Section A- Research Paper

COCRYSTALS OF FENBENDAZOLE WITH ENHANCED IN VITRO DISSOLUTION PERFORMANCE

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Article History: **Received:12/05/23** **Revised:29/05/23** **Accepted: 15/06/23**

ABSTRACT

The present study involves cocrystal preparation, characterization and solubility studies of Fenbendazole. Fenbendazole is a benzimidazole carbamate anthelminthic drug. Fenbendazole is chemically N- [6(Phenylsulfanyl) -1H-Benzimidazole-2-yl] hydrazine carboxamide. Cocrystal formation has been attributed to hydrogen bond interactions between fenbendazole and pharmaceutical conformers involving carboxylic-carboxylic or carboxylic-amino interactions. These cocrystals were created using the liquid-assisted grinding technique, and their distinctive thermal [Differential Scanning Calorimetry (DSC)] profiles served as the basis for their categorization. They were confirmed by Scanning Electron Microscopy (SEM). When compared to the pure medication, the cocrystals made with cinnamic, benzoic, and salicylic acids showed noticeably higher solubility. Improved dissolution profiles from their in-vitro dissolution experiments further support their support for raising Fenbendazole's oral bioavailability. among the three Fenbendazole carbamates that have been ready. The cocrystal of fenbendazole and salicylic acid performed well.

Keywords: Fenbendazole, Cinnamic acid, Benzoic acid, Salicylic acid, Co-Crystals, Solubility studies.

Doi: 10.31838/ecb/2023.12.Si8.826

INTRODUCTION

A solid made up of two or more distinct molecular and/or ionic compounds that are neither solvates nor simple salts, typically in a stoichiometric ratio, is known as a cocrystal. [1]. They are single phase neutral crystalline minerals. If at least one of the coformers is an API and the other is appropriate from a pharmacological perspective, the crystal is classified as a pharmaceutical cocrystal [2].

The current work includes the preparation of cocrystals as well as the characterization and solubility testing of fenbendazole. Fenbendazole is a benzimidazole carbamate anthelminthic drug. Chemically, Fenbendazole is N-[6(Phenylsulfanyl)-1H-Benzimidazole-2-yl] hydrazine carboxamide. By using conformers like salicylic, benzoic, and cinnamic acids and the liquid-assisted grinding technique (LAG), the current work aimed to increase the solubility of Fenbendazole [3,4].

MATERIALS AND METHODS

Materials

Fenbendazole, Cinnamic acid, Benzoic acid, Salicylic acid.

Methods

Preparation of cocrystals

Cocrystals were produced using the LAG method. While equimolar quantities of the API and conformers (benzoic acid, salicylic acid, and cinnamic acid) were put in a mortar and pestle at room temperature, methanol was added dropwise as a solvent during grinding. The resultant mass was dried and evaporated [5].

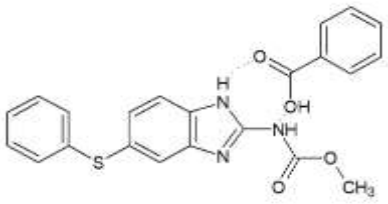
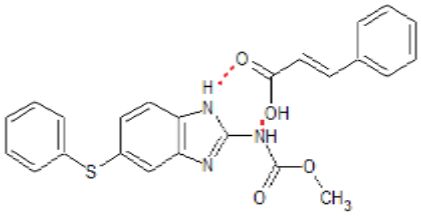
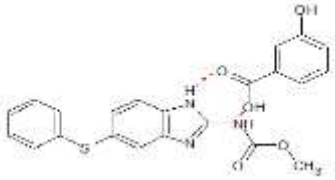


Fig 1: A: Fenbendazole-Benzoic acid



B: Fenbendazole-Cinnamic acid



C: Fenbendazole- Salicylic acid

Solubility studies

The dissolution solubility studies of Fenbendazole and its cocrystals were determined using a 4-hour shake flask method. In this study, surplus medication was injected into vials together with 10 ml of water [6]. This was shaken with a mechanical shaker at room temperature for 24 hours. Filtered, the solution was then examined spectrophotometrically at 293 nm to determine how much drug had been dissolved.

Scanning Electron Microscope (SEM) studies

SEM was used to study the surface morphology of pure medication, as well as Fenbendazole-Cinnamic acid, Fenbendazole-Benzoic acid, and Fenbendazole-Salicylic acid. Fenbendazole has cocrystallized into the characteristic fenbendazole crystalline structures, such as fenbendazole-cinnamic acid, fenbendazole-benzoic acid, and fenbendazole-salicylic acid [7].

Intrinsic Dissolution studies

The effectiveness of APIs in vivo can be determined by looking at their intrinsic dissolution rate. Utilising the paddle method, the dissolving rate investigations were carried out in 900 ml of buffer (pH 7.4) at 50 rpm and 37 ±0.5 ºC in a dissolution equipment (Electrolab dissolving Tester (USP), TDT-06L).The dissolution medium (7.4 pH buffer) was combined with 100 mg of the drug or its equivalent in cocrystals, and samples were taken at regular intervals for four hours. By substituting new medium, the dissolving medium volume was adjusted to 900 ml. The materials were immediately passed through a 0.40-m membrane filter, appropriately diluted, and subjected to a 293nm spectrophotometric analysis [8].

RESULTS

Solubility studies

By shaking the samples on a mechanical shaker for 24 hours at room temperature, the produced cocrystals and the pure drug were examined for saturation solubility in aqueous medium. After that, the samples were examined with a UV spectrophotometer at 293 nm.

Table 1 and Figure 3 showed that the concentration of pure Fenbendazole was 0.21 mg/ml, whereas the concentrations of Fenbendazole in cocrystals with benzoic acid, salicylic acid, and cinnamic acid were 0.985 mg/ml, 1.052 mg/ml, and 0.845 mg/ml, respectively. The results indicated that cocrystals made with salicylic acid showed a 50-fold improvement in solubility over pure API (fenbendazole) in aqueous conditions.

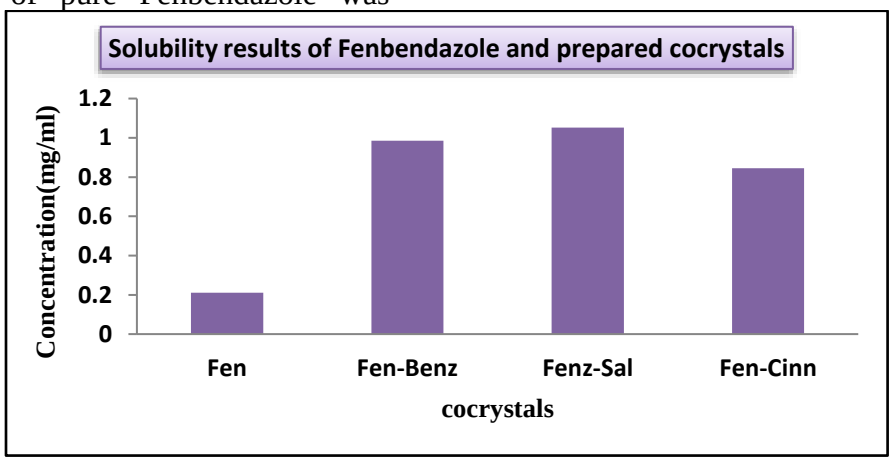
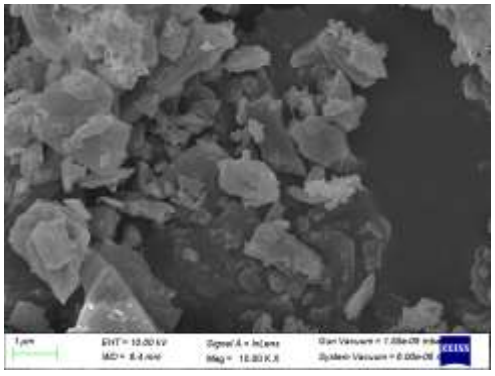


Figure 2: Solubility results of Fenbendazole and prepared cocrystals

SEM studies

The solid morphology of the Fenbendazole and its cocrystals are studied. The Fenbendazole- Benzoic acid cocrystals (Figure 3A) showed smaller irregular-sized particles, which may be due to the impaction mechanism involved in the process. The sample of Fenbendazole- Cinnamic acid cocrystals showed aggregated particles (Figure 3B) where Fenbendazole- Salicylic acid showed large irregular flat crystals (Figure 3C).



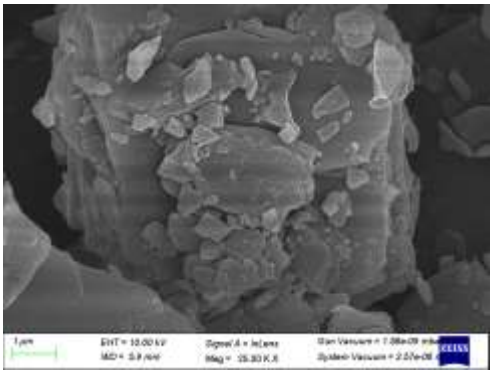
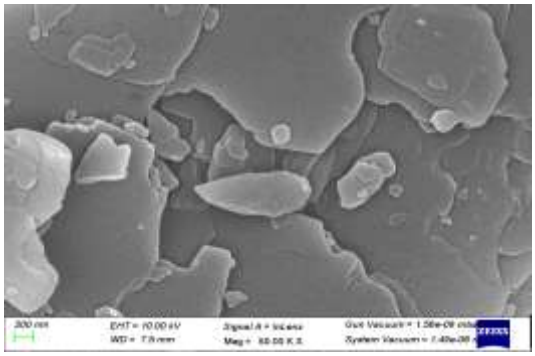


Figure 3: A: Fenbendazole –Benzoic acid B: Fenbendazole- Cinnamic acid



C: Fenbendazole- Salicylic acid

***In vitro* Dissolution Profile**

When compared to pure medication, Fenbendazole-Salicylic acid showed the highest cumulative % drug release of 38% and pure drug of 22 % in 15 minutes. This study unequivocally demonstrated that Fenbendazole cocrystals were superior to the pure drug. When compared to pure drug, which exhibited an 81% drug release after one hour, fenbendazole-salicylic acid obtained 100% drug release in under one hour since the drug was present in solubilized form. As a result, the amount of drug surface that might dissolve greatly increased.

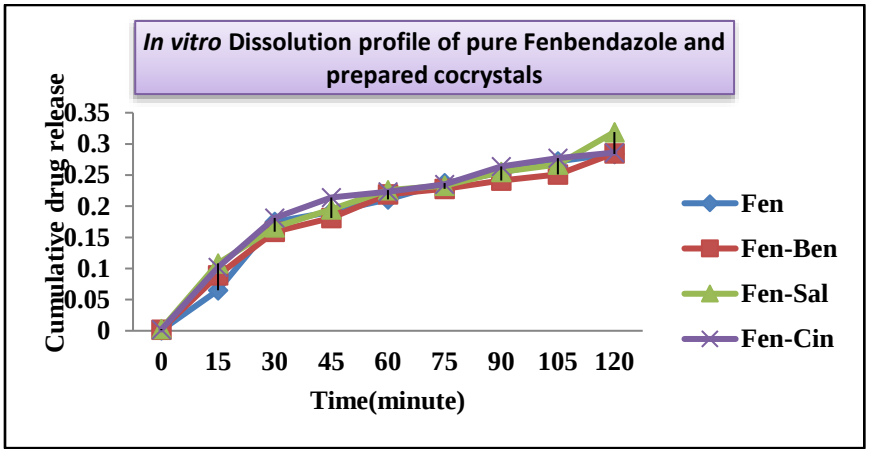


Figure 4: *In vitro* Dissolution profile of pure Fenbendazole and prepared cocrystals

DISCUSSION

To increase the solubility of the drug, a number of approaches are available that can be utilized singly or in tandem. Fenbendazole's co crystals were made using coformers like benzoic acid, cinnamic acid, and salicylic acid to further increase the drug's solubility. Using the LAG technique, three new Fenbendazole cocrystals with coformers were prepared, and SEM examinations were used to thoroughly characterize them. These results show that carboxylic-carboxylic or carboxylic-amino groups form hydrogen bonds as the basis for the majority of intermolecular interactions. These findings of this study will help us in advanced Fenbendazole cocrystals screening and synthesis.

DSC thermograms showed a single sharp melting endotherm at a position different from that of Fenbendazole and coformers suggested the formation of a novel crystalline phase. Before the genuine melting, there was a large desolvation

endotherm, which suggested that solvated cocrystals had formed. The crystalline structure of the prepared cocrystals was revealed in SEM images. The cocrystallization method clearly indicates increased bioavailability of the drug because the Fenbendazole-Salicylic acid crystals were more soluble than the other two crystals, with a solubility of 1.052 mg/ml. Salicylic acid appears to be the preferred coformer for the production of cocrystals of fenbendazole, according to this finding, which was further corroborated by intrinsic dissolution experiments carried out in buffer (pH 6.8).

CONCLUSION

The drug fenbendazole is an anti-helminthetic, insoluble and has a low bioavailability. Fenbendazole (F) and pharmaceutical coformers engage via hydrogen bonds with -NH from the donor (F) and two O atoms from the acceptor (conformers). These cocrystals were successfully formed using the liquid-assisted grinding process. SEM tests were used to further confirm them. Comparing these cocrystals to pure Fenbendazole (F), they showed noticeably higher solubilities (30–50 times higher). Additionally, they were assessed for their in-vitro dissolution experiments, where all of the cocrystals displayed noticeably high dissolution profiles (50%) and indicated that they were in favor of enhancing the oral bioavailability of fenbendazole.

Acknowledgement

The University College of Pharmaceutical Sciences (Kakatiya University) Warangal is acknowledged by author for offering first rate research facilities and encouraging research endeveavors.

Conflict of interest: None

Ethics statement: This is my original research work**.**

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