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Effect of Sonication on the Characterization of Dapsone Ethosomal gel

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ABSTRACT

Objective: The objective of the present study was to develop and evaluate an ethosome based topical gel for enhanced transdermal delivery of Dapsone in order to improve drug permeation, stability, and therapeutic efficacy of drug.

Methods: Ethosomal formulations (F1–F9) were prepared and optimized based on vesicle size, zeta potential, and encapsulation efficiency. Drug–excipient compatibility was assessed using Fourier transform infrared spectroscopy (FTIR). Optimized ethosomes were incorporated into Carbopol 934-based gels (G1–G9) and evaluated for physicochemical parameters including drug content, pH, viscosity, and spreadability. In-vitro drug release and ex-vivo skin permeation studies were conducted to evaluate transdermal performance. Morphological characterization was carried out using transmission electron microscopy (TEM) and scanning electron microscopy (SEM). Stability studies were performed for three months.

Results: The prepared ethosomes showed vesicle sizes ranging from 110.2 to 176.7 nm, zeta potential values between −13.2 and −21.7 mV, and high encapsulation efficiency. Among all formulations, F3 exhibited the smallest vesicle size and optimal release behavior. The optimized ethosomal gel (G3) demonstrated high drug content (77.15%), suitable pH (7.2), and good spreadability. In-vitro and ex-vivo studies indicated sustained drug release up to 89.45% over 24 hours with enhanced skin permeation compared to conventional gels. TEM and SEM confirmed spherical vesicles with uniform distribution. Stability studies showed no significant changes in formulation characteristics.

Conclusion: The optimized ethosomal gel proved to be a stable and effective transdermal delivery system for DAP, offering improved drug release, skin permeation, and potential therapeutic benefits..

Keywords: *Ethosomes, Topical delivery, Ethosomal gel, Encapsulation studies, Drug diffuse study, Stability*

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INTRODUCTION

Topical drug delivery systems offer several advantages over oral administration, including avoidance of first-pass metabolism, reduced systemic side effects, and targeted drug action at the site of application.[1] However, the stratum corneum acts as a major barrier, limiting the penetration of many therapeutic agents, especially drugs with poor permeability.[2]

Dapsone (4,4′-diaminodiphenyl sulfone) is a potent antimicrobial and anti-inflammatory drug used in the management of acne vulgaris, dermatitis herpetiformis, and leprosy.[3] Despite its therapeutic potential, topical delivery of Dapsone is associated with limited skin penetration and irritation due to frequent dosing.[4] Hence, an advanced delivery system is required to enhance its penetration through the skin layers while minimizing adverse effects.

Ethosomes are soft, malleable lipid vesicles composed mainly of phospholipids, high concentrations of ethanol, and water.[5] The presence of ethanol increases vesicle flexibility and disrupts the lipid bilayers of the stratum corneum, thereby enhancing drug permeation.[6] Ethosomal systems have been widely explored for improving the transdermal delivery of both hydrophilic and lipophilic drugs.[7]

Incorporation of ethosomes into a gel base further improves patient compliance, residence time on skin, and ease of application.[8] Therefore, the present investigation was undertaken to formulate and develop a Dapsone-loaded ethosomal vesicular gel and evaluate its potential for enhanced skin penetration. In long-term therapies, the use of Dapsone has been associated with adverse gastrointestinal effects and even serious hematological effects such as hemolytic anemia, methemoglobinemia and agranulocytosis.[9] In this study, Dapsone was incorporated in the same nanostructure aiming to avoid microbial resistance problems and increase efficacy. This association in the same topical formulation becomes advantageous in leprosy not only due to the possibility of synergism of action but also because of improvements in the healing process since skin lesions are common in patients with leprosy.[10]

MATERIALS AND METHODS:

2.1. **Materials**:

Dapsone was purchased from Yarrow Chem Products in Mumbai, India. Cholesterol and Soy Lecithin were purchased from Central Drug House in New Delhi. Polypropylene glycol (PPG), Polyethylene glycol (PEG 400), Carbopol 934, Isopropyle myristate, Triethenolamine and Ethanol were purchaesd from SD Fine Mumbai. Distilled water was prepared by our lab.

2.2. Preparation of Ethosomes:

Dapsone loaded ethosome were prepared by the “hot method” followed by sonication.[11] An organic phase was prepared by dissolving 50 mg of dapsone in calculative amount of ethanol. A hot lipid mixture of phospholipid and cholesterol, as detailed in Table 1, was combined with the organic phase under continuous stirring at 700 rpm at 40° C. Propylene glycol in given concentration, Table 1 was added to the above organic-lipid mixture under continuous stirring. On the other side, the aqueous phase is heated. Then aqueous phase is slowly introduced to the hot organic-lipid phase, with continuous mixing until an ethosomal suspension formed. This suspension was ultrasonicated for given time duration (table 1) to reduce ethosome size and allowed to stabilize for 30 minutes. The formulation was stored at 4-8 °C for later use.

Table 1: Formulation design of all ethosomal formulations

S.No.	F.Code	Ingredients							
		Ethanol (ml)	Propylene Glycol (ml)	Cholestrol (mg)	Phospholipid (mg)	Water (20ml)	DAP (mg)	Stirring RPM	Sonication Time
1.	F1	7.5	3	25	100	Q.S.	50	700	5
2.	F2	7.5	2	25	100	Q.S.	50	700	10
3.	F3	7.5	1	25	100	Q.S.	50	700	15
4.	F4	10	3	25	200	Q.S.	50	700	5
5.	F5	10	2	25	200	Q.S.	50	700	10
6.	F6	10	1	25	200	Q.S.	50	700	15
7.	F7	5	3	25	300	Q.S.	50	700	5
8.	F8	5	2	25	300	Q.S.	50	700	10
9.	F9	5	1	25	300	Q.S.	50	700	15

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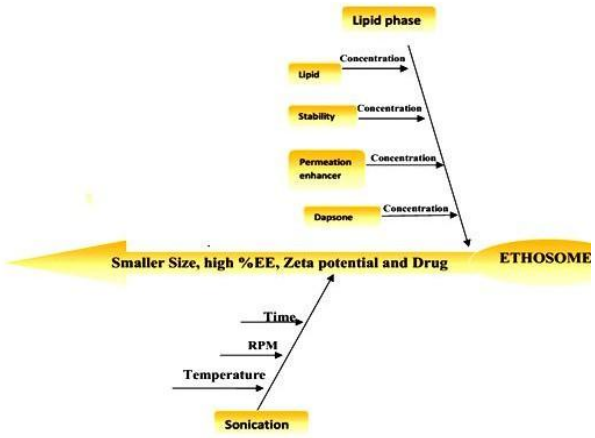

Figure 1: Effect of Sonication on Vesicles

2.3. Physicochemical characterization of ethosome formulation:

2.3.1. Drug-Excipient compatibility Analysis:

The infrared range is imperative evidence which provide an adequate data about the structural compatibility with the compound.[12] During analysis, physical mixture was placed under probe, FTIR spectrum was recorded to analyzed for the changes in peaks. The FTIR study was done by using Perkin Elmer Spectrum and the scanning range was fixed in the range of 400-4000 cm- [1] at room temperature.

2.3.2. Droplet size, size distribution, and zeta potential:

The aliquotes of ethosomes were diluted in ultrapure water (1 :10v/v) to determine the mean droplet size, PDI and Zeta potential using (Nano-ZS, Malvern instrument, Malvern, U.K.). Before loading the cell into the instrument, cautiously wipe the estimating windows with lens paper, it was recommended to keep running in manual mode and started at a low voltage.[13]

2.3.3. Encapsulation study:

The encapsulation efficiency was evaluated through the centrifugation technique. 10 ml of ethosomes dispersion was transferred into a cold centrifuge (R-4 C, Remi centrifuge, Vasai, India) at 15,000 rpm for 60 min at 4ºC. The untrapped drug is separated, and supernatant liquid is obtained. The amount of entrapped ethosomes was examined by U.V. Spectroscopy (Pharma spec 1700, Shimadzu, Japan) and was calculated by using this equation.[14]

$$\%\ \textbf{Entrapment Efficiency} = \frac{\textbf{Total amount of drug} - \textbf{amount of free drug}}{\textbf{Total amount of drug}} \times 100$$

2.3.4. *In-vitro* drug release study:

A Diffusion cell (Dinesh scientific, New Delhi) was used in this study, with cellophane membrane for the release profile.[15] 1ml of ethosomes was applied to the membrane, and the donor compartment was filled with 15ml 6.8 pH buffer. The setup was placed on a magnetic stirrer (Bharat Electrical Industries, Varanasi), where the solution 6.8 pH buffer in the receptor compartment was stirred at 50 rpm using a magnetic bead, maintaining a temperature of 37°C±5ºC. 1 ml samples were collected and replaced with an equal volume of fresh dissolution medium. The drug concentration of aliquote was withdrawn at different time intervals of 0, 0.5, 1, 2 upto 24hr and analyzed at 293 nm by using a UV spectrophotometer (Pharma spec 1700, Shimadzu, Japan) .[16, 17]

2.3.5. Vesicular shape and surface morphology:

The optimized samples are visualized by scanning electron microscopy (JEOL Jsm – 6490LV, scanning electron microscope, Japan.) to give 3D image of the globules.

2.4. Formulation of Ethosomal gel:

Optimized vesicle F3 is used for formulation of a gel by using dispersion method.[18] Carbopol 934 is add in aqueous phase (1% w/v) with continuous stirring at 25ºC followed by the addition of 1ml isopropyl myristate with continuous stirring at 500 rpm with due care to avoid air entrapment. The pH was adjusted by adding small amount of triethanolamine. [19] After that, final volume was adjusted by addition of PEG 400. Different formulation design was prepared as given in Table 2.

Table 2: Formulation design of gel formulation:

F.Code	F3 Formulation (100mg~01ml)	Carbopol 934(mg)	PEG 400(ml)	Isopropyle Myristate (ml)	Triethenolamine (0.5ml QS)	Water (10 ml QS)
G1	100	10	1.25	1	Q.S.	Q.S.
G2	100	10	2.5	1	Q.S.	Q.S.
G3	100	10	5.0	1	Q.S.	Q.S.
G4	100	30	1.25	1	Q.S.	Q.S.
G5	100	30	2.5	1	Q.S.	Q.S.
G6	100	30	5.0	1	Q.S.	Q.S.
G7	100	50	1.25	1	Q.S.	Q.S.
G8	100	50	2.5	1	Q.S.	Q.S.
G9	100	50	5.0	1	Q.S.	Q.S.

2.5. Evaluation of ethosomal gel formulation:

2.5.1. Drug content of ethosomal gel:

100 mg of optimized ethosomal gel is dissolved in a 10 ml of methanol by using probe sonicator (Hicon Products India Private Limited) until the complete solubility was not reached.[20] The solution was then filtered and analyzed using a UV spectrophotometer (Pharma spec 1700, Shimadzu, Japan) at 293 nm.

2.5.2. Spreadibility:

The spreadibility of gel is calculated by take 1g of the optimized ethosomal gel is placed between two glass plates, and a weight is applied to one of the plates to simulate pressure. The spreadability is determined by measuring the area covered by the gel after applying a 1gm force.[20]

2.5.3. pH:

The pH can be measured using a **digital pH meter (**Hicon, Grover Enterprises, New Delhi). 1g optimized ethosomal gel is dissolved in buffer solution 5.5 pH, and the pH of the resulting solution is measured.[18]

2.5.4. Viscosity:

Viscosity of prepared formulations was prepared carried out by Brookfield Viscometer (Synchro Electric Viscometer).10g of sample was taken in a appropriate beaker, and dipped it in spindle groove no. 4 at 0.3 rpm for a predetermined duration of 3 min. The spindle was then rotated in the gel until a constant reading in the viscometer was displayed. Repeat the method until average value is obtained.[21, 22]

2.5.5. In-vitro drug release study of ethosomal gel:

The drug release studies were carried out using modified franz diffusion cell.[23] The cellophane membrane was mounted on the Franz diffusion cell. 10 mg optimized ethosomal gel was applied through donor compartment on the cellophane membrane. The reservoir compartment was filled with 15 ml phosphate buffer of pH 6.8. The study was carried out at 37± 1°C at 50 rpm for 8 hrs. Samples were withdrawn from reservoir compartment at periodic interval of 24 hrs, solution was replaced with fresh buffer to maintain a sink condition. The content was analyzed was measured spectrophotometrically at 293 nm for Dapsone.

2.5.6. Stability studies:

Vesicles were stored in a glass vial under static conditions $40^0C \pm 3^0c$ at 75% RH in glass bottle over a period of 0, 1, 2 and 3 months. The samples were collected and evaluated for PDI, Particle size, Zeta potential and %EE.[24]

2.5.7. FTIR spectral analysis:
The FTIR of pure drug, physical mixture and optimized formulation was carried out to ascertain the identify of drugs. The 10 mg of the optimized sample was placed on the NaCl plate, and the FTIR spectrum was recorded to analyze the changes. The sample was scanned between wave number 400-4000 cm- [1] at room temperature, using Perkin Elmer Spectrum and.

2.5.8. TEM Analysis:
The surface morphology was determined by transmission electron microscopy (TEM; Tecnai 20, Philips, Eindhoven, The Netherlands). TEM provides detailed, high magnification quality and stability of vesicular drug delivery systems, helping to ensure their efficacy to examine the surface morphology, size and shape.

2.5.9. *Ex-vivo* permeation studies of ethosomal gel:
Ethosomal permeation was assessed using a Franz diffusion cell with an effective surface area of 1.76 cm² and a receptor volume of 15 ml. Conventional gel were used as reference to study the effect of ethosomal formulation on drug diffusion. The abdominal skin from male wistar rats was pre-equilibrated in PBS (pH 6.8) for 30min. The skin was mounted on the receptor compartment with the stratum corneum facing upwards into the donor compartment, which was then applied with the ethosomal formulation. 15 ml of PBS (pH 7.4) phosphate-buffered saline was used as the receptor medium, and 1% PEG 400 to maintain sink conditions. It was agitated continuously at 700 rpm at 37 ±2ºC throughout the experiment. The sample (~50mg drug) was placed in donor compartment, at specific time interval withdrawn and replacement with fresh buffer. The drug content of samples was analyzed using UV spectrophotometry.[25]

3. Result and Discussion:
3.1 : Compatibility study:
The compatibility study was confirmed with the help of FTIR. Individual samples of drug and excipient and a combination of physical mixture were prepared and analysed for any interaction. The FTIR spectra confirmed the absence of any chemical interaction between the drug and excipients, as shown in Figure 2.

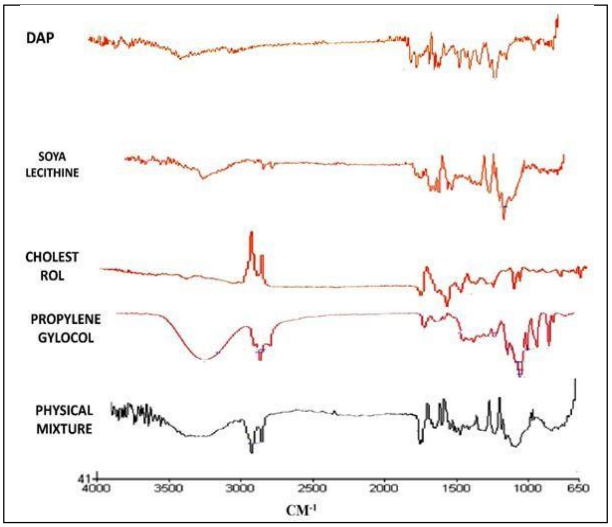

Figure 2: Drug-Excipient compatibility analysis by FTIR Spectra

3.2 Droplet size, size distribution, Zeta potential, pH and Encapsulation Efficiency
The vesicle size, size distribution, zeta potential of various formulation (F1-F3) was studied and presented in Table 3 and Figure 3. was ranges from 110.5 to 176.7 nm. Results show that as the concentration of alcohol increases, 5 to 10ml, the vesicle size decreases. Meanwhile, an increase in alcohol concentration from 7.5 to 10ml increases vesicle size; greater alcohol levels may promote bilayer leakage, resulting in a modest increase in vesicular size and a substantial reduction in % entrapment efficiency.[22] The phospholipid concentration increased from 100-300mg, and the vesicle size slightly increased due to increased phospholipid molecules in the vesicle bilayers where drug is situated.[22] However, all the ethosome formulations had PDI of 0.3 or less than 0.3 showing narrow vesicle distribution and good homogeneity. Due to the ethanol system, their vesicular charge was shifted from positive to negative, and the zeta potential values were found to be – 13.8, -17.9, -21.7mV. The encapsulation of the vesicles is shown in Table 3, at higher ethanol concentration (10ml), the %EE shows decrease in results (49.07 to 58.98%) in comparison to 7.5 ml of ethanol concentration. This could be due to the ethanol ability of leaking of entrapped drug.[23] This increased %EE i.e., 61.43 to 71.91% at 10ml concentration is likely due to the enhanced solubility of the drug in the ethanol within the ethosomes.[26] Owing to small vesicle size, low PDI, zeta potential lower than -30Mv, and high %EE the ethosome with F1-F3 was chosen for further development. The higher the effect of sonication time (15min) during preparation, the vesicle size is small, slightly increase in PDI is observed because the sonication round process breaks coarse drops into nanodroplets. Meanwhile, the zeta potential altered with the length of sonication time .[26] Therefore, ethosomal formulation (F1-F3) exhibiting a small vesicle size, low PDI, high zeta potential, and high entrapment efficiency (%EE) was selected as the optimized formulation.

Table 3: Entrapment, vesicle size and Zeta potential value of all formulations

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Size(nm)	110.2	176.7	116.3	132.7	145.5	134.2	158.4	171.5	154.7
PDI	0.25	0.25	0.32	0.39	0.37	0.21	0.32	0.27	0.34
ZP(MV)	-20.3	-17.9	-21.7	-13.8	-15.1	-13.2	-19.5	-16.4	-18.3
pH	4.7	5.6	4.2	7.1	6.8	5.2	4.9	5.3	6.9
%EE	61.43	65.29	71.91	58.98	49.07	52.19	68.85	71.04	70.06

(mean±SEM, n=3)

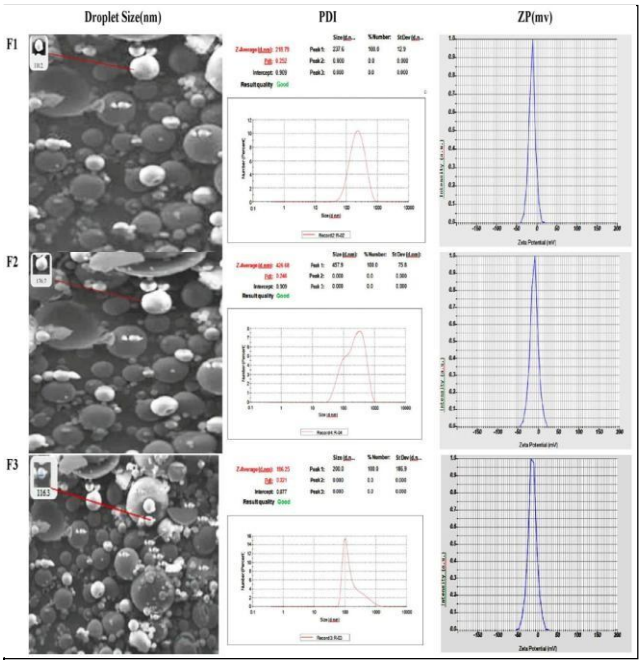

Figure 3: SEM, Particle size, PDI and ZP of optimised vesicle (F1-F3)

3.3 In-vitro drug release study
The in-vitro drug release profiles of Dapsone from the optimized batches (F1, F2, and F3) at ph 6.8 were measured by plotting the cumulative percentage of drug released over time, as shown in the Figure 4. The study showed an initial burst release of approximately 32.54%, 29.98%, and 20.58% in F1, F2 and F3, respectively, within the first hour. This was followed by a sustained release, with the maximum drug release observed over 24 hours. On the basis of results, F3 is selected to formulate as a gel.

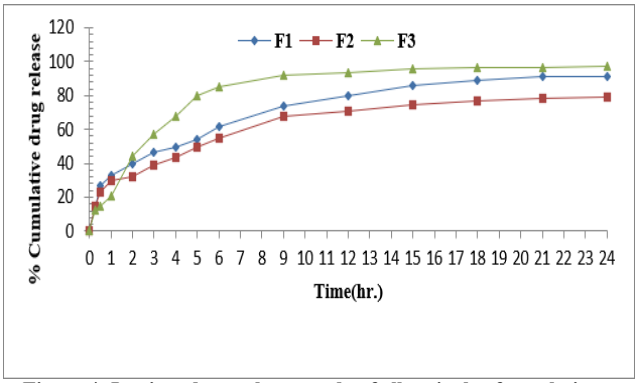

Figure 4: In-vitro drug release study of all vesicular formulations

3.4 Vesicular morphology:

Scanning electron microscopy of ethosome was shown in Figure 3, was spherical in shape with gnarled surface. By comparing all the vesicle sizes, we observed that F3 showed the smallest particle size, having a diameter in 110.3 nm. This confirms the existence of vesicular structure at 7.5 ml ethanolic concentration, resulted in decrease in vesicle size. However, ethanolic concentration interpenetrates the lipid bilayer leading to thinner of membranes. It also introduces a net negative energy to the ethosomal system and may alter steric stabilization contributing to the reduction in vesicular size.[27] The analysis also confirms the smooth surface of the ethosomes indicating uniformity and stability.

3.5 Characterisation of ethosomal gel

Ethosomal gel was prepared by using Carbopol 934 as a polymer, and the prepared gel was surface exhibits a notably smooth texture as shown in Table 4, free from any visible imperfections or roughness. The consistent texture enhances the overall appearance and indicates that the material has been carefully processed to achieve a refined, even finish. It was characterized by measuring % drug content, pH, viscosity, and spreadability are shown in Table 4. These values fall within the normal physiological pH range of the skin (3.0–9.0), indicating that the ethosomal gels are non-irritating and safe for topical application. The drug content plays a vital role in determining the effectiveness and performance of drug-loaded particles. It directly impacts the therapeutic potential and stability of the formulation. The drug content of the prepared formulation was found to be greater than 70% which revealed a uniform distribution of drugs throughout the formulation, and the drug loss during the gel formulation was minimal. From the results, it was observed that spreadability decreases (8.68g/cm^2 to 12.68g/cm^2) with increase in carbopol concentration (10-50mg). This indicates that Carbopol provided spreadable gels by shearing force of low magnitude. The gel prepared by 10mg Carbopol (G1-G3) showed viscosity of 35,758-45,223 cps while those prepared by 50mg Carbopol shows 47889 cps. However, increase in carbopol concentration results in greater restriction for the distance traveled by gel owing to the increased viscosity of the polymer. Furthermore, the result could be correlated to the mechanism of gelling occur by Carbopol, which bind with the solvent strongly, establishing cross-linking.[28]

Table 4: Evaluation parameter of ethosome loaded gels.

S.No.	Formulation Code	Visual Inspection	% Drug Content	Spreadability(g/cm^2)	pH	Viscosity(centipoises)
1.	G1	Smooth Texture	72.04	10.78	7.0	35758
2.	G2	Smooth Texture	79.51	12.05	7.4	34158
3.	G3	Smooth Texture	76.88	12.68	7.0	45223
4.	G4	Smooth Texture	81.28	11.05	6.8	45778
5.	G5	Smooth Texture	84.56	11.05	6.9	44158
6.	G6	Smooth Texture	69.24	11.78	6.0	42523
7.	G7	Smooth Texture	67.45	09.05	6.4	46115
8.	G8	Smooth Texture	64.21	10.05	6.8	47689
9.	G9	Smooth Texture	77.15	08.68	7.2	47889

(mean±SEM, n=3)

3.6 In-vitro drug release study of gel

The drug release profiles of optimized formulation (G1-G3) were assessed for predicting the in-vivo performance. Increased drug permeation indicates high vesicular penetration because of ethanol in the core, which solubilizes the lipid. The presence of ethanol in the ethosomal system imparts flexibility, enhancing membrane diffusion and reducing the hydration layer around vesicles, thereby facilitating drug permeation.[29] Figure 5, shows the release profile of optimised ethosomal gel, revealing % cumulative drug release from different formulations (G1-G3), ranging from 73.17 to 88.68%. These results revealed that reduced concentration of polymer (10mg) hinders drug release owing to multi-lamellar vesicles formed at lower polymer concentration. In contrast, greater concentration (5ml) of hydrophilic surfactant (PEG-400) with high HLB has a positive effect on drug release due to its great solubilising power on the hydrophobic drug. It may fasten the release due to more arrangement, stability, and sustained leakage of the prepared vesicle.[28] This release pattern shows first-order and Korsemeyer-Peppas kinetics, indicating that the release of drugs from the gels is regulated by Fickian diffusion and erosion as the drug release mechanism.[30] Based on the results, the formulation G3 released about 3/4th of the loaded drug in 9 hours, i.e., 60.42% was selected as the best formulation due to its ability to achieve the desired flux and demonstrate significantly higher cumulative drug release compared to the other formulations, as shown in Figure 6

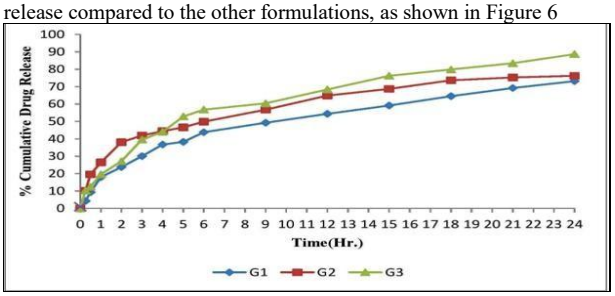

Figure 5: Drug release study of optimized gel formulation (G1-G3)

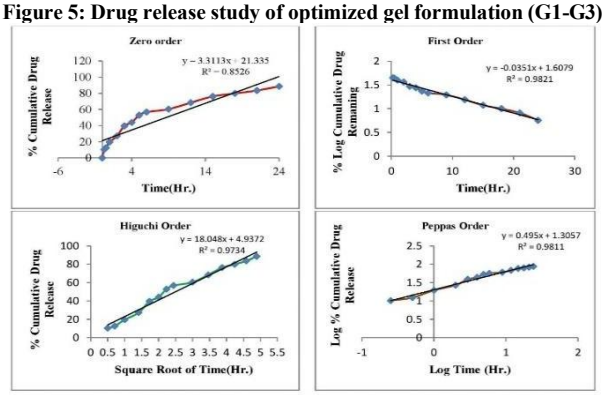

Figure 6: Release kinetics of optimized gel (G3) formulation

3.7 Stability study

The stability study was undertaken in the investigation of the stability of topical gel formulation strategies as per ICH guidelines .[31] The stability studies for the optimised the formulations G3 gel formulation were conducted for three months. The study results indicated that no significant changes were observed for the analyzed parameters, Figure 7. Additionally, no microbial contamination was found during the analysis period.

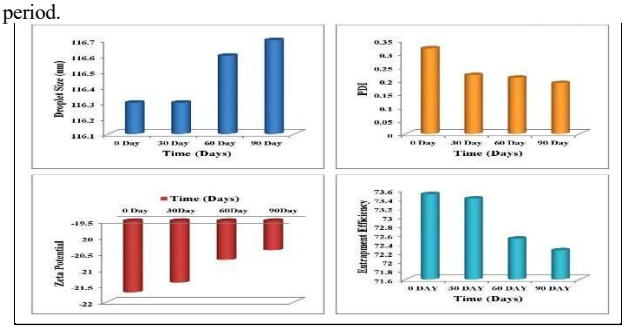

Figure 7: Droplet Size, PDI, Zeta potential and Entrapment Efficiency of G3 for three months at 40^{0}C ± 3^{0}c at 75% RH

3.8 FTIR Spectral Analysis:

To investigate the presence of organic functional groups in the optimized gels (G1-G3), FTIR studies were conducted. The results indicate the presence of characteristic absorption band of drug is present in optimized G3 formulation, shown in Figure 8. The spectrum also displays no major change in the position of peak of drug in the G3. This result revealed that there is no possible interaction between drug and excipient.

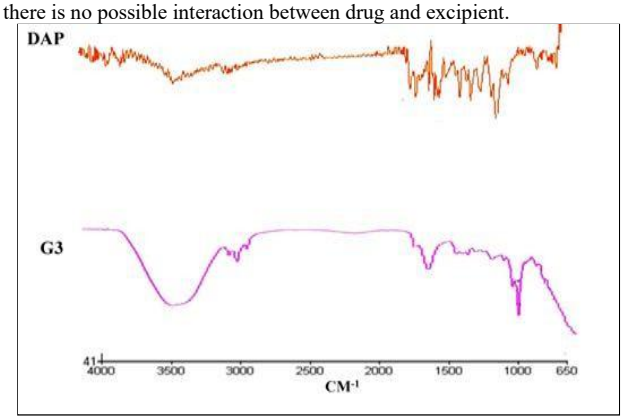

Figure 8: FTIR spectra of pure drug dapsone and optimised gel (G3)

3.9 TEM Analysis:

The photomicrograph of the optimized gel (G3) is shown in Figure 9. The globules exhibit a dark spherical disc appearance, with diameters ranging from 105 to 185 nm for G1, G2, and G3, respectively. Among the three formulations, G3 demonstrated the narrowest size distribution, which can be attributed to the inclusion of 10 mg of Carbopol and 5 ml of PEG 400. This combination contributed to a reduction in globule size, confirming the formation of a vesicular structure.

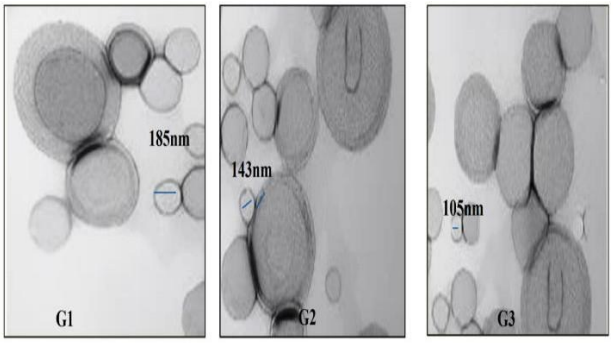

Figure 9: TEM Analysis of optimized gel (G1-G3)

3.10 Ex-vitro skin penetration study of optimized formulation:

To penetrate the stratum corneum is the use of vesicular systems, particularly ethosomes. Ethosomes were found to be capable of increasing the drug's residence time in the epidermis, which could potentially enhance its permeation.[32] In order to understand the ability of the ethosomal gel to aid drug permeation through the skin, ex-vitro studies were conducted for optimized formulation (G1-G3) and compared with conventional drug loaded gel (CG) to present better comparison of the permeation behaviour through the pig abdominal skin with franz diffusion cell as shown in Figure 10.

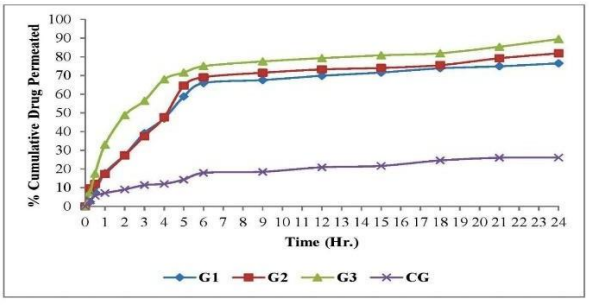

Figure 10: Cumulative percentage of drug permeated via pig abdominal skin vs time profile of ethosomal gel (G1-G3) and conventional gel (CG).

In contrast from the results that the ethosomal gel (G1-G3) have a significantly longer release (76.5±0.45, 81.5±0.33, 89.45±0.27%) in comparison to conventional gel, GG (26.09±1.17%) in 24hr. This demonstrated that prepared ectosomes had a controlled release characteristic. Results showed that as the concentration of permeation enhancer (PEG 400) in G3 may increases skin permeability, vesicular flexibility and improved their capacity to distort, permitting them to squeeze through the skin. This allowing for greater vesicle penetration. The amount of Carbopol (10mg) result in an enhanced residence period to drug at the absorption site through interacting with the stratum corneum. Moreover, the viscosity of gel formulation (G3) influences drug release significantly, as it influences the rate of drug diffusion from the carrier.[33,34]

4. CONCLUSION:

In this study evaluated an ethosomal gel system for the topical delivery of Dapsone, directing to improve drug permeation and sustain release with in the skin. The study involved the formulation of ethosomal vesicles using variable concentrations of ethanol and phospholipids, followed by their presence into gels using Carbopol 934. This analysis exposed that formulation F3 exhibited optimal vesicle characteristics, with small particle size (116.3 nm), low PDI (0.32), high zeta potential (–21.7 mV), and maximum encapsulation efficiency (71.91%).

FTIR analysis show the absence of any chemical interaction among drugs and excipients, supportive the compatibility of components. The vesicular preparations show desired morphological features, as confirmed through SEM and TEM analysis, with F3 forming spherical, uniformly distributed vesicles. In vitro drug release from F3 exposed a biphasic release pattern with an initial burst followed by release over 24 hours, indicating well-organized drug entrapment and sustained release behavior. F3 was further prepared into gels (G1–G3), with G3 selected as the optimized gel based on highest physic-chemical properties such as appropriate pH (7.0), high drug content (76.88%), viscosity (45223 cps), and high spreadability (12.68 g/cm²). PEG 400 enhanced drug solubilization and potential, whereas the low conc. of Carbopol confirmed high spreadability and drug release.

The in vitro release study of ethosomal gel G3 show a cumulative drug release of 88.68% over 24 hours, and higher than conventional preparation. The release followed Korsmeyer-Peppas and first-order kinetics, indicating Fickian diffusion as the major mechanism. The ex-vitro skin penetration study was conducted by using pig abdominal skin and show the superior penetration ability of G3 (89.45 ± 0.27%) compared to conventional gel (26.09 ± 1.17%). Stability studies shown over three months confirmed that G3 show its physic-chemical properties without microbial growth.

In conclusion, the ethosomal gel system, particularly G3, presented potential for topical delivery of Dapsone, offering increase penetration, sustained release, stability, and patient compliance.

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