

ORIGINAL ARTICLE

Design and evaluation of adapalene microemulsion for transfollicular drug delivery through guinea pig skin

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Abstract

Introduction: Acne vulgaris can be treated topically with adapalene, a synthetic derivative of naphthoic acid with retinoid activity. Adapalene has a very low rate of percutaneous absorption and is almost completely insoluble in water. To obviate this problem, microemulsion (ME) carrier is used. The study's goals were to create and characterize adapalene-loaded ME and assess the drug's transfollicular route of penetration to see if hair follicles can serve as a conduit for the drug to enter the skin.

Methods: Adapalene microemulsions (MEs) are made by combining the right amounts of the cosurfactant (propylene glycol), surfactant (Tween 80 and Span 20), and oil phase (oleic acid-Transcutol P (10:1)). Physical and chemical characteristics of MEs, including droplet size, stability, viscosity, drug release, and in vitro skin permeability via guinea pigs' hairy and non-hairy skin, were assessed.

Results: The range of 13.86–56.16 nm was found to be the average droplet size of ME formulations. The range of viscosities was 117–240 cps. The drug release profile reveals that 95.374 percent of the drug was released within the experiment's first 24 h. Compared to the adapalene control (aqueous suspension), all MEs enhanced the adapalene flow through both hairy and non-hairy skin. The surfactant/cosurfactant ratio had an impact on the amount of drug that passed through both skins because a larger ratio enhanced the adapalene affinity in the follicular route.

Conclusion: Furthermore, the proportions of the water and oil phases in formulations, as well as the S/C ratio, have a significant impact on the physicochemical characteristics and adapalene permeability across both pathways.

KEYWORDS

adapalene, microemulsion, phase diagram, skin, trans follicular delivery

1 | INTRODUCTION

In recent years, it has been shown that the transfollicular route is crucial for the percutaneous absorption of topically administered

medications. The important role of hair follicles as a way of penetrating and reservoir of topical agents has been confirmed in numerous animal and human models. Penetration of topical agents may occur through the stratum corneum or other accessory such as sweat

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glands and hair follicles. Initially, skin accessory were not considered as transdermal penetration because they only account for 0.1% of the skin's surface area. Further studies led to the discovery of a follicular pathway as a very complex route to absorb drugs.¹

Hair follicles stand in for the epidermis' deep dermal invagination, which provides a good surface area for potential absorption. Up to 10% of the skin's surface may be made up of hair follicles on the face and scalp, creating a bigger local surface area that makes it easier for more medicine to be absorbed through this route. Adapalene's target location is similarly thought to be the follicular duct. Drugs that are administered topically can be stored in the HFs. As a result, hair follicles offer a considerable potential for drug delivery into healthy skin layers. Microparticulate systems, in particular, have been exploited for follicular drug administration.

Colloidal dispersions called microemulsions (ME) are made up of an oil, water, and surfactant phase and have a thermodynamically stable system. MEs are thought to be cutting-edge and effective nano-carriers for transdermal and transfollicular distribution because they offer a number of benefits, including long-term stability, simplicity in synthesis, and a significant capacity for solubilizing hydrophilic and lipophilic medicines. By disturbing the stratum corneum barrier, ME components like oils and surfactants can improve the entry of medicines through the skin. The solubility of different medications is greatly increased by micro emulsions, which may also boost the drug's skin penetration and thermodynamic activity.²⁻⁴ Acne vulgaris can be treated topically with adapalene, a synthetic derivative of naphthoic acid with retinoid activity. Adapalene has a very low rate of percutaneous absorption and is almost completely insoluble in water. ($pK_a=4.23$ and $\log P=8.04$).⁵ Several studies have demonstrated the biological benefits of this medication in treating skin conditions with varied causes. Acne vulgaris can be effectively treated with the Therapeutic Formula 0.1 percent adapalene gel formulation. However, the therapeutic benefits may not become apparent for up to 4 weeks after application, and patients should continue using the medication for at least 6 months.⁶ The study's objectives included the development and characterization of adapalene-loaded ME as well as an assessment of the drug's transfollicular route of penetration to see if hair follicles may serve as a conduit for drug absorption into the skin.

2 | MATERIALS AND METHODS

Adapalene was bought from the ATRA firm in Iran, while Transcutol P (diethylene glycol monoethyl ether) was received as free samples from Gattefosse, Saint-Priest, France. Merck (Germany) gave propylene glycol (PG), Tween 80, Span 20, and oleic acid.

2.1 | Animal studies

We bought male adult guinea pigs from the Razi Institute in Karaj, Iran, whose weights ranged from 450 to 650g and were 20 to 22 weeks old. The tests were authorized by the Ahvaz Jundishapur University

of Medical Sciences ethical committee, and the animals were held for 5 days of acclimation before being handled in accordance with the recommendations for the handling and application of laboratory animals.

2.2 | Solubility of adapalene

Adapalene's solubility in various oils (oleic acid, oleic acid + Transcutol P (10:1)), surfactants (Tween 80, Span 20), and cosurfactants (propylene glycol) was examined by dissolving an excess of the compound in 5 mL of each oil, surfactant, and cosurfactant. The samples were mechanically agitated for 48 h at a temperature of $25 \pm 0.5^\circ\text{C}$ using a shaking water bath at 300 rpm to achieve equilibrium. The samples were centrifuged for 30 min at 1006g after equilibration to remove the medicine that had not yet dissolved. The clear supernatants were then filtered through a polytetrafluoroethylene membrane filter (φ 0.45 m), and the filtrates were then examined using UV spectrophotometry at a wavelength of 279 nm.⁷

2.3 | Adapalene ME preparation

Pseudoternary phase diagrams were constructed using the water titration method to determine the boundaries of ME formation.

Two phase diagrams with weight ratios of (Span 20–Tween 80/PG) of 1:1 and 3:1, respectively, were created. The oil phase's oleic acid + Transcutol P (10:1) to surfactant and cosurfactant ratio was altered as follows: 1:9, 2:8, 3:7, 5:5, 6:4, 7:3, and 8:2, and 9:1. Under moderate agitation, deionized water was added drop by drop to the combination of oil, surfactant, and cosurfactant. The translucent and homogeneous samples were regarded as an ME region in the phase diagram following equilibration.^{7,8}

Surfactant/cosurfactant ratio (S/C), water percent (%w), and oil percent (%oil) can all have an impact on the MEs' characteristics. Eight distinct formulations with 5 and 50 percent oil, 5–10 percent water, 4:1 and 6:1 S/C ratio, and 0.1 percent adapalene were created using a full factorial design with the three variables at two levels in this study. (Table 1).

TABLE 1 Composition of eight ME formulations of adapalene.

Formulation	Factorial	S/C	% Oil	% (S/C)	% Water
MEA-1	+++	3:1	50	40	10
MEA-2	++-	3:1	50	45	5
MEA-3	+ - +	3:1	5	85	10
MEA-4	+ - -	3:1	5	90	5
MEA-5	- - +	1:1	5	85	10
MEA-6	- - -	1:1	5	90	5
MEA-7	- + -	1:1	50	45	5
MEA-8	- + +	1:1	50	40	10

Abbreviations: +, High level; -, low level; S/C, surfactant/cosurfactant ratio.

The S + C mixture was combined with an oil phase containing 0.1 percent adapalene. After that, drop by drop of double-distilled water was added to the mixture while it was being stirred at room temperature to create a homogenous mixture.⁸

2.4 | Droplet size determination

At 25°C, the mean droplet size of samples was determined using the Scatter SCOPE 1 QUIDIX (South Korea).

2.5 | Viscosity measurement

The viscosity of the samples was measured at 25 ± 1°C using a Brookfield viscometer (DV-II+Pro Brookfield, USA) with spindle number 34 and a shear rate of 50rpm. Viscosity tests were conducted using a 5 mL volume sample.⁹

2.6 | Physical stability evaluation

Each ME formulation's physical stability was evaluated using centrifuge stress tests and temperature stability tests. The MEs were stored in accordance with ICH guidelines for 6 months at a range of temperatures (4°C, 25°C, 37°C, and 75 ± 5% RH) before being visually inspected by looking for changes in temperature- and time-dependent physicochemical properties like clarity, phase separation, viscosity, and droplet size. A high-speed centrifuge operating at 12.23g was also used to centrifuge Mes for 30min at ambient temperature. The degree of phase separation following centrifugation was utilized to evaluate the physical instability of the formulations.⁸

2.7 | In vitro drug release study

Franz diffusion cells with a cellulose membrane that were specially constructed and had an area of 4.906cm² were used to assess the rate of adapalene release from ME samples. Prior to each experiment, the cellulose membrane was hydrated in distilled water at 25°C for 24h. It was then fastened between the donor and receptor chambers. Adapalene-loaded microemulsion (3g ME) were weighed precisely and put on the membrane. Each diffusion cell was filled with 35mL of DMSO and phosphate buffer solution (PBS) pH = 7.4 (5:1 ratio). Throughout the experiment, 200rpm externally driven magnetic bars continuously swirled the receptor fluid. At predetermined intervals (0.5, 1, 2, 3, 4, 5, 6, 7, 8, and 24h), 2mL of receptor medium were taken out and promptly replaced with an equivalent volume of fresh receptor medium for spectrophotometric analysis for the drug content at 279nm. The cumulative proportion

of medication released over time was shown, and the pattern was explained by fitting to three different kinetic models, including the zero, first, and Higuchi orders. The maximum r^2 was considered as the most probable mechanism.¹⁰

2.8 | Permeability experiments

The hairy abdomen skin and the non-hairy pig ear skin sections are utilized to calculate the quantity of adapalene ME penetration through the follicular and epidermal pathways.¹¹ To find out how much fluid passed through guinea pigs with and without hair, two specifically created vertical diffusion cells (each with an effective diffusion area of roughly 4.906 and 0.3846cm²) were used. The receptor compartments was filled with 35 and 10mL and DMSO and PBS (pH7.4) (5:1 ratio), respectively. Prior to usage, the hydrated samples of hairy abdomen skin and non-hairy pig ears were positioned between the donor and receptor sections of the cells with the stratum corneum towards the donor medium. All of the adapalene ME samples were placed in the donor stages section (3 and 0.5g). The diffusion cells were set in a water bath with a thermostat set at 37 ± 0.5°C, and the receptor phase was continually stirred with a magnet stirrer at 200rpm using tiny magnetic bars. To maintain sink condition, a 2 and 1 mL sample were removed from the receptor mediums at each interval time interval (0.5, 1, 2, 3, 4, 5, 6, 7, 8, 24, and 48h) and replaced with an equivalent volume of DMSO and PBS (pH7.4) (5:1 ratio). The penetrated amount of adapalene in derived samples was found at a wavelength of 279nm using a UV spectrophotometer. Adapalene suspension (0.1%) was used as control.

The results were plotted as a cumulative permeated drug percentage versus time. Based on these plots, the apparent permeability coefficient (P_{app} , cm/s) (Equation 1), steady-state permeation flux (J_{ss}) (Equation 2) apparent diffusivity coefficient (D_{app} cm²/h) (Equation 3) were calculated.

$$P_{app} = \frac{dQ}{dt} \times \frac{1}{A \cdot C_0} \quad (1)$$

$$J_{ss} = C_0 \times P_{app} \quad (2)$$

$$D_{app} = h^2 / 6 T_{lag} \quad (3)$$

$\frac{dQ}{dt}$ is steady-state appearance rate on the acceptor side of the skin. A represents the area of the skin, C_0 represents the initial drug concentration in the donor phase, and h represents the thickness of the skin. The steady-state line was extrapolated to the time axis in order to calculate the lag time (t_{lag} , hr). The cumulative amount of Adapalene permeated per unit skin area plotted against time. The linear component of the permeation curve's slope was used to compute the skin permeation rate at steady state (J_{ss}).

3 | RESULTS AND DISCUSSION

3.1 | Adapalene solubility

The solubility amounts of adapalene in all excipients are presented in Table 2.

Two phase diagrams were created to determine the ME boundary depending on the various S/C ratios (Figure 1). A key factor impacting the phase characteristics of the ME is the weight ratio of S/C. A greater surfactant content was responsible for the rise in the ME area. The phase diagrams clearly showed that when the weight ratio of S/C rose, the ME existence area expanded and more water was incorporated into the ME structure. ($K_m = 1-3$).

3.2 | Characterization of the adapalene MEs

Table 3 displays the adapalene MEs' viscosity, mean droplet size, polydispersity index (PI), and other characteristics.

The average size of MEs ranged from 13.86 to 56.16 nm (Table 2). The ME-ADP7 formulation had the smallest average particle size, 13.86 nm, and a polydispersity index (PI) of 0.338 (Table 2). The homogeneity of droplet size was represented by the polydispersity value. All polydispersity values were <0.5 . Therefore, our findings suggest that MEs have a restricted droplet size distribution. Based on staining tests, All of MEs have water in oil (w/o) type.

TABLE 2 Solubility of adapalene in various oils, surfactants, and cosurfactants (mean $\pm$ SD, $n=3$).

Phase type	Excipient	Solubility amount (mg/ml)
Oil	Oleic acid	8.59 ± 0.07
	Transcutol P	18.53 ± 0.08
	Oleic acid +Transcutol P	10.43 ± 0.55
Surfactant	Tween 80	12.67 ± 0.09
	Span 20	4.09 ± 0.2
Cosurfactant	Propylene glycol	5.7 ± 0.54

According to the PI, the size distribution of ME formulations was restricted. According to the statistical research, there is a direct and substantial association between the average droplet size and the oil content (%Oil). However, a strong and indirect link between the mean particle size of MEs and a percentage of water (%W) was discovered. Our findings are in accordance with Bhatia et al.¹²

The statistical study revealed a substantial association between viscosity and the independent variables (%W, S/C, and %Oil), indicating that viscosity increases as oil percentages rise, water percentages fall, and S/C ratios rise. Newtonian behavior was suggested by the viscosity values in all of the ME formulations. Our findings are consistent with earlier studies by Yvan, et al.¹³ which show how all components of microemulsions alter viscosity.

A crucial aspect of the formulation that significantly affects therapeutic efficacy is the percentage of the drug that is released. The release profiles of the adapalene MEs are shown in Figure 2. The medication release profile indicates that 75.62%–95.37% of the adapalene was released throughout the course of the experiment's 24 h. Table 4 provides a summary of the percent of drug released and the release kinetics in the ME samples. The release data suited the first-order model the best.

3.2.1 | Investigations of in vitro permeation through guinea pig skin

As models for epidermal and follicular processes, the hairy abdomen skin and the non-hairy pig ear skin are employed.¹⁰ As a result, permeation tests in this study were conducted on guinea pig skin that was both hairy and hairless.

The obtained results are shown that adapalene MEs permeability parameters more than control.

The permeability characteristics of different MEs of adapalene from hairy Abdominal skin are less than non-hairy ear skin guinea pig. Adapalene is a lipophilic molecule so that did permeate through lipophilic barrier of pig ear skin. ME formulations are significantly affected on the lipid structures of pig ear skin.

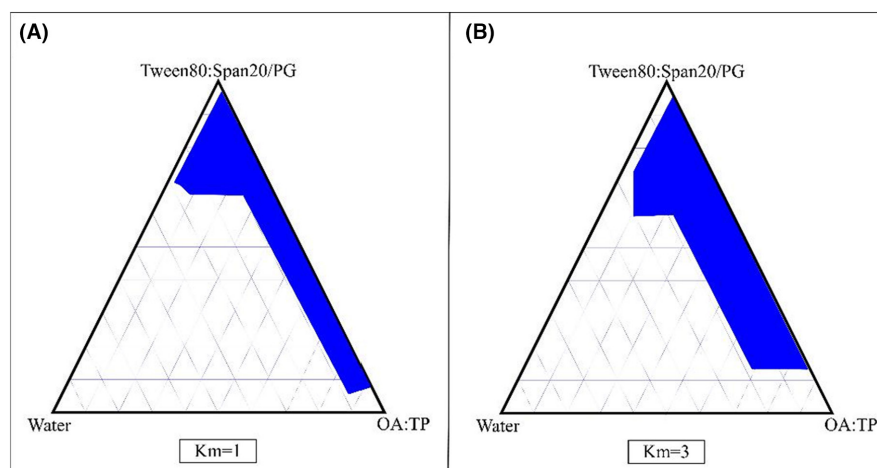


FIGURE 1 The pseudoternary phase diagrams of the oil-surfactant/cosurfactant mixture–water system at the 1:1 and 3:1 weight ratio of Tween 80–Span 20/propylene glycol at ambient temperature, blue area show ME boundary.

The permeability parameters of various MEs of adapalene from hairy Abdominal skin and non-hairy ear skin pig are presented in Tables 5 and 6.

In the hairy abdomen skin, ME-ADP5 had the maximum skin permeability among the MEs. Through a guinea pig's abdominal skin, the Jss of the ME-ADP5 (0.0057 mg cm⁻² h⁻¹) was 5.07 times higher compared to the control. Additionally, in guinea pigs with non-hairy ear skin, ME-ADP7 had the maximum skin permeability. The Jss of the ME-ADP7 was 4.07 times higher compared to the control through the non-hairy ear skin guinea pig (0.0179 mg cm⁻² h⁻¹). In this study, Table 7 provides other characteristics, including the percentage of permeability throughout a 24-h period. In guinea pigs with hairy abdominal skin and non-hairy ear skin, ME-ADP5 and ME-ADP4 exhibited the highest percentages of permeability, respectively. The findings demonstrate that any reduction in the percentages of the oil and water phases considerably raised the Jss parameter in the hairy abdomen skin. Additionally, the connection between Jss and independent factors in non-hairy ear skin guinea pigs statistically insignificant ($p > 0.05$). The findings indicated that the influence of oil and water is little and that the S/Co ratio has only a small impact on the percentage of permeability in the guinea pig with non-hairy ears. As a result, this effect may be observed in the first set of ME

formulations (Km=3). Additionally, the results revealed that the second group of ME formulations (Km=1) had a higher percentage of permeability through the pathway of the hairy abdomen skin. Our results agree with previous publications by Bhatia et al.,¹² Ma et al.,¹⁴ Salimi et al.¹⁵ and Lena Klein et al.¹⁶

Adapalene that had been loaded into ME was applied transfollicularly to guinea pig skin in research by BHATIA et al.¹² They demonstrated that compared to the adapalene solution, the adapalene flux offered by ME was greater. When an oil-in-water microemulsion changed to a bi-continuous microemulsion increasing the water content, the medication penetration in hair follicles increased. Adapalene permeates the follicular and epidermal pathways, as we are able to demonstrate in the current work. The permeability of adapalene is greatly influenced by ME components. As Hathout et al.¹⁷ and salimi et al.¹⁸ showed in their prior work, oleic acid is a penetration enhancer in MEs.

The difference between ME-ADP4 and ME-ADP5 is the S/C ratio and water percentage. Considering that the non-hairy skin had the largest percentage of permeability over the course of a 24-h period, ME-ADP4 had more surfactant than ME-ADP5. This indicates that the epidermal barrier was changed by ME-ADP4. More than the follicular pathway, the surfactant's impact on the

TABLE 3 Mean droplet size, polydispersity index, and viscosity of selected adapalene MEs (mean $\pm$ SD, $n=3$).

Formulation	Mean droplet size (nm)	Poly dispersity index	Viscosity (cps)
MEADP-1	33.76 $\pm$ 2.51	0.352 $\pm$ 0.009	147 $\pm$ 0.1.2
MEADP-2	34.2 $\pm$ 2.25	0.304 $\pm$ 0.001	151 $\pm$ 2.1
MEADP-3	39.4 $\pm$ 2.07	0.318 $\pm$ 0.028	220 $\pm$ 2.4
MEADP-4	56.16 $\pm$ 3.96	0.328 $\pm$ 0.021	240 $\pm$ 1.8
MEADP-5	32.86 $\pm$ 2.69	0.324 $\pm$ 0.034	136 $\pm$ 2.4
MEADP-6	19.83 $\pm$ 1.05	0.338 $\pm$ 0.015	197 $\pm$ 0.7
MEADP-7	13.86 $\pm$ 2.45	0.338 $\pm$ 0.030	127 $\pm$ 1.1
MEADP-8	29.4 $\pm$ 2.14	0.35 $\pm$ 0.011	117 $\pm$ 1.5

TABLE 4 Percentage release and kinetic release of chosen MEs (mean $\pm$ SD, $n=3$).

Formulation	% Release (24h)	Kinetic of release	r^2
MEA-1	79.10 $\pm$ 1.11	First	0.9944
MEA-2	75.62 $\pm$ 0.68	First	0.9905
MEA-3	95.37 $\pm$ 0.85	First	0.8645
MEA-4	86.85 $\pm$ 3.34	First	0.8092
MEA-5	89.79 $\pm$ 1.20	First	0.8272
MEA-6	80.08 $\pm$ 0.54	First	0.7979
MEA-7	90.71 $\pm$ 1.13	First	0.9495
MEA-8	87.79 $\pm$ 1.30	First	0.9776

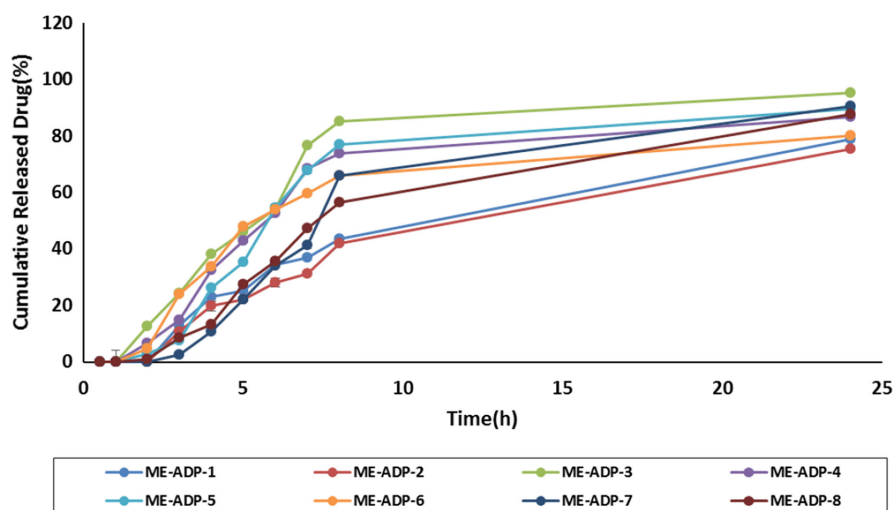


FIGURE 2 In vitro release profile of ME formulations of Adapalene.

TABLE 5 In vitro permeability parameters of adapalene ME formulations through non-hairy ear skin guinea pig (mean $\pm$ SD, $n=3$).

Formulation	J_{ss} (mg/cm ² .h)	P (cm/h)	T_{lag}	D_{app}	ER_D	ER_{flux}
Control	0.0044 $\pm$ 0.0001	0.0088 $\pm$ 0.0003	3.893 $\pm$ 0.244	0.0117 $\pm$ 0.0006	–	–
ME-ADP1	0.0114 $\pm$ 0.0012	0.0228 $\pm$ 0.0025	0.541 $\pm$ 0.394	0.0771 $\pm$ 0.005	7.197 $\pm$ 0.073	2.58 $\pm$ 0.206
ME-ADP2	0.0125 $\pm$ 0.0004	0.025 $\pm$ 0.0008	1.452 $\pm$ 0.1769	0.0288 $\pm$ 0.003	2.68 $\pm$ 0.16	2.84 $\pm$ 0.005
ME-ADP3	0.0127 $\pm$ 0.00007	0.0404 $\pm$ 0.0209	0.721 $\pm$ 0.09	0.058 $\pm$ 0.007	5.47 $\pm$ 1.06	2.89 $\pm$ 0.109
ME-ADP4	0.01675 $\pm$ 0.00063	0.0335 $\pm$ 0.0012	2.121 $\pm$ 0.189	0.0197 $\pm$ 0.001	1.83 $\pm$ 0.04	3.806 $\pm$ 0.02
ME-ADP5	0.0103 $\pm$ 0.00004	0.0206 $\pm$ 0.0008	2.145 $\pm$ 0.02	0.0194 $\pm$ 0.001	1.81 $\pm$ 0.09	2.34 $\pm$ 0.02
ME-ADP6	0.0062 $\pm$ 0.0005	0.0124 $\pm$ 0.0011	1.174 $\pm$ 0.24	0.0362 $\pm$ 0.007	3.36 $\pm$ 0.49	1.40 $\pm$ 0.083
ME-ADP7	0.0179 $\pm$ 0.001	0.0366 $\pm$ 0.0011	4.009 $\pm$ 0.06	0.0103 $\pm$ 0.001	0.97 $\pm$ 0.04	4.07 $\pm$ 0.109
ME-ADP8	0.0091 $\pm$ 0.0004	0.0182 $\pm$ 0.0008	0.607 $\pm$ 0.34	0.0817 $\pm$ 0.046	7.5 $\pm$ 0.385	2.06 $\pm$ 0.03

TABLE 6 In vitro permeability parameters of adapalene ME formulations through hairy abdominal skin guinea pig (mean $\pm$ SD, $n=3$).

Formulation	J_{ss} (mg/cm ² .h)	P (cm/h)	T_{lag}	D_{app}	ER_D	ER_{flux}
Control	0.00025 $\pm$ 0.00007	0.00005 $\pm$ 0.00001	2.75 $\pm$ 1.06	0.0419 $\pm$ 0.01616	–	–
ME-ADP1	0.0025 $\pm$ 0.00007	0.00051 $\pm$ 0.000014	0.506 $\pm$ 0.207	0.229 $\pm$ 0.094	12.87 $\pm$ 5.338	2.255 $\pm$ 0.738
ME-ADP2	0.00205 $\pm$ 0.00007	0.00041 $\pm$ 0.000014	1.426 $\pm$ 0.744	0.0865 $\pm$ 0.045	4.852 $\pm$ 2.565	1.811 $\pm$ 0.581
ME-ADP3	0.0037 $\pm$ 0.000141	0.00312 $\pm$ 0.00339	2.431 $\pm$ 0.599	0.0438 $\pm$ 0.001	2.454 $\pm$ 0.041	3.311 $\pm$ 1.288
ME-ADP4	0.0054 $\pm$ 0.000141	0.00108 $\pm$ 0.000028	2.841 $\pm$ 0.148	0.037 $\pm$ 0.0019	2.103 $\pm$ 0.126	4.777 $\pm$ 1.571
ME-ADP5	0.0057 $\pm$ 0.000212	0.00115 $\pm$ 0.000042	2.632 $\pm$ 0.111	0.0405 $\pm$ 0.001	2.268 $\pm$ 0.114	5.077 $\pm$ 1.618
ME-ADP6	0.00375 $\pm$ 0.00049	0.00075 $\pm$ 0.000099	2.197 $\pm$ 0.237	0.0488 $\pm$ 0.005	2.729 $\pm$ 0.274	3.411 $\pm$ 1.618
ME-ADP7	0.0041 $\pm$ 0.001	0.0022 $\pm$ 0.00195	1.609 $\pm$ 0.001	0.066 $\pm$ 0.001	3.706 $\pm$ 0.029	3.644 $\pm$ 1.288
ME-ADP8	0.0044 $\pm$ 0.000071	0.00089 $\pm$ 0.000014	1.414 $\pm$ 0.168	0.0759 $\pm$ 0.009	4.246 $\pm$ 0.471	3.966 $\pm$ 1.461

TABLE 7 In vitro percentage of permeability of Adapalene ME formulations in 24 h through hairy abdominal skin guinea pig and non-hairy ear skin guinea pig (mean $\pm$ SD, $n=3$).

Formulation	Hairy abdominal skin guinea pig (percent amount, %)	Non-hairy ear skin guinea pig (percent amount, %)
Control	0.8739 $\pm$ 0.0014	2.52 $\pm$ 0.001
ME-ADP1	3.58 $\pm$ 0.0012	7.91 $\pm$ 0.001
ME-ADP2	2.54 $\pm$ 0.0014	7.03 $\pm$ 0.001
ME-ADP3	8.21 $\pm$ 0.003	16.59 $\pm$ 0.003
ME-ADP4	8.8 $\pm$ 0.014	17.58 $\pm$ 0.001
ME-ADP5	9.83 $\pm$ 0.002	5.41 $\pm$ 0.001
ME-ADP6	8.19 $\pm$ 0.002	4.55 $\pm$ 0.004
ME-ADP7	8.54 $\pm$ 0.001	7.51 $\pm$ 0.0041
ME-ADP8	8.97 $\pm$ 0.004	8.72 $\pm$ 0.008

epidermis' barrier capacity was greater. The primary action sites of adapalene in acne are the follicular and epidermal pathways. Adapalene's primary acne-related action sites are the follicular and epidermal pathways. This study, which used ME-ADP5 with a greater water content, aimed to increase adapalene penetration in the hairy route.

4 | CONCLUSION

Low percutaneous absorption limits the therapeutic efficacy of the acne treatment adapalene. To improve solubility and investigate the permeation mechanism, adapalene-loaded MEs were employed in this work. Compared to the aqueous adapalene solution, the MEs enhanced adapalene penetration into the epidermal and follicular channels. ME formulations were shown different permeability parameter amounts in both pathways. When using MEs with a greater s/c ratio, adapalene is more likely to be absorbed through the epidermal pathway. The ME-ADP5 with a low level of S/C was the best ME that increased adapalene's follicular pathway affinity since the follicular pathway is the primary location for adapalene activity in acne.

ETHICS STATEMENT

Authors declare ethics approval was not required for this study.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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