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ORIGINAL ARTICLE

Dithranol Loaded Transethosomal Gel System for the Treatment of Psoriasis: *In-vitro* and *Ex-vivo* Characterization

Rai Prateek, Singhai Nidhi Jain*, Khatri Kapil
Ravishankar College of Pharmacy, Ayodhya Bypass,
Bhanpur Square, Bhopal, MP 462037, India

ABSTRACT

Dithranol, is the most commonly prescribed topical anti-psoriasis drug for the management and treatment of various skin diseases including psoriasis. However, in cases of severe psoriasis, steady state availability of this drug is important to inner layers of the skin. Available marketed formulations of dithranol comprise of conventional cream, ointment or gel, which suffers from poor skin permeation. In the present investigation we attempted to incorporate dithranol loaded nano-transethosomes into the carbopol gel matrix system to maintain a constant availability of this drug to deep skin tissues. Firstly, transethosomes were optimized using 3 factors 3 levels factorial design and prepared using different lipid blends, dithranol using a cold addition method. Secondly, the developed dithranol loaded transethosomes system was characterized for average size, size distribution, and surface charge. Thirdly, after evaluation, the optimized transethosomes was incorporated into carbopol gel system to obtain dithranol loaded transethosomal gel. Finally, the developed gel system was characterized for pH, viscosity, gel strength and mainly the in-vitro dithranol release from the slide-a-lyser and ex-vivo permeation findings using excised rat skin. The dynamic light scattering measurement confirms the average size, size distribution and zeta potential of the developed dithranol loaded transethosomes. Further, the FTIR spectroscopy, validated the successful loading of dithranol in transethosomes and also, entrapment efficiency was found close to 95%. Transethosomes containing 3% carbopol w/w (F4 formulation) were assessed to determine their physiochemical properties, including their visual appearance, pH, and viscosity. Resulting viscosity, pH and gel strength of the F4 formulation was found to be 2224±20 N-s/m², 6.89±0.4 and 250.7±4.13 lbf/100ft², respectively. In-vitro release of dithranol from developed gel system was found significantly higher (>80 % in 12 h; p<0.001) as compared to conventional gel system (< 80% in 4 h). Finally, the ex-vivo skin permeation investigation revealed higher transdermal flux of optimized dithranol loaded gel (2.42±0.08 µg/cm²/h) as compared to conventional gel system (1.67±0.098 µg/cm²/h; p<0.001). A solution to poor skin permeation of dithranol was successfully provided in the form of topical gel incorporating transethosomal formulation. Sequential analysis revealed that the developed gel system was efficient to penetrate the deep skin tissue, thereby increasing the drug availability at the site of interest.

***Keywords**: Dithranol, Transethosomes, Dynamic light scattering, Ex-vivo skin permeation, In-vitro release, Transdermal gel.*

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INTRODUCTION

Psoriasis is a skin condition that can cause skin cells to proliferate up to 10 times faster than normal [1, 2]. Therefore, the skin becomes red, rough, and covered with white scales as a result. They may develop anywhere, but most commonly appear on the scalp, elbows, knees, and lower back [3-5]. Psoriasis cannot be transmitted from one individual to another. It may occur occasionally among members of the same family [6-8]. In most cases, psoriasis manifests in early adulthood and mostly impacts a few specific regions for most individuals [9-11].

Psoriasis may spread to significant areas of the body in severe instances and over the course of a person's life, the patches may heal and then reappear [12]. Psoriasis is a frequent, persistent condition that has no guaranteed treatment [13-15]. In most cases, it flares up for a few weeks or months, then subsides for a while or goes into remission [16-18]. Psoriasis is genetically transmitted, chronic inflammatory, immune-mediated disease that damages the whole body and is prone to recurrence [19-21]. Histologically, the

most prominent changes are neovascularization, hyperplasia of keratinocytes, and infiltration of inflammatory cells [22].

An important treatment method for psoriasis is topical application of anti-psoriasis drugs [23, 24]. In order to alleviate the symptoms of psoriasis, drug is applied directly to the afflicted skin and may relieve inflammation. One of the most widely used drug for the treatment of psoriasis is the dithranol and since its discovery in 1916, this drug has been used to treat psoriasis in clinical settings [25]. Since dithranol interacts with the electron transport chain on the inner mitochondrial membrane, a reduction in ATP synthesis is expected to occur as a result of dithranol's therapeutic effect [26]. Compared to oral and intravenous administration, topical administration of certain medications with a limited therapeutic window may reduce systemic absorption, minimizing unwanted systemic effects [27]. In addition, medications administered topically are slowly absorbed into the skin, which results in a longer duration of action, a reduction in frequency of administration, and an increase in patient compliance [28].

Although the stratum corneum (SC) restricts the amount of medication that is absorbed via the skin, this results in a low level of clinical effectiveness and a significant amount of drug waste after topical administration [29]. It has become more important to formulate medications using nanocarriers, such as microemulsions, lipid nanoparticles, and liposomes, in order to avoid poor penetration of pharmaceuticals into irritated skin [30-32].

Liposomes are tiny vesicles encapsulated in a phospholipid bilayer. In the case of fat-soluble medications, the drug may be dispersed throughout the bilayer of lipids, while water-soluble medications may be kept in the aqueous core [33]. There is a wide range of medications that can be contained within liposomes, and they are very biocompatible [34]. Liposomes are primarily responsible for increasing the SC's hydration [35]. By fusing with the SC, liposomes alter the SC's structure and disrupt its lipid arrangement, allowing the drug molecules they are encapsulating to diffuse into the intercellular spaces and pass through capillaries, improving the percutaneous absorption of drugs [36]. Traditional liposomes, however, are not capable of penetrating deep layers of the skin or fissures of the SC because of their rigid membranes. Upon exposure to the edge activators cholic acid, tweens, and spans, the phospholipid membrane becomes softer and more malleable. However, the addition of surfactants may reduce the biocompatibility of the liposome [37].

In context, ethosomes can be a strong alternative to conventional liposomes, which contains high concentration of ethanol (20-40%) [37]. Ethosomes were first described by Touitou, who distributed liposomes in solutions containing 20–45 percent small-chain biocompatible alcohols such as ethanol, propylene glycol, and glycerol in order to form deformable liposomes [38]. As a result, the phospholipid membrane becomes more fluid. Unlike traditional liposomes, ethosomes have increased percutaneous permeability, and their contents are retained in the skin for longer periods of time [39]. The ethosome, on the other hand, is a simple nanocarrier designed for topical distribution and does not precisely target the location of skin disease, but instead promotes the accumulation and diffusion of drug during topical absorption [40].

In the present investigation, we encapsulated the dithranol inside the transethosomes and then incorporated the dithranol loaded transethosomes to a Carbopol gel matrix and *in-vitro* release studied and *ex-vivo* skin permeation from excised goat skin to determine its skin penetration capabilities. The permeability via skin can be intensified more by transethosomes, which is appropriate for transdermal and intracellular drug administration. Transethosomes are being prepared for improved dithranol transdermal drug delivery.

MATERIAL AND METHODS

Materials

Dithranol was purchased from Yarrow Pharma Pvt Ltd Mumbai, India. Phosphatidyl choline, cholesterol and ethanol (purity 99.5%) were obtained from Himedia, Ahmedabad, India. Propylene glycol (PG) and sodium cholate were purchased from SD fine chemicals, Mumbai, India.

Optimization Using Box-Behnken Design (3^3: 3 factors 3 levels)

Full factorial *Box-Behnken* design was employed for the present work considering concentration of cholesterol, phosphatidyl choline and ethanol as independent variables and entrapment efficiency (%), particle size (nm) and zeta potential (mV) as dependent variables [41]. A design matrix is presented in Table 1.

Table 1: Full Factorial Box-Behnken Design Used for Optimization of Transethosomes Formulations

Factors (Independent Variables)	**Levels**
X1: Cholesterol	Low, medium and high (0.5%, 0.75% and 1%)
X2: Phosphatidyl Choline	Low, medium and high (2.5%, 2.75% and 3.0%)
X3: Ethanol	Low, medium and high (35%, 37.5% and 40%))
Responses (Dependent Variables)	**Desirability Constraints**
Y1: Entrapment Efficiency (%)	Maximize
Y2: Particle Size (nm)	Minimize
Y3: Zeta Potential (mV)	Maximize (as absolute value)

Preparation of Dithranol loaded Transethosomal Formulation

Three different formulations of transethosomes were prepared using the cold dispersion technique as reported previously [41]. The organic phase was obtained by dissolving dithranol and surfactant (sodium cholate) in ethanol at 30°C for 30 min (GME500 heating mantle). The aqueous phase (ultrapure water and propylene glycol) was heated to 30°C and then added to the organic phase dropwise with continuous stirring at 1250 rpm using a magnetic stirrer. The mixing continued for 45 min to get the transethosomal dispersions that were further subjected to a size-reduction process by sonication method using probe sonicator for 10 min and passed through a 0.2 µm pore size membrane using PTFE syringe filters. Schematic representation of the different stages and different compositions involved in the dithranol loaded transethosomal formulation are shown in figure 1 and table 2, respectively.

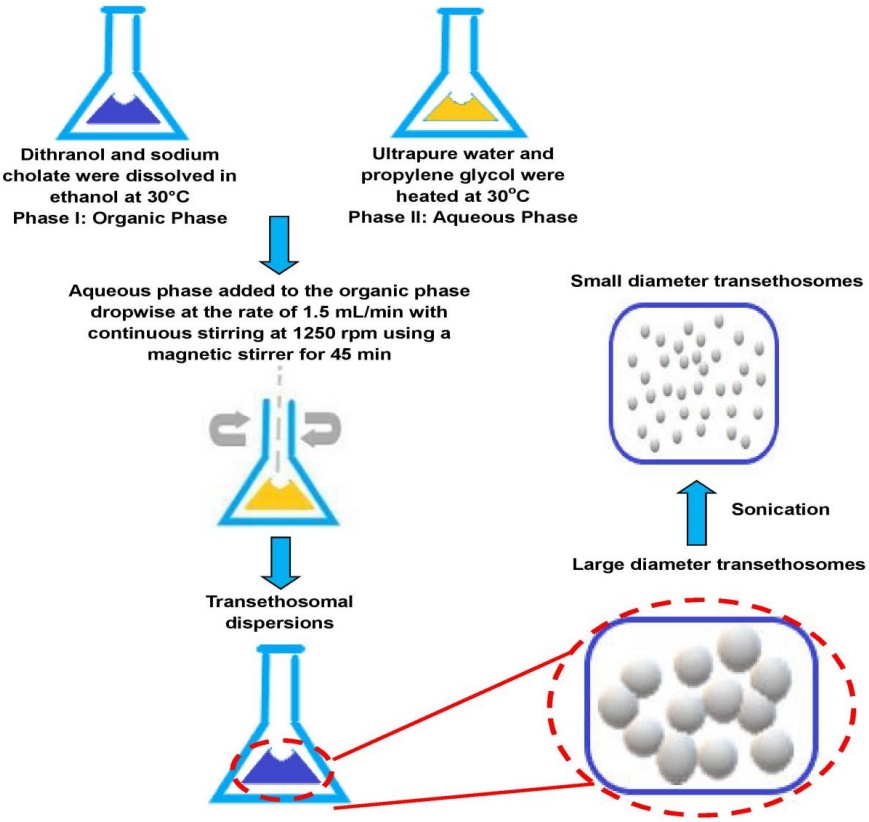


Figure 1: Step by step synthesis protocols for the formulation of transethosomes

Table 2: Composition of Different Transethosomes Formulation

Experimental Run	Cholesterol (% w/v)	Phosphatidyl Choline (%w/v)	Ethanol (%v/v)	Dithranol (%w/v)
ET1	0.5	2.75	35	1
ET2	0.5	3	37.5	1
ET3	1	2.5	37.5	1
ET4	**1**	**2.75**	**40**	**1**
ET5	0.75	2.5	40	1

Characterization of Dithranol Loaded Transethosomes

Attenuated Total Reflectance-Fourier Transform Infrared (ATR-FTIR) Spectroscopy

FTIR spectroscopy of dithranol loaded transethosomes were carried out using KBr pellet method using ATR-FTIR spectroscope (Prestige 21, Shimadzu Corp., Japan). The FTIR spectrum of dithranol loaded transethosomal gel was compared with FTIR peaks of reference literature. Various peaks in FTIR spectra were interpreted for the presence of different functional groups.

Vesicle Size, Size Distribution, and Surface Electric Charge Determination

The average particle size, size distribution (PDI) and zeta potential were analysed using Nano Partical zeta-sizer (Model No: SZ-100V2). Prior to the size and size distribution measurements, samples were diluted appropriately and then placed into quartz cuvette. Similarly, for surface charge determination, samples were diluted enough and were then placed into zeta cells. Dynamic light scattering technique was utilized by the instrument at backscattering at 90^0.

% Entrapment Efficiency

For the determination of entrapment efficiency, well-known ultracentrifugation technique was employed. Briefly, the different samples were first subjected to ultracentrifugation (Microspin TC-4815-D) at 25,000 g for 30 min at 4°C. The sediment was then collected and treated with triton X 100 (0.1% v/v). After filtration, the samples were analysed using UV spectroscopy (UV Spectrophotometer UV-1700 Shimadzu Japan) at 226 nm to estimate the concentration of dithranol.

Transmission Electron Microscope (TEM) Analysis

The surface topography and structural characteristics of developed formulation was seen under transmission electron microscope (TEM, TALOS F200S-FEI). Prior to the analysis, samples were made conducted using the coater and then kept aside for 24 h.

Preparation of Gel Using Dithranol Loaded Transethosomes

Gel base was prepared by dispersing carbopol 934 in distilled water and letting it stand overnight in the refrigerator [42]. After that, propylene glycol was dissolved in methyl paraben and propyl paraben, and then the mixture was added to the paraben solution. Triethanolamine was used in gel to maintain pH and regularity by dropwise mixing to get the final homogenous transparent gel base. Composition of different batches of gel containing dithranol loaded transethosomes are presented in Table 3.

Table 3: Composition of Different Gel Formulation Based on the Varying % of Carbopol 934, Methyl Paraben, Propyl Paraben and Propylene Glycol.

Formulation code	Carbopol 934 (%)	Methyl Paraben (%)	Propyl Paraben (%)	Propylene Glycol (%)
F1	2	4	4	2.5
F2	2.5	3.5	3.5	3.5
F3	2.75	4.5	4.5	2.25
F4	3	5	5	3
F5	2.25	3.5	3.5	2.75

In all the formulations transethosomes were added containing the 200mg equivalent of dithranol.

Physical and Biological Characterization of the Transethosomal Gel Containing Dithranol

Gel Viscosity Determination

For the determination of the viscosity, samples were analysed using digital Brookfield viscometer (DV-II, USA) equipped with spindle V-69 to 75. Briefly, the sample was placed in the beaker and then spindle was dipped up to the mark provided. After selecting the suitable range, and RPM, viscosity was measured as resistance to flow (% torque).

pH Measurement

pH of the different samples was measured using digital pH meter (ELICO.LI 610, Elico, Mumbai, India) at the room temperature. Briefly, the sample was placed in 10 mL beaker and the pH electrode was dipped into sample. The obtained readings on the digital display were recorded and experiments were repeated thrice to get average pH value.

Determination of Gel Strength

The gel strength was determined using the texture analyser (Brookfield CT3 Texture Analyzer, Mumbai, India). Briefly, the gel sample was placed in a 25 mL beaker and then, texture analyser probe was centrally immersed into it. The digital texture analyser was then set to 'gelling strength test' mode at test-speed of 0.5 mm/s and room temperature. As an important parameter, acquisition speed of 60 rotation per second with a trigger force of 5 g were chosen. A gel strength in terms of grams was calculated in order to determine the force required to penetrate the gel.

In-vitro Drug Release Investigation

The *in-vitro* drug release profiles of the dithranol from transethosomal gel and plain dithranol loaded gel formulations were studied using slide-a-lyser (Molecular weight cut-off 500 Da; 45 mL capacity; Thermo fisher scientific, Mumbai, India) membrane. For setting-up the assembly, the gel samples (1.5 mL each) were placed in the upper part of the lyser and the lower part was filled with citrate buffer (pH 5.8) as release medium. The lyser was kept rotating on magnetic stirrer at 100 RPM and temperature was set to 37±1°C throughout the investigation. Samples were withdrawn at different time intervals (0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 h) with subsequent analysis using UV spectrophotometer (UV-1700 Shimadzu, Japan) at 226 nm.

Ex-vivo Skin Permeation Investigation Using Excised Goat Membrane

For the *ex-vivo* skin permeation investigation, the excised goat intestinal membrane was used. Briefly, the excised goat intestinal membrane was first cleared from any excess fat and then stored in citrate buffer (pH 5.8) until use. A transethosomal gel containing 100 mg dithranol was applied to the excised skin and then stored in the donor compartment. A pH 5.8 citrate buffer was added to the receptor compartment and magnetic stirring was performed at 250 revolutions per minute at 37°C. Over the course of 8 h, the required sample was taken off at predetermined intervals and subsequently evaluated for dithranol concentration employing UV spectrophotometer at 226 nm. A similar procedure was carried out for the dithranol-loaded pain gel which was used for comparison purpose. The procedure adapted for the *ex-vivo* studies are duly approved by the institutional animal ethical committee as per the guidelines of the committee for the purpose of control and supervision of experiments on animals (CPCSEA), Govt of India vide letter no RCOP/IAEC/MARCH/2023/07.

Statistical Analysis

The statistical analysis investigation was conducted using the MS Excel 2019 and Graph Pad Instat® software's. The significance of the difference was estimated using 95 % probability values (P<0.05).

RESULT AND DISCUSSION

Optimization of Formulation Using Box-Behnken Factorial Design

Dithranol loaded transethosomal formulation was optimized by using 3^3 factorial designs. The results of the different experimental trails are shown in Table 4.

Table 4: Results of Optimization of Transethosomal Formulation Using Factorial *D*esign

Experimental Run	Particle Size (nm)	Zeta potential (mV)	PDI	Entrapment efficiency (%)
ET1	189 ± 2.3	-15.41 ± 1.6	0.48 ± 0.07	75.45 ± 2.13
ET2	193 ± 2.4	-17.30 ± 1.3	0.38 ± 0.06	67.23 ± 1.52
ET3	206 ± 2.6	-19.89 ± 2.1	0.36 ± 0.09	57.32 ± 1.42
ET4	**166 ± 1.8**	**-22.34 ± 2.3**	**0.18** ± 0.02	**83.48 ± 2.40**
ET5	181 ± 2.3	-22.40 ± 2.1	0.45± 0.07	73.38 ± 2.13

Date represented as mean ± SD (n=3)

The first step in the research process was to select three independent variables: cholesterol, phosphatidyl choline, and ethanol. A list of dependent variables was selected which included particle size, zeta potential, and entrapment efficiency. According to the design matrix, the model chosen was a 3^3 full factorial design. Based on our findings, all the tested parameters (response variables) except zeta potential showed a good correlation between the predicted and obtained values. Based on the negative predicted values of zeta potential, it is evident that the overall mean provides a more accurate representation of the response as compared to alone. This could be due to the fact that the surface charge

of the prepared transethosomes was not affected by the factors studied. In all responses, a precision greater than 4 is desirable as indicated in the 3D surface plot (Figure 1). The interaction factors plot is shown in Figure 2 were generated using the Design-Expert Software (Stat-Ease Inc., Minneapolis).

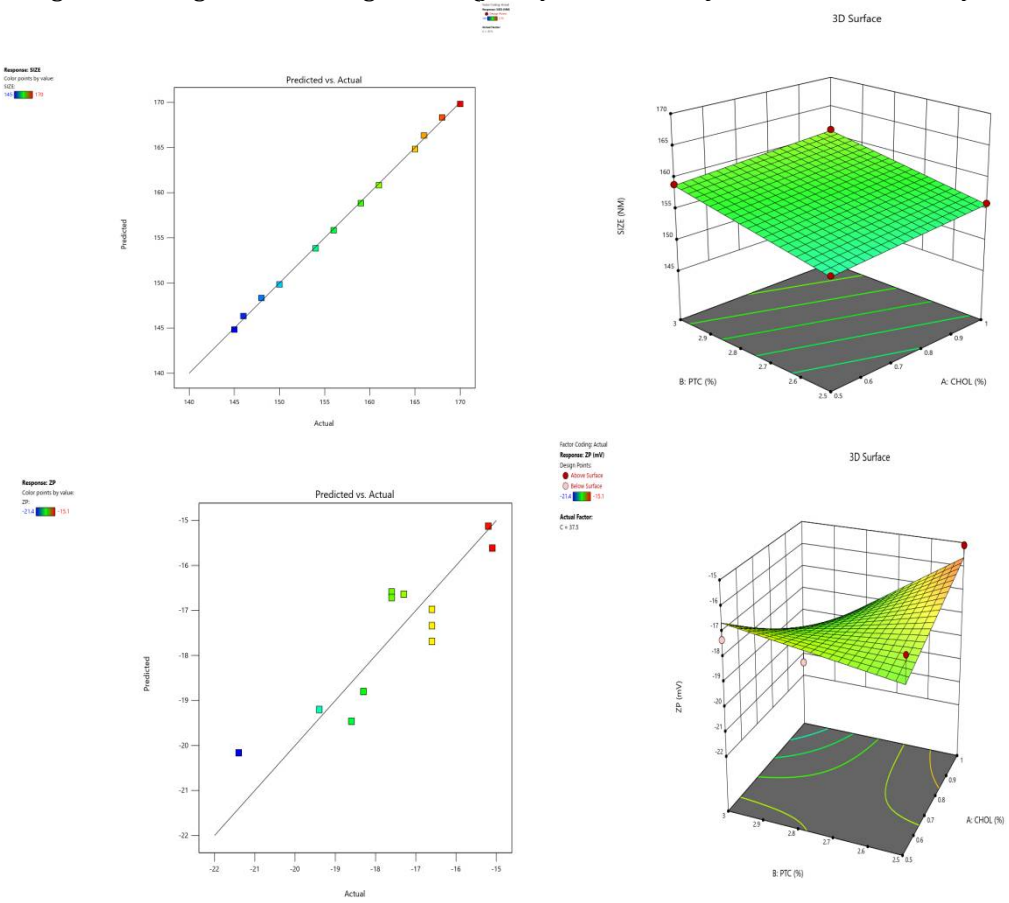


Figure 1. 3D Surface Response Plot

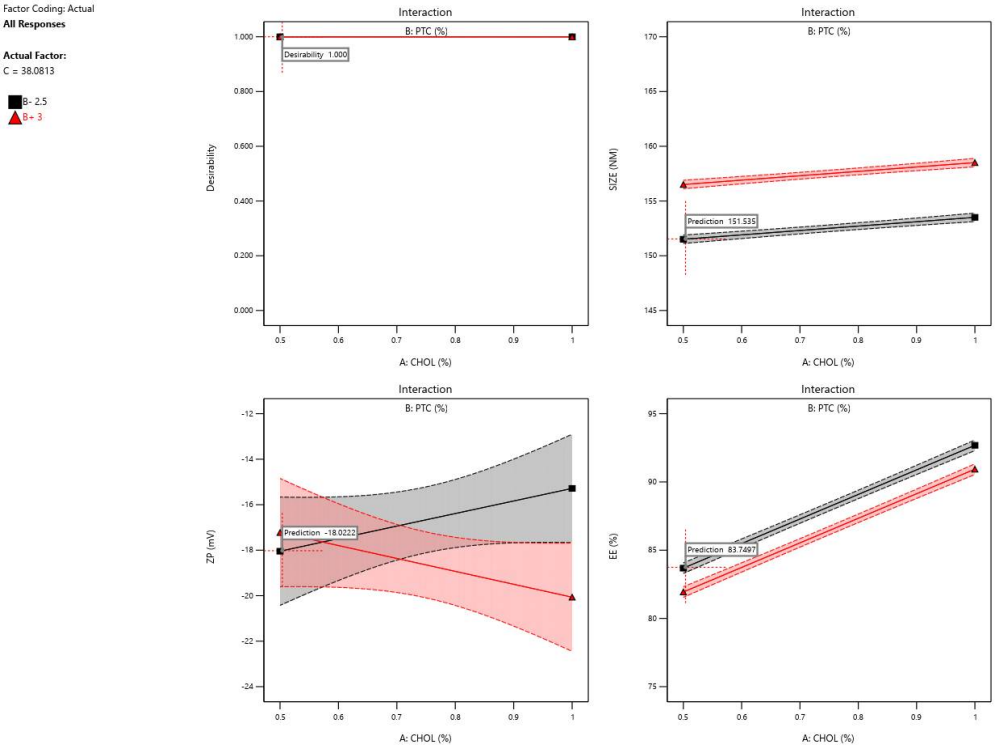
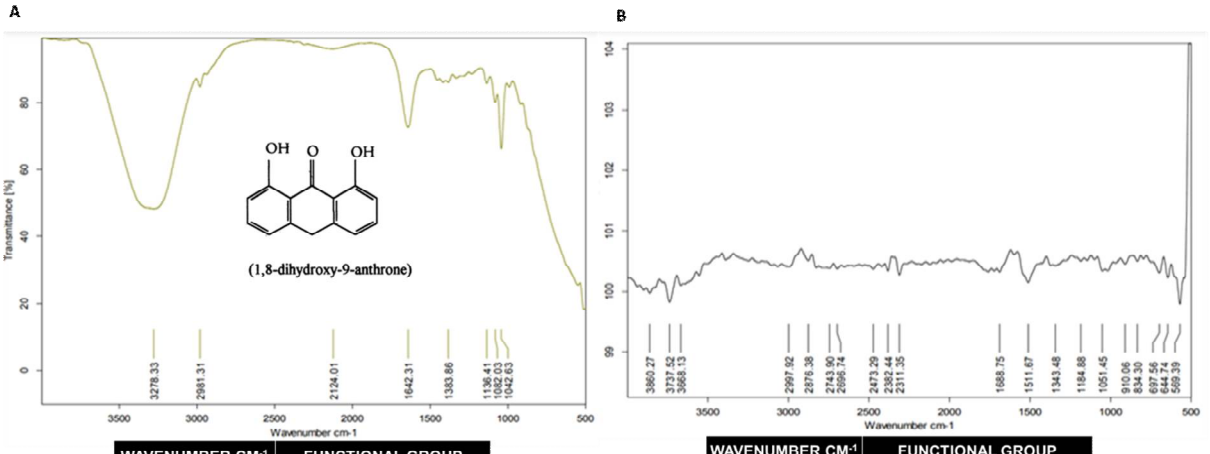


Figure 2. Interaction Plot

Formulation Characterization

FTIR Analysis

FTIR was carried out to confirm the formation of drug loaded transethosomes. As compared to Figure 3A (dithranol alone) the characteristic peaks of the dithranol are slightly invisible in Figure 3B (transethosomes), confirming the successful formation of the transethosomes and loading of dithranol in transethosomal vesicles. The data analysed using FTIR spectra are shown respectively with Figure 3A and Figure 3B.



WAVENUMBER CM^{-1}	FUNCTIONAL GROUP
1605.67	Aldehyde C-H stretching
1456.93	C=C str (aromatic)
1280.49	C=O stretching
1220.23	O-H bending (phenol)
1165.13	O-H bending (alcohol)

WAVENUMBER CM^{-1}	FUNCTIONAL GROUP
2940	C-H stretching
2865	C-H stretching
1729	C=O stretching
1626	C-H bending
1499	N-O stretching

Figure: 3A. FTIR spectra of dithranol alone. 3B. FTIR spectra of dithranol loaded transethosomes. Chemical structure of the dithranol is also given in the photograph A. ***Data represented as mean ± SD (n=3)***

Size, PDI and Surface Charge Determination

Size, PDI and surface charge results are shown in Table 3 and Figure 4 and Figure 5. As can be seen, formulation Et4 showed favourable results in terms of size (166 ± 1.8 nm), PDI (0.18 ± 0.02) and surface charge (-22.34 ± 2.3 mV).

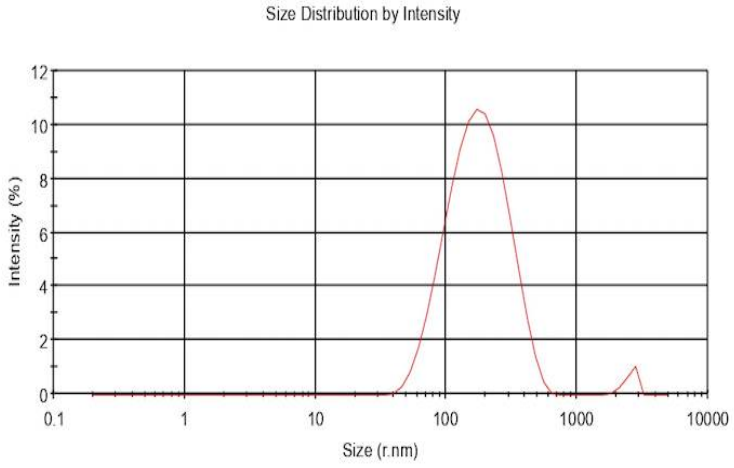


Figure 4: Particle Size of Optimized Dithranol Loaded Transethosomes (Et4)

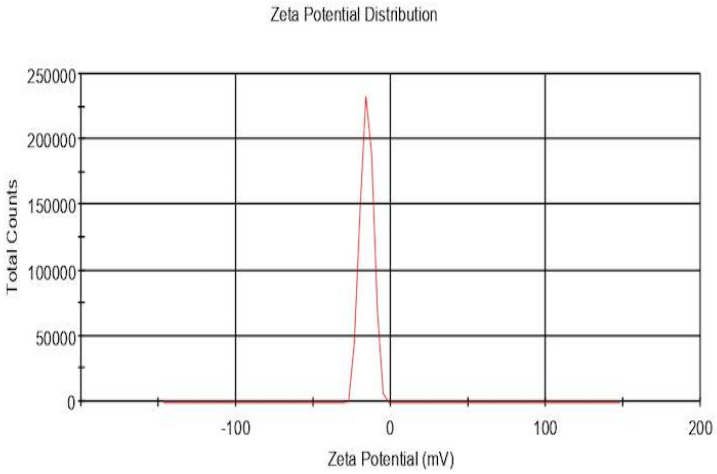


Figure 5: Zeta Potential of Optimized Dithranol Loaded Transethosomes (Et4)

Entrapment Efficiency

The ultra-centrifugation method was utilized for the estimation of entrapment efficiency of drug in developed formulations and the amount in transethosomes were calculated after taking absorbance of the samples using UV spectroscopy at 226 nm. As shown in Table 3, formulation Et4 displayed maximum entrapment (83.48 ± 2.4%), as compared to rest of the formulations.

Surface Morphology Analysis Using TEM

TEM revealed that the developed transethosomal formulation possesses the spherical structure (Figure 6). Also, the vesicles were found to be uniformly distributed in the suspension, further revealed its good PDI.

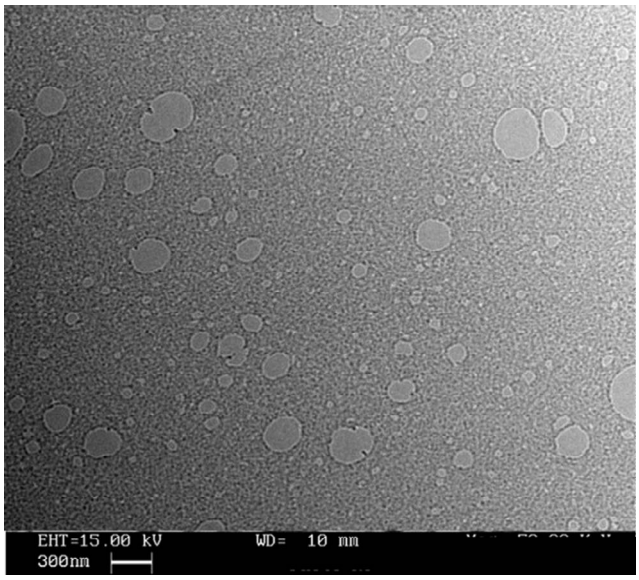


Figure 6: **TEM Photomicrograph of the Dithranol Loaded Transethosomes.** ***Data represented as mean ± SD (n=3)***

Optimization and Characterization of Transethosomal Gel

With the help of carbopol 934 as a gelling agent, a topical gel containing transethosomes loaded with dithranol was successfully formulated using a stirring method. We found that the method of preparing different transethosome gels was simple and robust. Initially, spectrophotometric measurements at 226 nm were conducted on transethosomal gels in an attempt to quantify the amount of dithranol entrapped. Transethosomes containing 3% carbopol w/w (F4 formulation) were assessed to determine their physiochemical properties, including their visual appearance, pH, and viscosity. Resulting data reveals that viscosity, pH and gel strength of the F4 formulation was found to be 2224 ± 20 N-s/m^2, 6.89±0.4 and 250.7 ± 4.13 lbf/100ft^2, respectively (Table 5).

Table 5: Rheological Properties of the Developed Drug Loaded Transethosomal Gel

Code	Viscosity at 50 RPM (N-s/m²)	pH	Gel strength (lbf/100ft²)
F1	1759 ± 25	6.12±0.2	175.1 ± 3.5
F2	1895 ± 64	6.32±0.3	170.53 ± 2.7
F3	2028 ± 24	6.78±0.2	350.23 ± 2.6
F4	2224 ± 20	6.89±0.4	250.7 ± 4.13
F5	1795 ± 36	6.78±0.1	190.18 ± 3.4

Data represented as mean ± SD (n=3)

In-vitro Release Investigation

Based on the optimization results of the transethosomal loaded gel formulations, F4 was further selected for the *in-vitro* release investigation. As can be seen in Figure 7, the dithranol from plain solution was completed released in just 4 h, revealing that dithranol requires a suitable matrix to hold it for getting continuous release. In contrast to the dithranol release from plain solution, only ~25 % was released in the same time (4 h). The release from the gel was less than ~50 % even after 8 h. The ~80 % of the dithranol was found to be released from the gel matrix in 12-13 h, revealing the capability of gel matrix to hold it comparatively for longer duration. This also signifies that the dithranol was well-encapsulated by the transethosomes for a longer period of time.

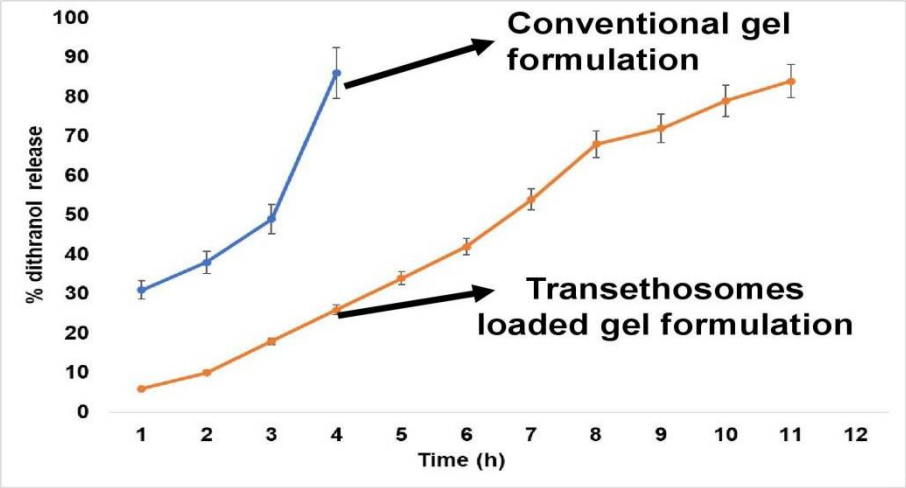


Figure 7: Comparative *In-Vitro* Release Investigation of Dithranol from Conventional Gel Formulation and Transethosomes Loaded Gel Matrix. *Data represented as mean ± SD (n=3)*

***Ex-Vivo* Permeation Studied Using Excised Goat Skin**

As can be seen in Table 6, the transdermal flux in case of conventional gel formulation was 0.321 ±0.03 µg/cm²/h after 10 h, whereas in the same time it was 0.689 ± 0.02 µg/cm²/h with the dithranol loaded transethosomes gel formulation. Similarly, the flux was 1.67 ± 0.098 µg/cm²/h after 24 h, whereas in the same time it was 2.42±0.08 µg/cm²/h with the dithranol loaded transethosomes gel formulation. The results clearly indicated the high capacity of the dithranol loaded transethosomes gel formulation to hold and release the drug constantly. The transethosomes are known to penetrate the skin owing to their small size, which contributed significantly in enhancing the transdermal flux through excised rat skin. Another reason for higher transdermal flux may be the presence of ethanol in the transethosomes, which is known to fluidize the skin, which in turn can increase the pore size and thereby enable the drug to permeate at faster rate.

Table 6: Transdermal Flux (µg/cm²/h) of Different Formulations.

Time (h)	Amount of Drug Permeated from Different Formulations (µg/cm²)	
	Dithranol in Conventional Gel Formulation (µg/cm²/h)	Dithranol Loaded Transethosomes Gel Formulation (µg/cm²/h)
0	0	0
10	0.321 ±0.03	0.689 ± 0.02
12	0.841 ± 0.11	1.14 ± 0.15
14	1.20 ± 0.05	1.68 ± 0.07
16	1.57 ± 0.10	2.1 ± 0.05
18	2.06 ± 0.09	2.68 ± 0.09
20	1.85 ± 0.08	2.53 ± 0.06
22	1.74 ± 0.12	2.48 ± 0.11
24	1.67 ± 0.09	2.42 ± 0.08

Date represented as mean ± SD (n=3)

CONCLUSION

Psoriasis is a genetically transmitted, chronic inflammatory, immune-mediated disease that damages the whole body and is prone to recurrence. In the present investigation, we attempted to delivery an FDA approved drug dithranol via first preparing its transethosomal nano-formulation and subsequently delivered it via fabricating carbopol gel system. Transethosomes were optimized using 3 levels full factorial design and then prepared using the cold addition method. The obtained nano-transethosomes were optimized for size, size distribution and surface electric charges. *In-vitro* dithranol release investigation showed its extended release over the 12 h using citrate buffer as media. Majorly, *Ex-vivo* skin permeation investigation on excised rat skin displayed a potential improvement in the dithranol permeation and transdermal flux in contrast to the dithranol loaded conventional gel. The permeation enhancing effect of transethosomes via gel system greatly contributed to the enhanced *ex-vivo* skin permeation. Our findings established that, transethosomes-mediated gel formulations may also be effective in delivering dithranol transdermally.

CONFLICT OF INTEREST

None

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REFERENCES

1. Armstrong, A.W., Read, C. (2020). Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. JAMA., 323(19):1945-1960.
2. Kamiya, K., Kishimoto, M., Sugai, J., Komine, M. & Ohtsuki, M. (2019). Risk Factors for the Development of Psoriasis. Int. J. Mol. Sci., 20(18):4347.
3. Armstrong, A.W., Mehta, M.D., Schupp, C.W., Gondo, G.C., Bell, S.J. & Griffiths, C.E.M. (2021). Psoriasis Prevalence in Adults in the United States. JAMA, Dermatol.,157(8):940-946.
4. Parisi, R., Iskandar, I.Y.K., Kontopantelis, E., Augustin, M., Griffiths, C.E.M., Ashcroft, D.M. & Global Psoriasis, Atlas. (2020). National, regional, and worldwide epidemiology of psoriasis: systematic analysis and modelling study. BMJ., 369:m1590.
5. Rendon, A., Schäkel, K. (2019). Psoriasis pathogenesis and treatment. Int. J. Mol. Sci., 20:1475.
6. Grän, F., Kerstan, A., Serfling, E., Goebeler, M. & Muhammad, K. (2020). Current Developments in the Immunology of Psoriasis. Yale J. Biol. Med., 93(1):97-110.
7. Raharja, A., Mahil, S.K., Barker, J.N. (2021). Psoriasis: a brief overview. Clin. Med. (Lond)., 21(3):170-173.
8. Sotiriou, E., Tsentemeidou, A., Bakirtzi, K., Lallas, A., Ioannides, D., & Vakirlis, E. (2021). Psoriasis exacerbation after COVID-19 vaccination: a report of 14 cases from a single centre. J. Eur. Acad. Dermatol. Venereol., 35(12):e857-e859.
9. Schadler, E.D., Ortel, B. & Mehlis, S.L. (2019). Biologics for the primary care physician: Review and treatment of psoriasis. Dis. Mon., 65(3):51-90.

10. Schäbitz, A., Eyerich, K. & Garzorz-Stark, N. (2021). So close, and yet so far away: The dichotomy of the specific immune response and inflammation in psoriasis and atopic dermatitis. J. Intern. Med., 290:27-39.
11. Strouphauer, E., Stolar, A., Tollefson, M. (2023). Manifestation of anxiety and depression among pediatric patients with psoriasis: A review, Pediatr. Dermatol., 40:11-18.
12. Uzelac, M. (2023). Diagnosis and management of psoriasis. AIDASCO Rev., 1(1):18-26.
13. Cather, J.C., Young, C.T., Young, M.S. & Cather, J.C. (2021). Ixekizumab for the treatment of pediatric patients with moderate to severe plaque psoriasis. Expert Opin. Biol. Ther., 21, 983-990.
14. Chen, Z., Wang, Y., Lan, X., Yang, M., Ding, L., Li, G., Hong, P., Bai, Y., Liu, Y. & Li, W. (2021). Nomogram for accurate and quantitative prediction of the risk of psoriatic arthritis in Chinese adult patients with moderate and severe plaque psoriasis. Eur. J. Dermatol., 499-507.
15. Gisondi, P., Geat, D., Pizzolato, M. & Girolomoni, G. (2019). State of the art and pharmacological pipeline of biologics for chronic plaque psoriasis. Curr. Opin. Pharmacol., 46:90-99.
16. Ji, C., Wang, H., Bao, C., Zhang, L., Ruan, S., Zhang, J., Gong, T. & Cheng, B. (2021). Challenge of nail psoriasis: an update review. Clin. Rev. Allergy Immunol., 61(3):377-402.
17. Naddei, R., Rebollo-Giménez, A., Burrone, M., Natoli, V., Rosina, S., Consolaro, A. & Ravelli, A. (2023). Juvenile Psoriatic Arthritis: Myth or Reality? An Unending Debate. J. Clin. Med., 12:367.
18. Narbutt, J., Niedźwiedź, M., Lesiak, A., Ceryn, J. & Skibińska M. (2023). Secukinumab for the Treatment of Psoriasis in Pediatrics: Patient Selection and Acceptability, Patient prefer. adherence., 17: 421-431.
19. Uppala, R., Tsoi, L.C., Harms, P.W., Wang, B., Billi, A.C., Maverakis, E., Michelle Kahlenberg, J., Ward, N.L. & Gudjonsson, J.E. (2021). "Autoinflammatory psoriasis"-genetics and biology of pustular psoriasis. Cell Mol. Immunol., 18(2):307-317.
20. Ogawa, K, Okada ,Y. (2020). The current landscape of psoriasis genetics in 2020. J. Dermatol. Sci., 99(1):2-8.
21. Winchester, R., FitzGerald, O. (2020). The many faces of psoriatic arthritis: their genetic determinism. Rheumatology (Oxford)., 59(Suppl 1):i4-i9.
22. Lowes, M.A., Suárez-Fariñas, M. & Krueger, J.G. (2014) Immunology of psoriasis. Annu Rev Immunol., 32:227-55.
23. Jyothi, S., Krishna, K.L., Ameena Shirin, V., Sankar, R., Pramod, K. & Gangadharappa, H.V. (2021). Drug delivery systems for the treatment of psoriasis: Current status and prospects. J. Drug Deliv. Sci. Technol., 62:102364.
24. Meng, S., Sun, L., Wang, L., Lin, Z., Liu, Z., Xi, L., Wang, Z. & Zheng, Y. (2019). Loading of water-insoluble celastrol into niosome hydrogels for improved topical permeation and anti-psoriasis activity. Colloids Surf. B. Biointerfaces., 182:110352.
25. Reich, K., Mrowietz, U. (2007). Treatment goals in psoriasis. J. Dtsch. Dermatol. Ges., 5(7):566-74.
26. Thaher, K.T.M.A. (2022). A Natural Anthraquinone Plants with Multi-Pharmacological Activities, Tex. J. Med. Sci., 10:23-32.
27. Song, Y., Yang, J., Wang, X., Chen, J., Si, D., Gao, H., Sun, M., Cheng, X., Wei, F. & Ma, S. (2022). Pharmacokinetics and metabolism of trans-emodin dianthrones in rats. J. Ethnopharmacol., 290:115123.
28. Kadian, V., Kumar, S., Saini, K., Kakkar, V. & Rao, R. (2020). Dithranol: An Insight into its Novel Delivery Cargos for Psoriasis Management. Curr. Drug Res. Rev., 12(2):82-96.
29. Benezeder, T., Painsi, C., Patra, V., Dey, S., Holcmann, M., Lange-Asschenfeldt, B., Sibilia, M. & Wolf, P. (2020). Dithranol targets keratinocytes, their crosstalk with neutrophils and inhibits the IL-36 inflammatory loop in psoriasis. Elife., 9:e56991.
30. Kapoor, D., Sharma, S., Verma, K., Bisht, A., Sharma, M., Singhai, N.J., Raval, N. & Maheshwari, R. (2022). Quality-by-design-based engineered liposomal nanomedicines to treat cancer: an in-depth analysis. Nanomed. (Lond)., 17(17):1173-1189.
31. Singhai, N.J., Maheshwari, R., Jain, N.K. & Ramteke, S. (2020). Chondroitin sulphate and α-tocopheryl succinate tethered multiwalled carbon nanotubes for dual-action therapy of triple-negative breast cancer. J. Drug Deliv. Sci. Technol., 60:102080.
32. Singhai, N.J., Maheshwari, R. & Ramteke, S. (2020). CD44 receptor targeted 'smart'multi-walled carbon nanotubes for synergistic therapy of triple-negative breast cancer. Colloids Interface Sci. Commun., 35:100235.
33. Maheshwari, R.G., Tekade, R.K., Sharma, P.A., Darwhekar, G., Tyagi, A., Patel, R.P. & Jain, D.K. (2012). Ethosomes and ultradeformable liposomes for transdermal delivery of clotrimazole: A comparative assessment. Saudi Pharm. J., 20(2):161-70.
34. Liu, P., Chen, G. & Zhang, J. (2022). A Review of Liposomes as a Drug Delivery System: Current Status of Approved Products, Regulatory Environments, and Future Perspectives. Molecules., 27(4):1372.
35. Nsairat, H., Khater, D., Sayed, U., Odeh, F., Al Bawab, A. & Alshaer, W. (2022). Liposomes: structure, composition, types, and clinical applications. Heliyon., 8(5):e09394.
36. Li, Y., Lofchy, L., Wang, G., Gaikwad, H., Fujita, M. & Simberg, D. (2022). PEGylated Liposomes Accumulate in the Areas Relevant to Skin Toxicities via Passive Extravasation across "Leaky" Endothelium. ACS Nano., 16(4):6349-6358.
37. Kuznetsov, D.M, Kuznetsova, D.A. & Zakharova, L.Y. (2022). Liposomes modified with borneol-containing surfactants for transdermal delivery of hydrophilic substrates. Russ. Chem. Bull., 71:1887–1896.
38. Jafari, A., Daneshamouz, S., Ghasemiyeh, P., & Mohammadi-Samani S. (2023). Ethosomes as dermal/transdermal drug delivery systems: applications, preparation and characterization. J. Liposome Res., 33(1):34-52.

39. Kumar, S., Kumar, A., Kumar, N., Singh, P., Singh, T.U., Singh, B.R., Gupta, P.K. & Thakur, V.K. (2022), *In vivo* therapeutic efficacy of Curcuma longa extract loaded ethosomes on wound healing. Vet .Res. Commun., 46(4):1033-1049.
40. Chauhan, N., Vasava, P., Khan, S.L., Siddiqui, F.A., Islam, F., Chopra, H. & Emran, T.B. (2022). Ethosomes: A novel drug carrier. Ann. Med. Surg. (Lond)., 82:104595.
41. El-Hashemy, H.A. (2022). Design, formulation and optimization of topical ethosomes using full factorial design: *in-vitro* and *ex-vivo* characterization. J. Liposome Res., 32(1):74-82.
42. Chandra, A., Aggarwal, G., Manchanda, S. & Narula, A. (2019). Development of Topical Gel of Methotrexate Incorporated Ethosomes and Salicylic Acid for the Treatment of Psoriasis. Pharm. Nanotechnol., 7(5):362-374.