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Research Article

Physical Characterization and Dissolution Study of Pentagamavunon-0 Loaded Self Nano-Emulsifying Drug Delivery System

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ABSTRACT

The recent work focuses on the physical characterization and dissolution study of PGV-0 loaded self-nanoemulsifying drug delivery system (SNEDDS). The PGV-0 SNEDDS was prepared by spontaneous emulsification method using oleic acid, tween 20:labrasol (1:1) and polyethylene glycol 400. The zeta potential of the PGV-0 SNEDDS was -34.4±7.66 mv. The nanoemulsion of PGV-0 SNEDDS was thermodynamically stable with forming droplet oil containing PGV-0 in it and spherical. The dissolution result showed that the dissolution profile of SNEDDS PGV-0 was dissimilar with the PGV-0 powder in AGF and AIF. The PGV-0 SNEDDS was able to increase the dissolution significantly ($p < 0.05$) compared with PGV-0 powder of 44.13% in AGF medium and 30.37% in AIF medium. It is concluded that SNEDDS formulation was able to improve the dissolution profile of PGV-0.

Keywords: PGV-0 SNEDDS, characterization, dissolution

INTRODUCTION

Administration of an antiinflammatory agent is very commonly used for a variety of inflammatory conditions and diseases. One of the potent antiinflammatory drug candidates is pentagamavunon-0. Unlike the NSAIDs that are known to have an irritating effect on the stomach, PGV-0 is safe for the stomach (Wahyuni, 1999).

PGV-0 is highly soluble in DMSO, easily soluble in 0.01-0.1N NaOH, poorly soluble in ethyl acetate, methanol and ethanol, and practically insoluble in water with a solubility of 7.04 x 10^{-7} M, n-hexane, carbon tetrachloride, benzene, toluene and diethyl ether (Soediman, 2003; Yuwono and Oetari, 2005). The molecular weight of PGV-0 is 352.13 (Nugroho *et al.,* 2009). PGV-0 is unstable in aqueous solution, its shelf life is only 45.3 hours, a half-life of 299 hours and its activation energy is 14.2 kcal mol-1 (Yuwono and Oetari, 2005). The molecular weight of PGV-0 is 352.13 (Nugroho *et al.,* 2009). PGV-0 is unstable in aqueous solution, its shelf life is only 45.3 hours, half-life of 299h. PGV-0 has a log value of permeability (log P) 1.84 (Yuwono and Oetari, 2005). According to Wahyuningsih, the apparent permeability constant (P_{app}) value of PGV-0 obtained from the in situ absorption test is 1.91x 10^{-4}cm/sec (Wahyuningsih, 2003), which means that PGV-0 has a high permeability (>10^{-5} cm/sec). Although it has a high permeability value, so it is easily absorbed orally, but its bioavailability is low. This is due to its low solubility in water and its high metabolism (Hakim *et al.,* 2006). PGV-0 undergoes glucuronidation and sulfation in vitro, whereas in vivo, the above two reactions only occur in the PGV-0 metabolite which still has a hydroxyl group (Sugiyanto *et al.,* 2005).

Poor dissolution is a prime determinant of the rate and extent of drug absorption. Hence, to improve the dissolution of PGV-0, a novel formulation technology called self nano-emulsifying drug delivery system (SNEDDS) was applied to PGV-0. In this regard, PGV-0 is dissolved in a nano-sized droplet of oil in the gastrointestinal tract so that the interface area in contact with gastrointestinal fluid and membranes is increased. Oil droplets containing PGV-0 as lipophilic drugs can be transported through the lymphatic system

which bypasses the liver to avoid first pass metabolism (Kohli, *et al.,* 2010). Along with the ability of the surfactant to modify the absorption of the gastrointestinal membrane in a reversible manner so that the membrane becomes more permeable (Bruesewit, *et al.*, 2007), these three result in an increase in the amount of absorbed and available drugs in the blood.

Bringing forward with the part one of the present studies, that particularly deals with the formulation development and optimization, part two demonstrates the physical characteristics and dissolution performance of the developed formulation. The characteristics of SNEDDS was assessed for the morphological and droplet size, the zeta potential and the physical stability of the nanoemulsion.

MATERIALS AND METHODS

The material used in this study was PGV-0 from Curcumin Research Center UGM. The excipients purchased from Bratachem were the oils (oleic acid, VCO, soybean oil, olive oil), surfactants (tween 20, span 80, and tween 80) and cosurfactants (PEG 400). Labrafil and labrafac as oils, labrasol (surfactant), and transcutol (cosurfactant) were kindly provided by Gattefosse (France) via PT Mensa Group (Jakarta). Myritol (oil) and kolliphor (surfactant) were purchased from PT BASF Indonesia (Jakarta). All excipients were pharmaceutical grade. Liquid chromatography grade of methanol and hydrochloric acid was purchased from Merck. Magnesium chloride, calcium chloride, potassium chloride, sodium chloride, sodium hydrogen chloride, all the reagents were pro analysis grade, were obtained from Laboratorium Penelitian dan Pengujian Terpadu (LPPT) UGM.

Excipients selection for SNEDDS formulation

The excipients selection for the PGV-0 SNEDDS formulation was reported by Astuti (2017). Briefly, the excipients were selected based on the ability to dissolve PGV-0 and self-nanoemulsifying properties. The PGV-0 solubility test was carried out by UV-Vis spectrophotometric method using methanol as the solvent. The oil, surfactant, and cosurfactant having the highest ability to dissolve PGV-0 were mixed and introduced to the water for the self-emulsification assessment. The dispersability, the time to complete emulsification and any phase separation were evaluated visually. The % transmittance of the emulsion was measured by visible-spectrophotometric method (Astuti, *et al.,* 2017).

Preparation of PGV-0 SNEDDS

Referring to the previous work (Astuti, 2017), the optimized PGV-0 SNEDDS formulation was prepared by using oleic acid, tween 20:labrasol (1:1) and PEG 400 as oil, surfactant, and cosurfactant, respectively. In a glass vial, a mixture of oleic acid (1.86 mL), tween 20:labrasol (1:1) (5.14 mL), and PEG 400 (3mL) was vortexed for 1min until homogenous. An accurately weighed of PGV-0 (163.5 mg) was added to the mixture, vortexed for 1min followed by sonication until the PGV-0 powder was dissolved.

Morphology imaging of nanodroplet by TEM

The morphology of PGV-0 SNEDDS droplet was observed by transmission electron microscope (TEM). Briefly, PGV-0 SNEDDS was diluted and carefully mixed with distilled water in the ratio of 1:25 to obtained an emulsion sample. The emulsion was passed through the 0.22 membrane filter and allowed to stand for 2h to achieve the equilibrium. The sample then negatively stained with 1% aqueous phosphotungstic acid. One drop of the sample was placed in a copper grid and visualized under the TEM.

Zeta potential measurement

Nanoemulsion sample of PGV-0 SNEDDS was prepared by adding 100µL of PGV-0 SNEDDS to 100mL of distilled water, mixed by magnetic stirrer until the emulsification point was reached. PSA instrument was prepared for zeta potential measurement. The zeta potential was measured at a wavelength of 633nm, temperature of 25°C, and a refractive index of dispersant was 1.33.

Physical stability determination

One hundred PGV-0 SNEDDS was added to 100 mL distilled water, artificial intestinal fluid (AIF), and artificial gastric fluid (AGF) respectively. The mixture then

homogenized with vortex for 30s. The resultant mixtures were observed every hour for 4h to determine their stability. The physical stability was characterized by the absence of aggregates, precipitates, and phase separation.

The AIF was containing 0.1523 $MgCl_2$, 0.1470g $CaCl_2$, 0.0931g KCl, 1.75850g NaCl, 0.4200g $NaHCO_3$ in 500mL distilled water CO_2 free. While the AGF was containing 1.00g NaCl and 1.3g HCl in 500mL distilled water CO_2 free.

Comparative dissolution profile

The dissolution profile of PGV-0 SNEDDS was compared with PGV-0 powder. PGV-0 SNEDDS sample was prepared by loading an accurately measured of 0.581mL PGV-0 SNEDDS equivalent to 9.5mg PGV-0 into a capsule size "0". As a comparison was 9.5mg of PGV-0 powder, loaded into capsule size "5". The dissolution assay was performed using apparatus type II (paddle) dissolution apparatus with 500mL of different dissolution media (AGF and AIF). The medium temperature was set to 37±0.5°C and the rotation speed was 50 rpm. At minute 0, the capsule was introduced into the medium, then at 5, 10, 15, 20, 30, 45 and 60min, 5mL of solution was taken and replaced again with an equivalent volume of the same dissolution medium type at the same temperature. The experiment was performed in a triple.

Data Analysis

The physical characteristics were evaluated based on the applicable requirements. The extent of PGV-0 released in the 45th-min value (C_{45}) were analyzed using IBM SPSS statistic 23 software. The normality of data distribution was determined by Kolmogorof-Smirnof test, followed by a one-way anova with 95% confidence level and Least Significant Difference (LSD). $P<0.05$ was considered as statistically significant difference. The dissolution profiles were compared using a similarity factor (f2) calculated by equation 1 (FDA, 2017).

$$f2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{i=1}^{n}(R_t - T_t)^2\right]^{-0.5} x100\right\} \quad \text{.....(1)}$$

Where R_t and T_t are the percentage of PGV-0 dissolved at each sampling time point for the PGV-0 SNEDDS and PGV-0 powder, respectively; n=number of sampling time point.

RESULT AND DISCUSSION

Excipient selection and PGV-0 SNEDDS preparation

Referring to the previous reports (Astuti, 2017), the best oil, surfactant, and cosurfactant for PGV-0 SNEDDS formulation was oleic acid, tween 20:labrasol (1:1), and PEG 400, respectively. The selected excipient showed the highest ability to dissolve PGV-0. When they were mixed as a SNEDDS blank then introduced to the water, in less than 2min the emulsion was formed completely. The emulsion showed a transparent appearance with the highest % transmittance, i.e 92.88%, 92.75% and 93.90% in water, AGF and AIF, respectively. The optimum formulation obtained based on the desirability value showed the optimum ability to dissolve PGV-0, droplet size and C_{45} (Astuti, 2017).

TEM image of PGV-0 SNEDDS

A TEM photograph of PGV-0 SNEDDS nanoemulsion (Figure 1) which shows the spherical droplets with the droplet size are about 50nm. This size is smaller than the droplet size measured by dynamic light scattering (DLS), ie 189.7nm (average size). A possible reason for this difference could be aggregating of the droplets in the dilute emulsion (1:1000) when observed under DLS. According to Kumar and Kumbhat, the comparison of size data obtained from DLS to TEM images can be used to determine the aggregation state. In an unaggregated emulsion, the DLS-measured diameter is similar or slightly larger than the TEM size, and much larger and often accompanied by high polydispersity index when particle aggregation occurs (Kumar and Kumbhat, 2016). The polydispersity index of PGV-0 SNEDDS measured by DLS was found to be 0.462±0.08, still below 0.5, so, the PGV-0 SNEDDS can be considered to have good stability. The inside of droplets are darker denotes PGV-0 dissolved in it. The spheric shape shows the low of the interface force droplet-water, that is beneficial for absorption process because of droplet

contact with enterocyte membrane surface become easier and increase the possibility for PGV-0 absorption.

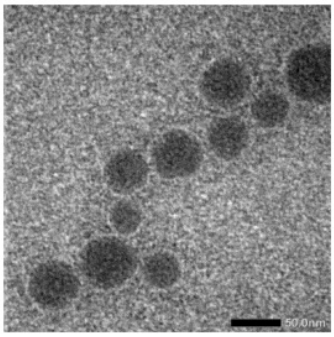

Figure 1. The morphology of PGV-0 SNEDDS droplet, observed by Transmission Electron Microscopy

Zeta potential

The potential zeta value can be used to estimate the surface characteristics of the nanoemulsion. In the range of more than 30mV or less than -30mV, nanoemulsion shows stability, because the attractive and repulsive forces prevent particles approaching each other closely. The obtained zeta potential of the PGV-0 SNEDDS was -31.5 to -34.4mv, so, the PGV-0 SNEDDS is considered pharmaceutically stable.

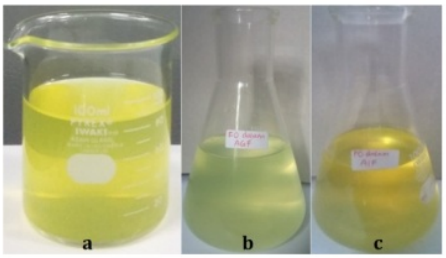

Figure 2. Physical stability of PGV-0 SNEDDS nanoemulsion at 25° C in medium (a) distilled water, (b) AGF, and (c) AIF.

Stability of the PGV-0 SNEDDS in distilled water, AGF, and AIF

The addition of PGV-0 SNEDDS into various media produces nanoemulsion which remains translucent without aggregation or precipitation up to 4h as (Figure 2. This indicates good physical stability of PGV-0 SNEDDS.

Dissolution profile of PGV-0 SNEDDS and PGV-0 powder comparison

The comparison of the dissolution profile of PGV-0 SNEDDS with PGV-0 powder (Figure 3). The PGV-0 SNEDDS is able to release PGV-0 in the faster time and in a greater extent than PGV-0 powder. Within the first 5min, 40% of PGV-0 has been released from SNEDDS, continuing to the 120min, more than 80% of PGV-0 has been released. In contrast, the PGV-0 powder is slow in releasing PGV-0, so until at the end of the study ie at 240min, the PGV-0 released from the powder is less than 4%. In the 240min, the ratio of PGV-0 released from SNEDDS PGV-0 and PGV-0 powder is 44.13 in AGF and 30.37 in AIF.

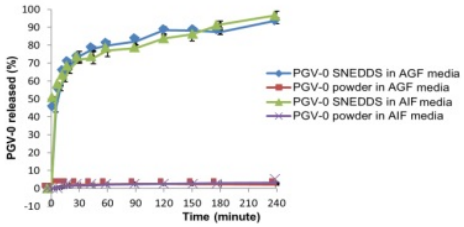

Figure 3. The comparison of dissolution profiles of PGV-0 SNEDDS with PGV-0 powder in AGF medium and AIF medium.

The C_{45} of PGV-0 SNEDDS in AGF is 78%. This extent of dissolution is meet the requirement set by WHO, i.e for the immediate release preparation, at least 75% of the active substance is dissolved in 45min (Kuwana, 2007).

ANOVA statistic analysis followed by LSD test on C_{45} parameter using SPSS program at 95% confidence level indicated that the C_{45} of PGV-0 SNEDDS in both AGF (78%) and AIF (73%) were significantly higher than PGV-0 powder in AGF (2.22%) and AIF (1.65%) (Table I). These results are in line with the similarity factor results. In the AGF medium, the dissolution profile of PGV-0 SNEDDS shows a lack of similarity with the PGV-0 powder (f2 <50), as well as in the AIF medium.

Table I. The significance value at the 0.05 level of LSD test of C_{45} and the similarity factor between two dissolution curves

No.	Curve		Significance of C_{45}	f2
	Curve 1	Curve 2		
1.	SNEDDS PGV-0 in AGF	PGV-0 powder in AGF	0.000#	7.62
2.	SNEDDS PGV-0 in AIF	PGV-0 powder in AIF	0.000#	7.95
3.	SNEDDS PGV-0 in AGF	SNEDDS PGV-0 in AIF	0.009#	65.86*
4.	PGV-0 powder in AGF	PGV-0 powder in AIF	0.435	81.73*

Note: * = similar ($50 \leq f2 \leq 100$); # = significantly different ($p < 0.005$)

This shows that the SNEDDS formulation could improve the dissolution profile of PGV-0.

The C_{45} of the PGV-0 powder in AGF did not differ significantly within AIF, in line with the similarity factor of both curves (f2 > 50). The similarity factor of dissolution profile of PGV-0 SNEDDS in AGF and in AIF also showed a similarity (f2>50). Although the C_{45} of both later curves is significantly different, overall it can be concluded that the dissolution profile of PGV-0 SNEDDS and PGV-0 powder was not affected by the medium difference (AGF and AIF). The C_{45} only measures the single point dissolution test, while the similarity factor in this study measured the 13 points dissolution test, so the dissolution profile comparison can characterize the formulation more precisely.

The dissolution of PGV-0 SNEDDS is much higher than that of PGV-0 powder because in aqueous media PGV-0 SNEDDS forms nanoemulsions that keep PGV-0 remained homogeneously dispersed for some time in the bulk medium in the form of nanodroplets. While the PGV-0 powder is almost insoluble in the medium and is mostly located at the bottom of the container as a precipitate. The enhancement in the dissolution of the SNEDDS dosage form was reported by many studies, among others by Cui (2009) who reported that within 20 minutes, 96% of the curcumin was detached from the SNEDDS preparation compared with the release of less than 2% of curcumin powder during 60 minutes of observation.

CONCLUSION

Formed PGV-0 SNEDDS was thermodynamically stable with forming droplet oil containing PGV-0 in it and spherical. The SNEDDS formulation was able to improve the PGV-0 dissolution profile.

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