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Research Article

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A bottom-up process approach for micronization of Ibuprofen

Stevanus Hiendrawan, Bambang Veriansyah and Raymond R. Tjandrawinata*

Dexa Laboratories of Biomolecular Sciences (DLBS), Industri Selatan V, Block PP no. 7, Jababeka Industrial Estate II, Cikarang, West Java, Indonesia

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ABSTRACT

Micronization of ibuprofen using bottom-up process via rapid expansion of supercritical solution (RESS) were conducted to investigate its effects on formation of micronized ibuprofen. Physicochemical properties of processed ibuprofen were analyzed using XRD, DSC, FT-IR, SEM, laser diffractometer and dissolution testing. Effects of extraction pressure, extraction temperature and nozzle diameter on particle size were optimized using Taguchi's orthogonal array and analyzed using analysis of variance (ANOVA). Processed ibuprofen retained its crystalline structure and has a similar chemical structure with unprocessed ibuprofen. The average particle size of ibuprofen was reduced from its original 48.549±2.304 μm into 3.765±0.024 μm under the optimum condition (T at 45°C, P at 200 bar and nozzle diameter at 200 μm). The processed ibuprofen showed an enhanced its dissolution rate by 1.79 times compare to unprocessed ibuprofen.

Keywords: ibuprofen, RESS, Taguchi, particle size, dissolution

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely prescription medication in the world [1]. Ibuprofen, a chiral NSAID belongs to class of propionic acid derivatives, is considered to be among the safest NSAIDs available [2]. The major mechanism for their anti-inflammatory action is inhibition of cyclooxygenase enzyme which result blocking prostaglandin generation. Racemic ibuprofen and S(+)-enantiomer are mainly used in treatment of mild to moderate pain related to dysmenorrhea, headache, migrane, postoperative and dental pain and management of spondylitis, osteo-arthritis, rheumatoid arthritis and soft tissue disorders. Ibuprofen has also anti-pyretic properties. Nevertheless, poorly aqueous solubility of ibuprofen affects on its dissolution rate and absorptions in gastrointestinal tract [3]. Dissolution rate is a function of particles surface area and solubility. The surface area can be improved by particle size reduction [4].

Micronization techniques are used for improvement the solubility and dissolution rate of poorly aqueous soluble drug by particle size reduction. Micronization process can be broadly classified into top-down and bottom-up processing. Top-down processing involves particle size reduction using various milling techniques such as ball milling, jet milling (fluid energy mill), pearl milling (wet milling) and high pressure homogenization [5-6]. The bottom-up processing involves growing the particles from a solution, such as supercritical fluid (SCF) technology, spray-freezing into liquid process, evaporative precipitation into aqueous solution (EPAS) and liquid solvent change process [7].

Recently, supercritical fluid technology for micronization processes, such as rapid expansion of a supercritical solution (RESS), supercritical anti-solvent (SAS) and particles from gas saturated solutions (PGSS), have gained increasing attention and may considered as interesting alternatives for micronization of active pharmaceutical ingredient (API) [8]. In particular, RESS process has some important advantages such as nano or microparticles with controllable particle size and possibility of providing a solvent-free product [8-10]. In RESS process, raw material is solubilized in a SCF at extraction unit, than supercritical solution is suddenly depressurised into precipitation

chamber through a nozzle to cause fast nucleation and fine particle formation. The combination of rapidly propagating mechanical perturbation and high supersaturation ratios is a distinguishing characteristic of RESS process, which lead to uniform condition within the nucleating medium for formation of small and monodisperse particles with a narrow size distribution [9]. The main limitation of RESS process is that the solute must have enough solubility in SCF [11].

Aim of this study was to investigate bottom-up processing via rapid expansion of supercritical solution (RESS) on formation of micronized ibuprofen and evaluate effect of processing method parameters. Micronization of ibuprofen by RESS process has previously been studied by several researchers. Charoenchaitrakool *et al*., [3] reported solubility ibuprofen in supercritical CO_2 and effect of pre-expansion pressure, spraying distance and the nozzle length on size and morphology of RESS process ibuprofen particles. Kayrak *et al*., [4] reported effects of extraction pressure, capillary length, spraying distance, collision angle and pre-expansion temperature on size and morphology of RESS processed ibuprofen particles. Hezave *et al*., [12] reported influence of effective diameter and length of nozzle on RESS processed ibuprofen particles. Pankaj Pathak *et al*., [13] and Michael Turk *et al*., [14] reported formation of micronized ibuprofen suspension using modification of the RESS process (RESOLV/ RESAS). From our knowledge there is no study that has been done on RESS micronization using statistical design of experiment (Taguchi methods) for ibuprofen. Therefore the aim of these present work is to study the feasibility of RESS process and to evaluate the effect of processing parameter on the ibuprofen particles using Taguchi design of experiment [9,15-17].

Analysis of variance (ANOVA) was used to determine contribution of each parameter in the RESS process. Physicochemical properties of the micronized ibuprofen particles were analyzed using X-ray diffraction (XRD), differential scanning calorimetry (DSC), Fourier transform infrared (FT-IR), scanning electron microscope (SEM), laser diffractometer (LD) and dissolution rate measurement.

EXPERIMENTAL SECTION

2.1. Materials

Ibuprofen was purchased from Shasun Chemicals and Drugs, Ltd (Chennai, India). High purity of carbon dioxide (CO_2, purity of 99.95%) was purchased from PT. Intergas (Jakarta, Indonesia). Potassium dihydrogen phosphate (KH_2PO_4), sodium hydroxide (NaOH) and sodium lauryl sulphate (SLS) were purchased from Merck (Darmstadt, Germany).

2.2 Apparatus and procedure for bottom up process via RESS

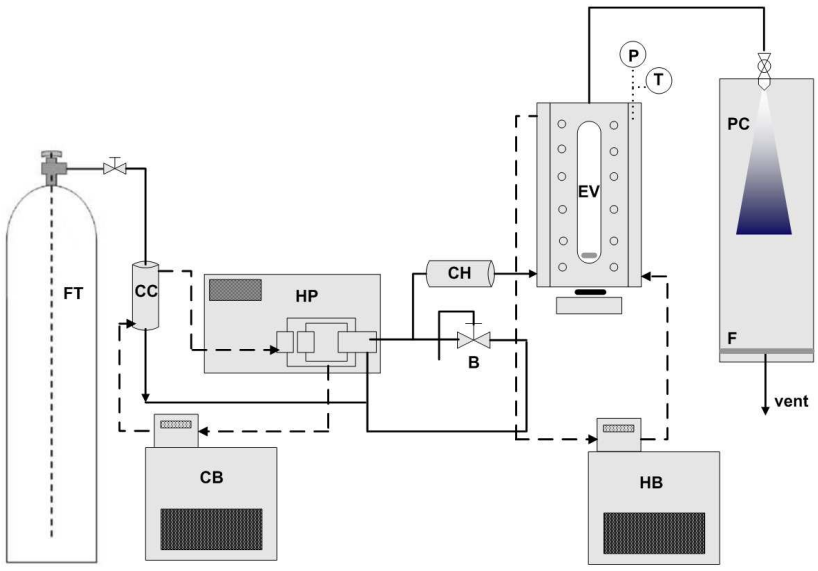

Figure 1. Schematic diagram of a custom-built RESS apparatus. B, back pressure regulator; F, frit filter; CB, cooling bath; CC, precooler; CH, preheater; EV, extraction vessel; FT, CO_2 cylinder; HB, heating bath; HP, high-pressure pump for carbon dioxide; PC, precipitation chamber

Micronization was conducted using a custom-built rapid expansion of supercritical solutions (RESS) apparatus. **Figure. 1** shows a schematic diagram of RESS system. Details of apparatus and experimental procedures were described in the previous paper [9]. Prior to each experiment, 10 grams of ibuprofen was loaded to Extraction

Vessel (EV) and then temperature of the EV was increased to experimental temperature. CO_2 was cooled in a precooler (CC) and pressurized by a high pressure pump (HP) to a desired pressure, heated to a desired extraction temperature by a preheater (CH) and allowed to enter the EV for extraction. After reaching the experimental temperature and pressure, the solution was kept in the EV until supercritical fluid CO_2 ($scCO_2$) was saturated with ibuprofen for one hour. This mixture was depressurized in a precipitation chamber (PC) at atmospheric pressure for 4 min by means of a nozzle. During the depressurization, the flow of HP was increase to 50 g/min to ensure the steady state condition of EV and the nozzle was also heated to avoid plugging by solid precipitation. The precipitated particles in the frit filter (F) were collected and analyzed.

2.3 Characterization

Morphology of unprocessed and processed ibuprofen was characterized by X-ray diffraction (XRD), differential scanning calorimetry (DSC), Fourier transform infrared (FT-IR), scanning electron microscope (SEM), laser diffractometer (LD) and dissolution rate measurement. Details on XRD, DSC, FT-IR, SEM and LD used in this study were described in the previous paper [9]. Dissolution rates of the unprocessed and processed ibuprofen were performed in DT-700 dissolution apparatus (Erweka, Germany) according to the USP paddle method [18]. The experiment was conducted in 900 ml phosphate buffer solution pH 7.2 with SLS 0.01%. Temperature of dissolution medium was kept at 37 ^oC and speed of agitator was at 50 rpm. A specific amount of ibuprofen powder (200 mg) was added into the dissolution medium. At specific time intervals, 5 mL of the solution was withdrawn and substitute with another 5 ml fresh dissolution medium to keep similar volume in the dissolution vessel. Assay of ibuprofen was measured using an UV spectrophotometer (model U-2900, Hitachi, Japan) at a wavelength of 223 nm.

RESULTS AND DISCUSSION

3.1. RESS process

Table 1. Parameters and their levels of the orthogonal array design

Parameters	Level 1	Level 2	Level 3
A : Extraction pressure (bar)	100	150	200
B : Extraction temperature (^oC)	35	40	45
C : Nozzle diameter (µm)	200	250	300

A Taguchi L-9 orthogonal array design (OAD) was used to investigate optimum conditions and examine the most influencing parameters in the RESS process. RESS experiments is carried out with 3 parameters and 3 levels (**Table 1**), namely extraction pressure (100, 150 and 200 bar), extraction temperature (35, 40 and 45^oC) and nozzle diameter (200, 250 and 300 µm).

Table 2. Orthogonal array design matrix L9 and experimental results

Run	A Extraction pressure (bar)	B Extraction temperature (^oC)	C Nozzle Diameter (µm)	Particle size ± SD (µm)	Span ± SD
1	100	35	200	4.405 ± 0.057	1.543 ± 0.018
2	100	40	250	4.545 ± 0.018	1.540 ± 0.011
3	100	45	300	4.756 ± 0.054	1.630 ± 0.100
4	150	35	250	4.346 ± 0.016	1.545 ± 0.004
5	150	40	300	4.289 ± 0.032	1.699 ± 0.003
6	150	45	200	4.001 ± 0.004	1.389 ± 0.074
7	200	35	300	3.926 ± 0.012	1.385 ± 0.077
8	200	40	200	3.891 ± 0.136	1.315 ± 0.018
9	200	45	250	3.778 ± 0.061	1.603 ± 0.993
K_1^*	4,569	4,226	4,099		
K_2^*	4,212	4,242	4,223		
K_3^*	3,865	4,178	4,324		
R^{**}	0,704	0,063	0,225		
Optimal level	200 bar	45 ^oC	200 µm		

$^*K_i^A = \sum$ *(mean particle size at* A_i*)/3, the mean values of mean particle size for a certain factor at each level*

$^{**}R_i^A = max\ (K_i^A)\text{-}min(K_i^A)$

Structure of Taguchi's L-9 OAD and experiment results are shown in **Table 2**. In the view of orthogonal analysis, we adopted statistical software to calculate the values of K and R. Based on the R value, it can be concluded that influencing parameters decreased in the order: extraction pressure > nozzle diameter > extraction temperature. Optimum conditions were achieved at extraction pressure 200 bar, extraction temperature 45^oC and nozzle diameter

at 200 μm. The experiment was conducted to confirm that optimum conditions obtained from statistical software gave the same optimum conditions with experiment. Result of this experiment result is micronized ibuprofen particles with particle size 3.765±0.024 μm and yield of the RESS process was about 86.5%.

Table 3 listed analysis of variance (ANOVA) of three parameters for the RESS process of ibuprofen, with 95% confidence interval using MINITAB v.15 (Minitab Inc., USA). Results showed that a change in level of extraction pressure, extraction temperature and nozzle diameter had no a significant effect on particle size (P>0.05).

Table 3. ANOVA analysis of three parameters for RESS micronization of ibuprofen

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Extraction pressure	2	0.742767	0.742767	0.371383	12.31	0.075
Extraction temperature	2	0.006508	0.006508	0.003254	0.11	0.903
Nozzle diameter	2	0.075985	0.075985	0.037992	1.26	0.443
Residual error	2	0.060320	0.060320	0.030160		
Total	8	0.885580				

Effect of extraction pressure was determined at three extraction pressure (100, 150 and 200 bar. **Figure. 2.1** showed that average particle size decreased from 4.569±0.043 μm to 3.865±0.070 μm when extraction pressure increased from 100 to 200 bar. CO_2 density increased as extraction pressure increased, hence, the solvating power of solvent is increased. As the results, solubility of ibuprofen in $scCO_2$ increased as the pressure increased. Charoenchaitrakool *et al*., [3] reported that solubility of ibuprofen (at 35°C-45°C) increased as pressure increased from 100 to 200 bar. Increasing ibuprofen solubility results in higher supersaturation in fluid upon expansion. The higher supersaturation may result in increasing nucleation rate, which lead to smaller particle size formation of ibuprofen. Similar result was reported by Hezave *et al*., [12] for other API.

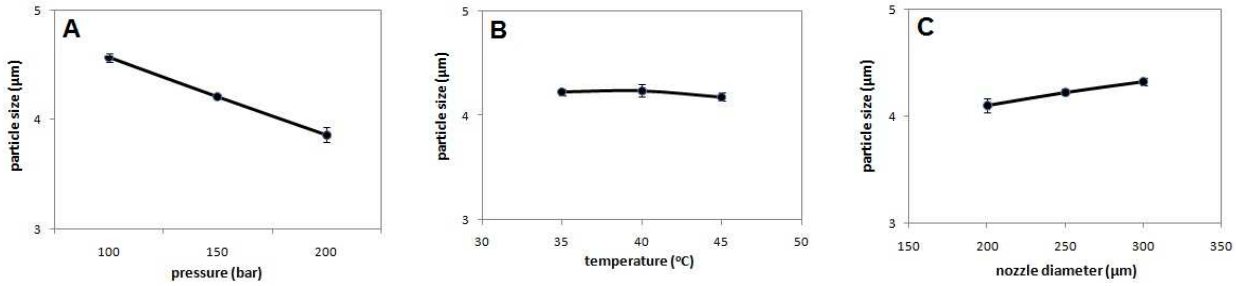

Figure 2. Effect of each parameter on RESS processed ibuprofen particle size: (1) extraction pressure ; (2) extraction temperature; (3) nozzle diameter

Effect of extraction temperature was determined at three extraction temperatures (35, 40 and 45°C). **Figure. 2.2** showed that extraction temperature had no significant effect on ibuprofen particle size. Ibuprofen particle size was decrease from 4.226±0.028 μm to 4.178±0.040 μm when extraction temperature increased from 35°C to 45°C. Increasing the extraction temperature leads to decrease in density of CO_2 and concurrent increase in solute's vapour pressure. Decrease of solvent density causes a decrease of solvent strength. On the other hand, a concurrent increase in solute's vapour pressure leads to an increase in the ibuprofen solubility in $scCO_2$. Effect of these two competing factors resulted in no significant particle size reduction with increasing temperature.

Effect of nozzle diameter was determined at three nozzle diameter (200, 250 and 300 μm). **Figure. 2.3** showed that particle size was increased from 4.099±0.066 μm to 4.324±0.033 μm when nozzle diameter increased from 200 to 300 μm. Increasing the nozzle diameter will result in slower jet velocity and increasing growth of crystal nuclei, which probably leads to increase particle size. Similar result also found by Chingunpitak *et al*., [19] when using dihydroartemisinin as a solute.

Figure. 3 showed PSD profile from the RESS process under optimum condition and unprocessed ibuprofen. Ibuprofen particles from the RESS process have narrower particle size distribution compare to unprocessed ibuprofen.

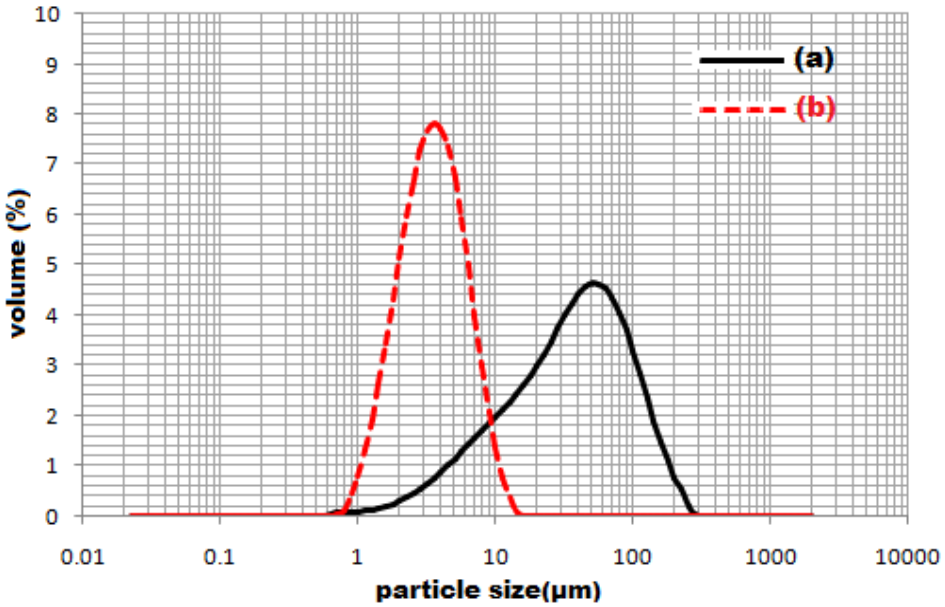

Figure. 3. Particle size distribution of of ibuprofen particles. (a) unprocessed; (b) RESS at optimum condition

3.2. Characterization of micronized ibuprofen

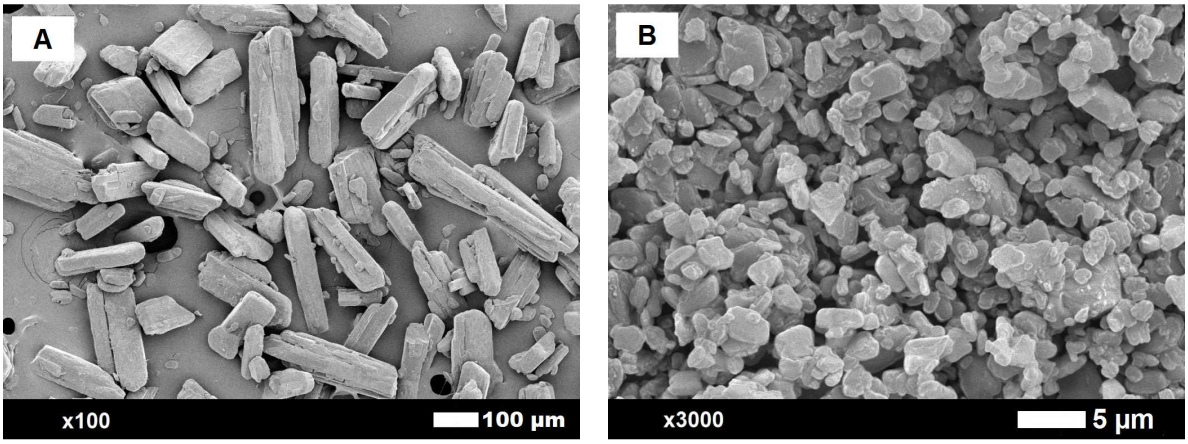

Figure. 4. SEM image of ibuprofen particles. (1) unprocessed; (2) RESS at optimum condition

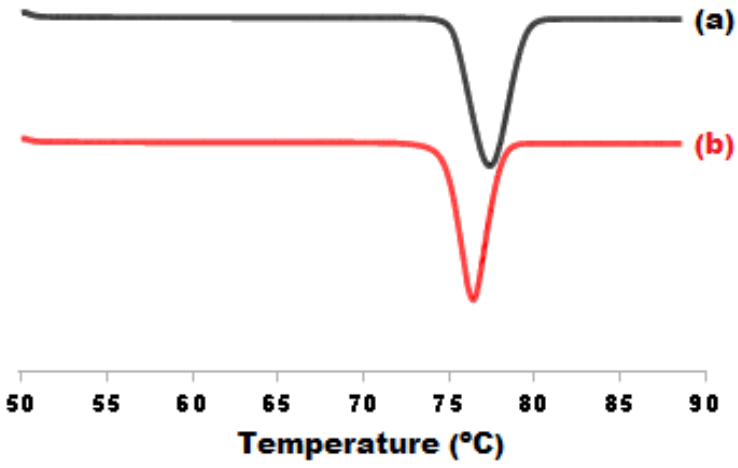

Figure. 5. DSC profile of ibuprofen particles. (a) unprocessed; (b) RESS at optimum condition

Unprocessed ibuprofen has irregular-shape particles with average particle size 48.549±2.304 µm is shown in **Figure. 4.1**. The smallest RESS processed ibuprofen obtained from optimum condition (extraction pressure 200 bar, extraction temperature 45^{o}C and 200 µm nozzle diameter) (**Figure. 4.2**) also has irregular-shape. Both unprocessed and processed ibuprofen particles was characterized using X-ray diffraction (XRD), differential scanning calorimeter (DSC), fourier transform infrared (FT-IR) and dissolution measurement.

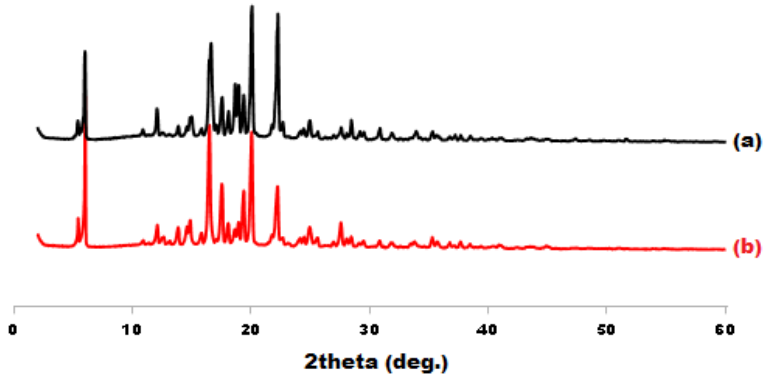

Figure. 6. XRD profile of ibuprofen particles. (a) unprocessed; (b) RESS at optimum condition

Figure. 5 and **Figure. 6** showed DSC and XRD patterns of unprocessed and processed ibuprofen. Melting point of unprocessed ibuprofen is 77.40^{o}C whereas RESS processed ibuprofen has melting point 76.16^{o}C , respectively. Slightly lower of DSC endothermic peak in processed ibuprofen particles due to particle size reduction after RESS process [19]. XRD patterns of processed ibuprofen were similar to unprocessed ibuprofen, indicating that same crystal structure was obtained after the RESS process. Slightly decreased of intensity XRD peaks due to crystallinity reduction after the RESS process [9].

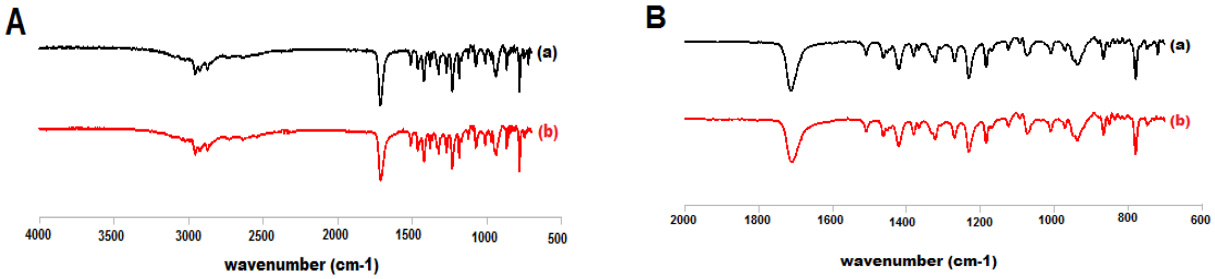

Figure. 7. FTIR profile of ibuprofen particles. (a) unprocessed; (b) RESS at optimum condition. (1) wavenumber 700-4000 cm^{-1}; (2) wavenumber 700-2000 cm^{-1}

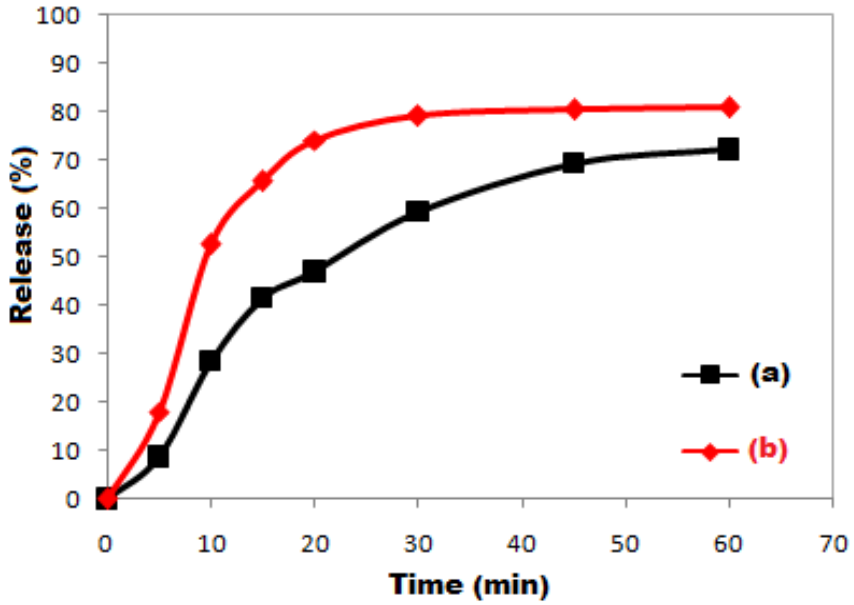

Figure. 8. Dissolution profiles of ibuprofen particles. (a) unprocessed; (b) RESS at optimum condition

Chemical structure of unprocessed and processed ibuprofen was characterized using FT-IR and results are shown in **Figure. 7.1** and **Figure. 7.2** FT-IR spectra of the processed ibuprofen showed similar absorption peak with FT-IR spectra of the unprocessed ibuprofen, indicating that RESS process did not affect chemical structure and modify the surface of ibuprofen.

Dissolution rate profile of the unprocessed and processed ibuprofen are shown in **Figure. 8**. An enhancement in dissolution rate was observed in the processed ibuprofen. In this study, an empirical Weibull equation [11,20] was used to correlate the dissolution profiles. The Weibull equation expressed accumulated fraction of the pharmaceutical compound in a dissolution medium at a specific time internal and is defined as Eq. [1]

$$m = 1 - \exp\left[\frac{-t^b}{a}\right] \quad (1)$$

where *m* is the accumulated fraction of drug in a dissolution medium at time *t. a* and *b* are two empirical parameters that were fitted using the experimental data. The dissolution rate coefficient (kw) was used for comparing the dissolution profile [11,20] and defined as the reciprocal of time interval where 63.2% of original amount of drug has been dissolved. It was calculated from the parameters in the Weibull model as:

$$kw = \frac{1}{\sqrt[b]{a}} \quad (2)$$

The kw value of the RESS processed ibuprofen were 0.0495 min^{-1} whereas the kw value of the unprocessed ibuprofen was 0.0277 min^{-1}. Based on this result, the dissolution rate of RESS processed ibuprofen was enhanced approximately 1.79 times due to reduce the particle size after the RESS process.

In order to compare the dissolution profile of unprocessed and processed ibuprofen, two factor, *f1* (different factor) and *f2* (similarity factor) analysis was also used

$$f1 = \frac{\sum_{j=1}^{n} |Rj - Tj|}{\sum_{j=1}^{n} Rj} \; x \; 100 \quad (3)$$

$$f2 = 50 \; x \; log\left\{\left[1 + \frac{1}{n}\sum_{j=1}^{n} |Rj - Tj|\text{^}2\right]^{-0.5} \; x \; 100\right\} \quad (4)$$

where *Rj* and *Tj* are the cumulative percentage dissolved at each of selected *n* time points of the unprocessed ibuprofen (reference) and processed ibuprofen (test product), respectively. In general, the dissolution profiles were taken as similar with f1 value lower than 15 and f2 value higher than 50. The comparison of dissolution profile using f1 and f2 has also been adopted by Food and Drug Administration (FDA) and European Medicines Agency (EMEA) in the assessment of the similarity between two dissolution profiles [11,20]. The difference factors (f1) and similarity factor (f2) for RESS processed ibuprofen compare to unprocessed ibuprofen particles were 45.41 and 36.14. This f1 and f2 value confirming that the dissolution character of the processed ibuprofen from RESS process was different than the unprocessed ibuprofen. From this result can be concluded that processed ibuprofen have higher aqueous solubility than unprocessed ibuprofen.

CONCLUSION

Micronization of ibuprofen was successfully performed using rapid expansion of supercritical solution (RESS). Processed ibuprofen with particle size of 3.765±0.024 μm was achieved using RESS process at extraction pressure of 200 bar, extraction temperature of 45^{o}C and a nozzle diameter of 200 μm. The size of RESS processed ibuprofen was dependent on processing parameters conditions. The results showed that particle size decreased as extraction pressure increased and nozzle diameter decreased. Extraction temperature had no significant effect on ibuprofen particle size. RESS process at optimum conditions produced narrower particle size distribution when compared with unprocessed ibuprofen. The processed ibuprofen particles retained similar crystallinity and chemical structure.

Dissolution measurement of the smallest processed ibuprofen from RESS process show an enhanced dissolution rate compare to unprocessed ibuprofen.

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