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# Dissolution Enhancement of Gendarusin A by Poloxamer 188 Addition in *Justicia gendarussa* Burm. f Ethanolic Extract Granule Matrix

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**ABSTRACT**

*Justicia gendarussa* Burm. f (Acanthaceae) is often used as folk medicine for many purposes in Indonesian indigenous tribes. Preclinical studies on *J. gendarussa* leaves indicated that the extract possessed the activity of male contraception. Gendarusin A was found to be the compound responsible for the activity. The purpose of this study was to prove that poloxamer 188 can increase the dissolution rate of gendarusin A in *Justicia gendarussa* Burm. f ethanolic extract granule (JEG) matrix, in an effort to find male contraceptives phytopharmaceutical product. In this research, we had made three JEG matrix types, which were type 1 (without the addition of surfactant poloxamer 188); type 2 (with the addition of 1% surfactant poloxamer 188), and type 3 (with the addition of 2% surfactant poloxamer 188). The three types of JEG matrix then examined by dissolution test to obtain the dissolution rate of gendarusin A. HPLC instrument was utilized to analyse the concentration of gendarusin A from dissolution mediums. The results showed that the gendarusin A in JEG matrix type 3 dissolved much faster compared to JEG matrix type 1 and type 2. The score of dissolution efficiencies of gendarusin A in JEG matrix type 1, type 2, and type 3 were 15,72%; 24,22%; and 31,83% respectively. It can be concluded that poloxamer 188 addition can increase the dissolution rate of gendarusin A in JEG matrix.

## INTRODUCTION

*Justicia gendarussa* Burm. f (Acanthaceae) is often used as folk medicine in Indonesia. The plant leaves are used as antinociceptive (Ratnasooriya et al., 2007; Shikha, 2010), antibactericidal (Sivasakthi and Vijayalakshmi, 2014), antioxidant (Mrunthunjaya and Hukkeri, 2007), antifungal (Sharma et al., 2011), antiarthritic (Paval et al., 2009), antiinflammatory (Shikha et al., 2010), antisickling (Mpiana et al., 2010), and anthelmintic (Saha et al., 2012). *J. gendarussa* is a plant that is used by imdigenous people of Papua as a male contraceptive. Preclinical studies on *J. gendarussa* leaves extract showed the activity of male contraception (Prajogo et al., 2009). *J. gendarussa* leaves containskaempferol, stigmasterol, sitosterol and sitosterol-D-glucoside glycosides (Rajakumar and Shivana, 2009), flavonoids gendarusin A-B with gendarusin A as a major compound (Prajogo et al., 2009), and justidrusamides A-D (Kiren et al., 2014). Gendarusin A or 6,8-di-C-α-L-arabinosil apigenin is the compound that responsible for the male antifertility activity, isolated from n-butanol fraction of *J. gendarussa* (Prajogo et al., 2009) as shown in figure 1.

Ethanolic extract of *J. gendarussa* leaves has a characteristic of a thick consistency and low level of gendarusin A (Prajogo et al., 2009), for that it is necessary to develop a carrier material for the extract so that a good granules characteristic can be obtained. Further, surfactant materials also necessary to be added to fasten the release the gendarusin A to overcome the active compound low concentration problem. Surfactants can improve the dissolution rate of the active ingredient due to a direct effect on improving the wetting and solubilization of the drug substance particles (Ansel et al., 1995).

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Poloxamer 188 is a solid non ionic surfactant which possesses a hydrophilic polioxy ethylene group and a lipophilic polioxy propylene group (Rowe et al., 2009). In an effort to produce a good male contraceptive phytopharmaceutical product of *J. gendarussa*, this research was aimed to determine the effect of surfactant poloxamer 188 addition on the dissolution rate of gendarusin A.

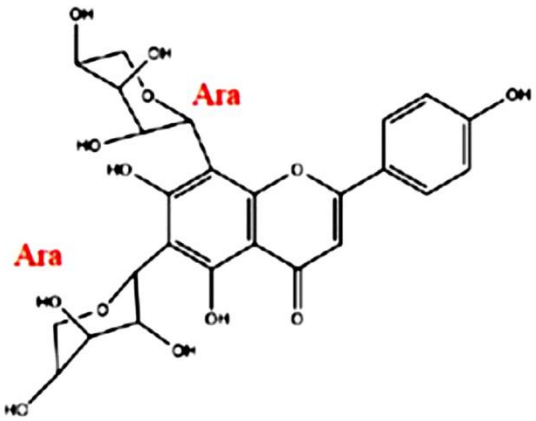


**Fig. 1:** Chemical structure of gendarusin A.

## MATERIALS AND METHODS

### Plant material

*J. gendarussa* leaves were collected from nine months old cultivated plants in Trawas, Indonesia. The specimen then authenticated by the Unit Layanan Pengujian Laboratory, Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia (herbarium number: 0780/SA/V/2014). The leaves were air-dried and powdered. The average value of moisture content (MC) of the samples was 9.6±1.7%, n = 105 (using Moisture Analyzer HB43-S, Mettler Toledo) (Ningsih et al., 2015). The maximum permitted level of MC of the herbal medicine is 12% (w/w) (Indonesian National StandardSNI 01-3709-1995, 1995).

### Preparation of ethanolic extract of *J. gendarussa* leaves

500 g of the dried and powdered leaves of *J. gendarussa* was extracted by maceration technique in 1 L of 70% (v/v) ethanol for 24 h with 3 repetitions (Prajogo et al., 2016). The solvent residues then removed by means of rotary evaporator at reduced temperature to obtain a solid mass of extract.

### Preparation of *J. gendarussa* ethanolic extract granule matrix (JEG's)

JEG's were made in three types, which previously had been optimized for their compositions of carrier materials Avicel PH 101 (Asahi Chemical), corn starch (Cargill Bio-Chemical), and cab-o-sil (Cabot Corporation). JEG type 1 is the granule matrix without the addition of surfactant poloxamer 188 (Pluronic F-68, Sigma-Aldrich, Singapore), while type 2 and type 3 are the granule matrices with the addition of the surfactant poloxamer 188 as much as 1% and 2% of the weight of the extract respectively (Rowe *et al*, 2009). All three types of JEG then sifted using mesh no. 16 sieve. The wet granules then dried in a drying cabinet at a temperature of 50°C for 6 hours, the dried granules then resifted with mesh no. 20 sieve. The granules obtained from the processes then evaluated fo r the physical parameters (angle of repose and number of fines) and the level of gendarusin A.

### Dissolution evaluation of gendarusin A in JEG

650 g of each JEG type were placed in a hard gelatin capsule shell. The dissolution test were done by using USP apparatus I (2008) basket method (DT-706 Erweka), at 37±0.5°C, 100 rpm. The dissolution medium used was pH 1.2, 500 mL HCl buffer. Samples were taken from the receptor compartment as much as 5.0 mL at t = 15, 30, 45, and 60 minutes, then filtered with a 0.2 µm nylon membrane filters (Whatman) and freeze dried. The dry filtrates then solved in 5 mL of methanol, and injected into HPLC (Shimadzu System Controller SCL–6A) to determine the level of gendarusin A.

### Gendarusin A assay

The HPLC assay used Shimadzu SPD-6AV UV-VIS spectrophotometer detector with wavelength of 254 nm, Shimadzu LC-6A pump, reverse phase Nova-pak® C18 3,9 x 150 mm column. The mobile phase was isocratic methanol : water (30:70) with a flow rate of 1 mL/min and stop time of 25 min. This assay has been validated previously by Asmara (2004).

### Statistical analysis of physical parameters and gendarusin A dissolution rate

The physical parameters and gendarusin A dissolution rate values of each JEG were compared statistically using one way ANOVA ($p<0.05$) followed by Tukey HSD test (SPSS 16.0;).

## RESULT AND DISCUSSION

### Physical parameters of JEG

According to the angle of repose and the number of fines, the three types of JEG were qualified for the criterias of granules with good physical parameters. The angle of repose valuesof type 1, type 2, and type 3 JEG were 27.70˚, 27.70˚, and 28.07˚, whereas the amount fines were 1.05%, 2.06%, 2.59%, respectively, as shown in Table 1. Granule will be able to flow properly when the angle of repose is less than 30˚, and the number of fines are less than 20% (Aulton, 2002).

Statistical one way ANOVA analysis showed that there was no significant difference ($p > 0,05$) in the angle of repose and the number of fines among the three types of JEG, therefore it can be concluded that the addition of poloxamer 188 has given no alteration on the values of those parameters.

**Table 1:** The mean scores of physical parameters of JEG (±SD).

| Physical parameters | JEG type 1 | JEG type 2 | JEG type 3 |
|---|---|---|---|
| Angle of repose (°) | 27.70±0.00 | 27.70±0.00 | 28.07±0.64 |
| Number of fines (%) | 1.05±0.23 | 2.06±0.64 | 2.59±0.73 |

n = 6

**Dissolution of gendarusin A in JEG**

Dissolution profiles of gendarusin A in JEG type 1, JEG type 2, and JEG type 3 are shown in figure 2. The dissolution rate of gendarusin A in JEG type 3 was more rapid compared to JEG type 1 and JEG type 2. At t= 60 min, gendarusin A in JEG type 1, JEG type 2, and JEG type 3 levels were 15,72 %, 24,22 % and 31,83 % respectively, as shown in Table 2. Tukey Honest Significant Difference analysis showed that there was a difference ($P<0.05$) between JEG type 3 and JEG type 1 ($P=0.000$), and between JEG type 3 and JEG type 2 ($P=0.000$).

**Table 2:** Dissolution rate of gendarusin A in various types of JEG.

| Time (min) | Dissolution | | |
|---|---|---|---|
| | JEG type 1 | JEG type 2 | JEG type 3 |
| 15 | 13.59±0.36 | 22.70±1.32 | 30.67±1.70 |
| 30 | 17.08±1.56 | 26.22±0.57 | 36.21±0.32 |
| 45 | 20.76±0.92 | 29.99±1.49 | 38.86±0.27 |
| 60 | 22.93±0.72 | 35.95±0.43 | 41.20±0.72 |
| Rate dissolution (%) | 15.72±0.61 | 24.22±0.58 | 31.83±0.36 |

n = 3

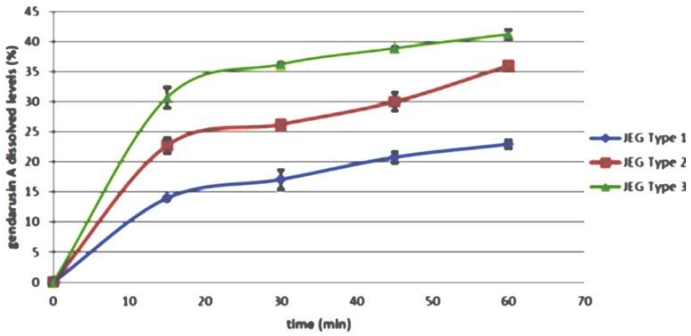


**Fig. 2:** Dissolution profile gendarusinAin HCl buffer pH 1.2. Blue line: JEG Type 1; Redline: JEG Type 2; and Green line: JEG Type 3.

## CONCLUSION

Surfactant poloxamer 188 was successfully applied for improvement of the dissolution rate of gendarusin A in JEG matrix. The dissolution rate of gendarusin A was more rapid in JEG matrix type 3 (with 2% poloxamer 188 addition) compared to JEG matrix type 1 and JEG matrix type 2.

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**Conflict of Interests**: There are no conflicts of interest.

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