Journal of Tropical Pharmacy and Chemistry

Journal homepage: https://jtpc.farmasi.unmul.ac.id

Optimization of Gelling Agents and Emulsifiers in Emulgel Bases, and Physical Evaluation of Emulgel containing Sepabang (*Melastoma malabathricum* L.) Leaves Extract

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Abstract

Emulgel preparations are a preferred product compared to other topical preparations due to their dominant penetration power, including antioxidant effects on human skin. The selection of gelling agents and emulsifiers is the main parameter in the formulation of emulgel, especially those containing natural substance compounds. Sepabang (*Melastoma malabathricum* L.) leaf has a high antioxidant activity, so it is potent to be developed in the form of emulgel preparation. This research aims to optimize and formulate an emulgel containing Sepabang leaf extract that physically stable. Emulgel preparations are each formulated using Carbopol and hydroxypropyl methylcellulose (HPMC) as gelling agents and Tween 60 – Span 60 and combination of triethanolamine and stearic acid as emulsifiers, with a concentration of methanol extract of Sepabang leaves of 0.25%. Physical characteristics of emulgel preparations include pH value, viscosity determination, and spreadability test evaluated at room temperature for four weeks. The physical stability test is done by the Freeze-Thaw method for six cycles, of which one cycle consists of 48 hours at 4°C and 48 hours at 40°C. The results showed that the Sepabang emulgel that meets physical characteristics and stability parameters is F1 with HPMC as gelling agents and emulsifiers of a non-ionic surfactant (Tween 60-Span 60) 3%.

Keywords: emulgel, Carbopol, HPMC, emulsifier, Sepabang

Submitted: 18 June 2020 **Accepted**: 21 July2020 **DOI**: https://doi.org/10.25026/jtpc.v5i2.261

Introduction

The research of *Melastoma malabathricum* L. leaves extract has been shown to have antibacterial, antifungal, antioxidant, and anti-inflammatory activities [1,2]. The preliminary assay showed that the antioxidant activity of methanol extract of Sepabang leaves is included in the powerful antioxidant group with a value of IC_{50} 14.47 ppm and have antibacterial and antifungal activities [1]. In the proliferation of tissue, antioxidant content helps to increase the strength of collagen fibers that can increase the velocity of the epithelization of tissues [3]. Therefore, Sepabang leaves can be developed in the form of pharmaceutical preparations, especially the preparations for skin and mucous applications, or known as a topical dosage form.

A topical dosage form for the drug delivery system is an ointment, cream, or gel, but these three dosage forms have many disadvantages. The ointments and creams usually have sticky properties and have a lower coefficient of dispersing, making it more difficult to apply to the skin. The use of gel dosage form is higher because the gel is more comfortable to apply and not sticky, thus providing more comfort to the patient's skin. However, the gel has limitations in the delivery of hydrophobic drugs and that is not perfectly dissolved in water. These limitations are addressed by a new topical dosage form, emulgel. Emulgel is an emulsion preparation mixed with a gelling agent. This preparation can deliver hydrophobic compound, but it has gel-like properties. A topical dosage form currently widely developed is an emulgel because it has a better penetration capability on the skin than a cream. Emulgel is an emulsion that is mixed with a gelling agent. Therefore an emulgel produces a better hydration effect compared to a cream. Moreover, the delivery of dermatological drugs has some desirable properties such as easy to spread, non-sticky, and feels oily, emollient, easy to wash, bio-friendly, and has a good appearance [4,5].

Emulgel preparations must meet physical characteristics including pH value, viscosity, and spreadability, as well as the physical stability evidenced by a series of tests. The main components in emulgel preparations to determine its physical characteristics and stability are gelling agents and emulsifiers. Both of these main components determine the stability of the emulsion system on emulgels. Gelling agents that commonly used in the topical dosage formulations are cellulose derivates i.e., hydroxypropyl methylcellulose and other polymers i.e., Carbopol [6,7]. Both gelling agents are evidenced to have many advantages to maintain the emulgel form of drug preparation [8]. Emulsifiers which are widely developed in topical dosage formulations are nonionic surfactants such as Tween 60-Span 60, and anionic surfactants such as triethanolamine (TEA) combined with a stearic acid doe to their superiority to maintain the emulsion stability [9,10,11]. Based on some of these, this research is conducted to optimize the emulgel bases, and formulate emulgel containing methanol extract of Sepabang (*Melastoma malabathricum* L.) leaves that meets the physical characteristics and stability parameters.

Experimental

Preparation of gel base formula

For a gel base formula with Carbopol as a gelling agent, the Carbopol is mixed with aquadest using stirrer at 300 rpm speed and then hydrated for about 24 hours until a homogeneous base is obtained. A homogeneous base is then added with triethanolamine bit by bit until the gel mass is formed. While for a gel base formula with hydroxypropyl methylcellulose as gelling agent, HPMC is developed using hot water (60-70ºC), evenly dispersed powder over hot water in containers, then allowed overnight to be completely moistened. HPMC has been developed to be mixed with a homogeneous gel base [6,7].

Table 1. The Design of Emulgel Base Formulas

Formula	Gelling Agent	Emulsifier
B1	HPMC	Tween 60 - Span 60 3%
B2	HPMC	Tween 60 - Span 60 4%
B3	HPMC	Tween 60 - Span 60 5%
B4	HPMC	TEA – Stearic acid 1%
B5	HPMC	TEA – Stearic acid 2%
B6	HPMC	TEA – Stearic acid 3%
B7	Carbopol	Tween 60 - Span 60 3%
B8	Carbopol	Tween 60 - Span 60 4%
B9	Carbopol	Tween 60 - Span 60 5%
B10	Carbopol	TEA – Stearic acid 1%
B11	Carbopol	TEA – Stearic acid 2%
B12	Carbopol	TEA – Stearic acid 3%

*3 replications of each formula

Preparation of Emulgel

The Sepabang extract dissolved to deionized water and propylene glycol. The water phase and oil phase are heated apart to 70°C, then mixed using a stirrer. Once the emulsion is formed, the previously prepared gels are added slowly, and the area in the emulsion mass is continuously stirring to form the emulgel [6]. When the emulgel reached a temperature of 40-50°C, the dispersions of Sepabang extract was added, and stirring continued until the extract and emulgel base homogenously mixed.

Physical evaluation of Emulgel

The emulgel evaluation includes organoleptic observation, the determination of viscosity and pH value, spreadability test, and physical stability test using the Freeze-Thaw method [6].

Organoleptic observation

Organoleptic observations include color, smell, and homogeneity. Homogeneity can be observed by applying emulgel preparations on the surface of the object-glass. Observations are conducted weekly for one month at room temperature [10, 11].

Determination of Viscosity

The Emulgel viscosity evaluation was performed using a digital Brookfield Viscometer with 28 spindles and a 2.5 rpm speed. Emulgel preparations are inserted into the container to measure the viscosity of up to three-quarters of the containers and dipped into emulgel, then the appliance is turned on and observed increased viscosity that reads to reach the highest number. The highest amount given indicates the viscosity of an emulgel in a Pa.s unit. A viscosity of the preparations is observed weekly for one month of storage at room temperature [6,9].

Spreadability test

This test is done by putting the emulgel on the transparent glass placed on the graph paper, then the glass is covered with another transparent glass, left for approximately 5 minutes, and added load then observed the diameter of the formed area [6,8].

Determination of pH value

This test is done by a pH meter that has been calibrated with standard buffer solutions of pH 4 and pH 7 [9,10,11].

Freeze-Thaw method

The Freeze-Thaw method is performed at two different temperatures that are 4°C and 40°C. The first step is to weigh as much as 4 grams of emulgel and put in a 10 mL vial, and each formula is prepared four vials each. The vial is inserted into the Freezer (4°C) and stored for 48 hours, then it moves into the climatic chamber (40°C) and stored for 48 hours, this is the first cycle. Afterward, the vial is inserted back into the Freezer (48 hours) and the climatic chamber (48 hours), this is the second cycle. So on until the sixth cycle. Each one cycle is issued one vial for each formula and is observed organoleptic and the possibility of emulsion instability [9,10].

■ Results and Discussion

Optimization of Gelling Agents and Emulsifiers in Emulgel Bases

A series of base optimization is done by varying two primary constituent materials of emulgel bases i.e., gelling agents and emulsifiers. Gelling agents used are hydroxypropyl methylcellulose (HPMC) and Carbopol, while emulsifiers used are Tween 60–Span 60 and a combination of triethanolamine (TEA) and stearic acid. The formula design of the emulgel bases can be seen in Table 1.

The physical characteristics data resulting from these 12 formulas of emulgel bases can be seen in Table 2. The best characteristics are shown in the formula (with Tween 60 – Span 60 as emulsifiers) i.e., formula B1, B2, B3, B7, B8, and B9. while emulgel bases (with emulsifier Triethanolamine-stearate) showed less good results wherein, formed foam on emulgel, namely in the formula B4, B5, B6, B10, B11, B12.

The next physical evaluations of emulgel formula are the determination of pH, viscosity, and spreadability of the preparations, performed over four cycles (4 weeks) at room temperature. As shown in Figure 1, The pH assignment results indicate that the best formula is B1 and B8. They were being chosen doe to met the skin pH criteria

in the range of 4.5–6.5. Besides that, the graphs also show that the pH changes of each formula are relatively stable during the 4 test cycles.

The results of a physical evaluation based on viscosity, as seen in Figure 2 indicate that all emulgel base formulas qualify for the ideal viscosity for a semisolid dosage of 2–50 Pa.s. Besides, viscosity changes also remain stable in 4 test cycles. Similarly, the spreadability test, as seen in Figure 3, is indicated that all emulgel bases are easy to spread and remain stable during the 4 test cycles.

The test results of the base physical stability of the emulgel with the Freeze-Thaw method for 6 cycles whereby one cycle consists of 48 hours at 4°C and 48 hours at 40°C, which is done to obtain the best base formula shown in Table 3. The test results show that all emulgel base formulas are physically stable, i.e., not experiencing discoloration, smell, consistency, or phase separation.

Table 2. The Observation Results of Emulgel Base Physical Characteristics

Formula*	Color	Homogenity	Consistency
B1	white	Homogeneous	Viscous, easy to smear
B2	white	Homogeneous	Viscous, easy to smear
B3	white	Homogeneous	Viscous, easy to smear
B4	white	Homogeneous, slightly foamy	Viscous, easy to smear
B5	white	Homogeneous, slightly foamy	Viscous, easy to smear
B6	white	Homogeneous, slightly foamy	Viscous, easy to smear
B7	white	Homogeneous	Viscous, easy to smear
B8	white	Homogeneous	Viscous, easy to smear
B9	white	Homogeneous	Viscous, easy to smear
B10	white	Homogeneous, slightly foamy	Viscous, easy to smear
B11	white	Homogeneous, slightly foamy	Viscous, easy to smear
B12	white	Homogeneous, slightly foamy	Viscous, easy to smear

*3 replications of each formula

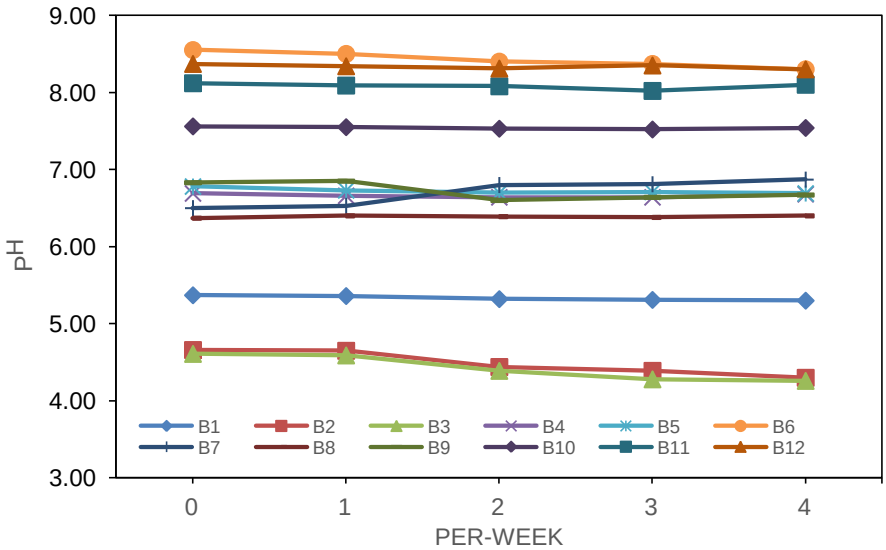

Figure 1. pH value profile of various emulgel bases for 4 weeks

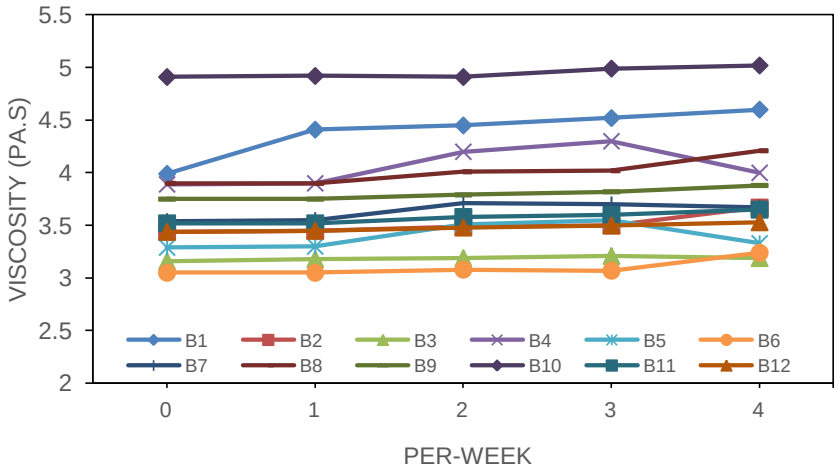

Figure 2. Viscosity profile of various emulgel bases for 4 weeks

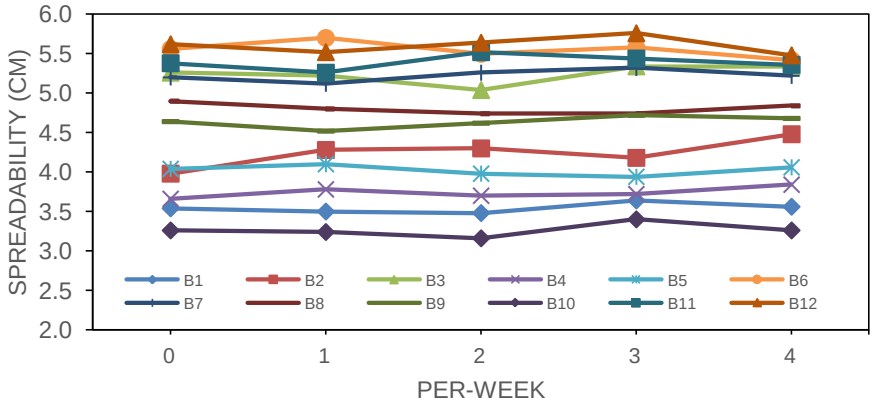

Figure 3. Spreadibility profile of various emulgel bases for 4 weeks

Table 3. The Result of Emulgel Base Stability Test with Freeze-Thaw Method

Formula	Physical Stability Test per-Week					
	1	2	3	4	5	6
B1	-	-	-	-	-	-
B2	-	-	-	-	-	-
B3	-	-	-	-	-	-
B4	-	-	-	-	-	-
B5	-	-	-	-	-	-
B6	-	-	-	-	-	-
B7	-	-	-	-	-	-
B8	-	-	-	-	-	-
B9	-	-	-	-	-	-
B10	-	-	-	-	-	-
B11	-	-	-	-	-	-
B12	-	-	-	-	-	-

(-) Does not occur organoleptic changes (color and smell), no separation of phases and consistency

Based on the physical evaluation of the emulgel base formula as a whole, it can be concluded that the emulgel base formula that meets all the criteria includes physical characteristics, pH determination, viscosity, spreadability, and stability testing are formulas B1 and B8. These two emulgel base formulas use nonionic surfactants i.e., Tween 60 and Span 60 as emulsifier.

Thus, based on those criteria of pH, viscosity, and spreadability parameters, both formulas are chosen to be continued at the formulation stage of the emulgel preparations containing 0,25% methanol extract of Sepabang leaves.

Table 4. The Observation Result of Physical Caratecteristics of Sepabang Emulgel

Parameters	The observation result	
	F1	F2
Color	Light green	Light green
Homogenity	homogeneous	homogeneous
Consistency	Viscous, easy to smear	Viscous, easy to smear

F1: Emulgel containing 0,25% Sepabang extract with B1 base
F2: Emulgel containing 0,25% Sepabang extract with B8 base

Table 5. The Result of pH, Viscosity, and Spreadability of Sepabang Emulgel

Parameters		Per-week				
		0	1	2	3	4
pH	F1	6,41 ± 0,03	6,37 ± 0,02	6,38 ± 0,06	6,40 ± 0,02	6,42 ± 0,05
	F2	6,48 ± 0,04	6,51 ± 0,04	6,51 ± 0,06	6,53 ± 0,08	6,54 ± 0,02
Viscosity (Pa.s)	F1	3,89 ± 0,02	3,81 ± 0,35	3,66 ± 0,31	3,53 ± 0,40	3,47 ± 0,45
	F2	9,82 ± 0,04	9,77 ± 0,35	9,63 ± 0,25	9,51 ± 0,20	9,41 ± 0,11
Spreadability (cm)	F1	5,38 ± 0,3	5,22 ± 0,3	5,60 ± 0,4	5,60 ± 0,4	5,48 ± 0,3
	F2	3,66 ± 0,2	3,86 ± 0,4	3,86 ± 0,3	3,5 ± 0,2	3,84 ± 0,3

* ẋ value ± SD (n = 3)

Table 6. Results of the stability test of Sepabang by using with Freeze-Thaw method

Formula	Physical stability test per-week					
	1	2	3	4	5	6
F1	-	-	-	-	-	-
F2	-	-	+	+	+	+

(+) Color change occurs
(-) Does not occur organoleptic changes (color and smell), no separation of phases and consistency

The physical characteristics result as Table 4 shows that both the formula is homogeneous and easily applied, with the light green color of Sepabang leaves.

The results of the physical stability test with the Freeze-Thaw method for six cycles as of Table 6 shows that the formula of methanol extract of Sepabang leaves (*Melastoma malabathricum* L.) is physically stable only F1, while F2 experiences discoloration since the 3rd cycle until the 6th cycle. Therefore, based on the results of overall physical evaluation covering physical characteristics, pH, viscosity, spread, and physical stability, it can be concluded that the most excellent and physically stable emulgel is the F1 formula.

It is possible because F2 uses Carbopol as a gelling agent, where this material is affected by susceptible to alters in environmental pH changes, especially after the addition of extracts. Moreover, Carbopol is known to have an incompatibility with phenolic compounds [12], wherein the phenolic compound contained by Sepabang (*Melastoma malabathricum* L.) extract [1]. In contrast, the F1 formula with HPMC as a gelling agent tends to be more stable to pH changes.

■ Conclusion

The emulgel base with nonionic surfactant (Tween 60 and Span 60) as an emulsifier is better than anionic surfactant (triethanolamine) and stearic acid, when combinate with Carbopol or HPMC as a gelling agent. The emulgel preparations containing 0.25% methanol extract of Sepabang leaves (*Melastoma malabathricum* L.) in formula F1 using HPMC as a gelling agent is more optimum and physically stable than formula F2.

Acknowledgments

Thanks to the B2P2TOOT Health Research and Development Agency of the Indonesian Ministry of Health as a grant of research drug and medicinal herbs (RISTOJA) for the implementation of this research.

References

[1] Mita, N., Arifuddin, M., Ardana, M., Priastomo, M., Farida, S., 2017. Determination of Extract Quality Parameters of Sepabang (*Melastoma malabathricum* L.) Leaves from Dayak Bahau and Abai Ethnics in Borneo and Its Antibacterial and Antifungal Activities, *3rd International Seminar on Natural Product*, April 1st 2017, Makassar, Indonesia

[2] Joffry, S.M., 2012. Melastoma malabathricum L. Smith Ethnomedicinal Uses, Chemical Constituents, and Pharmacological Properties: A Review, Evidence-Based Complementary and Alternative Medicine, *Hindawari Publishing Corporation, Evidence-Based Complenetary and Alternative Medicine*, Volume 2012, Article ID 258434, Page 1-48

[3] Thakur, R., Jain, N., Pathak, R., Sandhu, S.S.. 2011. Practices in Wound Healing Studies of Plants, Review Article Evidence-Based Complementary and Alternative Medicine, p. 1-15

[4] Yadav S.K., Mishra M.K., Tiwari A., Shukla A. Emulgel: A New Approach for Enhanced Topical Drug Delivery. Int J Curr Pharm Res, 2016, 9(1), 15-19. DOI: http://dx.doi.org/10.22159/ijcpr.2017v9i1.16628

[5] Prasad, Mahapatra Annada, et al, 2012. Formulation and Evaluation of Cream Prepared From Croton Sparsiflorus Morong And Their Wound Healing Activity. *International Journal Of Research In.*

[6] Handayani, M., Mita, N., & Ibrahim, A., 2015. Formulasi dan Optimasi Basis Emulgel Carbopol 940 dan Trietanolamin dengan Berbagai Variasi Konsentrasi. *Proceeding of Mulawarman Pharmaceuticals Conferences*, 1(1), 53-60. https://doi.org/10.25026/mpc.v1i1.8

[7] Pramita R, I., Fitriani, V. Y., Mita, N., & Ramadhan, A. M., 2017. Pegaruh Konsentrasi HPMC (Hidroxy Propyl Methyl Cellulose) Sebagai Gelling Agent dengan Kombinasi Humektan Terhadap Karakteristik Fisik Basis Gel. *Proceeding of Mulawarman Pharmaceuticals Conferences*, 5(1), 139-148. https://doi.org/10.25026/mpc.v5i1.230

[8] Ajazuddin, Alexander A., Khichariya A., Gupta S.,Patel R.J., Giri T.K.,Tripathi D.K. 2013. Review: Recent expansions in an emergent novel drug delivery technology: Emulgel. Journal of Controlled Release 171 (2013) 122–132, DOI http://dx.doi.org/10.1016/j.jconrel.2013.06.030

[9] Mita, N., 2015. Formulasi Krim dari Kulit Buah Kakao (Theobroma cacao L.) Berkhasiat Antioksidan, *Journal of Tropical Pharmacy and Chemistry*, 3(1), 12-21. https://doi.org/10.25026/jtpc.v3i1.83

[10] Anggraini, S., Mita, N., & Ibrahim, A., 2015. Formulasi Krim Antioksidan Daun Cempedak (Artocarpus champeden Spreng), *Proceeding of Mulawarman Pharmaceuticals Conferences*, 2(1), 8-15. https://doi.org/10.25026/mpc.v2i1.32

[11] Mita, N., Tarini D., S., & Damayanti, S. (2015). Evaluasi Formula Krim Minyak Biji Delima (Punica granatum L.) dan Uji Aktivitas Antioksidan dengan Metode Î²-Carotene Bleaching, *Journal of Tropical Pharmacy and Chemistry*, 3(2), 109-119. https://doi.org/10.25026/jtpc.v3i2.97

[12] Rowe R.C., Sheskey P.J., Owen S.C. 2006. Handbook of Pharmaceutical Excipients. Fifth Edition. *Pharmaceutical Press*, London UK. page 113