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Particle Processing of Acetaminophen Using the Cooling and Anti-solvent Crystallization Methods

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ABSTRACT

Several crystallization strategies are being implemented to enhance the solubility of acetaminophen, also known as paracetamol. Therefore, this study aimed to determine the effectiveness of the cooling and anti-solvent crystallization on the properties of acetaminophen. The results showed that the anti-solvent recrystallization produced achieved an impressive yield of up to 41.40%, while the cooling method yielded approximately 2–9%. Through FTIR, XRD, and DSC analysis on the samples, it was discovered that these methods had minimum effects on the molecular and thermal properties of the compound. Furthermore, the methods did not alter the crystallinity of acetaminophen, with crystal form I dominating the products. In addition, processing using the cooling and anti-solvent effectively reduced particle size of acetaminophen from 68.60 µm to 26.92 µm and 28.25 µm, respectively. In conclusion, the solubility of paracetamol in aqueous solutions experienced a significant enhancement. In the unprocessed samples, it measured 0.0107 gram/ml, while the recrystallized samples had an improved range of 0.0123 to 0.0167 g/ml.

Keywords: Particle, Acetaminophen, Crystallization, Cooling, Anti-solvent

INTRODUCTION

Acetaminophen, also known as paracetamol, is a widely utilized pharmaceutical compound available in tablet, syrup, and insert forms [1]. Functioning as both an antipyretic and analgesic agent, it is utilized independently and in conjunction with other medications or ingredients [2,3]. Significantly, the reputation of the drug is marred by poor solubility in aqueous solutions. At 30°C, the solubility of acetaminophen in water is approximately 1:70 mass ratio, categorizing it as low and underscoring the need for enhancements in solubility to facilitate further developments [4]. To address the challenge, additional substances such as propylene glycol have been introduced in the formulation [5]. However, the use of glycols as co-solvent in the formulation has posted issues due to associated side effects. In 2022, the inclusion of glycols in acetaminophen syrup was implicated in kidney failure cases among children in Indonesia [6].

A key strategy for altering the pharmaceutical property of a substance, includes crystallinity modification, which significantly impacts performance in practical applications. Achieving more precise control over this process is essential for enhancing processing effectiveness and subsequently, the solubility property of the powder [7]. Several technology platforms have been explored to modify the crystallinity of acetaminophen, including the

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cooling [8,9], solvent [10], anti-solvent [11], seeding [12], solution-mediated [13], and co-crystallization-based methods [14]. Reactive-based crystallization utilizing both cooling [15] and seeding [16], has been investigated to facilitate the continuous processing of acetaminophen.

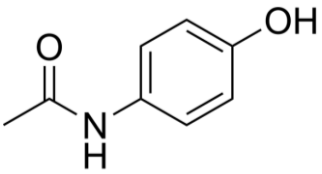

Figure 1. Molecular Structure of Acetaminophen

In this study, both the cooling and the anti-solvent were investigated. The effect of process parameters such as temperature and solvent/anti-solvent (S/AS) ratio were also explored. Furthermore, particle characteristics and dimensions including morphology, size distribution, crystallinity, thermal property, and solubility were examined to determine processing results. The yield was measured to evaluate the effectiveness of processing scheme.

EXPERIMENT

Chemicals

Acetaminophen used in this study had 99.6 % purity, as obtained from Anqiu Lu'an Pharmaceutical Co. Ltd. High purity grade ethanol was purchased from Merck, while distilled water was obtained from laboratory supplies. All reagents were applied as received.

Experimental procedure

Crystallization

Crystallization was conducted using the cooling and anti-solvent-based methods. In the cooling crystallization, acetaminophen solution was prepared by dissolving the solid in ethanol at a ratio of 1:3 (w/w). The solution was heated at 50°C using a hotplate and magnetic stirrer at 400 rpm. Subsequently, the cooling was conducted at 5^{o}C (378 K) for a predetermined period. Following crystal formation, the solution was filtered off through Whatman - Grade 93 filter paper to isolate the solid products.

In the anti-solvent crystallization, a feed solution was prepared by dissolving acetaminophen powder in ethanol at a ratio of 1:3 (w/w). Heating and stirring were then conducted at 50°C using a hotplate and magnetic stirrer at 400 rpm. The solution was cooled to room temperature and introduced into DI water in a certain quantity. The mixture was stirred using a magnetic stirrer at room temperature and a speed of 400 rpm for 15-45 minutes. Following crystal formations, the mixture was filtered through the Whatman - Grade 93 filter paper to obtain solid products.

Crystallization yields were used to evaluate the effectiveness of the selected methods. The following represents the calculation:

$$\% \text{ Yield} = \frac{\text{The crystals obtained from the recrystallization process}}{\textit{The initial crystals used for the recrystallization process}} \text{ x } 100\% \qquad (1)$$

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Characterizations and analysis

Product samples were characterized for morphology using the SEM method (Hitachi Flex-SEM 1000). To prepare for electron imaging, the samples were placed in carbon tape and coated with chromium. Spectroscopy analysis was performed through ATR/FTIR (Agilent Cary 630). Furthermore, crystallinity was examined using XRD analysis (X-Pert Pro Diffractometer), comprising the placement of sample powders in the XRD sample holders, followed by exposure to X-ray within the range of 2Θ: 0 - 90º. For analysis of the thermal property, specifically the melting point, DSC analysis (Mettler Toledo) was conducted. The procedure included subjecting the sample to heat (with a blank sample as a reference). The DSC measurement followed a temperature increase of 5ºC/min from ambient temperature up to 220ºC (493 K).

The samples were examined for solubility properties. The solubility of the products was determined by weighing some quantity of the solid in the vials. Meanwhile, the solids were added by distilled (DI) water gradually, until complete dissolution was obtained. The solubility was determined by measuring the ratio of solid product weight to the added DI water. Each experiment and analysis were conducted at least in duplicate to ensure reliability.

RESULT AND DISCUSSION

Crystallization

The effect of selected experimental parameters on crystallization process was examined. A summary of the result is presented in Tables 1 and 2. Based on the experimental data, the yield obtained from anti-solvent crystallization was higher. In the cooling crystallization, the maximum yield was achieved at 9.01%, obtained with crystallization time of 90 minutes. Whilst the anti-solvent crystallization generated a maximum yield of 41.40 % at 45 minutes.

Table 1. Summary of the cooling crystallization method

Initial Concentration (%)	Crystallization Time (min)	Yield (%)	dp (µm)	Solubility (g/ml)
25	30	2.50 ± 2.4	29.83 ± 3.24	0.0123 ± 0.02
25	60	3.80 ± 1.2	26.92 ± 2.95	0.0151 ± 0.02
25	90	9.01 ± 1.5	31.29 ± 2.21	0.0142 ± 0.03

This difference in yield can be attributed to the nature of anti-solvent method, which includes reducing the solubility of the solute in the solution and promoting rapid crystallization. In this context, anti-solvent is a substance that dissolves solute with very low solubility.

Upon adding an anti-solvent to a saturated solution, the solubility of the solute will decrease due to the interaction. As a result, the level of supersaturation in the solution increases. Supersaturation refers to a condition where a solution contains a higher concentration of solute than the amount to be dissolved under normal conditions. Its high level promotes nucleation (the formation of crystal nuclei) and rapid crystal growth, thereby having greater chances of contributing to the higher yield observed in the anti-solvent crystallization method compared to the cooling counterpart [17].

In the cooling-based method, crystallization is determined by temperature level, with a lower degree potentially leading to faster crystal growth. In this study, the process was

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conducted at 5°C (278 K), a condition that may not have supported optimum crystal growth [18].

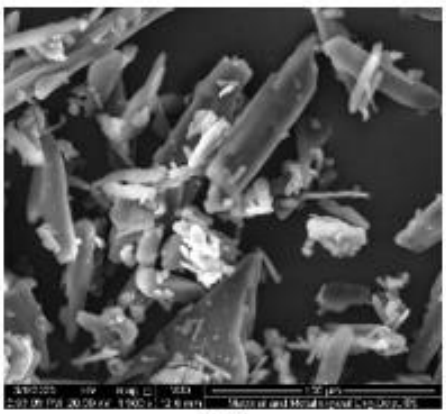
In the anti-solvent method, a yield of approximately 38.25 % was observed at solvent-to-anti-solvent ratio of 1:3, higher than that of 1:1. This shows the effect of anti-solvent on crystallization process. The appropriate solvent-to-anti-solvent ratio can result in optimal yield. However, excessive addition of anti-solvent can reduce the solution saturation level, thereby hindering crystallization of paracetamol and leading to slower crystal formations [7].

Table 2. Summary of anti-solvent crystallization method

Initial Concentration (%)	Solvent: Anti-solvent Ratio	Crystallization Time (min)	Yield (%)	dp (µm)	Solubility (g/ml)
25	1:1	30	28.20 ± 2.2	28.31 ± 1.75	0.0139 ± 0.010
25	1:2	30	34.47 ± 2.7	28.25 ± 2.34	0.0158 ± 0.002
25	1:3	30	38.30 ± 1.2	37.80 ± 0.23	0.0167 ± 0.003
25	1:4	30	28.60 ± 3.5	49.04 ± 3.71	0.0157 ± 0.001
25	1:5	30	31.00 ± 2.4	45.06 ± 3.31	0.0157 ± 0.002
25	1:6	30	22.40 ± 1.1	28.25 ± 2.89	0.0139 ± 0.004
25	1:3	15	26.90 ± 3.2	38.52 ± 3.39	0.0165 ± 0.002
25	1:3	45	41.40 ± 3.9	37.83 ± 2.50	0.0158 ± 0.002

Morphology

Acetaminophen particles of this study were subjected to visual testing using scanning electron microscope (SEM) machine. Figure 2 shows SEM images of the samples. Observation of SEM images showed that the samples predominantly consisted of elongated particles. The cooling crystallization yielded relatively smaller particles. Additionally, samples produced through this method had an increase in particle size with extended processing (cooling) time, indicating potential crystallization growth. This phenomenon was similarly observed in the anti-solvent method, as shown in Figure 2. The ratio of solvent to anti-solvent may also have affected particle dimensions. It is important to note that an increase in anti-solvent quantity produced larger particles as presented in Figure 2 (e - g).



(a)

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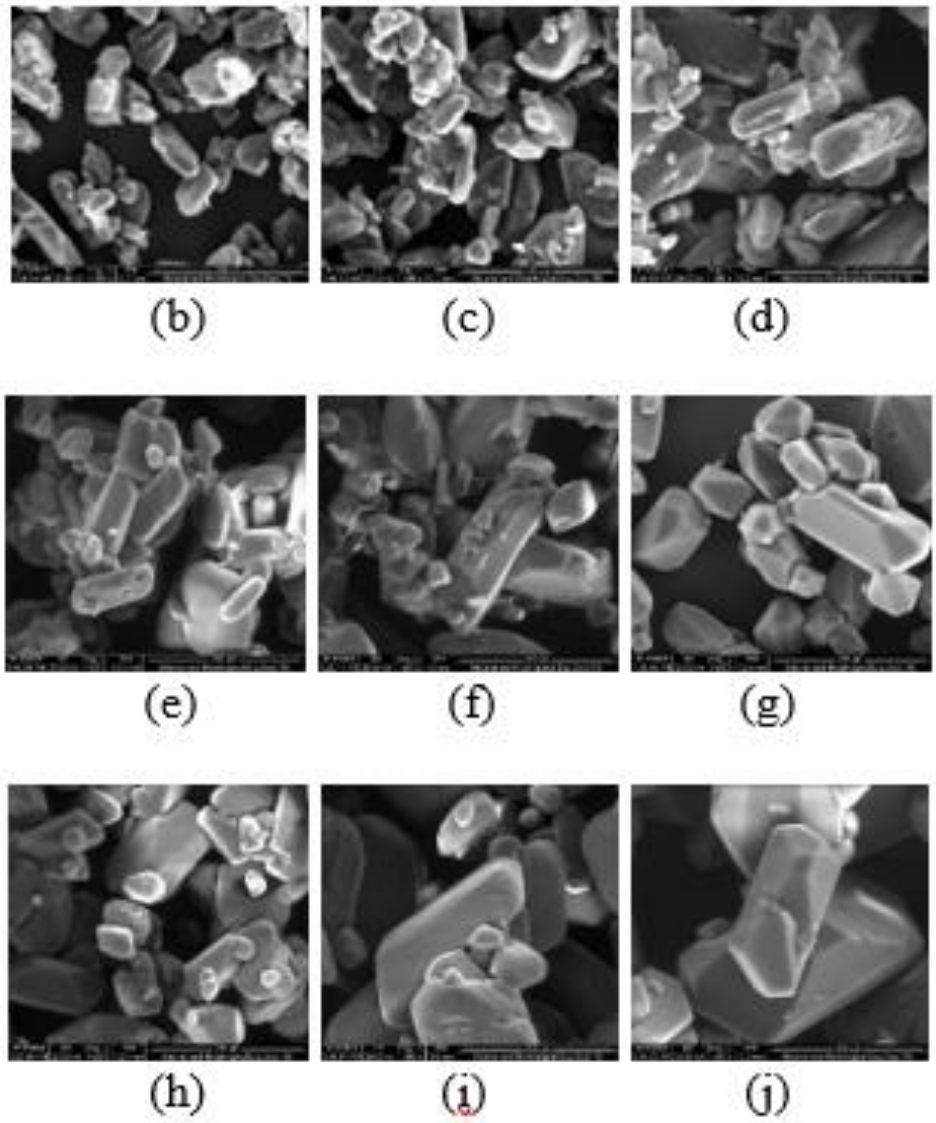

Figure 2. SEM images of acetaminophen: (a) unprocessed, (b) cooling 30 min., (c) cooling 60 min., (d) cooling 90 min., (e) solvent/anti-solvent ratio 1:1, (f) solvent/anti-solvent ratio 1:3, (g) solvent/anti-solvent ratio 1:5, (h) solvent/anti-solvent ratio 1:6, (i) solvent/anti-solvent 15 min., and (j) solvent/anti-solvent 1:3 (45 min).

Fourier Transform Infra-Red (FTIR) Analysis

Based on the FTIR analysis, both unprocessed and processed materials have similar signature peaks, showing only a slight change in the functional groups of the materials (Figure 3). Typical bonds of acetaminophen, such as O – H bond at 3200 - 3500 cm^{-1}, C = O amide at 1650 cm^{-1}, and C-O groups at 1150 - 1275 cm^{-1}, remain evident in all samples, as shown in Figure 3 [19,20]. However, a change in pattern, indicated by a green-dashed circle, was observed within the range of 3300 to 3700 cm^{-1}. This showed that the O - H straight bond experienced some effects of molecular vibrations, thereby inducing spectra differences between the unprocessed and processed samples. Another transformation was observed at 1100

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- 1250 cm^{-1}, representing the straight C - O attached to the O - H (phenol) bond of the compound [19].

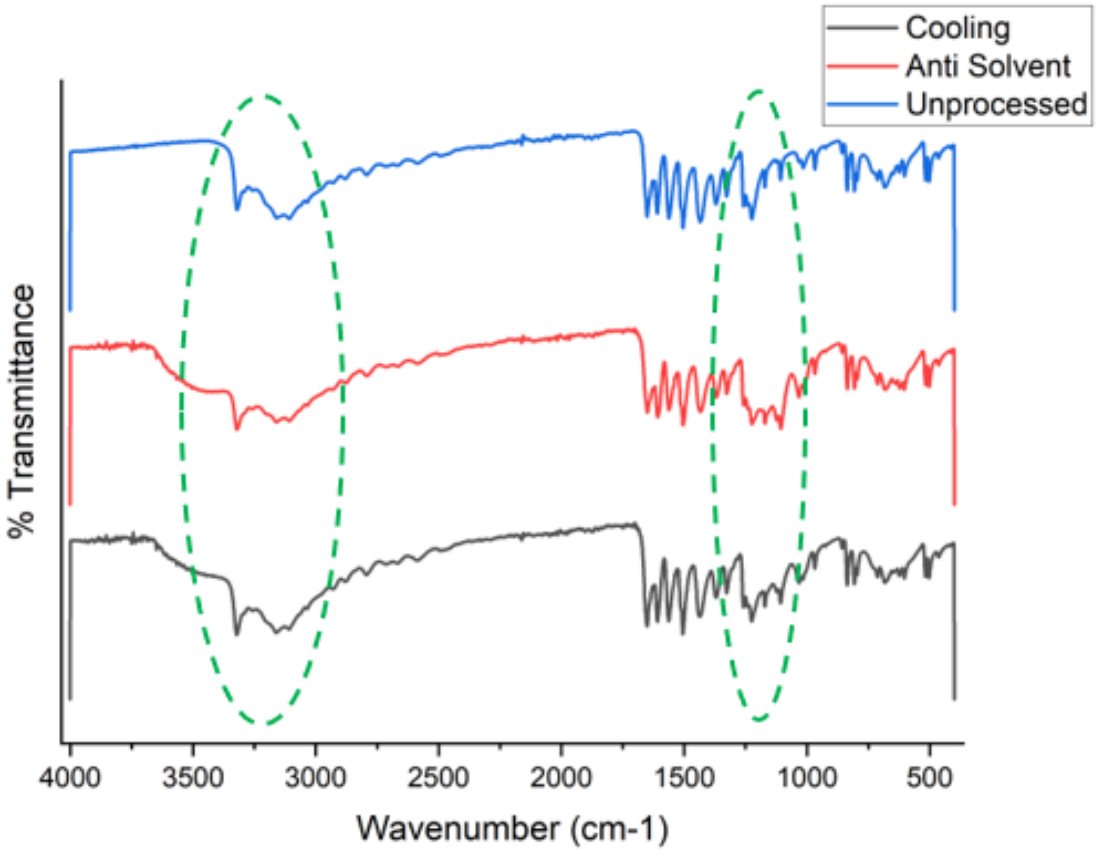

Figure 3. FTIR spectra of acetaminophen samples

Changes in the wavelength range of 3200-3400 cm^{-1}, might also be affected by N-H groups. Aliphatic primary amines have a weak N-H doublet in the IR spectrum around 3300 and 3380 cm^{-1}, originating from the 'out-of-phase' and 'in-phase stretching' vibrations of the amine group, respectively. In general, the change of peak patterns observed at a range of 3300-3380 cm^{-1} is attributed to various causes such as sample dilutions, ambient humidity, or some other effects from the experimental protocols [21]

The difference could potentially impact other powder properties. However, the spectra patterns of both - the unprocessed and processed materials at lower wavelength numbers (around 400 cm^{-1} and less), were similar. This suggests that the change in vibrational molecules does not affect the crystalline phases of both materials, reducing the chances of detecting polymorphisms [22].

Crystallinity analysis by XRD

The XRD analysis was performed to determine the degree of crystallinity of both the product and material crystals. Based on the powder characterization using the XRD method, the following results were obtained.

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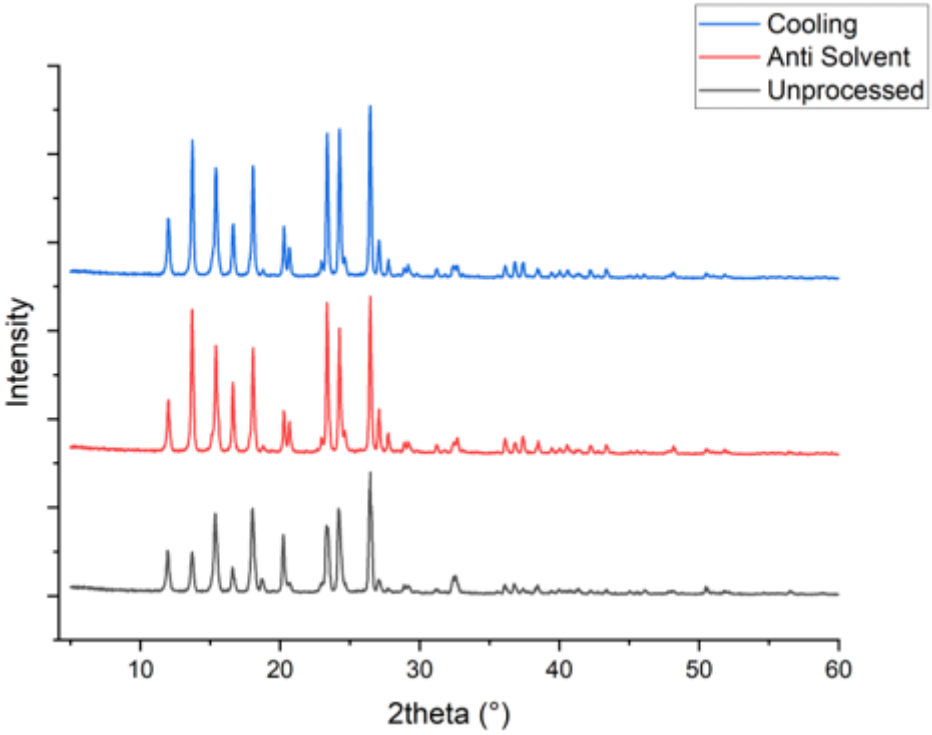

Figure 4. XRD diffractogram of unprocessed and processed acetaminophen in 30 min.

The crystal structure of recrystallized acetaminophen was analyzed using an XRD graph, as shown in Figure 4. The graph showed that the samples were in crystal Form I of acetaminophen. This showed the minimum effect of the crystallization process on the samples' crystalline form [23]. The XRD graphs are in accordance with the result of the FTIR spectra in the previous section, where drug crystal transformation was not observed in the samples.

Based on the powder XRD graph, peak positions and area in the graphs were used to estimate the degree of crystallinity. This parameter was calculated by comparing the fraction of crystalline area with the sum of the fraction of crystalline and amorphous area. The calculation was based on the measurement of the range between 2Θ: 0 – 90°. The XRD spectra showed a consistent flat horizontal curve between 2Θ: 60 – 90°. Furthermore, the crystalline area was contributed by the observation area prior to 2Θ: 60°. The following represents the calculation for the degree of crystallinity [24].

$$\text{Crystalinity} = \frac{\text{Crystalline fraction area}}{\text{Crystalline fraction area+Amorf fraction area}} \times 100 \qquad (2)$$

Based on the peaks obtained from the XRD results, the following shows the calculation of the degree of crystallinity for each sample. The calculation was performed using the software *Origin 2023*.

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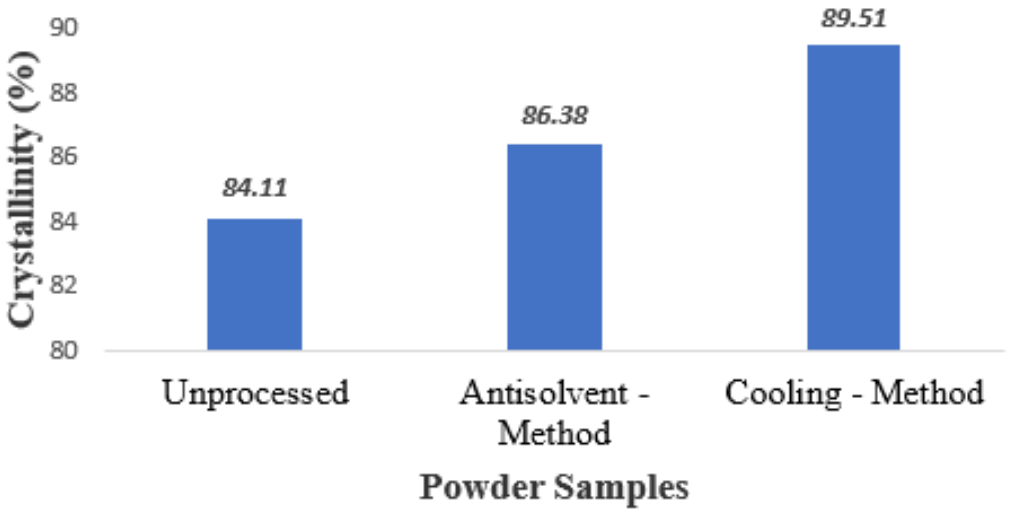

Figure 5. Crystallinity degree (%) of the unprocessed and processed acetaminophen in 30 min in different methods.

The data presented in Figure 5 suggests that samples obtained through cooling crystallization generally have higher crystallinity. It was recorded in 89.51% crystallinity. As a result, crystals obtained using this method possess greater crystallinity. Meanwhile, the anti-solvent method gives 86.38% crystallinity, and the unprocessed sample provides 84.11% crystallinity. The balance between crystalline and amorphous phases can significantly influence powder solubility. Compounds with a higher amorphous phase tend to show increased solubility. In simpler terms, compounds with higher degrees of crystallinity may potentially have lower solubility [7, 25, 26].

Thermal Properties (DSC Analysis)

The DSC analysis was conducted to determine the thermal properties of both the unprocessed and processed materials. The result is displayed in Figure 6. Based on the DSC observation, there was no difference in the melting point of the samples. Both unprocessed and processed acetaminophen had melting points at 169^{o}C (432 K), showing that the powders maintained the signature of acetaminophen crystal type I. Based on the results, recrystallization did not transform crystal types or compositions for both unprocessed and processed powders. Both anti-solvent and the cooling method were unable to facilitate crystal transformation. The condition is in line with the concept of congruent melting point production, where the produced crystals melt at a single temperature without any change in composition [27, 28].

Solubility

The results of solubility tests are presented in Tables 1 and 2. Particles produced from the cooling and anti-solvent method had solubility between 0.0123 - 0.0151 g/ml as well as 0.0139-0.0167 g/ml. Compared to the unprocessed and cooling processed acetaminophen, the solubility of anti-solvent particles was higher. According to the literature, unprocessed acetaminophen recorded a value of approximately 0.014 g/ml [4]. The measurement in this study showed that the unprocessed acetaminophen solubility was at 0.0107 g/ml, consistent with the literature data. Recrystallization led to a significant improvement, with increases of up to 40% and 56% observed for the cooling and anti-solvent methods, respectively. The higher

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value from anti-solvent method was caused by various factors, such as particle characteristics, including surface physicochemical properties. Referring to the result presented previously (crystallinity section), crystallinity degree might contribute to the result. The higher degree of crystallinity powder from the cooling method produced lower solubility particles than those of the anti-solvent. Another reason might come from a slight change in the molecular vibration pattern, as observed in the FTIR analysis. Further investigations are warranted to elucidate this phenomenon.

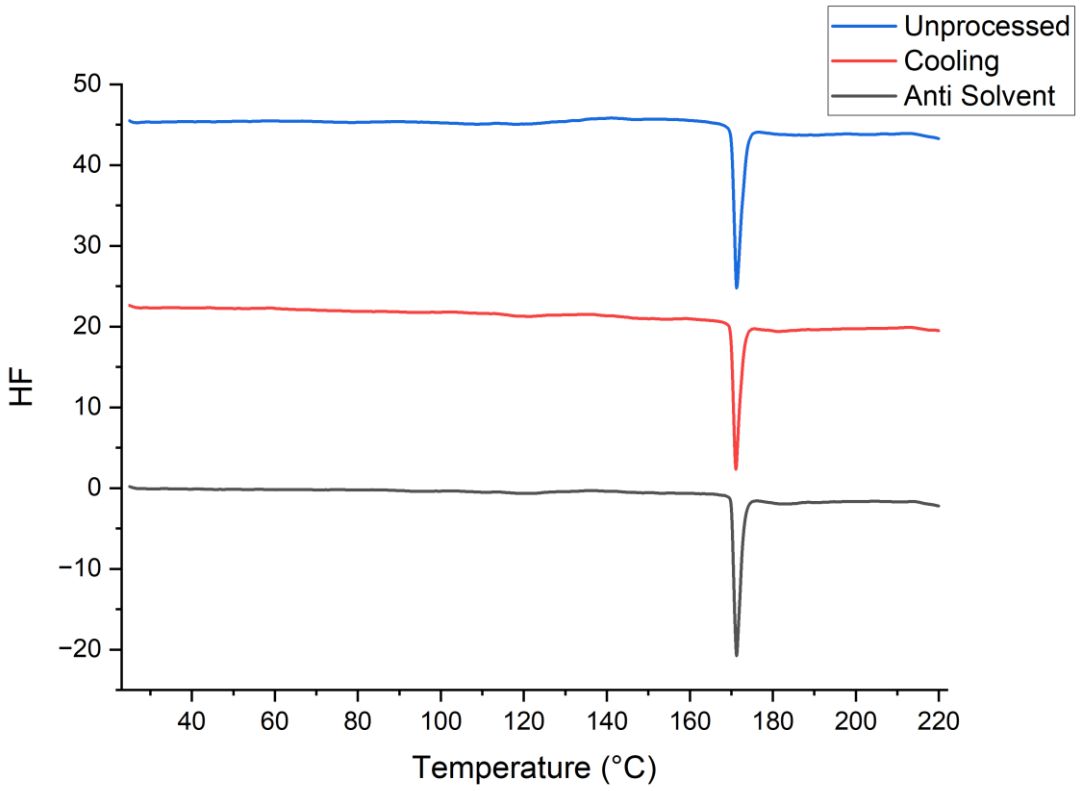

Figure 6. The DSC graph of acetaminophen samples

CONCLUSION

In conclusion, crystallization of acetaminophen through both cooling and anti-solvent methods resulted in the formation of crystals with improved solubility properties. The process, which may have affected crystallinity and molecular vibrations, proved advantageous in enhancing solubility. Particularly, the anti-solvent crystallization, using solvent-to-anti-solvent ratio of 1:3 for 30 minutes, showed a substantial increase, reaching 56%. While the cooling method generated smaller-sized crystals compared to the anti-solvent method, it was less efficient in terms of processing yield. On the other hand, the anti-solvent processing showed a yield of up to 41.40%, while the cooling method yielded a maximum of 9.01%. These results suggest that both methods were viable for processing acetaminophen particles. Furthermore, the selection of the specific method could significantly influence product characteristics, comprising particle dimensions, morphology, crystallinity, solubility properties, and processing yields.

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