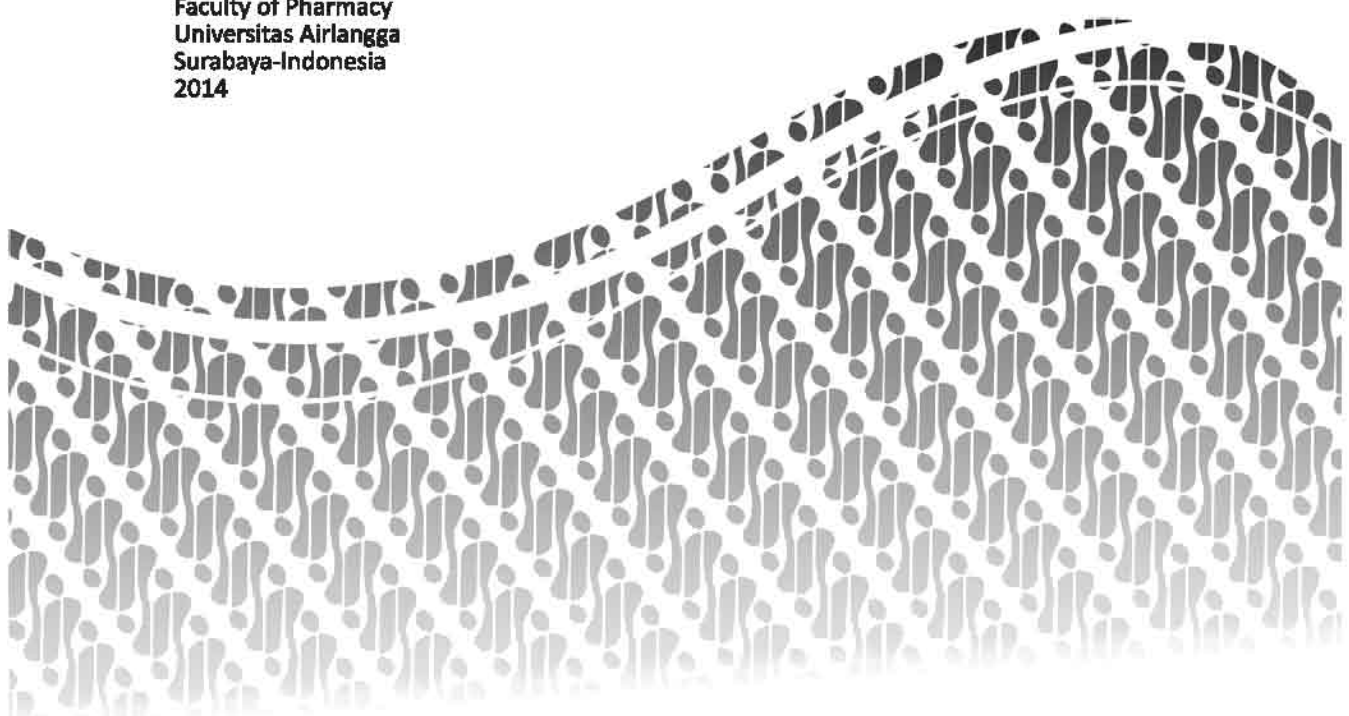


# Proceeding

## **The 1<sup>st</sup> International Conference on Pharmaceutics & Pharmaceutical Sciences**

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## **PREFACE From Chairman**

It is our pleasure to present you the proceedings of The 1st International Conference on Pharmaceutics and Pharmaceutical Sciences (ICPPS) organized by The Faculty of Pharmacy Universitas Airlangga Surabaya Indonesia.

The proceeding was produced based on papers and posters presented at The 1st International Conference on Pharmaceutics and Pharmaceutical Sciences (ICPPS), held in Surabaya, Indonesia, 14-15 November 2014.

The proceeding clearly reflects broad interest, from the participants that coming from all around the world.

The papers presented were pharmaceutics and biopharmaceutics; requirements on how to evaluate molecules in discovery and their appropriateness for selection as potential candidate; their development in context of challenges and benefits, together with associated time and cost implications and also requirements to progress through pre-clinical and clinical.

In this an opportunity, I would like to express my appreciation to the editorial team of the proceeding who have been working hard to review manuscripts, and making the first edition of this proceeding be possible.

I would like also to thanks to all invited speakers and presenters who participated in The 1st International Conference on Pharmaceutics and Pharmaceutical Sciences (ICPPS) and your contribution to this proceeding.

Finally, I hope this proceeding will give contribution to the Pharmaceutics and Pharmaceutical Sciences research.

Chairman,

Dra. Esti Hendradi, MSI., Ph.D., Apt

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## EFFECT OF $\beta$ -Cyclodextrin ON SPF VALUE AND INHIBITION OF KOJIC ACID TYROSINASE ACTIVITY IN VANISHING CREAM BASE FORMULATION (ON SUNSCREEN PRODUCT CONTAINED OXYBENZONE)

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### INTRODUCTION

Newly, we found many cosmetics combined of sunscreen substance and lightening agent in their ingredients.

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. Kojic acid is produced mainly by microbial fermentation using aspergillus and penicillium spp. In in vivo test, cream containing kojic acid compounds have been reported as effective in preventing pigmentation changes in human skin due to exposure to UVA and UVB. This inhibition has been shown to be due to chelation of Cu, a prosthetic group in tyrosinase (Barel et al, 2001). Cream contained 1 % of kojic acid showed steady but slow whitening effect. <sup>14</sup>C-labeled kojic acid cream was observed to be quickly absorbed from the skin to the liver, intestines, and kidneys in mice.

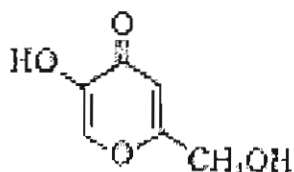


Fig 1. Properties of Kojic Acid  
5-hidroksi-2-hidroksimetil-4-pyron

MW: 142.1  
MP: 153-154°C  
pKa: 7.90-8.  
Log P (octanol-water): -0,64

When the absorption was thus quick, the depigmentation agent did not stay at the epidermis where it had its target organ, melanocytes, for a long enough time to inhibit melanogenesis. Therefore, kojic acid was mixed with  $\beta$ -cyclodextrin to slow the absorption into the dermis (Elsner and Maibach, 2005). 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  $\beta$ -cyclodextrin reported can decrease penetration of kojic acid (Nakayama et al., 2005).

Cyclodextrins are cyclic oligosaccharides with a hydrophilic outer surface and a somewhat hydrophobic central cavity. Cyclodextrins are able to form inclusion complexes with many drugs by taking up the drug molecule, or a lipophilic moiety of the molecule, into the cavity (Loftsson and O'Fee, 2003).

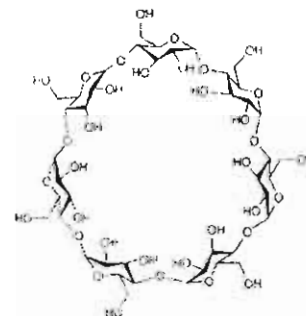


Fig 2.  $\beta$ -cyclodextrin (Sweetman, 2007)



Sunscreen agents, such as: oxybenzone and octyl dimethyl PABA, are commonly present in whitening products to compensate for the photosensitivity effect caused by the whitening agent. This combination is more efficient but may have a profound effect on the efficacy of the sunscreen agent.

Therefore, this study was aimed to investigate the SPF value of sunscreen product contained oxybenzone and octyl dimethyl PABA (3:7) with the addition of kojic acid 1% b/b as whitening agent and their complex with  $\beta$ -cyclodextrin in 1:1 molar equivalent. In this research, we also studied the effect of  $\beta$ -Cyclodextrin (BCD) on penetration of Kojic Acid, as lightening substance in Vanishing Cream Base Formulation (on Sunscreen Product Contained Oxybenzone), by determination of tyrosinase activity inhibition.

**MATERIAL AND METHODE**

**Material**

Oxybenzone, Octyldimethyl PABA and Kojic Acid were from Surya Dermato,  $\beta$ -cyclodextrin p.a (Sigma Aldrich), Stearic Acid, cetyl alcohol, span 80, tween 80), Methyl paraben Propyl paraben, sorbitol 70%, Isopropanol p.a., (Brataco Chemicals). All of the active ingredients used here were in a pharmaceutical grade except for the chemical reagent isopropanol and  $\beta$ - cyclodextrin which were in pro analytical grade. While material for inhibition of tyrosinase activity test is the Mushroom tyrosinase, L-Tyrosine, NaH<sub>2</sub>PO<sub>4</sub>. 2H<sub>2</sub>O (p.a) and Na<sub>2</sub>HPO<sub>4</sub> (p.a).

The SPF assay were carried out by using a Double Beam Spectrophotometer UV- Vis Perkin Elmer Lambda EZ 201, Ultrasonic Branson 3510, Hettich zentrifugen EBA 20, Mettler Toledo AL 204 analytical balance. Digital pH meter Schott CG 842 and spreading capacity measurer are also used for the organoleptic analysis.

**Method**

The sunscreen product contained oxybenzone and octyl dimethyl PABA (3:7) with the addition of kojic acid 1% w/w as whitening agent and their complex with  $\beta$ -cyclodextrin in 1:1 molar equivalent. Vanishing cream as base was made with inversion technique.

The characteristics of the finished product evaluated were emulsion type, pH, spreading-ability, and organoleptic such as colors, odors.

Table 1. Formula composition

Component	Percentage		
	F1	F2	F3
Kojic acid	1	1	1
$\beta$ cyclodextrin	4	-	4
oxybenzone	-	3	3
Octyl dimethyl PABA	-	7	7
Vanishing cream base	Ad 100	Ad 100	Ad 100

**Determination of SPF value**

The SPF value was determined by Petro correlation for in vitro method. 2 mg/cm<sup>2</sup> or 2  $\mu$ L/ cm<sup>2</sup> sunscreen agent for in vivo test was equivalent with 10 ppm sunscreen agent dissolved in isopropanol. An UV spectrum of this solution was then measured at 290-400 nm by using Double Beam UV-Vis Spectrophotometer Perkin Elmer Lambda EZ 201 at an interval of 2 nm which has absorbance for 0.05 or more. According to Petro, the absorbance was then converted into the absorbance for 10 ppm solution concentration for each wavelength. Then it was proceed in this following equation:

$$AUC_{\lambda_{p-\alpha}}^{\lambda_p} = \frac{A_{p-\alpha} + A_p}{2} \lambda_p - \lambda_{p-\alpha}$$

Whereas:

AUC = Area under curve

A<sub>p</sub> = Absorption on p wavelength

A<sub>p- $\alpha$</sub>  = Absorption on p- $\alpha$  wavelength



The total AUC were obtained by totaling each AUC between 2 wavelengths in series from 290 nm till 490 nm which has an absorbance value above 0.050 and the SPF value of a formula were obtained by inserting the total AUC into the equation below:

$$\text{Log SPF} = \frac{\text{Total area}}{\lambda_n - \lambda_1} \times 2$$

Whereas:

$\lambda_n$  = longest wavelength above 290 nm that has an absorbance higher than 0.050

$\lambda_1$  = shortest wavelength 290 nm

Determination of tyrosinase activity inhibition:

A. 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.

B. 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 ± 0.5°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 ±

0.5 °C then added 0.5 ml of 30% TCA. The solution is then inserted into cuvet and placed on the sample position in the spectrophotometer. 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 ± 0.5 °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:

$$\% \text{ Inhibition} = 100 - \frac{A \times 100}{B}$$

B

A = Absorbance at the maximum with the skin lightening

B = Absorbance at maximum  $\lambda$  without the skin lightening

## RESULT AND DISCUSSION

All the formulas had either pH in skins pH range or simillar spreadability.

The SPF value increased in formula 3. The complex formation of the sunscreen agent with BCD was suspected to be responsible for this phenomenon. It might becaused of complex formation of the sunscreen agent with  $\beta$ - cyclodextrin increased sunscreen agent solubity.

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 does not affect the inhibition percent of tyrosinase activity. Addition of BCD on combination kojic acid-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 or combination 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 acid molecule should released from base further more penetrate through the skin. Increasing viscosity will decrease the molecules mobility of active ingredient that caused barriers against the release of kojic acid.

Table 2. Average of pH

FORMULA	pH ± SD
1	4,51 ± 0,08
2	4,29 ± 0,03
3	4,04 ± 0,03

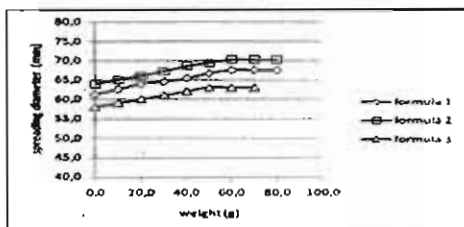


Figure 3. Profile of Spreading-ability

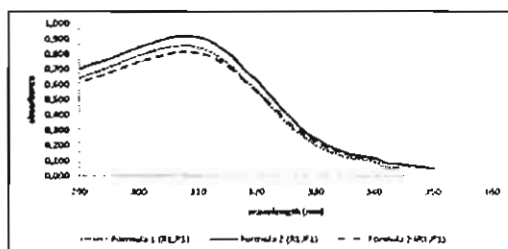


Figure 4. Profile of sunscreens absorbance measurement

Table 3. Average of SPF

Formula	SPF (average)
1	10,607 ± 0,432
2	11,741 ± 0,479
3	19,113 ± 0,295

Table 5. Average percent of tyrosinase inhibition

Formula	% tyrosinase activity inhibition
1	28,39 ± 0,51
2	60,50 ± 0,98
3	23,69 ± 0,61

### CONCLUSION

1. The complex formation of the sunscreen agent with BCD decreased the SPF value of sunscreen product.
2. BCD decrease penetration kojic acid based on inhibition of tyrosinase enzyme activity in invitro.
3. The existence of BCD 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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