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Sonocrystallization—Case Studies of Salicylamide Particle Size Reduction and Isoniazid Derivative Synthesis and Crystallization

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Abstract: Two case studies of salicylamide particle size reduction and isoniazid derivative synthesis and crystallization realized using sonocrystallization were investigated. The size, habit, structure, thermal behavior, and spectrometric properties of sonocrystallized crystals were analyzed through scanning electron microscopy (SEM), powder X-ray diffractometry (PXRD), differential scanning calorimetry (DSC), and Fourier transform infrared (FTIR) spectroscopy. The effects of the operating parameters, such as sonication intensity, sonication duration, and solution concentration, on sonocrystallization were compared. The crystal size of salicylamide was reduced from 595 μm (the original size) and was efficiently manipulated to be between 40 and 80 μm. Moreover, compared with the crystal habits of unprocessed crystals and recrystallized crystals fabricated through conventional methods, the crystal habit of salicylamide could be modified to present a regular shape. The structure, thermal behavior, and spectrometric properties of sonocrystallized salicylamide were found to be in agreement with those of an unprocessed sample. For producing isoniazid derivative crystals, *N′*-(propan-2-ylidene)-isonicotinohydrazide was synthesized using isoniazid in acetone at 318 K. The resulting solution was then cooled by applying power ultrasound to isolate *N′*-(propan-2-ylidene)-isonicotinohydrazide crystals. The solid-state properties of the synthesized *N′*-(propan-2-ylidene)-isonicotinohydrazide was verified through PXRD, DSC, and FTIR spectroscopy. The feasibility of particle size manipulation was then demonstrated through sonocrystallization.

Keywords: salicylamide; *N′*-(propan-2-ylidene)-isonicotinohydrazide; isoniazid derivative; solid-state properties; sonocrystallization

1. Introduction

The modification of solid-state properties and the synthesis of pharmaceutical compound derivatives are crucial steps in drug discovery and development. To identify potential drug candidates and novel solid forms such as cocrystals, structural analogs and derivatives must be synthesized. Moreover, appropriate particle size characteristics, crystal forms, and crystal habits should be designed to meet the requirements of easy dissolution, physical stability, and the downstream powder handling process. In conventional drug manufacturing processes, solution crystallization is frequently employed to isolate pharmaceutical compounds and modify the solid-state properties [1–5]. However, the conventional processes have disadvantages such as batch-to-batch variation and inefficient control

of crystal nucleation and growth. Therefore, several novel and advanced crystallization strategies have been developed for the efficient manipulation of the solid-state properties of crystals [6–10].

In sonocrystallization, an advanced crystallization process, power ultrasound is applied to influence the crystallization mechanism in several ways in order to reduce the induction time and metastable zone width (MSZW), to increase the rate of secondary nucleation, to enhance localized mixing, and to modify crystal growth. Sonocrystallization is utilized in chemical synthesis and crystallization to enhance crystal quality in terms of particle size, size distribution, habit, and purity. For example, Suslick summarized the application of power ultrasound to chemical reactions in both homogeneous liquids and in liquid-solid system [11]. Kim et al. developed a spray sonocrystallization for crystallization of salsalate that provides a tunable crystal size and narrow size distribution [12]. Sander et al. reviewed and discussed the effect of powder ultrasound in the crystallization of organic molecules [13]. Vishwakarma and Gogate improved oxalic acid crystallization by using ultrasonic reactors and reported the effects of operating parameters and ultrasonic reactor types on the crystallization [14]. Nguyen et al. employed sonocrystallization to enhance the crystal product quality of acetaminophen, particularly in terms of crystal purity in the presence of structurally similar impurities [15]. Ike and Hirasawa adopted antisolvent sonocrystallization to control the polymorph of L-arginine hydrochloride [16]. Gielen et al. applied ultrasound during crystallization to inhibit the agglomeration of active pharmaceutical ingredient and monitored the process using analytical tools such as focus beam reflectance measurements and Fourier transform infrared (FTIR) spectroscopy [17]. Using the Taguchi method, Gandhi et al. optimized process parameters for the production of sirolimus nanocrystals through sonication-based crystallization [18]. Li et al. investigated the effect of ultrasound on the reactive crystallization process of cloxacillin benzathine [19]. Crawford developed a solvent-free sonochemical organic synthesis in condensation reaction and found the particle size of the starting materials was one of the key parameters [20].

In our previous studies, sonocrystallization was employed for the recrystallization of two pharmaceutical compounds, phenacetin and sulfathiazole [21–23]. To further explore the applicability of sonocrystallziation to modify solid-state properties and synthesize pharmaceutical compounds, two case studies involving salicylamide particle size reduction and isoniazid derivative synthesis and crystallization were investigated in this study. Salicylamide is a nonprescription drug with analgesic and antipyretic properties. The drug therapeutic effectiveness of salicylamide can be improved by reducing the particle size and by employing a cocrystal design [24,25]. Isoniazid, a critical frontline antituberculosis drug, is one of the most effective drugs used to treat tuberculosis infections. However, bacterial strains that are resistant to isoniazid are becoming prevalent; thus, the development of antituberculosis agents from isoniazid derivatives is an imperative task. To this end, Hu et al. reviewed and summarized the advancement in the discovery of isoniazid derivatives as a novel antituberculosis agent [26]. Lemmerer et al. synthesized various isoniazid derivatives by using different ketone modifiers and designed the corresponding cocrystals [27]. Oruganti et al. designed different cocrystals using isoniazid and N'-(propan-2-ylidene)-isonicotinohydrazide, a derivative of isoniazid [28]. In this study, N'-(propan-2-ylidene)-isonicotinohydrazide, an isoniazid derivative, was synthesized and isolated through sonocrystallization. The effects of operating parameters such as sonication intensity, sonication duration, and solution concentration were investigated. Finally, to demonstrate the advantages of the proposed approach, the solid-state properties of sonocrystallized crystals were compared by applying power ultrasound during crystallization.

2. Materials and Method

Salicylamide with a minimum purity of 99% was obtained from Sigma-Aldrich (St. Louis, MO, USA). After analyzing the solubility data of salicylamide in methanol, acetonitrile, acetic acid, acetone, water, and ethyl acetate [29], methanol was selected as the solvent suitable for sonocrystallization given the considerable variation in solubility with temperature. Methanol with a minimum purity of 99.8% was purchased from Sigma-Aldrich. For the isoniazid derivative synthesis,

N′-(propan-2-ylidene)-isonicotinohydrazide ($C_9H_{11}N_3O$, CAS 4813-04-1) was synthesized through a reaction between isoniazid and acetone. The produced isoniazid derivative was then isolated through sonocrystallization to obtain the crystals and to manipulate the solid-state properties. The reactants, isoniazid and acetone with minimum purities of 99% and 99.8%, respectively, were purchased from Sigma-Aldrich. All chemicals were used without further purification. The specification of the chemicals used in this study are listed in Table 1.

Table 1. Specifications of the chemical samples used in this study.

Compound	CAS. No.	Formula	Mw (g/mol)	Supplier	Purity (%)
Acetone	67-64-1	C_3H_6O	58.08	Sigma-Aldrich	99.8
Isoniazid	54-85-3	$C_6H_7N_3O$	137.14	Sigma-Aldrich	99
Methanol	67-56-1	CH_3OH	32.04	Sigma-Aldrich	99.8
Salicylamide	65-45-2	$C_7H_7NO_2$	137.14	Sigma-Aldrich	99

The experimental apparatus of sonocrystallization has been detailed in our previous reports [21–23]; a brief description is presented herein. The schematic of the experimental apparatus is presented in Figure 1. The system comprised a sonication device, a magnetic stirrer, a jacket crystallizer, and a heating or cooling circulator. The sonication device (Branson Ultrasonics, St. Louis, MO, USA, S-450D) consists of an ultrasound probe, an ultrasound generator, and an ultrasound controller installed in the jacket crystallizer. The frequency and maximum power of the sonication device were 20 kHz and 400 W, respectively. The ultrasonic probe was positioned at the center of the jacket crystallizer, and approximately 1 cm of the probe was immersed in the solution. A magnetic stirrer was used to stir the solution, as presented in Figure 1. A temperature-programmed heating or cooling circulator was used to control the solution temperature. For reducing the particle size of salicylamide, it was dissolved in methanol maintained at a specific concentration, and the resulting solution was poured into the jacket crystallizer; a high temperature was maintained to ensure the total dissolution of salicylamide. The reaction scheme for the synthesis of *N*′-(propan-2-ylidene)-isonicotinohydrazide is presented in Figure 2. Isoniazid was dissolved in acetone and poured into the jacket crystallizer. In this case, acetone is used both as the reactant and solvent. The reaction temperature was controlled to be 318 K. After the total dissolution of salicylamide (or the reaction of isoniazid and acetone at a high temperature), the temperature of the jacket crystallizer was cooled to −5 °C at a rate of 20 °C/h. During cooling, power ultrasound was introduced at a programmed sonication intensity and duration. Subsequently, the produced crystals were filtrated using a filter paper, and the resulting wet cake was dried at 50 °C in an oven.

In this study, solid-state properties—such as the habit, particle size, crystal structure, thermal properties, and spectrometric properties—of sonocrystallized crystals were analyzed through scanning electron microscopy (SEM), powder X-ray diffractometry (PXRD), differential scanning calorimetry (DSC), and FTIR spectroscopy. To compare the crystal habits of the various synthesized crystals, the crystals were fixed on a conductive adhesive tape and sputtered with a thin gold film. Images of the crystals were then captured through SEM (Hitachi, Taipei. Taiwan, S-3000H), and these images were used to estimate the mean particle size of the sonocrystallized crystals by counting the length of the crystals on ImageJ software. To determine the crystal structure, PXRD data were collected from 5° to 50° at a scanning rate of 52°/min by using a PXRD instrument (PANalytical X'pert). To determine the thermal properties of crystals, DSC (PerkinElmer, Taipei, Taiwan, Jade DSC) was employed, in which the samples were heated at a rate of 10 °C/min. For comparing the spectroscopic properties of the formed crystals, FTIR spectroscopy (PerkinElmer, Spectrum 100) was conducted from 700 to 4000 cm^{-1}.

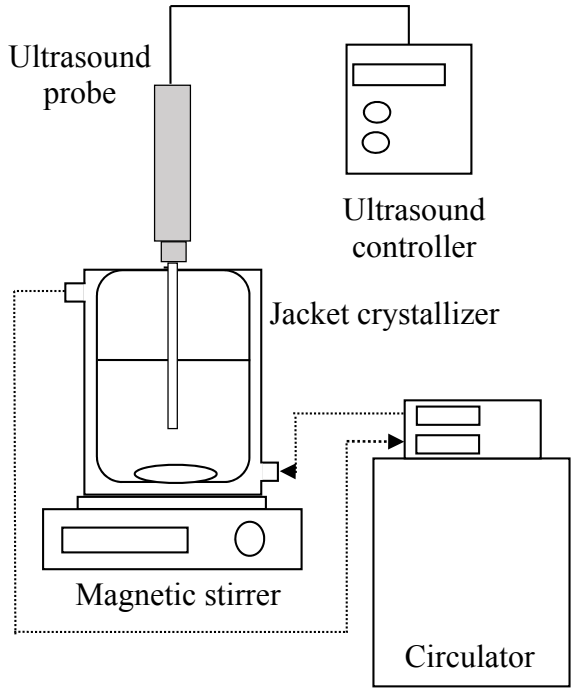


Figure 1. Experimental apparatus for sonocrystallization.

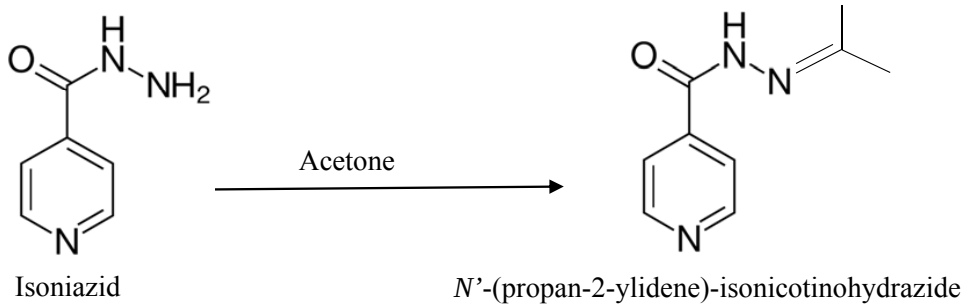


Figure 2. Reaction scheme for the synthesis of *N*′-(propan-2-ylidene)-isonicotinohydrazide.

3. Results and Discussion

3.1. Particle Size Reduction of Salicylamide

The operating condition and mean sizes of the salicylamide crystals obtained through sonocrystallization are listed in Table 2, as are the recrystallization results obtained without applying power ultrasound (Experiment B1). The effects of operating parameters, namely sonication intensity, sonication duration, and solution concentration, were investigated. To evaluate the effect of sonication intensity, 10%, 30%, and 50% intensities were employed while maintaining the other operating parameters constant. The trends of the sonication intensity effects are depicted in Figure 3a. Table 2 and Figure 3a (Experiment 1, 2 and 3) reveal that the mean particle size of sonocrystallized salicylamide decreases with increasing sonication intensity. The mean particle size could be controlled in the range of 68.5–39.9 μm by adjusting the sonication intensity between 10% and 50%. In general, the introduction of power ultrasound in the crystallization solution reduces the induction time and the MSZW. These reductions enhanced the nucleation rate benefits while, in turn, reducing the particle size. Moreover, high sonication intensity increases the probability of particle collision, especially in a high-crystal-density system; consequently, secondary nucleation is induced, and smaller crystals are produced.

Table 2. Particle size reduction of salicylamide.

Experiment No.	Intensity (%)	Duration (%)	Concentration (mg/mL)	Cooling Rate (°C/h)	Mean Size (μm)	S.D [a] (μm)
Ori	—	—	—	—	595.0	178.4
1	30	30	170	20	45.6	18.2
2	10	30	170	20	68.5	30.4
3	50	30	170	20	39.9	13.3
4	30	10	170	20	80.5	26.7
5	30	50	170	20	38.4	13.7
6	30	30	140	20	53.8	17.0
7	30	30	200	20	59.6	22.3
B1 [b]	0	0	170	20	432.5	176.5

[a] Standard deviation of particle size distribution; [b] Experiment without applying power ultrasound.

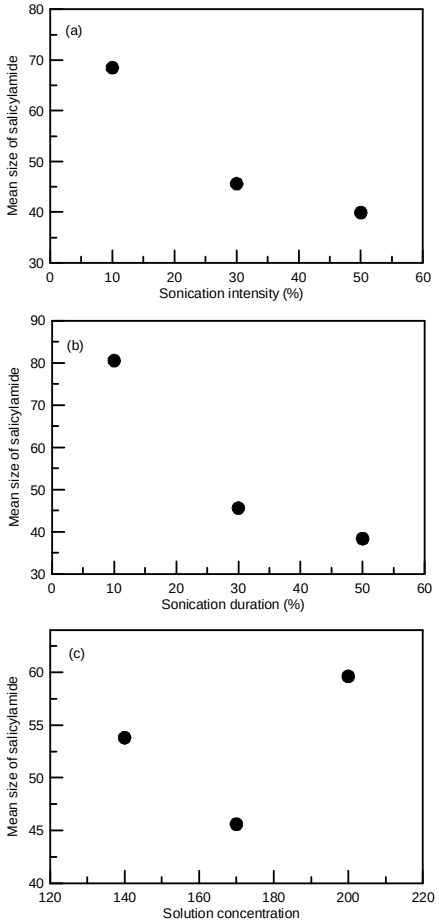


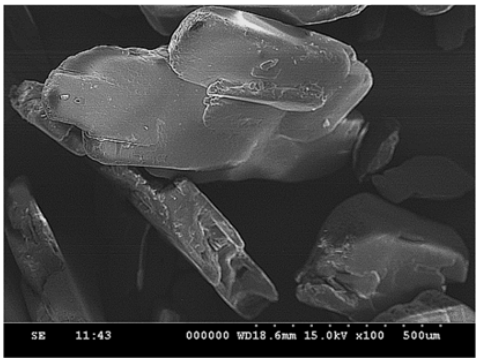
Figure 3. Illustration of the effect of the following operating parameters on the mean size of salicylamide: (**a**) sonication intensity; (**b**) sonication duration; and (**c**) solution concentration.

For investigating the effect of sonication duration, three programmed sonication durations were implemented: 1 s of sonication followed by 9 s of silence (10%), 3 s of sonication followed by 7 s of silence (30%), and 5 s of sonication followed by 5 s of silence (50%). The mean crystal sizes of sonocrystallized salicylamide obtained at these sonication durations are illustrated in Figure 3b. The figure reveals that an increase in the sonication duration is favorable for producing smaller crystals. As the sonication duration increased from 10% to 50%, the mean crystal sizes of salicylamide were reduced from 80.5 to 38.4 μm (Experiment 1, 4, and 5). Similar to the effect of sonication intensity, long sonication provides a high number of cavitation bubbles and increases the probability

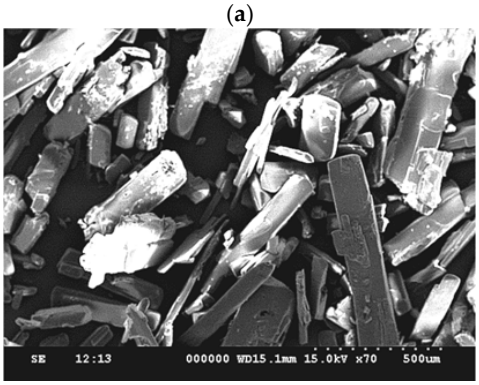
of particle collision; this generates a high number of nuclei, which in turn reduces the mean size of the produced crystals.

To investigate the effect of solution concentration on the basis of the solubility values reported in the literature [29], three solution concentrations were employed during sonocrystallization: 140, 170, and 200 mg/mL (Experiment 1, 6 and 7). Figure 3c evidences the presence of an optimum solution concentration for particle size reduction. The mean crystal size was reduced from 53.8 to 45.6 mm with increase in the solution concentration from 140 to 170 mg/mL; this is because the higher the solution concentration, the higher the driving force for nucleation, and thus the higher is the resulting particle size reduction. However, the reverse trend was observed when the concentration was further increased from 170 to 200 mg/mL; at this higher concentration, nuclei agglomeration may occur, and the crystals grown on the already agglomerated nuclei contribute to a higher mean crystal size. The effect of solution concentration on sonocrystallization was similar to that reported for the microparticle production of salbutamol sulfate [30].

The crystal size of salicylamide crystals grown through sonocrystallization (sonocrystallized crystals) was compared with those of salicylamide crystals as received (original crystals) and the salicylamide crystals grown through conventional cooling crystallization (conventional crystals) (Experiment B1). The crystal sizes of salicylamide crystals grown through sonocrystallization could be efficiently reduced up to 38.4 μm, a larger reduction than that observed for the original crystals (595 μm) and the conventional crystals (432.5 μm). The particle size distribution of sonocrystallized salicylamide is also graphically presented in the Supporting Information (Figure S1a). The crystal habits, obtained through SEM, of these three types of crystals are compared in Figure 4; the figure reveals that sonocrystallized crystals with smaller and regular crystal habits are suitable for use in pharmaceutical applications. To further explore the crystal form, the thermal and spectrometric properties of the original and sonocrystallized salicylamide crystals were evaluated through PXRD, DSC, and FTIR (Figures 5–7, respectively); the data for these two types of crystals were in agreement with each other.

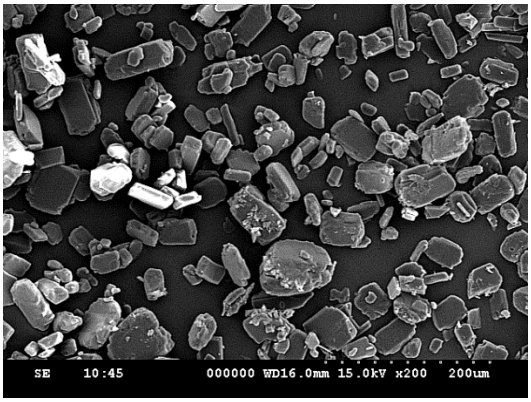


(**a**)



(**b**)

Figure 4. *Cont.*



(**c**)

Figure 4. SEM images of salicylamide: (**a**) original crystals; (**b**) crystals obtained in Experiment B1; and (**c**) crystals obtained in Experiment 5.

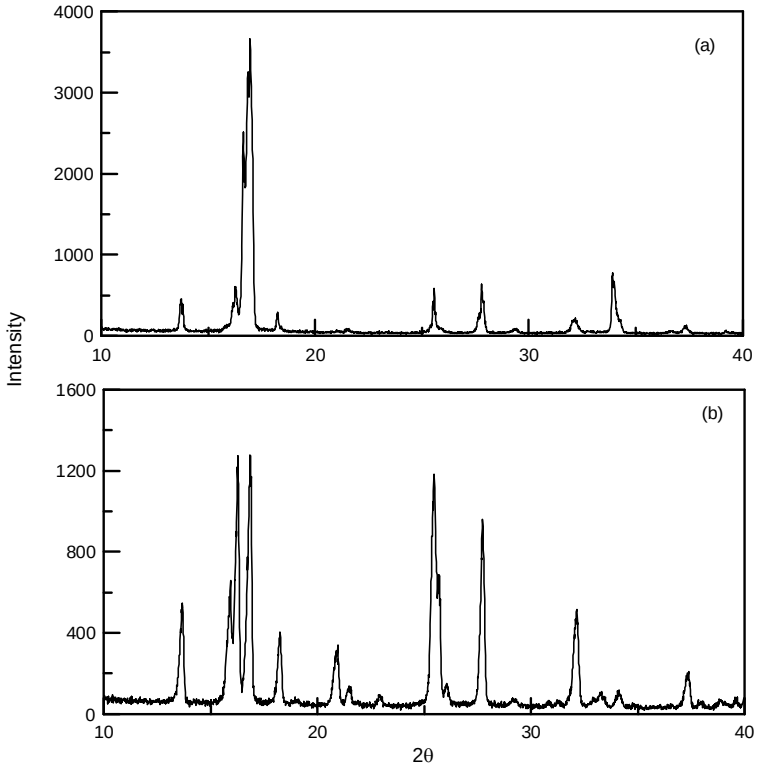


Figure 5. PXRD results of salicylamide: (**a**) original crystals and (**b**) salicylamide crystals obtained in Experiment 1.

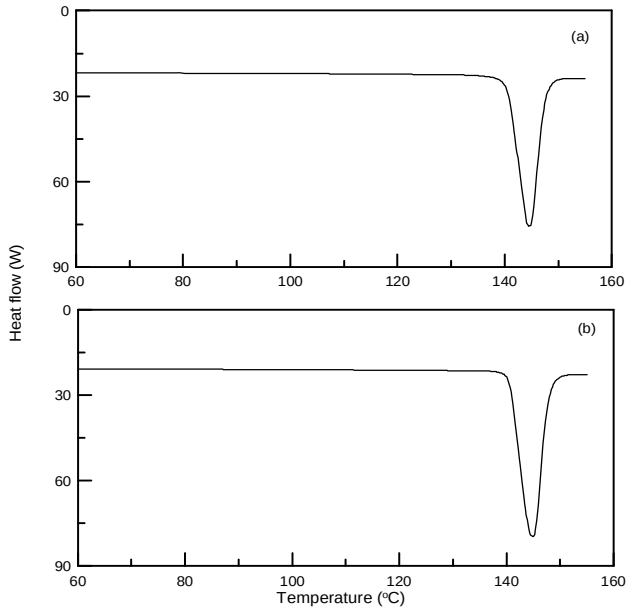


Figure 6. DSC results of salicylamide: (**a**) original crystals and (**b**) salicylamide crystals obtained in Experiment 1.

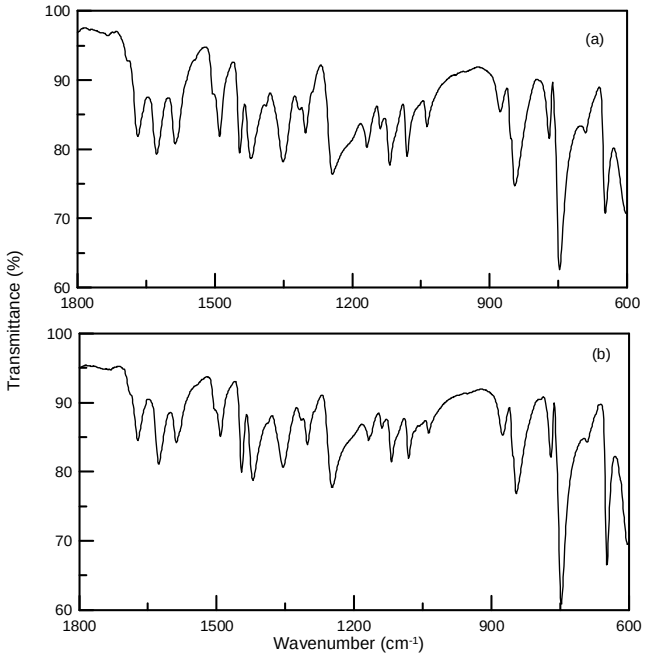


Figure 7. FTIR results of salicylamide: (**a**) original crystals and (**b**) salicylamide crystals obtained in Experiment 1.

3.2. Synthesis and Crystallization of N′-(Propan-2-ylidene)-isonicotinohydrazide

Table 3 summarizes the experimental conditions and the sonocrystallization results of *N′*-(propan-2-ylidene)-isonicotinohydrazide for synthesizing and producing crystals of the isoniazid derivative. As evidence for the synthesis of *N′*-(propan-2-ylidene)-isonicotinohydrazide, the analytical results of NMR (Nuclear magnetic resonance) for synthesized and crystallized crystals is shown in the Supporting Information (Figure S2). In addition, the analytical results of PXRD and FTIR for the crystals obtained from Experiment 8 are presented in Figure 8. A comparison of the

PXRD pattern obtained from Cambridge Crystallographic Data Center and the FTIR spectrum acquired from the SpectraBase database, presented in the Supporting Information (Figures S3 and S4), revealed that the crystal structures and spectrometric properties of the crystals obtained in this study are consistent with the data in the literature, confirming that the synthesis and isolation of *N′*-(propan-2-ylidene)-isonicotinohydrazide through sonocrystallization is feasible. Consistent PXRD and FTIR results were also obtained for the other sonocrystallization experiments listed in Table 3. Regarding the thermal properties of the crystals, a DSC thermogram of *N′*-(propan-2-ylidene)-isonicotinohydrazide crystals obtained after conducting Experiment 8 is presented in Figure 8c; the melting (onset) temperature was at approximately 160 °C, and an endothermic signal at approximately 135 °C indicated a crystal form transition.

Table 3. Data for the synthesis and crystallization of *N′*-(propan-2-ylidene)-isonicotinohydrazide.

Experiment No.	Intensity (%)	Duration (%)	Concentration (mg/mL)	Cooling Rate (°C/h)	Mean Size (μm)	S.D [a] (μm)
8	30	30	25	20	27.6	8.7
9	10	30	25	20	73.2	43.1
10	50	30	25	20	31.4	10.2
11	30	10	25	20	31.4	12.3
12	30	50	25	20	23.7	8.1
13	30	30	35	20	27.7	10.3
14	30	30	15	20	19.4	7.9
B2 [b]	0	0	25	20	78.1	41.6

[a] Standard deviation of particle size distribution; [b] Experiment without applying power ultrasound.

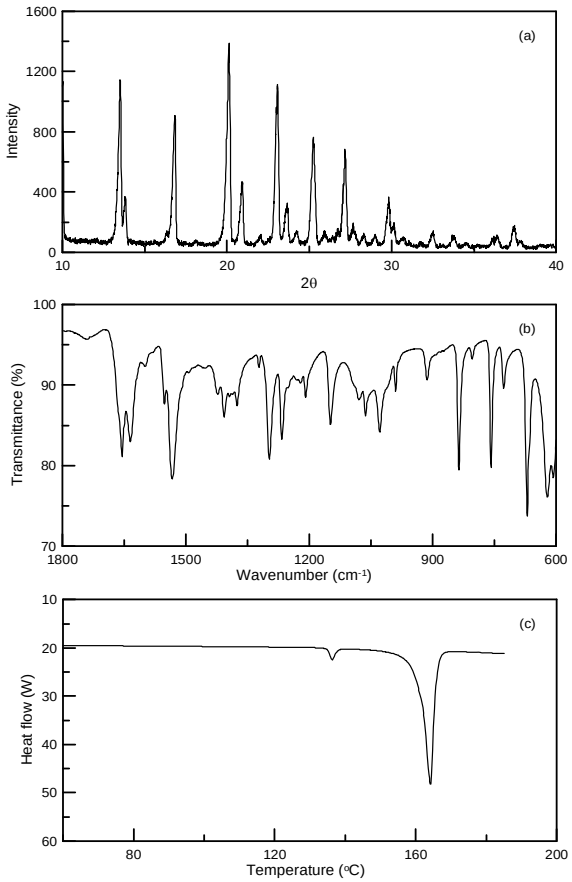


Figure 8. Analytical results of the following methods for the synthesized *N′*-(propan-2-ylidene)-isonicotinohydrazide crystals obtained after conducting Experiment 8: (**a**) PXRD; (**b**) FTIR; and (**c**) DSC.

Regarding the effect of the operating parameters on sonocrystallization, the effects of sonication intensity, sonication duration, and isoniazid concentration on the mean crystal size of the synthesized *N′*-(propan-2-ylidene)-isonicotinohydrazide are presented in Figure 9. To analyze the effect of sonication intensity (Figure 9a), three intensities of 10%, 30%, and 50% (Experiment 8, 9, and 10) were implemented. When the sonication intensity increased from 10% to 30%, the crystal size of *N′*-(propan-2-ylidene)-isonicotinohydrazide was reduced significantly from 73.2 to 27.6 μm. Similar to the results for salicylamide particle size reduction, a higher sonication intensity enhanced the nucleation rate benefits, resulting in particle size reduction; however, further increase in the intensity had the opposite effect, with the mean crystal size increasing from 27.6 to 31.4 μm as the sonication intensity was increased from 30% to 50%. These opposing trends could be due to the redissolution and recrystallization of the produced crystals: at a high sonication intensity (50%), considerable power is introduced, which increases the local temperature and consequently accelerates crystal redissolution and the subsequent recrystallization.

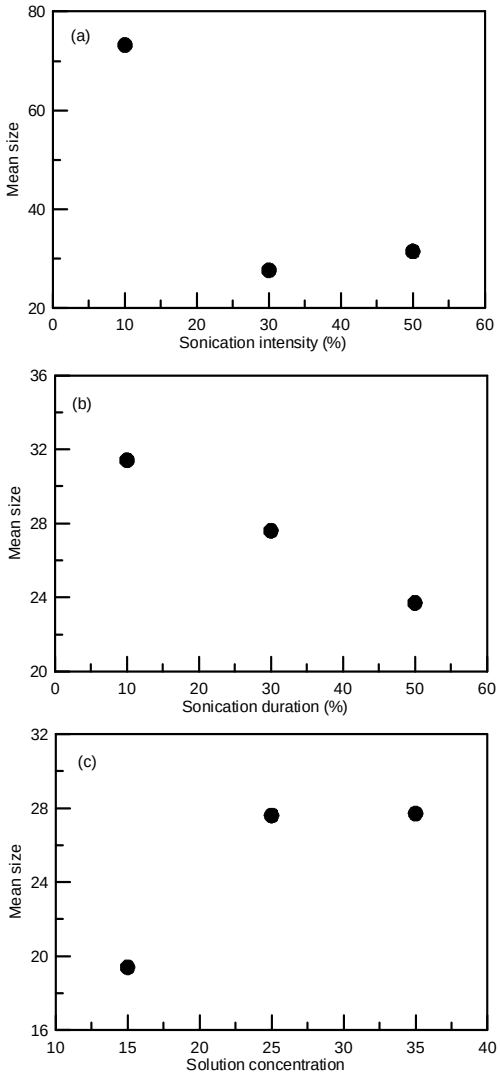


Figure 9. Illustration of the effect of the following operating parameters on the mean size of *N′*-(propan-2-ylidene)-isonicotinohydrazide: (**a**) sonication intensity; (**b**) sonication duration; and (**c**) solution concentration.

To investigate the effect of sonication duration, three sonication durations—10% (1 s of sonication followed by 9 s of silence), 30% (3 s of sonication followed by 7 s of silence),

and 50% (5 s of sonication followed by 5 s of silence)—were implemented. As presented in Figure 9b, with an increase in the sonication duration from 10% to 50%, the mean crystal sizes of *N′*-(propan-2-ylidene)-isonicotinohydrazide were reduced from 31.4 to 23.7 μm (Experiment 8, 11, and 12). Similar to the effect of sonication intensity for salicylamide, long sonication enhances particle size reduction and thus produces smaller crystals. To investigate the effect of isoniazid concentration, three concentrations—15, 25, and 35 mg/mL (Experiment 8, 13, and 14)—were adopted. Figure 9c demonstrates that a higher isoniazid concentration leads to a higher solution concentration of *N′*-(propan-2-ylidene)-isonicotinohydrazide during sonocrystallization; the mean crystal size increased from 19.4 to 27.7 μm with increase in the isoniazid concentration from 15 to 35 mg/mL. Narducci et al. reported a similar trend for the sonocrystallization of adipic acid [31]. To compare the crystal habit of the sonocrystallization crystals (Experiment 8) with that of the conventional crystal (Experiment B2), the crystals were subjected to SEM (Figure 10). The application of power ultrasound resulted in the formation of smaller crystals with a regular shape. The mean size of the conventional crystals was 78.1 μm. For the purpose of microparticle production, in this study, *N′*-(propan-2-ylidene)-isonicotinohydrazide crystals with mean size of 19.4 μm were produced and its particle size distribution is shown in the Supporting Information (Figure S1b).

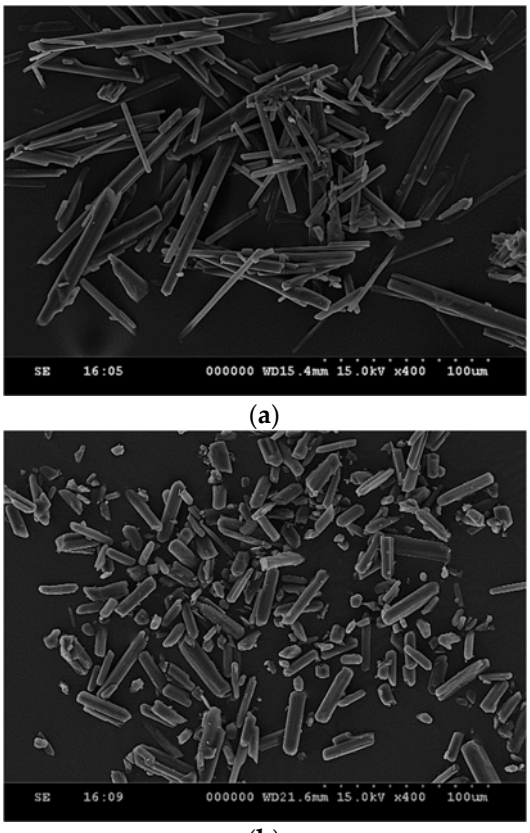


Figure 10. SEM images of *N′*-(propan-2-ylidene)-isonicotinohydrazide: (**a**) crystals obtained in Experiment B2 and (**b**) crystals obtained in Experiment 8.

4. Conclusions

Case studies of sonocrystallization for salicylamide particle size reduction and isoniazid derivative synthesis and crystallization were presented. Through sonocrystallization of salicylamide, the mean crystal size of the original crystals (595.0 μm) and that of the conventional crystals (432.5 μm) were successfully reduced to 38.4 μm. A higher sonication intensity, longer sonication duration, and intermediate solution concentration are suitable for

the production of small salicylamide crystals. Through sonocrystallization, small salicylamide crystals with a regular habit and consistent crystal structure were generated. For isoniazid derivative production, *N*′-(propan-2-ylidene)-isonicotinohydrazide was synthesized from isoniazid and acetone and crystallized through sonocrystallization. The feasibility for producing *N*′-(propan-2-ylidene)-isonicotinohydrazide was first confirmed through NMR, PXRD and FTIR analyses. The applicability of particle size modification of the synthesized *N*′-(propan-2-ylidene)-isonicotinohydrazide was then demonstrated by manipulating the sonication intensity, sonication duration, and isoniazid concentration. The experimental results indicated that an intermediate sonication intensity, longer sonication duration, and lower isoniazid concentration facilitates the generation of small *N*′-(propan-2-ylidene)-isonicotinohydrazide crystals. The crystal size of *N*′-(propan-2-ylidene)-isonicotinohydrazide can be manipulated to 19.4 μm through sonocrystallization, which is much lower than that realized through the conventional route (78.1 μm).

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4352/8/6/249/s1, Figure S1: Particle size distribution of sonocrystallized salicylamide crystals from Experiment 3 and sonocrystallized *N*′-(propan-2-ylidene)-isonicotinohydrazide crystals from Experiment 14. Figure S2: NMR results of the synthesized *N*′-(propan-2-ylidene)-isonicotinohydrazide crystals. Figure S3: Calculated PXRD pattern of *N*′-(propan-2-ylidene)-isonicotinohydrazide from The Cambridge Crystallographic Data Centre (CCDC number: 706025). Figure S4: FTIR spectrum of *N*′-(propan-2-ylidene)-isonicotinohydrazide from SpectraBase database.

Author Contributions: C.-S.S. designed the sonocrystallisation experiments; Z.-Y.Y., S.-K.Y., W.-S.H. and Y.-Z.H. performed the sonocrystallisation experiments and analyzed the data; C.-S.S. and T.-M.Y. prepared the original draft; C.-S.S. edited and revised the paper.

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Conflicts of Interest: The authors declare no conflict of interest.

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