Marmara Pharmaceutical Journal 21/4: 783-792, 2017
DOI: 10.12991/mpj.2017.30

RESEARCH ARTICLE

Enhancement of solubility and dissolution of ibuprofen microparticle prepared by ultrasonic spray drying

Revika RACHMANIAR, Camellia PANATARANI, I Made JONI, Marline ABDASAH, Taofik RUSDIANA

ABSTRACT

Ibuprofen (IBU) is one of the most commonly used non-steroidal anti-inflammatory drugs with high permeability and low solubility. The aims of this research is to improve the solubility and dissolution of the IBU by reducing particle size using ultrasonic spray drying method and utilizing water-soluble polymer (polyvinyl alcohol (PVA)) and surfactant (sodium lauryl sulphate (SLS)) for particles formulation. The results showed that increasing amount of PVA, smaller particle size of as-prepared IBU-PVA-SLS was obtained, 6.3-fold smaller than untreated IBU. The *in vitro* drug release study for simulated gastric fluid without enzymes (0.1 N HCl or Buffer pH 1.2) shows the dissolution of prepared IBU-PVA-SLS significantly increase 2.4-fold higher than untreated IBU for dissolution time of 30 minutes. While the solubility of the IBU-PVA-SLS was increased 4.7-fold compare to untreated IBU. In general, IBU possessing relatively high dissolution in intestinal fluid. In contrast, the finding of recent investigation on dissolution of IBU-PVA-SLS is significantly increase in gastric fluid, either due to smaller particles size or PVA-SLS. Thus, despite the PVA and SLS determine the particles formation during polymerization yielding smaller particle size, they also responsible for effective drug delivery system. It was concluded that PVA and SLS in ultrasonic spray drying technique for IBU preparation successfully reduces the particle size and effectively enhances the solubility and dissolution rate of poorly water-soluble IBU in 0.1 N HCl.

Key words: Ultrasonic spray drying ; ibuprofen ; polyvinyl alcohol ; sodium lauryl sulphate ; solubility ; dissolution.

Revika RACHMANIAR, Marline ABDASAH, Taofik RUSDIANA
Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Universitas Padjadjaran, Jl. Raya Bandung-Sumedang KM 21, Jatinangor 45363, West Java, Indonesia

Camellia PANATARANI, I Made JONI
Department of Physics, Faculty of Mathematics and Natural Science, Universitas Padjadjaran, Jl. Raya Bandung-Sumedang KM 21, Jatinangor 45363, West Java, Indonesia

Camellia PANATARANI, I Made JONI
Nanotechnology Research Center, Universitas Padjadjaran, Jl. Raya Bandung-Sumedang KM 21, Jatinangor 45363, West Java, Indonesia

Revika RACHMANIAR
Department of Pharmaceutics, Indonesian School of Pharmacy, Jl. Soekarno-Hatta No.354, Bandung 40266, West Java, Indonesia

Corresponding Author:
Taofik RUSDIANA
e-mail: t.rusdiana@unpad.ac.id

Submitted / Gönderilme: 03.06.2017 **Revised / Düzeltme:** 24.07.2017
Accepted / Kabul: 27.07.2017

How to cite this article : Rachmaniar R, Panatarani C, Joni IM, Abdasah M, Rusdiana T. Enhancement of solubility and dissolution of ibuprofen microparticle prepared by ultrasonic spray drying. Marmara Pharm J. 2017; 21 (4): 783-792

1. Introduction

Ibuprofen (IBU) [2-(4-isobutyl-phenyl) propionic acid] is a non-steroidal anti-inflammatory drug that is expected to provide immediate effect, however IBU has a low solubility and high permeability (class 2 drug in BCS system) preventing fast dissolution rates and high bioavailability. IBU also has a short half-life, 2.0 ± 0.5 hours. Because of its low solubility and short half-life, IBU is difficult to be absorbed into the blood circulation system hence IBU has relatively low bioavailability [1-3]. Thus, the dissolution rate is required to achieve high bioavaibility of IBU. The dissolution rate could be improved by decreasing the particle size, leads to higher surface area of reaction [3-7]. It is very common that pharmaceutical technology uses the micronization process to reduce the particle size in order to increase the dissolution rate of drugs [8-9].

Generally, spray drying is applied in the pharmaceutical industries for preparing micro- and/or nanoparticles, increasing the solubility of poorly water soluble drugs, drying heat-sensitive materials, and improving powder

flowability [6,9-14]. Many researchers apply spray drying for microparticle preparation of the drug to obtain reduced size to a specific size ranges (1-5 μm) [6, 5] and shapes [11, 16-18]. Pyo *et al*., Kim *et al*., and Puri *et al*. were using spray drying to control the amorphous states of the drugs because this state are often desired in order to achieve fast dissolution rates and high bioavailability [15, 19, 20-23]. Xu *et al.,* Li *et al*., and Shen *et al*. improved solubility and dissolution of IBU by spray drying technique with using various polymer [1, 21, 24]. At previous research, microparticle was prepared by spray drying using nozzle or rotary atomizer which produced particle size 2-30 μm [9, 25-27]. Another atomizer for spray drying process is ultrasonic atomizer. It commonly uses for preparation of nano- and submicrometer inorganic particle, such as ZnO particle, by using spray pyrolysis [26, 28-30]. By using ultrasonic atomizer which can produce fine droplet 1-10 μm, particle can be formed smaller than particle that produced by nozzle or rotary atomizer [30].

Despite successful in size reduction of drugs, effort in micronization may cause changes such as polymorphic transitions, particle agglomeration/aggregation, and statically charged particles [9]. Therefore, to prevent those, stabilizer is necessary. Mauludin *et al*. and Xu *et al*. applied polyvinyl alcohol (PVA) as a stabilizer for hesperidin and celecoxib respectively [1, 6]. In addition, an anionic surfactant such as sodium lauryl sulphate (SLS) was employed to prevent microcapsules from attaching to the inner wall of spray-drying chamber and to produce free-flowing powder. In the absence of SLS, strong electrostatic interaction among microparticle arisen from friction in spray drier making the powder fly in all directions [24]. Woo *et al*., Lee *et al*., and Mauludin *et al*., used SLS as a solubilizer or co-carrier for cyclosporin A and hesperidin by using spray drying [1, 9, 25].

In this study the novel method on microparticle preparation was proposed by combining PVA and SLS corresponding for stabilizer and surfactant in spray drying method. In addition, the ultrasonic nebulizer was also applied for obtaining smaller aerosols in spray drying. The objective of present investigation is to enhance solubility and dissolution of IBU by preparing microparticle using ultrasonic spray drying technique utilizing PVA as a stabilizer and SLS as a surfactant. Surface morphology, particle size, crystallinity, functional group, solubility, and dissolution of as prepared IBU-PVA-SLS particle were investigated.

2. Results and Discussion

2.1. Characteristic of particles

Figure 1 shows XRD patterns of IBU and IBU-PVA-SLS particle. XRD patterns revealed all the peaks of IBU-PVA-SLS similar to the untreated IBU. The x-ray diffractogram of untreated IBU has sharp peaks at diffraction angles showing typical crystalline pattern. In this case the untreated IBU and IBU-PVA-SLS were already being in a crystalline state. The narrow full width at half maximum (FWHM) of untreated IBU showed that IBU has high degree of crystallinity while wide FWHM of IBU-PVA-SLS showed that IBU-PVA-SLS have low degree of crystallinity. This is due to IBU dissolved in the cosolvent system before ultrasonic spray drying process. Cooling off after evaporation process of the solvent in reactor caused molecular structure of IBU cannot rearrange to crystalline arrangement (as expected) [31].

FTIR was used to examine interactions between IBU, PVA, and SLS. The mixing of components at a molecular level will cause changes in the frequency and bandwidht of interacting groups in the spectrum. Figure 2 displays FTIR spectrum of untreated IBU, PVA, SLS, and IBU-PVA-SLS. FTIR spectrum revealed the pattern spectrum of IBU-PVA-SLS similar to the untreared IBU, PVA, and SLS.Untreated IBU exhibit a peak about 860-830cm^{-1} due to the para C-H and a strong band at 1700 cm^{-1} due to the carboxylic C=O group. PVA exhibits a peak about 3334-3299 cm^{-1} due to O-H group. SLS exhibits a peak about 1219-1214 cm^{-1} due to sulphate covalent. In the same region, IBU-PVA-SLS exhibit the same peaks with untreated IBU, PVA, and SLS. FTIR spectrum is accordance to XRD pattern that IBU-PVA-SLS exhibit the present of untreated IBU, PVA, and SLS. IBU-PVA-SLS exhibit the shift of carboxylic C=O group to the larger wavenumber due to intermolecular hydrogen bonding between IBU and PVA. The O-H group which was exhibited by IBU-PVA-SLS have a different transmitance according to concentration of PVA. Lower concentration of PVA in IBU caused lower transmittance intensity of O-H group. The transmittance values of O-H group peak for IBU-PVA-SLS (2:1:2; 2:2:2; 2:3:2) were 79.08, 59.92, and 49.56%, respectively [32].

The result which was obtained from XRD and FTIR indicated that ultrasonic spray drying process did not damage the structure of each component of IBU, PVA, and SLS. The decreasing degree of IBU-PVA-SLS crystallinity and formation of hydrogen bonding in IBU-PVA-SLS attributed to the incorporation of IBU within the PVA at a molecular level.

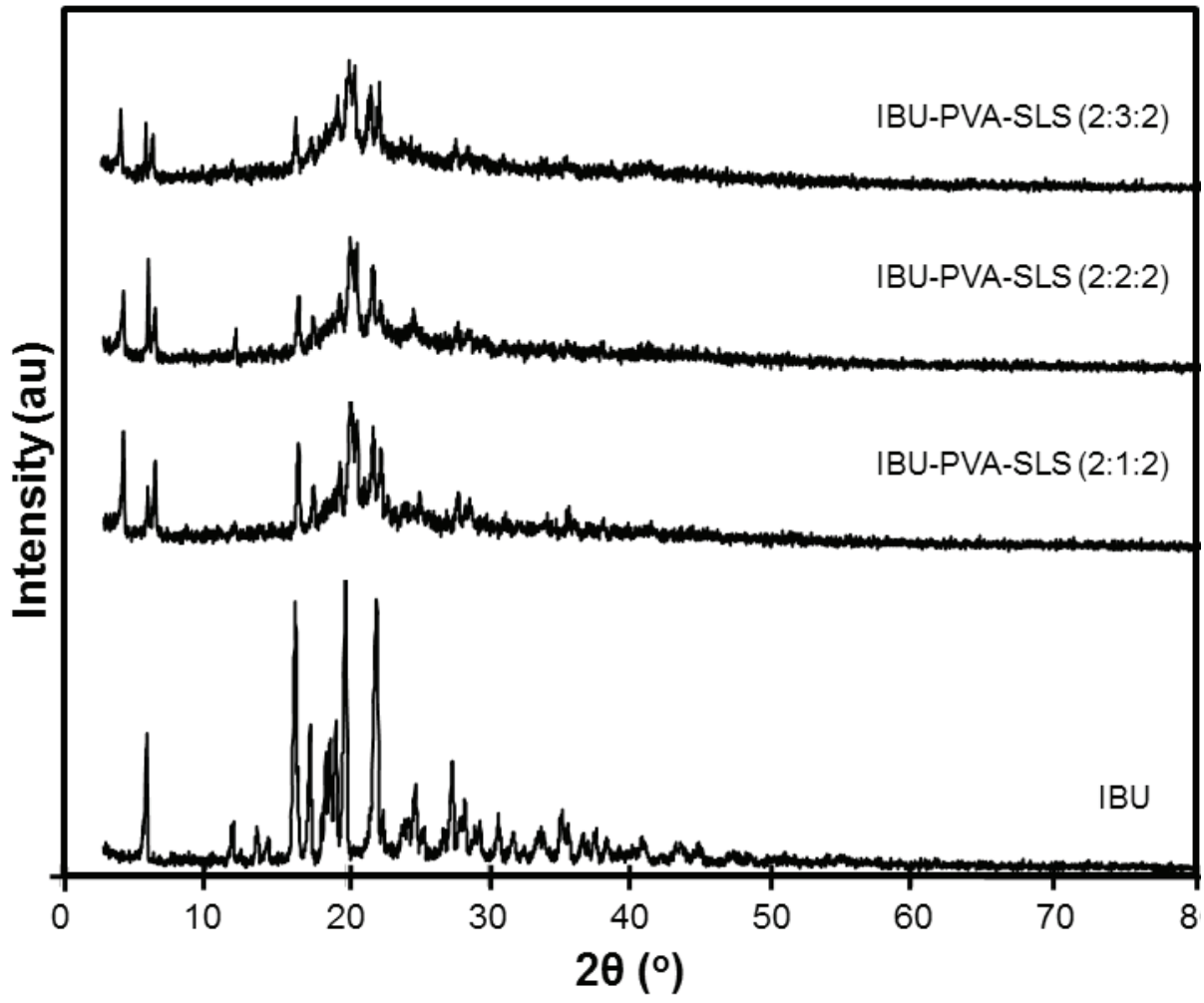

Figure 1. X-ray diffraction pattern of IBU-PVA-SLS 2:1:2, IBU-PVA-SLS 2:2:2, IBU-PVA-SLS 2:3:2, and untreated IBU.

SEM is one of the most common technique to identify structure morphology of particles. Scanning electron micrograph of untreated IBU and IBU-PVA-SLS showed that the major particles were a spherical in shape as shown in Figure 3. It was also observed that particle size decreased when the PVA concentration increased. Table represented the average particles size obtained IBU at different PVA concentration from SEM images. Smallest average particle size received from highest concentration of PVA formed a morphology of large agregate (Figure 3. D) due to high hygroscopic characteristic of PVA. IBU-PVA-SLS (2:3:2) has 6.3-fold smaller than untreated IBU. The SLS surfactant decrease the surface tension of IBU in ethanol-water solution allows IBU well dissolve and atomizer easily generate aerosol for spray drying process yielding smaller particles size [24]. The polymerization without SLS cause improved electrostatic interaction between particles, particles fly in all directions which caused difficulty in handling [33]. SLS alone were not suitable for preparation since they were relatively soft and not free flowing [25]. Thus PVA was utilized as stabilizer to prevent aggregation and smaller particles size are obtained in spray drying process [6].

Based on PSA analysis the particle size of IBU-PVA-SLS was larger when compared with SEM analysis. Because the suspension of the particles in water was done for PSA analysis in which case aggregation takes place between the particles before PSA measurement. This can be reaffirmed from the SEM image and polydispersity index (PI) value. It can also be ascertained that some IBU-PVA-SLS particles get attached to each other to produce large inhomogeneous particles as shown in Fig. 3 with an increase in the PI value.

The zeta potential observation of IBU-PVA-SLS suspensions exhibit a lower zeta potential (+30 to -30 mV) as given in the Table, usually a large aggregate particles in suspension has

Table 1. Particle size, polydispersity index, and zeta potential of untreated IBU and IBU-PVA-SLS

Comparison of IBU:PVA:SLS	Powder		Suspension			
	SEM		PSA			Zeta Potential (mV)
	Particle Size (μm)	Standard Deviation (μm)	Particle Size (μm)	Standard Deviation (μm)	Polydispersity Index	
1:0:0	62.93	25.73	N/A	N/A	N/A	N/A
2:1:2	3.27	1.32	21.06	3.787	4.047	0.09
2:2:2	1.45	0.93	7.40	2.024	2.288	-0.09
2:3:2	1.04	0.84	9.14	2.211	3.008	0.04

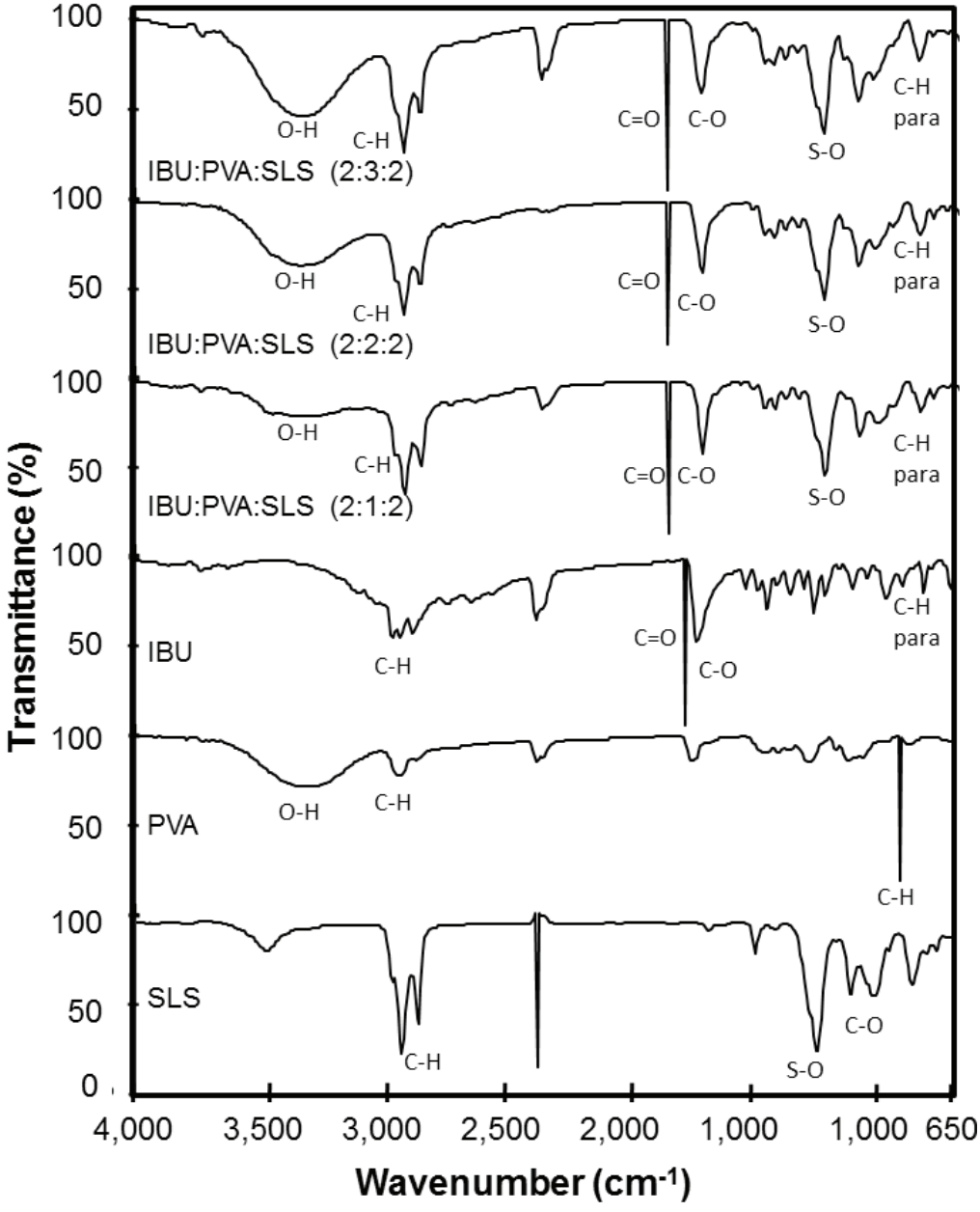

Figure 2. FTIR spectrum of IBU IBU-PVA-SLS 2:1:2, IBU-PVA-SLS 2:2:2, IBU-PVA-SLS 2:3:2, untreated IBU, PVA, and SLS.

low zeta potential. These zeta potential analysis represent a reduced repulsive force among particles causing aggregation [34] and Zeta potential value reveal that IBU-PVA-SLS particles were unstable.

Table also displays polydispersity index. IBU-PVA-SLS particles have a polydispersity index value more than 0.3 indicating wide particle size distribution was received [35] . The wide particle distribution of IBU-PVA-SLS showed the low uniformity of received particles size. Thus ultrasonic spray drying process sucessfully reduced particle size of IBU without any damage of each structure of IBU, PVA, and SLS, but received unstable suspension of IBU in water.

2.2. Solubility Study

Solubility of IBU-PVA-SLS was measured in water using UV-VIS spectrophotometer. Figure 4 present the solubility in water of untreated IBU, IBU-SLS physical mixture, IBU-PVA physical mixture, and IBU-PVA-SLS spray dried.

IBU-PVA-SLS have a higher solubility in water than untreated IBU due to IBU-PVA-SLS exhibit small particle size, low degree of crystallinity, and hydrogen bonding. Decreasing the particle size, leads to higher surface area of reaction so that the solubility in water of IBU-PVA-SLS increased. The change in degree of crystallinity was expected to enhance the solubility in water of IBU-PVA-SLS. Additional PVA in

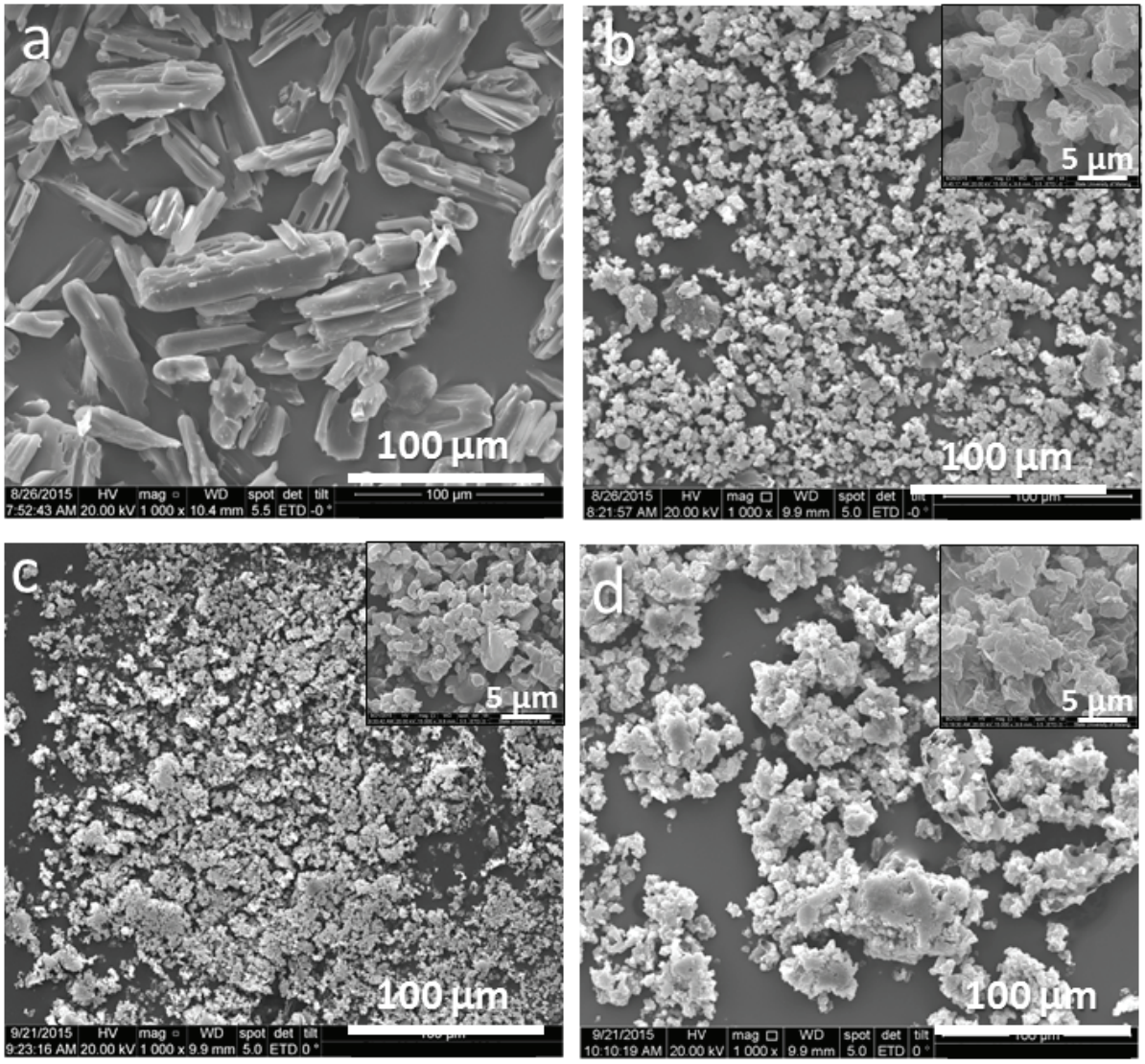

Figure 3. SEM image and corresponding magnification of (a) untreated IBU, (b) IBU-PVA-SLS 2:1:2, (c) IBU-PVA-SLS 2:2:2, (d) IBU-PVA-SLS 2:3:2

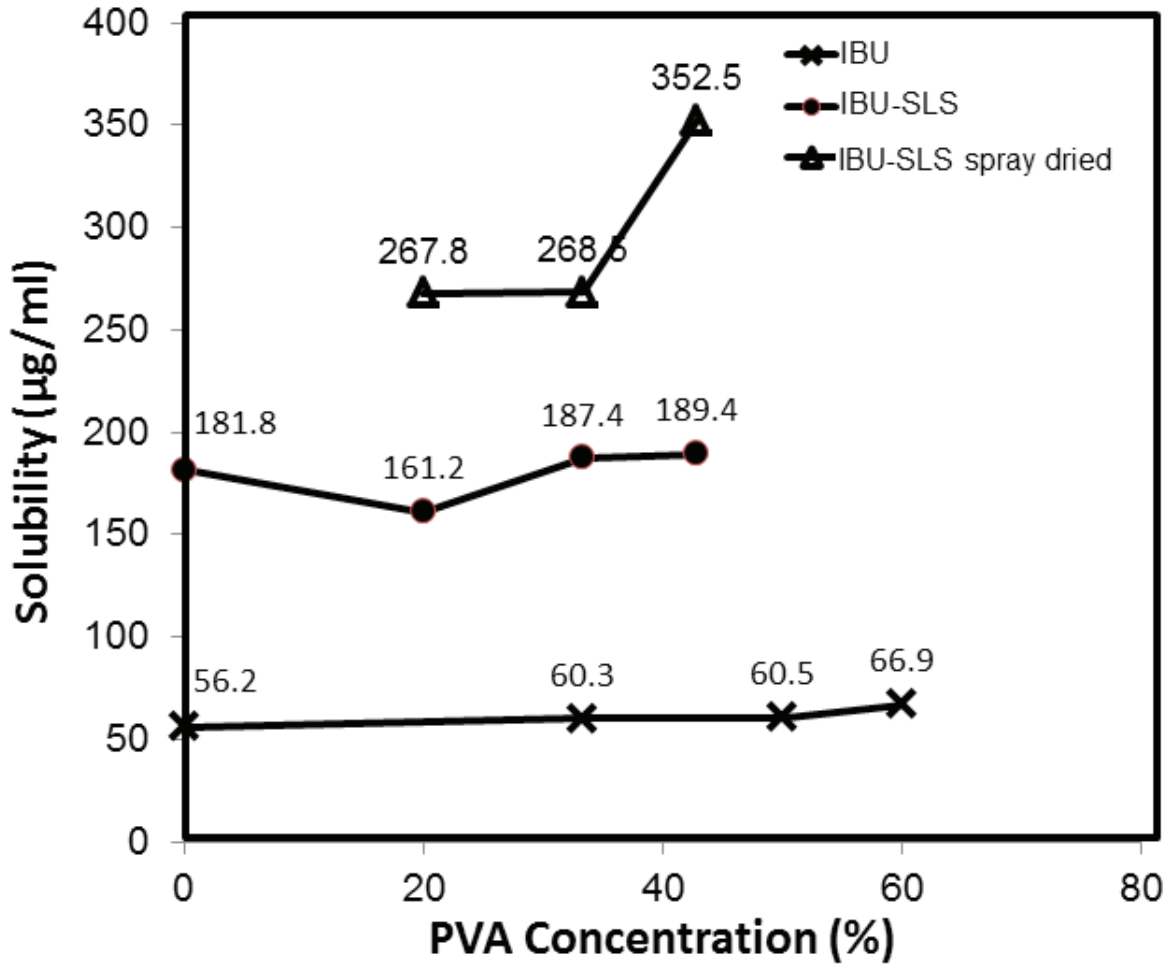

Figure 4. Solubility of IBU, IBU-PVA-SLS Physical Mixture, and IBU-PVA-SLS spray dried

IBU may cause improvement on solubility because PVA is a hydrophilic polymer. Thus it was observed that IBU-PVA-SLS with highest concentrations of PVA had the highest solubility in water. The solubility IBU-PVA-SLS in water increased significantly as displayed in Fig 4 where the increases are 5-, 5-, and 6-fold higher than the solubility of untreated IBU respectively for IBU-PVA-SLS 2:1:2; 2:2:2; 2:3:2.

The solubility of IBU-PVA physical mixture is 19% higher than the solubility of untreated IBU, whereas IBU-SLS physical mixture is 223% higher than the solubility of the untreated IBU. SLS is a surfactant that reduce the surface tension of water so as to facilitate ibuprofen to dissolve in water, whereas PVA only has a function as a water-soluble polymer that helps solubility of IBU in water, but does not have function as a surfactant.

When in a IBU-PVA physical mixture was added by SLS, the solubility of IBU-PVA-SLS was increased to 209% higher than the IBU-PVA physical mixture. The solubility of IBU-PVA-SLS spray dried is 86% higher than IBU-PVA-SLS physical mixture.

Ratio of surface area and volume of IBU-PVA-SLS spray dried is greater because the particle size of it is smaller than the untreated IBU. The surface area of large particles causes large surface of particle to contact with water. Crystallinity of IBU-PVA-SLS spray dried is lower than untreated IBU. Particles which has low crystallinity shows the irreguler arrangement of atoms in the particle, causing the particles more easily to react. The spray drying process produces particles that form hydrogen bonds. Hydrogen bonding between the IBU and PVA is indicated by the shift of C=O to a higher wavenumber. Smaller particle size, decreased crystallinity, and hydrogen formed cause IBU-PVA-SLS spray dried more soluble in water than the untreated IBU.

2.3. Dissolution Study

Based on guidance for industry, waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system - FDA, immediate release drug product is considered using *U.S. Pharmacopeia* (USP) Apparatus II (paddle) at 50 rpm in a volume of 900 ml or less in each of the following media 0.1 N HCl. The dissolution study used 0.1 N HCl in accordance with the simulated gastric fluid without enzymes. The temperature used in the dissolution study was 37±0.5 °C in accordance with the temperature of the human body. The dissolution profiles of untreated IBU and IBU-PVA-SLS are illustrated in Figure 5. It was observed that dissolution rate of IBU-PVA-SLS increased markedly from untreated IBU. After 30 min of dissolution, the released IBU-PVA-SLS (2:1:2; 2:2:2; 2:3:2) were 2.3-, 2.2-, and 2.1- fold higher than that of untreated IBU. Meanwhile, after 10 min of dissolution, the released IBU-PVA-SLS (2:1:2; 2:2:2; 2:3:2) were 4.05-, 4.32-, and 3.57- fold higher than that of untreated IBU, respectively.

The apparent dissolution rate constants (Kp) for different systems were shown in Figure 6. The PVA concentration determine the dissolution of IBU-PVA-SLS, lower PVA concentration increase the dissolution rate. Thus smaller particles size of the particles did not guaranty improve the dissolution rate; indeed the present of PVA was responsible for the increase of dissolution rate. In addition, the results indicated that the dissolutions rate of IBU-PVA-SLS were improved markedly from untreated IBU may due to low degree of crystallinity and the existence of hydrogen bonding, as confirmed in XRD pattern and shifted peak at wavenumber 1712.79-1713.40 cm^{-1}, respectively

The highest dissolution of IBU-PVA-SLS spray dried in HCl medium is the particles that containing the lowest PVA concentration (IBU-PVA-SLS with a ratio of 2:1:2). This is caused PVA less soluble in organic solvents such as HCl medium. The greater surface area to volume ratio of IBU-PVA-SLS spray dried particle because the smaller particle size. Similarly to solubility, smaller particle size, and lower crystallinity causes IBU-PVA-SLS dissolved higher than the untreated IBU.

Sampling during the dissolution process were using a filter to prevent the particles that have not yet fully dissolved are taken. Clogging of filters when sampling can affect The accumulative IBU release by time. So, at some time points the accumulative IBU release was decreased.

The use of PVA and SLS in preparation of IBU by spray drying is potential to improve solubility in water and dissolution in HCl 0.1 N. Therefore the selected water-soluble polymer and surfactant in preparing IBU by spray drying permits the formulation of dosage form and drug delivery system in gastric fluid.

3. Conclusion

The dissolution of IBU-PVA-SLS is significantly increase in gastric fluid, either due to smaller particles size or PVA-SLS. Despite the PVA and SLS determine the particles formation

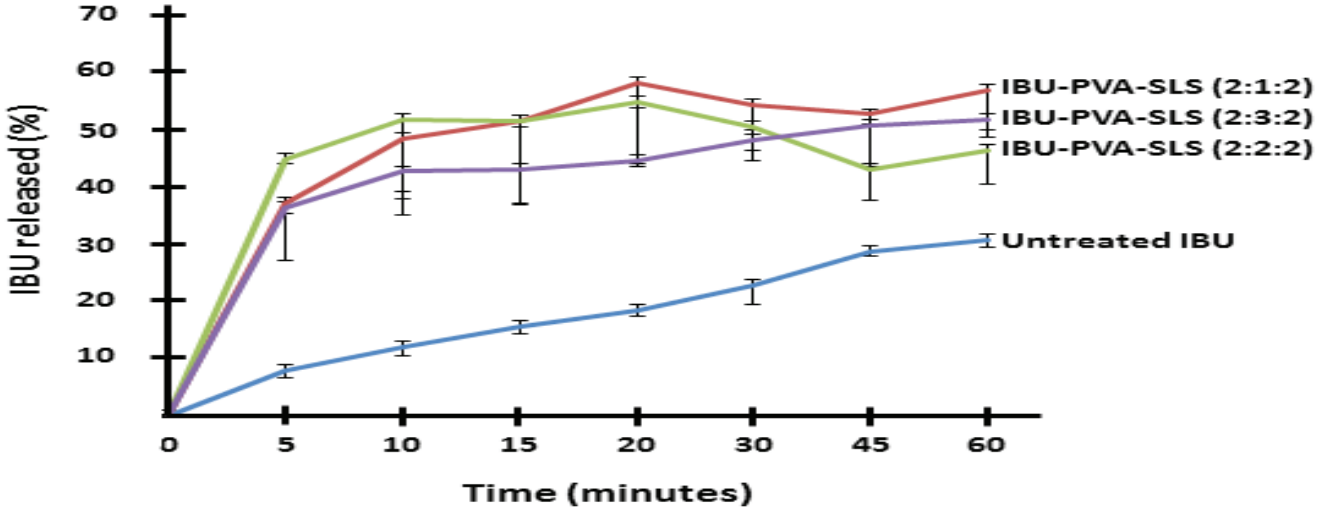

Figure 5. Dissolution profile of untreated IBU and IBU-PVA-SLS in 0.1 N HCl medium

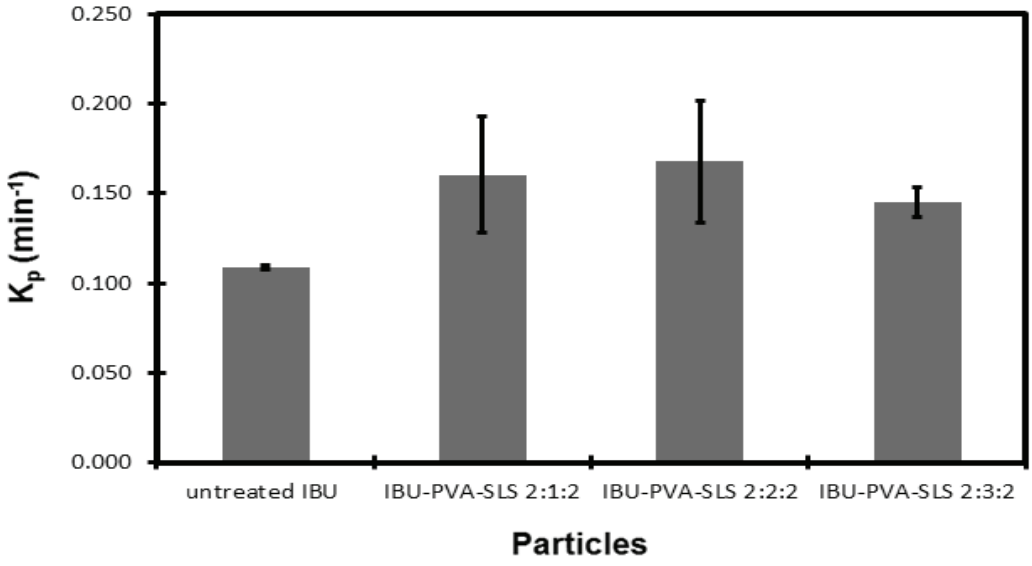

Figure 6. The apparent dissolution rate constant (Kp) for untreated IBU, IBU-PVA-SLS 2:1:2, IBU-PVA-SLS 2:2:2, and IBU-PVA-SLS 2:3:2

during polymerization yielding smaller particle size, they also responsible for effective drug delivery system. It was concluded that the selected water-soluble polymer (PVA) and surfactant (SLS) for IBU in ultrasonic spray drying technique successfully reduces the particle size of IBU and effectively enhances the solubility and dissolution rate of poorly water-soluble IBU in 0.1 N HCl (gastric fluid).

4. Materials and Methods

4.1. Materials

Ibuprofen BP/Ph. Eur (S250 Grade) were purchased from Shasun Pharmaceutical Ltd, India. Polyvinyl alcohol (PVA) were purchased from Shanghai Kaidu Industrial Development Co., Ltd, Shanghaim China, Sodium lauryl sulphate (SLS) were purchased from Changge Newborui Fine Chemical Facrori Co. Ltd, Henan, China.

4.2. Preparation of IBU-PVA-SLS solution

Ibuprofen BP/Ph. Eur (S250 Grade) (Shasun Pharmaceutical Ltd, India), polyvinyl alcohol (PVA), sodium lauryl sulphate (SLS) were used as source material. IBU and SLS (1:1) was dissolved in ethanol. PVA aqueous solution was added to IBU-SLS solution to obtain IBU-PVA-SLS clear solution. The weight ratio of component in the mixture IBU:PVA:SLS was 2:1:2. The weight ratio of component in the cosolvent system ethanol:water was 9:1. In order to investigate the effect of PVA on the solubility and dissolution of particle, the concentration of PVA was varied.

4.3. Ultrasonic Spray Drying Process

A spray drier was used for preparation of IBU-PVA-SLS particles. The clear solution of IBU-PVA-SLS was atomized by ultrasonic nebulizer (Corona Model: GL-899). Nebula of IBU-PVA-SLS was delivered at flow rate of air as carrier gas of 5L/min and thereafter spray-dried at inlet temperature of 70°C and at outlet temperature of 50°C. The obtained particles were collected in electrostatic precipitator (ESP) by voltage of 15 kV and at temperature of 50°C.

4.4. Characterization of Particle

Untreated IBU and IBU-PVA-SLS particles were characterized by means of x-ray diffractometry (XRD) Shimadzu 4.5 to characterize crystallinity of particle, fourier transform infrared spectroscopy (FT-IR) Thermo Scientific Nicolet iS5 spectrophotometer to characterize functional groups, and scanning electron microscopy (SEM) Phenom FEI to characterize surface morphology. IBU-PVA-SLS particles were also characterized by means of Nano C Particle Analyzer, Beckman Coulter to characterize polydispersity index and zeta potential.

4.5. Solubility and Dissolution Study

4.5.1. Solubility in water

IBU and IBU-PVA-SLS (equivalent to 80 mg of IBU) were added to 50 ml of water, shaken at speed of 400 rpm for 24 hours at temperature of 25±0.5°C. The sample was filtered through a 0.45 µm membrane filter then analyzed by UV-VIS spectrophotometer Analytic Jena at a wavelength of 221 nm.

4.5.2. Dissolution study

IBU and IBU-PVA-SLS (equivalent to 50 mg of IBU) were tested using dissolution tester Flight RC-3. Dissolution test was performed at 37±0.5 °C using the paddle method at 50 rpm with 900 ml 0.1 N HCl as a dissolution medium. At predetermined intervals, 5 ml of the medium was sampled and filtered. This sample then analyzed by uv-vis spectrophotometer at a wavelength of 221 nm. Similar volume (5 ml) of fresh medium was added into dissolution flask.

The apparent dissolution rate constant (Kp) was calculated by following equation:

$$\left(\frac{M}{Mo}\right)^{-\frac{2}{3}} = Kp.t \quad (1)$$

where Mo is the drug weight in samples (mg), M is the weight of undissolved drug (mg), Kp is the apparent dissolution rate constant (min^{-1}), and t is the dissolution time (min).

Acknowledgements

This research was supported by Nanotechnology Research Center, Universitas Padjadjaran and Endowment Fund for Education (LPDP) of Republic of Indonesia.

Authorship statement

Author contributions: Concept – R.R., C.P., T.R.; Design – C.P., I.M.J., T.R.; Supervision – R.R., C.P., I.M.J., T.R.; Resource – R.R., C.P., T.R.; Materials – R.R.; Data Collection and/or Processing - R.R., C.P., I.M.J., T.R.; Analysis and/or Interpretation - R.R., C.P., I.M.J., M.A., T.R.; Literature Search – R.R.; Writing – R.R., C.P., I.M.J., T.R.; Critical Reviews – C.P., I.M.J., M.A., T.R.

Conflict of interest statement

The authors declared no conflict of interest

References

1. Xu L, Li, S.M, Sunada, H. Preparation and evaluation of ibuprofen solid dispersion systems with kollidon particles using a pulse combustion dryer system. Chem Pharm Bull 2007;55:1545–50.
2. Rashid A, White ET, Howes T, Litster JD, Marziano I. Growth rates of ibuprofen crystals grown from ethanol. Proc Chemeca, Flash Drive, Adelaide, 2010.
3. Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. Int J Pharm 2011;420:1–10.
4. Wong SM, Kellaway IW, Murdan S. Enhancement of the dissolution rate and oral absorption of a poorly water soluble drug by formation of surfactant-containing microparticles. Int J Pharm 2006;317:61–8.
5. Macarron R. Critical review of the role of HTS in drug discovery. Drug Discov Today 2006;11:277–9.
6. Mauludin R, Müller RH. Physicochemical properties of hesperidin nanocrystal. Int J Pharm Pharm Sci 2013;5:954-60.
7. Siswandi S, Rusdiana T, Levita J. Virtual screening of co-formers for ketoprofen co-crystallization and the molecular properties of the co-crystal. J App Pharm Sci 2015;5:78-82.
8. Kesisoglou F, Panmai S, Wu Y. Nanosizing-oral formulation development and biopharmaceutical evaluation. Adv Drug Deliv Rev 2007;59:631–44.
9. Woo JS, Piao MG, Li DX, Ryu DS, Choi JY, Kim JA, Kim JH, Jin SG, Kim DD, Lyoo WS, Yong CS, Choi HG. Development of cyclosporin A-loaded hyaluronic microsphere with enhanced oral bioavailability. Int J Pharm 2007;345:134–41.
10. Re MI. Formulating drug delivery systems by spray drying. Drying Technol 2006;24:433–46.
11. Vehring R. Pharmaceutical particle engineering via spray drying. Pharm Res 2008;25:999–1022.
12. Heng D, Lee SH, Nga WK, Tan RB. The nano spray dryer B-90. Expert Opin Drug Deliv 2011;8:965–72.
13. Fontana MC, Durli TL, Pohlmann AR, Guterres SS, Beck RCR. Polymeric controlled release inhalable powder produced by vibrational spray-drying: One-step preparation and *in vitro* lung deposition. Powder Technol 2014;258:49–59.
14. Draheim C, De Crécy F, Hansen S, Collnot EM, Lehr CM. A design of experiment study of nanoprecipitation and nano spray drying as processes to prepare PLGA nano- and microparticles with defined sizes and size distributions. Pharm Res 2015;32:2609-24.
15. Kim JS, Kim MS, Park HJ, Jin SJ, Lee S, Hwang SJ. Physicochemical properties and oral bioavailability of amorphous atorvastatin hemi-calcium using spray-drying and SAS process. Int J Pharm 2008;359:211–9.
16. Chow AH, Tong HH, Chattopadhyay P, Shekunov BY. Particle engineering for pulmonary drug delivery. Pharm Res 2007;24:411-37.
17. Buttini F, Colombo P, Rossi A, Sonvico F, Colombo G. Particles and powders: Tools of innovation for noninvasive drug administration. J Control Release 2012;161:693-702.
18. Belotti S, Rossi A, Colombo P, Bettini R, Rekkas D, Politis S, Colombo G, Balducci AG, Buttini F. Spray dried amikacin

sulphate powder for inhalation in cystic fibrosis patients: The role of ethanol in particle formation. Eur J Pharm Biopharm 2015;93:165-72.

19. Pyo SH, Cho JS, Choi HJ, Han BH. Preparation and dissolution profiles of the amorphous, dihydrated crystalline, and anhydrous crystalline forms of paclitaxel. Dry Technol 2007;25:1759–67.
20. Puri V, Dantuluri AK, Kumar M, Karar N, Bansal AK. Wettability and surface chemistry of crystalline and amorphous forms of a poorly water soluble drug. Eur J Pharm Sci 2010;40:84–93.
21. Hen S, Nga WK, Chia L, Hu J, Tan RB. Physical state and dissolution of ibuprofen formulated by co-spray drying with mesoporous silica: effect of pore and particle size. Int J Pharm 2011;410:188–95.
22. Duret C, Wauthoz N, Sebti T, Vanderbist F, Amighi K. New respirable and fast dissolving itraconazole dry powder composition for the treatment of invasive pulmonary aspergillosis. Pharm Res 2012;29:2845–59.
23. Bianco S, Caron V, Tajber L, Corrigan OI, Nolan L, Hu Y, Healy AM. Modification of the solid-state nature of sulfathiazole and sulfathiazole sodium by spray drying. AAPS Pharm Sci Tech 2012;13:647–60.
24. Li DX, Oh YK, Lim SJ, Kim JO, Yang HJ, Sung JH, Yong CS, Choi HG. Novel gelatin microcapsule with bioavailability enhancement of ibuprofen using spray-drying technique. Int J Pharm 2008;355:277–84.
25. Lee EJ, Lee SW, Choi HG, Kim CK. Bioavailability of cyclosporin A dispersed in sodium lauryl sulphate–dextrin based solid microspheres. Int J Pharm 2001;218:125–31.
26. Panatarani C, Lenggoro IW, Okuyama K. The crystallinity and the photoluminescent properties of spray pyrolized ZnO phosphor containing Eu^{2+} and Eu^{3+} ions. J Phys Chem Solids 2004;65:1843-7.
27. Pasquali I, Bettini R, Giordano F. Solid-state chemistry and particle engineering with supercritical fluids in pharmaceutics. Eur J Pharm Sci 2006;27:299–310.
28. Panatarani C, Lenggoro IW, Okuyama K. Synthesis of single crystalline ZnO nanoparticles bysalt-assisted spray pyrolysis. J Nano Res 2003;5:47-53.
29. Alver U, Kılınç T, Bacaksız E, Küçükömeroğlu T, Nezir S, Mutlu IH, Aslan F. Synthesis and characterization of spray pyrolysis zinc oxide microrods. Thin Solid Films 2007;515:3448–51.
30. Joni IM, Panatarani C, Hidayat D, Setianto, Wibawa BW, Rianto A, Thamrin H. Synthesis and dispersion of nanoparticles, and Indonesian graphite processing. AIP Conf Proc 2013;1554:20-6.
31. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. J Pharm Sci 1997;86:1-12.
32. Supratman, U. Spektrometri Inframerah. In: Elusidasi struktur senyawa organik. Vol 1, First ed. Widya Padjadjaran, Bandung, 2010, pp. 66-106.
33. Elkordy AA, Essa EA. Effects of Spray Drying and Spray Chilling on Ibuprofen Dissolution. Iranian J Pharm Sci 2010;6:3-12.
34. Mohanraj VJ, Chen Y. Nanoparticles-a review. Trop J Pharm Res. 2006;5(1):561-573.
35. Yen F, Wu T, Tzeng C, Lin L, Lin C. Curcumin nanoparticle improve the physicochemical properties of curcumin and effectively enhance its antioxidant and antihepatoma activities. J Agric Food Chem 2010;58:7376-82.