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Increase adapalene delivery using chemical and herbal enhancers

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Abstract

Background: Acne is one of the skin diseases that include abnormalities in the production of sebum, changes in the microbial flora, abnormal keratinization, and inflammation. Adapalene is a good choice in the treatment of acne with fewer side effects and high effectiveness. However, the absorption of adapalene through human skin is low. We investigated the effect of several enhancers on the skin absorption of adapalene.

Methods: For the preparation of a topical formulation, this drug needs proper skin absorption. Therefore, to increase the effect of chemical absorption of the Adapalene skin permeability, it should first be put on the skin in a touch of some absorption like Eucalyptus, Urea, Clove oil, propylene glycol, and oleic acid for 1 and 2 hours and was then examined for the passing of the drug on the treated skin and for the effect of absorptions by calculating of the permeability parameters using DSC and FT-IR techniques.

Result and Conclusion: The results show that the enhancers used increased the permeability of the drug adapalene to water. Several mechanisms including lipid liquefaction, degradation of the fat structure, as well as irreversible denaturation of intracellular creatine caused by Eucalyptus, urea clove oil, PG, and oleic acid are the main mechanisms of drug penetration. Based on the results, it was found that among the enhancers studied, eucalyptus and urea had the highest and the lowest absorption effect in 2- and 1-hour pre-contact, respectively.

KEYWORDS

adapalene, DSC, enhancing absorption, FT-IR, skin permeability

1 | INTRODUCTION

Adapalene is a topical retinoid that is mainly used to treat acne and is chemically similar to retinoids. Studies of biochemical and medicinal properties have shown that adapalene regulates cell differentiation and inflammatory processes, all of which have important effects on the pathology of acne vulgaris.[1,2] Adapalene absorption through human skin is low. Only small amounts (0.25 ng/mL) of the main substance were found in the plasma of patients with acne after topical administration of adapalene in controlled trials.[3]

In terms of mechanism of action, adapalene binds to nuclear retinoic acid receptors (gamma and beta) and retinoid X receptors but does not bind to cytosolic receptor proteins.[4] Studies on the pharmacology of adapalene by in vitro and in vitro experiments have shown that adapalene is very active on cells as well as tissue proliferation and differentiation. Also, adapalene has anti-inflammatory properties. Adapalene interacts selectively with RARβ and RARγ

nuclear receptors. Because the role of RARβ in human keratinocytes is unclear, the effect of adapalene on epidermal stem cell types is evaluated for its interaction with RARγ.[5] It is suggested that topical adapalene may reduce the differentiation of follicular epithelial cells and reduce the formation of microcomedones.[5] Adapalene is chemically more stable and lipophilic than other retinoids. Its absorption through human skin is low. Excretion is mainly through biliary consumption. Some of the most important side effects of adapalene are erythema, dryness, and burning.[6]

The main barrier to pass through the skin is the stratum corneum, which is the outermost layer of the epidermis and consists of 10–25 layers of dead cells in the lipid layer. When a topical drug is placed on the skin, the active drug must pass through the stratum corneum and reach the living tissue. The limiting factor in this process is the slow penetration of the stratum corneum.[7] Under normal circumstances, the main pathway is intercellular or lipid bilayer. The main limitation in the dermal application is the impermeability of the epithelium of the human body to foreign substances. Therefore, today the most important challenge for the topical formulation is to provide a suitable increase in the penetration of the drug into the skin.[8,9]

In this study, we investigated the effect of five additives (oleic acid oil, eucalyptus oil, clove oil, urea, and propylene glycol) as well as their time on the skin (1 and 2 hours) on increasing the skin absorption of adapalene. It is expected that the obtained results can be effective on the optimal skin permeation of this drug and be effective in designing a new topical formulation.

Absorption of chemical additives includes compounds that penetrate the skin and reduce the reversible effects of the skin barrier by interfering with the structures in the stratum corneum in the skin. So far, about 400 chemicals have been identified as absorption enhancers, but due to their limited use in topical products, a small number of them are used.[10]

The chemical compounds in eucalyptus leaf extract, which are mainly phenolic, stop cell division, slow down photosynthesis and respiration, and disrupt growth regulators and enzyme activities in other plants, which ultimately lead to reduced plant growth.[7,11]

Urea can be used as a raw material to produce many chemical compounds, including; plastics, adhesives, potassium cyanate, and urea nitrate.[12]

Clove oil, which is obtained from its petals, has many medical applications and is used in the manufacture of medicines and cosmetics. Clove oil is known to be useful for treating wounds and injuries, the effects of insect bites or stings, especially on sensitive skin. This oil is used in the manufacture of anti-acne compounds and is effective in treating purulent acne.[13]

Oleic acid is a compound of a fatty acid with a molecular formula of $C_{18}H_{34}O_2$ with a molecular mass of 282.4614. This compound is a pale yellow oily liquid. Its density is 0.895 g/cm^3, and it's melting and boiling points are 286 and 633 K, respectively. This compound is insoluble in water but soluble in methanol and organic compounds.[14]

Propylene glycol is a chemical compound with the formula $C_3H_8O_2$ and a molar mass of 76.9 g/mol. It has a melting point of 59°C and a boiling point of 188.2°C.[15] It is soluble in water and ethanol. Propylene glycol is hydrolyzed by propylene oxide (C_3H_6O). Applications of propylene glycol include consumables such as drug solvents, food additives, cleansers, and disinfectants in the cosmetics industry.[16]

2 | MATERIALS AND METHODS

2.1 | Materials

Adapalene powder was prepared from Behsan Daroo Pharmaceutical Company. Eucalyptus oil, clove oil, and oleic acid were received from Kashan Barij Essential Oil Company, and urea, propylene glycol, sodium dihydrogen phosphate, disodium hydrogen phosphate from Merck Company.

2.2 | Animals

In this study, male Wistar rats were used. The rats used weighed about 150–170 g and were about 10–12 weeks old. Rats were facilitated under the supervision and approval of the ethics committee of the University. Rats were anesthetized and relieved with ketamine/xylazine (50 mg/kg). After killing the rats, the hairs of the abdomen were cut, and then the entire skin of this area was removed. Then the subcutaneous fat on the inner surface of the skin was removed with chilled pure acetone. Skin thickness was measured with a digital micrometer. It was stored in the freezer at minus 20°C until permeability tests. Before use, the skin samples were taken out of the freezer and kept at room temperature until they melted and reached room temperature.[7]

2.3 | Adapalene determination

To determine the amount of drug that passes through the skin, it is necessary to use a valid method to measure the drug. In this study, UV spectroscopy with a wavelength of 279 nm was used. The selection of the mentioned wavelength is based on the spectral absorption spectrum of adapalene in phosphate buffer solution pH = 7.4 and ethanol, which has been considered for permeability and release studies. At this wavelength, Adapalene had maximum light absorption. First, to prepare the adapalene wavelength, a concentration of five milligrams per 10 ml was made and its wavelength was obtained in a spectrophotometer, which showed the desired wavelength of 279 nm.[7]

2.4 | Investigation of adapalene permeability

To evaluate the permeability of adapalene in rat skin after skin preparation, it was placed on a Franz diffusion cell. Initially, the skin was exposed to 1 g of each of the various additives (oleic acid, clove oil,

TABLE 1 Results of different enhancer adsorption on different parameters of Adapalene permeability of whole rat skin (n = 3, mean ± SD)

Parameter	Flux (mg cm^{-2} h^{-1})	D (cm^2 h^{-1})	T_{lag} (h)	P (cm/h)
Control (water)	0.00095 ± 0.0008	0.011 ± 0.0004	4.875 ± 0.18	0.00002 ± 0.000001
PG (1 hour)	0.00295 ± 0.0001	0.023 ± 0.0002	2.302 ± 0.23	0.00006 ± 0.000001
PG (2 hours)	0.00520 ± 0.0001	0.257 ± 0.124	0.239 ± 0.116	0.00010 ± 0.000001
Clove oil (1 hour)	0.0045 ± 0.0006	0.664 ± 0.889	0.929 ± 0.850	0.00009 ± 0.000002
Clove oil (2 hours)	0.0082 ± 0.00028	0.110 ± 0.002	0.494 ± 0.008	0.00164 ± 0.000004
Urea (1 hour)	0.0084 ± 0.0001	0.0407 ± 0.0019	1.333 ± 0.062	0.00020 ± 0.000003
Urea (2 hours)	0.0165 ± 0.0004	0.207 ± 0.0044	0.261 ± 0.005	0.00033 ± 0.000007
Eucalyptus oil (1 hour)	0.0082 ± 0.0004	0.0260 ± 0.0013	2.088 ± 0.107	0.00016 ± 0.000008
Eucalyptus oil (2 hours)	0.0288 ± 0.001	0.108 ± 0.0016	0.500 ± 0.007	0.00058 ± 0.00002
Oleic acid (1 hour)	0.0073 ± 0.001	0.024 ± 0.0001	2.225 ± 0.089	0.00015 ± 0.00002
Oleic acid (2 hours)	0.0098 ± 0.0005	0.106 ± 0.0001	0.510 ± 0.0006	0.00020 ± 0.00001

eucalyptus oil, urea, and propylene glycol) for 1 and 2 hours. After removing the absorption enhancers from the skin surface, the receptor phase was filled with a volume of 35 mL of phosphate buffer solution pH = 7.4 and ethanol and the donor phase was filled with 5 mL of 0.05% drug solution.

The prepared cells were placed on a heater stereo at 37°C and 200 rpm. At the half, 1, 2, 3, 4, 5, 6, 7, 8, and 24 hours, two cells were removed from the receiving phase inside the cell each time. Two milliliters of phosphate buffer were replaced by pH = 7.4 and ethanol, and the sample absorbance in the UV device was read at 279 nm, with different absorptions. There is a need for a negative control in permeability. For this purpose, the rat skin was placed on the tuber, and in the donor phase, only distilled water was placed, and in the receptor chamber, phosphate buffer pH = 7.4 and ethanol to zero the device was used.[17]

2.5 | Statistics and calculations of permeability parameters

All studies were repeated three times and the values were expressed as mean standard deviation. A two-way *t* test and analysis of variance were used to statistically evaluate the results. Minitab 17 software was used to design the Full-Factorial test.

In this study, the permeability of Tadalafil from drug microemulsions to the whole skin of rats was investigated, and permeability parameters such as equilibrium velocity (J_{ss}), permeability coefficient (p), incubation time (T_{lag}), and apparent diffusion coefficient (D_{app}) were calculated. Also, the results for ER_{flux}, ER_D, and ER_p of drug-containing microemulsions compared to drug saturation control are given in Table 2. To calculate the permeability parameters, the cumulative value of the drug passing through the surface unit against time was plotted.

The permeability coefficient (p) was calculated from Equation (1).[17]

$$J_{SS} = P.C \quad (1)$$

C = drug concentration in the donor phase.

(T_{lag}) = The amount of commune time was obtained from the skin along the equilibrium line to the time axis in the cumulative drug curve:

The value of *D* was calculated from Equation (2).[17]

$$D = \frac{h^2}{6\mathrm{Tlag}} \quad (2)$$

Because *h* does not represent the actual length of the drug permeation, the *D* calculated from this formula is also the *D* apparent. Because all calculations are based on the Steady State area of the cumulative drug permeability diagram, it is necessary to establish the synchronous conditions for these parameters to be valid. In this study, the maximum concentration created in the receptor phase was less than 10% of the drug saturation solution in the receptor phase.

3 | RESULTS

In order to investigate the effect of adsorption on skin permeability, the permeability of adapalene after skin contact with absorption enhancers for 1 and 2 hours was investigated. Adapalene permeability diagrams for each component and its permeability parameters are given in Table 1. The effect of absorption of different additives in 1- and 2-hour skin contact on adapalene permeability (Table 2) as the ratio of drug permeation rate after pre-contact with pre-adsorption to desired (ER_{flux}) and drug release coefficient after pre-contact with adsorption to the desired enhancement before it (ER_D) and the permeability of the drug after contact with the absorption of the desired enhancement before it (ER_p) are shown. Hydrated skin and buffer phosphate and ethanol were used in the phase chamber as a control. Figure 1 shows Adapalene cumulative diagram crossing the surface unit after 1 and 2 hours of skin contact with eucalyptus, urea, propylene glycol, clove, and oleic acid from whole rat skin.

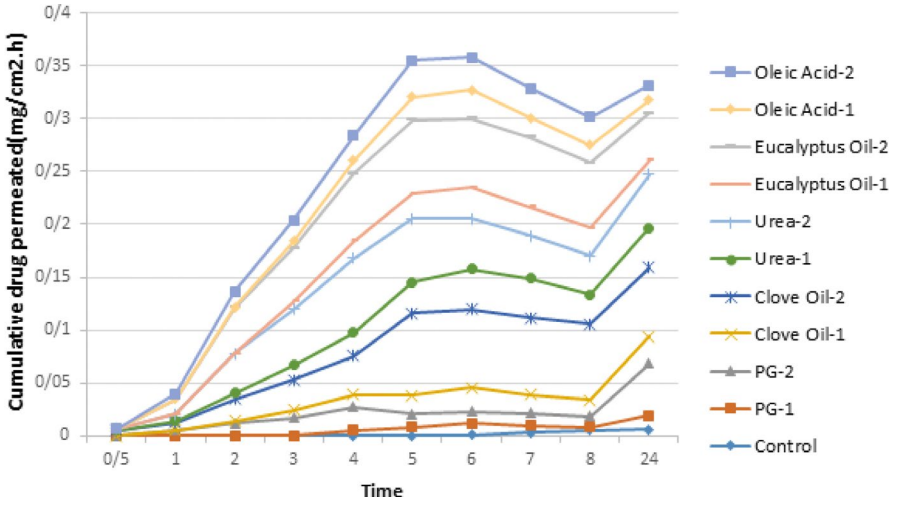

FIGURE 1 Adapalene cumulative diagram crossing the surface unit after 1 and 2 hours of skin contact with eucalyptus, urea, propylene glycol, clove, and oleic acid from whole rat skin

Enhancer	ER_{flux}	ER_D	ER_P
PG (1 hour)	4.716 ± 1.936	2.132 ± 0.292	4.716 ± 1.936
PG (2 hours)	8.325 ± 2.965	23.342 ± 2.067	8.325 ± 2.965
Clove oil (1 hour)	6.758 ± 4.937	58.329 ± 7.871	6.758 ± 4.937
Clove oil (2 hours)	13.167 ± 1.07	9.565 ± 0.189	13.167 ± 1.07
Urea (1 hour)	13.391 ± 1.11	3.665 ± 0.030	13.391 ± 1.11
Urea (2 hours)	26.275 ± 1.884	18.642 ± 2.275	26.275 ± 1.884
Eucalyptus oil (1 hour)	12.708 ± 2.958	2.334 ± 0.035	12.708 ± 2.958
Eucalyptus oil (2 hours)	46.241 ± 8.903	9.745 ± 0.209	46.241 ± 8.903
Oleic acid (1 hour)	12.200 ± 1.030	2.190 ± 0.008	12.2 ± 1.030
Oleic acid (2 hours)	15.883 ± 3.600	9.554 ± 0.335	15.883 ± 3.600

TABLE 2 Results for ER_{flux}, ER_D and ER_P, permeation (n = 3), mean ± SD)

TABLE 3 Peak height and percentage reduction of peak height -CH symmetric, asymmetric and C = O and C-N tensile groups due to component effect (n = 3, mean ± SD)

	Asymmetric C-H stretching		Symmetric C-H stretching		C = O stretching of lipid ester		C = O stretching of keratin		C-N stretching of keratin	
Enhancer	Peak height	D%	Peak height	Peak height	Peak height	D%	Peak height	% D	Peak height	% D
Control (water)	1.835	–	1.95	2.111	2.061	–	2.111	–	2.151	–
PG	0.224	87.79	0.13	0.96	0.212	89.71	0.96	54.52	0.141	93.44
Clove oil	1.227	33.15	0.464	1.889	0	100	1.889	10.52	1.94	9.81
Urea	0.021	94.68	0.023	0	0.327	N.S	0	100	0	100
Eucalyptus oil	0	100	0.001	0.02	0.038	N.S	0.02	83.3	0.01	98.6
Oleic acid	0.382	79.18	0.229	0.404	0.19	90.72	0.404	80.86	0.258	88

Analysis of the FT-IR spectrum of pre-contact skin with adsorption is a practical way to study the interactions between chemical absorption enhancers and the stratum corneum, which are revealed by the formation of absorption bands at different wavelengths. The FT-IR absorption spectrum bands represent the vibrations of lipid and protein molecules in the stratum corneum.[18] The FT-IR table obtained from the effect of adsorption on the whole skin of rats is shown in Tables 3–5.

In this study, rat skin was contacted with different absorption enhancers. The phase transition temperature in the values of changes (ΔH) related to each adsorption is shown in Table 5.

TABLE 4 The wavelengths related to –CH are symmetric and asymmetric and the C = O group stretches amid 1 and 2 in hydrated skin and skin pre-contacted with components (n = 3, mean ± SD)

Enhancer	C-H stretching asy	C-H stretching sym	C = Ostretching Of lipid ester	Amid I	Amid II
Control (water)	2918.77 ± 0.16	2856.34 ± 0.16	1731.68 ± 0.14	1667.04 ± 0.12	1547.67 ± 0.11
PG	2921.20 ± 0.22	2850.21 ± 0.13	1740.84 ± 0.21	1539.60 ± 0.96	1454.915 ± 0.14
Clove oil	2981.66 ± 0.15	2915.86 ± 0.11	-	1690.02 ± 0.21	1642.65 ± 0.17
Urea	2594.97 ± 0.1	2467.94 ± 0.1	1774.09 ± 0.1	–	–
Eucalyptus oil	-	2856.57 ± 0.1	1725.03 ± 0.1	1631.07 ± 0.1	1546.34 ± 0.10
Oleic acid	2921.40 ± 0.38	2955.43 ± 0.23	1745.12 ± 0.19	1632.12 ± 0.40	1564.81 ± 0.26

TABLE 5 Displacement of mean transfer temperatures and enthalpy values in rat skin with enhancers (n = 3, mean ± SD)

Enhancer	Tm_1	Tm_2	ΔH_1	ΔH_2
Control (water)	67.5 ± 2.1	112 ± 6.6	−7.01 ± 0.4	−551.35 ± 19.5
PG	59 ± **0.9**	153 ± **0.9**	0.915 ± **0.04**	2.714 ± **0.3**
Clove oil	36 ± **0.2**	116 ± **0.5**	0.906 ± **0.02**	2.204 ± **0.1**
Urea	38 ± **0.2**	88 ± **0.3**	−2.39 ± **0.01**	−3.86 ± **0.1**
Eucalyptus oil	37.5 ± **0.1**	120.1 ± **0.1**	−0.787 ± **0.001**	26.55 ± **0.8**
Oleic acid	63 ± **1.1**	124 ± **1.1**	0.906 ± **0.02**	2.204 ± **0.1**

Bold values are standard deviations and have been used to indicate data scatter.

4 | DISCUSSION

The effect of enhancers on drug permeation through rat skin was analyzed in comparison with the control by calculating ER_{Flux}, ER_P, and ER_D. The results showed that all the adsorption of Eucalyptus oil, Urea, Clove oil, Propylene glycol, and Oleic acid in 1- and 2-hour contact with the skin caused a significant increase in ER_{Flux}, ER_P, and ER_D. While propylene glycol in the 1-hour pre-contact model was not significantly different from control, the effect of a 2-hour pre-contact of this combination significantly increased the skin permeation rate of Adapalene.

The results also show a significant relationship between J_{ss} and the adsorption sample used in both two-1 and 2-hour modes compared to those in the control sample, indicating an increase in permeability using the adsorption under study.

The results showed that all adsorption of additives had more additive effects on drug permeation rate (flux) than drug release (D_{app}). Among them, urea and eucalyptus in 1- and 2-hour mode, respectively, show the most effect by increasing the permeability of rat skin.

The results also show a significant J_{ss} adsorption relationship of all compounds used in the 2-hour contact compared to that of the control sample, indicating an increase in permeability using these absorption enhancers.

As it was found from the present study, the highest and lowest absorption efficiency of the additives was related to the increase in the skin absorption of the drug, respectively.

Two hours: Propylene glycol > Clove oil > Oleic acid > Urea > Eucalyptus.

One hour: Propylene Glycol > Clove oil > Oleic Acid > Eucalyptus > Urea.

The relationship between the permeability parameters and the independent variables is shown. The results show that the amount of permeability coefficient has a significant relationship with the equation constant and the value of P is changed by changing the absorption of additives.

The relationship between the independent variables and the apparent diffusion coefficient shows that this parameter (D_{app}) has a significant water percentage, so that with increasing the water percentage, the D_{app} rate increases.

The results show that all adsorption of additives had more additive effects on drug permeation rate (flux) than the apparent drug diffusion coefficient.

The present study shows that any change in the amount of pre-contact absorption of additives with rat skin can change the parameters of drug permeability through rat skin.

The increase in ER_D by oleic acid indicates that this permeation causes liquefaction and extraction of lipids in the stratum corneum, which is an important contribution to increasing ER_D permeation in the treated skin on permeation.

The effect of different adsorption on adapalene permeability in Table 2 as ER_{flux} (ratio of drug permeation rate after pre-contact with the desired adsorption to before) and ER_D (drug release coefficient after pre-contact with the desired adsorption before) and ER_P (drug permeability after contact with the afferent permeation previously

shown) is shown. Hydrated skin and aqueous solution were used in the phase chamber as a control.

J_{SS}, D_{app}, and P of hydrated skin drug are 0.00095 mg/cm^2/h, 0.011 cm^2/h, and 0.00002 cm/h, respectively. Tables 1 and 2 show all the parameters of permeability to control.

The 2-hour eucalyptus oil has the greatest effect on drug flux, followed by a 2-hour urea, 2-hour oleic acid, 1-hour urea, 2-hour clove oil, 1-hour eucalyptus oil, 1-hour oleic acid, 2-hour propylene glycol, 1-hour clove oil, and 1-hour propylene glycol had less effect. Among the desired adsorption of clove oil, it had the greatest effect on ER_D of the drug and the same adsorption of eucalyptus oil also had the greatest effect on ER_P.

Previous studies by Salimi et al have shown an increase in permeation of meloxicam flux 16.54 and ER_P by 12.95 by eucalyptus oil.[19] Also, another study by this researcher increased the permeability of Octyl methoxycinnamte due to the use of eucalyptus to more than 48 times.[7]

A study by Joe M. Viljoen et al on the effect of penetration enhancers on the permeability of topical formulations by Oleic acid has one of the highest permeation effects on transdermal permeability, which is consistent with the present study.[20]

Another study by Carrer et al showed that propylene glycol was able to increase the permeation of drugs from logp-1.41 to 5.59, which, like the data in the present study, had an effect on the structure of the stratum corneum.[21]

The FT-IR results from clove oil show that it has increased the absorption wavelength in the asymmetric C-H region and increased the position of the absorption wavelength in the asymmetric CH, indicating liquefaction in the stratum corneum membrane followed by impaired barrier properties and possibly increased drug permeability. From the horny layer, this adsorption removes the wavelength of the C = O region of stress, indicating a complete weakening of the hydrogen bond between the lipid molecules. This increase in absorption also causes the absorption wavelength in the amide 1 region and decreases the absorption wavelength in the amide 2 region, indicating a disorder in amide 1 and no change in amide 2, respectively.

The results obtained from the height of the peaks with this adsorption show that clove oil reduces the percentage of surface area below the peak (decreases the peak height) of the symmetric and asymmetric CH region and C = O stressing also reduces the peak height in the amide 1 and amide 2 regions. These results indicate that this compound has an effect on lipid bilayers of stratum corneum and protein parts of this tissue, but the effect on lipid parts is more than the protein part. It appears that these compounds increase the permeability of the drug through the skin by disrupting the lipid group of the stratum corneum.

The results of a four-hour pre-contact skin FT-IR with increasing oleic acid permeation show that it increases the absorption wavelength in the asymmetric CH and symmetric CH regions, indicating a blue shift of bilayer liquefaction in the stratum corneum and impaired barrier properties and possibly increased drug permeation through the stratum corneum. This adsorption increases the C = O stress wavelength, indicating a weakening of the hydrogen bonds between the lipid molecules. Oleic acid also decreases the wavelength number of amide I and increases the wavelength number of amide II, which increases and decreases the barrier effects, respectively.

The results of 4-hour pre-contact skin FT-IR with propylene glycol show that C-H is asymmetric and C-H is asymmetric toward the absorption band. Indicating a redshift, PG indicates the orientation of lipid bilayer groups and ultimately prevents the drug from entering the skin. The results also show that PG causes an absorption band shift in the C = O region and amides I and II to a lower wavelength. This indicates the orientation of protein groups in the bilayer of the stratum corneum.

The DSC results obtained from the enhancing effect of clove oil show that this compound has reduced TM_1 and significantly reduced ΔH_1 and ΔH_2 .This compound appears to liquefy lipids in the bilayer layer of lipids and lipid complex protein in the stratum corneum through disruption of the fat layer and irreversible denaturation of protein structure in the stratum corneum. The results are consistent with the results of the FT-IR.

DSC results from the effect of oleic acid permeation show that this compound reduces TM_1 and significantly reduces ΔH_1 and ΔH_2, and it seems that this compound is caused by lipid layer disruption and irreversible denaturation on the protein structure in the stratum corneum. Due to the significant reduction in enthalpy, it causes lipids to liquefy in the lipid bilayer and lipid-protein complex in the horny tissue. The results are in line with the results of the FT-IR.

The results of the antipyretic effect of propylene glycol on the abdominal skin of rats in DSC show that PG decreased TM_1 phase transfer and increased TM_2 phase transfer temperature. This combination also shows that it significantly reduced ΔH_2. This indicates that PG disrupts the lipid layer as well as liquefies the lipid-protein complex in the aqueous tissue. Therefore, the results of pre-contact skin DSC are largely consistent with FT-IR results.

5 | CONCLUSION

Transdermal drug delivery has several problems. Overcoming the barrier of the cutaneous stratum corneum has challenges that can be overcome by the use of the transcutaneous drug delivery. All the absorption of chemical and herbal additives used in this study led to changes in the structure of the skin and increased therapeutic drug delivery. The use of absorption enhancers used in this study can greatly aid the dermal delivery of Adapalene.

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CONFLICT OF INTEREST

The publication has been approved by all co-authors and the responsible authorities at the institute where the work has been carried out.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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