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The International Conference on Pharmacy and Advanced Pharmaceutical Sciences

Faculty of Pharmacy UGM

PROCEEDING

The International Conference on Pharmacy and Advanced Pharmaceutical Sciences

Faculty of Pharmacy UGM
Yogyakarta Indonesia
October 2009

UNIVERSITI SAINS MALAYSIA

Nara Institute of Science and Technology NAIST

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Preface from the Editor

The proceeding was produced based on papers and posters presented at the international Conference on Pharmacy and Advanced Pharmaceutical Sciences, held in Yogyakarta, Indonesia, 5 – 6 October 2009.

The proceeding clearly reflects broad interest; from there are participants coming from all around the world. Many contributions on Pharmaceutical Sciences there are quite a substantial number of papers on Pharmacist role in general. The papers presented file into a broad spectrum in Pharmaceutical sciences including Pharmacology, Toxicology, Analytical Chemistry and Drug Design, Drugs Synthesis, Formulation of Drugs, Pharmacy Social, Pharmacoepidemy, Traditional Medicine Natural Product Chemistry and Phytochemistry, etc.

In addition there are substantial numbers of paper deal with professional aspect of Pharmacist in general health care.

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 International Conference on Pharmacy and Advanced Pharmaceutical Sciences and your contribution to this proceeding.

Finally, I hope this proceeding will give contribution to the advanced scientific research in the field of pharmaceutical sciences

Yogyakarta, July 2010

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Welcome Message
From the committee

Welcome to Yogyakarta

On behalf of the Scientific and Organizing Committees, it is a great pleasure for me to welcome all participants to Yogyakarta, to the International Conference on Pharmacy and Advanced Pharmaceutical Science 2009.
The international conference is organized by the faculty of Pharmacy UGM to celebrate its 63th anniversary and the Lustrum XII of Gadjah Mada University, as a collaboration work between the Faculty of Pharmacy UGM with the Nara Institute of Science and Technology (Japan) and the Universiti Sains Malaysia (Malaysia). In this conference 15 lectures within the field of Pharmaceutical Care and Advanced Pharmaceutical Science will be given by invited speakers. Besides, 55 posters and 75 paper will be presented in the parallels presentation sessions. Herewith, we express our gratitude to all speakers and presenter, who would like to share their advance knowledge in this scientific event.

The Organizing Committee gratefully acknowledges the Nara Institute of Science and Technology and the Universiti Sains Malyasia, for the nice collaboration in bringing forth this conference. A special acknowledgment is addressed to the Rector of Gadjah Mada University and the sponsors, for all supports that make this symposium possible. Furthermore, personally, I want to express my deep appreciation to the members of the Organizing Committee, for the good teamwork and their great effort given in the preparation for this symposium.

Finally, I wish all participants a scientifically rewarding and an enjoyable meeting in Yogyakarta.

Chairman

Dr. Hilda Ismail, M.Si., Apt.

Remark of the Dean Faculty

Assalamu'alaikum wr. wb.
Distinguished ladies & gentlemen.

First of all, on be half of the Faculty of Pharmacy Universitas Gadjah Mada, I would like come to all of you in Yogyakarta, thank you very much for your attention to come and to attend the international Symposium on Pharmacy and Advanced Pharmaceutical Sciences. I hope we are all in health condition.

Ladies and gentlemen,
The symposium is organized by the Faculty of Pharmacy UGM in collaboration with the Faculty of Pharmaceutical Sciences Universiti Sains Malaysia and the Nara Institute of Science and Technology Japan, and held as part to celebrate the 63th anniversary of the Faculty of Pharmacy UGM.
In the symposium , I hope we can communicate our recently information concerning social / clinical pharmacy and pharmaceutical sciences. I hope the symposium will be very fruitfull, very useful for all of us .
I addres special thanks to the plenary speakers both from domestic and aboard, the oral and poster presenters, as well as to those who come just to know the development of clinical or social pharmacy and pharmaceutical science. Your willingness to come , to communicate and to share your experiences is highly appreciated.

Special thanks also I address to my colleague the Dean of Faculty of Pharmacy USM who has been coordinating USM students to attend this symposium. The hope is not to set up networking between the pharmacy students of USM and UGM.

Therefore, during almost whole day discussing scientific matter related to human health and welfare, I hope we can make a wonderful opportunity to make a scientific closer relationship while we enjoy the cultural performances of Yogyakarta presented by our pharmacy student.

Finally, I hope that this meeting will give benefits to all of us, and we may see each other again in a similar event in the near future.

I look forward to thank you all for attending this event.

Wassalamu'alaikum wa rahmatullahi wa barakatuh,
Dean of Faculty of Pharmacy UGM

Prof. Dr. Marchaban, DESS., Apt.

Speech of the Senior Vice Rector
For Education, Research and Community Services,
Gadjah Mada University

Assalamu'alaikum wa rahmatulLahi wa barakatuh,

On behalf of the Rector, I would like to welcome all of you to our campus Gadjah Mada University and to our home town Yogyakarta. It is a great honor for me and Gadjah Mada University to host the Two-day International Conference on Pharmacy and Pharmaceutical Sciences that is conducted by the Faculty of Pharmacy, Gadjah Mada University. The increasing problems and new cases of some diseases in the world, both the infectious and the degenerative diseases, have demanded the development of medical and pharmaceutical sciences and technologies for supporting the developments of early detection methods of the diseases, the accurate diagnoses, as well as the appropriate and effective medications or therapy. Pharmaceutical Science and Technology have been developing very fast within recent years. The development trend shows using much more biotechnological approach in both diagnose establishment and medication administrations. For examples the usage of some serums, enzymes, hormones, vaccines, etc., and their recombinant products. The science and technology for finding prevention method against infectious diseases or degenerative diseases now have been developing so amazing, for example the usage of growth hormones, vaccines, and stem cells for it.

Gadjah Mada University has been committed to become World Class University; therefore international networking in education, research and publication is much needed. I really support to this international conference on Pharmaceutical Science and Technology which can keep us in touch with the state of the art of pharmaceutical science. I do believe that by conducting this kind of international meeting, we can get and exchange new information and best practices on pharmaceutical science and technology, and it is very important to inspire our young researchers and enhance our research networking internationally. In this occasion, I would like to express my great gratitude to all the guest speakers and speakers, who have contributed their advanced presentations in this international conference. I also would like to extend my gratitude to the Organizing Committee from the Faculty of Pharmacy, Gadjah Mada University, who has already successfully arranged this international conference. I would also thank to all institutions or companies who have sponsored and supported this conference.

Finally, have a fruitful conference and enjoy Yogyakarta. Thank you
Wassalamu'alaikum wa rahmatulLahi wa barakatuh,

Senior Vice Rector for Education, Research and Community Service
Gadjah Mada University

Prof. Dr. Retno Sunarminingsih, M.Sc., Apt.

CONTENTS

Influenced of Kojic Acid and B-Cyclodextrin on SPF Value Sunscreen Product Contained Oxybenzone and Octyl Dimetyl Paba (3:7) (In vanishing cream base formulation)

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Abstrack

The aim of this study was to investigate the SPF value of sunscreen product contained oxybenzone and octyl dimetyl PABA (3:7) with the addition of kojic acid 1% w/w as whitening agent and their complex with β-cyclodextrin in 1:1 molar equivalent. The SPF value was determined by Petro correlation for *in vitro* method. The result showed that the addition of kojic acid increased the SPF value of sunscreen product from 10,607 ± 0,432 became 11,741 ± 0,479. A different result showed with the addition of complex form of kojic acid with β-cyclodextrin. The SPF value decreased to 9,113 ± 0,295. The complex formation of the sunscreen agent with β-cyclodextrin was suspected to be responsible for this phenomenon. Moreover, it was suggested to make *in vivo* correlation with the result of this study.

Key words : oxybenzon, octyl dimetyl PABA, kojic acid, β-cyclodextrin, SPF, vanishing cream

Introduction

Sunscreen agents 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 UV filter.

UV filters are generally aromatic compounds conjugated with an electron receiving group or conjugated with a double bond and an electron-releasing group that is substituted in the ortho or para position of the aromatic ring. Chemicals of this configuration absorb the harmful short-wave (high-energy) UV rays (200 - 400 nm) and convert the remaining energy into innocuous longer wave (lower energy) radiation (>400 nm) (Shaath, 2005). The energy absorbed from the UV radiation corresponds to the energy required to cause a photochemical excitation in sunscreen molecule. Thus, cosmetic vehicles, such as pH, λ_{max}, and extinction coefficient (ε), which affect the electron delocalization, have a direct influence to the SPF (Shaath, 1986).

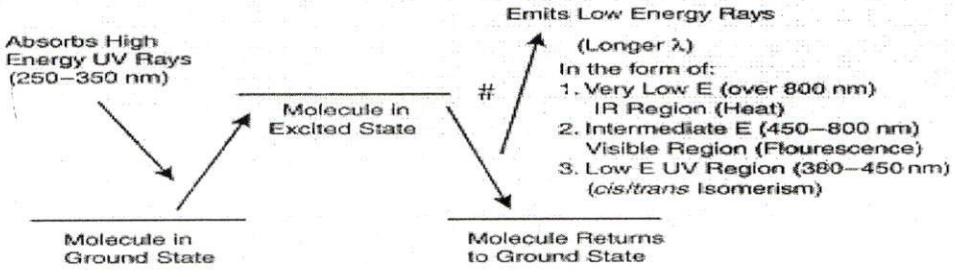


Fig 1. Schematic representation of the process in which a sunscreen chemical absorbs ultraviolet radiation (Shaath, 2005)

Octyldimetyl PABA and oxybenzone are one of kind UV filter that worked with the mechanism above (Shaath, 2005). They absorb UV rays and combined to provide wide range protection from UVA and UVB spectrum. Since they are influenced by the vehicle, their combination with whitening agent may impact their efficacy to protect the skin from harmful UV radiation (Widianingsih and lumintang, 2002).

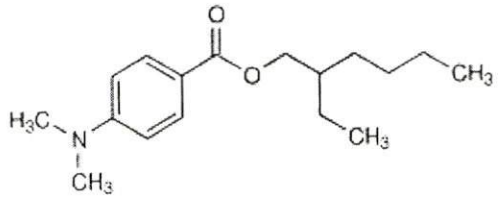


Fig 2. Octyldimetyl PABA (Sweetman, 2007)

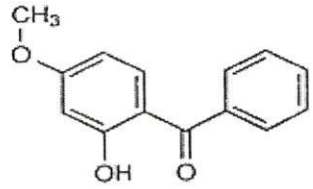
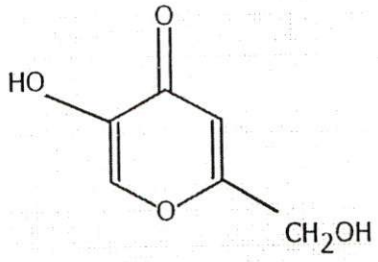


Fig 3. Oxybenzone (Sweetman, 2007)



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

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

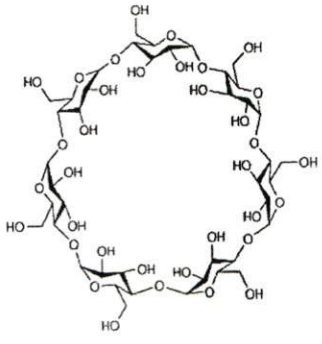


Fig 5. β-cyclodextrin (Sweetman, 2007)

Whitening agent that used in this experiment was kojic acid. 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 all*, 2001).

Cream contained 1 % of kojic acid showed steady but slow whitening effect. 14C-labeled kojic acid cream was observed to be quickly absorbed from the skin to the liver, intestines, and kidneys in mice. 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 β-cyclodextrin to slow the absorption into the dermis (Elsner and Maibach, 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).

Cyclodextrins can both enhance and hamper drug delivery through artificial and biological membranes. The composition of the drug formulation and the physicochemical and physiological composition of the membrane will determine what kind of effect obtained. Cyclodextrins will enhance drug delivery through a diffusion-controlled barrier but will hamper delivery through a lipophilic membrane-controlled barrier. It will either hamper or enhance drug delivery through porous membranes depending on the relative pore size compared with the effective diameter of the drug/cyclodextrin complex (Loftsson and O'Fee, 2003).

Alteration of SPF value is undesirable. Therefore, this study was aimed to investigate the SPF value of sunscreen product contained oxybenzone and octyl dimetyl PABA (3:7) with the addition of kojic acid 1% $^{b}/_{b}$ as whitening agent and their complex with β-cyclodextrin in 1:1 molar equivalent. Investigation was made in vanishing cream base preparation because it was elegant, smooth, and easy to be washed from our skin that made it preferable for a cosmetic preparation. Moreover, the formula's characteristics were tested to observe the differences between the formulas.

Methodology

Materials

The materials used in this experiment were as follows Oxybenzone (Surya Dermato), Octyldimethyl PABA (Surya Dermato), Kojic Acid (Surya Dermato), β-cyclodextrin p.a (Sigma Aldrich), Stearic Acid (Surya Dermato), cetyl alcohol (Surya Dermato), span 80 (Surya Dermato) tween 80 (Surya Dermato), Methyl paraben (Surya Dermato), Propyl paraben (Surya Dermato), Sorbitol 70% (Surya Dermato), Isopropanol *p.a.*, (Brataco Chemicals). All of the active ingredients used here were in a pharmaceutical grade except for the chemical reagent isopropanol and β- cyclodextrin which were in pro analytical grade. The qualitative analysis is carried out by using a *Fourier Transform Infrared Spectrophotometre* Jasco FT-IR 5300, *Melting Point Apparatus*, *Bausch and Lomb Refractometre* and the result were compared to the reference and substance certificate of analysis, while 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.

Preparation of the Formula

Formulas were made with inversion technique. Oil phase that made up with stearic acid, cetyl acohol, propyl paraben, and span 80 was heated until reached 70^{0}C on water heater, then, the remaining base ingredients which part of water phase in 75^{0}C temperature was added to the oil phase. It was mixed until it dispersed and smooth. Active ingredients were added to the base when its temperature reached 40-50^{0}C. Oxybenzone was dispersed in octyldimetyl PABA before they were added. Kojic acid was added in aqueous solution form,

and freeze dry complex form of kojic acid with β-cyclodextrin was added in dry condition and dispersed to the preparation.

Determination of Sunscreen Characteristics

The characteristics of the finished product evaluated were emulsion type, pH, spreading-ability, and organoleptic such as colors, odors, and consistency. The finished product was observed with microscope and stained using methylene blue and Sudan III to evaluate its emulsion type. To get the pH value, 2 gram formula was dissolved in 18 mL free-CO_2 aquadest. In order to determine the spreading capability, approximately 1 gram of the gels was weighed and put on a glass plate with a millimeter scale. This glass plate was then covered with another glass plate. And its change in spreading diameter was observed along with an increase of the given load.

Table 1. Formula

Material	Percentage (% w/w)			
	Base	Formula 1	Formula 2	Formula 3
Stearic Acid	14	14	14	14
Cetyl Alcohol	2	2	2	2
Methyl Paraben	0,1	0,1	0,1	0,1
Propyl Paraben	0,05	0,05	0,05	0,05
Span 80	0,5	0,5	0,5	0,5
Tween 80	4,5	4,5	4,5	4,5
Sorbitol 70%	3	3	3	3
Oxybenzone	-	3	3	3
Octyldimetil PABA	-	7	7	7
Kojik acid	-	-	1	1
β-Cyclodextrin	-	-	-	8
Aquadest	75,85	65.85	64.85	56,85

Determination of the SPF Value

The SPF value was determined by Petro correlation for *in vitro* method. 2 mg/cm^2 or 2 µL/ cm^2 sunscreen agent for *in vivo* test was equivalent with 10 ppm sunscreen agent dissolved in isopropanol.

First 100.0 mg preparation formula which contained 10 mg sunscreen's active ingredients dissolved in 2.0 ml isopropanol, the solution was then placed in ultra-sonicator and centrifuged for 15 minutes with 50 rpm speed. The 1.0 ml of filtrate was taken and poured into a 5.0 ml metered flask and shake well until it was homogenized (1000 ppm).

The 1.0 ml of mixture was then pipette, put into a 10.0 ml metered flask and diluted to acquire a 100 ppm solution. The 100 ppm solution that we acquired was pipette for 1.0 ml solution and moved into another 10.0 ml metered flask before isopropanol was added to dilute it and then it's shake well until it reach a concentration of 10 ppm . 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
Ap = Absorption on p wavelength
Ap-α = Absorption on p-α wavelength

The total AUC were obtained by totaling each AUC between 2 wavelengths in series from 290 nm till 400 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:

$$Log\ SPF = \frac{Total\ area}{\lambda n - \lambda 1} x\ 2$$

Whereas:
λn = longest wavelength above 290 nm that has an absorbance higher than 0.050
λ1 = shortest wavelength 290 nm
The Log SPF value obtained from the equation was then converted into SPF value.

Statistical Analysis

The value of pH and SPF obtained were analyzed with SPSS for windows using One-way ANOVA method and continued with Tukey HSD test to asses the significant differences in different formula given. Result where as $p<0.05$ was considered to be statistically significant. Organoleptic and emulsion type test were descriptive analyzed, and spreading-diameter's data was proceed to get its spreading-ability.

Results and Discussions

Organoleptics test showed no definite differences between the formulas. The formulas had yellowish white colors, with soft cream odors and semisolid consistency. These physical characteristics were determined by the active ingredients of sunscreen agents.

The result for emulsion type test was oil in water emulsion preparation. It was homogenous blue that could be seen in the microscope using methylen blue stained, and dispersed orange with Sudan III.

One of the important factors that influence SPF of a sunscreen is pH, besides extinction coefficient and solvent polarity and therefore, it's important to make sure what's the real cause of SPF changes in the treatment formula. The pH of a product is a measure of the free hydrogen ion content and can be a very important chemical characteristic. The value of pH is dependent on the materials used in the formulation and their interactions. The pH can affect the use properties of the product as well as the stability of the actives and stability of the overall formula. The pH value in table 2, compared with formula 1, was slightly increased in formula 2, but in formula 3 it decreased. The fluctuation was significant according to Tukey HSD test was shown in table 3.

Spreading-ability profile was relatively changed. As showed in figure 6, formula 2 had higher mean spreading diameter than formula 1. The reversed could be seen in formula 3, with relatively downward profile of the spreading-diameter.

Table 2. Average pH data

FORMULA	pH* ± SD
1	4,51 ± 0,08
2	4,72 ± 0,26
3	3,80 ± 0,03

* The result were obtained from an average of 3 times replication

Table 4 showed average value of SPF obtained. Compared to formula 1, formula 2 had higher SPF and formula 3 was lower. According to Tukey HSD test, the differences between the formulas were significant.

Profile of absorbance didn't show any remarkable bathochromic or hipsochromic shift. It has relatively constant λ_{max} at 308 nm. Changes of SPF value in formula 2 were possible because its absorbance was increased. It could be happened because kojic acid has chromophore and auksochrome group.

The SPF value decreased in formula 3. The complex formation of the sunscreen agent with β-cyclodextrin was suspected to be responsible for this phenomenon. The preparation contained water, that could served a good condition to make the reaction happened. Although there was a remarkable fell of SPF value in formula III that observed in this experiment, efficacy of this preparation wasn't definitely decreased. Advanced study about complex formation of the sunscreen agent with β- cyclodextrin was needed to solve this problem. Moreover, it was suggested to make in vivo correlation with the result of this study.

Table 3. Result of HSD test of the sunscreens pH

FORMULA	N	Subset for alpha = .05		
		1	2	2
Formula 3	9	3,8022		
Formula 1	9		4,5056	
Formula 2	9			4,7189
Sig.		1,000	1,000	1,000

a. Uses Harmonic Mean Sample Size = 9,000

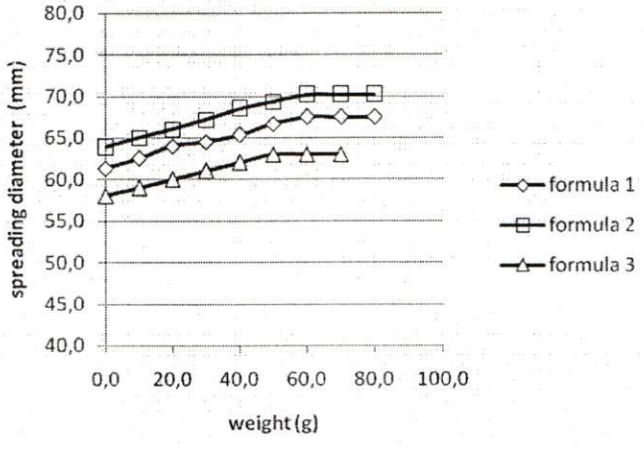


Fig 6. Profile of the Sunscreen's Spreading-ability

Table 4. Spreading-capacity of sunscreen

Formula	Average Slope ± SD (mm/g)	% CV
1	0.100 ± 0.003	3.10
2	0.107 ± 0.006	5.38
3	0.100 ± 0.000	0.00

* The result were obtained from an average of 3 times replication

Table 5. The SPF Value

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

Table 6. Result of HSD test of the sunscreens SPF

FORMULA	N	Subset for alpha = .05		
		1	2	3
Formula 3	9	9,113		
Formula 1	9		10,607	
Formula 2	9			11,741
Sig.		1,000	1,000	1,000

Means for groups in homogeneous subsets are displayed
a. Uses Harmonic Mean Sample Size = 9,000

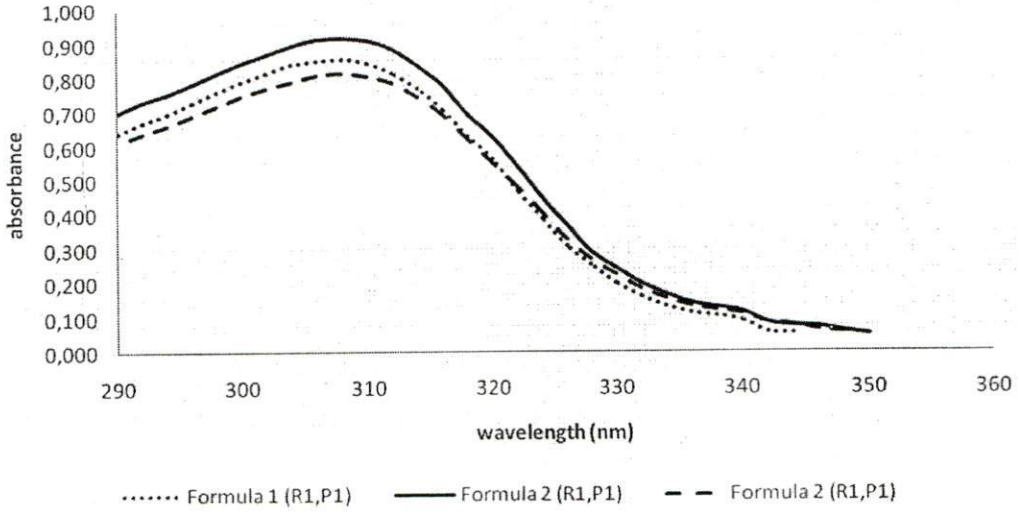


Fig 7. Profile of sunscreens absorbance in formula1, 2, 3 at first replication and measurement.

Conclusion

The result showed that the addition of kojic acid increased the SPF value of sunscreen product from 10,607 ± 0,432 became 11,741 ± 0,479. A different result showed with the addition of complex form of kojic acid with β-cyclodextrin. The SPF value decreased to 9.113 ± 0.295. The complex formation of the sunscreen agent with β-cyclodextrin was suspected to be responsible for this phenomenon. Moreover, it was suggested to make *in vivo* correlation with the result of this study.

Acknowledgement

This study was supported financially by Project Grant Faculty of Pharmacy Airlangga University. We would also like to thank Surya Dermato Medica for providing the materials needed for the sunscreens preparation.

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