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A Screening of Permeation Enhancers for Transdermal Delivery of Propofol

Abhishek Singh Kushwaha*

TranSkin Research Pvt. Ltd, Bhopal, Madhya Pradesh, India

Abstract

Propofol is a highly lipophilic anesthetic drug used to induce sedation, predictable amnesia and anxiolysis. In this project, several permeation enhancers were screened to improve the permeation of propofol across the porcine full thickness skin. The screening studies of permeation enhancers was performed in two phases. As a result of the first phase of screening studies, DMSO, Laureth-4 and transcutol were found to be the potential penetration enhancers which improved the permeation of propofol across the skin ~ 4, 3.5 and 4.5-fold more compared to control. A 100% propofol was used as a control. In the second phase, the combination of DMSO and Laureth-L4 (F1) delivered 278.6 ± 20.3 µg/cm^2 propofol across the skin which were found to be ~ 18 more compared to control (15.68 ± 2.6 µg/cm^2). The studies in this project concluded that the combination of DMSO and Laureth-L4 can be used for the development of transdermal propofol product in the future.

Keywords: Propofol; DMSO; Permeation enhancers

Introduction

Propofol is an anesthetic, widely used to induce sedation, predictable amnesia and anxiolysis. Propofol is clinically recommended due to its rapid onset of action with minimum side effects [1]. It is highly used in pediatric population, as it is safe and efficacious. Propofol provides similar level of anesthesia accomplished by inhalation anesthetic [2]. It is a slightly yellow oily liquid with lipophilic in nature. Propofol is available in the form of injectable emulsion that contains lipid ingredients such as soybean oil and egg phosphatide [1,3].

Propofol emulsion is very painful at the side of injection and can be associated with side effect such as anaphylactic reactions with high lipid uptake [1,4]. Propofol shows poor oral bioavailability (~ 5%) due to its high hepatic extraction ratio (0.8-0.9) [5,6]. The pulmonary delivery of propofol is also challenging, as it is viscous and water insoluble. Thus, there is a need to deliver propofol from different routes.

Transdermal delivery of propofol seems to be a promising alternative, as it avoids the first pass metabolism of the drug, maintains drug levels in the systemic circulation for prolong period and reduces the unexpected side effects [7,8]. However, transdermal delivery of drugs is limited due to the presence of stratum corneum as a main barrier. Therefore, this project was designed to screen several chemical penetration enhancers to improve the transdermal delivery of propofol. Penetration enhancers are widely accepted and used to alter the barrier layer of skin to enhance the permeation of drugs. They work by several mechanisms such as, disruption of the lipids of stratum corneum, modification and interaction with keratin protein and improving the partition of drugs or solvents into the stratum corneum [9-11].

In the first step of this project, all the penetration enhancers were investigated individually to improve the permeation of propofol across the porcine full skin. In the second step, the best six formulations were prepared using different combinations of potential penetration enhancers selected based on the results of first study.

Materials and Methods

Materials

Propofol, polyethylene glycol 400 (PEG-400), Tween 80 and DMSO (dimethyl sulfoxide) was purchased from Sigma–Aldrich (St. Louis, Missouri). Diethyl sebacate, diisopropyl adipate, dimethyl isosorbide, di-propylene glycol and isopropyl palmitate were procured from Spectrum chemical (New Brunswick, NJ). Transcutol® P was gifted by Gattefosse´ (Saint-Priest Cedex, France). Levulinic acid was obtained from TCI America (Montgomeryville, PA). Kolliphore EL and Cremophore RH 40 were gifted by BASF Corporation (Tarrytown, NY).

Methods

Experimental design

Phase I: All the penetration enhancers were investigated individually to improve the permeation of propofol across the porcine full thickness skin. The test formulations were prepared with a 5-10% w/w of penetration enhancer and 80-95% w/w of propofol. A 100% propofol was used as a control. All the penetration enhancers are listed in the Table 1.

Phase II: Three potential penetration enhancers were selected based on the results of first study. The best six formulations were prepared using different combinations of these three permeation enhancers.

Penetration enhancer	%w/w
Diethyl sebacate	10
Diisopropyl adipate	10
Dimethyl isosorbide	10
Dimethyl sulfoxide	10
Transcutol	10
Polyethylene glycol 400	10
Ethanol	10
Tween 80	5
Laureth-4	5
Oleic acid	5

Table 1: A list of penetration enhancers used in the screening studies.

***Corresponding author:** Abhishek Singh Kushwaha, TranSkin Research Pvt. Ltd, Bhopal, Madhya Pradesh, India, Tel: +91 9981983734; E-mail: askushwaha@transkinresearch.com

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***In vitro* permeation studies of propofol:** The permeation studies were performed across the porcine full thickness skin for 12 h using Franz diffusion cells having a 0.64 cm^2 active diffusion area. Before starting an experiment, the skin was completely thawed and dermatomed to the thickness of 500 µm. Dorsal surface of the skin was cleaned properly with phosphate buffer saline and pat dried with kimwipes®. The skin was sandwiched between donor and receiver compartments using pinch clamp. The receiver compartment of the Franz cell was filled with a 5 ml of phosphate buffer saline containing 10% w/v methanol. The skin was hydrated with the receptor fluid for 30 min. Then, a 10 µl aliquot of propofol formulation was applied on the active diffusion area of the skin. Magnetic stir bar (3 mm) was used to stir the receptor fluid to distribute the permeated amount of drug homogenously. The samples from the receiver compartment was collected at definite time interval and analyzed by HPLC method [1,3].

Extraction of propofol from the skin: After permeation studies of propofol, active diffusion area of the skin was washed 5 times with water containing 50% ethanol and then pat dried with kimwipes®. Active diffusion area of the skin was excised using dermal punch having diameter of 8 mm. Each piece of skin was shaken in a 3 ml of DMSO (dimethyl sulfoxide) using a centrifuge tube rotator. After 24 h, samples were collected, and analyzed using HPLC.

Analytical method: Shimadzu Prominence-i 2030C plus HPLC system consisted of quaternary pump, auto sampler and UV-VIS Detector was used to analyze the samples. A phenomenex Luna® 5 µm C18 column (150 x 4.6 mm) was used to elute propofol. The mobile phase was prepared with water and methanol (20:80 v/v). The flow rate of mobile phase was maintained at 1 ml/min. Propofol was detected at a wavelength of 254 nm. The method was validated from propofol concentration of 0.1 µg/ml to 10 µg/ml [1].

Statistical analysis: One-way Anova test was performed using SPSS software for the analysis of data. The data was considered statistically significant if p value was found to be less than 0.05.

Results

First Phase

In the first phase, the total amount of propofol quantified in the receptor fluid in the case of diethyl sebacate, diisopropyl adipate, dimethyl isosorbide, dimethyl sulfoxide (DMSO) and transcutol and Laureth-4 was ~ 3, 2, 3, 4, 3.5 and 4.5-fold ($p<0.05$) more compared to control. There was no significant improvement observed in the permeation of propofol in the case of PEG 400, ethanol, tween 80, and oleic acid. As a conclusion, DMSO, laureth-4 and transcutol were selected as the potential penetration enhancers to perform the phase II permeation studies. Table 2 shows the cumulative amount of propofol found in the receptor fluid after first phase of permeation study, a bar graph representation shown in Figure 1.

Second phase

Permeation studies: The best six formulations were prepared using different combination of DMSO, Laureth-4 and transcutol. The cumulative amount of propofol permeated across the skin in the case of formulations F1, F2, F3, F4, F5 and F6 was 278.6 ± 20.3 µg/cm^2, 170.59 ± 24.6 µg/cm^2, 150.78 ± 18.9 µg/cm^2, 201.25 ± 30.9 µg/cm^2, 158.2 ± 23.6 µg/cm^2 and 173.5 ± 26.3 µg/cm^2 which were found to be ~ 18, 12, 10, 14, 11 and 12 ($p<0.05$) more compared to control (15.68 ± 2.6 µg/cm^2). As a result of this study, F1 was found to be the potential formulation that enhanced the significant delivery of propofol compared to other formulations as shown in Table 3 and Figure 2.

Penetration enhancer	The cumulative amount of drug permeated (µg/cm^2)
Control	10.68 ± 1.3
Diethyl sebacate	28.317 ± 2.5
Diisopropyl adipate	19.08 ± 2.6
Dimethyl isosorbide	31.32 ± 3.7
Dimethyl sulfoxide	40.64 ± 2.4
Transcutol	35.37 ± 2.9
Polyethylene glycol 400	9.56 ± 1.1
Ethanol	15.61 ± 1.7
Tween 80	12.90 ± 0.8
Laureth-4	45.20 ± 6.3
Oleic acid	13.72 ± 1.4

Table 2: The cumulative amount of propofol permeated across the skin in first phase of screening studies (µg/cm^2).

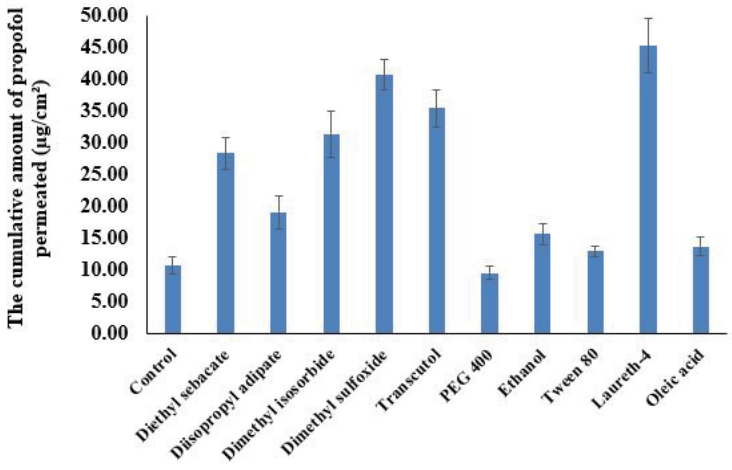

Figure 1: A bar graph representation of a result of the first phase of screening studies (µg/cm^2).

Extraction of propofol: The amount of propofol extracted from the skin in the case of formulations F1, F2, F3, F4, F5, F6 and control were 123.22 ± 23.06 µg/mg, 103.95 ± 17.26 µg/mg, 90.65 ± 13.63 µg/mg, 55.36 ± 19.26 µg/mg, 71.26 ± 12.96 µg/mg, 101.63 ± 26.32 µg/mg and 28.65 ± 10.26 µg/mg. The amount of propofol quantified in the skin after application of F1, F2, F3, F4, F5, and F6 were found to be ~ 4, 4, 3, 2, 2 and 4-fold ($p<0.05$) more compared to control. As a result of an extraction of propofol from the skin, F1 formulation showed the potential to deliver a significant amount of propofol into the skin, shown in Figure 3.

Discussion

Chemical penetration enhancers are widely used to improve the topical and transdermal delivery of drugs due to their patient compliance and lower cost [7,12]. In this project, ten penetration enhancers were investigated to improve the permeation of propofol across the porcine full thickness skin. Penetration enhancers were selected based on their miscibility with propofol. Diethyl sebacate and diisopropyl adipate were chosen as the permeation enhancers which are the fatty acid diesters [13-16]. These fatty acids improve the fluidity of the lipid of the stratum corneum. Fatty acid dieters have been investigated previously to improve the skin permeation of hydrocortisone butyrate propionate, ketoprofen, nicorandil and leukotriens antagonist. Dimethyl isosorbide is commonly used as a solvent and penetration enhancer in the pharmaceutical and cosmetic products [13,14]. It disrupts the lipid layer of the stratum corneum. Dimethyl sulfoxide (DMSO) is a strong permeation enhancer, it disrupts the disulfide bond of the keratin protein in the stratum corneum to improve the permeation of drugs15. Transcutol is a bivalent alcohol diethylene glycol [13,14]. It is reported to improve the delivery of broad-spectrum antiparasitic agent ivermectin across the porcine skin. PEG 400 is commonly used in the topical products as solvent and skin-conditioning agent. Polysorbate 80 is a non-ionic surfactant that has been used to improve the permeation of chloramphenicol, hydrocortisone and lidocaine across the skin. Oleic acid has previously been used to improve the transdermal delivery of trazodone hydrochloride. Laureth-4 is used as the emulsifier for the preparation of emulsion [13,14].

Ingredients	F1 %w/w	F2 %w/w	F3 %w/w	F4 %w/w	F5 %w/w	F6 %w/w
Propofol	80	80	80	80	80	80
DMSO	15			10	10	10
Laureth-4	5	5	5			5
Transcutol		15		10		10
Dimethyl isosorbide			15		10	

Table 3: Propofol formulations for a second phase of screening studies.

Machida et al., reported that 30% w/w propylene glycol improved the permeation of propofol ~ 4-fold more compared to control (100% propofol) [5]. They also reported that the combination of a 5% (w/w) menthol and a 10% (w/w) propylene glycol significantly improved the plasma concentration level of propofol. Oleic acid is another enhancer which was reported to improve the permeation of propofol across the epidermis. Juluri et al., reported to enhance the permeation of propofol using iontophoresis technique after pre-treatment application of permeation enhancers [3]. In this project, formulation F1 was able to deliver ~18 fold more amount of propofol compared to control which might be helpful in the development of transdermal propofol product.

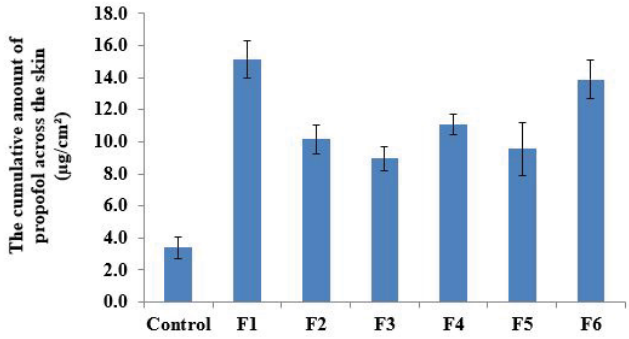

Figure 2: The cumulative amount of propofol permeated across the skin in second phase screening studies (µg/cm²).

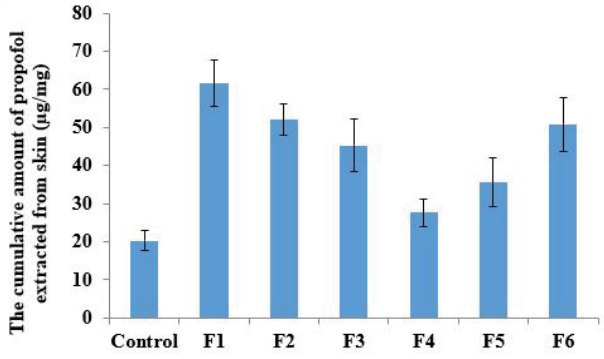

Figure 3: The cumulative amount of propofol retained in the skin (µg/mg).

Conclusion

DMSO, Laureth-4 and transcutol were found to the potential penetration enhancers. F1 was found to be the best formulation that delivered significant amount of propofol into and across the skin. For the future studies, F1 might be a good candidate to investigate on animals and in the transdermal propofol product development.

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