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Utilization of co-crystallization technology to enhance the solubility and the dissolution profiles of famotidine

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ABSTRACT

Background: Co-crystallisation is a useful technique that can be used to improve important physicochemical properties of drugs that have solubility troubles, without any chemical modification. *Aim:* This study investigates the co-crystallization of the poorly soluble drug famotidine (FMT) with either nicotinamide (NIC) or urea as co-formers. *Methodology:* The method employed for preparation was solvent evaporation at a predetermined stoichiometric ratio. The prepared formulations were evaluated for their solubility, while a selected co-crystal (FMT1) was also assessed through the undertaking of *in vitro* dissolution, differential scanning calorimetry, and Fourier transform infrared spectrometry. *Results:* All the prepared formulations demonstrated an improvement in drug solubility compared to the pure drug. However, FMT1, which contains a 1:1 ratio of FMT to NIC, yielded the best results. *Conclusion:* The findings of this study can suggest that the solubility and dissolution profile of FMT might be successfully enhanced by this technique.

KEYWORDS

co-crystals, famotidine, nicotinamide, urea, solvent evaporation technique

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1. INTRODUCTION

Pharmaceutical co-crystals are used for the improvement of the critical physicochemical properties of drugs, without resorting to chemical modifications. These properties include solubility, dissolution rate, micrometric characteristics, as well as pharmacokinetic and pharmacodynamic attributes [1-4]. Pharmaceutical co-crystallization uses a system that combines a drug with the right co-former with non-covalent bonding, like stacking, hydrogen bonds, van der Waals force, and electrostatic interactions, at specific stoichiometric ratios [5,6]. Co-formers that can be used in co-crystallization may include excipients or other drugs. Many co-crystals exists, containing co-crystal formers selected from the list of GRAS (generally recognized as safe) compounds that contains different food additives, preservatives, or pharmaceutical excipients [7,8].

Generally, different methods can be used in the preparation process of co-crystals. These

methods are subdivided into two types: solid-based and solvent-based methods. Solid-state methods or solvent-free methods may use some or no solvent, and they are always supported by the use of mechanical energy for the delivery of the co-crystallization. This category includes neat grinding, liquid-assisted grinding, polymer-assisted grinding, and hot melt extrusion [9,10]. On the other hand, the solvent-based method is a technique commonly used for co-crystallization and involves the use of a solvent or a solvent mixture. Examples in this category include solvent evaporation, cooling co-crystallization, adding anti-solvents, and slurrying [9].

Famotidine (FMT) is a white-pale yellow powder that is very slightly soluble in water, practically insoluble in alcohol and ethyl acetate, freely soluble in glacial acetic acid, and slightly soluble in methyl alcohol [11]. The aim of this study was to modulate the physicochemical properties of FMT by using two different co-formers (Figure 1).

2. METHODOLOGY

2.1. Materials

FMT powder and urea were provided by Pioneer (Iraq) as a gift sample for study. Nicotinamide (NIC) was provided by CDH (India), while potassium dihydrogen orthophosphate was provided by GCC (UK) and glacial acetic acid was provided by Chem-Lab (Belgium).

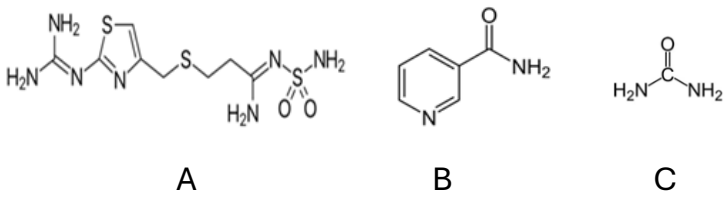

Figure 1. Chemical structures of famotidine (A), nicotinamide (B), and urea (C).

2.2. Method of co-crystallization

The co-crystallization process was conducted by using the solvent evaporation technique. In brief, 338 mg of FMT and co-formers (NIC or urea) in a stoichiometric ratio (as shown in Table 1) were dissolved in an appropriate volume of glacial acetic acid while stirring until all the solvent had completely evaporated [13,14]. The resulting co-crystals were collected and stored in a desiccator.

2.3. Characterization of the obtained co-crystals

2.3.1. Determination of saturated solubility

Excessive amounts of FMT and prepared co-crystals were put separately in 10-mL tubes of distilled water. These tubes were then agitated in a water bath shaker (50 rpm/min) for 48 h, at 25°C.

Table 1. Formulation of different co-crystals of famotidine (FMT). *Abbreviations used:* NIC, nicotinamide.

Formula	Composition	Ratio
FMT1	FMT : NIC	1:1
FMT2	FMT : NIC	1:2
FMT3	FMT : NIC	1:3
FMT4	FMT : Urea	1:1
FMT5	FMT : Urea	1:2
FMT6	FMT : Urea	1:3

The solution was then filtered by a 0.45-μm filter membrane and the solubilized drug was subsequently read by a spectrophotometer at 280 nm [15].

2.3.2. *In vitro* dissolution study

The *in vitro* dissolution study was conducted by using a USP type 2 apparatus with 50 rpm as the rotating speed. The dissolution conditions included 900 mL of a phosphate buffer (pH 4.5) at 37ºC. At 5-min intervals, samples were taken and replaced with an equal volume of the same dissolving medium. Each removed sample was promptly filtered, and it was then analysed by a UV spectrophotometer at 266 nm. In order to explore the impact of the co-former on the drug release profile, comparative dissolution tests of FMT and of the formulation with increased solubility were performed [16].

2.3.3. Fourier transform infrared (FTIR) spectroscopy

FMT and certain FMT co-crystal samples in powder form were combined with KBr crystals at a constant 1:10 ratio. They were grinded until being homogeneous, then compressed at a 20-psi pressure. Finally, they were analysed over a range of 4,000 to 400 cm^{-1} through FTIR with attenuated total reflectance (Shimadzu, Japan) [17].

2.3.4. Thermal properties' analysis

A differential scanning calorimetry (DSC) - thermogravimetric analysis (TGA) device (SDT Q600 in V20.9 Build 20; TA Instruments, USA) was utilized in order to perform the thermal analysis. The objective was to examine the thermal action of FMT, the co-former, and specific co-crystals. These samples were heated at 10ºC/min, beginning at 50ºC and rising to 300ºC. The heating process took place in hermetically sealed aluminum pans within a nitrogen flow (30 mL/min) [18].

2.4. Statistical analysis

The solubility study data are presented as a mean ± standard deviation and were analyzed by using the one-way analysis of variance (ANOVA) in order to identify any significant results (p<0.05). The dissolution data, on the other hand, were analyzed by using DDsolver for Excel.

3. RESULTS

Table 2 displays the saturated solubility values obtained from this study of pure FMT and FMT co-crystals. Figure 2 compares the FMT and FMT1 dissolution profiles. In order to check for hydrogen bonds in the synthesized formula (FMT1) and eliminate any potential chemical interactions between FMT and NIC, the FTIR spectroscopy was analysed. The formula's spectra showed widened bands at wavenumbers 3,356 to 3,155 cm^{-1} (Figure 3). The DSC results demonstrated endothermic peaks of FMT and NIC at 167.05ºC and 129.13ºC, respectively (Figures 4A and 4B). In the DSC thermogram of the selected co-crystal, a peak appeared at 84.34ºC. In addition to that, TGA revealed that a weight loss occurs at the melting point of these three samples.

Table 2. Solubility data for the formed famotidine (FMT) co-crystals. *Note:* Results expressed as mean ± standard deviation (n=3).

Formula	Saturated solubility (mg/mL)
Pure drug	0.99 ± 0.09
FMT1	16.58 ± 0.92
FMT2	8.29 ± 0.13
FMT3	8.61 ± 0.06
FMT4	8.15 ± 0.60
FMT5	13.32 ± 1.94
FMT6	14.23 ± 0.07

4. DISCUSSION

4.1. Determination of saturated solubility

When compared to the pure drug, the co-crystals of both NIC and urea with FMT demonstrated an increase in saturated solubility. These results can be attributed to favourable hydrogen bond interactions between the drug and the co-former, as shown in previous studies [19-22] and as confirmed by the FTIR spectroscopy results.

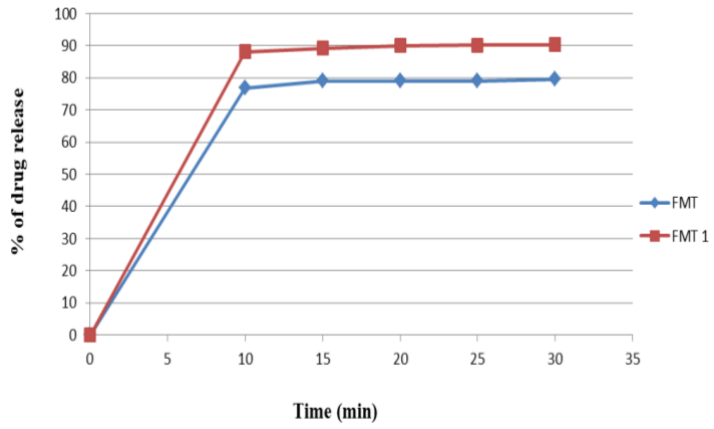

Figure 2. *In vitro* dissolution profiles of famotidine (FMT) and of FMT1 in phosphate buffer (pH 4.5), at 37ºC.

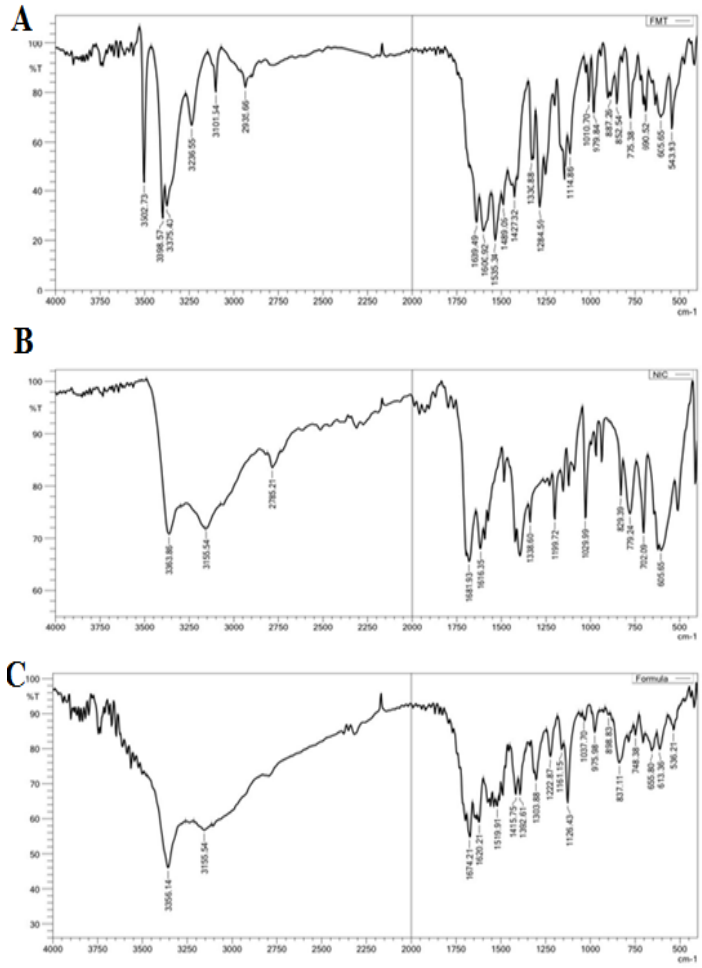

Figure 3. Fourier transform infrared spectrum of famotidine (A), nicotinamide (B), and their co-crystal formula FMT1 (C).

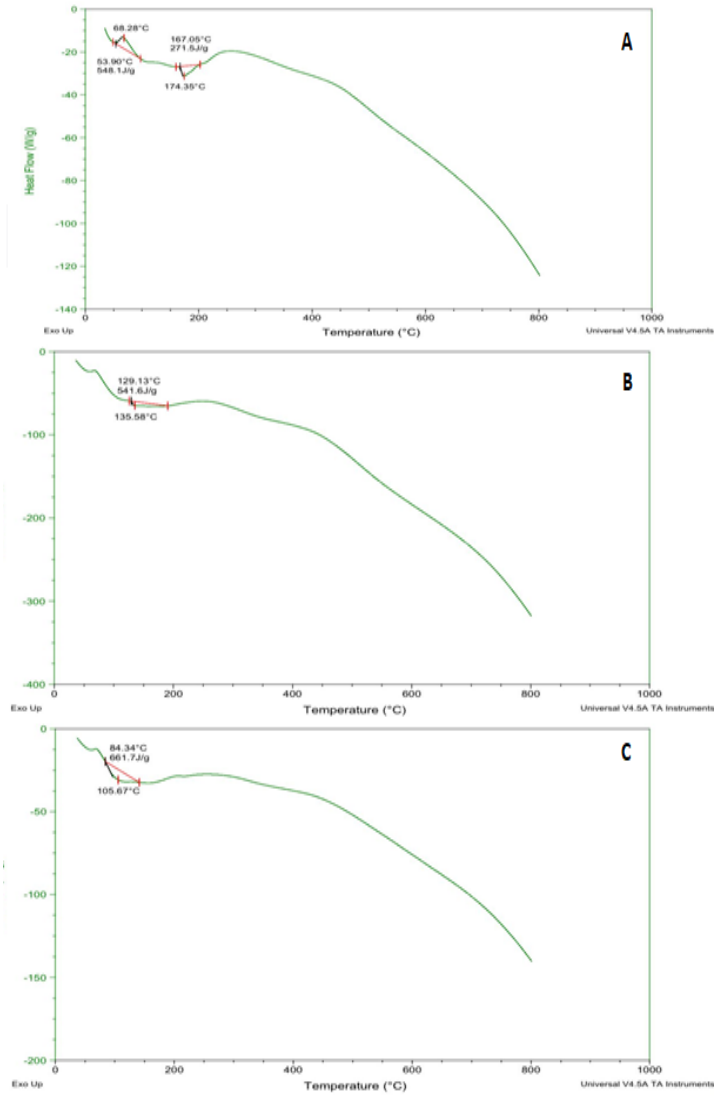

Figure 4. Differential scanning calorimetry and thermogravimetric analysis curves of famotidine (A), nicotinamide (B), and their co-crystal formula FMT1 (C).

However, the most significant enhancement was observed in the 1:1 FMT:NIC formulation, showing a 16-fold increase. In addition, improvements in FMT solubility were observed through a co-crystallization with malonic acid [23]. Previous reports have demonstrated enhanced solubility of FMT through a co-crystallization with sorbic acid and syringic acid [24].

4.2. *In vitro* dissolution study

Figure 2 shows that FMT released 79% of the drug after 30 min, whereas its prepared co-crystals released 90% of the drug after the same time. The similarity factor, f_2, was calculated to be 48.18. This study reveals a significant rise in the drug dissolution percentage of the co-crystals in comparison with that of the pure FMT, as also demonstrated in previous studies [24]. This increase in drug release might be attributed to an enhancement in drug solubility within the prepared co-crystals [18].

4.3. FTIR spectroscopy

The formula spectrum showed widened bands at wavenumbers 3,356 to 3,155 cm^{-1}, which belong to intermolecular hydrogen bonding [18,25-27].

This hydrogen bonding occurs between the N-H of FMT and the N atoms of NIC. Meanwhile, the pure drug had sharp peaks in its spectrum, as well as additional peaks at 3,375 and 3,398 cm^{-1} for the NH_2 group of FMT.

4.4. Thermal properties' analysis

DSC is a good thermoanalytical technique for the description of solid-solid interactions of drugs with co-formers, if present. The interactions can be proved in the form of appearance, shifts, or disappearance of endothermal or exothermal effects or variations in related enthalpy [28]. The obtained DSC results show the crystalline nature of FMT and NIC [19,29]. The drop in the melting point of the co-crystal (84.34^{o}C) might be because of how FMT and the co-former interact, which changes how crystallized the molecules are. This leads to a new crystal form with altered physical properties, including melting point and solubility [30-32]. Furthermore, the undertaken TGA has revealed that weight loss occurs at the melting point of the samples, thereby indicating the thermal stability, compatibility, and purity of the prepared co-crystals [33].

5. CONCLUSION

Co-crystallization represents an interesting technique for the enhancement of the solubility and dissolution profiles of medications having solubility issues. It involves combining the drug with the co-former of the co-crystal through non-covalent interactions, primarily hydrogen bonding. These co-formers, which are polar in nature, increase the drug's affinity for water molecules, leading to improved drug solubility and release profiles.

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CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

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