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Analysing the Effect of Permeation Enhancers on the In Vitro Skin Permeability of Propranolol: A Mechanistic Study

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ABSTRACT: Propranolol hydrochloride is a non-selective beta-adrenergic blocker. Due to extensive first pass metabolism, it shows variable bioavailability. Up to now, several researches has been conducted regarding its effect on wound healing. Hence, transdermal delivery of this drug could be helpful to overcom the first pass metabolism and delivery of the drug into skin. In this study, the effect of different permeation enhancers namely Isopropyl myristate, Labrafac, Labrafil, Olive oil and Plurol oleique on skin permeability of propranolol through rat skin has been analysed through a Franz cell and by evaluating the parameters like J_{ss}, ER_{flux}, ER_D and ER_p. The effect of enhancers on skin structure was studied by using FT-IR and DSC techniques. Enhancement mechanisms were evaluated through comparing FT-IR peak intensities for asymmetric and symmetric C-H stretching, ester C=O stretching and Amide peaks. Mean transition temperature (Tm) as well as their enthalpies (H) studied by DSC technique. It was shown that all the permeation enhancers improved permeability of the drug through rat skin. Among them, Labrafac had more effect on flux having ER_{flux} value of 9.24 and plurol oleique had more effect on ER_D having value of 13.99 due to the positive effects on skin lipid-protein structure while Isopropyl myristate has shown the least effect. According to the obtained results, the use of chemical permeation enhancers due to changes the structure of the skin to increase the permeability of the drug can be considered as suitable excipients in transdermal delivery of propranolol.

KEYWORDS: Propranolol; Permeation Enhancers; Transdermal Drug Delivery.

1. INTRODUCTION

Propranolol hydrochloride is a nonselective beta-blocker used for various conditions such as angina, arrhythmias, hypertension, myocardial infarction prophylaxis, and migraine. It is a highly lipophilic drug that exhibits high first-pass metabolism and therefore has variable bioavailability [1,2]. Several studies on the effect of propranolol on wound healing, including burns and diabetic wounds, have demonstrated its efficacy [3-7]. Transdermal administration has many advantages, including avoiding first-pass metabolism of the drug, controlled and continuous administration of the drug, reducing dosing frequency, improving patient compliance, localization at the target site, avoiding the risks of injections, and reducing the toxic content of drugs [8,9]. Therefore, topical administration of propranolol could be beneficial to avoid adverse effects, improve bioavailability, and deliver the drug directly to the site of action. Human skin provides a physical barrier to drug delivery to the body. It consists of the stratum corneum and the epidermis. The lipid matrix of the stratum corneum plays an important role in the permeation of drugs through the skin [10]. It is well known that the physiological properties of the drug and the carrier influence the percutaneous absorption of drugs [11,12]. Skin permeation can be improved by several strategies: Increasing the diffusivity in the skin by disturbing the lipid matrix of the stratum corneum (SC), improving the solubility of the drug in the skin, increasing the degree of saturation of the drug in the formulation [13,14]. Permeation enhancers such as olive oil, DMSO, and surfactants increase the permeation of drugs through the skin by various mechanisms such as disrupting the organized intercellular lipid structure of the stratum corneum, liquefying

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membrane lipids, altering cellular proteins, and extracting intercellular lipids by mostly nonpolar solvents [13, 14]. For the development of transdermal drug delivery systems, the study of the microstructure of the intercellular or lipids in the SC layer of the skin is required. In recent studies, lipid organization and skin microstructure have been investigated using various techniques, including differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FT-IR). In this study, an attempt was made to investigate the effect of different permeation enhancers on the skin permeability of propranolol through the skin.

2. MATERIALS AND METHODS

2.1. Materials

Propranolol hydrochloride was purchased from Tolid Darou company (Tehran, Iran). Olive oil was purchased from Barij Essence (Kashan, Iran) Labrafil, plurol oleique and labrafac were obtained as gift from Gattefosee company (Saint-Priest, France).

2.2. Animal experiments

Male adult Wistar rats (weighing 150 - 175 g) and aged 10 - 12 weeks were purchased from Animals Laboratory, Jundishapur University of Medical Sciences, Ahvaz, Iran. The hair on the abdominal skin was removed with an electric clipper, taking care not to damage the skin. The rats were anaesthetized with ether prior to sacrificing them. Abdominal full-thickness skin was removed and any extraneous subcutaneous fats cleaned from the dorsal side using cooled pure acetone solution with 4^0C. Whole skin thickness was measured using a digital micrometer. The animals were treated according to the principles for the care and use of laboratory animals, and approval for the animal studies was obtained from the Ethical Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.ABHC.REC. GP96054). The procedures followed complied with standard international guidelines [15].

2.3. Solubility studies

The solubility of propranolol was determined in water, olive oil, labrafac, plurol oleique, labrafil. and isopropyl myristate. An excess amount of propranolol was added to 5 ml of the enhancer. The mixture was immersed in a water bath for 24 h at 37 ^{0}C and allowed to equilibrate. Then, obtained mixture was centrifuged for 30 min at 3000 rpm, filtered, and the dissolved drug measured by a validated UV spectrophotometric method at 290 nm.

2.4. Differential Scanning Calorimetery(DSC) studies

The changes in structure of whole skin induced by permeation enhancers were examined using a DSC (Mettler Toledo DSC^1 system) equipped with a refrigerated cooling system (Hubert Tc45). Approximately 5 - 10 mg of sample was placed in hermetically sealed aluminum pans. Simultaneously an empty hermetically sealed pan was used as a reference. Skin samples were exposed to heat ranging from 20 to 200 ^{0}C (scan rate: 5 ^{0}C/min). All experiments were at least in triplicate. In order to ensure accuracy and repeatability of data, DSC analyzer was calibrated and checked with indium standard. Enthalpy (ΔH) values were calculated from endothermic and exothermic transitions of the thermograms as in following Eq. (1):

ΔH = peak area/sample weight (Eq. 1)

2.5. FT-IR spectroscopy

The excised rat skin samples were treated with olive oil, labrafac, labrafil, plurol oleique and water for 4h, vacuum-dried (650 mm Hg, 25 ± 1 ^{0}C) for 1 h and the stored in desiccators to remove traces of permeation enhancer materials. The samples scanned in the range 4000 to 500 cm^{-1} using an FT-IR facility.

2.6. In-vitro Permeation Studies

In-vitro permeation studies were carried out using vertical glass Franz diffusion cells with an approximated effective diffusion area of 3.46 cm^2. The receptor compartment volume contained 30 mL Whole skin sample was hydrated and then mounted between the donor and receptor compartments of the cell with the stratum corneum facing the donor medium. For pretreatment of skin samples, fully skin samples were pre-treated with putting 2 mL of a chemical enhancer on the surface of skin in the donor phase for 4 hours. Then, propranolol (1% w/v), dissolved in water, was in the donor compartment and the

receptor cell was filled with phosphate buffer (pH: 7). The Franz diffusion cell was placed and clamped in a 37±0.5°C water bath with a magnetic stirrer. The receptor medium was stirred with a small magnetic bead. At predetermined time intervals (0.5, 1, 2, 3, 4, 5, 6, 7, 8 and 24 h), a 2mL sample was withdrawn from the receptor medium and immediately exchanged for an equivalent volume of fresh phosphate buffer (pH:7) to maintain sink condition. The samples were filtered and the permeated amount of propranolol was analyzed by UV spectroscopy method at 290 nm. Each of the test solvents was used as blank. Skin permeability parameters were measured using obtained data including flux (Jss), permeability coefficient (P), lag time (Tlag), and diffusivity coefficient (D). The permeation rate at steady state (Jss, mg/cm^2 h) was determined from the linear portion of the slope of the permeation curve. The lag time (tlag, hr) was determined by extrapolating the steady-state line to the time axis. Permeability coefficient (Kp, cm/h) of carvedilol through the skin was calculated as in Eq (2):

$Kp = Jss/C^0$ (Eq. 2)

where Jss is steady-state flux and C^0 the initial concentration of propranolol in the donor compartment. Enhancement ratios (ER) were calculated from permeation parameters after enhancer treatment divided by the same parameters before enhancer treatment.

3. RESULTS AND DISCUSSION

3.1. Solubility of propranolol

The solubility of propranolol in various enhancers is presented in Table 1. The results indicate the highest solubility in labrafac followed by plurol oleique, olive oil, labrafil,and Isopropyl Myristate .

Table 1. Solubility of propranolol in different enhancers

Enhancer	Solubility (mg/ml)
Water	0.08 ± 0.001
Olive Oil	425± 1.2
Labrafac	765.8 ± 2.5
Plurol oleique	586 ± 2.3
Labrafil	415 ± 1.3
Isopropyl Myristate	51.6 ± 1.4
Buffer Phosphate (pH 7)	61±0.5

3.2. *In-Vitro* permeation of Propranolol

The effect of solvents on Propranolol skin permeability (hydrated skin as control) is expressed in Table 2, 3 and Figure 1 as ERflux (ratio of drug flux after and before skin pretreatment with solvents) and ERD (drug diffusion coefficient after and before skin pretreatment with solvent). It was observed that labrafac, labrafil and plurol oleique increased drug permeability while isopropyl myristate has shown the least effect. ER_{flux} for labrafac and labrafil was more than ER_D meaning they increased diffusion more than they did flux.

Table 2. Results of different absorption enhancers on different parameters of propranolol permeability from full rat skin (Mean ± SD, n=3)

Enhancer	**J_{ss}(mg/cm^2.h)**	**D_{app}(cm^2/h)**	**P(cm/h)**	**T_{lag}(h)**
Control	0.1474±0.00036	0.02306± 0.0079	0.0029±0.00007	2.4967± 0.80061
Olive oil	0.4566±0.00049	0.2342±0.00231	0.0091±0.00009	0.2322±0.0229
Labrafac	1.3621±0.0003	0.0792±0.0064	0.0272±0.00006	0.6857±0.0055
Isopropyl Myristate	0.2986±0.00016	0.0091±0.0004	0.0059±0.00003	5.9243±0.02976
Labrafil	1.2501±0.00171	0.0681±0.00493	0.0250±0.00003	1.0779±0.00780
Plurol oleique	0.9618±0.0004	0.3275±0.0139	0.0192±0.000009	0.1819±0.00776

Table 3. Enhancement Ratios of skin permeability parameters of propranolol after pretreatment with various penetration enhancers compared with control (Mean ± SD, n = 3)

Enhancer	ER_{flux}	ER_D	ER_p
Olive Oil	3.1±0.04	10.98±1.7	3.1±0.04
Labrafac	9.24±0.25	3.71±1.56	9.24±0.25
Isopropyl Myristate	2.03±0.038	0.426±0.16	2.03±0.038
Labrafil	8.48±0.09	2.75±0.19	8.48±0.09
Plurol oleique	6.53±0.15	13.99±1.23	6.53±0.15

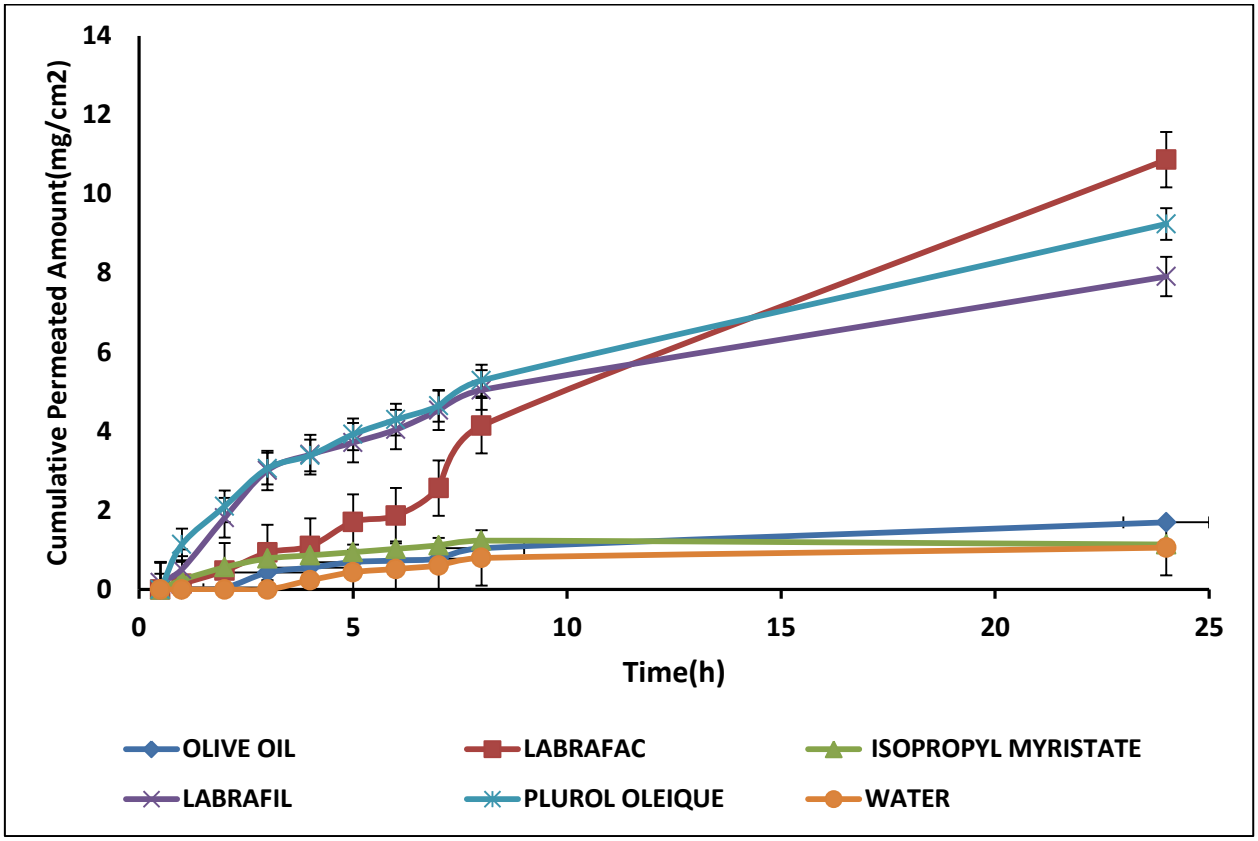

Figure 1. Cumulative permeability profile of propranolol through a surface area with water, labrazol, labrafil, labrafac and oleic oil, and Isopropyl Myristate from the whole skin of the rat. (Mean ± SD, n=3)

3.2. FT-IR Spectroscopy

The FTIR analysis of skin can be practical tool for studying the interaction between enhancers materials with SC that provides bands at different wave numbers. The rationale for use of FTIR technique to understand mechanism of penetration modifier was that the treatment with enhancers/retardants, sometimes yield a shift in specific band position to higher or lower wavenumber or lead to change in the intensity of the signal observed at that band position. If the shift is to higher wavenumber (blue shift), it indicates SC membrane (lipid bilayer) fluidization that in change contribute to disruption of the barrier properties that probably causes the substance permeation enhancement through the SC. On the other hand, lipid groups are oriented again, a phenomenon that that causes a shift to lower wave number (e.g., red shift) and strengthening of subcutaneous barrier properties which finally slows down the entrance of permeant through the skin. If the penetration modifier performs by affecting on lipid pathway, the phase transition of the lipids is showed by increase/decrease in the band position (wavenumber) of the signals at 2920, 2850,

and near1738 cm−1. [17]. Spectral analysis has been done involved examination of changes in peak position and their intensities from 4200-500 cm^{-1} (Table 4,5,6). In this study, untreated whole rat skin served as control. It showed bands at 2914.94, 2840.90, 1691.36, 1643.19 and 1536.30 cm^{-1}. The bands observed in the range of 3000 - 3600cm^{-1} represent O-H and N-H stretching from lipid, protein and water while the peaks near 2914.94 and 2840.90 cm-1 represent asymmetric and symmetric stretching bands of the terminal methyl groups of lipids in rat skin. The lipid ester carbonyl stretching (C=O stretching of lipid ester) in SC showed at 1691.36 cm^{-1} position while the bands observed at 1643.19 and 1536.30 cm^{-1} represent amide I (C=O stretching of keratin) and amide II (C-N stretching of keratin) linkage of the helical secondary structure found in epidermal keratin [16]. The FT-IR spectra of whole rat skin treated with labrafac showed significant decrease in peak height at 2775.59, 2666.5, 2032.76, 1756.31 and 1555.98 cm^{-1} showing formation of weakening of hydrogen bonds in lipid groups. According to the findings, labrafac interacts mostly with lipids and proteins in the SC layer. The findings of the permeability parameters after labrafac pretreatment correlate with FT-IR and DSC measurements. The IR spectra of whole skin rat treated with Labrafil displayed decrease in peak height of the wave numbers 1787.65 cm^{-1} and disappearance of the peaks in 1643.19, 1536.30 cm^{-1} positions showing lipid extraction. According to the findings, labrafil interacts mostly with lipids and proteins in the SC layer. The spectrum for whole skin rat treated with plurololeique presents a blue shift at 2914.94,2840.90, and 1691.36cm^{-1} that show interacts mostly with lipids in the SC layer. The skin treated with isopropyl myristate showed a blue shift at 2840.9 2914.9,1691.36, and1643.19 cm^{-1} and decrease in peak height at 1643.19 cm^{-1}. The whole rat skin treated with olive oil showed a blue shift at 1643cm^{-1} and drcrease in the peak heights at 2914.94,2840.90,1691.36,1643.19, and1536.30 cm^{-1}. According to the results, olive oil interacts mostly with lipids in the SC layer.

Table 4. FT-IR Peak wave numbers (cm^{-1}) changes compared with control (untreated skin) and abdominal hydrated whole skin rat following treatment with various enhancers. (mean ± SD, n = 3)

Enhancer	C-H stretching Asy	C-H stretching Sym	C=O stretching of lipid ester	Amide I	Amide II
Water	2914.94±0.12	2840.90±0.30	1691.36±0.60	1643.19±0.21	1536.30±0.25
Olive Oil	Deleted	Deleted	1735.26±0.29	1679.70±0.60	1505.72±0.58
Labrafil	Deleted	Deleted	1787.65±0.11	Deleted	Deleted
Labrafac	2775.59±0.32	2666.5±0.25	2032.76±0.57	1756.31±0.86	1555.98±0.98
Plurololeique	2976.31±0.43	2913.16±0.47	1738.37±0.73	1620.29±1.23	1558.17±0.12
Isopropyl myristate	2946.84±0.11	2876.32±0.58	1743.03±0.60	1631.35±1.48	1491.26±0.35

Table 5: Decrease in mean peak height (± SD), compared with control (untreated skin) of assymmetric (Asy) and symmetric (Sym) C-H stretching and C=O stretching absorbance of abdominal hydrated whole skin rat following treatment with various enhancers (mean ± SD, n = 3)

Enhancer	C-H stretching Asy		C-H stretching Sym		C=O stretching of lipid ester	
	Peak height	%D	Peak height	%D	Peak height	%D
Water	0.360±0.001	-	0.558±0.28	-	1.722±00.35	-
Olive Oil	0	100	0	100	0.003±0.17	99.8
Labrafil	0	100	0	100	0.087±0.02	94.94
Labrafac	0.043±0.003	88.05	0.116±0.001	79.21	0.011±0.000	93.61
Plurololeique	0.185±0.001	48.61	0.310±0.000	44.44	1.427±0.001	17.13
Isopropyl Myristate	0.395±0.002	Not seen	0.475±0.001	14.87	2.026±0.002	Not seen

Table 6: Decrease in mean peak height (± SD), compared with control (untreated skin) of C=O stretching of keratin and C-Nstretching of keratin absorbance of abdominal hydrated whole skin rat following treatment with various enhancers (mean ± SD, n = 3)

Enhancer	C=O stretching of keratin		C-Nstretching of keratin	
	Peak height	%D	Peak height	%D
Water	1.723±0.010	-	0.311±0.002	-
Olive Oil	0.004±0.000	99.76	0.003±0.000	99.03
Labrafil	0	100	0	100
Labrafac	0.795±0.002	53.85	0.116±0.01	62.70
Plurololeique	0.822±0.003	52.29	0.636±0.008	Not seen
Isopropyl Myristate	0.948±0.002	44.97	0.363±0.000	Not seen

3.3. DSC Studies

The DSC technique is widely used for characterization the melting of lipids and the phase transition of lipid bilayers and protein denaturation in SC layer. By comparing mean transition temperature (Tm) and enthalpies (H), thermotropic behavior of treated skin was assessed. Any transition in Tm to lower degrees may be due to lipid disruption in bilayer and irreversible protein denaturation in SC. While, enthalpy decrease was related to lipid fluidization in lipid bilayers and protein – lipid complexes. [18]. Thermotropic behavior of skin treated with different enhancers evaluated by comparing for mean transition temperature (Tm) and their enthalpies (H). Kaushik et al. studied the SC of human skin and observed three endothermic transition peaks at temperatures 59 - 63°C (Tm1), 75 - 82°C (Tm2) and 99.5 - 120°C (Tm3), suggesting It has been shown that Tm1 corresponded to lipid transformation from a lamellar to disordered state, Tm2 is due to the melting of lipid – protein complex [17,19] In this study, two endothermic transitions were obtained at around 57.5 (T1) and 123 ^{o}C (T2) were obtained in thermogram of hydrated whole rat skin. T1 and T2 transitions appeared to be due to melting of lipids and irreversible denaturation of intracellular keratin, respectively. The results obtained are shown in Table 7; It was observed that Tm1 and Tm2 as well as H_1 and H_2 were shifted to lower temperatures by all of enhancers showing their interaction with lipid layer and possible denaturation of skin protein. Tm_1, mean transition temperature of lipids; Tm_2, mean transition temperature of irreversible denaturation of intracellular stratum corneum keratin; H_1, transition enthalpy of lipid phase; H_2, transition enthalpy of keratin phase.

Table 7. Effect of solvents on the thermal properties of hydrated rat skin (mean ± SD, n = 3)

Enhancer	Mean Transition temperature		Transition enthalpy	
	Tm1	Tm2	H1	H2
Control	67.5±2.1	112±2.9	7.01±0.4	551±16.5
Olive Oil	38.1±0.3	115±0.1	0.81±0.2	6.45±0.1
Labrafil	38±0.1	123±0.1	5.86±0.1	3.306±0.1
Labrafac	38.4±0.3	118±0.3	7.74±0.1	2.66±0.2
Plurololeique	40.2±0.8	110±0.1	3.84±0.3	5.12±0.4
Isopropyl myristate	38.5±0.4	120±0.2	1.54±0.1	3.16±0.1

4. CONCLUSION

The results show that the enhancers Labrafac and Labrafil have a better effect on skin permeability compared to other enhancers. It was also found that isopropyl myristate had the least effect on skin permeability of propranolol. It is suggested that lipid fluidization and protein denaturation are the main modes of action of labrafac and labrafil, while olive oil and plurololeique interact mainly with lipids in the SC layer.

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