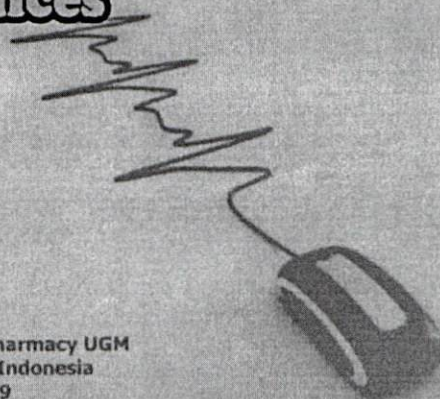


PROCEEDING

The International Conference on
**Pharmacy and Advanced
Pharmaceutical
Sciences**



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The Effect Of β -Cyclodextrin And Oxybenzone-Octyl Dimethyl Paba (3:7% W/W) Addition On The Penetration Of Kojic Acid In Vanishing Cream (Based on Activity Inhibition of Tyrosinase)

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Abstract

This research was aimed to investigate the effects of the addition of β -cyclodextrin (BCD) and a combined of oxybenzone and octyl dimethyl PABA (3:7% w/w) on the penetration of kojic acid based on inhibition activity of tyrosinase. The presence of BCD was expected to make the preparation effective, while the addition of oxybenzone and octyl dimethyl PABA was intended to overcome photosensitive properties of kojic acid. Effectiveness determination of vanishing cream preparation was conducted by testing activity inhibition of tyrosinase that was expressed as percentage inhibition. Tyrosinase was an enzyme that plays an important role in the process of melanin formation in human skin. Inhibition activity of tyrosinase by kojic acid was determined in vitro by observing absorption values of dopachrome (an intermediate product of melanin formation) using spectrophotometer. Based on results of effectiveness tests of kojic-acid vanishing cream preparation by means of measurement of activity inhibition of tyrosinase, it was found that addition of sunscreen (oxybenzone and octyl dimethyl PABA without BCD) had no significant effect on the activity inhibition of tyrosinase. While, addition of BCD or combined of BCD-sunscreen significantly reduced inhibition of tyrosinase activity in vitro.

Keyword : kojic acid, β -cyclodextrin, oxybenzone, octyl dimethyl PABA, tyrosinase, enzym, inhibition

Introduction

Kojic acid is a skin lightening agent which has very small molecular size, so easily absorbed up through the basal membrane. Because of its small molecule, kojic acid hardly absorbed through the lipid membrane of its target sites, the melanocytes (Manosroi et al, 2005) and can penetrate into the systemic (Nakayama et al., 2005). It is likely absorbed through voids between cells on the skin. Losses due to kojic acid to the systemic is not able to work effectively inhibits melanin formation took place in the basal membrane of skin that results are not optimal lightening effect. Addition of β -cyclodextrin reported can decrease penetration of kojic acid (Nakayama et al., 2005). BCD can be used in a number of 0,5-10 parts per 1 weight part of kojic acid, which is the optimal composition of 4 parts cyclodextrin every a part of kojic acid (Hatae et al, 1988).

Generally, skin lightening maybe caused the skin more photosensitive, so in cosmetics usage needed the sun-rays filter (Zulkarnain, 2003). To obtain maximum protection, frequently sunscreen used in combination of anti UV-A with anti UV-B, ei: oxybenzone and octyl dimethyl PABA. In this study used the composition (3:7) % w/w which is the optimum composition in accordance with the results of previous studies (Wati, 2005).

This research investigated the effects of the addition of β -cyclodextrin and a combined of oxybenzone and octyl dimethyl PABA (3:7% b/b) on the penetration of kojic acid based on activity inhibition of tyrosinase. Effectivity determination of vanishing cream preparation was conducted by testing activity inhibition of tyrosinase that was expressed as percentage inhibition. Tyrosinase was an enzyme that played an important role in the process of melanin formation of human skin. Activity inhibition of tyrosinase by kojic acid was determined in vitro by observing absorption values of dopachrome (an intermediate product of melanin formation) using spectrophotometer.

Methodology

Materials

The materials used in this study if no others have mentioned pharma-ceutical grade standards. Materials for the manufacture of test preparations including Kojic acid, Oxybenzone, Octyl dimethyl PABA, BCD (p.a), stearic acid, Cetyl alcohol, Span 80, Tween 80, and 70% sobitol solution. While material for inhibition of tyrosinase activity test is the Mushroom tyrosinase, L-Tyrosine, $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ (p.a) and Na_2HPO_4 (p.a).

Instrument

Double beam UV-VIS Spectrophotometer, Fourier Transform Infrared Spectrophotometer, Micropipet various volumes, Pumpkin measure, Research Hanson dissolution testing, thermo-meters, pH meter CG SCHOOT Glass 842 Mainz, Milipore Membrane Filters, Tue diffusion, Analytical scales, Vortex, light microscopy, Electrothermal Melting Point Apparatus.

Preparations :

Vanishing cream base

14% stearic acid, 2% cetyl alcohol, Methyl paraben 0.1%, Propyl paraben 0.05%, 0.5% Span 80, 4.5% Tween 80, 3% sorbitol solution 70%, Aqua ad 100%.

Table 1 Formulation

Component	Percentage (% b/b)			
	F ₁ (control)	F ₂	F ₃	F ₄
Kojic acid	1	1	1	1
β -cyclodextrin	-	4	-	4
Oxybenzone	-	-	3	3
Octil dimethyl PABA	-	-	7	7
Vanishing cream base(F ₀)	Ad 100	Ad 100	Ad 100	Ad 100

Characteristics Determination of the cream preparation:

Determination of the physical quality of cream preparations include organoleptic (shape, colour, odour, texture), pH and spreading-ability.

Determination of the spreading-ability:

Determination of cream spreading-ability was performed using a pair of glass plate (20 X 20 cm). The cream preparation (1 gram) was put in the middle of the first glass plate that given the scale. Then put the second glass plate on the first glass plate and measured the diameter of cream spreading. After that put ballast on the second glass plate then measured the diameter spreading-ability of the cream. The weight of ballast that put on the second plate was increased until spreading-ability of the cream was constant.

Determination of tyrosinase activity inhibition

Preparation of a solution of the reaction components.

The solution should be prepared for the implementation of this study was 0.1 M phosphate buffer pH 6.5, solution of tyrosinase (5370 units / mg solid in 0.1 M phosphate buffer pH 6.5 to 100.0 ml volume), a solution of 5.52 mM L-tyrosine, and 30% TCA.

Preparation of test sample solution.

The cream (around 3 grams) was put in the diffusion cell then covers with the Millipore membrane which was impregnated with isopropyl-myristate as modified lipid membrane. Then the preparation of cream in diffusion cell was put into the penetration chamber contain 500 ml of phosphate buffer pH 6.5 ± 0.05 at $37 \pm 0.5^\circ\text{C}$ as diffusion medium, and then the paddle was stirred 100 rpm. The sample solution around 3 ml was collected at 6 hours after it penetrated.

Determination of the dopakrom maximum wavelength

L-tyrosine solution of 5.52 mM has taken a number of prepared and then added 0.5 ml 3 ml of buffer solution pH 6.5 ± 0.05 . Then the mixture add with 1.0 ml of tyrosinase and oxygenated for 5 minutes. The mixture was incubated for 15 minutes at $26 \pm 0.5^\circ\text{C}$. Then added 0.5 ml of 30% TCA. The solution is then inserted into cuvet and placed on the sample position in the spectro-photometer. Used as a blank solution 0.1 M phosphate buffer pH 6.5. Then do the reading of absorbance values from a wavelength of 400 nm to 500 nm, and the selected wavelength that gives the greatest absorption.

Inhibition Tyrosinase Activity Determination

L-tyrosine solution 5.52 mM added with 0.5 ml 3 ml of sample solution. Then the mixture added with 1.0 ml of tyrosinase and oxygenated for 5 minutes. The mixture was incubated for 15 minutes at $26 \pm 0.5^\circ\text{C}$. Then add 0.5 ml of TCA 30% and observed the absorbance at dopacrom maximum wavelength. Inhibition tyrosinase activity is the percent inhibition values obtained from the later absorbance value calculated by the equation:

A = Absorbance at the maximum with the skin lightening
 B = Absorbance at maximum λ without the skin lightening

Results and Discussions

Characteristics Test Results

Based on the results of organoleptic test, all formulas have the same smell and texture. Meanwhile, in terms of different colours. Formula that contains sunscreen cream white yellowish colours, while others are white.

Table 2. Organoleptic test results

Formula	Replication	Organoleptic		
		Color	Odor	Texture
F ₁	1	White	-	Semisolid, smooth
	2			
	3			
F ₂	1	White	-	Semisolid, smooth
	2			
	3			
F ₃	1	White yellowish	-	Semisolid, smooth
	2			
	3			
F ₄	1	White yellowish	-	Semisolid, smooth

Cream Type

The results of cream type test using water-soluble reagents (methylene blue) showed that the type of cream is O/W.

The pH Test Result

Based on the pH results in table 3, it was known that all formulas in the skin pH range (4 - 6.8).

Table 3. The pH test result

Formula	*pH	% CV
F ₁	4,46 ± 0,01	0,34
F ₂	4,24 ± 0,03	0,68
F ₃	4,29 ± 0,03	0,70
F ₄	4,04 ± 0,02	0,62

*) The average obtained from 3 replicates it, each determined 3 times at different places.

Spreading-ability

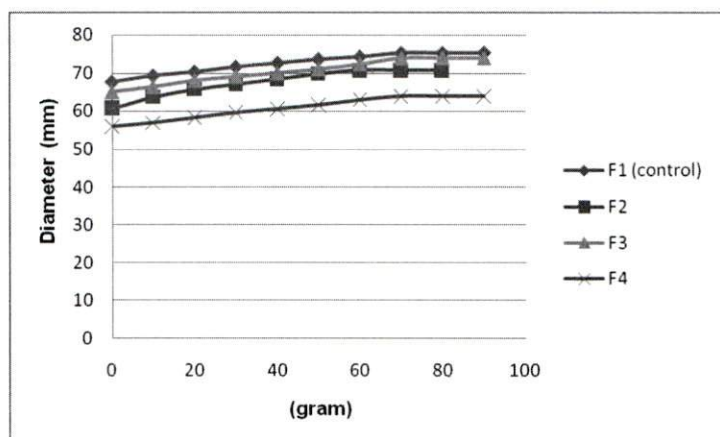


Figure 1. Profile of spreading-ability kojic acid cream on various formulas

Table 4. Spreading-ability result

	Replication	Dispersability (mm/g)	Average ± SD
F ₁ (Control)	1	0,1179	0,1067 ± 0,01
	2	0,1083	
	3	0,0940	
F ₂	1	0,1786	0,1595 ± 0,02
	2	0,1393	
	3	0,1607	
F ₃	1	0,1083	0,1226 ± 0,01
	2	0,1369	
	3	0,1226	
F ₄	1	0,1179	0,1155 ± 0,02
	2	0,0964	
	3	0,1321	

Based on the results of one way ANOVA test, the addition of BCD (F₂) decreased its spreading-capacity, as well as addition of BCD on combination kojic-sunscreen (F₄)

Table 5. Spreading-capacity results

	Replication	Diameter at 60 g (mm)	Average \pm SD
F₁ (Control)	1	75	74,33 \pm 0,58
	2	74	
	3	74	
F₂	1	70	70,67 \pm 0,58
	2	71	
	3	71	
F₃	1	73	74,00 \pm 1,00
	2	74	
	3	75	
F₄	1	64	63,00 \pm 1,00
	2	62	
	3	63	

Test Results Activity Inhibition of Tyrosinase

Table 6. Inhibition percent tyrosinase activity

Formula	% Inhibition			Average (%) \pm SD	CV (%)
	Replikation				
	I	II	III		
F ₁	61,73	62,10	63,07	62,3 \pm 0,69	1,11
F ₂	28,39	28,40	29,28	28,69 \pm 0,51	1,78
F ₃	60,50	60,65	62,26	61,14 \pm 0,98	1,60
F ₄	23,69	23,33	24,52	23,63 \pm 0,61	2,56

Based on one way ANOVA test, known that the addition of BCD decreased inhibition percent compared to the control constraints. Nevertheless the addition of sunscreen alone does not affect the inhibition percent of tyrosinase activity.

Addition of BCD on combination kojic-sunscreen preparations showed the same phenomena such as decreased its inhibition percent of tyrosinase activity.

Decreasing of inhibition percent of tyrosinase activity after addition of BCD alone or BCD-sunscreen was might be caused by decreasing of kojic acid penetration. It was probably caused by some of the things that the release process of kojic acid from base and in the process of penetration through the membrane. Before reach basal membrane where the kojic acid site of action, kojic molecule should released from base further more penetrate through the skin.

From spreading-ability test was known that the addition of BCD alone and also BCD on combination with sunscreen preparations reduced spreading-capacity, it means increasing viscosity. Increasing viscosity will decrease the mobility of active ingredient molecules that caused barriers against the release of kojic acid.

After the release process, kojic acid has to penetrate through trans-epidermal route through diffusion mechanism and trans-appendageal. One of the factors affecting the diffusion of the active ingredient is a molecule characteristic, which is the size of molecules. In the research on the use of drug fendeline with BCD, showed that the diffusion through a semi-permeable membrane decreased which was caused by increasing its molecule size

(Duchene et al, 1986). In this case decreasing kojic acid penetration by BCD addition might be caused by increasing of molecules the size of kojic acid. There for it expected would inhibit its penetration to the systemic, and make it survive longer in basal membrane, which is synthesis of melanin site. While the addition of BCD on combination kojic-sunscreen (F₄) reducing inhibition tyrosinase enzyme activity significantly compared with the control, as well as formula with the addition of a single BCD (F₂). This is probably due to the interaction between these materials so that the amount of kojic acid penetrated decreased and tyrosinase activity in vitro also declined.

Conclusion

Based on research results can be concluded that:

1. Combination of sunscreen oxybenzone and octyl dimethyl PABA (3:7) % w/w in the preparation of the skin lightening 1% kojic acid in a vanishing cream base does not affect the penetration kojic acid based on inhibition of tyrosinase enzyme activity in *invitro*.
2. β -cyclodextrin decrease penetration kojic acid based on inhibition of tyrosinase enzyme activity in *invitro*.
3. The existence of β -cyclodextrin and combination sunscreen oxybenzone and octyl dimethyl PABA (3:7)% w / w decrease penetration kojic acid based on inhibition of tyrosinase enzyme activity in *invitro*.

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