

Microemulsion-based hydrogel formulation for transdermal delivery of dexamethasone

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The purpose of this study was to construct a microemulsion-based hydrogel formulation for the transdermal delivery of dexamethasone. Almond oil, olive oil, linseed oil, and nutmeg oil were screened as the oil phase. A microemulsion-based system was chosen due to its good solubilizing capacity and skin permeation capabilities. The pseudoternary phase diagrams for microemulsion regions were constructed using various oils, egg lecithin as the surfactant, isopropyl alcohol (IPA) as the cosurfactant, and distilled water as the aqueous phase. Microemulsion gel formulations were prepared using Carbopol and filled into a reservoir-type transdermal system. The ability of various microemulsion formulations to deliver dexamethasone through the rat skin was evaluated *in vitro* using Keshary Chien diffusion cells. In order to enhance permeation, the skin was treated with an abrading gel (apricot seed powder in hydrogel base). The *in vitro* permeation data showed that microemulsions increased the permeation rate of dexamethasone compared with the control. The optimum formulation consisting of 0.1% dexamethasone, 10% olive oil, 70% egg lecithin:IPA (2:1), and water showed a permeation rate of 54.9 $\mu\text{g}/\text{cm}^2/\text{h}$. The studied microemulsion-based hydrogel was stable toward centrifugation test and was nonirritating to the skin. The pharmacodynamic studies indicated that microemulsion based on nutmeg oil demonstrated a significantly ($P < 0.05$) higher anti-inflammatory potential. The nutmeg oil-based transdermal microemulsion gel system demonstrated 73.6% inhibition in rat paw edema. Thus, microemulsion-based transdermal systems are a promising formulation for dermal delivery of dexamethasone.

Key words: Carbopol, dexamethasone, hydrogel, microemulsion, transdermal

INTRODUCTION

Microemulsion is defined as a dispersion consisting of oil, surfactant, cosurfactant, and aqueous phase, which is a single optically isotropic and thermodynamically stable liquid solution with a droplet diameter usually within the range of 10–100 nm.^[1] Microemulsions have several advantages, such as enhanced drug solubility, good thermodynamic stability, and enhancing effect on transdermal ability over conventional formulations.^[2] There are several permeation enhancement mechanisms of microemulsions, such as an increased concentration gradient and thermodynamic activity toward skin and the permeation enhancement activity of the components of microemulsions.^[3] So far, much attention has been focused on the dermal delivery of drugs such as estradiol and lidocaine using microemulsions.^[3,4] Recently, different hydrogel matrices such as carbomer 934, Carbopol, and carrageenan have been used to

increase the viscosity of microemulsion for dermal application.^[3,5-7] The addition of hydrogel matrix into the microemulsion resulted in the formation of the microemulsion-based hydrogel, which is more suitable for dermal application when compared with microemulsion.^[8]

Dexamethasone is a synthetic glucocorticoid^[9] widely used in inflammatory condition^[10] and to enhance the normal immune response.^[11] It is used as a therapeutic agent in alcohol withdrawal syndrome,^[12] cerebral edema,^[13] congenital adrenal hyperplasia,^[9] nausea, and vomiting, especially associated with a high dose of anticancer agents,^[14] high altitude disorder,^[13] cerebral malaria, opportunistic mycobacterial infections, respiratory disorders, skin disorders,^[9] and rheumatism.^[15] Dexamethasone possesses most of the desirable physicochemical and biological properties, e.g. half-life of 2 and 5 h, plasma protein binding is about 67%, and a small daily dose ranging from 0.5 to 9 mg, while the associated drawbacks like hepatic first-pass effect of the drug and gastric irritation upon oral administration can also be overcome by transdermal delivery.^[16] Researchers have also reported methodologies for increasing

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DOI: 10.4103/0973-8398.49172

the transdermal absorption of drugs from formulation by employing deformable carriers,^[17] transfersomes,^[18] patches,^[19] transdermal system,^[20] ointment,^[21] ocular microemulsion,^[22] iontophoresis,^[23-25] and phonophoresis.^[26,27]

The goal of this work was to develop a reservoir-type transdermal delivery system with the drug core being formed of a microemulsion-based hydrogel and to evaluate the permeation-enhancing potential of an abrading agent. The present study was focused on the screening of dexamethasone-loaded microemulsions and formulation of a microemulsion-based hydrogel.

MATERIALS AND METHODS

Materials

Dexamethasone was provided as a gift sample by Arbro Pharmaceuticals, New Delhi, India. Almond oil was procured from Fluka Chemicals Corp., Switzerland, and linseed oil and nutmeg oil were from Aldrich Chemicals Company, USA. Egg lecithin was purchased from HiMedia Laboratories, Mumbai, India, IPA from Ranbaxy Chemicals Pvt. Ltd., New Delhi, India, and olive oil and Carbopol 934 from CDH Pvt. Ltd., New Delhi, India. Hydroxy propyl methyl cellulose (HPMC K₁₅M) was gifted by Gattefosse, France, through Colorcon Asia Pvt. Ltd., Goa, India. All chemicals used were of analytical grade. Animal experiments were approved by the institutional animal ethical committee.

Pseudoternary phase diagram study

Almond oil, olive oil, linseed oil, and nutmeg oil were selected as the oil phase. Egg lecithin and IPA were selected as surfactant and cosurfactant, respectively. Distilled water was used as an aqueous phase. Surfactant-cosurfactant mixture (S:CoS) of different weight ratios (1:3, 1:2, 1:1, 1:0, 2:1, 3:1, and 4:1) were chosen. These S:CoS ratios were chosen in both increasing concentration of cosurfactant with respect to surfactant and increasing concentration of surfactant with respect to cosurfactant. Pseudoternary phase diagrams of oil, S:CoS, and aqueous phase were developed using the aqueous titration method under magnetic stirring at 20 rpm. Slow titration with the aqueous phase was performed to each weight ratio of oil and S:CoS. After being equilibrated, the mixtures were assessed visually and determined as being microemulsions by virtue of their clarity and transparency. The physical state of the microemulsion was marked on a

pseudo three-component phase diagram with the aqueous phase, oil phase, and mixture of surfactant and cosurfactant representing the three axes.

Screening of oils for microemulsions

To find out the suitability of oil to be used as the oil phase in microemulsion, the solubility of dexamethasone was determined. Microemulsions were prepared with each oil, S:CoS (almond oil-1:1, olive oil-1:3, linseed oil-3:1, and nutmeg oil-2:1), and water in a 1:7:2 ratio. Egg lecithin and IPA were selected as surfactant and cosurfactant, respectively. Excess amount of dexamethasone was added to 2 ml of the selected microemulsions in 5 ml capacity vials. It was placed in a shaker water bath maintained at $37 \pm 1.0^\circ\text{C}$ for 72 h. The equilibrated samples were removed from the shaker, centrifuged, and the supernatant was filtered through Whatman filter no. 4. The concentration of dexamethasone was determined UV spectrophotometrically at 244 nm.

Preparation of the transdermal microemulsion-based hydrogel formulation of dexamethasone

Preparation of the microemulsion of dexamethasone

Dexamethasone was added to the mixtures of oil and S:CoS with a varying component ratio as described in Table 1, and then the appropriate amount of water was added to the mixture drop by drop and the microemulsion containing dexamethasone was obtained by stirring the mixtures. All microemulsions were stored at $30 \pm 2^\circ\text{C}$. Dexamethasone at 0.1% w/w was incorporated in all formulations.

Preparation of the microemulsion-based hydrogel of dexamethasone

Carbopol was selected as the gel matrix to prepare the microemulsion-based hydrogel formulation. Carbopol was slowly mixed with the microemulsion under stirring. After Carbopol had swelled, it was kept overnight to obtain the microemulsion-based hydrogel. The control formulation was prepared by adding 0.1% w/w dexamethasone to phosphate-buffered saline (PBS) at pH 7.4 and was gelled by the addition of Carbopol (1% w/w) and triethanolamine.

Fabrication of the reservoir-type patch of microemulsion gel of dexamethasone

Transdermal patches (reservoir type) of dexamethasone were fabricated by encapsulating the dexamethasone gel preparation within a shallow compartment made of a hollow

Table 1: Compositions of the selected microemulsion formulations (% w/w)

Microemulsion components (% w/w)	Formulation codes				
	C	AO	OO	LO	NO
Dexamethasone	0.1	0.1	0.1	0.1	0.1
Oil	-	10	10	10	10
Egg lecithin	-	35	17.5	52.5	46.6
IPA	-	35	52.5	17.5	23.3
Distilled water q.s.	100	100	100	100	100
Vehicle	Distilled water	Almond oil	Olive oil	Linseed oil	Nutmeg oil

ring-shaped device and drug-impermeable backing membrane (laminated aluminum foil). A microporous tape of a larger area was stuck onto the impermeable-backing membrane to bring the transdermal patch in intimate contact with the skin. The device was closed by a release liner on the open side. The various formulations were designated as C, AO, OO, LO, and NO for formulations prepared from distilled water (control), almond oil, olive oil, linseed oil, and nutmeg oil, respectively.

Preparation and method of application of the abrasive gel

The abrasive gel was prepared by heating distilled water to 80°C and adding to it crushed apricot seeds (*Prunus armeniaca*). The polymer (HPMC) 2% w/w was then added slowly and allowed to disperse uniformly. It was then cooled to form a viscous gel into which was entrapped crushed apricot seed pieces.

One gram of the gel was topically applied with the help of the index finger on the depilated site of application of formulation and was gently massaged onto the skin for a period of 2 min. The crushed apricot pieces were dusted off with a soft cloth.

The above-mentioned formulations were also applied after pretreatment of the site of application of the patch by an abrading gel and these were designated as CA, AOA, OOA, LOA, and NOA for formulations prepared from distilled water (control), almond oil, olive oil, linseed oil, and nutmeg oil, respectively.

Characterization of the dexamethasone-loaded microemulsion preparation

Droplet size determination

The droplet size distribution and the average droplet size of the microemulsion were measured using a Zetasizer Nano ZS (Malvern Instruments, UK) using water as the dispersant at 25°C.

Viscosity measurements

The viscosity measurements were performed at 25 ± 0.1°C using a Brookfield viscometer DV-II+ Pro (Middleboro, MA, USA) (Spindle: T-bar and torque >30%).

Stability of the microemulsion-based hydrogel

The stability of the studied microemulsion-based hydrogel containing dexamethasone was studied via clarity and phase separation observations. The centrifuge tests were carried out to assess the physical stability by subjecting the microemulsion to centrifugation at 3000 rpm for 15 min (RCF ≈ 1200).

Determination of dexamethasone concentration in the receptor media

The drug content in the diffusion media, i.e. poly ethylene

glycol (PEG) 400 and PBS pH 7.4 (20:80), was measured UV spectrophotometrically at 244 nm. The assay was linear in the concentration range of 1–30 µg/ml for dexamethasone ($y = 0.0395x + 0.0023$, $R^2 = 0.9999$).

In vitro skin permeation studies

The full-thickness rat skin was used for the permeation experiments. After the hair was removed with a depilatory, the skin was rinsed with physiological saline and then washed with PBS (pH 7.4). The skin was clamped between the donor and the receptor chamber of a Keshary Chien diffusion cell with an effective diffusion area of 1.0 cm² and 11-ml receptor cell volume. The receptor chamber was filled with freshly prepared 20% PEG 400 in PBS (pH 7.4). The diffusion cell was maintained at 37 ± 2°C and the solution in the receptor chambers was stirred continuously with a magnetic bead. Two grams of the microemulsion-based hydrogel was placed in the donor chamber. In case of pretreatment with abrading gel, the skin was clamped and to it was applied 1 g of the abrading gel and was massaged onto the skin for 2 min. The crushed apricot seed debris was dusted off with a soft cloth, the donor chamber was mounted, and the experiment was carried as outlined. At 1, 2, 4, 6, 8, 10, 12, 20, 22, and 24 h, 2 ml of the sample from the acceptor chamber was removed for determination of the drug concentration and replaced immediately with an equal volume of the receptor fluid. All experiments were performed in quadruplicate. The cumulative amount of dexamethasone permeated through the rat skin was plotted as a function of time. The permeation rate (flux) of dexamethasone at the steady state (J_{ss} , µg/cm²/h) and the lag time (T_{lag} , h) were calculated from the slope and the intercept of the straight line obtained by plotting the amount of dexamethasone permeated versus time in steady state conditions, respectively. Permeability coefficient (K_p , cm/h) was calculated by dividing the flux obtained by the initial concentration of drug in the donor compartment. The enhancement ratio (ER) was calculated from the following equation:

$$ER = \frac{J_{ss} \text{ of test formulation}}{J_{ss} \text{ of control formulation}}$$

Pharmacological studies

Skin irritation study

Various preparations, when applied dermally, might elicit skin irritation. Therefore, to assess the skin-sensitizing potential, dexamethasone patch was applied onto the dorsal skin of albino Wistar rats. The animals were housed in polypropylene cages, with free access to standard laboratory diet and water. Animals were acclimatized for at least 7 days before experimentation. The dorsal abdominal skin of the rats was shaved 24 h before study. The formulations were applied and the site of application was occluded with gauze and covered with a nonsensitizing microporous tape. Erythema values for formulations with and without pretreatment with abrading gel were recorded. The patch was removed after 24 h and the

score of erythema was recorded as follows: mild erythema–1; moderate erythema–2; severe erythema–3.^[28]

In vivo anti-inflammatory studies

Wistar albino rats (220–250g) were assigned to weight-balanced groups ($n = 4$). The experimental groups received the different formulations while the control group was treated with placebo only. Two grams of the different formulations were spread over 9 cm² of dorsal skin after removing the hair with a clipper. After 2 h, 0.05 ml of a 0.5% carrageenan suspension was injected into the subplantar area of the left hind paw. The activity was measured by measuring the changes in paw volumes with a screw gauge (Mitutoyo, Kanagawa, Japan) 4 h after carrageenan injection. The right hind paw served as a control and was treated with physiological saline solution without carrageenan.^[29] Four hours after the carrageenan injection, the degree of paw swelling was calculated as follows:

$$\text{Swelling (\%)} = \frac{V_t - V}{V} \times 100$$

where, V_t is the volume of the carrageenan-treated paw and V is that of the nontreated paw.

$$\text{Inhibition (\%)} = \frac{S_c - S_t}{S_c} \times 100$$

where, S_c is the swelling of the control paw and S_t is that of the test formulation-treated paw.

Statistical analysis

All skin permeation experiments were repeated four times and data were expressed as the mean value \pm SD. The results were analyzed by Student's *t*-test using Statistica for windows (version 5.0) from StatSoft Inc., USA.

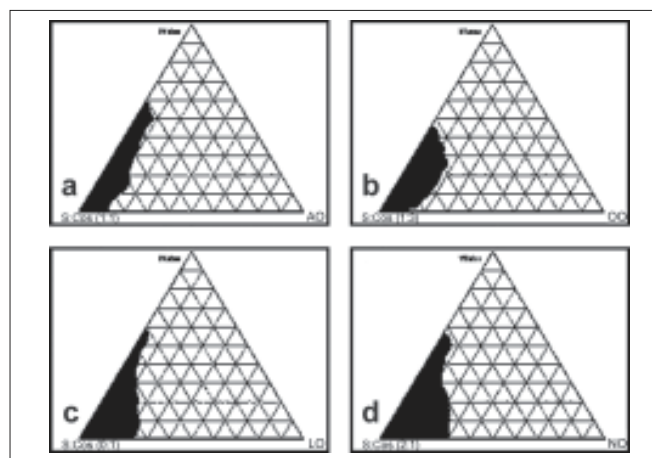


Figure 1: The pseudoternary phase diagrams of the oil, surfactant cosurfactant mixture, and water system at 1:7:2 weight ratios of oil, egg lecithin–isopropyl alcohol mixture and distilled water at 25°C. (a) Almond oil, (b) olive oil, (c) linseed oil, and (d) nutmeg oil (shaded portion represents the microemulsion region)

RESULTS AND DISCUSSION

Phase studies

The aim of construction of pseudoternary phase diagrams was to find out the existence range of microemulsions. The phase diagrams of the four selected systems are presented in Figure 1. It can be seen that the oil/water (o/w) microemulsion region was slightly larger for olive oil and nutmeg oil while linseed oil and almond oil had comparatively smaller areas. However, all ternary phase diagrams revealed that at least a 10% w/w oil phase could be incorporated using egg lecithin and IPA as surfactant and cosurfactant, respectively. The dark-shaded region in the phase diagram marks the clear transparent microemulsion phase.

There was occurrence of distinct phases, the immiscible phase, the translucent phase, and the clear transparent phase. The conversion from turbid phase to oil-in-water (o/w) microemulsion phase was observed. The major region on the phase diagram represents the turbid and the conventional emulsion. The microemulsion region changed slightly in size with the increasing ratio of surfactant to cosurfactant. It was observed that the amount of oil that could be incorporated varied with the type of oil and also on the ratio of S:CoS. The S:CoS ratio yielding largest areas was selected for each oil. The selected phase diagrams are shown in Figure 1.

Because the order of the addition of the ingredients has a significant influence on the preparation of microemulsions,^[30,31] the dexamethasone was first dissolved/dispersed in the oil phase and to it was added the S:CoS mixture of selected ratio at defined concentrations and then slowly titrated with water. The concentrations of the components are represented in Table 1.

Solubility of dexamethasone

In order to develop microemulsion formulations for dermal delivery of poorly water-soluble dexamethasone, the optimum oil was selected by determining the concentration of dexamethasone that would dissolve. Four different microemulsions were prepared using oil, S:CoS (egg lecithin–IPA) mixture, and distilled water in a 1:7:2 ratio. The solubility of dexamethasone in microemulsions of various oils is reported in Table 2.

The solubility of dexamethasone was highest in microemulsions of olive oil (14.2 ± 0.36 mg/ml), followed

Table 2: Solubility of dexamethasone in microemulsions of various oils at 25°C (mean \pm SD, $n = 4$)

Microemulsion oil (S:CoS)	Solubility (mg/ml)
Almond oil (1:1)	10.6 ± 0.1
Olive oil (1:3)	14.2 ± 0.3
Linseed oil (3:1)	9.4 ± 0.2
Nutmeg oil (2:1)	11.8 ± 0.4

by nutmeg oil, almond oil, and linseed oil. The solubility of dexamethasone in microemulsions of various oils decreased slightly when compared with that in olive oil. The addition of egg lecithin and IPA to oil would probably positively influence drug solubility. It was therefore inappropriate to study the solubility of dexamethasone in the oil phase. Microemulsions were therefore chosen for assessing the solubility. Dexamethasone demonstrated high solubility in microemulsions of various oils. As per the observed solubility, olive oil and nutmeg oil could be the most appropriate oils for the development of the microemulsion. In order to verify the selection of the oil, the *in vitro* skin permeation rate of dexamethasone from the microemulsions containing dexamethasone, oil, egg lecithin-IPA mixture, and water was also determined.

Preparation of the transdermal microemulsion-based hydrogel formulation of dexamethasone

After addition of carbomer 934 followed by addition of triethanolamine, it was observed that the microemulsion structure was disturbed. However, a clear gel could be obtained by omitting triethanolamine. The microemulsion-based hydrogels with 1.0% w/w Carbopol were stable at 40°C. No phase separation and degradation was observed during 3 months. The microemulsion-based hydrogel with 1.0% Carbopol formulated as a reservoir-type transdermal device could be applied to the skin as such or after treating the area of the skin with an abrading gel.

Characterization of the dexamethasone-loaded microemulsions

The droplet size of all microemulsions ranged from 4 to 13 nm. The droplet size of the microemulsion was found to vary with the oil. Olive oil and nutmeg oil produced microemulsions of 10–13 nm in diameter while almond oil and linseed oil microemulsions had a droplet size of 4–6 nm. The small droplet sizes are very much a prerequisite for drug delivery as the oil droplets tend to fuse with the skin thus providing a channel for drug delivery.

The viscosities of the microemulsion-based Carbopol gels ranged from 160 to 200 Poise for the micro emulsion gel and the conductivities were in the range of 8×10^{-6} – 10×10^{-6} S/cm. The conductivities of the microemulsion revealed that water was the external phase and the microemulsion was o/w type. The microemulsion formulations had pH values varying from 4.1 to 4.7 [Table 3].

Incorporation of different oils did not greatly affect the pH

of the microemulsions. The centrifuge test showed that the microemulsion had good physical stability.

In vitro skin permeation studies

The high permeation rate of microemulsions might be attributed to several factors. Microemulsions could act as a drug reservoir, where drug is released from the inner phase to the outer phase and then further on to the skin.^[3] Secondly, because of the small droplet size, droplets settled down to close contact with the skin and a large amount of the oil phase in the microemulsions might penetrate into the skin.^[3] In addition, because of the small droplet diameters of the microemulsions, the probable mechanism may also be the permeation of dexamethasone directly from the droplets into the stratum corneum without microemulsion fusion to the stratum corneum and subsequent permeation enhancement. The concentration of the mixtures of egg lecithin and IPA was 70% w/w in all preparations but their ratio probably influenced the permeation rates. Higher fluxes were observed for OO and NO formulations ($40.734 \mu\text{g}/\text{cm}^2/\text{h}$ and $36.0 \mu\text{g}/\text{cm}^2/\text{h}$). These microemulsion had S:CoS ratio of 1:3 and 2:1, respectively. Despite the fact that nutmeg oil had a larger droplet size, its permeation rate was not much affected, a phenomenon which needs to be analyzed. A microemulsion gel-based system of almond oil and linseed oil had a lower flux, i.e. 28.9 and $21.8 \mu\text{g}/\text{cm}^2/\text{h}$, respectively. IPA has a strong permeation enhancing effect by virtue of its ability to enhance the solubility of dexamethasone in the skin by disrupting the lipid bilayer of the skin.

The lecithin and IPA present act not only as a surfactant and stabilize the microemulsion but they also act as permeation enhancers. They probably interact with the intercellular lipids in the stratum corneum. IPA tends to fluidize the lipids thus increasing the permeation of dexamethasone.

Figure 2 shows the release profile of microemulsion formulations of dexamethasone in different oils and control preparations. Two sets of experiments were performed, i.e. without pretreatment of the skin with an abrading hydrogel (C, AO, OO, LO, and NO) and after pretreatment with an abrading hydrogel (CA, AOA, OOA, LOA, and NOA). It was observed that use of an abrading gel significantly increased the permeation rate of dexamethasone across the rat skin ($P < 0.05$).

The use of an abrading hydrogel of crushed apricot seed probably assisted in enhancing the drug permeation by removing the upper dead layer of skin, i.e. the stratum corneum. There was a 1.3–1.4-times increase in the

Table 3: Physicochemical parameters of tested dexamethasone-loaded microemulsions

Microemulsion oil	Droplet size (nm)	Viscosity (Poise)	Conductivity (S/cm, 10^{-6})	pH
Almond oil	4.2	172.5	9.1	4.5
Olive oil	10.8	162.9	8.9	4.1
Linseed oil	5.0	193.8	8.2	4.4
Nutmeg oil	12.7	166.3	9.6	4.7

permeation of dexamethasone across the rat skin after abrading the skin compared with the same formulation when applied without pretreatment. The flux of dexamethasone formulation NOA increased from 36.0 to 50.2 $\mu\text{g}/\text{cm}^2/\text{h}$, while that of formulation OOA increased from 40.7 to 54.9 $\mu\text{g}/\text{cm}^2/\text{h}$. Formulation OO showed an ER of 2.2 without pretreatment as compared with 1.2, 1.6, and 1.9 for LO, AO, and NO. The ERs and permeability coefficient values are reported in Table 4.

A maximum flux of 54.9 $\mu\text{g}/\text{cm}^2/\text{h}$ was achieved for formulation OOA after pretreatment with abrading gel and the total amount of drug delivered across the rat skin was 1283.5 $\mu\text{g}/\text{cm}$. The observed lag time reduced from 0.8 to 0.6 h after pretreatment of skin. There was a significant ($P < 0.05$) reduction of lag time on pretreatment of the skin with the abrading hydrogel.

This may be probably because the primary pathway of transdermally delivered drugs is paracellular, i.e. around the cells than through the elastin. Elastin is composed of collagen and hyaluronic acid and other lipids, which occupies the interstices between the cells of the top-most layer of the skin (i.e. the epidermis, including, e.g. stratum corneum,

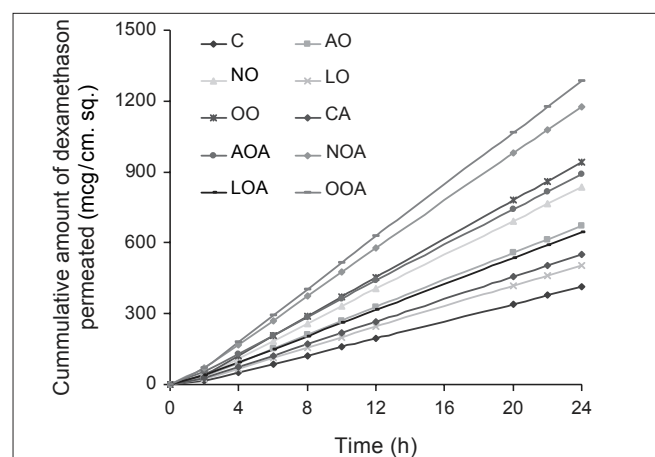


Figure 2: Permeation profiles of dexamethasone through the excised rat skins from the microemulsion-based gel formulations with different oils (mean \pm SD, $n = 4$)

lucidum, granulosum, spinosus) and must be dissolved and/or disrupted in order for the drug to be able to transverse through the viable skin to the subcutaneous tissues where the cutaneous plexi of the capillary net can be reached. Permeation of oil into the lipid layers of the skin may lead to the change in the lipid barrier properties. Further disruption of the stratum corneum barrier by the abrading agent might enhance the permeation by removing the upper dead stratum corneum.

In case of human subjects, it is desirable that the formulation delivers 0.5–9 mg of dexamethasone in 24 h. Therefore, the desired plasma levels can be achieved by employing a patch of size 6.8 cm^2 .

Pharmacological studies

Skin irritation studies

The skin irritation studies revealed that all formulations were nonsensitizing and safe for use.

In vivo anti-inflammatory effect

The microemulsion-based transdermal system showed a significant ($P < 0.05$) response in the carrageenan-induced paw edema inflammation model. The formulation demonstrated significantly improved activity compared with that of the control ($P < 0.05$) and improvement was measured in terms of paw edema volume 4 h after carrageenan injection.

The anti-inflammatory potential revealed that there was a significant reduction of paw swelling when compared with the results from the nonabraded skin. There was 62.2 and 73.6% reduction of paw volume for the microemulsion gel-based transdermal device for OOA and NOA, respectively, when applied after the pretreatment of the site of application with the abrading gel. NOA demonstrated a significant reduction ($P < 0.05$) in paw edema compared with OOA.

Comparative reductions in edema volume with respect to control are shown in Figure 3. A 32.7% decrease in paw inflammation was recorded when the control formulation was applied dermally after abrading the skin with the abrading gel thus clearly indicating the role of the abrading gel

Table 4: The permeation parameters of the dexamethasone-loaded microemulsion-based gel transdermal system

Microemulsion formulation code	Enhancement ratio		Permeability coefficient $\text{Kp}10^{-4}$ (cm h^{-1})	Lag time T_{lag} (h)
	w.r.t. control formulation	w.r.t. unabraded application		
C	1.0	1.0	18.1	1.1
CA	1.3	1.3	23.7	0.7
AO	1.6	1.0	28.9	0.7
AOA	2.0	1.3	37.9	0.4
OO	2.2	1.0	40.7	0.8
OOA	3.0	1.3	54.9	0.2
LO	1.2	1.0	21.8	0.8
LOA	1.5	1.2	27.4	0.5
NO	1.9	1.0	36.0	0.7
NOA	2.7	1.4	50.2	0.5

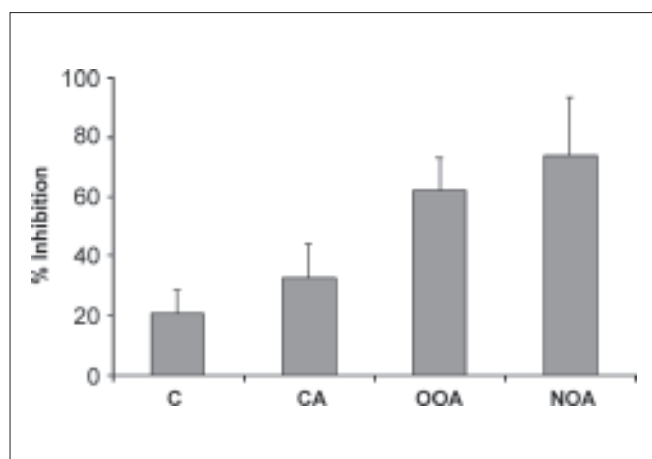


Figure 3: Anti-inflammatory activity of the microemulsion-based transdermal formulations of dexamethasone (mean \pm SD, $n = 4$)

enhancing the permeation. The effect of nutmeg oil over that of olive oil was more pronounced. NOA microemulsion formulation demonstrated 11.7% higher activity as compared with the olive oil-based microemulsion formulation. The transdermal microemulsion gel-based system thus has due potential to deliver dexamethasone at therapeutically effective concentrations.

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Source of Support: Nil, **Conflict of Interest:** None declared.