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Formulation and Evaluation of Ketoprofen Gel Preparations using Sesame Oil, Soybean Oil and Oleic Acid as Enhancers

Rugun Clara Samosir[1], Iyan Sopyan[1,2,*], Dolih Gozali[1]

[1]Departemen of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, Indonesia, 45363
[2] Research Center of Drug Delivery and Disposition, Faculty of Pharmacy, Universitas Padjadjaran. Bandung, 45363

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ABSTRACT

Permeation is a measurable profile in drug penetration in the skin. Adding increasing permeation substance (enhancer) in drug formulation is an important thing in pharmaceutical and toxicology in nowadays. The purpose of this research was to evaluate the effect of sesame oil, soybean oil, and oleic acid as an enhancer in ketoprofen gel permeation. Six formulas were prepared by varying concentration of sesame oil, soybean oil, and oleic acid respectively 5% and 10% and one blank, without enhancer. Permeation test was evaluated by in vitro permeation test using Franz diffusion cell method and shed snake skin of reticulated python as a membrane. Permeation test was carried out for 6 hours. The result showed that sesame oil, soybean oil, and oleic acid were able to increase ketoprofen permeation. B1 formula that contains 5% sesame oil had the greatest percent permeation after 6 hours is 5.913%, while blank that contain no enhancer is 0.623%.

Keywords: Ketoprofen, permeation, enhancer, soybean oil, sesame oil, oleic acid

1. Introduction

Permeation is a profile should be measured in the penetration of the medication on the skin. The addition of the substance (enhancer) permeation Enhancer at medication dosage is crucial on the research of pharmaceutics and Toxicology at the moment [1].

Permeation-enhancing compounds (enhancer) can modify or impair the lipid composition of the stratum cornea intercellular so that the transfer of drugs through the skin can be improved. Penetration-enhancing compounds that are widely used are dimethyl sulfoxide (DMSO), dimethylacetamide (DMA), dimethylformamide (DMF), propylene glycol, glycerol, and others [2].

The use of organic solvents such as DMSO and DMF are proven effective in increasing the penetration of drug compounds like the barbiturates, steroids, and griseofulvin, but has a weakness among them are irritants, leaving only the morphological changes significantly on the skin, can be denatured ceratin of skin causing keratolysis, and toxic [3].

Therefore, sought relatively safe permeation enhancers for the body. Based on United States Patent by Sharma, *et.al* [4], it is said that the plant oils can function as enhancers in transdermal preparation. In this study, we used enhancers of sesame oil (sesame oil), soybean oil (soybean oil), and oleic acid (oleic acid) which are expected to enhance permeation of drugs without causing toxic effects on the skin. In addition, this plant is the excess oil that can be metabolized by the body, the price is affordable and easy to obtain.

Active substances which are used in this research is that ketoprofen is a propionic acid have activity as a bitter taste with non-steroid analgesic and antipyretic power working to inhibit the synthesis of prostaglandins. The time of elimination ketoprofen crusts quickly, i.e. 1.5–2 hours cause these drugs must often be consumed when used per oral and on the use of ketoprofen in high doses (300 mg >) can cause bleeding in the stomach. One way of overcoming these weaknesses is by giving ketoprofen topically so as to reduce the side effects of the drug.

*Corresponding author,
e-mail : i.sopyan@unpad.ac.id (I. Sopyan)

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2. Method

2.1. Tools

The tools used in this research are analytic scales (Dragon 204), the Franz diffusion cell has been modified, UV-spectrophotometer Visible (Analytic Jena Specord 200-222U179), pH meter (Metrohm Type 744), and viscometer (Brookfield HBDV-II CP+P).

2.2. Materials

Ketoprofen (Hexpharm), carbopol 940 (Quadran), sesami oil (Lansida), soybean oil (Lansida), oleic acid (Brataco), ethanol (Brataco), triethanolamine (Quadran), tween 80 (Quadran), span 60 (Quadran), n-octanol p.a. (Brataco), aquabidest (IPHA), sodium hydroxide (Merck), potassium phosphate (Merck), ketoprofen gel preparations available on the market (® Profenid gel) (Sanbe), and snake membranes swell (Reticulated Python Python) (from the Bandung Zoo).

2.3. Organoleptic identification material observation

Examination materials are organoleptic, which includes description and solubility are then compared with the monograph listed in the Pharmacopoeia Indonesia Edition IV and Handbook of Pharmaceutical Excipients.

2.4. Formulation of ketoprofen gel

Formulation of ketoprofen gel with sesame oil enhancers, soybean oil, and oleic acid was designed based on Table 1.

2.5. Evaluation of ketoprofen gel

Evaluation of ketoprofen gel includes organoleptic observations, pH, the viscosity, determination of the levels of ketoprofen in the gel, in-vitro testing and release of ketoprofen from preparations gel using cell method Franz diffusion and as well as the calculation of the partition coefficient of ketoprofen from the gel.

2.6. Statistical analysis data

Statistically, data analysis using random complete block design using the ($\alpha = 0.05$, DBLA), with a confidence level of 95%.

3. Result

3.1. Results of material identification

The results of the examination of materials showing the materials used comply with the standards contained in the Indonesia Pharmacopoeia Edition IV and Handbook of Pharmaceutical Excipients.

3.2. Results of gel ketoprofen formulation

Formulation of ketoprofen gel is made in three variations with each enhancer comprising 2 variations in concentration. Results formulation of ketoprofen gel preparations can be seen in Figure 1 and the results of observations of the organoleptic preparations can be seen in Table 2.

Table 1. Gel formulation

Materials	Formulation (%w/w)						
	Blank	A1	A2	B1	B2	C1	C2
Carbopol 940	1	1	1	1	1	1	1
Ketoprofen	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Triethanolamine	3	3	3	3	3	3	3
Soybean oil	-	5	10	-	-	-	-
Sesame oil	-	-	-	5	10	-	-
Oleic acid	-	-	-	-	-	5	10
Tween 80	0.1	0.1	0.2	0.1	0.2	0. 4	0.8
Span 60	0.4	0.4	0.8	0.4	0.8	0.1	0.2
Na_2EDTA	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Aquadest (ad)	100	100	100	100	100	100	100

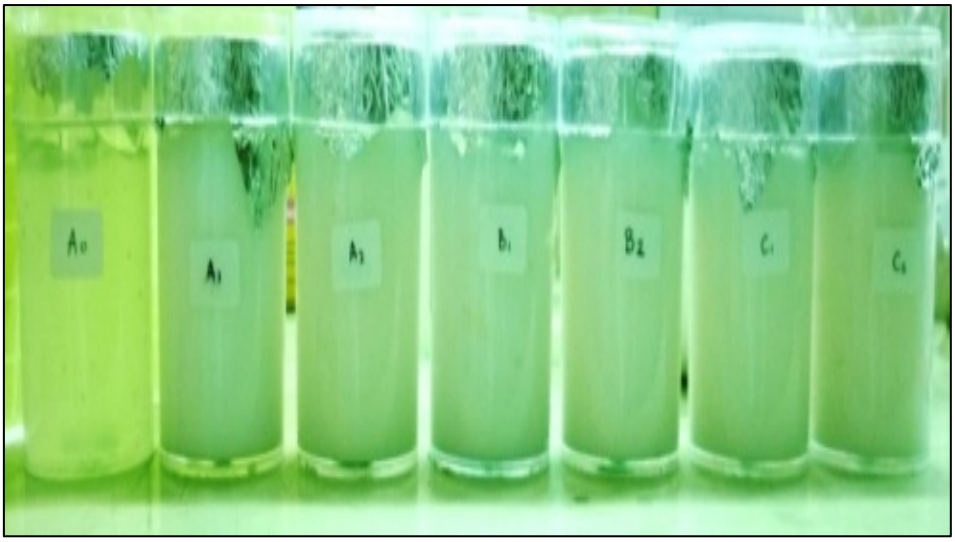

Figure 1. Ketoprofen gel formulation

Table 2. Observations of organoleptic ketoprofen gel

Formulation	Viscosity	Color	Smell
Blank	Viscous	Clear	-
A1	Viscous	White	Soybean oil
A2	Viscous	White	Soybean oil
B1	Viscous	White	Sesame oil
B2	Viscous	White	Sesame oil
C1	Viscous	White	Oleic acid
C2	Viscous	White	Oleic acid

Blank: ketoprofen gel with sesame oil without enhancers, soybean oil, and oleic acid
A1: ketoprofen gel with enhancer soy oil 5%
A2: ketoprofen gel with 10% soybean oil
B1: ketoprofen gel with sesame oil 5%
B2: ketoprofen gel with sesame oil 10%
C1: ketoprofen gel enhancer with oleic acid 5%
C2: ketoprofen gel enhancer with oleic acid 10%

3.3. The Evaluation Material of Ketoprofen Gel

The evaluation material of gel includes organoleptic observations, measurements, measurement of pH, viscosity determination of ketoprofen in inventory levels, testing the release preparation of ketoprofen in in-vitro using diffusion cell method of Franz, and results in partition coefficient calculation of ketoprofen from preparations.

3.4. Observation organoleptic preparations

Ketoprofen gel with an enormous variety of enhancers does not experience a change in organoleptic, good consistency, color, and odor during the 56 days of storage.

3.5. Observation viscosity of preparations

The graph between the storage time and the viscosity of the material at room temperature can be seen in Figure 2.

3.6. Observation pH preparations

The results of measurements of the pH of the material can be seen in Figure 3.

3.7. Results of the determination of the levels of ketoprofen in preparation

Determination of the levels of ketoprofen gel preparations done in order to ensure that the resulting preparations contain ketoprofen concentration homogeneity. The results of the determination of the levels of ketoprofen in preparations can be seen in Table 3.

3.8. Determination of partition coefficient

The result of a determination partition coefficient exhibited in Table 4.

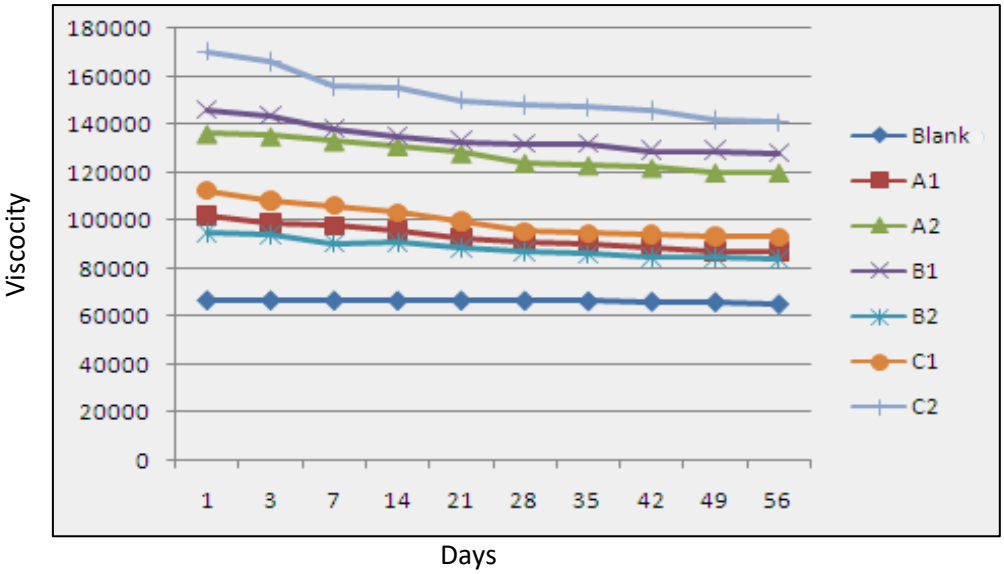

Figure 2. The results of measurements of the viscosity during storage

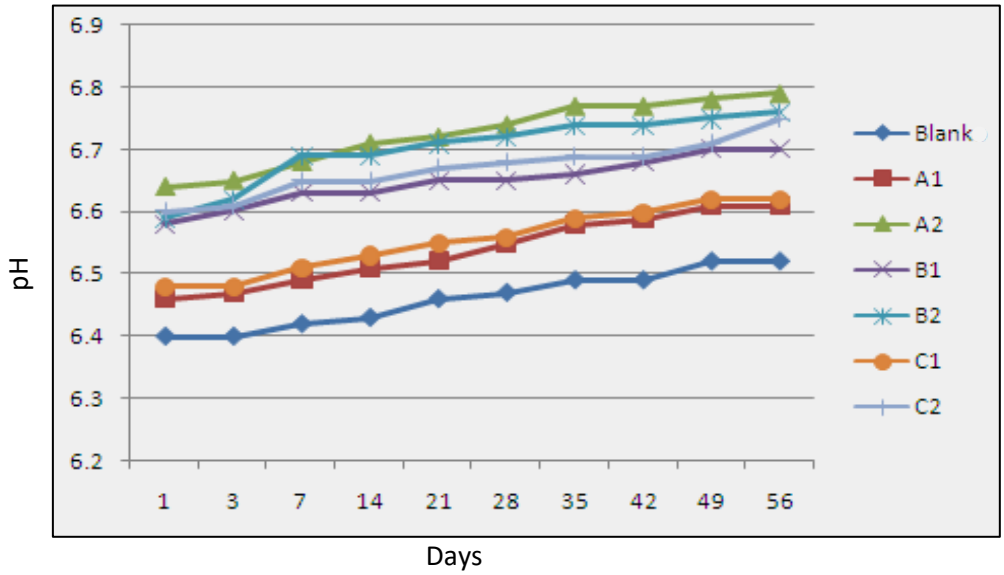

Figure 3. The results of pH measurements during storage

3.9. Evaluation of In vitro permeation

Preparation of ketoprofen permeation testing using diffusion cells Franz in a way measure the concentration of the active ingredients in the liquid receiver on a specific time interval. Permeation test in vitro preparations of ketoprofen gel formula sixth blank and compared against existing products in the market presented in Figure 4 and Table 5.

4. Discussion

During the period of storage are happening decreased viscosity preparations. It is thought to be caused by the presence of the influence of air from the outside causing material tends to absorb water from the environment. However, the viscosity of the material made it still meets the standards of the viscosity of semisolid preparations that are in the range of 500-5000 Poise [5].

Based on these images can be observed that an increase in pH during storage preparation compared to the initial pH of the preparations. An increase in the pH of the material occurs in amounts that are not too large. This show the preparations relatively stable during storage and an increase in pH that occurs likely caused by the

Table 3. Results of the determination of the levels of ketoprofen in preparation

Formulation	Theoretical Concentration (mg)	Concentration (mg) (n=3)
Blank	25	2442.93± 22.54
1	25	2422.03±23.97
A2	25	2580.57±71.12
B1	25	2512.20± 80.83
B2	25	1797.99±10.90
C1	25	2442.94±13.65
C2	25	2569.83±52.80

Table 4. Partition coefficients of ketoprofen test results against a solvent of n-octanol and water

Samples	Partition coefficient
Ketoprofen	3.12
Blank	3.63
A1	3.59
A2	3.35
B1	3.28
B2	3.35
C1	3.46
C2	3.23

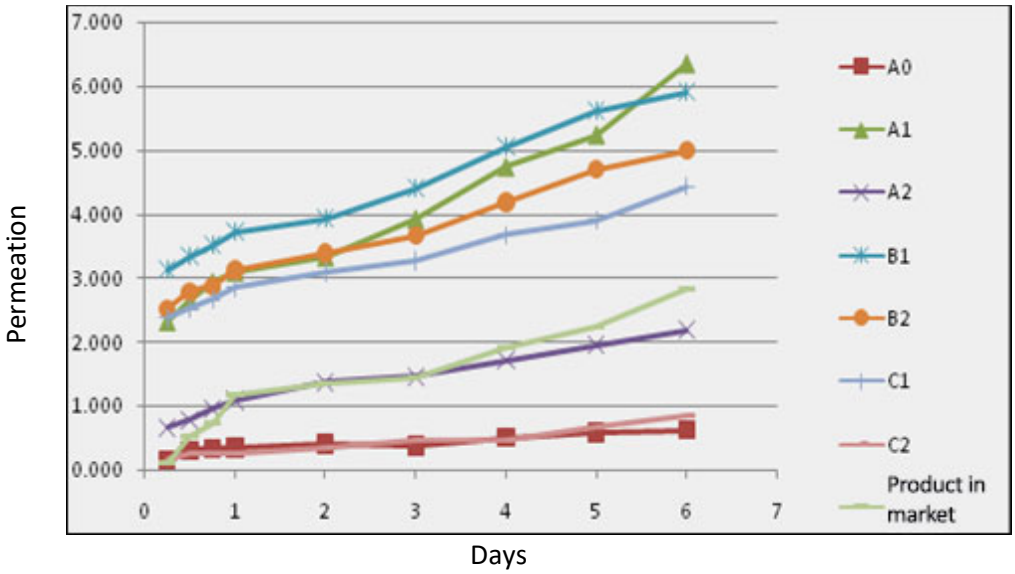

Figure 4. Ketoprofen gel preparations permeation results

presence of an excipient which is alkaline in the preparations. Based on the data obtained during the storage preparations pH 58 days ranges from 6.40–6.77, and pH for topical preparations a pH range between 5–8. Thus it can be concluded that the preparations that have been made are quite safe to use.

Determination of coefficient of partition 1-octanol/water, P o/w, is useful as relative lipophilicity drug information. Although the 1-octanol is not a biological molecule, the solvent is better and more appropriate for drug partition coefficient study between phospholipids and water, $P_{membrane}$, which can be calculated using the membrane lipid bilayer. Optimum partition of the drug on the lipid layer is one of the key pharmaceuticals in product development [6].

Table 5. Percent of dosage permeation for 6 hours

Time (hours)	Permeation of ketoprofen (%)							
	Blank	A1	A2	B1	B2	C1	C2	Marketed product
0.25	0.164	2.329	0.657	3.135	2.535	2.383	0.156	0.108
0.5	0.303	2.656	0.771	3.347	2.790	2.520	0.249	0.532
0.75	0.339	2.945	0.943	3.517	2.877	2.667	0.250	0.739
1	0.354	3.106	1.085	3.716	3.134	2.849	0.257	1.163
2	0.404	3.346	1.365	3.935	3.389	3.098	0.330	1.345
3	0.379	3.930	1.456	4.413	3.668	3.265	0.451	1.451
4	0.513	4.744	1.707	5.058	4.180	3.669	0.459	1.910
5	0.580	5.246	1.957	5.614	4.690	3.902	0.672	2.219
6	0.623	6.358	2.182	5.913	4.985	4.418	0.844	2.824

Blank: gel with sesame oil without enhancers, soybean oil, and oleic acid
A1: ketoprofen gel with soybean oil 5% as an enhancer
A2: ketoprofen gel with 10% soybean oil as an enhancer
B1: ketoprofen gel with sesame oil 5% as enhancer
B2: ketoprofen gel with sesame oil 10% as enhancers
C1: ketoprofen gel with oleic acid 5% as an enhancer
C2: ketoprofen gel with oleic acid 10% as an enhancer

Active substances from stocks to rise compared to the partition coefficient of active substances without preparations. It is influenced by the effect given by an excipient which is in preparation. Partition coefficients of ketoprofen preparations obtained are at 3.28 ranges up to 3.63. Based on these data it can be concluded that such material is eligible in ketoprofen for preparations transdermal. The price of the partition coefficient of the substance to be used as the material of transdermal is the range between 2.5-4.

According to the analysis of the data are statistically random complete block design using the (α= 0.05, DBLA), with a confidence level of 95% oil addition sesami oil, soybean oil, and oleic acid in ketoprofen gel preparations will affect the increase in concentration of ketoprofen the permeated of preparations (H_0 is rejected). Therefore, a further test carried out using the method of Duncan. Based on the results of further trials Duncan retrieved that formula A1, A2, B1, B2, and C1 differs markedly with a blank. This shows that an increase in ketoprofen permeation with the addition of soybean oil, soybean oil, and oleic acid. Meanwhile, the formula C2 revealed no different with a blank. This shows that in the formula C2 with oleic acid 10% did not provide a significant permeation enhancement compared blank.

5. Conclusion

It could be concluded that sesame oil, soybean oil, and oleic acid can improve the profile of ketoprofen gel permeation. The formula containing 5% sesame oil gave a most excellent permeation profile i.e. 5.913% during 6 hours permeation.

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