
Comparison of carbopol 934 and 941 as thickeners on ketoconazole microemulsions based on physical stability

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ABSTRACT

As a drug delivery system, ketoconazole microemulsion in virgin coconut oil (oil phase) is added with a thickening agent to create transdermal dosage form. This study aimed to compare the physical stabilities of ketoconazole microemulsions formed with different thickeners, namely Carbopol 934 and Carbopol 941. The formula used varying concentrations of Carbopol 934 and Carbopol 941, i.e., 0.15% and 0.25%. The stability was observed during eight-week storage in which the conditions were controlled by different degrees of temperature, i.e., 4⁰C, 25-30⁰C (room temperature), and 40⁰C. The stability tests included organoleptic observation, pH, surface tension, viscosity, particle size, and zeta potential. Based on the Kruskal-Wallis test results, ketoconazole microemulsion with Carbopol 941 that had been stored in different temperature showed a significant difference in particle size (significance value < 0.05), but it did not apply to Carbopol 934. The evaluation revealed that compared to 0.25% of Carbopol 934, microemulsion with 0.15% of Carbopol 934 had a smaller difference between the time intervals. This research concluded that the use of 0.15% of Carbopol 934 as a thickener in ketoconazole microemulsion had better physical stability compared to Carbopol 941 due to the influence of temperature and length of storage.

Keywords: physical stability, ketoconazole microemulsion, thickener, Carbopol 934, and Carbopol 941

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INTRODUCTION

Ketoconazole is a topically and orally administered antifungal. In oral administration, ketoconazole may inhibit the liver enzyme CYP3A4 cytochrome P450 isoenzyme, causing hepatotoxicity when used in large doses for more than one month. Meanwhile, in topical application, it is not associated with hepatotoxic risk because the amount absorbed by the body is considerably low (Sweetman, 2009). To optimize drug absorption in the skin, ketoconazole is created in the form of microemulsion and treatment with large doses is reduced to minimize hepatotoxic side effects. Microemulsion is a thermodynamically stable system with transparent (translucent) color and low viscosity; it is a dispersion of oil and water stabilized by the film of surfactant molecules (Agoes 2012).

As a drug delivery system, ketoconazole microemulsion in virgin coconut oil (oil phase) is added with a thickening agent to create a transdermal dosage form. The addition of Carbopol as a thickener aims to improve physical stability, avoid the use of Tween 80 with large concentration, and increase the viscosity of ketoconazole microemulsions; hence, increasing the comfort in topical application. Aside from being stable at high temperature, Carbopol is a good and efficient thickening agent even when used in low concentration, which allows its use as a suspending agent and stabilizer in emulsions, pastes, ointments, and gels (Jeon, 2007 in Ben *et al.*, 2013). Carbopol 941 and Carbopol 934 are used because at the same concentration their viscosity is lower than Carbopol 940 (Rowe *et al.*, 2009). Carbopol 941 is cross-linked with allyl ethers of pentaerythritol, while Carbopol 934 is cross-linked with allyl ethers of sucrose (United States Pharmacopeial Convention, 2007). Carbopol gives dosage form a high viscosity capable of slowing the droplet movement, which consequently reduces the rate or speed of dosage form separation and induces stability (Ben *et al.*, 2013).

MATERIALS AND METHODS

Material

The materials used in this research were virgin coconut oil from PT Herban Bagoes, Carbopol 934 from PT Shrec Chemicals, and Carbopol 941 from PT Zhongtang (Dalian) Materials.

Method

Examining the characteristics of virgin coconut oil

This examination included organoleptic analysis and specific gravity test of virgin coconut oil. The organoleptic analysis was carried out by observing the shape, color, and odor.

Creating microemulsion dosage form (Arfiani 2010)

Table I. The formula of virgin coconut oil (VCO) microemulsion

Components	%	Functions
Ketoconazole	0.4	Active substance
VCO	5	Oil phase
Tween 80	35	Surfactant
Sorbitol	10	Cosurfactant
Nipagin	0.18	Preservative
Nipasol	0.02	Preservative
Aquadestilata ad	100	Water phase

Tween 80 was dissolved in aquadest that was heated to 60°C (M1). Nipagin and Nipasol were dissolved also dissolved in heated aquadest (M2). Ketoconazole was dissolved in virgin coconut oil (oil phase). M2 was mixed with M1 (water phase). The oil phase was added to the water phase and stirred with a magnetic stirrer at 500 rpm for 15 minutes. The temperature was maintained lower than

or equal to 40°C. Then, sorbitol was added dropwise while stirred with a magnetic stirrer at 500 rpm for 15 minutes.

Creating microemulsion dosage form with thickening agent (Arvindbhai *et al.*, 2014)

Table II. The formula of ketoconazole microemulsion with Carbopol as thickener

Components	F1	F2	F3	F4	F5	Functions
Carbopol 934	-	0.15g	0.25 g	-	-	Thickening agent
Carbopol 941	-	-	-	0.15g	0.25g	Thickening agent
50% TEA Solution	-	0.3mL	0.6mL	0.3mL	0.6mL	pH neutralizer
Aquadest	-	ad 10mL	ad 10mL	ad 10mL	ad 10mL	Dispersant
Microemulsion	100 mL	90mL	90mL	90mL	90mL	Microemulsion

Carbopol was dispersed in aquadest and left for 24 hours. Afterward, it was added with 50% TEA solution until the pH reached 5.5 and, then, stirred until homogeneous. The microemulsion produced in Point 2 was mixed with the thickening base using a magnetic stirrer at 300 rpm for 15 minutes at room temperature.

Measuring diameter in spreadability test (Lateh, 2015)

A sample of 0.5 gram was placed in the middle of the first petri dish, which was attached to a graph (millimeter) paper. The diameter was measured by placing a 46-gram petri dish on top of the first petri dish. The spreadability was determined based on the diameter of the sample that had spread to two directions after 1 minute. Then, another weight (i.e., 50 gram) was added to it until a constant spreadability was obtained. The diameter of the spread was measured after 1 minute.

Examining the physical stability of microemulsion

Phase separation (Gozali *et al.*, 2009)

This test was performed with six cycles (cycling test). Each cycle consisted of a dosage form stored at 4°C ± 2°C for 48 hours. It was later stored at the same temperature for the next 48 hours. In this test, the indications of separation were observed organoleptically.

Physical stability (Natalia, 2012)

In this test, the dosage forms were stored at different temperatures, namely 4°C ± 2°C, 25-30°C ± 2°C (room temperature), and 40°C ± 2°C, for eight weeks. Afterward, they were evaluated every two weeks. The evaluation included organoleptic test, pH, surface tension, viscosity, zeta potential, and particle size.

Organoleptic test

The microemulsion dosage form was observed for any discoloration, changes in odor and clarity, as well as any changes that might occur during storage.

pH measurement (Departemen Kesehatan RI, 2014)

The pH was measured with pH meter at a temperature of 25°C ± 2°C by washing the electrode, rinsing it with distilled water, and letting it dry. The pH meter was calibrated using standard buffer solutions with pH 4 and pH 7. The electrode was inserted into the microemulsion, and the pH was recorded.

Viscosity test

The viscosity of the dosage form was measured using the Brookfield LVDVE Viscometer at room temperature ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}$). The microemulsion was put into a 250 mL beaker glass, attached with Spindle No. 63 for F1 and Spindle No. 64 for F2-F5, and set until the fill line of the spindle was covered with the samples. The speed for F1 was 20 rpm, while the one for F2-F5 was 10 rpm. The viscosity was recorded after 2 minutes, and three readings were performed.

Surface tension measurement (Voigt, 1995)

The surface tension was measured with the Du Noüy ring method, which used a tensiometer that had been calibrated previously. The ring was attached to the latches of the measurement system without contact with the test liquid. The table with the test liquid was raised toward the holder until the ring was 2-3 mm below the surface of the ring. The table and the test liquid were moved downward slowly until the ring was lifted from the solution. The force was determined by measuring the turning angle of the circular wire used to pull out the platinum-iridium ring from the effect of interfacial forces.

Particle size and zeta potential (Martin *et al.*, 1993; Voigt, 1995)

The sample (1 mL) was diluted with aquadest (9 mL). The particle size and the zeta potential were measured with DelsaMax PRO light scattering analyzer. The solution was put into the flow cell, which then inserted into the cell in the equipment. The analyzer was turned on, and the DLS & PALS (Simultaneous) menu was selected. After 9 minutes, it produced a set of data consisting of particle size and zeta potential.

RESULTS AND DISCUSSION

The characteristics of virgin coconut oil

The characteristics of the virgin coconut oil met the requirements or the standards set in the Farmakope Indonesia Edition III.

Table III. The evaluation results of the characteristics of virgin coconut oil

Evaluations	Results	Standard of FI III
Organoleptic Test	a. Shape: Liquid	Liquid
	b. Color: Clear	Clear
	c. Smell: Weak smell, typical of coconut oil	Odorless or weak smell
Specific Gravity	0.9496 g/mL	0.940 – 0.950 g/mL

Spreadability

The spreadability of microemulsion without thickening agent (F1) was higher (i.e., 6.80 cm) than with thickening agent (F2-F5= 4.4-6.3 cm).

Table IV. The spreadability test results of ketoconazole microemulsion with Carbopol as thickener

Formulas	Diameters with 46-gram Weight (cm±SD)	Diameters with 50-gram Weight (cm±SD)
F1	6.30±0.4	6.80±0.4
F2	6.00±0.2	6.30±0.4
F3	4.20±0.2	5.00±0.3
F4	4.50±0.2	5.30±0.2
F5	3.80±0.2	4.40±0.2

There is a structural difference between Carbopol 941 and 934. Carbopol 941 is cross-linked with allyl ethers of pentaerythritol, while Carbopol 934 is cross-linked with allyl ethers of sucrose (United States of Pharmacopeial Convention, 2007). The decrease in spreadability occurs because the viscosity of the dosage form increases (Prमितasari, 2011). A high viscosity makes the dosage form difficult to flow and, thereby, spread.

Organoleptic observation results

At a temperature of 4⁰C, microemulsion without thickening agent (F1) became more viscous in Week 2. At the same temperature, microemulsion with 0.15% of Carbopol 934 gelatinized in Week 4. It had a higher viscosity than before it was stored at 4⁰C. The particles tended to merge and form bonds with denser ones, resulting in increased viscosity and decreased flow rate (Dewi, 2010). However, when the microemulsion was restored at room temperature, it returned to its original state, i.e., dilute and easily poured. Microemulsion with 0.25% of Carbopol 934 showed formal changes at 40⁰C in Week 8. It had a lower viscosity than before it was stored at 40⁰C. The particles of the microemulsion tend to stretch at high temperature and, thereby, widen the space between them. Consequently, viscosity decreases as flow rate increases.

Phase separation

This research used cycling test with six cycles. The physical feature, particularly the occurrence of phase separation, of the microemulsion was then observed. After the six cycles, there was no difference between the microemulsions prepared with different formulas. They remained clear in color, indicating that all formulas in this research produced stable microemulsions with reversible change.

Surface tension

Microemulsion without thickener had lower surface tension (i.e., 30.3 dyne/cm) than the one with a thickening agent (i.e., 39.5-57.1 dyne/cm). Microemulsion with Carbopol 934 had stronger surface tension than Carbopol 941 because, even with the same concentration, the viscosity of Carbopol 934 was higher than Carbopol 941. Changes in surface tension occurred in all three temperatures. The surface tension decreased every two weeks (time interval of observation). The results of nonparametric analysis showed that the length of storage affected the surface tension of microemulsion, except for the one without a thickening agent. This analysis also found that microemulsion with a thickener (F2, F3, and F5) was not dependent on temperature, except for the one with 0.15% of Carbopol 941 (F4) and without a thickening agent (F1).

Table V. The surface tension of ketoconazole microemulsion with carbopol as thickener at a temperature of 4°C

Formulas	Time (week)				
	0	2	4	6	8
F1	30.3±0.25	31.0±0.61	34.6±0.51	35.1±0.66	35.8±0.25
F2	39.5±0.12	36.1±0.12	34.5±0.76	32.9±0.60	28.1±1.01
F3	57.1±0.38	50.8±0.25	45.8±0.23	43.5±0.47	42.4±0.10
F4	42.8±0.21	41.1±0.29	37.1±0.10	33.6±0.06	32.6±0.35
F5	47.0±0.35	46.2±0.36	42.8±0.75	40.2±0.32	38.6±0.87

Table VI. The surface tension of ketoconazole microemulsion with Carbopol as thickener at room temperature (25 - 30°C)

Formulas	Time (week)				
	0	2	4	6	8
F1	30.3±0.25	32.5±0.44	33.5±0.61	34.4±1.00	35.1±0.76
F2	39.5±0.12	38.8±0.25	36.5±0.20	34.2±0.80	33.5±1.15
F3	57.1±0.38	52.8±0.55	47.2±0.49	38.6±0.51	36.5±0.42
F4	42.8±0.21	42.2±0.26	41.8±0.29	39.0±0.50	38.0±0.17
F5	47.0±0.35	46.5±0.25	44.5±0.51	41.1±0.74	40.5±0.45

Table VII. The surface tension of ketoconazole microemulsion with carbopol as thickener at a temperature of 40°C

Formulas	Time (week)				
	0	2	4	6	8
F1	30.3±0.25	29.5±0.36	27.5±0.31	26.4±0.45	24.9±1.33
F2	39.5±0.12	35.9±0.46	34.6±0.79	31.3±1.18	28.1±1.68
F3	57.1±0.38	53.7±1.01	48.7±3.34	35.8±0.21	34.9±1.14
F4	42.8±0.21	41.9±0.44	41.5±0.47	38.6±0.51	37.1±0.58
F5	47.0±0.35	42.3±0.52	41.8±0.32	41.1±0.55	39.7±0.26

Viscosity

Microemulsion without thickener had a lower viscosity (i.e., 1,268 cps) than the one with a thickening agent (i.e., 4,364-46,197 cps). The viscosity of microemulsions stored at three different temperatures changed in every time of observation. It increased because the structure of microemulsion became more dense during the storage. The globules were difficult to move due to the narrow space between the particles. Meanwhile, the decreased viscosity was affected by the temperature rise. High temperature can reduce viscosity (Ben *et al.*, 2013).

Table VIII. The viscosity of ketoconazole microemulsion with carbopol as thickener at a temperature of 4°C

Formulas	Time (week)				
	0	2	4	6	8
F1	1,268±79	3,334±120	3,977±56	4,788±22	5,653±10
F2	4,364±42	9787±42	13,540±67	15,866±16	20,108±17
F3	46,197±23	285,433±13	357,633±14	459,633±18	503,888±35
F4	27,450±35	33,743±53	51,517±67	56,277±11	58,655±32
F5	43,950±20	48,357±61	71,400±62	81,443±55	89,519±11

Table IX. The viscosity of ketoconazole microemulsion with Carbopol as thickener at a temperature of 25-30°C

Formulas	Time (week)				
	0	2	4	6	8
F1	1,268±79	939±39	889±23	781±15	709±12
F2	4,364±42	3,366±12	2,664±28	1,844±13	1,745±45
F3	46,197±22	30,630±11	25,323±61	17,220±38	15,187±46
F4	27,450±35	27,117±46	26,737±12	19,987±45	16,638±36
F5	43,950±20	34,197±50	34,003±470	29,643±50	29,103±32

Table X. The viscosity of ketoconazole microemulsion with carbopol as thickener at a temperature of 40°C

Formulas	Time (week)				
	0	2	4	6	8
F1	1,268±79	378±39	361±33	324±38	302±24
F2	4,364±42	3,574±9	2,406±88	1,642±95	945±10
F3	46,197±22	11,627±39	10,636±50	10,467±67	8,400±23
F4	27,450±35	21,458±243	15,533±50	14,407±72	13,473±94
F5	43,950±20	40,070±11	38,470±20	38,030±27	34,503±66

Globular size

Microemulsion without thickener had a smaller particle size (i.e., 12.63 nm) compared to the one with a thickening agent (i.e., 21.53-57.67 nm). The dosage form with Carbopol 934 had a smaller particle size than the one with Carbopol 941. The structural difference between these two thickening agents affects the particle size of the dosage form even when they are applied with the same concentration. Particle size increases in temperature and time because the smaller particles merge into larger ones. Moreover, the closer distance between the adjacent particles enables the merging. The polydispersity index of microemulsions formed with different formulas and stored in varying degrees of temperature was 0.571, categorized as monodisperse and relatively uniform. The nonparametric analysis results showed that the particle size in all formulas was not dependent on storage temperature, except in F4 and F5. It was dependent on the length of storage.

Table XI. The globular size of ketoconazole microemulsion with carbopol as thickener at a temperature of 4°C

Formulas	Time (week)				
	0	2	4	6	8
F1	12.63±1.10	15.47±0.23	18.13±1.04	19.37±1.39	22.37±3.25
F2	21.53±1.19	33.80±0.61	38.20±0.10	40.83±0.85	44.67±1.33
F3	26.27±1.39	52.37±1.24	60.30±0.44	71.47±0.85	77.47±0.25
F4	36.77±1.42	44.87±0.40	45.43±0.15	46.77±0.40	48.33±0.21
F5	57.67±0.58	58.13±0.35	60.60±0.62	62.03±0.57	68.33±0.61

Table XII. The globular size of ketoconazole microemulsion with carbopol as thickener at a temperature of 25 – 30°C

Formulas	Time (week)				
	0	2	4	6	8
F1	12.63±1.10	20.00±0.95	26.23±0.35	66.67±2.32	74.03±1.11
F2	21.53±1.19	41.30±0.66	43.03±0.31	43.30±0.40	44.60±0.26
F3	26.27±1.39	64.13±1.06	67.83±0.23	69.30±0.17	70.00±0.10
F4	36.77±1.42	47.57±0.93	49.47±1.10	53.50±0.10	55.03±0.40
F5	57.67±0.58	64.17±0.32	68.97±0.38	70.97±0.60	72.50±0.40

Table XIII. The globular size of ketoconazole microemulsion with carbopol as thickener at a temperature of 40°C

Formulas	Time (week)				
	0	2	4	6	8
F1	12.63±1.10	16.03±1.80	18.90±2.46	60.17±1.07	74.20±0.53
F2	21.53±1.19	28.97±2.98	36.67±0.51	40.27±0.38	55.20±1.84
F3	26.27±1.39	41.00±1.66	49.17±0.95	62.10±0.53	76.47±2.46
F4	36.77±1.42	46.93±0.84	55.13±0.71	84.33±4.97	98.00±1.32
F5	57.67±0.58	123.57±1.89	146.20±1.18	164.17±2.50	170.47±6.60

Microemulsion without thickener had smaller zeta potential (i.e., -7.97) compared to the one with a thickening agent (i.e., -9.33 to -14.51). The zeta potential in this research does not meet the desired criteria. The stability of an emulsion is categorically poor when its zeta potential is less than 30. On the contrary, an emulsion is stable when the zeta potential is larger than 30. The positive (+) and negative (-) values in zeta potential indicate the pH of the dosage form. The positive (+) value represents low pH (acid), while the negative (-) one shows high pH (base) (Ben *et al.*, 2013). The zeta potential in this research was negative because the pH of the dosage form was 6.26-6.92 (base). The statistical analysis of the zeta potential showed that the microemulsion with thickener (F2, F3, F4, and F5) was not affected by temperature and length of storage. Meanwhile, the zeta potential of microemulsion without thickener (F1) was dependent on temperature and length of storage.

CONCLUSION

This research concludes that the use of 0.15% of Carbopol 934 as a thickening agent in ketoconazole microemulsion gives better physical stability than Carbopol 941.

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