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Enhancing Dissolution of Febuxostat: Novel Febuxostat–Syringic Acid Multicomponent Crystals via Liquid-Assisted Grinding

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Abstract: Gout is a chronic inflammatory disease characterized by the deposition of monosodium urate crystals in the joints, and its global prevalence continues to increase. Febuxostat, a selective xanthine oxidase inhibitor, serves as an alternative therapy for patients who cannot tolerate allopurinol. Although effective, its clinical performance is limited by very low aqueous solubility and slow dissolution due to its Biopharmaceutics Classification System (BCS) Class II characteristics. Enhancing its solubility is therefore essential to improve oral absorption. This study aimed to prepare and characterize a febuxostat–syringic acid multicomponent crystal using the liquid-assisted grinding (LAG) method and to evaluate its impact on dissolution behavior. Multicomponent crystals were prepared using various molar ratios and optimized based on differential scanning calorimetry (DSC) results. Further characterization was conducted using powder X-ray diffraction (PXRD), Fourier-transform infrared spectroscopy (FTIR), and scanning electron microscopy (SEM). Dissolution studies were conducted with three replicates (n=3) in phosphate–citrate buffer pH 5.5 containing 1% sodium lauryl sulfate followed by HPLC analysis. The formation of a multicomponent crystal was evidenced by a reduced melting point and decreased peak intensity, along with distinct diffraction patterns indicating lower crystallinity compared to the febuxostat and syringic acid components. FTIR analysis revealed shifts in the absorption of wave numbers, while SEM showed smaller and rougher particles, indicating improved wettability. Statistical analysis using one-way ANOVA showed that the febuxostat–syringic acid multicomponent crystal demonstrated significantly enhanced dissolution (99.21% at 60 minutes) compared with pure febuxostat (76.00% at 60 minutes) ($p < 0.05$). The febuxostat–syringic acid multicomponent crystal prepared via the LAG method improved the physicochemical characteristics and dissolution performance of febuxostat. This approach provides a potential strategy to enhance the bioavailability of poorly soluble BCS Class II drugs.

Keywords: febuxostat, gout, liquid-assisted grinding, multicomponent crystal, syringic acid

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1. INTRODUCTION

Gout is a chronic inflammatory joint disease caused by the formation and deposition of monosodium urate crystals in the joints and surrounding tissues due to blood saturation. Consequently, the condition is characterized by hyperuricemia and recurrent acute arthritis attacks, affecting 1–2% of the global population with an increasing prevalence (Pisaniello et al., 2018). The current treatment options for chronic gout include drugs that enhance the overall clearance of uric acid from the body (uricosuric agents) or reduce uric acid production (xanthine oxidase inhibitors) (Alirezaei et al., 2017). Febuxostat (FEB) is a weakly acidic active pharmaceutical ingredient with pKa values of 3.42 and 0.39. It acts as a non-purine, selective xanthine oxidase inhibitor, reducing uric acid production (Ghallab et al., 2022). FEB has several significant limitations. It is a compound with very low aqueous solubility (12.9 µg/mL) and is classified as a Biopharmaceutical Classification System (BCS) Class II . Solubility plays a crucial role in determining the rate of drug absorption into systemic circulation. Low solubility can result in a slow dissolution rate and incomplete absorption, which can lead to reduced oral bioavailability. Several approaches have been explored to enhance the solubility of poorly soluble drugs, including particle size reduction, formation of multicomponent crystals, solid dispersions, the use of surfactants, and

complexation techniques. Improving the solubility and bioavailability of BCS Class II drugs remains a significant challenge in the development of effective oral formulations (Deshpande et al., 2023). One of the key challenges in developing new solid forms of FEB with higher solubility and bioavailability lies in producing a pharmaceutically effective, easily formulated, and stable product with practical manufacturing and storage requirements (Jagia et al., 2022).

Several studies have reported various approaches to overcome the solubility issues of FEB; however, the outcomes have remained unsatisfactory. Traditional methods, such as salt formation, are only applicable to ionizable compounds, presenting a challenge for molecules with poor ionization potential (Santenna et al., 2019). Polymorph formation is not always desirable, as polymorphic transformation may alter the properties of the formulated product. Solid dispersions are often prone to instability over time; amorphous drug forms, although typically exhibiting higher solubility, may recrystallize during storage, leading to reduced solubility and bioavailability (Pandi et al., 2020). Meanwhile, eutectic systems can be susceptible to environmental conditions such as temperature and humidity, which may affect the stability and performance of the product during storage and transportation (Yu et al., 2021). The formation of multicomponent crystals has emerged as an effective strategy to enhance the solubility of poorly soluble drugs. This approach can modify the physical properties of an active pharmaceutical ingredient (API) without altering its pharmacological activity (Berry and Steed, 2017). A previous study reported the formation of febuxostat multicomponent crystals via the liquid-assisted grinding method using p-toluenesulfonic acid as a coformer (Ungur et al., 2023).

Syringic acid was selected as a potential coformer based on crystal engineering principles. The molecule contains one carboxylic acid group together with phenolic hydroxyl and methoxy substituents, providing multiple hydrogen-bond donor and acceptor sites capable of forming robust supramolecular synthons with febuxostat. Such intermolecular interactions are expected to modify crystal packing, reduce lattice energy, and consequently improve the dissolution behavior of febuxostat.

The preparation method plays a vital role in determining the final crystal characteristics. Among the commonly used techniques, the liquid-assisted grinding (LAG) method, also known as solvent-drop grinding, has gained attention for its efficiency and simplicity. This method combines neat grinding and solvent evaporation by grinding the two components in a stoichiometric ratio with a small amount of solvent (Ying et al., 2021). This study aimed to develop a new multicomponent crystal solid form of FEB and investigate its potential to improve the solubility and dissolution rate of FEB. The resulting multicomponent solid form was characterized to identify the functional groups involved, thereby providing insight into the intermolecular interactions that occur and how these interactions influence the solubility and dissolution properties (Guo et al., 2021).

To the best of our knowledge, Although several studies have reported febuxostat multicomponent crystals using various coformers, no previous study has reported the preparation of febuxostat–syringic acid multicomponent crystals by liquid-assisted grinding or evaluated their influence on the physicochemical characteristics and dissolution behavior of febuxostat. Therefore, this study introduces a new coformer candidate in multicomponent crystal engineering for poorly soluble drugs crystals and evaluate their effect on the dissolution performance of febuxostat.

2. MATERIAL AND METHODS

2.1 Materials

Febuxostat (Lupin, India), syringic acid (TCI, Japan), asetonitril pro analysis (Merck, Germany), CO_2 free distilled water , asetonitril grade for liquid chromatography (Merck, Germany), metanol pro analysis (Merck, Germany), aquabidest (Ikapharmino, Indonesia), Na_2HPO_4 (Merck, Germany) citric acid, (TCI, Japan), Sodium lauryl sulfat (Kao, Indonesia).

2.2 Methods

a. *Preparation of multicomponent crystal febuxostat-syringic acid*

To determine the optimal ratio between the active pharmaceutical ingredient and the coformer, various molar ratios were prepared, namely 1:1, 1:9, 2:8, 3:7, 4:6, 4.5:5.5, 5.5:4.5, 6:4, 7:3, 8:2, and 9:1, in order to identify the ratio that produced a single peak. The febuxostat multicomponent crystals were then prepared at equimolar ratios of febuxostat and syringic acid of 1:1, 4:6, 4.5:5.5, 5.5:4.5, and 6:4. The mixtures were transferred into a mortar and ground manually for 30 minutes using a pestle while adding 30 µL of acetonitrile (pro analysis grade) dropwise with a micropipette. The samples were stored in tightly sealed containers and placed in a desiccator.

b. *Differential Scanning Calorimetry (DSC) Analysis*

A calibrated DSC instrument was used for thermal analysis. The analysis was performed on samples of FEB, syringic acid, and the FEB–syringic acid multicomponent crystal. Approximately 3 mg of each sample was placed in an aluminum pan, sealed, and heated from 50°C to 250°C at a rate of 10°C per minute.

c. Powder X-ray Diffraction (PXRD) Analysis

Samples of FEB, syringic acid, and the FEB–syringic acid multicomponent crystal were placed on an X-ray diffractometer sample holder under the following conditions: Cu metal target, Kα filter, voltage of 40 kV, and current of 30 mA. The diffraction patterns were recorded over a 2θ range of 5° to 50°. The results were presented as diffraction intensity versus 2θ angle plots.

d. Fourier Transform Infrared (FT-IR) Analysis

Samples of FEB, syringic acid, and the FEB–syringic acid multicomponent crystal (5 mg each) were placed on an aluminum plate, sealed, and analyzed using an FT-IR spectrophotometer within a wavenumber range of 4000–600 cm^{-1} to obtain their absorption spectra.

e. Scanning Electron Microscopy (SEM) Analysis

Samples weighing approximately 10 mg were mounted on aluminum stubs and coated with a thin layer of gold. The accelerating voltage was set at 20 kV with a current of 12 mA. The surface morphology of FEB, syringic acid, and the FEB–syringic acid multicomponent crystal was examined at different magnifications using SEM.

f. Dissolution Test

The dissolution studies were conducted in triplicate (n = 3). Comparative analyses were performed using pure febuxostat, the febuxostat–syringic acid physical mixture, and the febuxostat–syringic acid multicomponent crystal to assess the influence of multicomponent crystal formation on the dissolution behavior and solid-state characteristics of febuxostat. The dissolution profiles of pure febuxostat the febuxostat–syringic acid physical mixture and the febuxostat multicomponent crystal were evaluated. A sample equivalent to 40 mg of pure febuxostat (weighing 65.05 mg) was analyzed using a type II dissolution apparatus (paddle method). The dissolution medium consisted of 900 mL of 0.1 M phosphate-citrate buffer at pH 5.5 containing 1% SLS, maintained at 37 ± 0.05°C with a stirring speed of 50 rpm.At predetermined time intervals (5, 10, 15, 30, 45, and 60 minutes), 5 mL of the sample solution was withdrawn. After each sampling, an equal volume of fresh dissolution medium was added to maintain a constant volume. The amount of dissolved febuxostat was then analyzed using High Performance Liquid Chromatography (HPLC).

Prior to dissolution analysis, the HPLC method was validated according to guidelines. Linearity was evaluated over the concentration range of 10-50 μg/mL. These validation results confirmed that the analytical method was suitable for quantitative determination of febuxostat during dissolution testing. One-way ANOVA of the dissolution data demonstrated that the febuxostat–syringic acid multicomponent crystal exhibited significantly higher dissolution (99.21% at 60 minutes) than pure febuxostat (76.00%) ($p < 0.05$).

3. RESULTS AND DISCUSSION

Optimization results shown in Figure 1 illustrate the influence of different molar ratios on the formation of the multicomponent crystal. The ratio of 4.5:5.5 (febuxostat : syringic acid) produced the most stable and uniform phase, which is evident from the sharp and well-defined endothermic peak on the DSC thermogram. The visual comparison in Figure 1 clearly supports that this composition provides the most consistent thermal behavior among all ratios tested. Table 1 presents the effect of various solvents used during liquid-assisted grinding. Acetonitrile produced the most homogeneous and stable multicomponent product, as its intermediate polarity effectively facilitates hydrogen bonding between febuxostat and syringic acid .This observation is consistent with prior findings that solvent polarity and limited solvation in liquid-assisted grinding (LAG) enhance molecular diffusion and accelerate the nucleation of multicomponent crystals (Guo et al., 2021).

The DSC thermograms showed that pure febuxostat and syringic acid exhibited sharp endothermic peaks at 208.9 °C and 210.9 °C, respectively, while the physical mixture retained two distinct melting peaks corresponding to the parent components. In contrast, the febuxostat–syringic acid multicomponent crystal displayed a single endothermic peak with a lower melting temperature and reduced enthalpy, indicating the formation of a new crystalline phase. The melting point depression suggests that intermolecular hydrogen bonding disrupted the original crystal lattice and reduced lattice energy. Similar thermal behavior has been reported for febuxostat multicomponent systems prepared with salicylic acid and other pharmaceutical coformers, where melting point reduction was considered evidence of successful multicomponent crystal formation and was associated with improved dissolution characteristics (Jagia et al., 2022)

The PXRD patterns (Figure 2) supported the DSC findings. Pure febuxostat exhibited sharp diffraction peaks characteristic of a highly crystalline material, whereas syringic acid showed its own distinct diffraction pattern. Following liquid-assisted grinding, the multicomponent crystal displayed new diffraction peaks together with the disappearance or reduction of several characteristic peaks of febuxostat, confirming the formation of a crystalline phase rather than a simple physical mixture. These changes indicate crystal lattice reorganization caused by intermolecular interactions between febuxostat and syringic acid and are consistent with previous reports on febuxostat multicomponent systems (Jagia et al., 2022)

FTIR spectra (Figure 3) revealed shifts and broadening of the characteristic carbonyl (C=O) and hydroxyl (O–H) absorption bands, indicating the formation of hydrogen-bonding interactions between febuxostat and syringic acid. These intermolecular interactions likely contributed to the formation of stable supramolecular synthons, partial disruption of the original crystal lattice, and enhanced dissolution behavior. Similar spectral changes have been reported for febuxostat–salicylic acid multicomponent systems, supporting the successful formation of a new solid phase in the present study (Srivastava et al., 2019)

SEM micrographs (Figure 4) revealed distinct morphological differences between pure febuxostat, syringic acid, and the multicomponent crystal. Pure febuxostat exhibited rod-shaped crystals with smooth surfaces, whereas syringic acid appeared as irregular granules. Following liquid-assisted grinding, the multicomponent crystal displayed smaller and irregularly aggregated particles, indicating crystal reconstruction during multicomponent crystal formation. Similar morphological changes have been reported for febuxostat multicomponent systems prepared with other coformers and are associated

with increased surface area and improved wettability, which contribute to enhanced dissolution performance (Jagia et al., 2022; Pindelska et al., 2025)
Table 2. showed that the assay of febuxostat content in the multicomponent crystal yielded 100.22 ± 0.005 %, falling within the acceptable range (98–102%) (The Commitee on the Japanese Pharmacopoeia, 2021). It indicates that the grinding and crystallization process did not cause degradation or loss of the active ingredient.

Figure 5 and Table 3 demonstrate that the febuxostat–syringic acid multicomponent crystal exhibited superior dissolution compared with pure febuxostat and the physical mixture. At 60 min, the multicomponent crystal achieved a dissolution rate of 99.21 ± 2.28%, significantly higher than pure febuxostat (76.00 ± 1.14%) and the physical mixture (92.01 ± 1.02%) ($p < 0.05$). These findings indicate that multicomponent crystal formation effectively enhances the dissolution behavior of febuxostat.

The improved dissolution can be attributed to the combined effects of reduced lattice energy, intermolecular hydrogen bonding, decreased crystallinity, and modified particle morphology, as confirmed by the DSC, PXRD, FTIR, and SEM analyses. Comparable improvements in dissolution have been reported for febuxostat multicomponent systems prepared with salicylic acid and other pharmaceutical coformers, where crystal engineering modified the crystal packing and facilitated drug release (Jagia et al., 2022; Srivastava et al., 2019). These results demonstrate that syringic acid is a promising coformer for enhancing the dissolution performance of febuxostat

The one-way ANOVA results ($p < 0.05$) confirmed a significant enhancement in dissolution performance. The ~1.3-fold increase compared to pure febuxostat is likely driven by multiple mechanistic factors, including reduced crystallinity supported by DSC and PXRD data, improved wettability and molecular dispersion arising from hydrogen-bonding interactions, decreased particle size with a rougher surface morphology observed in SEM images, and enhanced interfacial energy associated with partial amorphization induced during the LAG process.

The enhanced dissolution observed for the febuxostat–syringic acid multicomponent crystal is consistent with previous reports demonstrating that multicomponent crystal engineering effectively improves the dissolution behavior of febuxostat. Srivastava et al. reported that the febuxostat–salicylic acid eutectic exhibited superior dissolution compared with pure febuxostat owing to improved intermolecular interactions and modified crystal packing. Likewise, Jagia et al. demonstrated that febuxostat co-crystals and eutectics prepared with suitable coformers significantly increased dissolution performance through reductions in lattice energy and changes in crystal habit. Therefore, the dissolution enhancement observed in the present study further supports the effectiveness of syringic acid as a promising coformer for febuxostat (Jagia et al., 2022; Srivastava et al., 2019). Co-crystallization reduces lattice energy barriers and increases thermodynamic activity in solution, thereby promoting faster drug release and potentially improving bioavailability Jessica, et al , 2021).

Nevertheless, this study has several limitations. Long-term solid-state stability and scale-up feasibility of the liquid-assisted grinding process were not evaluated. In addition, the enhanced dissolution observed in vitro has not yet been correlated with in vivo pharmacokinetic performance. Therefore, further investigations are necessary to confirm the clinical relevance and pharmaceutical applicability of this multicomponent crystal system

Table 1. Melting point and enthalpy of fusion data for various ratios of febuxostat and syringic acid

Ratio of febuxostat: syringic acid	Melting point (°C)	Enthalpy of fusion (ΔH, J/g)
1: 1	176.98	99.64
4: 6	176. 74	111.85
4.5: 5.5	177.31	114.72
5.5: 4.5	177.10	136.71
6: 4	176.50	114.26

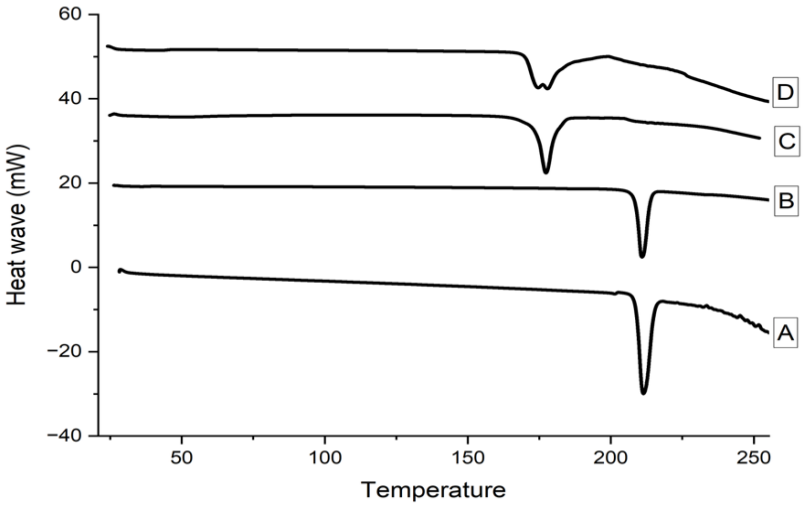

Figure 1. Thermograms of (A) febuxostat, (B) syringic acid, (C) febuxostat–syringic acid multicomponent crystal, and (D) physical mixture

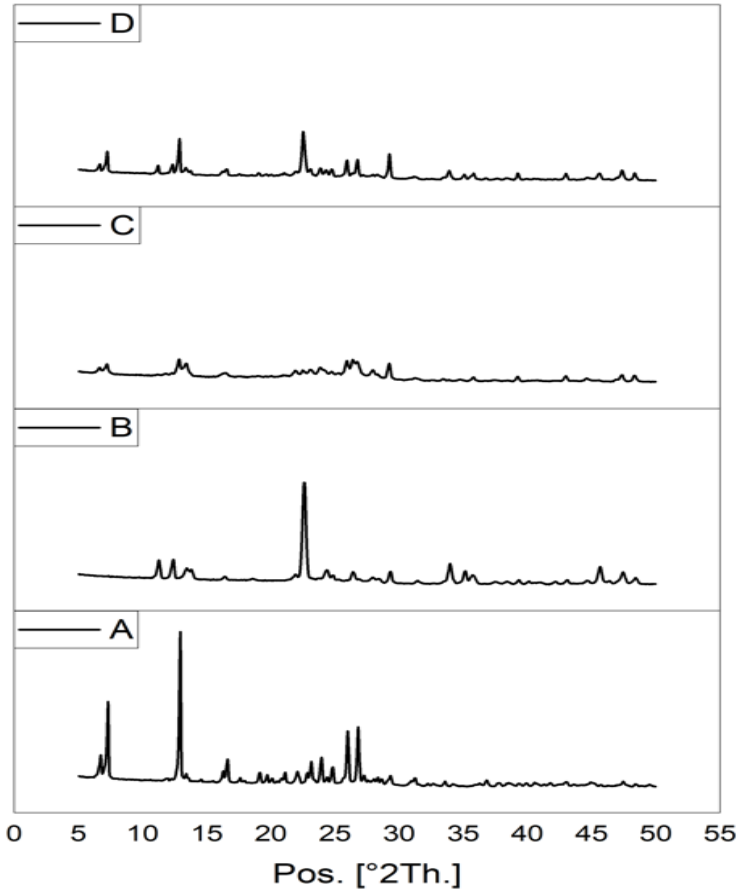

Figure 2. XRD patterns of (A) febuxostat, (B) syringic acid, (C) febuxostat–syringic acid multicomponent crystal, and (D) physical mixture

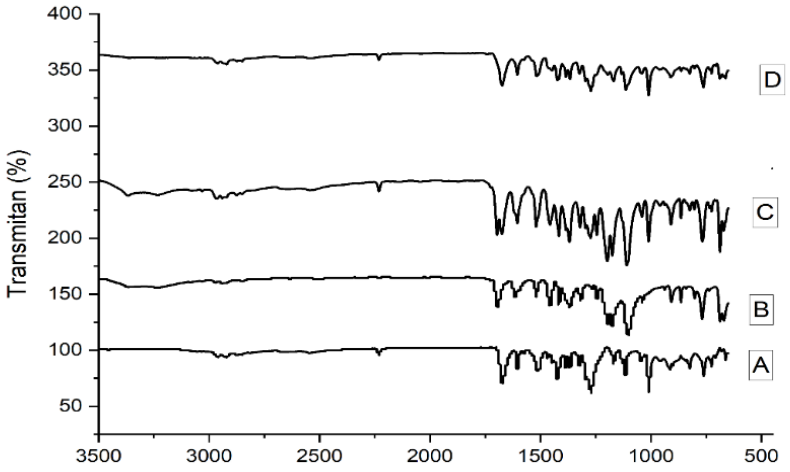

Figure 3. Spectrum FTIR of (A) febuxostat, (B) syringic acid, (C) febuxostat–syringic acid multicomponent crystal, and (D) physical mixture

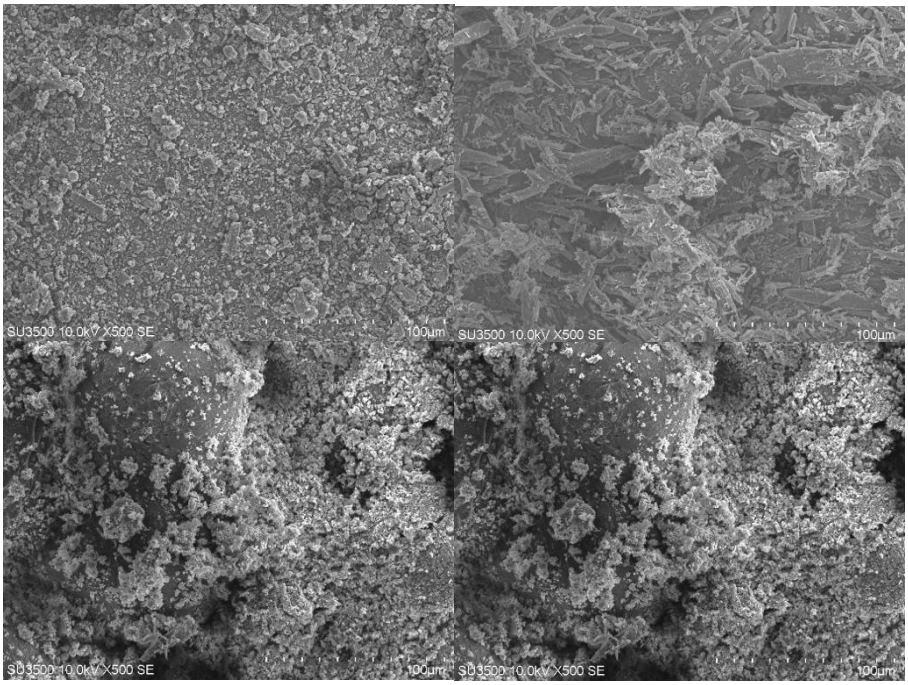

Figure 4. SEM of (A) febuxostat, (B) syringic acid, (C) febuxostat–syringic acid multicomponent crystal, and (D) physical mixture

Table 2. Determination of febuxostat content in the febuxostat–syringic acid multicomponent

Sample	Peak area	Measured Concentration (µg/mL)	Assay {%)	Mean Assay (%) ± SD
Febuxostat–Syringic Acid Multicomponent Crystal	7439.683	501.110	100.222	100.222 ±0.005237
	7439.252	501.081	100.216	
	7440.215	501.145	100.229	

Table 3. Percentage of dissolved febuxostat (%) in pure febuxostat, febuxostat–syringic acid multicomponent crystal, and physical mixture as mean ± SD.

Time	Percentage of dissolved febuxostat (%)		
	Febuxostat	Febuxostat–Syringic Acid Multicomponent Crystal	Febuxostat–Syringic Acid Physical Mixture
0	0	0	0
5	40.492 ± 2.556	41.950 ± 0.660	39.642 ± 0.829
10	30.561 ± 0.684	37.464 ± 1.451	34.000 ± 2.570
15	37.063 ± 3.283	45.047 ± 2.049	39.376 ± 1.225
30	41.925 ± 1.584	63.780 ± 2.257	61.201 ± 3.396
45	55.891 ± 0.865	77.606 ± 1.221	68.081 ± 1.902
60	76.004 ± 1.140	99.205 ± 2.279	92.006 ± 1.015

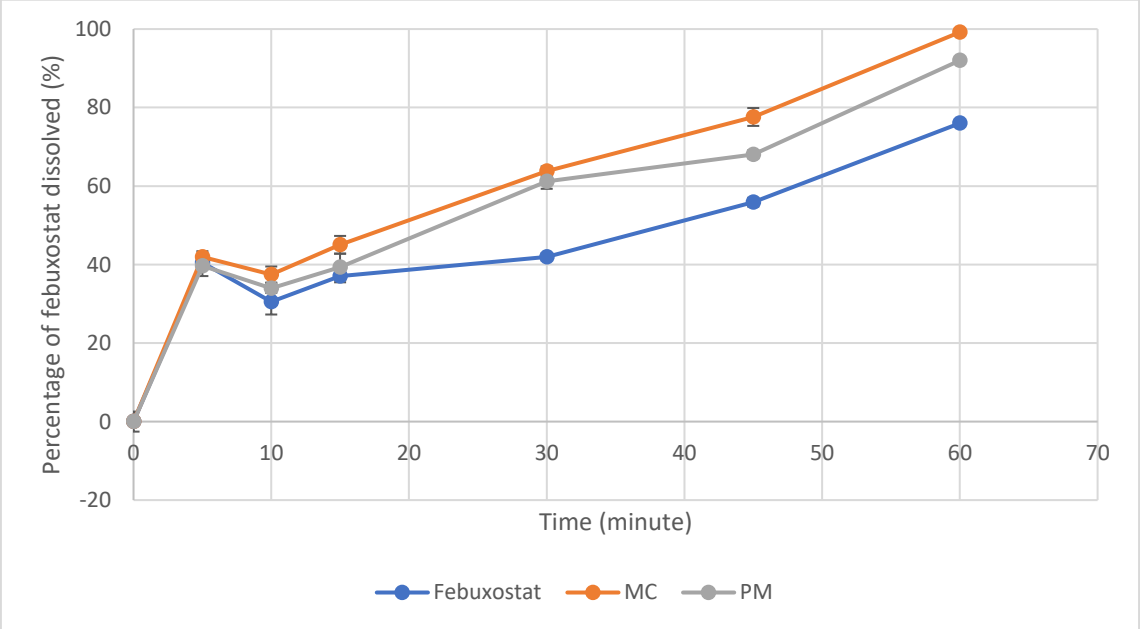

Figure 5. Dissolution profile of febuxostat (% dissolved) for pure febuxostat, febuxostat–syringic acid multicomponent crystal, and physical mixture. Data are presented as mean ± SD

4. CONCLUSION

A novel febuxostat–syringic acid multicomponent crystal was successfully prepared using the liquid-assisted grinding method. Solid-state characterization by DSC, PXRD, FTIR, and SEM confirmed the formation of a new crystalline phase through intermolecular interactions between febuxostat and syringic acid. The multicomponent crystal exhibited potentially improved dissolution compared with pure febuxostat, these findings indicate that syringic acid is a promising coformer for enhancing the physicochemical performance of febuxostat. These findings demonstrate the potential of multicomponent crystal engineering as an effective strategy to improve the dissolution of poorly water soluble drugs. Further studies on solid state stability and in vivo performance are required to confirm its pharmaceutical applicability.

5. ACKNOWLEDGMENT

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