618 | 1620 | 1618 | C=C aromatic stretching |
| 1506 | 1516 | 1516 | C=N stretching of triazole |
| 1421, 1139 | 1421, 1139 | 1421, 1139 | C-F stretching |
| 1209w | 1226m | 1307 | C-O stretching |
| 1274 | 1274 | 1274 | C-N stretch of triazole ring |
| 968 | 968 | 968 | C=C bending |

Key: sh= shoulder, w= weak, m= medium

**Fig.4.** FTIR spectra of fluconazole (FLU), urea-fluconazole (UFLU) and succinic acid-fluconazole (SFLU) co-crystals (shown is the region 1700-400) cm-1)

**4. Conclusion**

In this research, new co-crystals of an anti-fungal drug (fluconazole) were successfully synthesized. These co-crystals were prepared by solution method to enhance the physiochemical properties of these co-crystals. The co-crystals were characterized using UV and FT-IR spectrophotometery by comparing the spectra of the API’s and co-crystals. The UV and FTIR spectra confirm the formation of the co-crystals by hydrogen bonding formation between the O-H group of fluconazole with the coformers. The new co-crystals are stable at ambient laboratory conditions.

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***Competing Interests Statement***

*The authors have declared that no competing financial, professional or personal interests exist.*

***Consent for publication***

*Both authors contributed to the manuscript and consented to the publication of this research work.*

***Availability of data and material***

*Supplementary information such as the raw files of the UV and FTIR spectra are available from the authors upon reasonable request.*

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