INDONESIA INTERNATIONAL INSTITUTE FOR LIFE SCIENCES

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TITLE

In Vitro Percutaneous Absorption Study of Glycols as Penetration Enhancers towards Niacinamide against Skin Models

Study Sponsor : PT. Paragon Innovation and Technology
Laboratory : Skinovation Centre, Indonesia International Institute for Life Sciences
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The investigators, data collector, author and everyone involved in this study hereby certify the validity of the data presented in the report and has come to an agreement to the conclusions written at the end of the report.

The Head of Laboratory and Laboratory Coordinator also certifies that a quality control has been performed at each stage of the method described in a specific protocol. This control leads to accurate investigations to the tested product and to guarantee the reliability of analyzed data in accordance with this standard procedure. The present report constitutes a precise description of the performing of experimentation, processing of data and detailed procedure that have been used.

Any information concerning products to study such as patents, formulae, raw materials, manufacturing procedures etc. directly or indirectly provided by the sponsor of the study, will be regarded as confidential, will remain his property and will not be disclosed without his express consent.

Date : 9 Desember 2021

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Table of Contents

1. Introduction

Human skin is the largest organ that covers 16% of the body weight. Normally, skin comprises a multilayer membrane that is known as hypodermis, dermis, and epidermis (Kahraman, et al., 2019). Stratum corneum (SC) is known as the outermost layer of epidermis. It is made up from the binding interaction between corneocytes and lipid interface which includes free fatty acids, cholesterol, and ceramides (Elias & Wakefield, 2010). Stratum corneum also works as the permeability barrier and antimicrobial defenses. In general, the mechanism of barrier function as the permeability is by the regulation of IL-1α, Ca++, pH, liposensors, serine proteases signaling through the PAR2, TRPV1 and 4 as the receptors. Meanwhile, the antimicrobial activity of the skin barrier is regulated by the signaling of 1,25 (OH)2D3, an IL-1α. The signaling pathway of SC as the permeability barrier and antimicrobial defense are occured in lamellar bilayer (Elias, 2008). Moreover, skin is known as the important route for topical and systemic administration (Praça, et al., 2018).

Skin naturally is able to regulate the passage of a certain compound to pass through the skin layer, scientifically known as percutaneous absorption. In general, percutaneous absorption is classified into three steps, starting from penetration, permeation, and resorption (Bartosova & Bajga, 2012). Penetration is known as the entry of a particular substance to the SC. Following that, the compound is penetrated from the SC to a deeper layer which has a different function and structure. This process is called permeation. This step is carried out by a diffusion process. The skin permeation is known to be slower than penetration due to the binding of various types of ions (e.g. metal ions, ammonium ions), sulfonium salts, acrylates, etc. SC is mainly used as the rate limiting barrier due to the high resistance to diffusion rate. Meanwhile, resorption is known as the process of uptake of a particular substance into a vascular system.

The chemical transport into the skin involves three mechanisms (Bartosova & Bajga, 2012). Transcellular absorption is the process when the particular compound is transferred throughout the keratin-packed corneocytes by a cell membrane partitioning. The mechanism is followed by the intercellular absorption pathway. It occurs when the chemical is moving around the corneocytes which happens in lipid-rich extracellular regions. The end of the second pathway is indicated by the chemicals bypassing the corneocytes and entering the shunts that are provided by the hair follicles, sebaceous glands, and sweat glands. In the percutaneous absorption, a compound that is contacted with skin is generally crossed the diffusional barrier, followed by the uptake by the capillary network that is intended for systemic circulation. However, the compound might undergo evaporation from the surface of the skin. The binding and penetration to SC also possibly occurred as well as the compound is able to be metabolized.

Due to the external and internal environment, skin faces some challenges that might decrease its properties. Cosmetics appear as the solution to overcome many skin problems. It is defined as a preparation that is used to clean, beautify, promote attractiveness, alter the body appearance, and also maintain the skin and hair condition (Misui, 1997). Cosmetics are generally classified into skin care, hair care, oral care, and body cosmetics with various pharmacological activities such as anti-aging, anti-wrinkle, whitening agent, cleansing agent, etc. It has been proven that the presence of an active ingredient in cosmetics is expected to exert protective activity, resulting in an improvement of the skin (Kraeling, et al. 2015). However, many of the active ingredients have limited penetration due to many factors, resulting in reduced activity. Therefore, to ensure adequate activity, percutaneous absorption study of the penetration enhancers are important to determine the ability of the penetrant to stimulate the API to penetrate into a deep layer.

Percutaneous absorption study is an evaluation of the ability of a certain ingredient to pass through the upper skin membrane. Penetration study is commonly carried out either by *in vitro* or *in vivo* test. *In vitro* penetration test is carried out by applying the cosmetic formulation into multiple types of either human or

animal skin models. It is designated to measure the ability of chemicals to cross the skin membrane into a fluid reservoir. It is appropriately used to predict human dermal penetration study. *In vitro* method is preferred due to a lower cost, time needed, reproducibility, and less restricted parameters.

AIM OF STUDY : to study the effects of penetration enhancers towards the API in a cosmetic formulation through *in vitro* penetration testing by using MatTek Permeation Fixture (EPI-200-FIX).

2. Material and Methods

2.1. In vitro model

- In vitro model/Subject
- Device : MatTek Permeation Fixture (EPI-200-FIX)
- Skin Model : EpiDermTM Skin Model (EPI-200-X)
- Buffer : Phosphate Buffer Saline (PBS) pH 7.4
- Donor Solution : Liquid or semi-solid dosage form for topical use

2.2. Test Compound (Groups of study or experimental design)

Sponsor	Product Reference	Reception Date of The Study	Aspect	Product Storage	Study Date
PT Paragon Technology and Innovation	Negative Control	22/03/22	Semi-solid	In an aluminum foil-covered bottle, protected from light	22/03/2022 to 22/05/2022
	F1 (Base Value)				
	F2 (Glycerin free)				
	F3 (dose response to concentration				
	F4 (PG)				
	F5 (BG)				
	F6 (PeG)				
	F7 (PDO)				

2.3. Method

2.3.1. Method Origin

Prior to the penetration testing, the calibration curve of the API were constructed in order to find the Limit of Detection (LOD) and Limit of Quantification (LOQ) to define the lowest concentration of the API that can be detected and quantified (Kumar, et al., 2018). The in vitro percutaneous absorption study is conducted with Mattek Permeation Device (MPD) to determine the effect of penetration enhancers towards the API (). The method was mostly developed by Mattek Company with some adjustment for semi-solid dosage form. PBS solution pH 7.4 was chosen due to its abundant availability and numerous studies of penetration testing using PBS.

2.3.2. Method Principle

The principle of the method is similar to Franz-diffusion cells, where the donor solution is inserted to the device equipped with a membrane. The API is expected to pass through the membrane and fall into a receiver solution. To prove the presence of the API, the receiver solution is analyzed through the UV-Vis spectrophotometer at the selected wavelength to obtain the

absorbance. The data then will be processed with the selected formula to find the cumulative drug release and the average flux of the API to penetrate. The experiment was conducted in three biological and technical replicates.

2.3.3. Description of The Method

2.3.3.1. Determination of LOD and LOQ of Niacinamide

UV-Vis Spectrophotometer Shimadzu 1280 was used as the detector to analyze the unknown concentrations of the active ingredients. The assay was performed by making a 2000 ppm stock solution. Following that, the solution was diluted into 1, 2, 4, 8, 16, and 24 ppm accordingly. Several concentrated API solutions were measured through the detector at 262 nm. The standard curve of the API was constructed following the measurement as well as the standard error, standard deviation, LOQ and LOD.

2.3.3.2. EpiDerm Skin Model (EPI-200-X) Preparation

Prior to cell treatment, the EPI-200-X was given a pre-treatment to allow its full recovery from shipment stress. This was done by transferring the EPI-200-X cell inserts into 6-well plates containing 900 µL pre-warmed MatTek assay medium under sterile conditions, then incubating in a humidified 5% CO_2 incubator at 37°C overnight prior to treatment.

2.3.3.3. *In vitro* Penetration Testing

The formula below was distributed accordingly into three different groups of analyses. Different types of glycols namely PG, BG, PeG, PDO, and glycerin were renamed accordingly as penetrant 1 to 5 respectively. The tests were carried out with Whatman filter paper CA 0.45 um; 47 mm and the EPI-200-X as the epiderm. The first analysis was conducted in order to determine the ability of penetrant 5 to induce the API to permeate the skin surface. Control (-), F1, and F2 were grouped into the analysis. In order to find the dose response to the concentration of penetrant, control (-), F2, and F3 will be combined to find whether the different concentration of penetration enhancer affects the release of drug. Control, F4, F5, F6, and F7 were grouped in order to analyze whether the different isomer of glycol affects the penetration profile of the active ingredient.

Table 1. *Formulation of donor solution used for the penetration study*

Ingredient	Control (-)	F1	F2	F3	F4	F5	F6	F7
Base	95%	81%	91%	91%	93%	93%	93%	93%
Active	5%	5%	5%	5%	5%	5%	5%	5%
Penetrant 1 (PG)	-	-	-	-	2%	-	-	-
Penetrant 2 (BG)	-	2%	2%	1%	-	2%	-	-
Penetrant 3 (PeG)	-	2%	2%	1%	-	-	2%	-

Penetrant 4 (PDO)	-	-	-	-	-	-	-	2%
Penetrant 5 (Glycerin)	-	10%	-	-	-	-	-	-

Prior to the experiment, 5 ml of PBS solution were transferred into the 6-well plates. It was needed to ensure that the PBS which acts as the receiver solution touched the bottom part of the membrane. The 200 mg of each formula was weighed accordingly. Following that, the donor solution was placed on the membrane by putting the donor solution above the skin models. The analysis was carried out into time points as the following: 0.5, 1, 2, 4, 6, and 8 hours. The entire receiver solution was replaced for every time point. The taken receiver solution was needed to be diluted 20x in order to obtain a desired absorbance. The measurement was done by UV-Vis Spectrophotometer at 262 nm.

Standard calibration curve of API was also made on the same day with the penetration testing by utilizing the PBS as the buffer solution in order to find the concentration of API in the receiver solution. Following the penetration testing, the amount of drug release in order to find the value of API that was penetrated through the skin models by the equation below:

Amount of Drug Release (ug) = Concentration of sample (ug/ml) x Total receiver solution (ml) x Dilution FactorTotal amount of API in the donor solution (ug)

By knowing the amount of drug release, the cumulative drug release was calculated by the following formula:

Cumulative Drug Release (%) = Σ p(t-1) + p(t)

Where the p(t - 1) represented the percentage of the API that penetrated at the certain time points before t. Meanwhile, the p(t) represented the percentage of the API that penetrated at a certain time. This formula was applied since the total volume withdrawn and total bath volume was equal.

Average flux is defined as the rate of flow of molecules across the membrane. It was calculated according to the formula below:

Average Flux (ug/hr) = Amount of drug release (ug)Time (hr)

2.3.4. Materials and Equipment

The materials and equipment used in this study were listed in **table 2.3.4.1**.

Table 2.3.4.1. The list of materials and equipment utilized and incorporated in the study.

No.	Materials	Equipment
1	6 well plate	Biosafety Cabinet
2	1000 µL micropipette tips	Micropipette
3	200 µL micropipette tips	UV-Vis Spectrophotometer

4	10 µL micropipette tips	Analytical Balance
5	EpiDerm Skin Model (EPI-200-X)	Forceps
6	MatTek Permeation Fixtures (EPI-200-FIX)	Autoclave Sterilizer
7	Dulbecco's Modified Eagle Medium	
8	PBS sterile solution	
9	Whatman Filter Paper CA 0.45 um 47 mm	

2.4. Data Management, Calculation, and Statistical Analysis

All of the data obtained were processed through one-way ANOVA method, followed by the post hoc testing. The significant difference was achieved when the p value is less than 0.05. GraphPad 8.0.1 was utilized as the software to determine whether the result was statistically significant.

3. Result

3.1. Calibration Curve of API

Prior to the measurement of LOD and LOQ, the calibration curve was plotted to know the equation and find the r value to determine the linearity after the absorbance was measured at 262 nm. Figure 3.1. shows the calibration curve of the niacinamide.

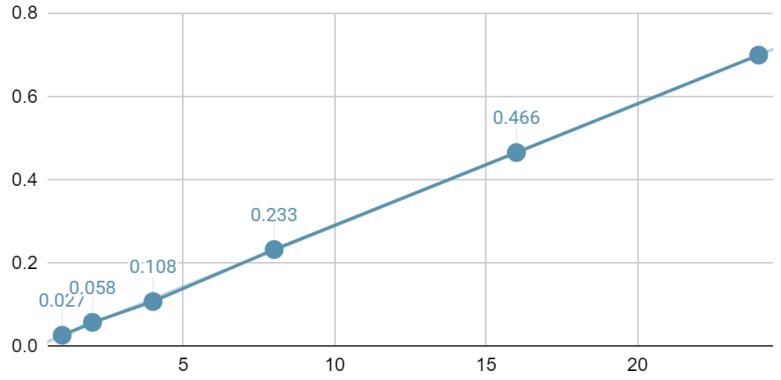

Figure 3.1. *Calibration Curve of Niacinamide*

The equation was found to be y = 0.0293x + 0.00338 and the linearity was found to be 0.9994. The result showed that the concentration of API is directly proportional to the absorbance. According to the requirements, the r value should be > 0.995, meaning that the linearity was achieved. Furthermore, the LOD, and LOQ should be measured in order to know the lowest concentration of the niacinamide that can be detected and measured. The value of LOD and LOQ of niacinamide were reported to be 0.48 and 1.44 ppm respectively.

3.2. *In vitro* Penetration Testing

3.2.1. Whatman Filter Paper CA 0.45 um; 47 mm

3.2.1.1. Effect of Penetrant 5 (Glycerin)

Control (-), F1, and F2 were plotted in the same graph to see whether the addition of penetrant 5 significantly increased the drug release of the API. According to Figure 3.2., The drug is highly penetrated through the skin models for the first 4 hours before it reaches the steady state. It was shown that the F1, which contains the addition of penetrant 5 have a higher release compared to the control and F2, which only have penetrant 2 and 3. The p value was observed to be less than 0.05, meaning that the addition of penetrant 5 significantly affects the penetration rate of the API due to the additional -OH group in the carbon parent chain. However, the F2, which only contains penetrant 2 and 3 did not significantly improve the drug release.

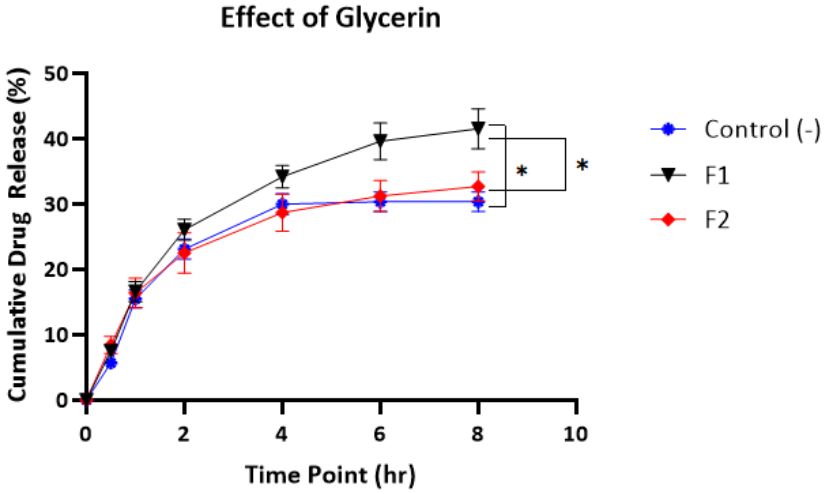

Figure 3.2. ***Cumulative drug release of the effect of penetrant 5 in Whatman filter paper CA 0.45 µm; 47 mm.*** *The results were compared as mean ± standard deviation of a triplicate sample. * indicate statistical significant difference ($p < 0.05$)*

Referring to **Table 3.2,** the addition of penetrant 2 and 3 in a different sample may cause a slight increase in drug release. It was shown that the F2's drug release is approximately 4% higher compared to the control (-). Meanwhile, the addition of penetrant 5 significantly affects the drug release since it is able to increase the rate by approximately 7%.

Table 3.2. *Cumulative drug release of the effect of penetrant 5 after 8 hours in whatman filter paper CA 0.45 µm; 47 mm*

Formula	Cumulative Drug Release (%)
Control (-)	30.37 ± 1.54
F1 (FS02)	41.52 ± 3.01
F2 (FS03)	34.10 ± 4.08

Average flux is defined as the speed of the API to pass through the skin models after a certain time point. The graph was plotted against time points. Referring to **Figure 3.3.,** the

highest flux was achieved after 1 hour, before it gradually decreased due to the less amount of API penetrated. It was also observed that the addition of penetrant 5 significantly increased the average flux. The high average flux is also affected by the amount of penetrated API.

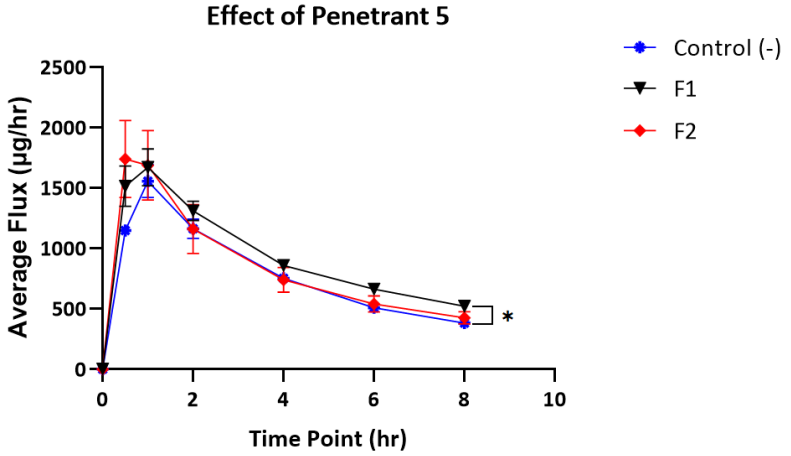

Figure 3.3. ***Average Flux of the effect of penetrant 5 in Whatman filter paper CA 0.45 µm; 47 mm.*** *The results were compared as mean ± standard deviation of a triplicate sample. * indicate statistical significant difference (p < 0.05)*

3.2.1.2. Effect of Dose Response to Concentration

Control (-), F2, and F3 were plotted in order to observe whether the concentration of penetrant significantly affected the cumulative drug release of the API. Referring to **Figure 3.4.,** the drug is highly penetrated for the first 4 hours before the steady state is achieved. Unfortunately, the results showed that the amount of penetrant added to the formulation does not significantly improve the drug release of API. According to Paragon Technology and Innovation, the viscosity of F2 and F3 were reported to be 9183 and 9000 cps respectively. The higher viscosity might indicate the lower release since it may block the API to pass through the API.

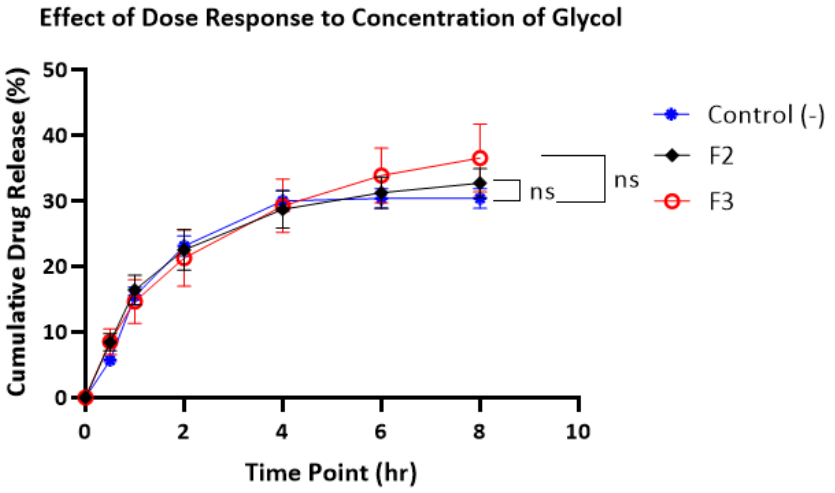

Figure 3.4. ***Cumulative drug release of the effect of concentration of glycol in Whatman filter paper CA 0.45 µm; 47 mm.*** *The results were compared as mean ± standard deviation of a triplicate sample. ns indicate no statistical significant difference (p > 0.05)*

According to **Table 3.3,** the addition of penetrant 2 and 3 in a different sample may cause slight increase in drug release. It was shown that the F2's drug release is approximately 4% higher compared to the control (-). Surprisingly, F3 which contains less concentration of penetration enhancers exert the best activities. It was able to increase the penetration rate by approximately 8%.

Table 3.3. ***Cumulative drug release data of the effect of concentration of glycols after 8 hours in Whatman filter paper CA 0.45 µm; 47 mm****. The Tests were conducted n = 3. The data were provided average ± SD*

Formula	Cumulative Drug Release (%)
Control (-)	30.37 ± 1.54
F2 (FS03)	34.10 ± 4.08
F3 (FS04)	38.00 ± 2.87

Figure 3.5. shows that the highest flux was achieved at the time point of 0.5 to 1 hour. The high average flux occurred due to the huge difference in concentration of donor and receptor compartment. As the time passed by, the flux gradually decreased since the concentration of both compartments reached the equilibrium state. Therefore, the steady state is achieved.

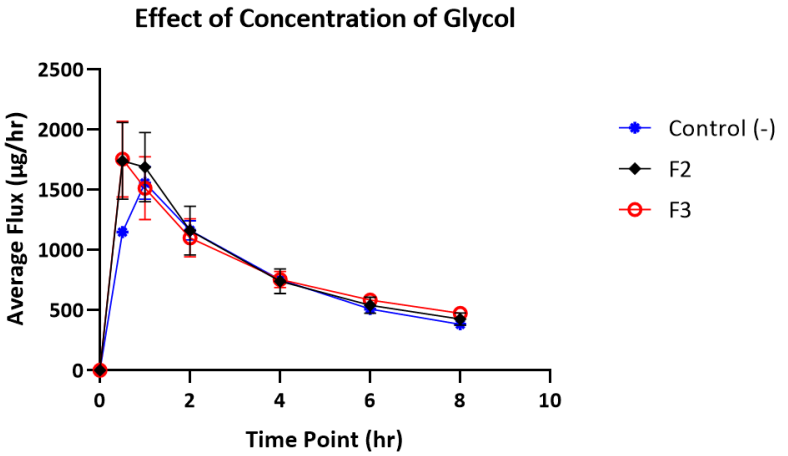

Figure 3.5. *Average flux of the effect of concentration of glycol after 8 hours in Whatman filter paper CA 0.45 µm; 47 mm.*

Figure 3.5. showed that the concentration of penetration enhancers does not significantly affect the flux. However,. the average flux of F3 is reported to be the highest after 8 hours. It was caused by the huge amount of API that was penetrated in a certain time slot.

3.2.1.3. Effect of Different Chemical Structure

Control (-), F4, F5, F6, and F7 were plotted in order to observe whether the length of the carbon chain and the different placement of the -OH group significantly affected the cumulative drug release of the API. In general, the drug is highly penetrated for the first 4 hours before the steady state is achieved. However, the F6 reaches a steady state after 2 hours. Referring to **Figure 4.6,** it was shown that the different chemical structures affect the penetration profile of the API.

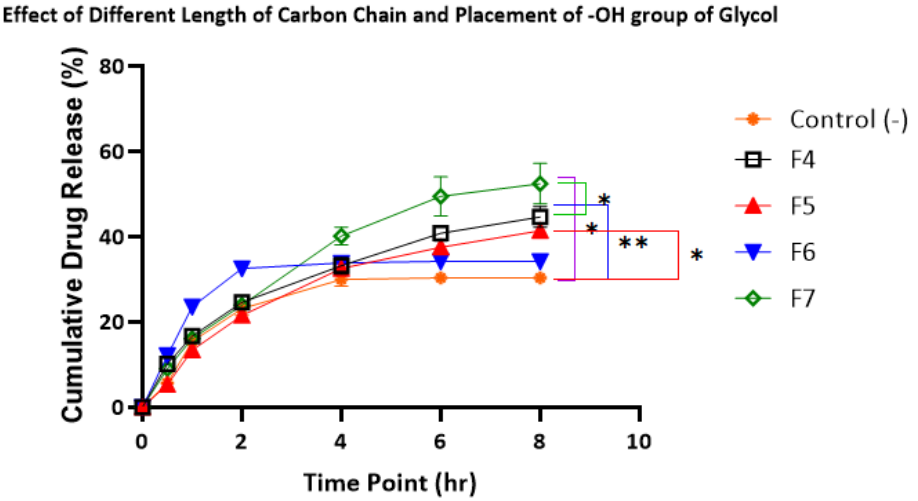

Figure 3.6. ***Cumulative drug release of the effect of different chemical structure of glycol in Whatman filter paper CA 0.45 µm; 47 mm.*** *The results were compared as mean ± standard deviation of a triplicate sample. * indicate statistical significant difference (p < 0.05). ** indicate statistical significant difference (p < 0.01)*

According to **Table 3.6.**, the drug release of F4, F5, and F6 were 46.8 ± 4.85%; 41.41 ± 1.12 %; and 34.21 ± 1.43 % respectively. It was reported by Paragon Technology and Innovation that the length of the carbon chain of glycol used were as follows: F6 > F5 > F4. Interestingly, the F7 shows the highest cumulative drug release, meaning that the different placement of -OH group and a shorter carbon chain significantly affect the release of the API. It was observed that F7 (propanediol) is able to initiate the hydrogen intermolecular binding towards the lipophilic surface (Hadgraft, et al., 1996). The presence of primary alcohol in PDO is able to improve drug release. However, It was found that the longer carbon chain resulted in a less penetration rate. The larger molecular size of carbon might affect the penetration rate. In addition, It was shown that the LogP of Penetrant 2 and 3 were found to be higher. The lower LogP were able to improve the solubility of the vehicles due to its hydrophilicity.

Table 3.6. ***Cumulative drug release data of the effect of different chemical structure of glycols after 8 hours in Whatman filter paper CA 0.45 µm; 47 mm.***
The Tests were conducted n = 3. The data were provided average ± SD

Formula	Cumulative Drug Release ± SD (%)
Control (-)	30.37 ± 1.54

F4 (FS05)	46.86 ± 4.85
F5 (FS06)	41.41 ± 1.12
F6 (FS07)	34.21 ± 1.43
F7 (FS08)	52.39 ± 5.03

Similar to previous analysis, the highest average flux of all groups is achieved after 0.5 - 1 hour before it gradually decreases due to the lower amount of API that passes through the skin model. It was shown that there is a significant difference between control (-) and F4, F5, and F7. However, it was clearly observed that F6 has no significant effect.

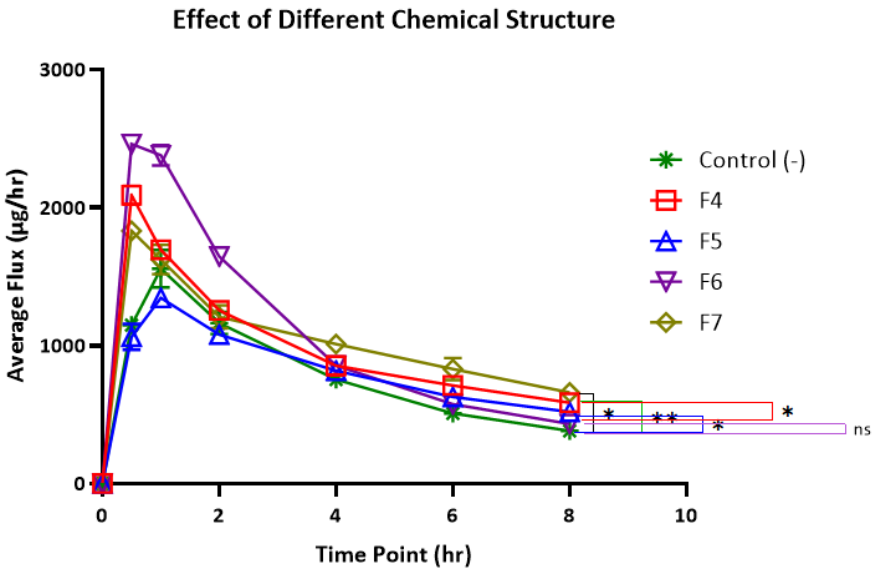

Figure 3.7. ***Average flux of the effect of different chemical structure in Whatman filter paper CA 0.45 µm; 47 mm.*** *ns indicate no statistical significant difference ($p > 0.05$)* indicate statistical significant difference ($p < 0.05$). ** indicate statistical significant difference ($p < 0.01$)*

3.2.2. Epiderm

3.2.2.1. Effect of Different Chemical Structure

Selected groups are chosen based on the variable that showed clear significant differences among all of the analyses. Based on the result of the preliminary penetration study using the artificial membrane, the variable on different chemical structure of glycols was chosen as the one that underwent further study.

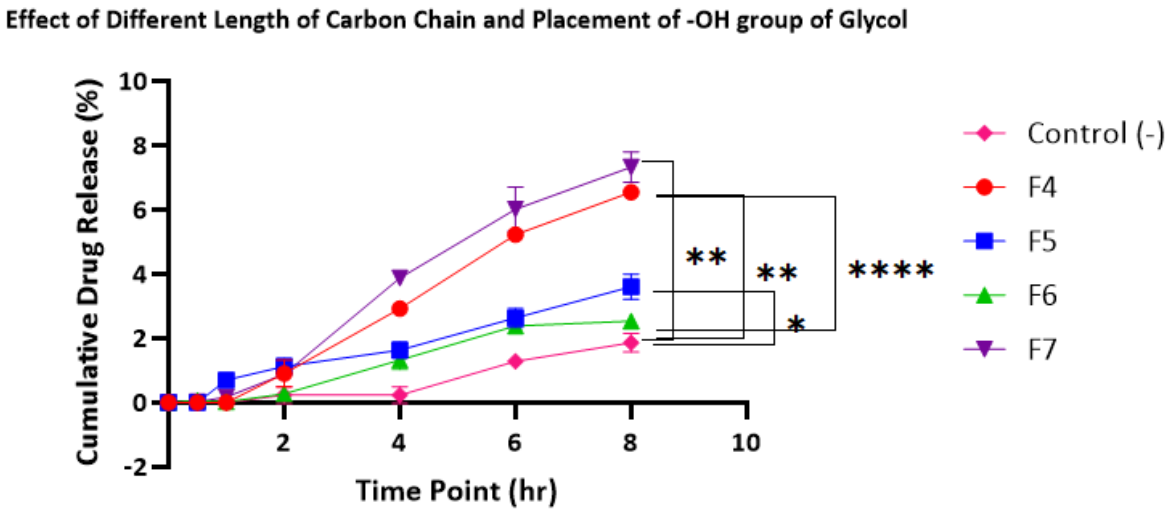

Figure 3.8. ***Cumulative drug release of the effect of different chemical structure of glycol in epiderm****. The results were compared as mean ± standard deviation of a triplicate sample. * indicate statistical significant difference (p < 0.05). ** indicate statistical significant difference (p < 0.01). **** indicate statistical significant difference (p < 0.0001)*

Figure 3.8. depicted a significant difference between control and all groups tested since the p values were reported to be less than 0.05. All formulas achieved a significant release after 2 - 4 hours. Referring to **Table 3.7.**, F7 resulted in a higher release compared to the other group of formulas. Similar to the previous results, the addition of -OH is able to initiate the release of niacinamide. However, It was stated that the release of the API of all groups with epiderm was compared to whatman filter paper. It was observed that ceramide content in the epidermis is robust, making the formula harder to decrease the barrier resistance.

Table 3.7. ***Cumulative drug release data of the effect of different chemical structure of glycols after 8 hours in the epiderm.*** *The Tests were conducted n = 3. The data were provided average ± SD*

Formula	Cumulative Drug Release (%)
Control (-)	1.87 ± 0.30
F4 (FS05)	6.54 ± 0.13
F5 (FS06)	3.61 ± 0.39
F6 (FS07)	2.53 ± 0.12
F7 (FS08)	7.33 ± 0.47

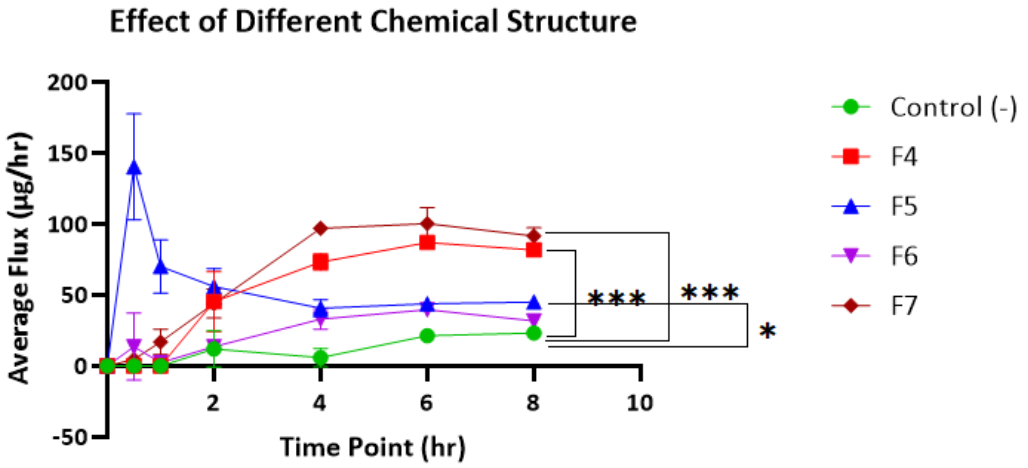

Figure 3.9. ***Average flux of the effect of different chemical structure of glycol in the epiderm****. The results were compared as mean ± standard deviation of a triplicate sample. * indicate statistical significant difference (p < 0.05). *** indicate statistical significant difference (p < 0.001)*

Figure 4.11. above visualized that all of the formulas generally achieved the highest flux after 4 – 6 hours. However, F5 reached the highest flux after 1 hour. The graph showed a significant difference between the control and F4, F5, and F7 respectively. The slower release of API was observed in the epiderm membrane compared to the previous membrane.

3.2.2.2. Additional Formula

Following the trial of penetration testing using Whatman Filter Paper Cellulose Acetate. Some of the formulations are added in order to observe the effect of glycerin and dipropylene glycol in a single dose. The specified formula are presented as follow:

Ingredient	Control (-)	FS10	FS11
Base	95%	93%	93%
Active	5%	5%	5%
Penetrant 5 (Glycerin)	-	2%	-
Penetrant 6 (Dipropylene Glycol)	-	-	2%

3.2.2.2.1. Cumulative Drug Release

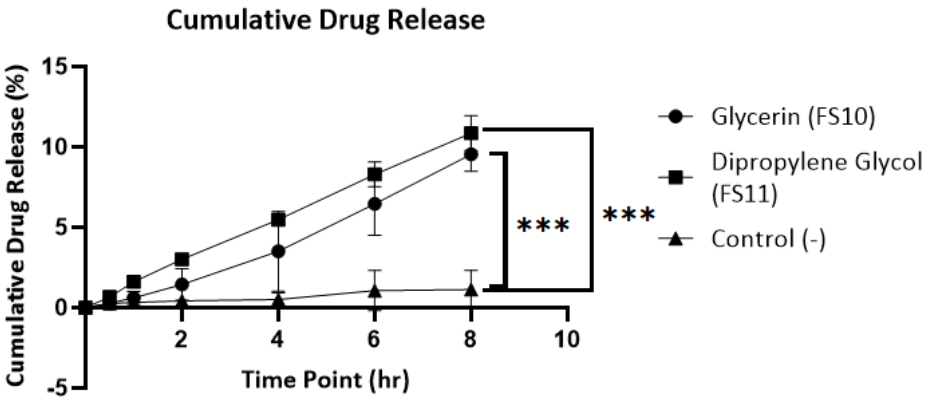

Figure 3.10. ***Cumulative Drug Release of the additional formula in the epiderm****. The results were compared as mean ± standard deviation of a triplicate sample.. *** indicate statistical significant difference (p < 0.001)*

Figure 3.10 showed that Dipropylene glycol exerted the greatest drug release compared to the glycerin single dose. Differs from propylene glycol, dipropylene glycol comprise of additional ether groups. Alkyl ether is proven to enhance the drug release by disrupting the lipid packaging formation. Therefore, the skin becomes fluidized and allows the active ingredient to penetrate the skin models (Park, *et al.,* 2000). Meanwhile, according to Pratama, *et al.* (2020), the single dose of glycerin significantly increases the drug release by increasing the solubility of niacinamide and hydrating the skin models.

Formula	Cumulative Drug Release (%)
Control (-)	1.12 ± 1.20
FS 10	9.34 ± 1.06
FS 11	10.85 ± 1.09

3.2.2.2.2 Average Flux

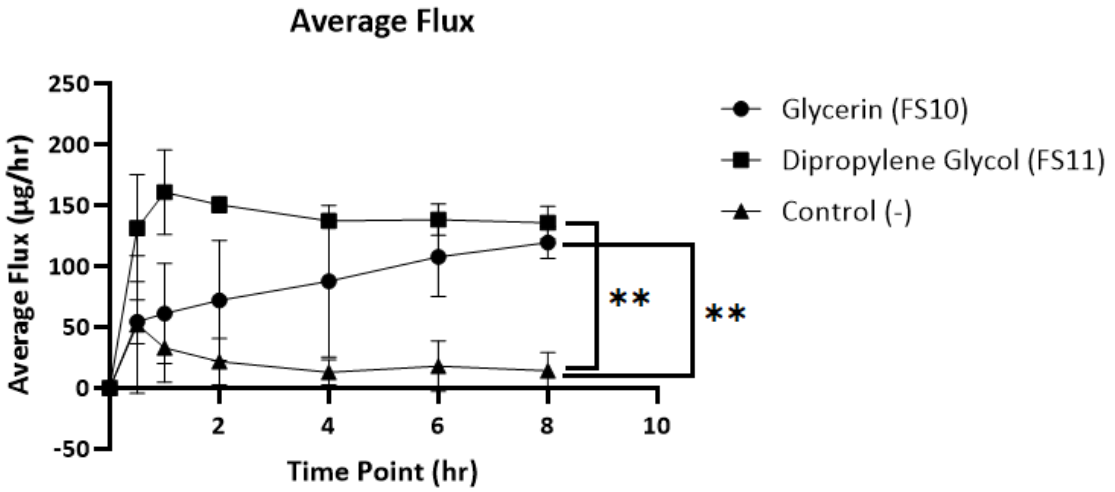

Figure 3.11. ***Average Flux of the additional formula in the epiderm****. The results were compared as mean ± standard deviation of a triplicate sample.. ** indicate statistical significant difference (p < 0.01)*

Figure 3.11. showed the average flux of the formula towards the epiderm. It was shown that the flux significantly increased after 2 hours of treatment. The higher flux was potentially caused by the more niacinamide penetrated. The higher flux indicates the receiver and donor solution reached the equilibrium state.

The cumulative drug release and the average flux of the selected penetration enhancers in a single dose were depicted in **Figure 3.12.** and **Figure 3.13.** respectively.

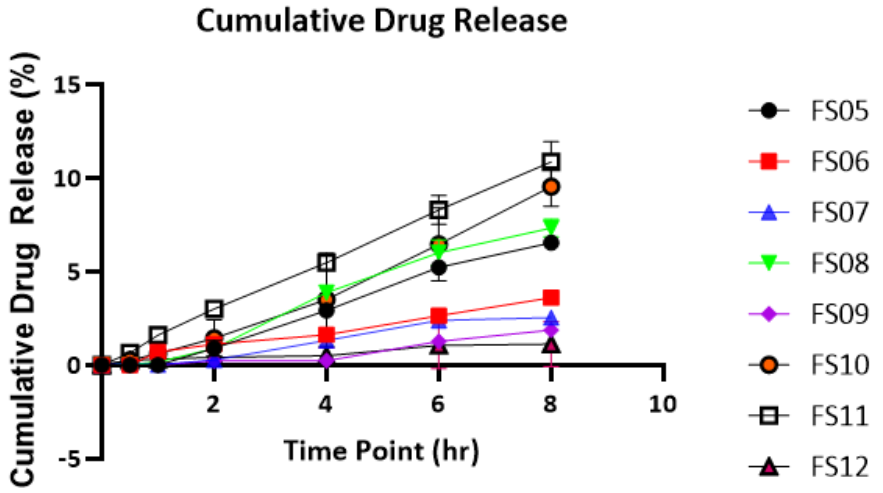

Figure 3.12. *Cumulative drug release of the all penetration enhancers as a single dose*

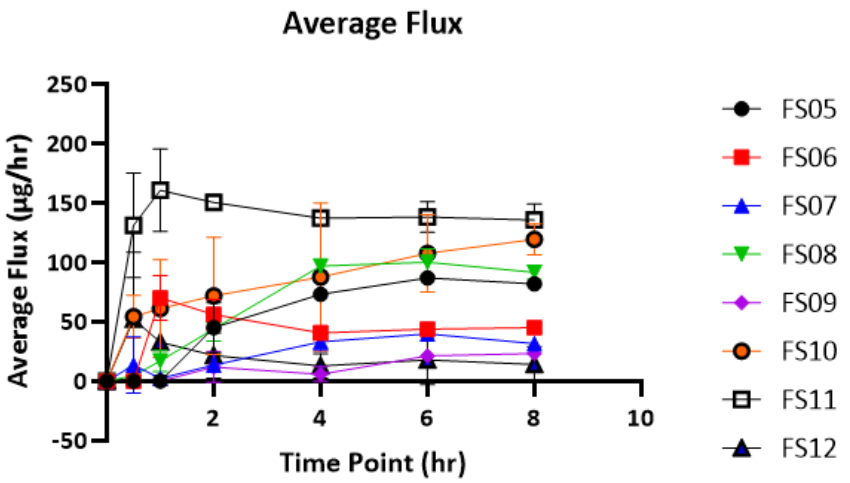

Figure 3.13. *Average Flux of the all penetration enhancers as a single dose*

4. Conclusion

In conclusion, this study has shown that the addition of glycerin significantly improves the penetration profile of the API. Also, the different concentration of glycols significantly affect the rate of release. Propanediol (Penetrant 4) were found to be able to exert the highest release, It was caused by the extra one hydrogen that attached in the carbon, hence initiating the hydrogen intermolecular binding to the stratum corneum. Longer carbon chains resulted in a lower release due to the larger molecular size and lower LogP. Unfortunately, the different concentrations of glycols were not found to be significant. The higher viscosity in the formula containing higher concentration of penetrants might affect the penetration rate. However, the new formula containing dipropylene glycol resulted in the highest release compared to the other penetrants in a single dose since the alkyl ether is able to disrupt the lipid bilayer and allow the niacinamide to penetrate.

The cumulative drug release was found to be lower in the epiderm due to the excessive amount of the ceramide in the inserts. Meanwhile, the greater porosity of the Whatman Filter Paper CA 0.45 um 47 mm were found to be higher compared to real human epidermis. The test is able to be carried out with animal skin models due to its similarity in terms of anatomical and physiological properties.

5. References

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