Tropical Journal of Pharmaceutical Research November 2024; 23 (11): 1797-1806
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v23i11.1

Original Research Article

Dissolution enhancement of ketoprofen using melt-sonocrystallization technique

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Sent for review: 1 March 2024 *Revised accepted: 2 November 2024*

Abstract

Purpose: *To investigate the effect of melt-sonocrystallization technique (MS) on the physicochemical characteristics and dissolution of a poorly soluble drug (ketoprofen).*
Methods: *Ketoprofen was heated in paraffin oil bath at 97 °C and then poured into a beaker containing 25 mL deionized water at 25 °C and immediately treated using a probe ultrasonicator at different ultrasonic times, and varying amplitudes at frequency of 20 KHz. Prepared suspensions were evaluated for the effect of temperature and energy of production. Powders were characterized using differential scanning calorimetry (DSC), scanning electron microscopy (SEM), X-ray diffraction (XRD), and Fourier transform infra-red spectrophotometry (FTIR). The Heckle plot, Carr's compressibility index, and Hausner's ratio were used to determine compressibility properties. Furthermore, the angle of slide was used to evaluate flow characteristics.*
Results: *There was a significant reduction in particle size characteristics following melt-sonocrystallization ($p < 0.05$). The SEM micrographs revealed needle-shaped particles with smooth surfaces. There was no significant difference in DSC thermograms with peaks ranging from 97.3 to 98.1 °C ($p < 0.05$). The FT-IR spectra showed two specific sharp and symmetrical peaks at (1654.5 cm^{-1}) and (1697.3 cm^{-1}). Also, distinctive peaks of ketoprofen remained detectable in XRD patterns, indicating that the substance had not undergone structural modification. The solubility increased by 15 %. There was no improvement in flowability or compressibility. Dissolution was greatly improved from 67 to 85 %.*
Conclusion: *Melt-sonocrystallization reduces particle size, solubility, and dissolution with no structural modification to ketoprofen. In vivo investigation of drug bioavailability from the generated powders would be required.*

Keywords: *Melt-sonocrystallization, Ketoprofen, Physico-chemical properties, Dissolution*

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INTRODUCTION

Drugs categorized into Class II in the biopharmaceutical classification system (BCS) have low gastrointestinal fluid solubility and high intestinal membrane permeability. Thus, their bioavailability is controlled by solubility and rate of dissolution [1]. Reducing particle size increases the surface area, which leads to higher dissolution rate. Particle manufacturing approaches are developed to modify the micrometrical, physicochemical, and biopharmaceutical characteristics of drugs. One of the promising technologies that use ultrasonic power is melt-sonocrystallization. Melt-Sonocrystallization with a frequency range of 20 to 100 KHz is utilized to control the crystallization process by cavitation phenomenon and acoustic streaming [2].

Cavitation is either transient or stable depending on the intensity of the energy input [3]. When the energy intensity given is insufficient to produce bubble collapse, stable cavitation occurs. This causes mild effects via a process known as acoustic streaming and leads to uniform micro-mixing [3]. At high intensities, bubbles that have outgrown the capacity to absorb gases violently collapse, causing transient cavitation. This results in a massive emission of energy densities from 1 to 1018 kW/m^3 in a very localized hot spot [4]. This occurs in an extremely brief time under 400 ns (the collapse is faster than thermal transport) [5], at a temperature of about 5000 K [6], a pressure of approximately 1000 bar [7], and a heating and cooling rate above 10^{10} K/s [8].

Melt-sonocrystallization was first introduced by Manish *et al* [9]. It was employed to produce small particles with improved solubility, and dissolution rate. It was also utilized to improve secondary properties of drugs with poor water solubilities, such as ibuprofen [9], flurbiprofen [10], Rosiglitazone [11], paracetamol, indomethacin and mefenamic acid [12]. Melt-sonocrystallization was used to prepare amorphous particles of celecoxib [13], and to identify thermodynamically preferred polymorph when dealing with a polymorphic system [14]. In this present study, melt-sonocrystallization was applied to the non-steroidal anti-inflammatory drug (NSAID) ketoprofen (2-(3-benzoylphenyl)-propionic acid), for which rapid bioavailability is preferred. The MS-prepared samples were investigated for particle size, flowability, compressibility, solubility, extent and rate of dissolution.

EXPERIMENTAL

Materials

Ketoprofen, hydrochloric acid and paraffin oil were provided by Xiamen Fine Chemical Ltd (China), Unichem (India), and Supplier Chemicals (Holland), respectively.

Preparation procedure

Ketoprofen (1 g; Xiamen Fine Chemical Ltd., China), was heated until it completely melted in a paraffin oil (Xiamen Fine Chemical Ltd., China), bath, at 97 °C. The molten was poured into a beaker containing 25 mL deionized water at 25 ^{o}C and immediately treated using a probe ultrasonicator (Model VC 505, Sonics and Materials, USA) with a tip diameter of 2.5 cm at different ultrasonic times, and varying amplitudes at frequency of 20 KHz. Prepared suspensions were allowed to cool for 2 h at room temperature. Crystallized ketoprofen was filtered and then dried at 40 ^{o}C for 24 h (Table 1). Temperature and energy of the suspension were subsequently recorded at the end of each experiment.

Table 1: Representative preparation of MS samples

Sample	Ultrasonic amplitude (%)	Ultrasonic time (min)
Pristine ketoprofen	-	-
MS1	**50**	**4**
MS2	75	4
MS3	100	4
MS4	75	5
MS5	75	8

Evaluation of parameters/indices

Percentage yield

Percentage yield was calculated using Eq 1.

Yield (%) = (w_g*100/(w_i-w_l) …….. (1)

And, $w_u = w_i - w_l$

Where w_u is the weight of the drug's melt poured into the beaker, w_i is the initial weight (1 g) and w_l is weight of the melt lost in the test tube.

Particle size measurement

A laser diffraction particle size analyzer (model S3500, Microtrac, USA) was employed for particle size measurement for both the pristine and MS-prepared ketoprofen samples.

Surface area measurement

A mercury porosimetry analyzer (Micrometrics, GA, USA) with a maximum mercury pressure of 50 PSI was used to determine the surface areas of MS-prepared powders and pristine Ketoprofen.

Solubility tests

An excess amount of both pristine and MS-prepared ketoprofen powders were separately introduced into a pH 1.2 hydrochloric acid (Xiamen Fine Chemical Ltd., China), solution, and then agitated for 48 h in a water bath shaker (model 1083, Germany) at 37 ± 0.1 °C. The sample was centrifuged until excess powder precipitation occurred and passed via a 0.45 µm filter. Concentration of the filtrate solution was appropriately adjusted and analyzed using a UV spectrophotometer (Cintra 5, GBC scientific equipment, Australia) at 256 nm. Determination was done in triplicates.

Differential scanning calorimetric analysis (DSC)

Using a differential scanning calorimeter (Mettler-Toledo-Schwerzenbach, Switzerland), small amounts of pristine and MS-prepared ketoprofen powders were heated at temperatures ranging from -30 to 140 °C in closed aluminum pans. An unfilled pan served as a baseline. The scan rate was set to 10 °C/min and a 5 min isotherm step at -30 °C.

X-ray diffraction analysis (XRD)

Powder X-ray diffraction patterns for pristine and MS-prepared drugs were made using an X-ray powder diffractometer (PW 1729, Philips, Holland) employing cobalt radiation.

Fourier transform infrared analysis (FTIR)

Pristine and MS-prepared ketoprofen samples were individually combined with potassium bromide (1 % w/w) and then mixed until the samples were evenly distributed.

A small portion of each resulting mixture was examined using a Fourier transform infrared spectrophotometer (Model IR Affinity-1, Shimadzu, Japan) across a 4000 - 400 cm^{-1} frequency range with 0.04 cm^{-1} resolution.

Scanning electron microscopy (SEM)

Surface morphology of pristine and MS-prepared ketoprofen powders was analyzed using a scanning electron microscope (model Inspect F50, Holland). The powders were placed on an aluminum stub using double adhesive carbon layers, and subsequently covered with platinum to enhance electrical conductivity.

Angle of slide

Pristine ketoprofen (10 g) and MS2 samples were positioned on a uniformly thick stainless-steel surface that was progressively inclined until the particles began to slide, and the corresponding sliding slope was recorded. The determination was done in triplicate.

Carr's compressibility index and Hausner's ratio

A total of 50 mL pristine ketoprofen and MS2 powders were poured separately into a cylinder and tapped 1000 times with a Copley Jolting Volumeter. Tapping volume was documented after completion. Determination was done in triplicate. Carr's index (C) was calculated using Eq 2. Hausner's ratio (HR) was calculated using Eq 3.

$$\text{Carr's index } (\%) = ((\rho_{tap}-\rho_{bulk})100/\rho_{tap}) \quad \ldots\ldots\ldots (2)$$

$$HR = \rho_{tap}/\rho_{bulk} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

where ρ_{tap} is tapped density and ρ_{bulk} is the bulk density.

Compressibility study

Untreated ketoprofen and MS2 samples weighing 200 mg each were compressed by an IR hydraulic press (Shimadzu Corporation) at different forces ranging from 20 to 100 kg/cm^2. Resulting compacts were placed in a desiccator with silica gel for 24 h to facilitate elastic restoration. Determination was done in triplicate. Porosity of the compacts was determined using Eq 4.

$$\varepsilon = (\rho_t-\rho)/\rho_t \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

Where (ρ) is tablet density calculated by determining its thickness with an electronic micrometer, while (ρ_t) is true density measured with an ultrapycnometer (Quantachrome Instruments, USA). The results were analyzed using Heckel Eq 5.

$$\text{Ln}(1/\varepsilon) = (K*P)A \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (5)$$

Where K and A are constants, while ε represents porosity at pressure P. Average yield pressure is the inverse of K.

Dissolution studies

Dissolution assay for pristine and MS-produced powders (50 mg) was conducted in pH 1.2 hydrochloric solutions (900 mL) at 50 rpm for 2 h utilizing a type II USP dissolution device (Erweka, Germany). At predetermined intervals, 5 mL was extracted, filtered and quantified using UV spectrophotometer (GBC scientific equipment, Australia) at 256 nm. Similarity factor (f_2) was calculated to evaluate the dissolution profiles using Eq 6.

$$f_2 = 50\log([1+(1/n)\sum_1^n(R_t-T_t)^2]^{-0.5}\times 100) \quad \text{..... (6)}$$

Where: n represents the number of dissolution time points (t), R_t and T_t denote the reference and test dissolution readings at any given time. When (f_2) value exceeds 50, the two profiles under comparison are considered identical.

Statistical analysis

All determinations were done in triplicate. Outcomes were presented as mean ± standard deviation (SD) and analyzed using GraphPad Prism version 5 (GraphPad Software, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Temperature and energy

During preliminary studies, initial results revealed that the melt is predominantly precipitated; hence, high ultrasonic energy was required to effect crystallization. Ultrasonic duration required for complete melt-sonocrystallization varied depending on the applied ultrasonic amplitudes. The suspensions obtained on completion of the process appeared milky and homogeneous. As the applied ultrasonic amplitude and duration increased, the temperature at the end of the process rose between 65 °C and 84 °C (Table 2).

Process yield, surface area, and solubility

There was a significant difference in yield, and surface area of the MS samples compared to untreated ketoprofen ($p < 0.05$; Table 3).

Particle size determination

Average size of the crystals was significantly lower for all applied amplitudes (50, 75, and 100 %; Figure 1 A) and ultrasonic durations (4, 5, and 8 min), (Figure 1 B) from 129 µm to 10 µm ($p < 0.05$).

Table 2: Temperature and energy recorded at the end of the process (mean ± SD, n = 3)

Sample	Temperature (ºC)	Energy (Joule)
MS1	66.66±0.57	8218±24.33
MS2	77.16±0.28	12276.33±158.86
MS3	81.66±0.76	15826.67±206.93
MS4	79.33±0.57	14237.67±35.23
MS5	83.16±1.04	23251±650.54

Scanning electron microscopy (SEM)

The SEM (Figure 2) showed that the pristine ketoprofen particles were irregular in size and had a crystal structure with a rough surface (Figure 2 A). However, the scanning electron micrographs of the MS powders showed smaller particles with smooth surfaces and a crystal habit dependent on the applied ultrasonic energy (Figure 2 B - F).

Table 3: Surface area, solubility and yield of MS powders (mean ± SD, n = 3)

Sample	Surface area (m^2/g)	Solubility* (mg/mL)	Yield* (%)
Prestine ketoprofen	0.142	0.157 ±0.003	-
MS1	**0.575**	**0.175±0.012**	**31.27±6.11**
MS2	0.663	0.176±0.006	73.18±3.39
MS3	0.505	0.186±0.005	82.03±3.13
MS4	0.519	0.186±0.002	79.29±5.60
MS5	0.530	0.185±0.007	**80.39±3.16**

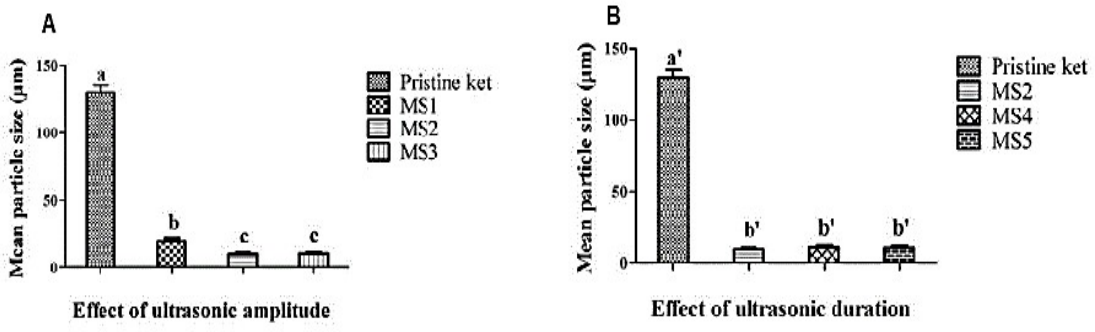

Figure 1: Effect of ultrasonic energy on the mean particle size of MS powders produced at different ultrasonic amplitudes and times

At ultrasonic amplitude of 50 %, the particles were characterized by a plate-like shape (Figure 3 A), whereas, at higher ultrasonic amplitudes (75 % and 100 %), the particles were smaller and needle-shaped (Figures 3 B - D). However, MS particles (MS3, MS4, and MS5), prepared at high ultrasonic energy, were agglomerated. No significant alteration was observed at the ultrasonic duration of 8 min. Therefore, the ultrasonic duration of 4 min was sufficient for the complete release of supersaturation.

Fourier transform infrared-red (FT-IR) analysis

The FT-IR spectra of untreated drug and MS-produced powders exhibited two distinct parallel acute peaks (1654.5 cm^{-1}) and (1697.3 cm^{-1}), corresponding to the drug carboxylic and carbonyl stretching vibrations (Figure 4).

X-ray diffraction (XRD) patterns

The XRD patterns of both pristine ketoprofen and MS samples, produced under various operation settings, exhibited distinct peaks that are characteristic of the crystalline state. However, certain peaks in MS samples had different intensities at specific 2 θ values. However, there was a significant reduction in peak intensities at 2 θ values of 14.10 and 18.04, while that at 6.04 and 27.80 increased (Figure 5).

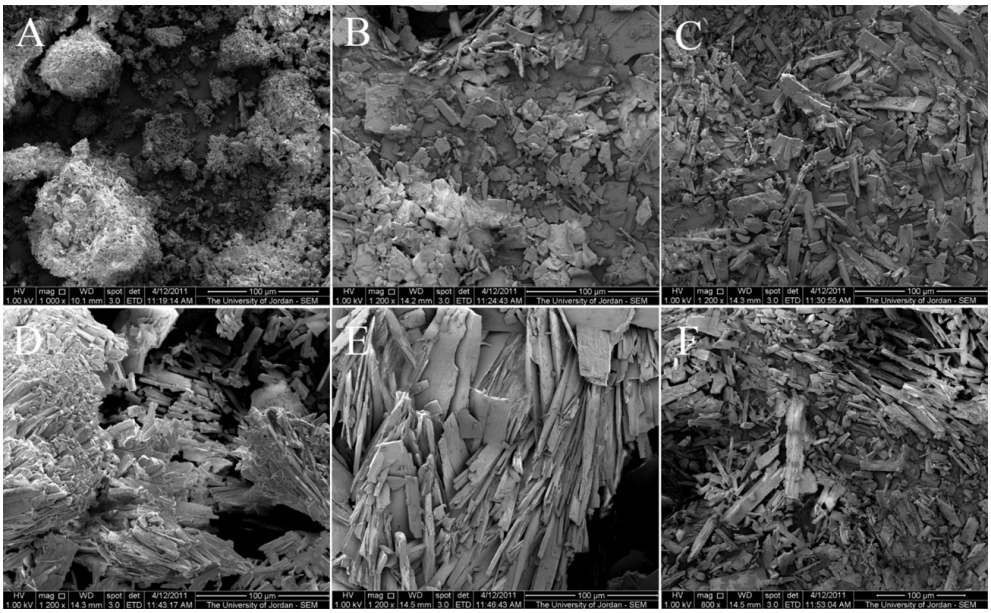

Figure 2: SEM micrographs of (A) Pristine ketoprofen; (B) MS1 (50 %, 4min); (C) MS2 (75 %, 4min); (D) MS3 (100 %, 4min); (E) MS4 (75 %, 5min); and (F) MS5 (75 %, 8min) powders (Magnification x1200)

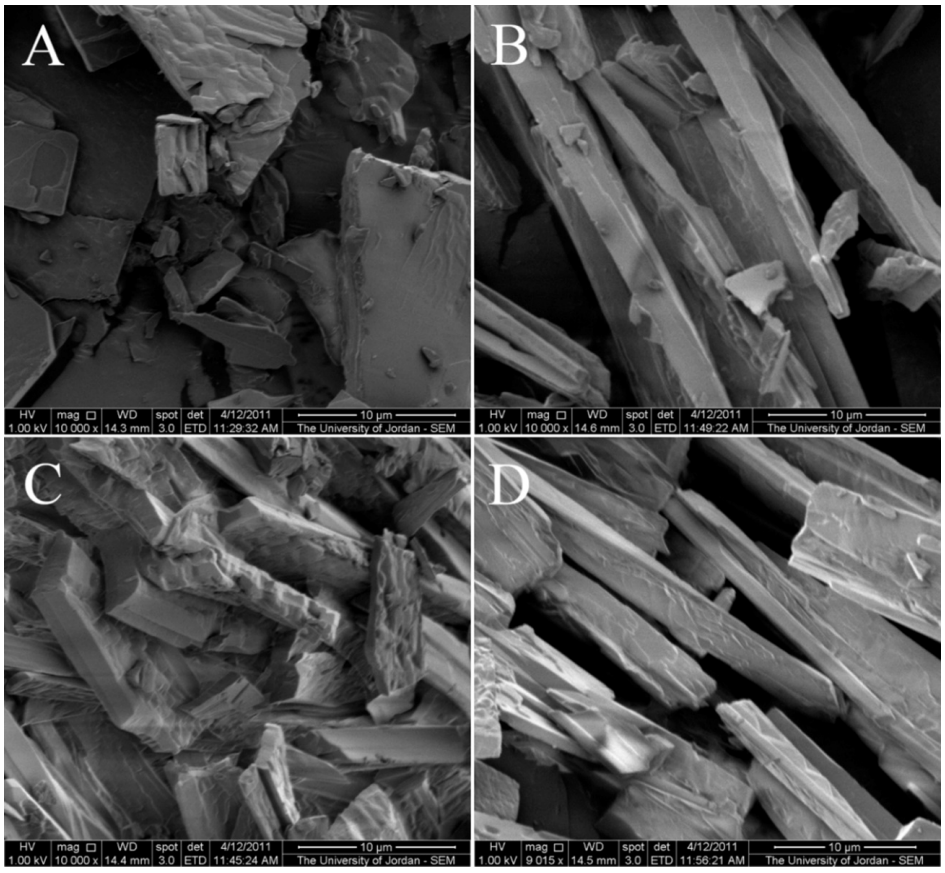

Figure 3: SEM micrographs of (A) MS1 (50 %, 4min); (B) MS4 (75 %, 5min); (C) MS3 (100 %, 4min); and (D) MS5 (75 %, 8min) powders (Magnification x10000)

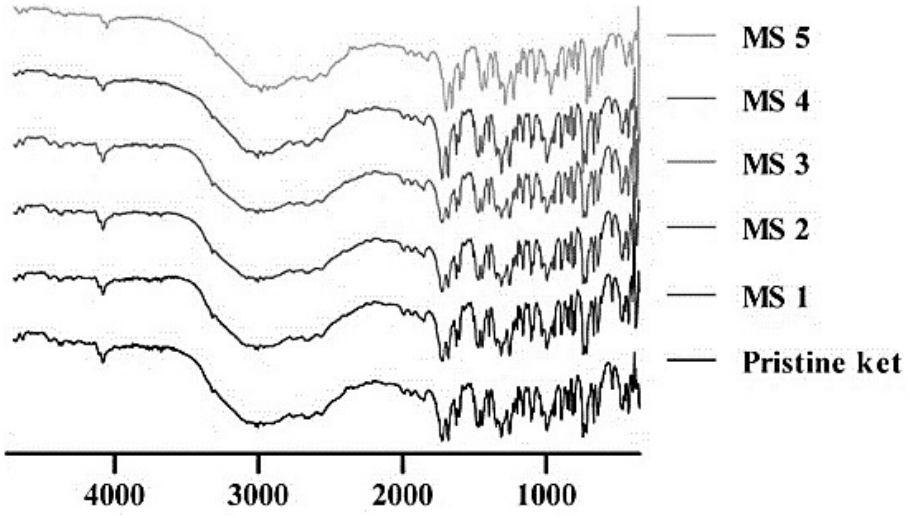

Figure 4: FTIR spectra of pristine ketoprofen and MS samples

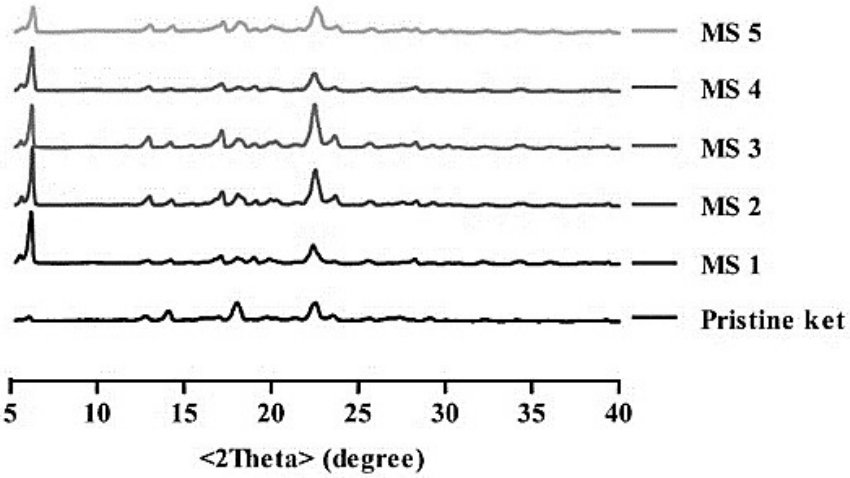

Figure 5: X-ray diffraction patterns of pristine ketoprofen and MS powders

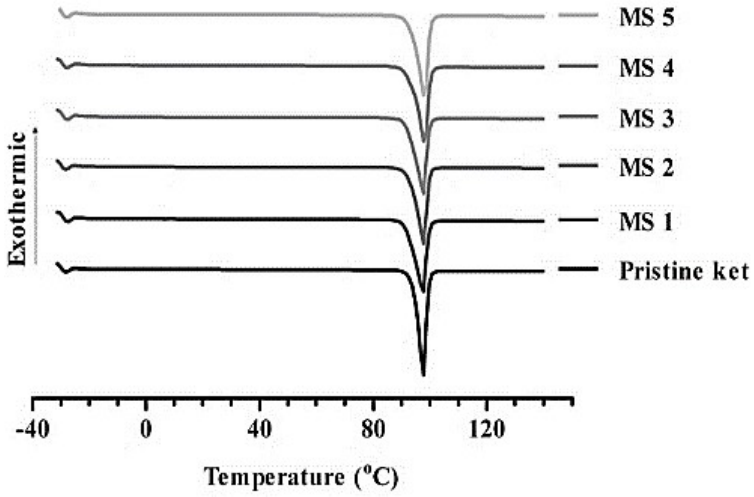

Figure 6: DSC thermograms of pristine ketoprofen and MS samples

Differential scanning calorimetry (DSC) thermograms

The DSC thermograms of both untreated drug and MS powders generated under various operating conditions revealed comparatively wide and asymmetrical melt endotherms ranging from 97.3 to 98.1°C (Figure 6).

Flow properties

The angle of slide Carr's index and Hausner's ratio for the drug and MS2 samples are presented in Table 4.

Dissolution profiles

In vitro dissolution profiles were determined for both untreated and MS samples in hydrochloric solution at pH 1.2 and 37 °C. Figure (7 A) showed that the rate and amount of ketoprofen dissolution increased at all applied ultrasonic amplitudes. After 30 min, MS-produced powders released 67 to 85 % of ketoprofen, compared to 30 % for untreated drugs. Figure (7 B) showed that the rate and extent of ketoprofen dissolution were considerably increased at all applied ultrasonic durations. Almost 50 to 85 % of the drug was released within 30 min

DISCUSSION

Melt-sonocrystallization technique was used for ketoprofen, which undergoes slow and shear-dependent crystallization [15], and results in an undesired oiling-out phenomenon, where a second liquid phase forms instead of solid crystals [16]. Ketoprofen is thermally stable up to 235 °C [17]. The melt properties of the drug and its glass transition temperature (Tg) are important parameters. Ketoprofen is a good

candidate for this study since it has a low tg (about -4 °C). Melt-sonocrystallization was conducted at an ambient temperature (25 °C), which is well above the tg, so the poured melt remained in the liquid state for a sufficient amount of time, enabling crystallization to be effected by applying ultrasonic power [9,13]. All experiments were conducted at 20 KHz, as the ultrasonic apparatus didn't permit alteration of this parameter. Therefore, only the effect of ultrasonic amplitude and duration were investigated in this study. The recorded temperature and energy for each experiment carried out in triplicate, showed good reproducibility using this technique [2].

The relatively low yield was due in part to the adhesion of the melt to the probe and the beaker's walls. However, as ultrasonic amplitude and duration increased, the yield also increased. The resultant energy was insufficient to affect the entire melt at low applied amplitude (50 %) and duration (4 min).

Table 4: Angle of the slide Carr's index and Hausner's ratio of pristine ketoprofen and MS2 powders (mean ± SD; n = 3)

Sample	Angle of slide (°)	Carr's index (%)	Hausner's ratio	Flow character
Pure ketoprofen	31.33±0.57	24.33±0.61	1.32±0.01	Passable
MS2	37.5±0.50	34.53±1.28	1.52±0.03	Very poor

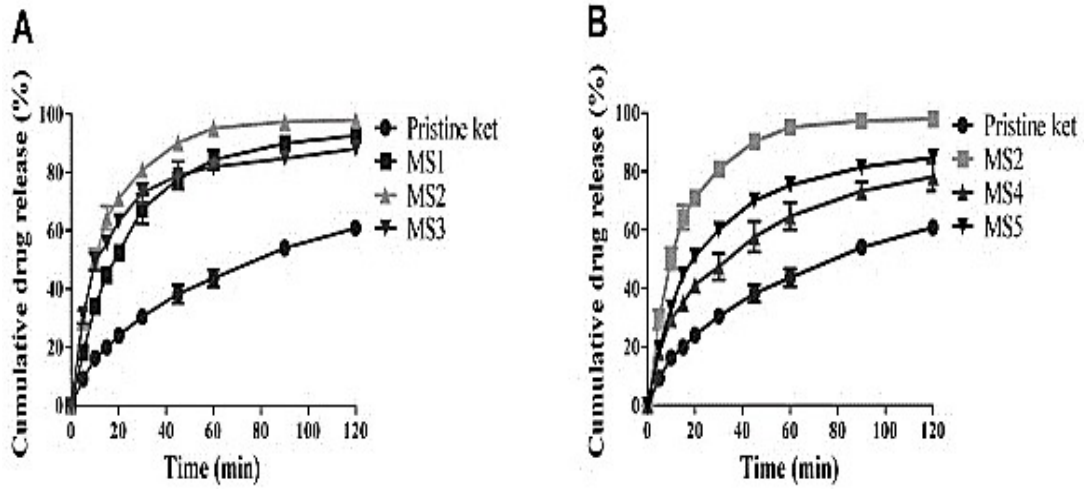

Figure 7: Dissolution profiles of pristine ketoprofen and MS powders at different US amplitudes (A) and times (B).

The resultant energy increased as the amplitude and duration increased, leading to improvement in process yield. The increase in solubility may be attributed to reduction in the size of the resulting particles, and as a result, higher surface area. However, there was no significant variation in solubility among the different conditions (p > 0.05). Decrease in particle size was due to transitory cavitation, which causes the release of an important amount of energy densities following bubble collapse. This resulted in an increase in kinetic energy of the molecules and several collisions, thus leading to the creation of a large number of tiny particles [10]. The key explanation for the reduction in mean particle size as the ultrasonic amplitude increased is that at high intensities, the resulting energy increased, leading to increased number of primary nuclei being generated. Thus, the number of molecules settling on every primary nucleus decreases during its growth stage, ending at a lower particle size [18]. However, raising the amplitude from 75 to 100 % did not affect the mean particle size (p > 0.05). As a result, more experiments were conducted at an ultrasonic amplitude of 75 %.

The FT-IR spectra of all MS-produced powders at various ultrasonic energies overlap, indicating that the application of ultrasonic power maintains the chemical integrity of ketoprofen. Therefore, it is a non-destructive technique [6]. Variation in intensity of some peaks in the XRD patterns may be attributed to changes in crystal shape, combined with a reduction in the size of particles [9]. Nonetheless, the detectability of characteristic peaks of ketoprofen implies that the drug did not undergo structural modifications

[6,19]. Furthermore, no significant difference in melting points was observed, implying that ketoprofen wasn't impacted by polymorphic transitions upon crystallization [19].

Improved flowability was associated with lower values of angle of the slide and Carr's index. Also, the closer the Hausner's ratio is to 1, the better the flowability. In this study, the flowability of ketoprofen powder did not improve after MS technique. However, the mean yielded pressure, as determined by the slope of the straight Heckle curve of MS2 powder was lower compared to pristine ketoprofen, implying that the compressibility was not improved. The similarity factor (f_2) was used for comparing the resulting dissolution profiles. This is assigned to rise in surface area owing to reduction in the size of particles as described by the Noyes-Whitney equation. The similarity factor (f_2) values demonstrated no significant variations in dissolution profiles among MS samples.

Rate and extent of ketoprofen dissolution were significantly increased at all applied ultrasonic durations as a result of a rise in surface area. However, maximum release was observed for samples produced at a short ultrasonic duration (4 min). This may be due to particle agglomeration resulting from decrease in surface area when the duration was increased. This phenomenon was observed in SEM micrographs of MS4 and MS5 samples. Particle agglomeration may be due to an increase of particle surface energy as a result of particle size reduction and/or to the cavitation and shockwaves accelerating particles to extremely fast speeds sufficient to cause particle agglomeration [8,20]. The Melt-sonocrystallization application using ultrasonic horn, however, is mainly recommended for laboratory-scale experiments [3]. For large-scale applications, multiple transducers [21], and continuous sonocrystallization [22] may be challenging.

CONCLUSION

Melt-sonocrystallization produces needle-shaped small particles of ketoprofen with a smooth surface, and significantly smaller mean particle size, and improves solubility, and dissolution rates with no structural modifications during ultrasonic treatment. Finally, future work should include an *in vivo* investigation of drug bioavailability from the generated powders, as well as a study of the application of this intriguing technology to other potential active pharmaceutical components with low water solubility.

DECLARATIONS

Acknowledgement

None.

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Nassim Belkacem, Mutaz Sheikh Salem, and Hatim Alkhatib conceived and designed the study. Nassim Belkacem and Chiraz Soumia Amrine analyzed the data and wrote the manuscript. All authors read and approved the manuscript for publication.

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