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Development and In-vitro Characterization of Fish Oil Oleogels Containing Benzoyl Peroxide and Salicylic Acid as Keratolytic Agents

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Key words
- fish oil
- penetration enhancer
- oleogel
- anti-inflammatory

Abstract

Topical keratolytic agents such as benzoyl peroxide (BP) and salicylic acid (SA) are one of the common treatments for inflammatory skin diseases. However, the amount of drug delivery through the skin is limited due to the stratum corneum. The purposes of this study were to investigate the ability of fish oil to act as penetration enhancer for topical keratolytic agents and to determine the suitable gelator for formulating stable fish oil oleogels. 2 types of gelling agents, beeswax and sorbitan monostearate (Span 60), were used to formulate oleogels. To investigate the efficacy of fish oil oleogel permeation, commercial hydrogels of benzoyl peroxide (BP) and salicylic acid (SA) were used as control, and comparative analysis was performed using Franz diffusion cell. Stability of oleogels was determined by physical assessments at 20 °C and 40 °C storage. Benzoyl peroxide (BP) fish oil oleogels containing beeswax were considered as better formulations in terms of drug permeation and cumulative drug release. All the results were found to be statistically significant ($p < 0.05$, ANOVA) and it was concluded that the beeswax-fish oil combination in oleogel can prove to be beneficial in terms of permeation across the skin and stability.

Abbreviations

BP	Benzoyl peroxide
SA	Salicyclic acid
EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid

Introduction

Oleogels are semisolid systems formed by the addition of a suitable gelling agent with an organic or lipophilic liquid [1]. The gelling agent will form aggregates and linkages between those aggregates result in the formation of 3 dimensional networks that will immobilize the liquid phase [2]. Poor water solubility of many drugs has become a major problem for the development of highly potent pharmaceutical formulations. Moreover, pharmaceutical companies had discovered that some potential new drugs' clinical translations have been greatly hindered due to their poor solubility in water [3]. The oleogels can be a potential drug delivery vehicle for the poor aqueous soluble drugs such as benzoyl peroxide and salicylic acid. They are capable of accommodating both hydrophilic and lipophilic compounds, having a longer shelf life, thermoreversible nature and easy to be prepared [4]. The aqueous phase is more likely to support microbial growth. Therefore, oleogels which use non-aqueous medium as solvent are more stable and resistant to microbial contamination [2].

Fish oil is known to enhance the anti-inflammatory properties of corticosteroids such as betamethasone and can also enhance the penetration of the drug across the skin [5]. Fish oil consists of omega-3 polyunsaturated fatty acids which are the essential fatty acids and are also associated with the anti-inflammatory activity itself [6–8]. Based on this fact, studies have been conducted to investigate the capability of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in alleviating inflammatory processes in several skin diseases. For example, the Omega-3 fatty acid administration is effective in improving the clinical condition of psoriasis [9,10]. The combined action of fish oil as an anti-inflammatory agent and as a penetration enhancer across the stratum corneum makes it a potential candidate to utilize it as a drug delivery vehicle in topical formulations [11–13].

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Keratolytic agents are often employed as part of a therapeutic regimen in the treatment of skin disease such as acne, psoriasis, dermatitis and warts [14–16]. The mechanisms of action of common keratolytic agents are reducing stratum corneum cellular cohesion by undergoing proteolysis of desmosomes which forms the junction between keratinocytes [17, 18]. Benzoyl peroxide (BP) and salicylic acid (SA) are examples of keratolytic agents that have anti-microbial and anti-inflammatory effect. Although these keratolytic agents are associated with several side effects such as erythema, skin dryness, itchiness and irritation but the use of fish oil along with these agents may potentially ameliorate the inflammatory side effect associated with keratolytic usage [19].

In this study, oleogels from fish oil were prepared and their ability as drug delivery vehicles was investigated. The permeation studies of commercial BP and SA hydrogels as control were also conducted to compare and determine the penetration enhancing effect of fish oil based oleogels across the membrane. To find an appropriate gelling agent for formulating fish oil oleogels, 2 different gelling agents, beeswax and sorbitan monostearate (Span 60) of different concentrations found in the literature were used to formulate oleogels [20–22].

Materials and Methods

Materials

Fish oil capsules (Blackmores, Australia), benzoyl peroxide, salicylic acid, sodium methylate, methanol, hexane (Merck, Germany), beeswax (White), d-limonene (R&M Chemicals, United Kingdom). Sorbitan monosterate, butylated hydroxyanisole (Sigma-Aldrich, USA). Cetrimide (Kofa chemical works, Malaysia), cellulose acetate membrane 0.45 µm (Advantec MFS Inc, USA), Benzac AC® 5% benzoyl peroxide (Galderma Laboratory, France) and T3™ salicylic acid hydrogel (HOE Pharmaceuticals, Malaysia).

Preparation of oleogels

Oleogels from fish oil were prepared by using a hot plate magnetic stirrer (Daihan Scientific, South Korea). First the gelling agent was added to the fish oil and heated at 60 °C with constant mixing at 300 rpm by using a magnetic stirrer. The composition of each oleogel is given in ➲ **Table 1**. After complete mixing of gelling agent butylated hydroxyanisole (BHA), as an antioxidant, and limonene to mask the smell of fish oil were added into the mixture. Once the mixture was homogenous, heating was stopped and cooled down to room temperature as it gradually solidifies to form oleogel. 2 types of gelling agents, beeswax and sorbitan monostearte (Span 60), were used for formulation of fish oil-oleogels. Formulations containing benzoyl peroxide (BP) were labeled as "B" and the formulations containing salicylic acid (SA) were denoted by "S".

Physical characterization

Fourier transform infrared spectroscopy (FTIR-ATR)

To determine any interaction present between drug and fish oil FTIR-ATR studies were conducted using Perkin Elmer FTIR-ATR (USA) instrument. Mixtures containing equal amounts of drug and fish oil were prepared using vortex mixing and scanned from 4000 to 500 cm^{-1}.

Stability studies

The physical assessments of each gel formulation were carried out after 24 h of preparation. Each gel formulation was stored in an incubator at 20 °C and 40 °C to evaluate the behavior and quality of the product at different temperature. The physical characteristics of the oleogels in both storage temperatures were monitored for any sign of abnormal feature which can be labeled as instability of formulation. The inspection was carried out till 12 weeks all the changes in physical appearance of oleogel formulation were evaluated and recorded again. The stability studies will help to determine the storage conditions and the shelf life of the manufactured oleogels.

pH determination

The universal pH indicator strip was used to perform pH evaluation test of gel formulation which has been stored at room temperature. The gel formulation was smeared on the pH strip. Then, the change in color of pH strip was compared with the reference color in order to determine the pH value of the gel. The pH value was recorded and the pH evaluation test was carried out after 24 h of gel preparation and followed by week 12.

Table 1 Composition of benzoyl peroxide (BP) and salicylic acid (SA) fish oil oleogel.

Constituent	Formulation						
	B1	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**
BP (% w/w)	5	5	5	5	5	5	5
Fish oil (% w/w)	87.35	84.85	82.35	79.85	74.85	72.35	77.35
Beeswax (% w/w)	7.5	10	12.5	15	–	–	–
Span 60 (% w/w)	–	–	–	–	20	22.5	17.5
BHA (% w/w)	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Limonene (% w/w)	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Constituent	**Formulation**						
	S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**
SA (% w/w)	2	2	2	2	2	2	2
Fish oil (% w/w)	90.35	87.85	85.35	82.85	79.85	75.35	82.35
Beeswax (% w/w)	7.5	10	12.5	15	–	–	–
Span 60 (% w/w)	–	–	–	–	20	22.5	17.5
BHA (% w/w)	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Limonene (% w/w)	0.1	0.1	0.1	0.1	0.1	0.1	0.1

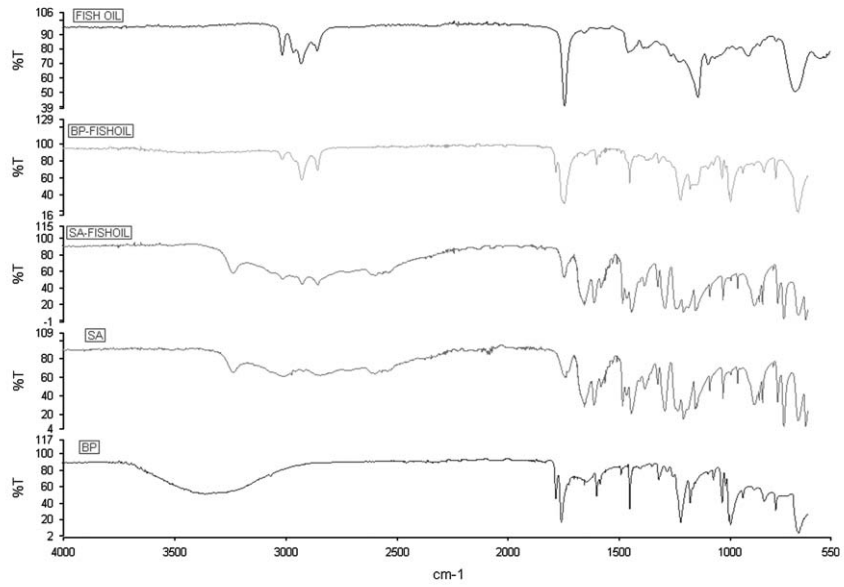

Fig. 1 FTIR spectra of fish oil, benzoyl peroxide (BP), salicylic acid (SA) and 1:1 ratio mixture of drug and fish oil.

Drug release studies

In vitro permeation studies

The oleogel formulations were subjected to in vitro permeation study using Franz diffusion cell (Permegear, Inc, USA), in order to determine the release of drug from the gel formulations. The 9 mm borosilicate glass Franz diffusion cell with 5 ± 0.2 ml of receptor chamber was used in this permeation study. Cellulose acetate membrane with a pore size of 0.45 µm and a diameter of 1.3 cm were used as permeation membrane. A 30 mg/ml cetrimide solution was prepared as a receptor phase used in Franz cell permeation studies. The whole setup was equilibrated at 37 °C for 30 min prior to dosing of the gel samples into the donor chamber. The temperature of the receptor medium was maintained at 37 °C temperature throughout the study. 1 g of weighed gel sample was placed into the upper donor chamber and then the donor chamber and the end of sampling port were covered with parafilm to avoid oxidation of the oleogel and evaporation of gel sample from the receptor medium. 1 ml of aliquot was withdrawn after predetermined time intervals (30, 60, 90, 120, 180, 240, 300, 360, 420 and 480 min) and replaced with equal amounts of fresh receptor solution maintained at 37 °C. To determine the UV absorbance of the prepared standard solutions, UV spectrophotometer 1800 (Shimadzu, Japan) set at a wavelength of 227 nm (BP) and 300 nm (SA) was used to determine the concentration of BP (benzoyl peroxide) and SA (salicylic acid).

Comparison between fish oil oleogel and commercial hydrogel products

The commercial hydrogel products of BP (Benzac AC® 5%) and SA (T3™ salicylic acid hydrogel) were also subjected to the same conditions as of fish oil based oleogels, and the drug permeation across the Franz cell membrane was measured using the same methodology as of oleogels.

Statistical analysis

All of the data obtained were presented as mean ± standard deviation. The data of drug cumulative amount release and flux were analyzed using one way-ANOVA by SPSS 17 software. In one way-ANOVA, the $p < 0.05$ showed a significance difference between the groups tested. If a p value is less than 0.05 it is considered as statistically significant.

Results and Discussion

Physical characterization

Fourier transform infrared studies

The FTIR spectra from 4000 to 500 cm^{-1} for benzoyl peroxide (BP), salicylic acid (SA) and fish oil mixtures are shown in **Fig. 1**. There were no appreciable changes in the nature and position of the function group bands of the spectrum for both BP-fish oil and SA-fish oil mixture. This suggests that the drug was not affected by the fish oil and the mixture did not exhibit any interaction.

Stability studies

Each gel formulation was stored in an incubator at 20 °C and 40 °C and was monitored regularly for any appearance of abnormal features or instability until a period of 12 weeks. The physical characteristics of the oleogels were recorded in terms any changes in their physical appearance. At 20 °C, all the formulations containing beeswax as gelling agent were appeared to be smooth, homogenous with no signs of any instability or abnormal features. This state of stability continued even after the 12 weeks of storage at the same temperature (**Table 2**). The formulations containing Span 60 as a gelling agent initially appeared to be stable with no signs of any physical abnormality but after 12 weeks of storage at 20 °C, the formulations were stiffer and S7 also produced unpleasant rancid odour. At 40 °C, initially the formulations containing beeswax as a gelling agent were stable, but as the time progresses and after 12 weeks, the B1 showed signs of liquid separation with unpleasant rancid odour and loss of homogeneity. As in the case of formulations containing Span 60, all the formulations exhibited abnormal features such as liquid separation, unpleasant rancid odour and loss of homogeneous state (**Table 3**).

The loss of homogenous state and the presence of oil layer on the surface may be due to the syneresis process, considered as a physical aging process of gel in which liquid separates out

Table 2 Changes appeared during storage period of 6 weeks and 12 weeks in fish oil oleogels at 20 °C.

	6 Weeks		12 Weeks	
Formulation & gellator	**Sign of instability**	**Appearance**	**Sign of instability**	**Appearance**
B1-beeswax	No	Homogenous	No	Homogenous
B2-beeswax	No	Homogenous	No	Homogenous
B3-beeswax	No	Homogenous	No	Homogenous
B4-beeswax	No	Homogenous	No	Homogenous
B5-Span 60	No	Homogenous	No	Homogenous
B6-Span 60	No	Homogenous	No	Homogenous
B7-Span60	No	Homogenous	Unpleasant odour	Homogenous
S1-beeswax	No	Homogenous	No	Homogenous
S2-beeswax	No	Homogenous	No	Homogenous
S3-beeswax	No	Homogenous	No	Homogenous
S4-beeswax	No	Homogenous	No	Homogenous
S5-Span 60	No	Homogenous	No	Homogenous
S6-Span 60	No	Homogenous	No	Homogenous
S7-Span 60	No	Homogenous	Unpleasant odour	Homogenous

Table 3 Changes appeared during storage period of 6 and 12 weeks in fish oil oleogels at 40 °C.

	6 Weeks		12 Weeks	
Formulation & gellator	**Sign of instability**	**Appearance**	**Sign of instability**	**Appearance**
B1-beeswax	No	No	Unpleasant odour	Phase separation
B2-beeswax	No	Homogenous	No	Homogenous
B3-beeswax	No	Homogenous	No	Homogenous
B4-beeswax	No	Homogenous	No	Homogenous
B5-Span 60	Unpleasant odour	Phase separation	Unpleasant odour	Phase separation
B6-Span 60	Unpleasant odour	Phase separation	Unpleasant odour	Phase separation
B7-Span60	Unpleasant odour	Phase separation	Unpleasant odour	Phase separation
S1-beeswax	No	No	Unpleasant odour	Phase separation
S2-beeswax	No	Homogenous	No	Homogenous
S3-beeswax	No	Homogenous	No	Homogenous
S4-beeswax	No	Homogenous	No	Homogenous
S5-Span 60	Unpleasant odour	Phase separation	Unpleasant odour	Phase separation
S6-Span 60	Unpleasant odour	Phase seperation	Unpleasant odour	Phase separation
S7-Span 60	Unpleasant odour	Phase separation	Unpleasant odour	Phase separation

spontaneously from the gel matrix [23]. Temperature may also cause the syneresis, as temperature may cause elastic contraction of polymer molecule in the gel and results in separation of oil layer from the gel [24]. In this study, Span 60 fish oil-oleogels which were stored at 40 °C for 3 months showed significant syneresis and this phenomenon may be due to the sol-gel transition temperature for Span 60 gels (54.8 ± 0.5 °C), which is close to the storage temperature. This is because the structural constitution of these physical gels is usually considered as a heterogeneous three-dimensional network of fibers and it exhibits sharp decrease and loss of interconnectivity of the cross-linked matrix at higher temperature and this phenomenon can be observed in low molecular mass gelators like sorbitan monostearate [21].

pH determination

The pH test of gel samples was carried out till week 12. Triplicate analysis (n = 3) was performed for each formulation and the pH at 20 °C and 40 °C is summarized in **Fig. 2a, b** respectively. Generally, the pH of gels ranged from 3.5 to 4.5. After 12 weeks observation, most of the pH readings for gel formulation were stable throughout the storage period except gel B1, B5 and S1. The pH of gel B1 and B5 were reduced from 4 to 3.5 whereas the pH of gel S1 was reduced from 4.5 to 4. The skin pH is range from 4 to 6 and this means that skin's surface is acidic which can act as a barrier to prevent infection from microorganisms [25]. Therefore, a formulation which used for skin application should not affect the acidic skin surface pH [26]. Since all of the gel formulations in this study are acidic, they are suitable to be used for skin application. In general, all of the fish oil oleogels except gel B1, B5 and S1 were stable as there were no changes in pH throughout 12 weeks of storage at room temperature.

In vitro permeation study

The in vitro permeation study is a way to measure the amount of drug permeation and the value can be expressed in terms of flux. Flux is the rate of release of drug and it is measured from the linear portion of the drug release profile in this study. Cetrimide 30 mg/ml which contained 0.05 % w/w BHA was chosen as the receptor medium in this Franz cell diffusion study. Cetrimide 30 mg/ml is an optimal receptor phase to study permeation of lipophilic substances [27]. Cetrimide does not only provide an effective sink condition to fish oil and lipophilic drug, but also inhibit decomposition of fish oil. A good sink condition is able to allow a drug to dissolve completely and it is important in measuring the release rate of the drug so that the properties of delivery system can be described [28]. Triplicate analysis (n = 3) was performed for each formulation. The lag time and cumulative drug release (Q8) for each formulation is shown in **Table 4**.

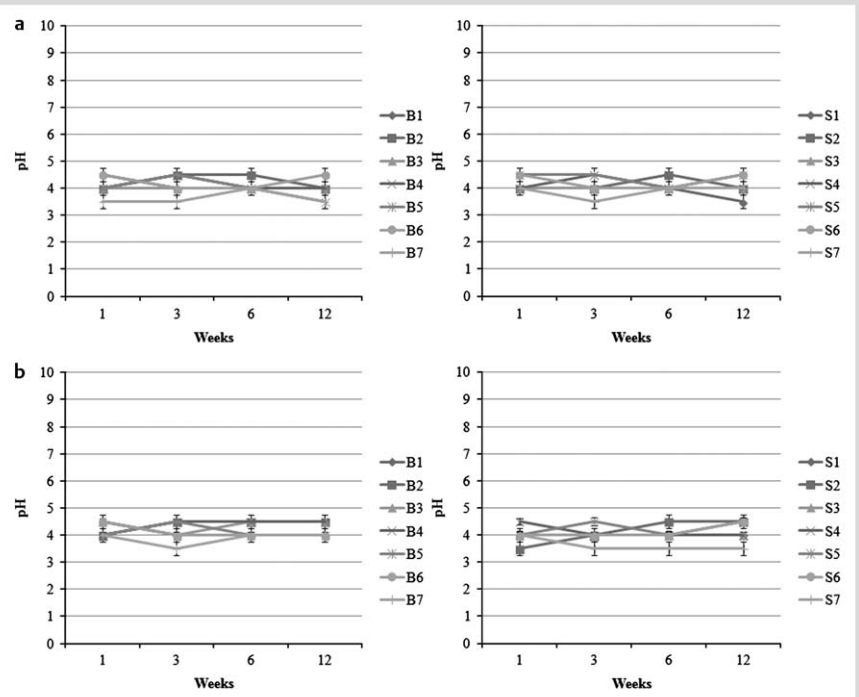

Fig. 2 **a** The pH result of each oleogel formulation over 12 weeks of storage. **a** pH of BP-formulations **b** pH of SA-formulations at 20 °C, n = 3. **b.** The pH result of each oleogel formulation over 12 weeks of storage. **a** pH of BP-formulations **b** pH of SA-formulations at 40 °C, n = 3.

Table 4 Lag time and cumulative permeation for each formulation.

Formulation	Lag time (Min)	Cumulative permeation (Q8) mg/cm²	Formulation	Lag time (Min)	Cumulative permeation (Q8) mg/cm²
B1	60	1.18 ± 0.03	S1	120	1.55 ± 0.02
B2	60	1.67 ± 0.03	S2	120	1.51 ± 0.02
B3	60	1.27 ± 0.02	S3	120	1.29 ± 0.07
B4	60	0.93 ± 0.04	S4	129	1.34 ± 0.17
B5	60	1.01 ± 0.02	S5	120	1.23 ± 0.02
B6	60	1.00 ± 0.01	S6	120	1.23 ± 0.01
Control	60	0.53 ± 0.02	Control	120	5.51 ± 0.07

Permeation of BP from fish oil oleogel vs. BP commercial hydrogel

In vitro permeation studies of BP containing fish oil oleogels along with commercial BP hydrogels were performed and it was observed that all the formulations showed a similar drug release pattern and there was an increase in the cumulative amount of BP with time for all of the gel formulation. BP-oleogel, B2, released the highest amount of BP throughout 8h as compared to other gel formulation, which was 1.67 ± 0.03 mg/cm². Control gel was the commercial hydrogel formulation which released the lowest amount (0.53 ± 0.02 mg/cm²) of BP throughout the 8h (**Fig. 3**). The gel formulation which had the highest flux value was gel B2 (0.1541 ± 0.0046 mg/cm²/h) whereas the gel formulation had the lowest flux value was control gel (0.0590 ± 0.0014 mg/cm²/h) as shown in **Table 5**. There was a significant difference in terms of cumulative amount and flux for all fish oil oleogels (gel B1, B2, B3, B4, B5 and B6) when compared to control gel ($p < 0.05$, ANOVA).

All of the BP-fish oil oleogel showed significant difference ($p < 0.05$) in drug flux and cumulative release as compared with commercial BP hydrogel. It was observed that all of the BP oleogel showed greater flux than BP commercial hydrogel and this significantly better permeation may be attributed to the permeation enhancing ability of the fish oil [5,27]. This is because, the fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in fish oil are not in the free form, but exist as triacylglycerol which will enhance the absorption of oil and a lipophilic substance across the skin [27]. Oily topical formulation such as ointment is believed to have the ability to increase permeation and potency of the drug by moisturizing the stratum corneum due to their occlusive nature [29]. Fatty acids can interact and disrupt the tightly packed lipid regions of the stratum corneum and this will reduce the resistance of the skin barrier and enhance drug absorption through skin [30].

Permeation of SA from fish oil oleogel vs. SA commercial hydrogel

Drug permeation analysis of SA-fish oil oleogels were also performed by comparison of SA commercial hydrogel as a control. It was observed that all of the SA gel formulations showed a similar drug release pattern and there was an increase in the cumulative amount of SA with time for all of the gel formulation (**Fig. 4**). In this part of a study, commercial SA hydrogel released the highest amount of SA (5.51 ± 0.07 mg/cm²) throughout 8h as compared to SA-fish oil oleogels and S5, oleogel, released the lowest amount of SA (1.23 ± 0.02 mg/cm²). The gel formulation which had the highest flux value was also commercial SA-hydrogel (0.4944 ± 0.0040 mg/cm²/h) whereas the lowest flux value SA-fishoil oleogel was S6 (0.1171 ± 0.0018 mg/cm²/h) as shown in **Table 5**. There was a significant difference in

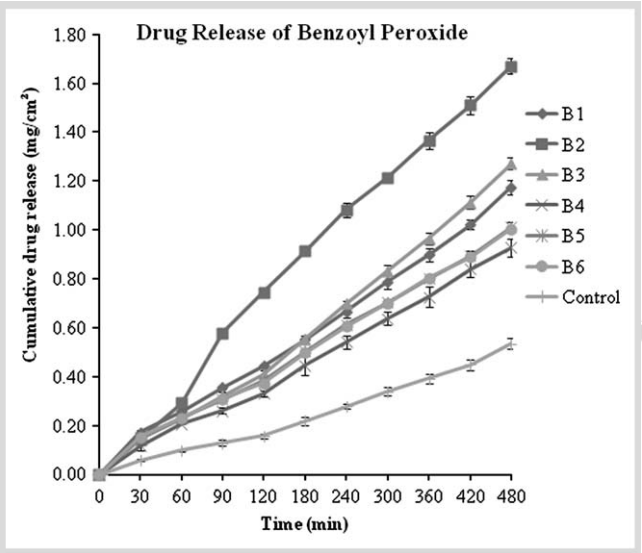

Fig. 3 Comparative drug release profile of BP from the fish oil oleogels and BP commercial hydrogel (control), n = 3.

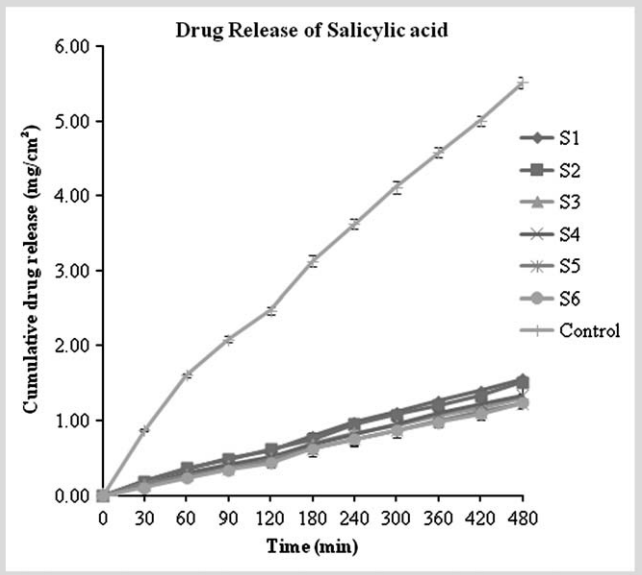

Fig. 4 Comparative drug release profile of SA from the fish oil oleogels and SA commercial hydrogel (control), n = 3.

terms of cumulative amount and flux for all SA-fish oil oleogels (S1, S2, S3, S4, S5 and S6) when compared to commercial hydrogel ($p < 0.05$, ANOVA).

It was observed that SA commercial hydrogel which act as a control showed significant difference ($p < 0.05$) in drug flux and cumulative amount release as compared with all of the SA fish oil oleogel. The enhanced penetration commercial SA-hydrogel was perhaps because of the ingredients such as propylene glycol, *Aloe barbadensis* leaf extract. Both of these ingredients have been penetration enhancing properties [31]. Apart from a natural moisturizing factor, *Aloe barbadensis* is believed to increase skin permeability by hydrating the stratum corneum [32,33]. SA-commercial hydrogel have the ability to act as chemical penetration enhancer. Since there are several penetration enhancers found in the commercial gel, the efficacy of fish oil acting as penetration enhancer is not significantly proved.

Table 5 Flux rate of oleogel formulations containing benzoyl peroxide and salicylic acid.

Formulation	Flux rate mg/cm²/h	Formulation	Flux rate mg/cm²/h
B1	0.1167 ± 0.0036	S1	0.1563 ± 0.0012
B2	0.1541 ± 0.0046	S2	0.1459 ± 0.0006
B3	0.1371 ± 0.0060	S3	0.1267 ± 0.0036
B4	0.0972 ± 0.0051	S4	0.1362 ± 0.0040
B5	0.1009 ± 0.0033	S5	0.1247 ± 0.0035
B6	0.1025 ± 0.0011	S6	0.1171 ± 0.0018
Control	0.0590 ± 0.0014	Control	0.4944 ± 0.0040

Conclusion

This research study showed that fish oil significantly enhanced the topical delivery of BP across the skin. BP fish oil oleogels with 10% w/w beeswax had a greater drug flux and cumulative release compared to other oleogel formulations and BP commercial hydrogel. But in SA-oleogel formulations, fish oil did not show significant penetration enhancing effects as compared with SA commercial hydrogel. This may be due to the presence of multiple penetration enhancers included in the formulation of commercial SA-hydrogel. The penetration effect of fish oil on SA can be carried out by modifying the composition of oleogel formulation. Based on the physical assessment and stability studies of oleogels, it was concluded that beeswax is a better option as a gelling agent for fish oil-oleogels. As Span 60 containing oleogels displayed characteristics such as liquid phase separation, heterogeneity and unpleasant rancid odour, they could be termed as unstable formulations. Span 60 fish oil-oleogels also showed significant syneresis at 40 °C and this phenomenon may be due to the sol-gel transition. By taking the physical assessment test and in vitro permeation study into consideration, 10% w/w beeswax is an ideal concentration of gelling agent to formulate BP fish oil oleogels. It is because 10% w/w beeswax BP fish oil oleogel not only possessed stable physical characteristics after storage of 12 weeks at temperature 20 and 40 °C, but also having the greatest flux (0.1541 ± 0.0046 mg/cm²/h) as compared with other fish oil oleogels and BP commercial hydrogel. In conclusion, fish oil oleogel (with beeswax as gelator) has shown its ability to act as a topical delivery system for BP. Besides, fish oil has the potential to act as a penetration enhancer for BP and by increasing permeation, the therapeutic efficacy of BP may be increased. Although fish oil showed permeation enhancing capabilities, the presence of limonene and BHA inside the formulation may or may not exert their own effects in terms of penetration enhancing, therefore such factors should be considered during the determination of penetration enhancing properties. For further studies, effect of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in fish oil on penetration of BP can be investigated and adhesive tape stripping test on skin can be carried out in order to investigate the keratolytic properties of BP fish oil oleogel.

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Conflict of Interest

The authors have no conflict of interest to report.

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