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Formulation and pH-Physical Stability Evaluation of Gel and Cream of *Plantago major* Leaves Extract

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ABSTRACT: *Plantago major* has been widely used for wound healing. This activity is supported by empirical as well as preclinical data. The aims of this study were to (1) formulate *Plantago major* leaves extracts (PMLE) into topical dosage forms i.e. creams and gels and; (2) evaluate the pH and physical stability of the products. The results showed that creams and gels of PMLE were able to maintain the pH, visual appearance, flow properties, droplet size, and type of emulsion under accelerated ($40\pm 2^\circ\text{C}$; $75\pm 5\%$ RH for 1.5 months) as well as room temperature (27°C ; 85% RH for 1.5 months) stability testing conditions. However, viscosity of creams significantly changed under those conditions. Even though the viscosity of gels was unstable under accelerated condition, it was stable under room temperature storage. It is concluded that PMLE could be formulated into creams or gels dosage forms and further optimisation should be conducted.

Keywords: formulation; gels; creams; *Plantago major*; physical stability

1. Introduction

Plantago major L. (Figure 1) is a perennial plant which belongs to the Plantaginaceae. Its height reach about 15 cm, but the size varies a lot depending on the growth habitats. The leaves grow in rosettes, and they are ovate to elliptical with parallel venation. The leaves are glabrous and have an entire or irregularly dentate margin. The flowers are small, brownish-green on long non-ramified spikes (1).



Figure 1. *Plantago major* L.

Plantago major is ubiquitous plant, including in Indonesia. This plant grows at a very wide range of regions, from 0 up to 3,300 m above sea level. However, most of them grow at 700 m above sea level or more. Their habitats include grasslands, agricultural areas, sides of roads and river side, forests and others, mainly on open fertile and rather hard land (2, 3).

More recent ethnopharmacological studies show that *P. major* is used in many parts of the world and in the treatment of a number of dis-

eases, such as: skin diseases, infectious diseases, problems concerning the digestive organs, respiratory organs, reproduction, the circulation, against tumors, for pain relief and for reducing fever. Furthermore, in skin diseases this plant empirically used for treatment of abscesses, acne, inflammation, bee, wasp and nettle stings, bruises, burn, cutaneous leishmaniasis, cuts, dermatitis, wound (as disinfectant, haemostatic), emollient, exanthema, poison ivy dermatitis, pruritus, pusformation in impetigo, rosen, soothing effect and wound healing (1).

Related with the wound healing activity, a number of researches have been conducted on *P. major*. Mahmood & Phipps proved that an aqueous extract of *P. major* leaves stimulated wound healing in vivo using a rat model (4). Leaf extracts of *P. major* showed enhancement of cell proliferation and migration in vitro (5). Methanol and aqueous extracts of *P. major* leaves showed stimulating effects on the healing of burn wounds in rats (6). Extracts of *P. major* leaves stimulated cell proliferation and migration in an in vitro scratch assay. Both ethanol and water extracts of fresh and dried leaves had stimulating effects which makes *P. major* an interesting source of different bioactive substances with wound healing potential. Polyphenol-rich ethanol-based extracts had stronger effects than water extracts (7). Aucubin, one of chemical compounds of *P. major*, exhibited an oral wound healing effect on mice. Re-epithelization and matrix formation of the aucubin-treated group occurred earlier than that of the control group. In addition, the number of inflammatory cells of the aucubin-treated group was fewer than that of the control group. It was concluded that aucubin may be useful for oral wound healing and can be applied as a topical agent to oral wounds (8).

Considering the availability, empirically and scientifically uses, it is valuable to develop *P. major* extract as an "active compound" of herbal medicine products for wound healing. For this indication, *P. major* extracts can be formulated into topical dosage forms such as creams and

gels. These dosage forms can be directly applied on wound and enable fast delivery of the active compound(s) to the site of action. In addition to efficacy, herbal medicine products have to comply the requirements of safety and quality. Quality of the products can be assured by stability tests. Therefore, the aims of this study were to (1) formulate *Plantago major* leaves extracts (PMLE) into topical dosage forms i.e. creams and gels and; (2) evaluate the pH and physical stability of the products.

2. Method

2.1. Chemicals and equipments

Chemicals used in this study were pharmaceutical grade, i.e.: cetyl alcohol, stearic acid, isopropyl palmitate, methylparaben, propylparaben, sorbitan monostearate, sorbitol, polysorbate 60, carbomer, NaOH, BHA, BHT, and destilated water. Analytical grade solvent, ethanol, was procured from Merck KGaA (Darmstadt, Germany). Equipments used consisted of climatic chamber (KBF 240), pH meter (Schott Lab 850), microscope (Olympus), analytical balance (Ohaus), viscometer cone and plate (Brookfield type cone and plate seri AT 71362), homogenizer (Multimix), mortar and stamper, waterbath (Mettler), exicator, and laboratory glass ware.

2.2. Preparation of extracts

Air dried of *Plantago major* leaves were collected from Tawangmangu, Center of Java. Authentication of the plants (No. 1101/D.T/XI/2013) was conducted by Center of Information and Development of Traditional Medicine, University of Surabaya, Indonesia. Crude drugs were powdered (2 mm) before use. Three hundreds g of sample was macerated with 3 x 1 L ethanol for 3 x 24 h. The ethanol extract was then evaporated under vacuum to yield a thick extract (10 g).

2.3. Preparation of creams and gels of *Plantago major* leaves extracts (PMLE)

Creams of PMLE was prepared using standard creams base according to Lachman with composition as shown on Table 1 (9). Water phase (methylparaben, propylparaben, sorbitol, polysorbate 60, BHA, and water) was dissolved in water and the oil phase (cetyl alcohol, stearic acid, isopropyl palmitate, BHT, and sorbitan monostearate) was melted on a waterbath. These two phases were gently mixed until cool and homogenous, then added gradually into PMLE.

Table 1. Composition of PMLE creams

Materials	Composition (%)
PMLE	0.9
Cetyl alcohol	2.0
Stearic acid	20.0
Isopropyl palmitate	1.0
Methylparaben	0.1
Propylparaben	0.01
Sorbitan monostearate	2.0
Sorbitol	3.0
Polysorbate 60	1.5
BHA	0.02
BHT	0.1
Destilated water to	100

Meanwhile, the standard gel base for PMLE was prepared according to Remington (10) with composition as shown on Table 2. Methylparaben was dissolved in hot water. After getting room temperature, it was divided into two parts. The first portion was added by carbomer and then quickly stirred using high-speed stirrer. NaOH was dissolved subsequently to the second portion, and followed by BHA. Those solutions were mixed using high-speed stirrer. Finally, the gels base was added gradually into PMLE.

Table 2. Composition of PMLE gels

Materials	Composition (%)
PMLE	0.9
Carbomer	4.0
NaOH	1.6
Methylparaben	0.3

Materials	Composition (%)
BHA	0.02
Destilated water to	100

2.4. pH and physical stability test

pH and physical stability tests were carried out under accelerated (45 days; $40\pm 2^\circ\text{C}/75\pm 5\%$ RH) and long-term (45 days; $27\pm 2^\circ\text{C}$) testing. Parameters evaluated were pH, visual appearance (color, odor, consistence), viscosity, flow properties, type of emulsion, and droplet size. The last two parameters are only applied for the creams.

2.5. Statistical analysis

All values were presented as mean \pm standard deviation, $n = 3$. Data were analyzed by ANOVA followed by LSD Post Hoc Test when necessary using GraphPad Prism statistical software (GraphPad Software Inc., Sandiego, California, Windows Version 5.01). Differences were considered statistically significant at $P < 0.05$

3. Result and discussion

3.1. Visual appearance

Visual appearance of PMLE creams and gels were evaluated every 15 days and the result is presented on Figure 2. Both of them did not show any visual degradation during 45 days as shown on Table 3. The creams and gels were able to maintain their consistence, green color, and characteristic odor.



Figure 2. Creams (a) dan gels (b) of PMLE

3.2. pH

pH of PMLE creams and gels are presented on

Table 4. It is concluded that PMLE creams and gels were able to maintain the pH under accelerated and room temperature condition ($P > 0.05$). A good topical preparation should have a suitable pH with the skin, i.e. 4.2-6.5 (11). Therefore, PMLE creams with pH 4.33-5.71 is considered more suitable than PMLE gels. This dosage form should be further optimized since too alkaline gels will cause the skin to be scaly. At the other hand, if the pH is too acidic it will make the skin becomes irritated.

3.3. Viscosity

Viscosity is a physical properties of dosage forms which affect the flocculation rate. Flocculation may occur when there is an increase in viscosity too early. Table 5 indicated that creams was not stable under both accelerated and room temperature condition. At the other hand, viscosity of the gels did not significantly change under room temperature storage.

3.4. Flow properties

Flow properties of PMLE creams and gels can be seen on Figure 3 and 4. The flow properties of the PMLE cream and gel preparations are pseudoplastic, i.e. the viscosity will decrease with the increase of rate of shear (12).

3.5. Type of emulsion and droplet size of PMLE creams

PMLE creams showed oil in water (O/W) type emulsion (Figure 5), which was stable under storage condition. Changes in the average droplet size or globul size distribution are important parameter for evaluating an emulsion. Table 6 demonstrated that droplet size of PMLE creams was unchanging during observation.

4. Conclusion

Gels and creams of *Plantago major* leaves extracts were able to maintain stable pH, visual appearance, flow properties, droplet size, and type of emulsion under accelerated stability testing condition ($40\pm 2^\circ\text{C}$; $75\pm 5\%$ RH for 1.5 months).

Table 3. Visual appearance of PMLE creams and gels

Storage	Dosage form	Parameters	Day*			
			0	15	30	45
Accelerated	Creams	Consistence	Creams	Creams	Creams	Creams
		Color	Green	Green	Green	Green
		Odor	Characteristic	Characteristic	Characteristic	Characteristic
	Gels	Consistence	Gels	Gels	Gels	Gels
		Color	Green	Green	Green	Green
		Odor	Characteristic	Characteristic	Characteristic	Characteristic
Room temperature	Creams	Consistence	Creams			Creams
		Color	Green			Green
		Odor	Characteristic			Characteristic
	Gels	Consistence	Gels			Gels
		Color	Green			Green
		Odor	Characteristic			Characteristic

*data were observed from three replications; Samples from room temperature storage were collected on day of 0 and 45 only.

Table 4. pH of PMLE creams and gels under stability testing conditions

Dosage form	pH (40±2°C/75±5% RH)*				pH (27±2°C)*	
	Day 0	Day 15	Day 30	Day 45	Day 0	Day 45
Creams	4.80±0.25 ^a	4.33±0.28 ^a	4.64±0.39 ^a	5.10±0.71 ^a	5.11±0.31 ^b	5.71±0.48 ^b
Gels	12.98±0.61 ^c	13.68±0.07 ^c	12.80±0.44 ^c	13.45±0.53 ^c	13.44±0.06 ^d	13.46±0.04 ^d

*data are presented as mean ± SD, n = 3 and the values with different superscript letters within a row in the same condition testing were significantly different (LSD Post Hoc Test, P < 0.05).

Table 5. Viscosity of PMLE creams and gels under stability testing conditions

Dosage form	Viscosity (cP; 40±2°C/75±5% RH)*				Viscosity (cP, 27±2°C)*	
	Day 0	Day 15	Day 30	Day 45	Day 0	Day 45
Creams	2240±1157 ^a	5170±752 ^b	3512±758 ^c	2765±682 ^d	4272±1054 ^e	2825±134 ^f
Gels	1950±733 ^g	2780±124 ^h	2675±1165 ^h	3341±478 ⁱ	3086±851 ^j	3720±646 ^j

*data are presented as mean ± SD, n = 3 and the values with different superscript letters within a row in the same condition testing were significantly different (LSD Post Hoc Test, P < 0.05).

Table 6. Droplet size of PMLE creams under stability testing conditions

Day	Droplet size (µm)	
	40±2°C/75±5% RH*	27±2°C*
0	6.83±0.03 ^a	0.81±0.02 ^b
15	6.84±0.02 ^a	-
30	6.83±0.03 ^a	-
45	6.84±0.02 ^a	6.83±0.03 ^b

*data are presented as mean \pm SD, $n = 3$ and the values with different superscript letters within a column were significantly different (LSD Post Hoc Test, $P < 0.05$).

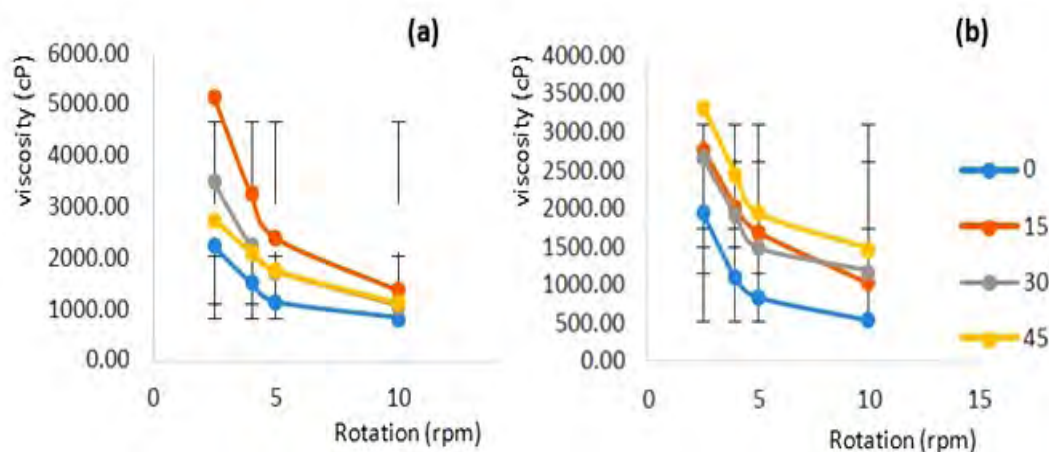


Figure 3. Flow properties of PMLE creams (a) and gels (b) under accelerated stability testing

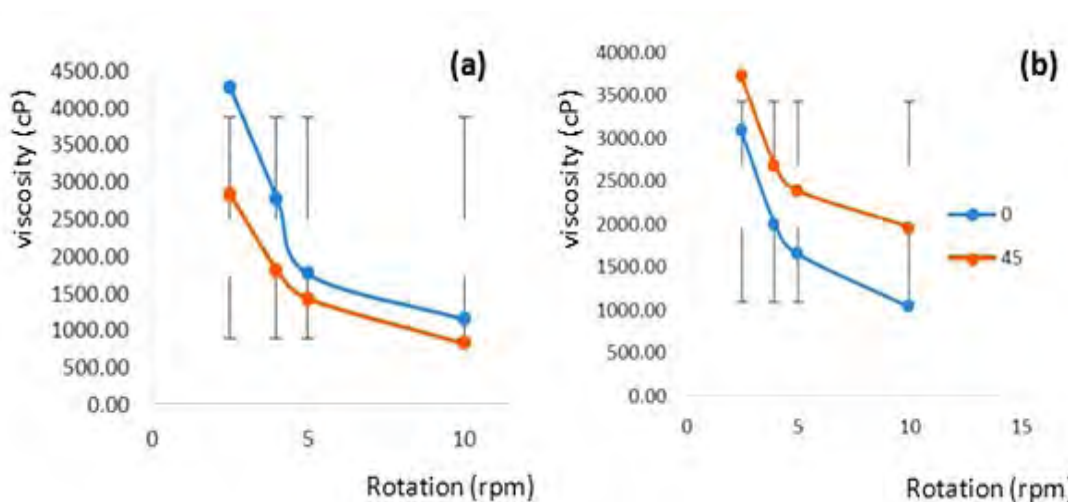


Figure 4. Flow properties of PMLE creams (a) and gels (b) under room temperature stability testing

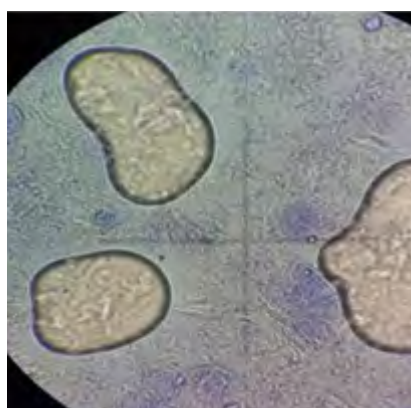


Figure 5. Oil in water (O/W) type emulsion of PMLE creams

However, viscosity of creams significantly changed under those conditions. Even though the viscosity of gels was unstable under accelerated condition, it was stable under room temperature storage. It is concluded that PMLE could be for-

mulated into creams or gels dosage forms and further optimisation should be conducted.

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