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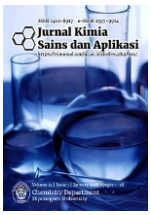

Physicochemical and Mechanical Characterization of Meloxicam-Fumaric Acid Co-Crystals Synthesized by Ultrasound-Assisted Solution Method

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Abstract

Meloxicam (MLX) is a class II BCS non-steroidal anti-inflammatory drug (NSAID) with low solubility and manufacturing challenges due to its needle-like crystal habit, which causes poor flowability and high elasticity. These mechanical characteristics often trigger capping and lamination during direct compression. This study aims to perform physicochemical characterization and mechanical property evaluation of MLX co-crystals with fumaric acid (FUM) co-former, synthesized using the ultrasound-assisted solution co-crystallization (USSC) method. The co-crystals were synthesized at a 1:1 molar ratio in ethanol solvent using ultrasonication. Characterization was performed using a polarizing microscope, PXRD, DSC, and FTIR, followed by evaluation of flow properties, compressibility, and tabletability. The results of PXRD, DSC, and FTIR analyses confirmed the formation of a new co-crystal phase via intermolecular hydrogen-bonding interactions. A morphological transformation was observed from a needle habit to a more isodiametric or plate-like habit. The MLX-FUM co-crystal showed significant improvements in flow rate (0.134 g/sec), angle of repose (33.86°), and compressibility index (38.92%) compared to pure MLX. Tabletability analysis showed a fivefold increase in tensile strength (2.70 MPa) at a pressure of approximately 2.94 MPa (30 kg/cm^2), which correlated with a decrease in elastic recovery from 3.18% to 1.96%. This study concludes that co-crystal synthesis by USSC holistically improves the mechanical profile of MLX, showing an improved mechanical profile that demonstrates potential for tablet manufacturing processes using the direct compression method.

1. Introduction

Tablets are the most preferred pharmaceutical dosage form due to their ease of use, accurate dosing, and good physicochemical stability compared with other dosage forms [1]. Direct compression is the preferred method in the pharmaceutical industry due to its high process efficiency, low operating costs, and minimization of heat and moisture exposure, which can damage the active ingredient [2]. However, the success of this method depends heavily on the mechanical properties of the pharmaceutical active ingredient, particularly its flowability and compressibility, which must meet certain standards to produce uniform and strong tablets [3].

Meloxicam (MLX) is a selective COX-2 non-steroidal anti-inflammatory drug (NSAID) that is widely used to treat chronic joint disorders. Pharmaceutically, MLX is classified as a Class II drug in the Biopharmaceutical Classification System (BCS), which has high permeability but very low water solubility [4]. In addition to solubility issues, MLX faces significant manufacturing challenges due to its needle-like crystal habit, which results in poor flowability and high elasticity [5]. These poor mechanical characteristics often trigger capping and lamination

phenomena during the pressing process, making it difficult to implement direct compression methods [6].

Current formulation development places a strong emphasis on crystal engineering, particularly the formation of pharmaceutical co-crystals, to modify the physical properties of active ingredients without altering their pharmacological activity [7] . Co-crystals are formed through the combination of API and neutral co-formers in the same crystal lattice through non-covalent interactions, such as hydrogen bonds [8]. One compound used as a co-former is fumaric acid. The selection of fumaric acid (FUM) as a co-former is based on the ability of its two carboxylate groups to form strong, stable hydrogen bonds with MLX, and on its rigid molecular structure, which facilitates the formation of a new, more regular crystal lattice that induces plastic deformation.

Previous research has demonstrated the successful formation of MLX-FUM mixed crystals with distinctive physicochemical characteristics through a liquid-assisted milling process, thereby establishing a strong precedent for FUM as a viable mixed crystal former [9]. Furthermore, FUM is prioritized due to its rigid, planar trans geometry, which facilitates the formation of layered 2D crystal lattices that support the formation of shear planes. Recent literature on crystal shape engineering confirms that transforming needle-shaped particles into spherical or plate-like structures drastically reduces handling and compaction issues in subsequent stages. This structural transformation is capable of overcoming physical constraints during the direct compaction process [10, 11].

Various studies have proven that co-crystallization can significantly improve the solubility, dissolution rate, and physical stability of poorly soluble drugs by utilizing measurable molecular interactions [12, 13]. One technique in co-crystal synthesis is the Ultrasound-Assisted Solution Co-crystallization (USSC) method. The use of ultrasonic energy triggers acoustic cavitation, which accelerates nucleation and yields crystals with a more uniform size distribution and more regular morphology than conventional methods such as solvent evaporation or grinding [14].

Although research on MLX co-crystallization has been extensively conducted to improve the solubility and dissolution of MLX [15, 16] without a detailed analysis of flow properties, density, and tabletability. Investigations focused on modifying the mechanical properties of the resulting powder, which are essential for direct compression, remain scarce. Therefore, this study not only confirms the formation of the MLX-FUM co-crystal phase through USSC but also provides a quantitative and comprehensive evaluation of mechanical properties, particularly compressibility behavior and flowability after co-crystallization with FUM. Understanding the mechanical parameters related to crystal habit changes through the USSC method is crucial to ensuring the industrial-scale use of active materials.

This study aims to characterize the physicochemical properties and evaluate the mechanical properties of MLX-FUM co-crystals synthesized using the USSC method to facilitate direct compression. This study not only confirms the formation of a new crystal phase through thermal analysis and diffraction characterization but also quantitatively evaluates improvements in mechanical parameters, such as the Carr Index and tabletability. This research is expected to provide innovative solutions for the pharmaceutical industry to process MLX into more efficient, high-quality tablet preparations.

2. Experimental

2.1. Tools and Materials

The tools and instruments used in this study consisted of an analytical balance (Mettler Toledo LA204, Switzerland), ultrasonic cleaner (WUS22, Beijing), polarizing microscope (Olympus BX-53, Japan), UV-Visible spectrophotometer (Shimadzu UV-1800, Japan), fourier transform infrared (Shimadzu IRAffinity-ORS8000, Japan), differential scanning calorimeter (Shimadzu DSC-60 Plus, Japan), powder X-ray diffractometer (Rigaku Miniflex, Japan), tapped density tester (TDTF ZS-2E, China), granule flow tester (GFT-100-AU), hardness tester (Erweka TBH 125, Germany), and glassware commonly used in laboratories. The materials used were meloxicam (PT. Kimia Farmas, Tbk., Indonesia), fumaric acid (Merck, Germany), 96% ethanol, and distilled water, all of which were selected as pharmaceutical-grade solvents.

2.2. Preparation of MLX-FUM Co-Crystal by USSC

MLX and FUM were weighed in a stoichiometric molar ratio of 1:1 and dissolved in 30 mL of 96% ethanol solvent. The mixture was sonicated using an ultrasonic cleaner (WUS22, Beijing) for 20 minutes at 25°C. Solid sample mixtures were taken every five minutes and observed under a polarizing microscope until crystals formed. The crystals that formed were then separated from the solution by filtration, dried at room temperature, and stored in a desiccator. They were subsequently evaluated and characterized [17].

2.3. Characterization of MLX-FUM Co-Crystal

2.3.1. Morphology of Crystals

MLX-FUM crystals were observed visually using a polarizing microscope (Olympus BX-53, Japan). The same treatment was also performed on MLX and FUM. A small amount of each sample was placed on a glass slide, followed by the addition of 2–3 drops of ethanol. The crystal morphology was then observed under appropriate magnification using the polarized light microscope, and the resulting micrographs were recorded digitally using a computer device [18].

2.3.2. Powder X-ray Diffraction (PXRD)

PXRD analysis was performed on MLX, FUM, and MLX-FUM co-crystals using a powder X-ray diffractometer (Rigaku Miniflex, Japan). The X-ray diffractometer used Cu Kα radiation (γ = 1.5406 Å). The system was operated at a current of 30 mA and a voltage of 40 kV, with a 2θ range of 3–50° and a scan rate of 2° (2θ) per minute with a step size of 0.02° [19].

2.3.3. Differential Scanning Calorimetry (DSC)

Thermal analysis characterization was performed using DSC (Shimadzu DSC-60 Plus, Japan) on MLX, FUM, and the MLX-FUM co-crystal. Each sample (1–3 mg) was placed in a sealed aluminum pinhole pan and heated over a temperature range of 50–300°C at a heating rate of 10°C/min. Nitrogen at a flow rate of 20 mL/minute was used to purge the air and prevent oxidation [19].

2.3.4. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy was performed to identify the functional groups of MLX, FUM, and the MLX–FUM co-crystal using an FTIR spectrometer (Shimadzu IRAffinity-1S, Japan). Approximately 2 mg of each sample was thoroughly mixed with 200 mg of KBr and compressed into a pellet prior to analysis. The FTIR spectra were recorded over the wavenumber range of 400–4000 cm^{-1} in transmittance mode. The characteristic absorption bands were analyzed to identify the functional groups and evaluate possible changes in intermolecular interactions resulting from co-crystal formation [9].

2.4. Evaluation of Mechanical Properties

2.4.1. Flow Rate and Angle of Repose

The flow rate and angle of repose of MLX powder and MLX–FUM co-crystals were evaluated using a granule flow tester (GFT-100-AU). Approximately 40 g of each sample was placed in a funnel with a 10 mm orifice diameter equipped with a damper to control powder discharge. The damper was opened to allow the powder to flow freely onto a flat surface, forming a conical heap. The flow time was recorded using a stopwatch from the moment the powder began to flow until complete discharge from the funnel [20]. The angle of repose (α) was then calculated from the height of the powder heap (h) and the diameter of the heap (D) using Equation 1.

$$\tan(\alpha) = \frac{h}{0.5D} \quad (1)$$

2.4.2. Compressibility Index

The compressibility index of MLX powder and MLX–FUM co-crystals was determined from their bulk and tapped densities using a tapped density tester (TDTF ZS-2E, China). Approximately 50 g of each sample was placed into a 250 mL graduated cylinder, and the initial volume was recorded as the bulk volume. The cylinder was then tapped 500 times using the tapped density tester, and the final volume was recorded as the tapped volume. The bulk density (ρ_b) and tapped density (ρ_t) were calculated by dividing the sample mass by the corresponding bulk and tapped volumes (g/mL) [21]. All measurements were performed in triplicate (n = 3). The compressibility index was calculated using Equation 2.

$$Compressibility\ Index\ (\%) = \frac{\rho_t - \rho_b}{\rho_t} \times 100\% \quad (2)$$

2.4.3. Tabletability

The tabletability of MLX powder and MLX–FUM co-crystals was evaluated using a hydraulic press equipped with an 11 mm punch and die set. Approximately 300 mg of each powder sample was placed into the die and compressed into tablets at compression pressures of 10, 20, 30, 40, and 50 kg/cm² with a compression speed of 100 mm/s. A dwell time of 10 s was applied by maintaining the maximum compression pressure before decompression to allow sufficient plastic deformation and particle rearrangement. Before each change in compression pressure, the punch and die were lubricated with 2% (w/v) magnesium stearate in ethanol.

The diameter (D), thickness (T), and hardness (F) of the freshly prepared tablets were measured immediately after compression using a tablet hardness tester (Erweka TBH 125, Germany). The diameter, thickness, and hardness were measured again after storage at room temperature for 24 h. The tablet tensile strength (σ) at each compression pressure was calculated using Equation 3.

$$\sigma = \frac{2F}{\pi DT} \quad (3)$$

The elastic recovery (ER) was determined to evaluate the compaction behavior of the powder and the dimensional recovery of the tablets after compression. The percentage of elastic recovery was calculated using Equation 4.

$$ER\ (\%) = \frac{h - h_0}{h} \times 100 \quad (4)$$

where h is the tablet thickness measured after 24 h of storage and h_0 is the initial tablet thickness measured immediately after compression [22].

3. Results and Discussion

3.1. Synthesis and Morphology of MLX-FUM Co-crystals

The preparation of MLX–FUM co-crystals was carried out using the USSC method by dissolving MLX and FUM in ethanol at a 1:1 molar ratio. Although the percentage yield was not the primary focus of this characterization study, the USSC process consistently produced a sufficient amount of co-crystal powder for all subsequent characterization and mechanical evaluations, including compressibility index and tabletability tests. The application of ultrasonic irradiation promotes acoustic cavitation, which enhances nucleation and crystal growth, facilitating efficient co-crystal formation [23].

The main advantage of the USSC technique over conventional crystallization methods lies in its ability to produce large quantities and a more uniform distribution of identical crystal sizes, as well as a more mechanically advantageous crystal habit. This occurs because ultrasonic irradiation and acoustic cavitation reduce the induction time and narrow the metastable zone width, enabling highly controlled secondary nucleation and fragmentation, which ultimately yields a narrower particle size distribution and an altered crystal habit [24].

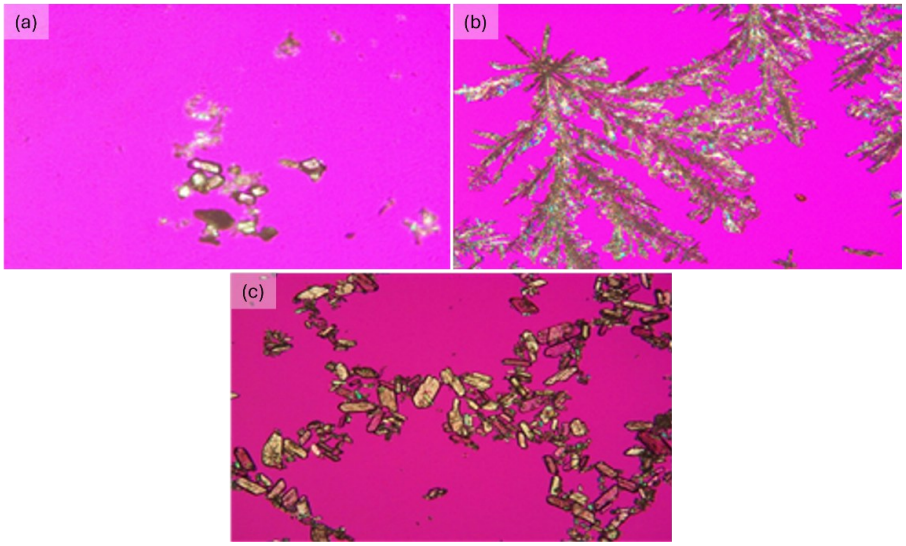

Figure 1. Crystal morphology of (a) MLX, (b) FUM, and (c) MLX-FUM co-crystal under a polarizing microscope at 200× magnification

Morphological characterization of the crystals using a polarized light microscope is presented in Figure 1. Both MLX and the MLX–FUM co-crystals exhibited birefringence under polarized light, appearing as bright, colorful crystals, which is characteristic of crystalline materials [25]. Qualitative observations at 200× magnification revealed a distinct morphological transformation after co-crystallization. Pure MLX exhibited a long needle-like crystal habit, whereas the MLX–FUM co-crystals displayed a more isodiametric or plate-like morphology following preparation by the USSC method [27]. Although particle size was not quantitatively determined, the observed change in crystal habit suggests a modification of the crystal packing and particle morphology. Such a morphological transformation has been reported to improve powder flowability and compaction behavior by reducing interparticle friction and promoting more efficient particle packing during compression, which may contribute to higher tablet tensile strength and lower elastic recovery [26].

3.2. Powder X-ray Diffraction (PXRD)

The PXRD diffractogram analysis can be seen in Figure 2. The PXRD results confirm the formation of a new crystalline phase in the MLX-FUM co-crystal, marked by the appearance of characteristic interference peaks at angles of 2 theta: 5.84°, 11.68°, and 14.46°, as well as a shift in the intensity of the dominant MLX peaks at 13° and 25.76° [27]. This transformation indicates a fundamental change in the crystal lattice parameters due to the integration of FUM into the MLX structure through non-covalent interactions, which is consistent with previous findings [9]. While the diffraction pattern primarily displays the characteristic peaks of the new co-crystal phase, indicating a high degree of conversion, the possible presence of minor traces of unreacted components cannot be entirely ruled out due to detection limits and minor peak overlaps. These diffraction pattern characteristics collectively prove that the resulting product is not merely a simple physical mixture but a new molecular entity in the form of a co-crystal with a more stable internal structural arrangement that is advantageous for the physicochemical properties of the material [28].

3.3. Differential Scanning Calorimetry (DSC)

The DSC thermograms of MLX, FUM, and the MLX–FUM co-crystal are presented in Figure 3. Pure MLX and FUM exhibited endothermic melting peaks at 257.94°C and 273.71°C, respectively, whereas the MLX–FUM co-crystal showed a single endothermic peak at 245.38°C. The appearance of a single melting endotherm at a temperature distinct from those of the parent components indicates the formation of a new crystalline phase with different thermal properties and lattice energy [29]. These results are consistent with the PXRD analysis, which also supports the formation of the MLX–FUM co-crystal. Previous studies have reported that co-crystals exhibiting a new crystalline phase may possess improved compaction behavior due to changes in crystal packing and intermolecular interactions, which can contribute to enhanced plasticity and reduced elastic recovery during compression [30].

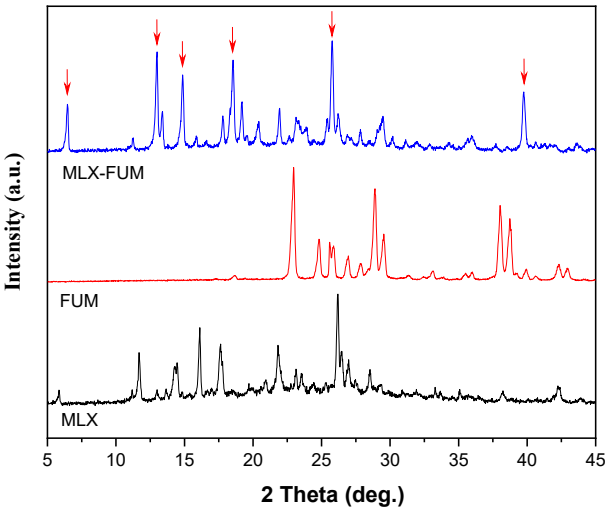

Figure 2. PXRD diffraction pattern of MLX, FUM, and the MLX-FUM co-crystal

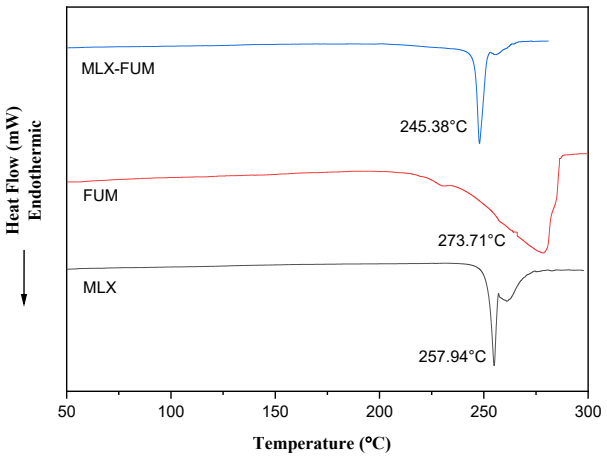

Figure 3. DSC thermograms of MLX, FUM, and the MLX–FUM co-crystal

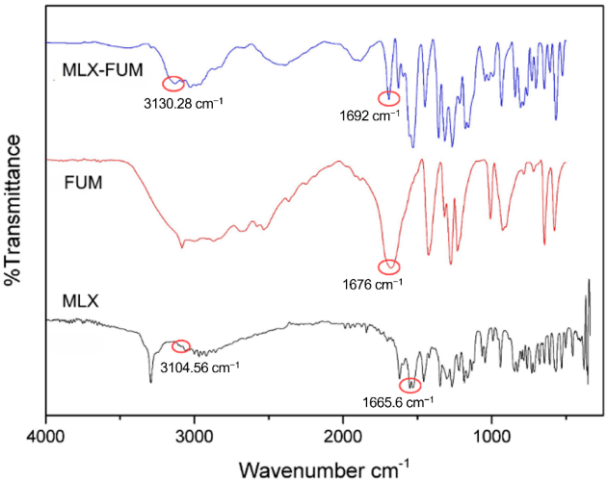

Figure 4. FTIR spectra of MLX, FUM, and MLX-FUM co-crystals

3.4. Fourier Transform Infrared (FTIR) Spectroscopy

The FTIR spectra of MLX, FUM, and the MLX–FUM co-crystal are presented in Figure 4. The FTIR analysis provided supporting evidence for the formation of the MLX–FUM co-crystal through changes in the characteristic absorption bands of the parent compounds, indicating intermolecular interactions between MLX and FUM. The O–H stretching band shifted from 3104.56 cm^{-1} in pure MLX to 3130.28 cm^{-1} in the MLX–FUM co-crystal, while the amide carbonyl (C=O) stretching band shifted from 1665.60 cm^{-1} to 1692 cm^{-1} [31]. These spectral shifts suggest the involvement of the hydroxyl and amide groups of MLX and the carboxyl group of FUM in intermolecular hydrogen bonding, leading to the formation of supramolecular synthons within the co-crystal lattice [32]. The observed band shifts indicate changes in the hydrogen-bonding environment following co-crystallization and are consistent with the solid-state transformation evidenced by the PXRD and DSC analyses [33].

3.5. Analysis of Powder Flow Properties and Tabletability

Based on the results of flow and compressibility testing, the MLX-FUM co-crystal showed a significant improvement in mechanical profile compared to MLX, with the flow rate increasing from 0.052 g/s to 0.134 g/s, and producing a change in the angle of repose from 41.65° to 33.86°, and a decrease in the compressibility index from 48.09% to 38.92%, indicating a significant relative improvement in flow properties [34]. However, it should be noted that a compressibility index of 38.92% is still considered sub-optimal for absolute industrial-scale flowability, thereby necessitating the addition of flow-enhancing excipients in future tablet formulations. Nonetheless, this relative increase in compressibility serves as the fundamental foundation for the superior tabletability performance shown in Table 2.

This transformation shows a strong correlation with the change in crystal habit from a needle-like shape to a more isodiametric shape after the USSC process, which effectively reduces the surface contact area between particles and decreases interparticle cohesive forces. These findings explain that crystal structure modification through co-crystal engineering can significantly alter the mechanical behavior of powders by optimizing molecular interactions in the new crystal lattice [35]. The use of ultrasonic energy in the USSC method can produce a more uniform particle size distribution and more regular morphology, with acoustic cavitation efficiency in improving the fluidity and bulk density of pharmaceutical active ingredients that initially have poor flow characteristics [36].

Tabletability analysis showed that MLX–FUM co-crystallization markedly increased the tensile strength, reaching 2.707 ± 0.05 MPa, approximately five times higher than that of pure MLX (0.534 ± 0.01 MPa) at the same compression pressure (30 kg/cm^2), as presented in Table 2. This improvement was accompanied by a reduction in elastic recovery from 3.185% to 1.965%, indicating a greater contribution of plastic deformation during the decompression process [37].

This behavior is consistent with previous studies reporting that carboxylic acid co-formers can promote the formation of slip planes within the crystal lattice. The rigid, planar geometry of fumaric acid facilitates the formation of layered hydrogen-bonded structures, allowing adjacent layers to slide more readily under compression, thereby promoting permanent particle rearrangement and plastic deformation [38]. Consequently, less elastic energy is retained after compaction, reducing the tendency for interparticle bond separation and minimizing the risk of mechanical failure, such as capping [39].

The enhanced tabletability is consistent with the improved micromeritic properties shown in Table 1, including a higher flow rate, a lower angle of repose, and a lower compressibility index for the MLX–FUM co-crystal. Overall, these findings demonstrate that co-crystallization via the USSC method improved both the powder flowability and compaction behavior of MLX, thereby enhancing its suitability for tablet formulation.

Table 1. Evaluation of the flow properties and compressibility of MLX powder and MLX-FUM co-crystal

Evaluation	MLX	MLX-FUM
Flow rate (g/s)	0.052 ± 0.01	0.134 ± 0.01
Angle of repose (°)	41.657 ± 2.67	33.865 ± 1.75
Bulk density (g/mL)	0.461 ± 0.00	0.461 ± 0.01
Tapped density (g/mL)	0.887 ± 0.01	0.753 ± 0.01
Compressibility index (%)	48.090 ± 1.11	38.928 ± 0.77

Table 2. Tensile strength and % elastic recovery of MLX and MLX-FUM co-crystals

Compressive strength (kg/cm^2)	Tensile strength (MPa)		Elastic recovery (%)	
	MLX	MLX-FUM	MLX	MLX-FUM
10	0.44 ± 0.04	0.63 ± 0.22	2.90 ± 0.04	1.72 ± 0.00
20	0.49 ± 0.03	1.02 ± 0.49	3.38 ± 0.19	1.98 ± 0.02
30	0.53 ± 0.01	2.70 ± 0.39	3.18 ± 0.24	1.96 ± 0.03
40	-	2.70 ± 0.05	-	1.96 ± 0.00
50	-	2.66 ± 0.00	-	1.13 ± 1.13

Note: The applied compaction pressures of 10, 20, 30, 40, and 50 kg/cm^2 are mathematically equivalent to approximately 0.98, 1.96, 2.94, 3.92, and 4.90 MPa, respectively. Dashed lines (-) for pure MLX at pressures >2.94 MPa indicate mechanical failure due to catastrophic capping and lamination, preventing hardness evaluation.

4. Conclusion

The MLX-FUM co-crystal was successfully synthesized using the USSC method, as confirmed by PXRD, DSC, and FTIR characterization analysis. This study highlights the transformative impact of co-crystallization on the mechanical properties of MLX. The solid phase of this co-crystal can improve the powder's flow properties and compressibility, as well as its tabletability, as characterized by higher tensile strength and lower elastic recovery compared to pure MLX. This study confirms that co-crystallization with the co-former FUM is a reliable strategy not only for improving solubility but also for holistic engineering of pharmaceutical materials. To bridge the gap between the improved Carr's index (38.92%) and true industrial flowability, future formulation studies are recommended to include glidants (e.g., colloidal silicon dioxide) and coarse, free-flowing diluents (e.g., direct-compression grade microcrystalline cellulose or spray-dried lactose). Therefore, the MLX-FUM co-crystal offers a potentially viable strategy for improving MLX tablet manufacturing through direct compression, with significant potential benefits in process efficiency, cost reduction, and final product quality.

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