The Application of β-Cyclodextrin and Polyethylene Glycol 6000 in The Micronisation of Drug – Polymer Composite With Particle From Gas Saturated Solutions (PGSS) Method

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Abstract :

Particle design is presently a major development of supercritical fluida applications, mainly in the pharmaceutical and speciality chemical industries. Micronisation technology provides more possibilities to deliver drug in human body either through gastrointestinal track. That experiment has a purpose to create drug-polymer microparticle composite with Particles from Gas-Saturated Solutions (PGSS) technology. Different pressures (80-200 bar) and polymers (PEG 6000 and β cyclodextrin) were applied to get microparticle with narrow size distribution, discrit morphology and fast drug release profile. Ketoprofen-PEG 6000 and ketoprofen-β cyclodextrin was saturated with supercritical fluid in saturated vessel and the liquified time was 2 hours, then depressured the solution pass through nozzle as microparticles. The composite's morphology is various by the effect of saturation pressure and type of polymer which used. Microparticle morphology indicate that higher saturation pressure create irregular microparticle product and on the contrary lower saturation pressure create sphere microparticle product. The average diameter of the particles obtained by PGSS at different conditions was about 0.83-7.74 µm and release profile of composite Ketoprofen-PEG 6000 was faster than ketoprofen-β cyclodextrin.

Keywords: drug release, microparticle,PGSS, and supercritical fluid

1. Introduction

A well suitable way to improve the bioavailibility is the reduction of particle size to increase the dissolution velocity. In the pharmaceutical industry, several conventional techniques (milling and grinding, spray-drying, freeze-drying) have been utilized for particle size reduction. The disadvantages of usingthese techniques are thermal and chemical degradation of the product, aboard particle size distribution, and cumbersome solids handling. Therefore, different supercritical fluid (SCF) based micronisation process have been applied to overcome these problem. Such processes can take advantage of the specific properties of SCFs such as a liquid like densities, and viscosities and diffusivities lying between dlute gas at ambient conditions, SCF based processes can offer a solvent free final product **[1]**.

Drug is generally a compound intended to treat disease or to overcome the body's physiological abnormalities. It is expected that disease healed after a drug taken for some time. Ketoprofen was one of *non-steroidal anti-inflammatory drug* (NSAID) commonly used today that has good analgesic properties, but possess a poor water solubility (0,13 mg/mL at 25^{o}C). Performance of drug delivery in the human body is determined by the ability to deliver therapeutic agents (healer) to illness location. Production drug in micron scale was the one of the most popular ways to improve the therapeutic effects. Micronisation technology provides more possibilities to deliver drug in human body either through gastrointestinal track. In the drug delivery system, the particle size, morphology and drug release profile of the drug particle are the most important thing to be controlled. It can be the parameter to ensure optimum amount of therapeutic agents delivered to human body. A controlled drug release can be obtained by using polymers as drug delivery. Controlled drug release generally formulated from drug-polymer composites in which the active pharmaceutical ingredients (API) is distributed in the polymer matrix and resulting microspheres or micro particles **[2-5]**.

In the Particle From Gas Saturated Solutions (PGSS) technique, the SCF is dissolved in a solute matrix resulting in viscosity reduction and melting point depression of the solute. A gas-saturated is thus formed as the gas concentration in the molten solute increases with increasing pressure. The gas-saturated solution is then expanded through a capillary nozzle to induce the particle precipitation. The molten solute precipitates out of the gas-saturated solution as fine particles due tothe high level of supersaturation. The PGSS technique has been

demonstrated as one ofthe SCF-based microencapsulation process to produce thermally sensitive polymer composites containing active materials **[5,6]**.

The aim of this study is to create drug-polymer microparticle composite with Particles from Gas-Saturated Solutions (PGSS) technology. The PGSS process have been successfully used to obtain drug-polymer composites, which comprise an active compound (drug) loaded into a matrix of a carrier material (polymer), in order to improve product preservation as well as controlling the dissolution rate of the active compound.

2. Material and Methods

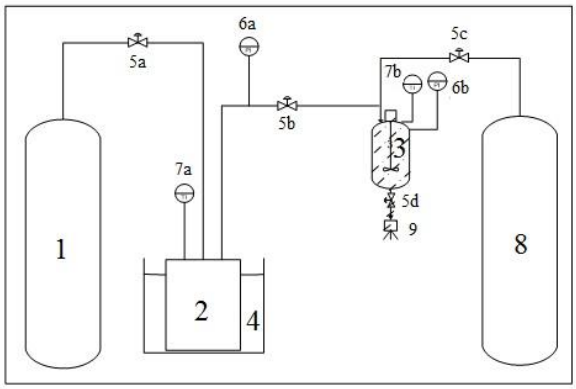


Figure 1. Schematic Diagram of Microparticle Drug-Polymer Formation. (1) CO_2 storage, (2) Gas supply, (3) Saturation vessel, (4) Water bath, (5) Valve, (6) Pressure Indicator, (7) Temperature Indicator, (8) N_2 storage, (9) Nozzle

2.1. Material

Ketoprofen with purity of 99,85% kindly donated by PT. Kimia Farma (Indonesia). Polyethylene Glycol 6000 was purchased from *Merck* (Indonesia). β-Cyclodextrin was purchased from Roquette (France). CO_2 and N_2 with purities 99% were purchased from PT. Tri Gases (Indonesia).

2.2. SC-CO_2 Production

The process flow diagram of the PGSS equipment used to produce drug-polymer composite is shown in Fig. 1. All of the valve were closed except valve 5a in order that CO_2 were flow into gas supply. Fill the chamber with ice and mix salt into the water until the temperature reached ± 0 ° C. This condition was maintained for about 2 hours. And then close valve 5a, and replaced the cold water in the chamber with hot water until temperature reached 70-80° C or pressure (PI 6a) through the CO_2 critical pressure (73.83 bar), so that the supercritical fluid is formed.

2.3. Particle Formation

Drug and polymer were weighted for about 3 gr with composition 1:3 (%w/w). Then put it into saturation vessel. Drug-polymer sample (3 gr) was loaded into the 0.5 L saturation vessel. Valve 5b were opened to fill supercritical fluid in vessel until the variable pressure achieved according to the pressure indicator (PI 6b), then close the valve 5b. Liquidified mixtures by supercritical CO_2 for 2 hours until the solution became homogen. After that open valve 5c and 5d simultaneously, then solution is expanded through a nozzle. The resulting product was collected on the bottom of the nozzle.

2.4. Analysis of Particle by Scanning Electron Microscopy (SEM)

Sample of drug-polymer composites were observed by *Scanning Electron Microscopy* (EVO MA 10, Carl Zeiss, Jerman). The SEM samples were covered with gold using a sputter coater (Emitech, Dubai). This analysis was conducted to determine the morphology of the resulting composite microparticles and the dispersion pattern of particles produced.

2.5. Analysis of Particle Size by Particle Size Analyzer (PSA)

The size distribution of the composite powder was measured by particle size analyzer (Zetasizer ZS90, Malvern, United Kingdom). The result from the analysis is the size distribution by number of particles in the range of size classes. From particle size analysis can be determined the diameter and size distribution of composite microparticles.

2.6. Drug Release Analysis by Spectrophotometer UV-Vis

Analysis of drug release is used to determine the performance of drug delivery in drug-polymer composites. Analyzes were performed by using UV-Vis spectrometer (Genesys 10uV scanning, Thermo Scientific, United States).

3. Result and Discussion

3.1. Characterization of Particle's Morphology

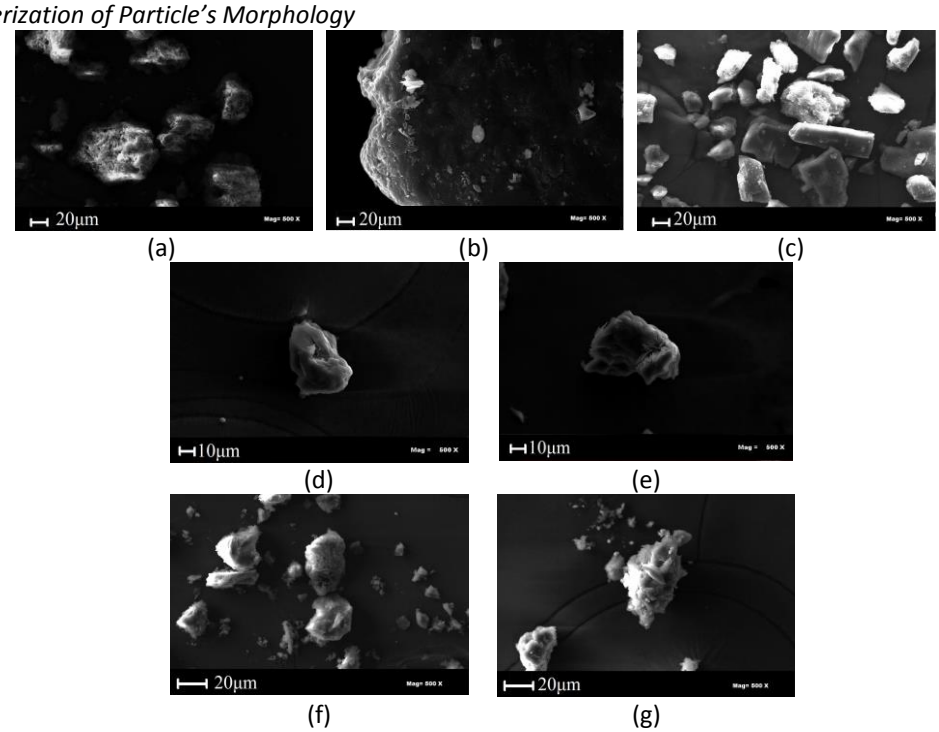
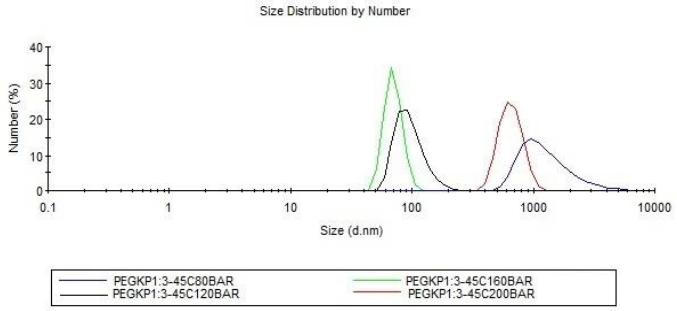


Figure 2. SEM analysis result : (a) Ketoprofen unprocess, (b) PEG unprocess, (c) β – *Cyclodextrin* unprocessed; (d)Ketoprofen-PEG 6000 composite (45°C; 80 bar); (e) Ketoprofen-PEG 6000 composite (45°C ;160 bar); (f) Ketoprofen-β Cyclodextrin composite (45˚C; 80 bar); (g) Ketoprofen-β Cyclodextrin composite (45˚C; 160 bar)

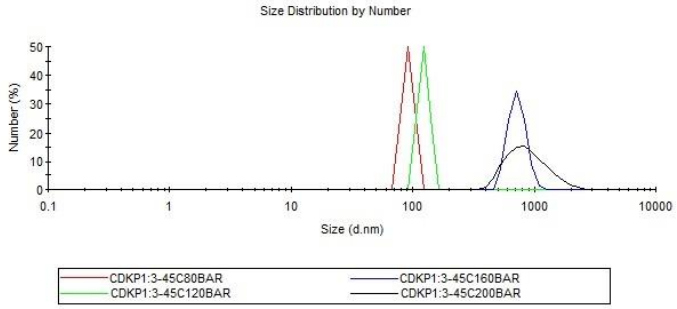
Figure 2 (a,b,c) is SEM image results for each of the unprocessed material. The image shows the irregular shape of the three materials**.** These materials are used in this study is to be formed into a drug-polymer composites. Formation of drug-polymer micro particles can be done by using PGSS technology as seen in Figure 2 (d, e, f, g). Figure 2 (d, 3) shows the shape of ketoprofen-PEG 6000 composite and Figure 2 (f, g) shows the shape of Ketoprofen-β Cyclodextrin composite. Visible morphological changes experienced by both the composite when compared to the pure form of the materials used**.** Both of images are compared to know the composite morphology, Ketoprofen-PEG 6000 composite is more like a single particle as compared with Ketoprofen-β Cyclodextrin composite. This is due to the supercritical CO_2 dissolved in the PEG 6000, so the melting temperature of PEG 6000 are went down which led the superc`ritical CO_2 to fill matrix of PEG 6000 in large numbers. The bonds between the polymer chains apart and it becomes easy to move and melt. Therefore, the drug can be distributed homogeneously in the polymer matrix . But this does not happen on a system using β-Cyclodextrin.

Table 1. Average diameter (µm) of drug-polymer composite at 45 °C

Composition of drug:polymer	Pressure (bar)			
	80	120	160	200
Ketoprofen : PEG 6000 (1:3)	1,836	4,793	5,172	0,958
Ketoprofen : β Cyclodextrin (1:3)	7,741	6,307	1,829	1,054



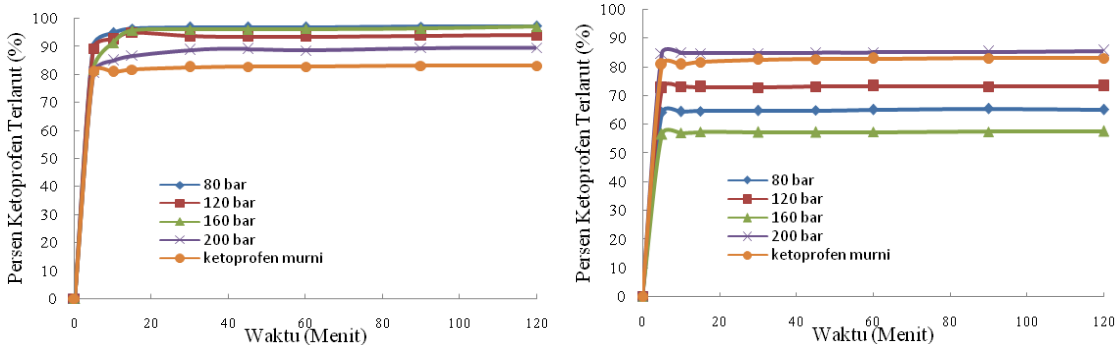
(a)



(b)

Figure 3. Size distribution of (a) Ketoprofen–PEG 6000 composite (b) Ketoprofen–β Cyclodextrin composite

From Table 1, shown that average diameter of Ketoprofen-PEG 6000 composite are smaller than Ketoprofen-β Cyclodextrin composite. The average diameter size of Ketoprofen-PEG 6000 composites ranged between 0.958-5.172 µm and 1.054-7.741 µm for Ketoprofen-β Cyclodextrin composites. From size distribution result analysis (Figure 3), Ketoprofen-PEG 6000 composites narrowest size distribution on pressure 160 bar, and for Ketoprofen-β Cyclodextrin composites at a pressure 80 bar.



(a) (b)

Figure 4. Drug release profile of (a) Ketoprofen-PEG 6000 composite (b) Ketoprofen- β Cyclodextrin composite

Drug release conducted to determine how fast the drug can be dissolved in the dissolution medium. Figure 4(a) shows a graph of the relationship between time versus release rate of ketoprofen from ketoprofen-PEG 6000 composites, dissolution rate of ketoprofen in ketoprofen-PEG 6000 composites is faster than pure ketoprofen (unprocessed). It causes the presence of PEG 6000 as an active ingredient increases the dissolution rate of drug. In addition, the use of supercritical CO_2 in this study could lead to drugs to fill the polymer's matrix. Figure 4(b) shows a graph of ketoprofen's release profile from the ketoprofen-β Cyclodextrin composites. Dissolution rate of ketoprofen in the ketoprofen-β Cyclodextrin composites were slower than the dissolution rate of pure ketoprofen (unprocessed). Dissolution rate is also influenced by physical and chemical properties of the component. Because the process condition on this experiment can't decrease the melting point of β Cyclodextrin so the formation of composite can't be perfect.

4. Conclusion

Drug-polymer composites can be produced using PGSS methods. Interaction between drug and polymer gives different drug perform from the pure drug component. Ketoprofen-PEG 6000 composites produces more discrete particle morphology than composite Ketoprofen- β Cyclodextrin because composite Ketoprofen- β Cyclodextrin are still agglomerated. Release profile of Ketoprofen-PEG 6000 composite better than Ketoprofen- β Cyclodextrin due to fast release ketoprofen in human body.

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