

Effects of Tablet Crushing Methods on Solid-State Properties, Dissolution Behavior, and Dispensability of Acetaminophen Tablets

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Abstract

Purpose

In clinical practice, tablets are often crushed and administered to patients with dysphagia or children, typically using a mortar and pestle, tablet crusher, or other methods of administration. Clinical tablet crushing may alter the physicochemical properties of drugs; however, the effects of crushing methods on pharmaceutical quality remain unclear. The present study demonstrated that different crushing methods affected not only the particle size but also the morphology, crystallinity, molecular state, and pharmaceutical performance of acetaminophen (AA) tablets.

Methods

Physicochemical properties of crushed samples, such as particle size distribution, SEM, PXRD, DSC, FTIR, dissolution, flowability, and dispensability were evaluated.

Results

All crushing methods reduced crystallinity, with oscillatory ball mill (OBM) the greatest solid-state alteration. In contrast, the tablet crusher produced the finest particles and the fastest dissolution, whereas excessive grinding by OBM caused particle aggregation and altered intermolecular interactions.

Conclusion

Crushing methods significantly influence solid-state properties and pharmaceutical performance of AA tablets.

1 Introduction

Oral dosage forms, such as tablets, capsules, and syrups, are commonly used in medical treatments because of their convenience [1]. However, few commercial formulations are available for pediatric or older patients with limited or impaired swallowing ability. Children often cannot swallow solid foods, whereas older adults may struggle to swallow because of decreased physiological function. In these cases, pharmacists often prepare crushed tablets or unsealed capsules for administration in hospitals and community pharmacies [2]. These practices are considered "compounding," which the U.S. Food and Drug Administration (FDA) defines compounding as the process of combining, mixing, or altering ingredients to create a medication tailored to an individual patient's needs [3]. However, the FDA has issued warnings that such practices can lead to significant drug quality issues. Although tablet crushing is widely practiced, the crushing method is often selected according to local practice or equipment availability. The mechanical stress applied during crushing differs substantially among methods and

may affect pharmaceutical quality attributes, including particle size, dissolution behavior, and powder handling characteristics.

Several studies have examined the impact of these methods on the physicochemical properties of crushed tablets and unsealed capsules, including their stability and dissolution behavior [4–8]. Herman et al. used commercially available tablet splitters, screw-cap crushers, manual crushers, and electric crushers to split tablets into two halves and measured the weight difference. They demonstrated that splitting tablets into two halves is difficult [4]. Court et al. reported that when anti-tuberculosis drugs, including pyrazinamide, ethambutol, and isoniazid, were crushed and administered, the area under the concentration-time curve (AUC) of crushed isoniazid decreased. They attributed this to the reduced dosage caused by crushed particles adhering to the container during administration [5].

The simplest method for crushing tablets involves using a mortar and pestle, and tablet crushers are among the most commonly used tools for this purpose. Recently, desktop ball milling has been adopted for tablet grinding purposes. Typically used to process crystals or biological samples, ball milling can crush tablets when a few balls are placed in the mill [9]. However, ball milling has been shown to change the crystallinity by converting crystalline components into an amorphous state in pharmaceutical applications. This technique has been used to improve the solubility of poorly water-soluble drugs [10], and it has been found to affect their physicochemical properties and efficacy [11].

Grinding pharmaceuticals into powder is a common practice in medical treatment; however, there are very few studies on how variations in grinding methods, such as shear force strength and grinding duration, affect the physical and chemical properties of the ground material.

Acetaminophen was selected as a model drug because it is widely prescribed and frequently administered as a crushed preparation in pediatric and geriatric patients. In addition, its solid-state properties are known to be affected by mechanical processing, making it a suitable model for evaluating the influence of crushing procedures on pharmaceutical quality. Therefore, the aim of this study was to investigate how different tablet-crushing methods affect the particle size distribution, solid-state characteristics, dissolution behavior, flowability, and dispensability of acetaminophen tablets. By clarifying the relationship between crushing procedures and pharmaceutical quality attributes, this study seeks to provide practical information for the safe and effective preparation of crushed medications in clinical settings.

2 Material and methods

2.1 Materials

Tablets containing AA crystals were obtained from Kaken Pharmaceutical Co., Ltd. (Tokyo, Japan). The components are listed in Table 1. AA crystals were purchased from FUJIFILM Wako Chemicals Co., Ltd. (Osaka, Japan). Lactose hydrate was obtained from Yoshida Pharmaceutical Co., Ltd. (Tokyo, Japan). Anhydrous lactose and hydroxypropyl cellulose (HPC-SL) were supplied by DFE Pharma (Goch, Germany).

and Nippon Soda Co., Ltd. (Tokyo, Japan). Methanol and distilled water used for high-performance liquid chromatography (HPLC) were obtained from Kanto Chemical Co., Inc. (Tokyo, Japan). All chemicals and solvents were of analytical grade.

Table 1
Composition of AA Tablet

Material	Concentration (%)
AA	20
HPC-SL	1.56
Cornstarch	23.24
Magnesium stearate	1
Lactose hydrate	54.2

2.2 Preparation of Crushed Samples

AA tablets were crushed using a mortar and pestle, tablet crusher (HTS-160; Takazono Co., Tokyo, Japan), or oscillatory ball mill (OBM, MM400; Retsch, Haan, Germany) with a stainless ball with a diameter of 12 mm. The grinding was performed at 30 Hz, and the stainless jars were refrigerated under liquid nitrogen for 5 min before grinding.

The conditions were as follows: crushing with a mortar and pestle for 10, 30, and 50 rounds, or using a tablet crusher at 10,000 rpm, and using the MM400 for 0.5, 1, 3, and 5 min. The resulting samples were sieved through a 48-mesh sieve as part of the dispensing procedure and used in subsequent experiments.

Similarly, the AA crystals were ground and sieved as required. In this study, crushed samples are referred to as compounds.

2.3 Evaluation of physicochemical properties of samples

2.3.1 Powder X-ray diffractometry (PXRD)

The crystallinities of the samples were assessed using PXRD. Diffraction patterns were recorded using a RINT 2000 diffractometer (Rigaku Co., Tokyo, Japan) at room temperature ($25 \pm 1^\circ\text{C}$) under the following settings: Cu target with Ni filter, 40 kV voltage, 40 mA current, 1.5418 Å wavelength, $4^\circ/\text{min}$ scan speed, and a diffraction angle range of $5\text{--}40^\circ$, with three repeated scans. The PXRD measurements were performed by evenly spreading the sample on a glass sample plate and securing it in a horizontal holder.

2.3.2 Differential Scanning Calorimetry (DSC)

Thermal analysis of various samples was conducted using a DSC instrument (DSC-60plus; Shimadzu Co., Ltd., Kyoto, Japan) under a nitrogen gas flow of 50 mL/min at a heating rate of $2^\circ\text{C}/\text{min}$. Samples (~

6 mg) were placed in alumina pans and heated from 25°C to 300°C.

2.3.3 Fourier transform infrared spectroscopy (FT-IR)

The interactions among the materials in the ground samples were analyzed using an FT-IR spectrometer (PerkinElmer Co., Ltd., MA, USA). The spectra were collected using single-bounce diamond anvil cells.

Each sample had a thickness of 1.0 mm, and the scanning range was 500–4,000 cm^{-1} .

2.3.4 Scanning Electron Microscopy (SEM)

The surface characteristics of the samples were observed using a scanning electron microscope (JSM-6060LA, JEOL Ltd., Tokyo, Japan). The samples were affixed to the sample stage using adhesive tape. After uniformly coating it with platinum using a sputtering device (JFC-1600 Auto Fine Coater, JEOL Ltd., Tokyo, Japan), the sample stage was secured in the sample chamber for the observation. Observations were conducted at magnifications of 1000–5000 $\times$ and an acceleration voltage of 20–25 kV.

2.4 Dissolution test

The dissolution behavior of AA in each sample was evaluated using the JP 18th edition paddle method. The paddle speed was set at 100 rpm, with 500 mL of distilled water containing 0.1% (v/v) Tween 80 as the test fluid and maintained at $37 \pm 0.5^\circ\text{C}$. A 20 mg AA sample was added to each vessel, and 5 mL of solution was withdrawn at specified intervals and replaced with an equal volume of fresh test fluid. The collected solution was filtered through a 0.45- μm membrane and then measured via HPLC (SSC-3461; Senshu Scientific Co., Ltd., Tokyo, Japan) under the following conditions: λ_{max} , 243 nm; flow rate, 1.0 mL/min; mobile phase, methanol: distilled water = 1:3 (v/v); and measurement temperature, 40°C. Samples (5 μL) were injected into a C18 column (Shodex® C18M 4D, 4.6 mm $\times$ 150 mm; Showa Denko K.K., Tokyo, Japan). The percentage of released AA at each time point was calculated based on the theoretical value of AA and the average of three measurements.

2.5 Evaluation of dispensability

2.5.1 Calculation of Weight Loss Rate by Packaging

Approximately 2 g of the sample was divided into 10 packets using a V-Mass Automatic Dividing and Packaging Machine (PM-SL21S, Takazono Co., Ltd.) and a Disc-Type Automatic Dividing and Packaging Machine (CAR-MU45S, Takazono Co., Ltd.). Glassine paper was used as the packaging material for both machines. During packaging with the V-shaped powder dispensing machine (VSPM), a plastic spatula was used to level the contents evenly. For packaging using the rotary disc-type dispensing machine (RDPM), the feeder vibration was set to 3, and automatic packaging was performed. The weight-loss rate (%) was calculated using Eq. (1).

Weight loss rate (%) = [(Weight of sample loaded into the packaging machine) – (Weight of sample after packaging)] / 100 ... (1)

2.5.2 Evaluation of Flowability

The angle of repose, spade angle, agglomeration degree, and compressibility of the samples were measured using an angle of repose tester (AOR-14, Tsutsui Scientific Instruments Co., Ltd.), powder tester (PT-R, Hosokawa Micron Corporation), and powder reduction degree tester (TPM-1A, Tsutsui Scientific Instruments Co., Ltd.). Flowability was evaluated using Carr's index [12].

2.6 Statistical analysis

Data were analyzed using Dunnett’s multiple comparison tests for apparent solubility measurements and permeability evaluation of the mucin layer. Statistical significance was set at *P < 0.01 and *P < 0.05. Each graph shows the mean ± standard deviation (n = 3).

3 Results and discussion

3.1 Particle Size Distribution

The particle size distributions of samples obtained by crushing AA crystals and AA tablets under various conditions are shown in Fig. S1, and the results of particle size measurements are presented in Table 2.

Table 2
Particle Diameter of AA Crystals and Crushed AA Tablets Prepared with Various Methods

Sample	Methods	Time/Round	D10 (mm)	D50 (mm)	D90 (mm)
AA crystals	-	-	233.3	291.4	362.6
AA tablets	Mortar and Pestle	10 rounds	13.78	86.25	250.6
		30 rounds	6.894	84.92	268.9
		50 rounds	4.565	43.25	120.9
	Tablet crusher	30 sec	8.421	53.69	120.4
		1 min	8.191	36.24	104.4
		3 min	7.769	37.32	108.4
		5 min	8.955	43.11	118.2
	OBM	30 sec	4.713	51.34	121.1
		1 min	4.110	39.57	127.6
		3 min	9.675	88.62	184.3
		5 min	9.386	77.51	137.9

When ground using a mortar and pestle, the particle size distributions of the samples obtained after 10 and 30 agitation cycles exhibited a bimodal distribution; however, the sample obtained after 50 cycles showed a nearly unimodal distribution, and the average particle size also decreased [Fig. S1(b), Table 2].

Furthermore, the samples obtained using a tablet crusher exhibited a nearly unimodal particle size distribution when crushed for 30 seconds to 3 minutes [Fig. S1(c)].

On the other hand, the particle size distribution of the sample obtained by grinding with a tablet mill showed a nearly unimodal distribution after 3 minutes or more of grinding, but the average particle diameter was smallest for the sample ground for 1 minute [Fig. S1(d)]. The optimal grinding time for tablets using a benchtop ball mill is generally considered to be 30 seconds to 2 minutes [6]; in the 3- and 5-minute grinding trials conducted in this experimental system, it is presumed that the average particle size increased because particles that had initially been finely ground in a short time agglomerated as the grinding time was extended (Table 2).

A trend toward a decrease in the average particle size was observed with grinding, and among the three methods examined in this study, it was found that grinding with a tablet crusher was the most efficient method for grinding the samples (Fig. S1, Table 2).

3.2 SEM Observation

The AA crystals exhibited polyhedra with large, well-defined crystal faces (Fig. 1(1)). As the number of grinding cycles increased from 10 to 30 to 50, the particles became finer, but their shape remained relatively isotropic (rounded, irregular particles). Furthermore, as observed in the particle size distribution, the sample obtained by grinding AA tablets in a mortar contained a mixture of fine powder and coarse particles (Fig. S1(b)).

In samples of AA crystals ground using a tablet crusher (Fig. 1(1b)), elongated needle-like or plate-like particles were observed in all samples processed for 30 seconds to 5 minutes. Furthermore, cleavage planes of the crystals were observed, revealing that although the crystals were fractured by crushing, their crystal morphology was largely preserved.

Regarding the grinding process using the OBM (Fig. 1(1c, 2c)), the sample in which AA crystals were ground for 30 seconds still contained large particles. However, rapid pulverization was observed after 1 minute of grinding, and in the sample ground for 5 minutes, the number of large particles decreased, with mainly fine particles observed (Fig. 1(1c)). On the other hand, when AA tablets were ground, the proportion of fine particles increased as the grinding time was extended; however, coarse particles were also observed in the sample ground for 5 minutes (Fig. 1(2c)).

These results reveal that the AA crystals ground in a mortar and that ground using the OBM were refined into finer particles owing to the grinding action caused by the collision of stainless-steel balls within the mortar and pestle or pot. In contrast, because the tablet crusher breaks the crystals using high-speed rotating blades, cleavage occurs, with the crystals splitting along a specific direction, resulting in a needle-like morphology [13]

On the other hand, for AA tablets (Fig. 1(2b)), it was found that while coarse particles remained after a crushing time of 30 seconds, the particles became finer after 1 to 5 minutes. Furthermore, the particles

were more uniformly dispersed, suggesting that the pattern of refinement due to crushing in tablets containing additives differs significantly from that observed in crystals.

3.3 Effect of crushing methods on the crystallinity of the crushed AA tablets

Figure 2 shows the PXRD patterns of the AA crystals and crushed tablets prepared using different crushing methods. Furthermore, for comparison, Fig. S2 shows the PXRD patterns of lactose hydrate, the crystalline additive in AA tablets, ground using various methods. The lactose hydrate used in this experiment was crystalline, and no amorphization was observed during grinding.

As shown in Fig. 2, the peak intensity of each sample decreased as the crushing time increased. In the AA crystals used in this study, specific peaks were observed at $2\theta = 15.6^\circ$, 16.6° , and 24.3° . When the AA crystals were ground using a mortar and pestle or OBM, their peak intensities decreased, and new peaks were observed at $2\theta = 20.8^\circ$ for the samples ground with a mortar and pestle and OBM (Fig. 2(a)). This is thought to be caused by lattice strain or partial amorphization resulting from the grinding and shear forces generated during the grinding process [14].

Fig. 2(b) shows the PXRD patterns of the crushed AA tablets prepared using a mortar and pestle. The intensities of the diffraction peaks of the AA crystals decreased with increasing grinding time. Additionally, in the PXRD patterns of the crushed AA tablets produced using a tablet crusher (Fig. 2(c)), the diffraction peak intensities of decreased as the grinding time increased. This reduction was especially noticeable at grinding durations of 3 and 5 min. A peak at $2\theta = 21.3^\circ$ appeared after grinding.

Fig. 2(d) shows the PXRD patterns of various compounds ground with OBM. Similar to other grinding methods, the intensities of the diffraction peaks decrease with increasing grinding time, indicating a loss of crystallinity.

3.4 Effect of crushing methods on the thermal behavior of the crushed AA tablets

Figure 3 shows the DSC curves for the AA crystals, lactose monohydrate, and tablet powder ground using a mortar and pestle, tablet crusher, and OBM.

In the DSC curve of lactose monohydrate, an endothermic peak attributed to dehydration was observed near 140°C (Fig. 3(a)). Furthermore, in the DSC curve of the AA crystals, an endothermic peak attributable to melting was observed at 168°C (Fig. 3(b)).

In contrast, in the DSC curve of the AA tablet ground with a mortar and pestle, new endothermic and exothermic peaks appeared at approximately 145°C and 160°C , respectively (Fig. 3(c)).

It has previously been reported that anhydrous lactose exhibits an endothermic peak at approximately 145°C [15–17]. As hydrated lactose was used as an excipient in this study, this peak is presumed to be

attributable to hydrated lactose. Although the origin of the exothermic peak at 160°C is unknown, it is presumed to be due to crystallization.

Figure 3(d) shows the DSC curves of AA tablets crushed in a tablet crusher. The curve for the AA crystals did not change regardless of the crushing time. These exothermic peaks were likely due to the dehydration of α -lactose monohydrate, which was used as an excipient in the AA tablets [16, 17]. This is thought to reflect the fact that partial amorphization occurred because of the high grinding energy and greater disruption of the AA crystal lattice.

The DSC curves of the various compounds prepared using the OBM are shown in Fig. 3(e). The endothermic peak originating from the AA crystals, observed at approximately 170°C, decreased with prolonged grinding time. However, for the compounds treated with OBM, an endothermic peak was observed at approximately 140°C and an exothermic peak at approximately 143°C. These exothermic peaks are likely attributable to the dehydration of α -lactose monohydrate, an excipient used in AA tablets [16, 17]. In the DSC curves of the ground tablet materials prepared in this experimental system, no clear endothermic peak attributable to the melting of AA was observed. Furthermore, after grinding, the complex thermal behavior of the additives containing lactose was observed. These complex changes can be verified using a system capable of simultaneous PXRD and DTA or DSC measurements, which will be the topic of future investigation.

3.5 Effect of crushing methods on the molecular state of AA in the crushed AA tablets

FT-IR was used to analyze the intermolecular interactions between the AA molecules and the additives across various samples, as shown in Fig. S3 and Fig. 4. These figures show the FT-IR spectra of the AA crystals, a physical mixture of AA tablet components, and the ground mixtures of AA tablets prepared using various methods. Broad bands due to the stretching vibration of the hydroxyl group of crystalline lactose were observed at 3600–3200 cm^{-1} . The weak band at 1650 cm^{-1} is due to the bending vibration of the hydroxyl groups of the crystal water, and the band at 1200–1070 cm^{-1} is due to the asymmetric stretching [18].

Figure 4(a) shows the FT-IR spectra of the samples with a focus on the carbonyl groups of AA crystals. No shifts in the carbonyl peaks were observed for any sample prepared with a mortar and pestle, indicating no significant interactions between AA molecules and the additives.

Additionally, the crushed tablet using a tablet crusher showed no shifts in the carbonyl group peaks (Fig. 4(b)). This suggests that grinding with the tablet crusher did not induce any significant interaction between AA molecules and the tablet additives.

In contrast, in the FTIR spectra of the crushed tablets processed with OBM, the carbonyl group peaks shifted to higher wavenumbers for all compounds (Fig. 4(c)). This shift indicates that the AA molecules may have interacted with the additives via hydrogen bonding, suggesting that significant grinding energy

was imparted during the process. However, a slight shift ($\sim 3\text{ cm}^{-1}$) in the carbonyl stretching vibration seemed to be within the instrumental resolution, and definitive evidence of intermolecular interactions could not be concluded solely from the FTIR analysis.

3.6 Effect of crushing methods on the dissolution behavior of AA crystals from the crushed AA tablets

Figure 5(a), (b) and (c) illustrate the dissolution behavior of AA crystals and AA from various crushed samples. The dissolution rate of AA increased with increasing number of grinding rounds or time.

AA crystals were 100% dissolved 10 min after the start of the test. When the AA tablets were crushed using a mortar and pestle, the dissolution rate of AA increased rapidly with the number of crushing rounds (Fig. 5(a)). However, while the 10-round sample reached 100% dissolution in 5 min, the 30- and 50-round samples exhibited similar dissolution behavior, reaching 100% in 2 min. We hypothesized that the increased surface area may have contributed to the heightened dissolution rate.

The dissolution behavior of AA in the tablet-crusher compounds is shown in Fig. 5(b). The initial dissolution rate was higher than that of the other samples, and all samples reached nearly 90% elution within 30 s of the start of the test.

Figure 5(c) shows the dissolution behaviors of various compounds prepared using OBM. All compounds ground with OBM exhibited rapid early dissolution, and the dissolution rate generally increased with grinding time. These results align with those of other grinding methods, indicating that the dissolution rate was affected by particle size reduction. However, grinding time did not affect the dissolution rate.

Comparing the dissolution profiles resulting from different grinding methods in Fig. 5(a)–(c), the sample ground using a tablet crusher exhibited the fastest dissolution rate, followed by the samples ground using the OBM and the mortar and pestle. Because the blades of the tablet crusher rotate at a high speed, it is believed that the shearing action of the blades resulted in finer humate particles. The particle size of the compounds produced with the tablet crusher may be smaller than that of any other sample, supporting the idea that the increased particle surface area contributed to the higher dissolution rate of the tablet-crushed sample. Compounds prepared using the OBM exhibited lower crystallinity in both AA and the additives. However, the particle size increased with longer grinding times owing to particle aggregation, which likely affected the dissolution rate of AA.

3.7 Evaluation of flowability

To investigate the effects of powder adhesion and flowability on tablet press design, the flowability of the active ingredients and excipients in the tablets was evaluated. Okuma et al. stated that Carr's flow index is an effective method for evaluating the dispensing characteristics of powdered pharmaceuticals [19]. The angle of repose, agglomeration, and compressibility of the active ingredients and excipients were measured, and the flowability of the samples was evaluated using Carr's flow index [12]. Table 3 shows the flowability results for the AA tablet components. The flow indices for AA crystals, HPC-SL,

and cornstarch were 56.7, 47, and 40, respectively, indicating “poor” flow properties. The flow index of lactose monohydrate was 21, indicating “extremely poor” flow properties.

Table 3
Evaluation of the Flowability of AA Tablet Components.

Material	Angle of repose (°)	Angle of spatula (°)	Compressibility (%)	Agglutination (%)	Carr's Fluidity index
AA crystals	42	58	0.8	ND	56.7
HPC-SL	54	80.9	24.2	27.4	47
Cornstarch	52	82.6	32.8	9.2	40
Magnesium stearate	58	79.2	41.2	5.7	31
Lactose hydrate	57	78.9	46.1	39.2	21

As the AA tablets prepared in this study contained more than 50% lactose monohydrate, the flowability of the powders used in tablet manufacturing was considered low. Therefore, in a disc-type tablet press, the sample falls automatically owing to the vibration of the feeder in the powder hopper, and the higher the flowability of the sample, the faster the weight-loss rate. However, because the rate of weight loss varies depending on the grinding method, it is necessary to further evaluate the flowability of powders ground using different methods.

To evaluate the effect of different grinding methods on the flowability of AA tablets, Table 4 presents the powder characteristics after 50 strokes with a mortar and pestle and after 5 min of grinding with a tablet crusher and a bench-top ball mill. The flow indices of the samples

Table 4
Evaluation for Powder Flowability of AA Tablet by various methods

Method	Angle of repose (°)	Angle of spatula (°)	Compressibility (%)	Agglutination (%)	Carr's fluidity index
Mortar and pestle (50 rounds)	43.5	80.3	29.1	36.1	42.0
Tablet crusher (%)	41.0	84.7	31.9	17.4	45.5
OBM	46.0	85.1	35.6	60.5	30.5

ground with a mortar and pestle and a tablet crusher were 42 and 45.5, respectively, and their flowability was rated as “not very good.” In contrast, the flow index of the sample ground with a bench-top ball mill

was 30.5, and its flowability was rated as “poor.” This suggests that the flowability of the powders affected the residue, that is, the loss in weight, in the rotary disc powder filling machine, as the powders fell due to vibration and were dispensed within the rotary tablet press. It is presumed that agglomeration occurred in the bench-top ball mill, which likely also affected the flowability index of the powders. In future experiments, this should be verified by varying the vibration frequency of the powder-feeding device in the dispensing machine.

Furthermore, in actual clinical settings, powdered formulations are stored under various conditions. Crushed tablets are expected to have a larger surface area owing to the crushing process, making them more susceptible to moisture absorption. Moving forward, it will be necessary to investigate changes in the physical properties of these materials when they are stored under various humidity and temperature conditions.

3.8 Evaluation of compounding dispensability

Powder formulations are the third most common oral dosage forms, after tablets and capsules. They are packaged using blister-packaging machines, and their dispersibility depends on the physical properties of the powder. To evaluate the dispensing characteristics of crushed tablets, the weight loss during packaging was measured and compared across different packaging machines. In this study, weight loss during packaging refers to the proportion of the powder formulation intended for packaging that is lost due to moisture in the air, moisture present between particles, or particle agglomeration causing them to adhere to the equipment and is therefore not packaged.

Table 5 shows the weight loss rates when AA tablet powder was divided into 10 packets using a V-mass automatic powder dosing machine (V-shaped powder dosing machine, VSPM) and a disc-type automatic powder dosing machine (rotary disc-type powder dosing machine, RDPM). In VSPM filling, the number of agitation cycles during grinding with a mortar and pestle did not affect the weight-loss rate. Furthermore, for tablets crushed with a tablet crusher, the weight loss rate decreased as the crushing time increased; however, at 30 s, 1 min, and 3 min, the weight loss rate was higher than that with the other crushing methods.

However, for samples crushed using a tabletop ball mill, no significant difference in the rate of weight loss was observed at any crushing time (Table 5).

The VSPM used in this study operates by horizontally homogenizing the powder using a plastic spatula within a V-shaped powder receptacle, after which the powder falls into partitioned compartments at the bottom of the hopper for its packaging. In contrast, in the RDPM, when

Table 5
Deviation of Separation and Packaging of Crushed AA Tablets.

Grinding Method	Time	Decrease rate of weight (%)	
		VSPM	RDPM
Mortar and Pestle	10r(30s)	1.0 ± 0.5	3.9 ± 1.7
	30r(1min40s)	1.8 ± 0.2	4.0 ± 1.0
	50r(2min30s)	1.3 ± 0.7	3.3 ± 1.2
Tablet crusher	30s	3.0 ± 0.5	3.8 ± 0.7
	1min	3.3 ± 0.7	5.5 ± 0.1
	3min	2.3 ± 0.7	8.0 ± 0.5
	5min	1.2 ± 0.7	10.0 ± 0.5
OBM	30s	1.2 ± 0.8	1.5 ± 0.5
	1min	1.2 ± 0.3	1.2 ± 0.3
	3min	1.5 ± 0.5	6.2 ± 1.3
	5min	1.5 ± 0.5	8.5 ± 1.7
Data are expressed as mean ± S.D. (n = 3)			

powder is fed into the powder supply hopper, a vibrating feeder automatically drops it onto a rotating, donut-shaped container. When the set weight is reached, the rotation of the donut-shaped container stops, and a scraping device removes a specific amount of powder at a fixed angle for portioning and packaging purposes. Owing to these structural differences, it is presumed that the powder's adhesion and flowability affect weight loss in the RDPM.

3.9 Impact of crushing energy on solid-state properties and pharmaceutical performance

The present study demonstrated that different crushing methods affected not only the particle size but also the morphology, crystallinity, molecular state, and pharmaceutical performance of acetaminophen tablets. These changes appeared to depend on the magnitude and mode of mechanical energy applied during crushing.

Grinding with a mortar and pestle reduced particle size while maintaining relatively high crystallinity in AA. The relatively small decrease in diffraction intensity suggested that the mechanical stress applied by manual grinding was insufficient to induce extensive crystal disorder.

Although the crystallinity of the AA crystals decreased somewhat as a result of processing with a tablet crusher, the crystal morphology was generally maintained, as evident from the needle-like particles observed by SEM. It is believed that the high-speed rotating blades promoted cleavage along the preferred crystal orientation, producing fine particles with a large specific surface area while minimizing crystal disruption; compared to other grinding methods, this may explain the rapid dissolution observed in the tablet-crushing samples.

On the other hand, when AA tablets were crushed using a tablet crusher, fine particles were observed, unlike with AA crystals. While needle-like crystals were observed in AA crystals because they fracture along their cleavage planes, in AA tablets, it is thought that intense mixing and collisions between the additives and the AA crystals lead to the formation of high-energy interfaces along the cleavage planes of the AA crystals. It is believed that the adhesion of additives to these interfaces led to the observation of fine particles in which the cleavage planes were not visible. This surface adsorption onto the cleavage planes was observed as a decrease in crystallinity via XRPD; however, since this interaction was limited to the cleavage planes, it may not have been detected by FTIR. It is believed that the adsorption of additives onto these cleavage planes prevented the agglomeration of finely ground particles and improved wettability, which in turn led to the high dissolution rate observed.

OBM induced the greatest changes in the solid-state properties of AA tablets. SEM images revealed extensive particle size reduction accompanied by particle aggregation. These morphological changes corresponded well with the PXRD results, which showed marked decreases in diffraction intensity and the appearance of additional peaks, suggesting reduced crystallinity and partial lattice disorder. Furthermore, FTIR spectra showed slight shifts in the carbonyl stretching vibration, implying possible changes in intermolecular interactions between AA crystals and excipients.

Despite the greatest reduction in crystallinity, OBM did not produce the fastest dissolution. These findings indicate that dissolution behavior is governed not only by crystallinity but also by particle aggregation and changes in intermolecular interactions induced by excessive grinding energy.

This phenomenon has also been observed when preparing mixtures of telmisartan and various excipients via liquid-solid compaction; it has been reported that while the crystallinity of telmisartan decreases, its surface area increases and its solubility improves, there are no intermolecular interactions between telmisartan and the excipients [20]. As discussed above, it is presumed that during sample preparation via liquid-solid compaction, an extremely thin film of excipients forms on the crystal surface, resulting in an increase in surface area and improved wettability in the dispersion medium.

Taken together, these findings suggest that the pharmaceutical performance of crushed tablets is governed not simply by particle size reduction but by a combination of morphological changes, crystallinity, intermolecular interactions, and particle aggregation. Therefore, selecting an appropriate crushing method is essential to maintain the quality, stability, and pharmaceutical performance of compounded powdered medications in clinical practice.

4 Conclusion

This study demonstrated that crushing methods significantly influence the solid-state properties, dissolution behavior, and dispensing characteristics of AA tablets. Among the methods examined, OBM induced the greatest reduction in crystallinity and altered intermolecular interactions, whereas tablet crusher treatment produced the finest particles and the fastest dissolution. These findings suggest that the selection of crushing methods is an important factor in ensuring the quality and clinical performance of compounded powdered medications [21].

Abbreviations

Acetaminophen: AA

Powder X-ray diffractometry: PXRD

Food and Drug Administration: FDA

Differential scanning calorimetry: DSC

Japan Pharmacopeia: JP

V-shaped powder dispensing machine: VSPM

Rotary disk-type powder dispensing machine: RDPM

area under the concentration-time curve: AUC

Scanning Electron Microscopy: SEM

oscillatory ball mill: OBM

Declarations

Declarations: The authors declare no conflicts of interest.

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visualization, T.T., Y.K.; supervision, T.H.; project administration, T.H., K.H., and Y.K.; funding acquisition, T.H. All authors have read and agreed to the published version of this manuscript.

Ethics, Consent to Participate, and Consent to Publish declarations: Not applicable.

Clinical trial number: not applicable

Data availability: No datasets were generated or analyzed in this study.

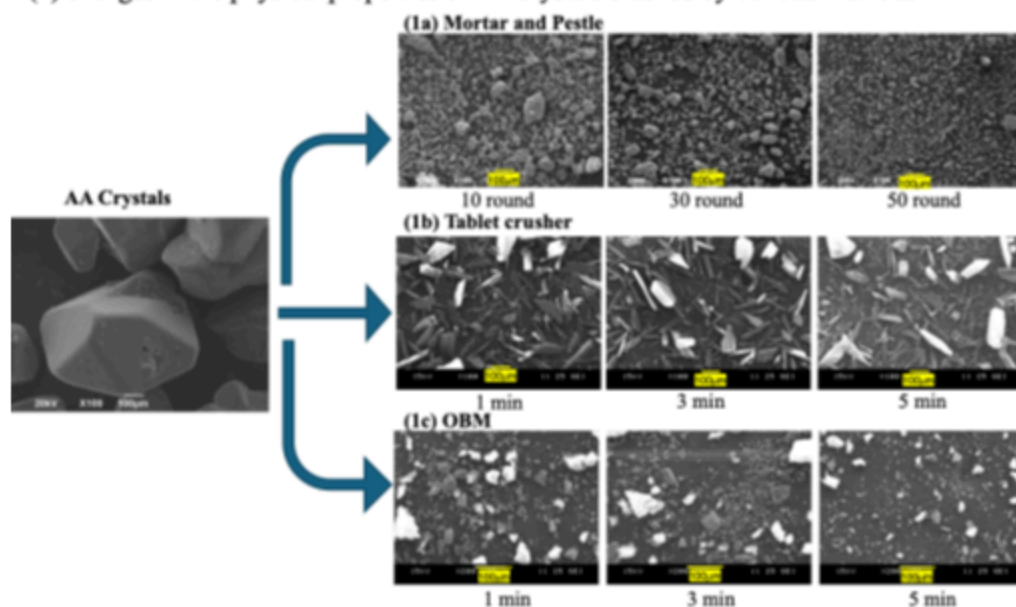
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Figures

(1) changes in the physical properties of AA crystals crushed by various methods



(2) changes in the physical properties of AA tablets crushed by various methods

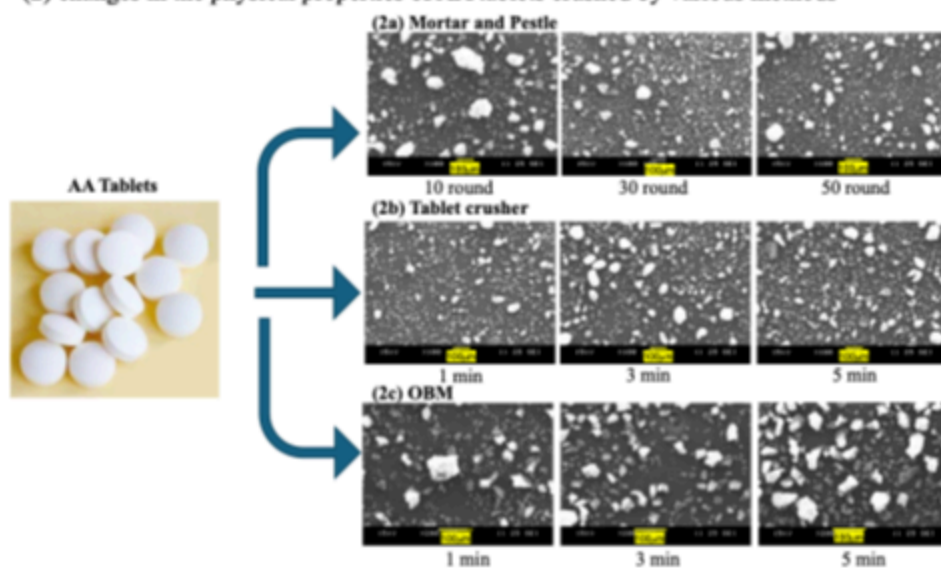
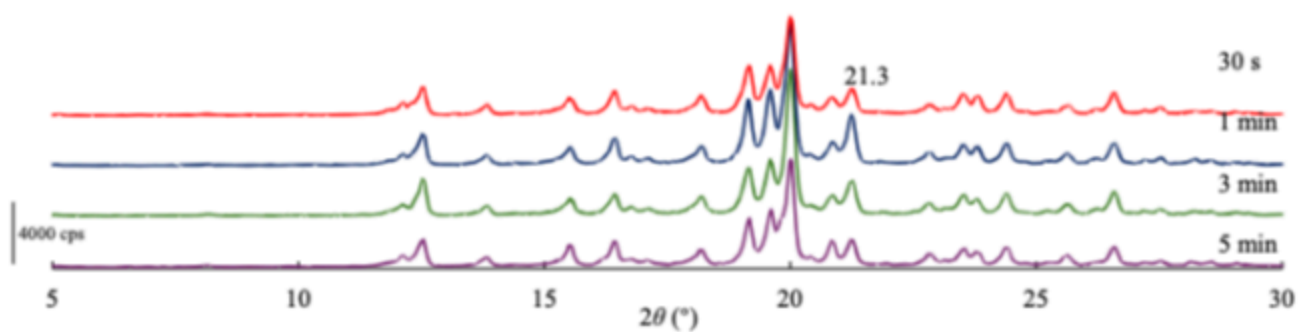


Figure 1

Changes in the Physical Properties of AA Crystals or Tablets Crushed by Various Methods

(c) Ground AA tablets prepared by tablet crusher



(d) Ground AA tablets prepared by OBM

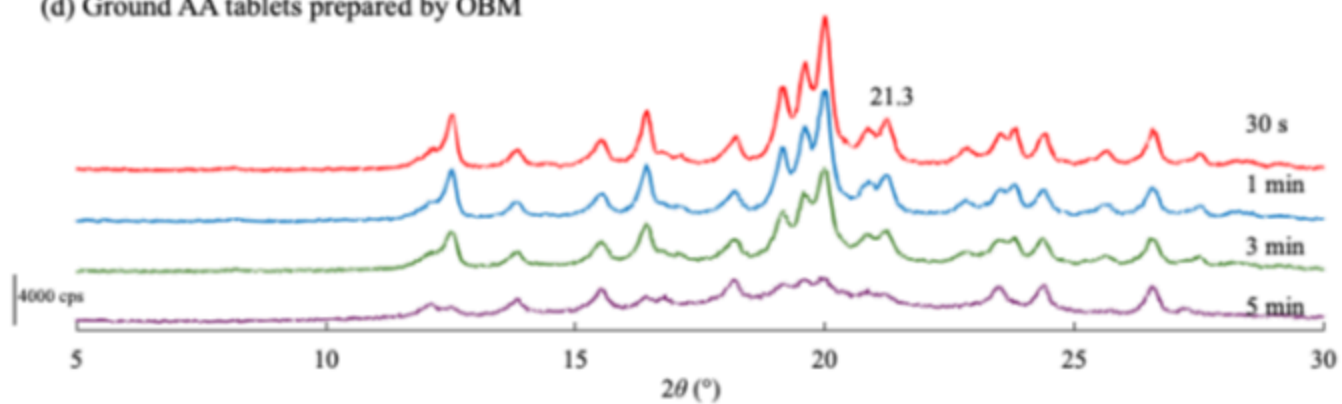


Figure 2

PXRD Patterns of Crushed AA Crystals and Crushed AA Tablets Prepared with various Methods.

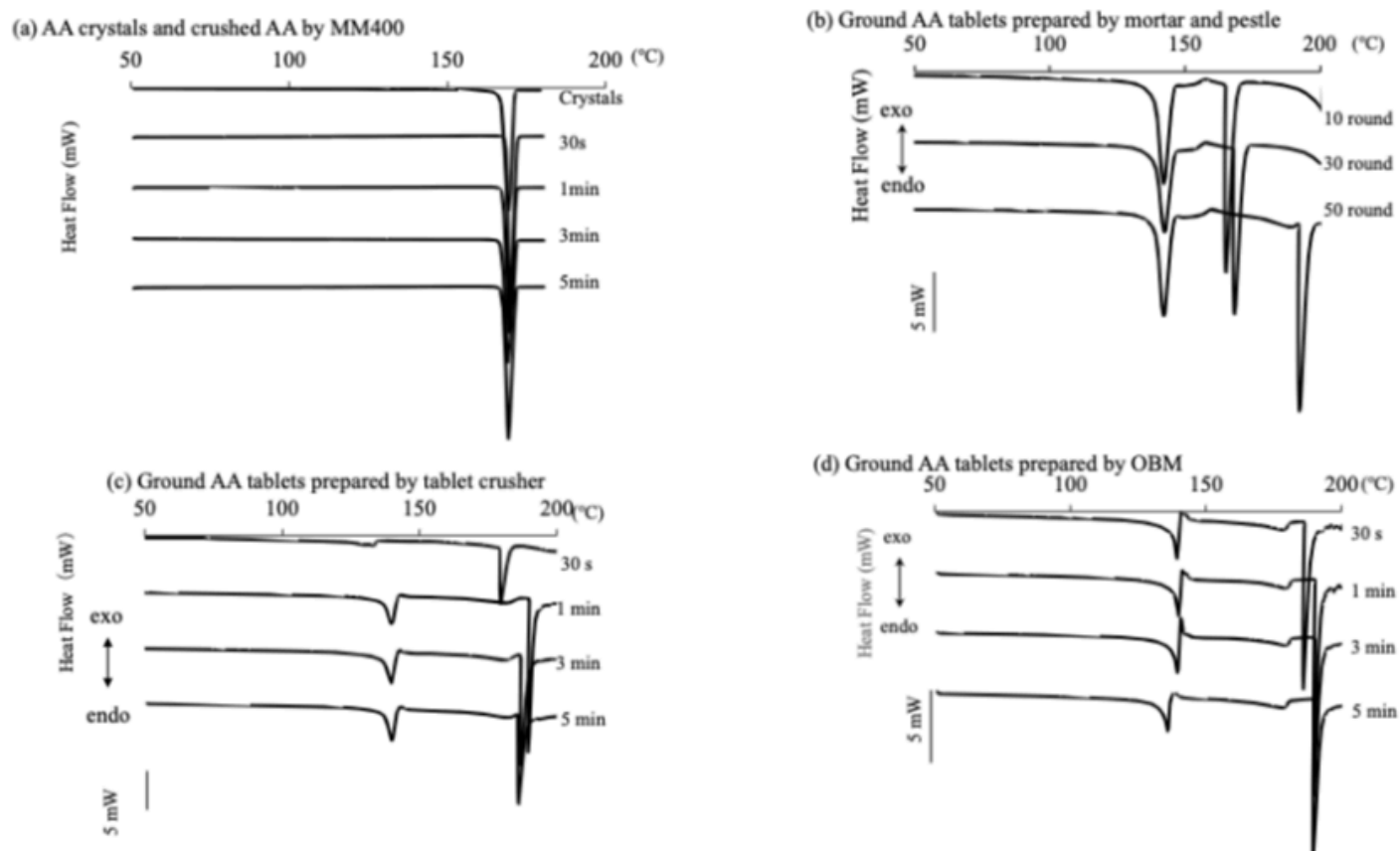


Figure 3

DSC Curves of Various Samples

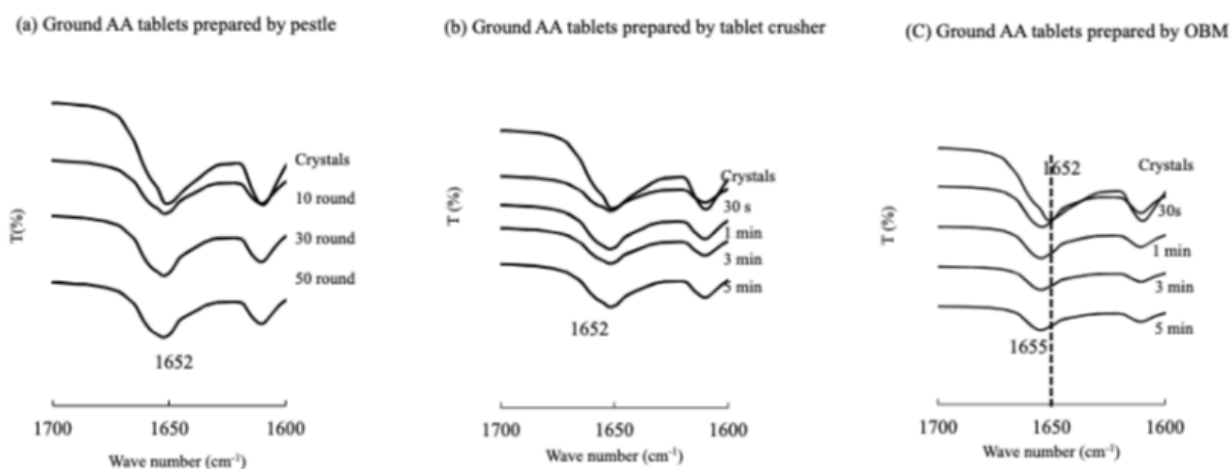


Figure 4

FTIR Spectra of Crushed AA Tablets Prepared with Various Methods.

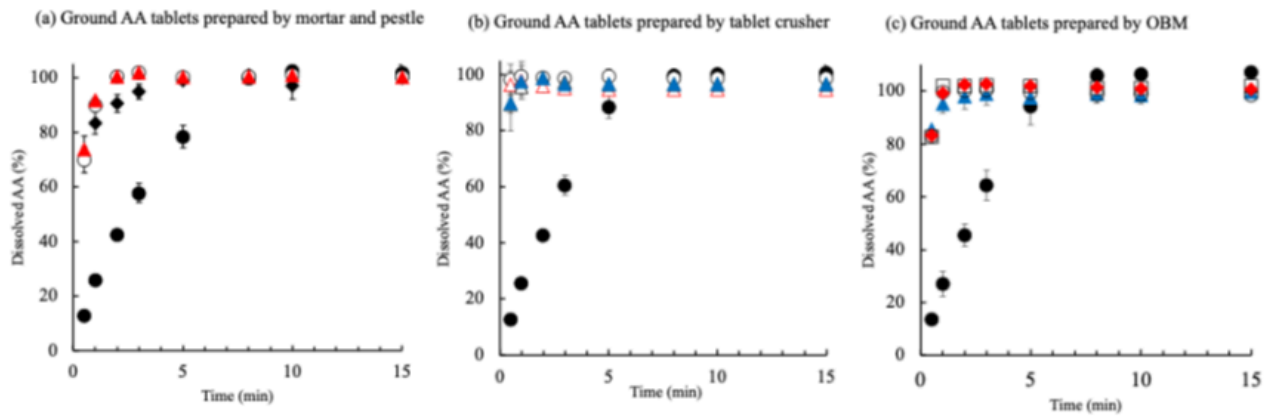


Fig.5 Dissolution Profiles of AA from Various Samples

a), ●; AA crystals, Ground AA tablets prepared with mortar and pestle , ◆; 10round, ○; 30round, ▲; 50round
 (b), (c), ●; AA crystals, Ground AA tablets prepared with tablet crusher or MM400, ○;30s, □; 1min, ▲; 3min, ◆; 5min

Mean $\pm$ SD, $n=3$

Figure 5

See image above for figure legend.

Supplementary Files

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