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Kojic Acid Penetration: Effect of Carbomer - Tween 80 Agregate Formation

N. Rosita, S. E. Jayanti, T. Erawati

Department of Pharmaceutics, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia

*Corresponding author: T. Erawati (era_ffua@yahoo.com)

ABSTRACT: Kojic acid is well known as a depigmentation agent is used for hyper-pigmentation therapy. The objective of this study was to determine the effect of Carbomer-Tween 80 aggregate on kojic acid penetration. Kojic acid is quickly absorbed through the skin, remaining on the epidermis not long enough to inhibit melanogenesis activities; Carbomer-Tween 80 aggregate was used to control the release of kojic acid. Tween 80 was added in different concentrations (0.01% for F1, 0.02% for F2, and 0.04% for F3) to carbomer (0.25%) dispersion to create aggregate, then the aggregate was added to a vanishing cream base. Kojic acid penetration was observed by measuring the inhibition activity of tyrosinase. The inhibitor activity was determined by measuring the absorbance of dopachrome, a product of tyrosinase reacting to L-tyrosine as a substrate, and with kojic acid as an inhibitor. The value of inhibition percentage for the formulas without Carbomer-Tween 80 aggregates, F1, F2, and F3 was 64.8367 ± 3.16, 67.2833 ± 1.89, 71.0867 ± 4.05, and 49.2867±2.75%, respectively. The inhibition percent of F3 (with addition of 0.04% Tween 80) was significantly lower than the others, demonstrating that increasing Tween 80 concentrations decreases kojic acid penetration.

Keywords: kojic acid, carbomer-tween 80 aggregation, penetration

1. INTRODUCTION

Kojic acid, 5-hydroxy-2-hydroxymethyl-4H-pyran-4-one, has been widely used in topical preparations as a depigmentation agent because of its inhibition of tyrosinase activity in melanin synthesis. Tyrosinase enzyme activity is diminished by the removal of its associated copper ion by chelation between the ketone group at position 4 and the hydroxyl group at position 5 of kojic acid (Cabanes et al. 1994).

The effect of whitening was steady but too slow with this initial 1% preparation of kojic acid; in mice, 14C-labeled kojic acid cream was observed to be quickly absorbed from the skin to the liver, intestines, and kidneys. When the absorption was this rapid, the depigmentation agent did not stay within the epidermis long enough to inhibit melanogenesis of its target organ, melanocytes (Nakayama et al. 2005). The absorption of kojic acid needed to be slowed.

In order for a depigmentation effect, kojic acid had to penetrate through the skin membrane to reach its target organ in the stratum basale of the epidermis. Before penetration through the skin, kojic acid first had to release from the bases. Many factors influence drugs being released from the bases, such as the amount of the drug in the donor phase, the base viscosity, and the affinity of the drug for its bases (Martin, 1993).

Iglesias et al. showed that Carbomer-surfactant aggregate could control the release of solubilized estradiol, and that Carbomer-Tween 80 aggregate had the greatest capability to inhibit estradiol released. Furthermore, the interaction between polymer and surfactant may cause dramatic changes in drug diffusion and penetration through the skin and mucous. Critical Aggregation Concentration (CAC) is usually lower than the surfactant Critical Micelle Concentration (CMC), especially when the polymer and the surfactant are oppositely charged. The CAC value of Carbomer-Tween 80 dispersion is 0.076 mM (0.01%) and the CMC value of Tween 80 solution is 0.153 mM (0.02%) (Iglesias et al. 2003).

The objective of this study was to determine the influence of Tween 80 (0.01; 0.02; and 0.04% w/w) on Carbomer (0.25% w/w), and its aggregate's effect on kojic acid (1% w/w) penetration, as observed through the inhibition of tyrosinase activity in vitro.

2. MATERIALS AND METHODS

2.1 Materials

Kojic acid, Tween 80, stearic acid, cetyl alcohol, stearyl alcohol, methyl paraben, propyl parabene, triethanolamine, and sorbitol liquid 70% were obtained from Surya Dermato. Carbomer 940 was obtained from Brataco Chemicals. Mushroom tyrosinase was purchased from Sigma Chemical Company. L-tyrosin, monobasic sodium phosphate and dibasic sodium phosphate were purchased from Merck. All material were pharmaceutical grade except mushroom tyrosinase, L-tyrosin, monobasic sodium phosphate and dibasic sodium phosphate were pro analytical grade.

2.2 Preparation of the kojic acid cream as a depigmentation agent

The kojic acid in vanishing cream base formulas as depigmentation cream was shown in Table 1. In this research vanishing cream base contained stearic acid, cetyl alcohol, and stearyl alcohol as oil components, methyl paraben and propyl paraben as preservative, triethanolamine as alkali, sorbitol liquid 70% and distilled water as water components.

Carbomer (0.25%) dispered into distilled water then neutralized with triethanolamine until it reaches pH 5.5. Kojic acid (1%) was solubilized to Carbomer solution and mixed with surfactant (Tween 80) in different concentration (0.01%, 0.02%, and 0.04%) solution to produce aggregate then storage for a night. And then the aggregate was added to the vanishing cream base named F1, F2, and F3 respectively. The Vanishing cream base and kojic acid 1% w/w in vanishing cream base used as blank and control respectively.

2.3 The characteristics determination of the kojic acid cream

The Characteristics determination of kojic acid cream included pH value and spreading-ability

1. Determination of cream pH

The kojic acid cream (1 gram) diluted with destilate water up to 50 ml, pH value measured by pH-meter.

2. Determination of the spreading-ability

The cream spreading-ability was performed using a pairs of glass plates (20 X 20 cm). The kojic acid cream (1 gram) was placed at the center of the glass plate which has scale, then covered by another glass plate. After that put ballast on the glass plate then measured the diameter spreading-ability of the cream. The weight of ballast was increased until spreading-ability of the cream was constant.

Table 1. Formulas of depigmentation cream.

Material	Consentration (% w/w)				
	Blank	Control	F1	F2	F3
Kojic acid	0	1	1	1	1
Carbomer	0	0	0.25	0.25	0.25
Triethanolamine	0	0	0.10	0.10	0.10
Tween 80	0	0	0.01	0.02	0.04
Vanishing cream base up to	100	100	100	100	100

2.4 Evaluation of kojic acid cream penetration (United Stated Pharmacopoeia, 2002)

The penetration of kojic acid in a vanishing cream base was measured by the modification method of the penetration test USP XXV and British Pharmacopoeia, 2002 with diffusion apparatus ERWEKA DT 700.

The kojic acid cream (around 3 grams) was put in a diffusion cell and then covered with a Millipore membrane, which was impregnated with isopropyl-myristate as a modified lipid membrane. The kojic acid cream in this diffusion cell was then put into a penetration chamber containing 500 ml of phosphate buffer pH 6.5 ± 0.05 at 37 ± 0.5°C as a diffusion medium, and stirred at 100 rpm. A sample solution of approximately 5 ml was collected at 360 minutes penetration.

2.5 Determination of enzyme tyrosinase activity

L-tyrosine solution, 0.5 ml, was added to 3.0 ml of the sample solution, which was collected from the compartment receptor after 360 minutes, and which had penetrated through a Millipore membrane impregnated

with isopropyl-myristate. The mixture was oxygenized for 5 minutes and then 1.0 ml tyrosinase solution was added. The mixture was then incubated for 10 minutes at 25°C and subsequently inactivated with 0.5 ml TCA solution. Finally, the absorption value was determined by measuring the maximum wavelength of dophacrome (Avanti, 2003).

2.6 Evaluation of tyrosinase enzyme activity inhibition

The inhibition of tyrosinase enzyme activity was defined by percent of inhibition. This was determined from calculating the absorption value per second of the enzymatic reaction with inhibitor, compared with the absorption value per second of the enzymatic reaction without inhibitor, using the following equation (Luanratana & Gritsadapong, 2005):

$$inhibition(\%) = 100 - \frac{(Ax100)}{B}$$

Whereas:
A = absorption value (A/second) at dophacrome λ maximum with inhibitor
B = absorption value (A/second) at dophacrome λ maximum without inhibitor

The data (inhibition %) were analyzed with ANOVA one-way method ($p<0.05$).

3. RESULT AND DISCUSSION

From the HSD test result of each formula's pH value, as shown in Table 2, it can be concluded that the pH of formula blank > control > F2 = F3 but between control and F1, F1 and F2, and between F2 and F3 no significant differences were shown. Based on the pH data it was known that all formulas were in a range of skin pH.

Table 2. The pH values of kojic acid creams.

Formula	Mean pH ± SD *	% CV
Blank	6.41 ± 0.16	2.51
Control	6.00 ± 0.01	0.17
F1	5.80 ± 0.09	1.60
F2	5.64 ± 0.01	0.18
F3	5.55 ± 0.05	0.90

*The results represent an average of 3 replications

The result of ANOVA one-way test of the pH value of kojic acid creams found the value of $F_{calculation}$ (47.210) > F_{table} (3.48) as seen in Table 3. It can be concluded that there was minimal significant difference between data a pair of pH value of formulas. Honestly Significant Difference (HSD) tests were performed to determine which pH value formulas had significant differences.

Table 3. HSD test result of pH value of kojic acid creams.

Formula	N	Value groups of pH			
		1	2	3	4
Blank	3				6.41
Control	3			6.00	
F1	3		5.80	5.80	
F2	3	5.64	5.64		
F3	3	5.55			

Figure 1 shows the spreading profile of kojic acid creams at various preparations; the spreading-capacity of kojic acid cream at 60 gram ballast is shown in Table 4. Spreading-capacity was formulated from the spreading-diameter at same ballast weight. The result of an ANOVA one-way test of spreading-capacity found that the value of $F_{calculation}$ (112.314) > F_{table} (3.48). It can be concluded that there was minimal significant difference between data of pairs of spreading-capacity formulas. Honestly Significant Difference (HSD) tests determined which spreading-capacity formulas had significant differences. From the result of HSD tests as shown in Table 5, it can be concluded that the spreading-capacity of formula blank < F3 = F2 < control, but between F1 and F2, and between F2 and F3 no significant differences were shown.

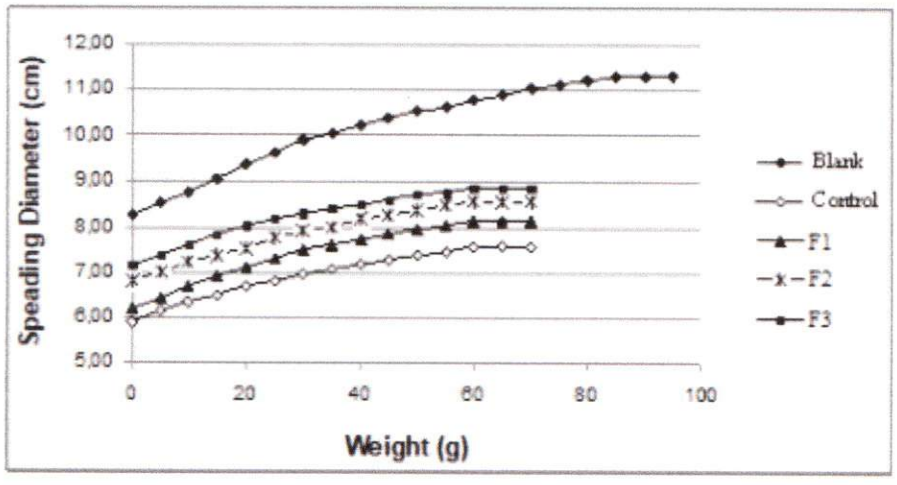

Figure 1.The spreading profile of kojic acid cream with various concentrations of Tween 80. Each value represents an average of 3 replications.

Table 4. Spreading-capacity of kojic aid creams at 60 grams ballast.

Formula	Spreading Diameter (cm)* at 60 grams ballast
Blank	10.77 ± 0.32
Control	7.57 ± 0.15
F1	8.13 ± 0.15
F2	8.57 ± 0.15
F3	8.87 ± 0.15

*The result were obtained from an average of 3 replications

Spreading-ability, as represented by the slope of linear-regression between spreading-diameter (cm) and ballast weight (gram), is shown in Table 6. The slope value of all formulas, as tested by the ANOVA one way method, found that the value of $F_{calculation}$ (17.053) < F_{table} (3.48). It can be concluded that there was minimal significant difference in the data between pairs of spreading-ability formulas.

Table 5. HSD test result of spreading-capacity value of kojic acid creams.

Formula	N	Value groups of spreading-capacity (cm)			
		1	2	3	4
Blank	3				10.7667
Control	3	7.5667			
F1	3		8.1333		
F2	3		8.5667	8.5667	
F3	3			8.8667	

Honestly Significant Difference (HSD) tests determined which spreading-ability formulas had significant differences. It can be concluded from the results of HSD tests, as shown in Table 7, that the spreading-ability of blank formula was significantly different from the other formulas.

Table 6 Kojic acid creams spreading-ability.

Formula	Spreading-ability (cm/g)*
Blank	0.0360 ± 0.0010
Control	0.0241 ± 0.0008
F1	0.0281 ± 0.0013
F2	0.0263 ± 0.0024
F3	0.0245 ± 0.0034

*The results were obtained from an average of 3 replications

Table 7. HSD test result of spreading-ability value of kojic acid creams.

Formula	N	Value groups of spreading-ability (cm)	
		1	2
Blank	3	0.0360	
Control	3		0.0241
F1	3		0.0281
F2	3		0.0263
F3	3		0.0245

The effectiveness of kojic acid as a depigmentation agent was calculated by measuring its inhibition percent (%) of tyrosinase enzyme activity. The result of kojic acid inhibition percent (%) with Carbomer/Tween 80 in vanishing cream is shown in Table 8.

The result of an ANOVA one-way test of inhibition percent (%) found the value of $F_{calculation}$ (29.340) > F_{table} (4.07). It can be concluded from the data that there was minimal significant difference between pairs of inhibition percent (%) formulas. Honestly Significant Difference (HSD) tests were utilized to determine which inhibition percent (%) formulas had significant differences. The result of these HSD tests, as shown in Table 9, shows that the inhibition percent (%) of formula F3 was significantly different from the other formulas. Interaction between the Carbomer and surfactant formed aggregate, in a critical aggregation concentration (CAC) value, may cause changes in the drug solubility, the rheological properties of polymer aqueous dispersions, and in drug diffusion and penetration through the skin and mucous (Iglesias et al. 2003). The inhibition percent (%) of the F1 and F2 formulas was not significantly different from the control formula; as the estimated amount of aggregates that formed were not adequate to entrap kojic acid, meaning the amount of kojic acid inside the Carbomer/Tween 80 aggregate was less than the amount of kojic acid outside of the aggregate (free), kojic acid release was not inhibited.

The inhibition percent (%) of F3 (with addition of 0.04% tween 80) was significantly lower than the others, demonstrating that the amount of kojic acid which penetrated through the membrane was decreased, as measured by the increased dopachrome that was formed.

Table 8. Kojic acid effectiveness (inhibition %) in vanishing cream formulas.

Formula	Inhibition (%)			Mean ± SD	% CV
	R1	R2	R3		
control	61.62	67.93	64.96	64.8357 ± 3.16	2.10
F1	69.19	65.40	67.26	67.2865 ± 1.89	1.27
F2	75.25	67.17	70.84	71.0894 ± 4.05	1.73
F3	46.21	51.52	50.13	49.2850 ± 2.75	7.11

Table 9. HSD test result of inhibition percent (%) value of kojic acid creams.

Formula	N	Value group of inhibition (%)	
		1	2
Control	3	64.8367	
F1	3	67.2833	
F2	3	71.0867	
F3	3		49.2867

Because of excessive surfactant added, it was estimated that the polymer saturated with surfactant increased the amount of free surfactant until its concentration was the same as the CMC value, forming a micelle that covered the kojic acid outside of the Carbomer/Tween 80 aggregate. Kojic acid remaining inside the micelle had difficulty being released from the matrix bases thereby decreasing its penetration.

4. CONCLUSION

The addition of Tween 80 (0.04% w/w) to a Carbomer/Tween 80 aggregate in a vanishing cream base effectively decreased the penetration of kojic acid.

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