

## Formulation and physical stability test of oleanolic acid cream and gel

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### ABSTRACT

*Plantago major* has been empirically used for wound healing. One of its chemical compounds, oleanolic acid, exhibited wound healing activity on hyperglycemic rats. This study aimed to (1) formulate oleanolic acid into topical dosage forms, i.e., cream and gel and (2) evaluate the physical stability of the products. Oleanolic acid was formulated into the dosage forms using stearic acid, isopropyl palmitate, and cetyl alcohol as the cream base and carbomer as the gel base. The cream and gel were then evaluated with accelerated stability test ( $40\pm 2^{\circ}\text{C}/75\pm 5\% \text{RH}$ ) and stability test at room temperature ( $27\pm 2^{\circ}\text{C}/73\pm 5\% \text{RH}$ ) for six weeks. The physical stability was determined using the following parameters: the visual appearance, density, viscosity, and flow properties of cream and gel, as well as the emulsion type and particle size of the cream. Data analysis were performed using one sample *t*-test and paired *t*-test. The results showed that the oleanolic acid cream and gel were able to maintain their visual appearance, density, viscosity, and flow properties during the six-week storage. Also, the oleanolic acid cream was able to keep its particle size and emulsion type during the tests.

**Keywords:** formulation, stability test, cream, gel, oleanolic acid

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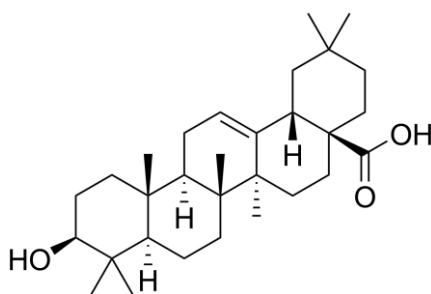
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## INTRODUCTION

Oleanolic acid (Fig. 1) is a secondary metabolite from the group of triterpenoids contained in several plant species, such as *Olea europaea*, *Plantago major* (Chiang *et al.*, 2003b; Kartini *et al.*, 2014), *Mentha piperita* (Rais and Ali, 2010), and *Ocimum basilicum*. Oleanolic acid together with its isomer, ursolic acid, has exhibited various pharmacological activities, namely COX-2 and cholinesterase inhibitor (Kolak *et al.*, 2011; Ringbom *et al.*, 1998; Stenholm *et al.*, 2013), immunomodulator (Chiang *et al.*, 2003a), and cancer prevention and treatment (Chiang *et al.*, 2003b; Kolak *et al.*, 2011; Lee *et al.*, 2005; Liu, 1995; Liu, 2005; Pollier and Goossens, 2012; Ringbom *et al.*, 1998; Shanmugam *et al.*, 2013; Stenholm *et al.*, 2013). Previous studies have concluded that oleanolic acid exhibits cytotoxicity against SiHa and Hep G2, KB, MCF-7, MDA-MB-231, HeLaS3, and A549 cancer cell line, and inhibit the productions of TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IFN- $\gamma$  (Kartini *et al.*, 2014; Kartini *et al.*, 2017). Also, it has been empirically proven to have anti-inflammatory and wound healing activities (Kuonen *et al.*, 2013).



**Figure 1. The chemical structure of oleanolic acid**

In wound treatment, oleanolic acid is formulated first into a dosage form. The appropriate dosage form for wound healing is topical, i.e., applied to the skin surface for both local and systemic purposes. The combination of active ingredients and bases gives a wide range of opportunity for topical application. Topical dosage forms come in several types, including ointment, paste, cream, and gel. Cream is an emulsion containing one or more active dissolved drug substances and has relatively fluid consistency, while gel is a good transparent vehicle because it liquefies on contact with skin and gives cooling sensation (Yanhendri, 2012).

Among the conditions that have to be met for a good dosage form is physically stable. Inability to maintain physical properties under storage conditions fails to comply with the acceptance criteria for dosage forms. Their stability can be evaluated with accelerated stability test and stability test at room temperature (Guideline, 2003). Based on this background, research aiming to formulate oleanolic acid into cream and gel dosage forms and to test their stability is necessary. In this research, accelerated stability test and stability test at room temperature were performed with the following parameters: organoleptic properties, density, viscosity, flow properties, emulsion type, and particle size.

## MATERIALS AND METHODS

### Materials

The materials used in this research were pharmaceutical grade products, namely stearic acid, cetyl alcohol, isopropyl palmitate, Nipagin, Nipasol, Span 60, sorbitol, and Tween 60 (obtained from CV. Tristar Chemical, Surabaya). Additional materials were oleanolic acid (Sigma, St. Louis, MO, USA) and Aqua purificata.

### The formulation of oleanolic acid creams and gels

The concentration of oleanolic acid formulated into cream and gel was 0.00375%. It referred to the ursolic acid content, i.e., the isomer of oleanolic acid that exhibits wound healing activities (Mukherjee *et al.*, 2013). The oleanolic acid cream was prepared using the formula in Table 1. The water phase (Nipagin, Nipasol, sorbitol, BHA, and Tween 60) was heated in a water bath (70°C) until properly mixed, while the oil phase (stearic acid, cetyl alcohol, isopropyl palmitate, BHT, and Span 60) was heated in a water bath until melted completely. Both phases were mixed in a hot mortar and then crushed until a homogeneous mass of cream was formed. The oleanolic acid was poured into a different mortar, added with the cream base a little at a time, and mixed until homogeneous. The cream was then stored in a primary container, i.e., plastic pot.

The oleanolic acid gel was prepared using the formula in Table II. Paraben and BHA were dissolved in hot water. Carbomer was added to it by dispersion, allowed to expand, and then stirred in high speed with a homogenizer. NaOH solution was then poured into the resultant gel base. Finally, the oleanolic acid was added to the base and stirred until homogeneous. The gel was then stored in a primary container, i.e., plastic pot.

**Table I. The formula of oleanolic acid cream (Lachman *et al.*, 1986)**

Ingredients	Composition (%)
Oleanolic acid	0.00375
Stearic acid	14.0
Cetyl alcohol	1.0
Isopropyl palmitate	1.0
Methylparaben	0.1
Propylparaben	0.01
BHA	0.02
BHT	0.1
Span 60	2.0
Sorbitol	3.0
Tween 60	1.5
Aqua purificata ad	100

**Table II. The formula of oleanolic acid gel (Remington and Beringer, 2000)**

Ingredients	Percentage (%)
Oleanolic Acid	0.00375
Carbomer	4
BHA	0.02
NaOH	1.6
Methylparaben	0.3
Aqua purificata ad	100

### The physical stability test of oleanolic acid cream and gel

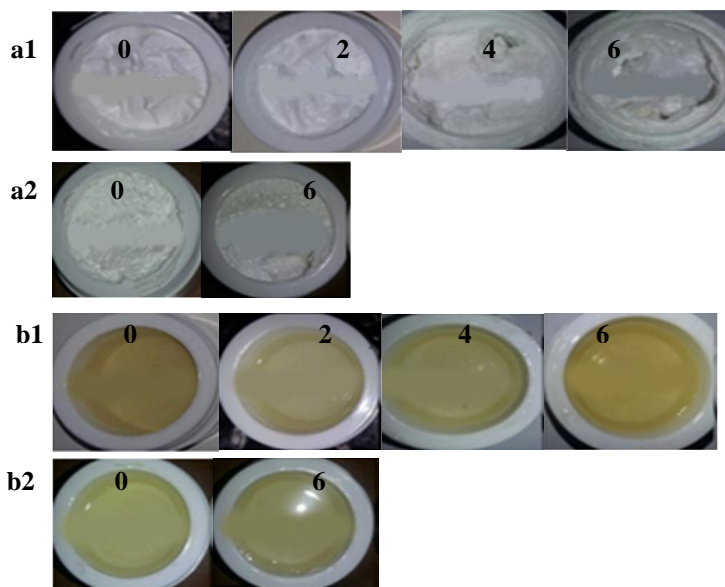
The physical stability of the oleanolic acid cream and gel was evaluated using accelerated stability test (climatic chamber, 40±2°C/75±5% RH) and stability test at room temperature (27±2°C/73±5% RH). It was determined according to the following observation parameters: organoleptic properties, emulsion type, particle size, viscosity, and flow properties. The dosage forms in the accelerated stability test were evaluated in weeks 0, 2, 4, and 6, while the ones in the stability test at room temperature were observed in weeks 0 and 6.

In this research, the organoleptic indicators included smell, color, and shape. The emulsion type of the cream was identified by applying it to a microscope slide, dyeing it with methylene blue, and observing the change in the background of the dosage form on the slide. The particle size was identified by applying the cream to a microscope slide and conducting continuous observations on particle size until 500 data were obtained. The viscosity was measured using a Brookfield cone and plate viscometer (Engineering Laboratories INC, Stoughton MA, USA). The gel flow was measured at room temperature. One-gram sample was placed on the cone. The measurements were performed by increasing the shear rate from 0.5/sec to 100/sec, and the viscosity was read at every rotation per minute (rpm). The density of the dosage forms was measured with beaker glass. Empty beaker glass that had been calibrated with a given volume was weighed using an analytical scale. The dosage forms were poured into the beaker glass up to the calibration mark and then scaled using an analytical balance. The densities ( $\rho$ ) of the dosages forms were calculated using the equation  $\rho = (m_1 - m_2)/v$ , where  $m_1$ : the mass of beaker glass filled with the dosage form,  $m_2$ : the mass of empty beaker glass, and  $v$ : the volume of the dosage form.

## RESULTS AND DISCUSSION

### Organoleptic properties

The results of organoleptic observations showed that the cream was homogeneously white and had a distinctive smell (Figure 2a). Meanwhile, the gel was homogeneous and clear yellowish and had a specific scent (Figure 2b). The stability of the oleanolic acid cream and gel under different temperature was tested at high and room temperature for six weeks.



**Figure 2. The results of organoleptic observations on oleanolic acid cream (a) and gel (b) stored in a climatic chamber (1) and at room temperature (2). The numbers in the figure (0, 2, 4, and 6) showed the duration of storage in weeks**

The results showed that both dosage forms did not experience separation when stored at either elevated or room temperature. Different temperature treatments were necessary to see the ability of the dosage forms to maintain their properties during the time of storage. Cream is an emulsion system in which high temperature can increase the kinetic energy of droplets, constituting the dispersed phase, and induce the merging of globules and the swelling of globular diameter. On the contrary, cold

temperature decreases the solubility of the emulsifier in the oil phase and the water phase that the effectiveness of emulsifier to coat the globules diminishes (Lachman *et al.*, 1986).

### Densities

The observation results of the densities of oleanolic acid cream and gel stored in a climatic chamber are presented in Table III. The storage duration (weeks) and the density of each replication were plotted into a graph. The slope of the graph was calculated and then examined with one sample *t*-test using zero test point. The statistical analysis of the oleanolic acid cream and gel, as well as their bases, resulted in  $p > 0.05$ , indicating the absence of change in the densities of the dosage forms during the six-week storage.

**Table III. The densities of the dosage forms stored at temperature  $40 \pm 2^\circ\text{C}$ / RH  $75 \pm 5\%$**

Weeks	Densities (g/ml)			
	Cream	Cream Base	Gel	Gel Base
0	$1.07 \pm 0.07$	$0.90 \pm 0.02$	$1.20 \pm 0.02$	$1.23 \pm 0.01$
2	$0.78 \pm 0.18$	$0.89 \pm 0.05$	$1.25 \pm 0.08$	$1.08 \pm 0.09$
4	$0.84 \pm 0.05$	$0.87 \pm 0.03$	$1.77 \pm 0.05$	$1.09 \pm 0.12$
6	$0.82 \pm 0.14$	$0.82 \pm 0.12$	$1.21 \pm 0.04$	$1.03 \pm 0.11$

The observation results of the densities of oleanolic acid cream and gel stored at room temperature are presented in Table IV. The data were analyzed with paired *t*-test using  $\alpha = 0.05$ . This statistical analysis produced  $p > 0.05$ , indicating the absence of change in the densities of the dosage forms during the six-week storage.

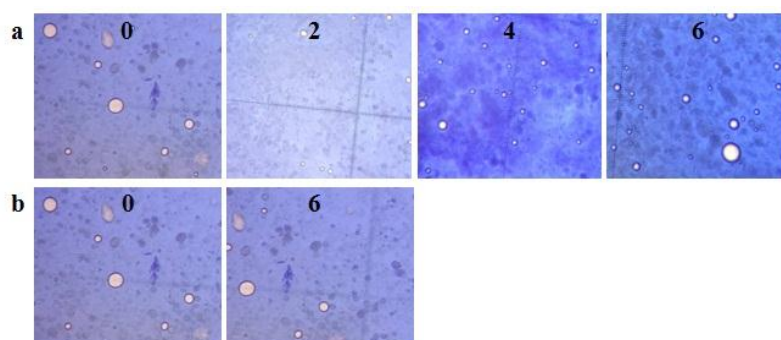
The absence of change in the densities of both oleanolic acid cream and gel shows that they remain homogeneous during the time of storage. This stability is a guarantee that the active substances are dispersed evenly throughout the dosage forms. In other words, the homogeneity is controlled correctly (Yoshioka and Stella, 2000).

**Table IV. The densities of the dosage forms stored at room temperature ( $27 \pm 2^\circ\text{C}$ /RH  $73 \pm 5\%$ )**

Weeks	Densities (g/mL)			
	Cream	Cream Base	Gel	Gel Base
0	$1.07 \pm 0.07$	$0.90 \pm 0.02$	$1.20 \pm 0.03$	$1.23 \pm 0.01$
6	$1.09 \pm 0.02$	$0.97 \pm 0.006$	$1.19 \pm 0.06$	$1.20 \pm 0.02$

### Emulsion type and droplet size

The observation results showed that the emulsion type of oleanolic acid cream was an oil-in-water emulsion (M/A, Figure 3) during the six-week storage both in a climatic chamber and at room temperature. It was evidenced by the blue (water) and not-blue (oil) colors on the background of the observation. Also, this emulsion type was in line with the expected specification, i.e., oil-in-water emulsion.



**Figure 3.** The observation results of the emulsions of oleanolic acid cream stored in a climatic chamber (a) and at room temperature (b). The numbers in the figure (0, 2, 4, and 6) represent the storage duration in weeks

The observation results of the particle size of oleanolic acid cream stored in a climatic chamber are presented in Table V. The storage duration (weeks) and particle size of each replication were plotted on a graph. The slope of the graph was calculated and then examined with one sample *t*-test using zero test point. The statistical analysis of the cream and cream base resulted in  $p > 0.05$ , indicating the significant difference of particle size during the six-week storage in a climatic chamber.

The observation results of the particle size of oleanolic acid cream stored at room temperature are presented in Table VI. Based on the observations, a statistical analysis, namely paired *t*-test with  $\alpha = 0.05$ , was performed. It showed a significance value of more than 0.05, indicating the absence of significantly different particle size during the six-week storage at room temperature.

**Table V.** The particle size of oleanolic acid cream stored at temperature  $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$

Weeks	Particle Size ( $\mu\text{m}$ )	
	Cream	Cream Base
0	$6.96 \pm 0.02$	$6.97 \pm 0.09$
2	$6.85 \pm 0.10$	$6.83 \pm 0.07$
4	$6.78 \pm 0.03$	$6.81 \pm 0.03$
6	$6.82 \pm 0.10$	$6.86 \pm 0.09$

**Table VI.** The particle size of oleanolic acid cream stored at room temperature ( $27 \pm 2^\circ\text{C}/73 \pm 5\% \text{RH}$ )

Weeks	Particle Size ( $\mu\text{m}$ )	
	Cream	Cream Base
0	$6.96 \pm 0.02$	$6.97 \pm 0.09$
6	$6.93 \pm 0.10$	$6.77 \pm 0.14$

The particle diameter of the oleanolic acid cream formulated in this research was in line with previous studies, i.e.,  $0.5\text{-}10 \mu\text{m}$  (Martin *et al.*, 1993). The droplet shape and size of an emulsion are influenced by the amount and efficiency of the emulsifier and the mixing and stirring processes. Observations on the cream showed that the droplet was present in the forms of not only balls but also

other shapes. This form is believed to be caused by stirring during the formulation and the merging of two or more droplets spontaneously, resulting in irregular shapes.

### Viscosity and flow properties

The observation results of the viscosity of oleanolic acid cream and gel stored in a climatic chamber and at room temperature are presented in Table VII and VIII, respectively. The storage duration (weeks) and viscosity of each replication were plotted on a graph. The slope of the graph was calculated and then examined with one sample *t*-test using zero test point. The analysis of oleanolic acid cream and gel, as well as their bases, produced  $p > 0.05$ , indicating the absence of statistically different viscosities during the six-week storage.

**Table VII. The viscosity of oleanolic acid cream and gel stored at temperature  $40 \pm 2^\circ\text{C}/75 \pm 5\%$  RH**

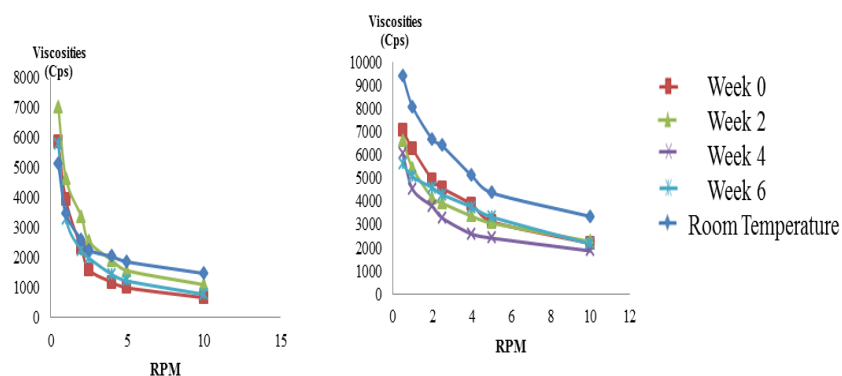
Weeks	Viscosity (cPs)			
	Cream	Cream Base	Gel	Gel Base
0	$1591 \pm 354.31$	$775 \pm 92.11$	$4566 \pm 505.55$	$920 \pm 54.50$
2	$2534 \pm 374.53$	$794.67 \pm 75.86$	$3919 \pm 299.44$	$919 \pm 38.79$
4	$2501 \pm 722.71$	$859 \pm 21.66$	$3282 \pm 680.12$	$905 \pm 49.80$
6	$1979 \pm 608.76$	$885 \pm 23.25$	$4293 \pm 659.85$	$956 \pm 55.43$

**Table VIII. The viscosity of oleanolic acid cream and gel stored at room temperature ( $27 \pm 2^\circ\text{C}/73 \pm 5\%$  RH)**

Weeks	Viscosity (cPs)			
	Cream	Cream Base	Gel	Gel Base
0	$1591 \pm 354.31$	$775 \pm 92.11$	$4566 \pm 505.55$	$920 \pm 54.50$
6	$2240 \pm 442.27$	$928 \pm 32.08$	$6383.67 \pm 2065.12$	$923.33 \pm 30.62$

The viscosity of oleanolic acid gel and cream was the same as the expected specification, i.e., 1000-5000 cPs. It was also in line with previous research (Yuliani *et al.*, 2012), which found that the viscosity of the gel of *Anredera cordifolia* (mignonette vine) using carbomer as the gelling agent was more stable than using Ca-alginate or CMC-Na. Carbomer can maintain the viscosity of a system through its capacity to keep the network formation. Therefore, a higher concentration can reduce the change (the difference) in the viscosities of the dosage forms.

The graphs of the observed flow properties are presented in Fig. 4. Based on the measurements of the viscosities of cream and gel at various rpm, the viscosity value decreases as the rpm (shearing stress) increases. As a conclusion, the flow properties of oleanolic acid cream and gel were pseudoplastic. This characteristic was due to the addition of pressure and shear rate, causing the molecules that were previously irregular to start to order themselves and form a straight line so that the flow resistance became smaller (Singh, 2006).



**Figure 4. The profile of the flow properties of oleanolic acid cream (a) and gel (b) at temperatures  $40\pm 2^{\circ}\text{C}/75\pm 5\% \text{RH}$  and  $27\pm 2^{\circ}\text{C}/73\pm 5\% \text{RH}$**

## CONCLUSION

Based on this research, it can be concluded that the two dosage forms of oleanolic acid, namely cream and gel, did not experience any changes in their organoleptic properties, densities, viscosities, and flow properties during the six-week storage. Also, the oleanolic acid cream was able to maintain its particle size and emulsion type during the tests.

## ACKNOWLEDGMENT

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EPICATEKINOLIN HCl DENGAN MINYAK ATSIRI  
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TERHADAP Escherichia coli ATCC 25922  
Sulastika Triandhi, Nur Milla, Taufiq Fauzan

PENGUJIAN PEMERIKSAAN EKSTRAK ETANOL AKAR  
SAMBUDZI (Andropogon squarrosus) (Burm. f.)  
MAYAL TERHADAP KADAR ASAM URAT SERUM  
BENYOT JANTAN GALUR SWISS YANG DIINDUKSI  
JUS MATI KIRAM DAN DIINTERAKSI DENGAN  
FLAVONOID. Azzahra Azzah, Nurul

AKTIVITAS ANTIPROLIFERASI SELULAT 3 EKSTRAK  
PETROLEUM ETER BAWANG MUDA (Allium  
cepa) BUNGA BAWANG (Allium cepa) DAN  
MAYAL (Allium cepa) TERHADAP  
MAMMARY TUMOR

EFEK EKSTRAK ETANOL BAWANG TERHADAP  
Cytosine Fosforase HASIL TERHADAP KADAR  
TERHADAP. Nurul Fauzan

UJI KEMAMPUAN UJI HASIL FASEM  
MENDAPILKAAN DI MAMMARY KADAR HASIL  
MAMMARY TERHADAP. Nurul Fauzan

UJI PEMERIKSAAN EKSTRAK ETANOL BAWANG  
MUDA TERHADAP HASIL PUTIH JANTAN  
GALUR SWISS YANG DIINDUKSI MAMMARY  
TUMOR

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<p><u>Uji aktivitas antibakteri ekstrak etil asetat daun binahong (Anredera scandens (L.) moq.) terhadap Shigella flexneri beserta profil kromatografi lapis tipis</u> LK Wardhani, N Sulistyani Jurnal Ilmiah Kefarmasian 2 (1), 1-6, 2012</p>	75
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