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Formulation and Statistical Optimization of Mupirocin Transferosomal Loaded Gels

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ABSTRACT

Background: Topical Mupirocin is the drug of choice for Impetigo, which is a common bacterial skin infection. There are conventional formulations with limited efficacy due to poor penetration through the barrier of skin.

Methods: The present study is an investigation of transferosomes as a novel delivery system for mupirocin. We have formulated and optimized transferosomes using various lipids, edge activators and preparation methods. The factors like drug content, drug release, drug entrapment efficiency (%EE) and zeta potential (ZP) were evaluated. A 3-level factorial design was employed to optimise the most promising formulation among all the compositions. The significant results were obtained from MF3. Hence, it was incorporated into a gel and drug delivery into the skin layers was evaluated by using Confocal Laser Scanning Microscopy (CLSM).

Results: The optimized transferosome formulation (MF3) demonstrated superior drug %EE, drug content and a stable ZP. The mupirocin-loaded gel containing MF3 exhibited better drug release properties compared to conventional formulations. CLSM confirmed enhanced skin permeability of mupirocin delivered through the optimized transferosomes.

Conclusion: These findings suggest that mupirocin-loaded transferosomes have the potential to improve drug delivery for impetigo treatment. The enhanced skin penetration achieved with this method could lead to more effective therapy and potentially shorter treatment durations.

Keywords: Mupirocin, Transferosomes, Hydrogenated Soya Phosphatidylcholine (HSPC) and Cetomagragol.

1. INTRODUCTION

Impetigo is a highly contagious infection induced by bacteria that are gram-positive like Staphylococcus aureus, Streptococcus pyrogens [1]. In this infection, red, itchy sores appear on sensitive parts of skin which further burst and form a honey-coloured crust [2]. It spreads easily through direct contact with infected sores or contaminated objects [3]. Topical antibiotics like, Mupirocin, Fusidic acid and the oral antibiotics like Dicloxacillin, Cephalexin, Clindamycin, Amoxicillin-clavulanate, Trimethoprim-sulfamethoxazole etc., are the drugs available for treating Impetigo. Symptomatic care is also required with the use of antibiotics. Even though there many potent conventional formulations available in the market, because it is not easily absorbed by the skin, its use in therapeutic settings is

restricted. Hence, the attention was drawn towards the formulation and optimisation of mupirocin into a novel drug delivery system called transferosomal preparation to improve the permeability. They are vesicular drug carrier systems which contain phospholipids and surfactants as excipients and enhance the permeability and drug retention [4-9]. This research primarily aims to prepare and statistically evaluate mupirocin-loaded transferosomal vesicle and studying characteristics employing a factorial design as a topical formulation to enhance the permeability resulting in drug retention.

2. MATERIALS AND METHODS

2.1 Materials

The following ingredients were sourced from various sources: Mupirocin from Glenmark Pharmaceuticals in Mumbai, Capmul and Captex 200 from MCM Abitec Group in the USA, Tween 20, Span 20, Tween 80, Egg lecithin, PEG 200 and PEG 400, Propylene glycol from Merck in Mumbai, Labrafac LipophileWL1349, Labrasol Gattefosse, Cremophor EL, and Labrafil from Gattefosse in France. Following the regulations set forth by the CPCSEA, Government of India (Registration No. 1219/PO/Re/S/08/CCSEA), the Institutional Animal Ethics Committee (IAEC) gave its stamp of approval to the study's experimental methods. Analytical grade reagents and substances were used at every step.

2.2 Methods

2.2.1 Determination of Wavelength [10, 11]

100 mg of Mupirocin dissolved in a buffered ethanol solution of pH 5.5 exhibited a maximum absorbance peak at 224nanometers (λmax).

2.2.2 Construction of Calibration Curve of MUP in PH 5.5 Buffer Solution [12]

Five concentrations (5, 10, 15, 20, and 25 µg /ml) of mupirocin were prepared using a stock solution whereas their absorption was assessed at the λmax of 224 nm. The data accumulated was used to plat the calibration curve for mupirocin (Fig 2).

2.2.3 Screening studies [13-15]

Solubility of Mupirocin in various phospholipids like olive oil, peanut oil, soyabean oil, soya phosphatidylcholine linseed oil, Hydrogenated soya phosphatidylcholine (HSPC) and different surfactants like Tween20, span 20, Labrasol, cremophor EL, Labrafil, Tween 80, Cetomagragol were also studied. Ethanol, Methanol, and Chloroform are used as solvents for formulation studies.

2.2.4 Optimization of Transfersomes [16, 17]

The edge activator was fine-tuned such that it could pass easily through a dialysis membrane with a molecular weight between 12,000 and 14,000 kDa. Table 2 shows that several ratios of chosen lipid and edge activator were employed in the formulation. The medication amount was 10 mg, the organic solvent quantity was 10 ml, and the water for hydration was 0 ml. Dialysis membranes with molecular weights between 12,000 and 14,000 kDa were considered while determining the optimal lipid to edge activator ratio.

2.2.5 Method of Preparation (Thin film film hydration method) [18]

Mupirocin-loaded transferosomes were prepared using the thin film hydration method. HSPC, Cetomacrogel, and Mupirocin were dissolved in ethanol and the solvent was evaporated to form a lipid film. Using PBS, the film (pH 5.5) was hydrated to create large multilamellar vesicles (MLVs), which were then sonicated. The transferosomes were separated by high-speed centrifugation and the precipitate was resuspended in phosphate buffer for evaluation of entrapment efficiency, zeta potential, polydispersity index and particle size analysis. The formulations were stored below 4°C for further studies [19-21]

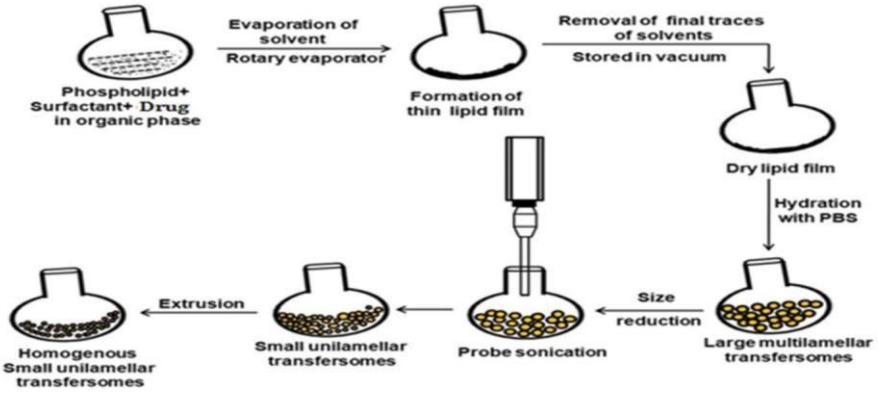


Table 1: Levels of 3^2 Factorial Design Variables for Formulation of Mupirocin Loaded Transfersomes

Factor	Actual coded levels		
Independent variable	**Low(-1)**	**Medium(0)**	**High(+1)**
X1: Hydrogenated soya phosphatidylcholine	85	87.5	90
X2: Cetomagragol	15	17.5	20
Dependent variable			
Y1: Vesicle size (nm) Y2: Entrapment efficiency (%)	Minimize Maximize		

2.2.6 In Vitro Drug Release

Franz diffusion cells with an effective surface area of 3.14 cm2 and a 15 ml capacity were used to conduct in vitro drug release experiments from transfersomes. The donor compartment was supplied with one milliliter of transferosomal suspension. A UV-Vis spectrophotometer was used to measure the drug concentrations in aliquots at various time intervals relative to a suitable blank at 224 nm.

The surface appearance and form of the optimized batch were observed employing an accelerating voltage of 200 kV with an electron microscope (JEOL/JM 2100, Source LaB6).

2.2.7 Compatibility Studies

The compatibility studies were performed using, FTIR Studies, Differential Scanning Calorimetry, XRD

2.2.8 Optimization of Transferosomal Gel

It was performed based on the concentration of Carbopol 934 (0.5%, 1%, 1.5%, and 2%) as described in the table 3 below

Table 2: Formulation of Transferosomal Gel

Ingredients	MF3(F1)	MF3(F2)	MF3(F3)	MF3(F4)
Mupirocin Transferosomes (gm)	0.4	0.4	0.4	0.4
Carbopol (% w/w)	0.5	1.0	1.5	2

Propylene Glycol(%)	0.1
Methyl Paraben	0.02%
Trietanolamaine	0.1%
Distilled water	QS

A 1 g sample of the gel was applied over two 20 cm × 20 cm horizontal plates after 1 minute to find the formulation's spreadability.

The drug content in Mupirocin loaded Transferosomal gel was evaluated by taking 500 mg of the gel into 50 ml of PBS (pH 6.4). After filtering, the filtrate was diluted with 3.5 ml of distilled water. Then, the drug concentration was determined by comparing the spectrophotometric reading at 224 nm with the respective gel concentration.

2.2.9 Flux of Gel Formulation

A graph was produced showing the quantity of Mupirocin that was absorbed by the goat skin as a function of time. Regression was used to generate the linear component of the plot's slope and intercept. The flux (J, lg/cm2/h) was determined by dividing the slope by the skin surface area.

2.2.10 Rheological Studies

In order to determine the gels' rheological characteristics, a Brookfield cone and plate viscometer (type LV DV-III+ Rheometer) was used. Using the CP 52 spindle and Rheocalc software, 0.5 ml of the sample was put onto the viscometer plate and its viscosity, shear stress, and rate of shear were measured at different speeds. Additionally, it was examined for thixotropic occurrences at 25°C.

2.2.11 Extrudability Test

The quantity of gel (g/cm2) that was pressed out of the lacquered aluminum collapsible tube was determined after putting the weight in grams required to eject a gel ribbon of no less than 0.5 cm in 10 seconds.

2.2.12 Skin Irritation Test

We assessed the location as 0, 1, 2, 3 for no response, modest patchy erythema, slight but confluent, moderate but patchy erythema, severe erythema with or without oedema, and each reaction that occurred after 7 days of using the produced transpersonal gel.

2.2.13 Diffusion Studies

Experimental permeation of transferosomal gels through a clipped rat abdomen skin were performed in vitro utilizing the Franz diffusion cell. We used 20 cc of pH 5.5 PBS in the receptor compartment and enough sample in the donor compartment. After removing the samples at various intervals, they were mixed with the same amount of new buffer, filtered, and properly diluted. A UV spectrophotometer was then used for analysis at 224 nm.

2.2.14 CLSM Studies

The goat skin preserved in formalin solution was used for permeability study. An investigation was conducted utilizing CLSM to determine the mechanisms and depth of skin penetration of the vesicle loaded with MF3. A 100:1 M ratio of Rhodamine and DHPE was used to produce the MF3-loaded vesicles and label them bilayer. After being applied to the hairless goat skin for 12 hours, the marked vesicles were removed (2, 4, 6, 8, 10, 12). Various increments along the z-axis of the CLSM were used to optically scan the complete thickness of the skin.

3. RESULTS AND DISCUSSION

3.1 Determination of λ_{max} of Mupirocin

Fig. 1 shows that the maximum value of λmax for MUP in a PBS (pH 5.5) was 224 nm. Based on the findings, the

provided sample meets the criterion as the values are consistent with those found in the literature.

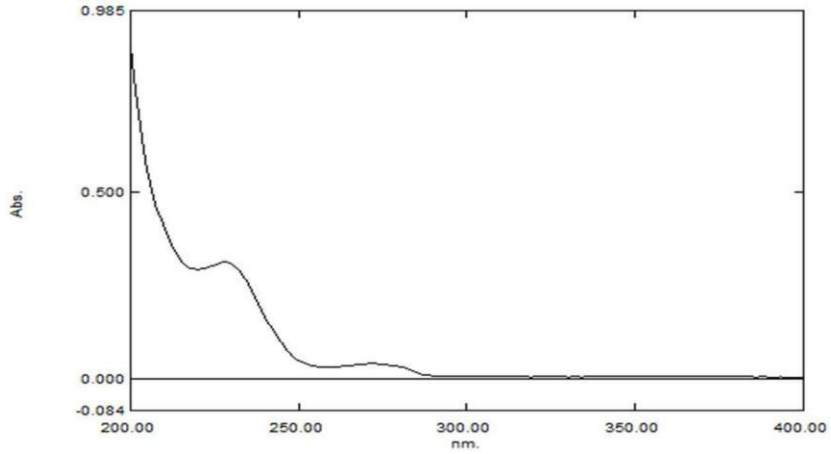


Figure 1: λ_{max} of MUP in 6.4 pH Phosphate Buffer.

3.2 Calibration Curve of Mupirocin

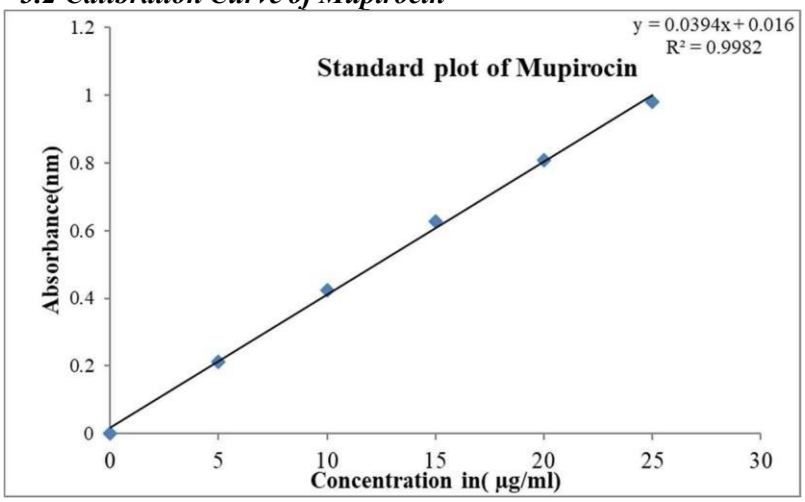


Figure 2: Standard Plot of Mupirocin

3.3 Screening studies

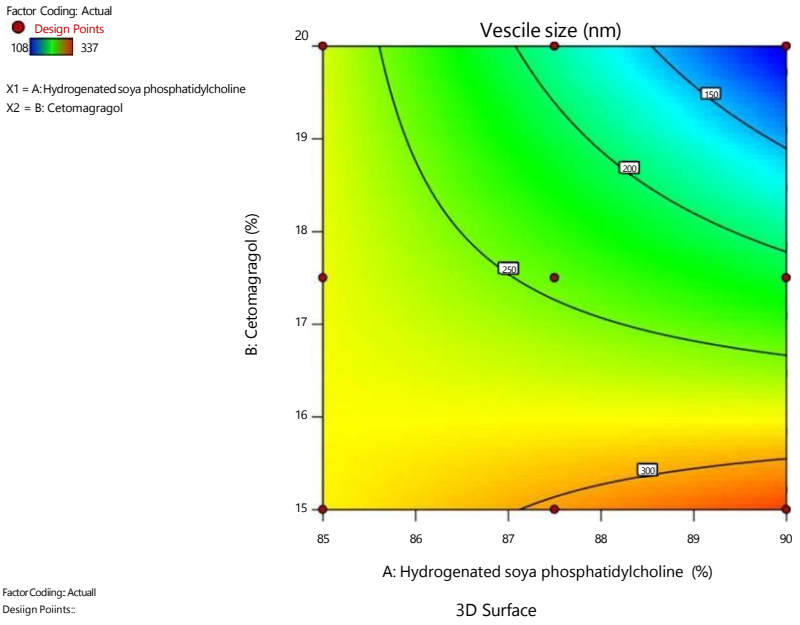
Solubility of Mupirocin in different phospholipids was investigated and discovered that it dissolved well in Hydrogenated soya phosphatidylcholine (HSPC) of 37.9 mg/ml and several surfactants were also investigated and found elevated solubility in Cetomagragol of 123mg/ml as shown in Table 4**.**

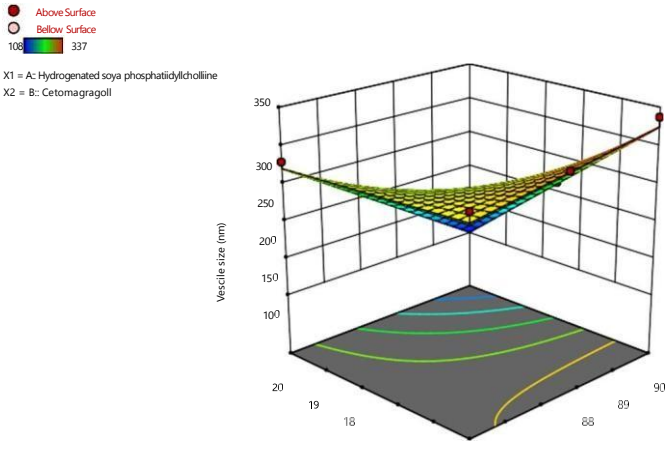
Table 4: Solubility of Mupirocin in Oils and Surfactants

Phospholipids /Surfactants	**Solubility of MPN in mg/ml Mean±S.D.***
Phospholipids	
Olive oil	1.3±0.13
Peanut oil	3.5±0.33
Sesame oil	5.2±0.65
Capmul MCM	7.3±0.71
Arachis oil	8.2±0.28
Castor oil	9.1±0.59
Linseed oil	12.0±0.33

Soyabean Oil	15.1±0.15
Labrafac LipophileWL1349	23.1±0.19
HSPC	37.9±0.31
Dimyristoly phosphatidylcholine (DMPC)	43.1±0.42
Hydrogenated soya phosphatidylcholine (HSPC)	52.2±0.61
Surfactants	
Tween 20	75.3±0.51
Span 20	81.3±0.74
Labrasol	82.9±0.66
Cremophor EL	90.2±0.34
Labrafil	91.5±0.25
Tween 80	96.5±0.19
Cetomagragol	123±0.13
(HSPC)+Cetomagragol	219.3±0.15

Vesicle size (nm)





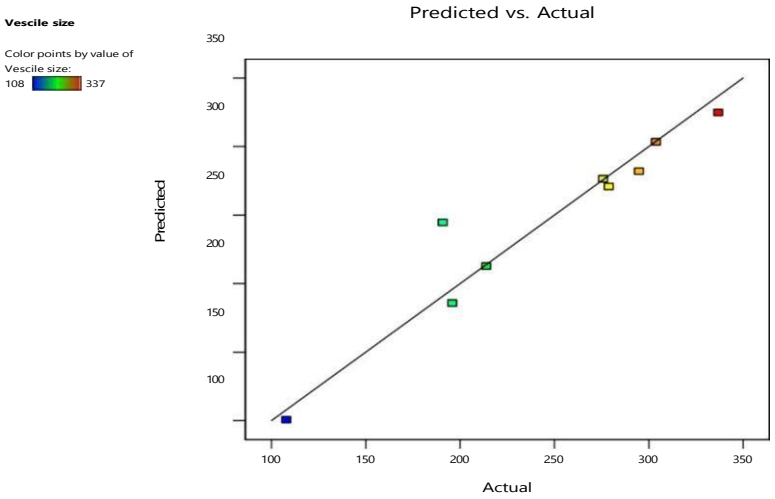
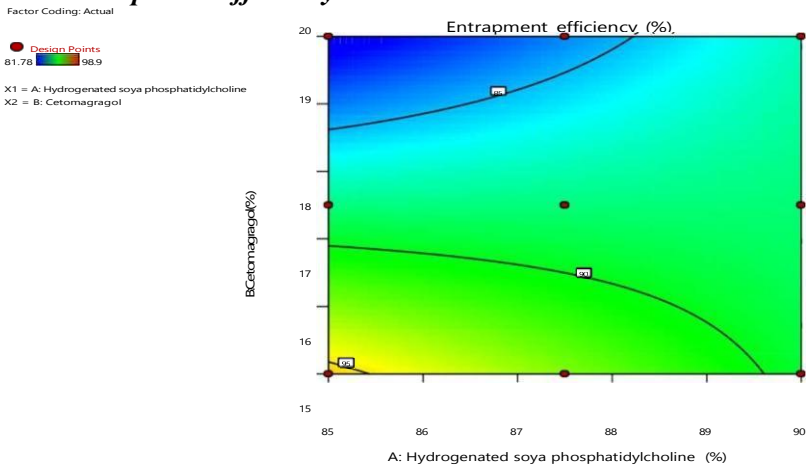


Figure 3: D-Response Surface Graphs and Their Corresponding 2D-Contour Plots

The 3D- response surface graphs and 2D- contour plots graphs (Figures 13 A and13 B) showed that %EE rises in proportion to the quantity of phospholipid from 375 mg to 475 mg. Moreover, the % EE of Mupirocin initially increased in proportion with the amount of Cetomagragol from 15% to 20%. However, a further increase in the amount of Cetomagragol to 20% resulted in a drop in the % EE. We displayed the perturbation graph to locate the elements. that influence the entrapment efficiency most. For entrapment efficiency, factor A shows a slight bend, and factor B displays a steep slope. It shows that the quantity of Cetomagragol was the most significant factor determining the drug %EE.

3.4 Entrapment Efficiency



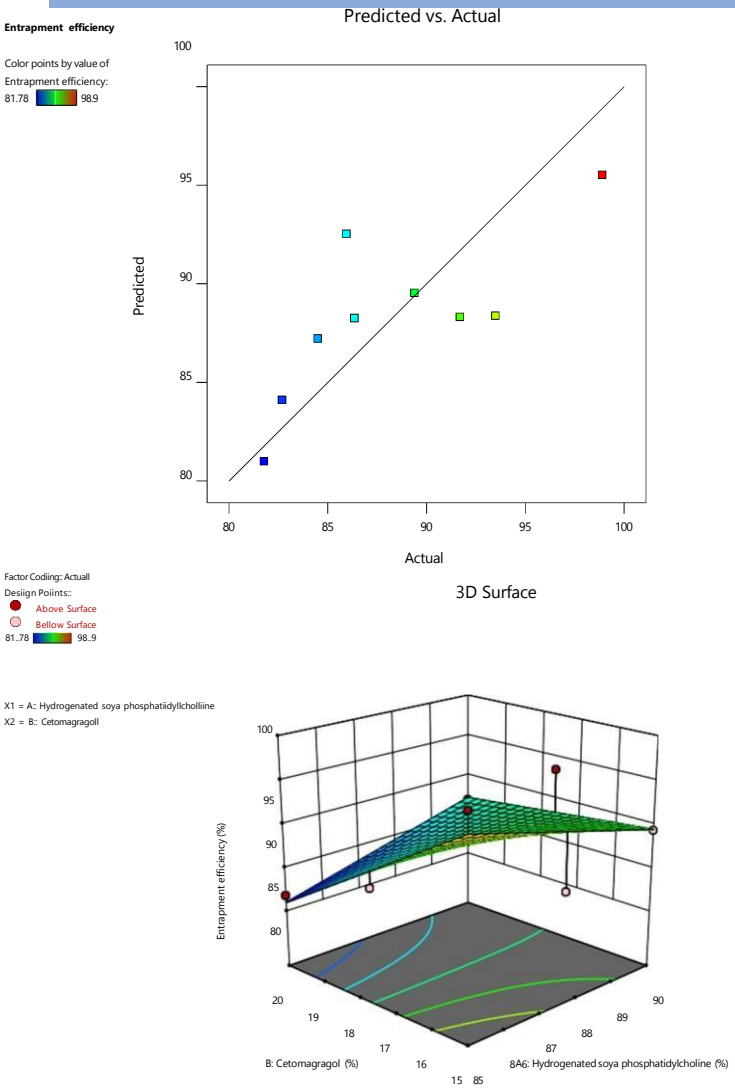


Figure 4: 3D-Response Surface Graphs and Their 2d-Contour Plots

3.5 Entrapment Efficiency

Entrapment efficiency of Mupirocin Transferosomal formulations were calculated and the highest entrapment effiency was obtained for MF3 formulation which was found to be 91.4%
Containing lipid/surfactant ratio of (85:15) as seen in table 8.

%EE, Vesicle Size, PDI, And ZP of Mupirocin transferosomal Preparations

Form code	%EE	Vesicle size (nm)	PDI	ZP (mV)
MF1	57.5±0.20	302±12	0.44±0.052	-39.0
MF2	62±0.32	295±14	0.63±0.038	-39.2
MF3	91.4±0.71	295±13	0.56±0.024	-43.3
MF4	70.5±0.64	270±8	0.39±0.033	-35.6
MF5	42.5±0.33	345±15	0.41±0.035	-38.2
MF6	78±0.48	330±19	0.29±0.037	-35.2

MF7	90.01±0.51	295±12	0.10±0.021	-40.3
MF8	77.03±0.36	275±10	0.47±0.027	-36.2
MF9	59.01±0.49	300±11	0.37±0.031	-41.1
MF10	70.01±0.25	290±13	0.26±0.033	-19.3
MF11	76.70±0.36	285±14	0.39±0.049	-28.9
MF12	68.14±0.44	260±11	0.46±0.025	-35.0

3.6 Zeta potential

We used a Zeta sizer to determine the transferosomal formulations' ZP at 25oC. (Nano-ZS, Malvern instrument,Malvern, U.K.).

The zeta potential of MF3 was in negative charge 43mV, Particle size was 295nm with PDI 0.103. The values obtained were correlating with the values shown during statistical optimization. (Fig 11).

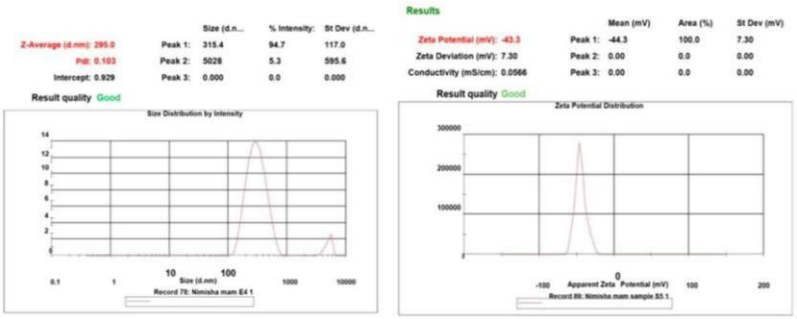


Figure 11 : ZP and Particle Size of Mupirocin Transferosomes

3.7 Compatibility Studies

- **FTIR**: From the ftir studies performed on pure drug of mupirocin shown in (fig.6) as well as optimised mupirocin transferosomes shown in (fig.7) it was clearly evident that the presence of functional groups C-O, C=O (carbonyl groups), O-H(alcohol) in the absorption locations of 1233.62 cm^{-1}, 1774.60cm^{-1}, 3456.35 cm^{-1} in the pure drug were also present in the optimised formulation. From the ftir studies it was concluded that Mupirocin is compatible with other excipients showing no deviation in the wave number range.
- **FTIR**

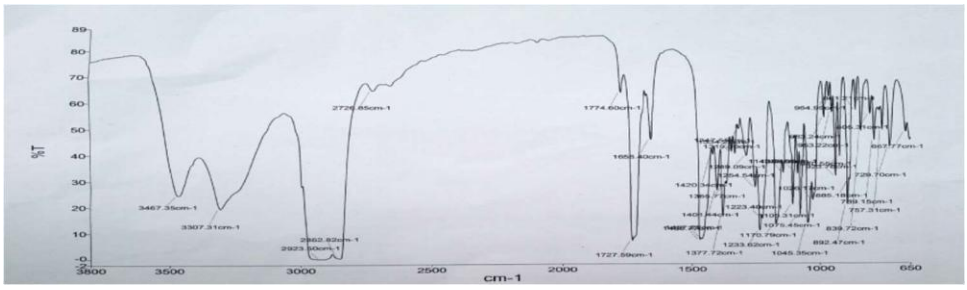


Figure 6: FTIR Spectra Mupirocin Pure Drug

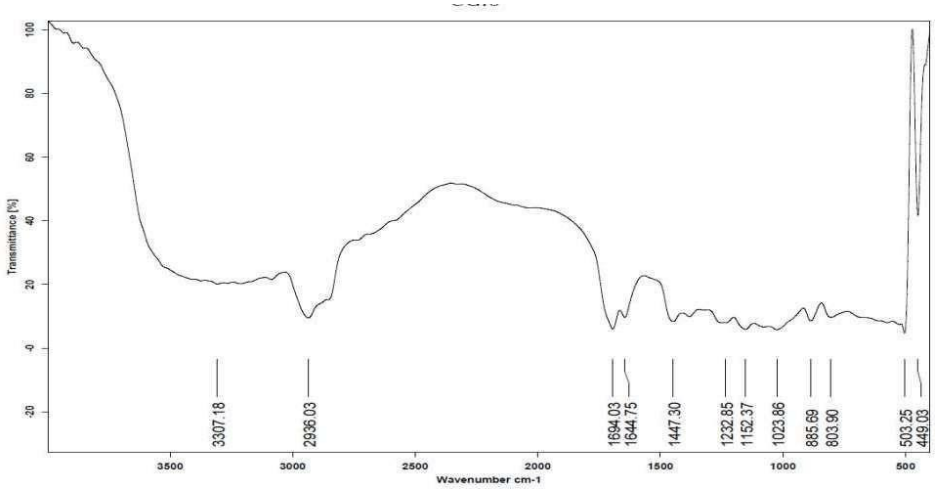
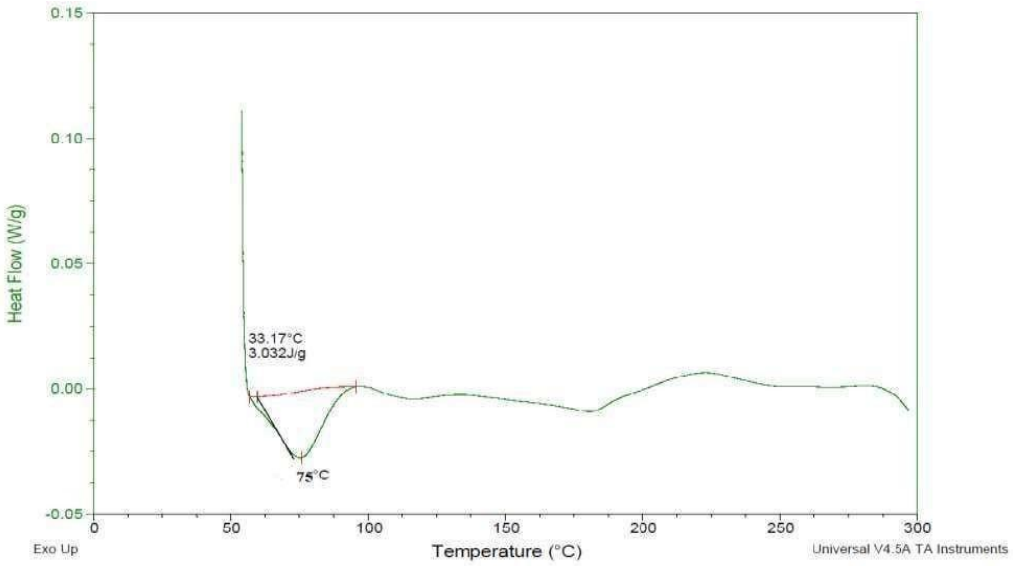


Figure 7: FTIR Spectra Of Mupirocin optimised formulation (MF3)Transferosomes

- **DSC:** From the dsc graphs it was shown that mupirocin melts at 75^0c(exothermic peak) shown in (fig 8) .In case of optimised formulation from the dsc graph the melting point of phospholipid was shown as 169.7^0c (exothermic peak) shown in (fig 9) showing no deviation from the pure phospholipid.

Figure 8: DSC graph Of Mupirocin Pure Drug



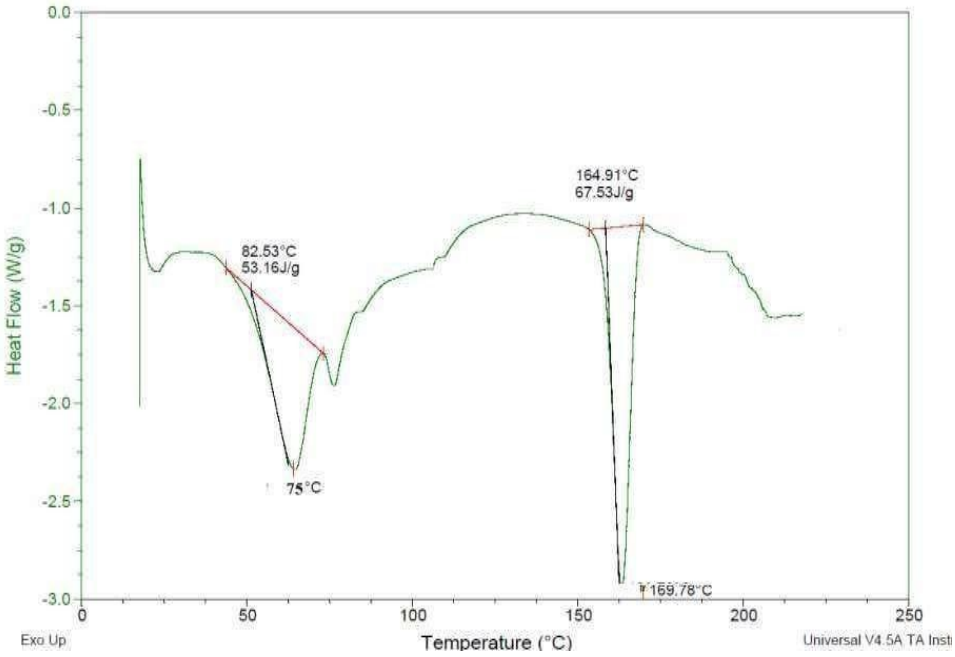


Figure 9: DSC graph of Mupirocin Optimized Formulation(MF3)

- **XRD:** Figure 10 displays XRD signals that indicate the presence of MUP crystal peaks. Lower peak intensities in the XRD spectra of Mupirocin Transferosomes relative to the pure drug (Figure 11), suggesting either amorphous phase transitions or reduced crystallinity.

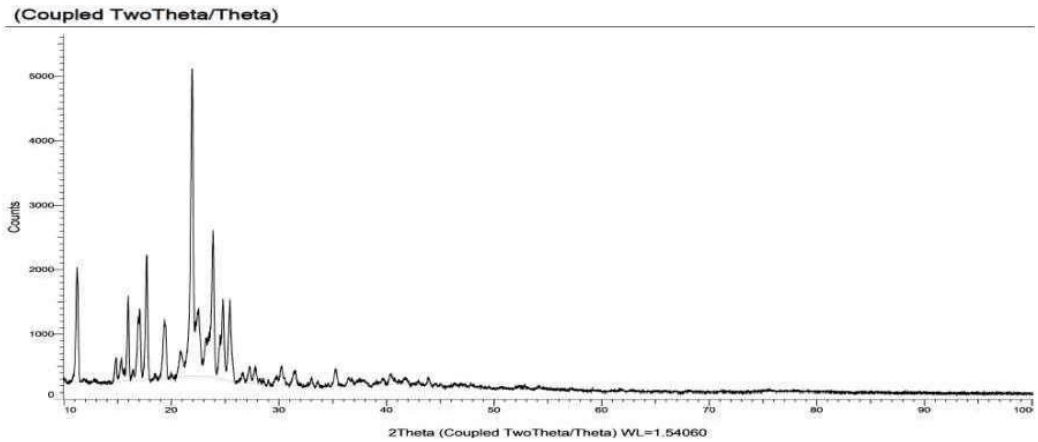


Figure 10: XRD of Mupirocin Pure Drug

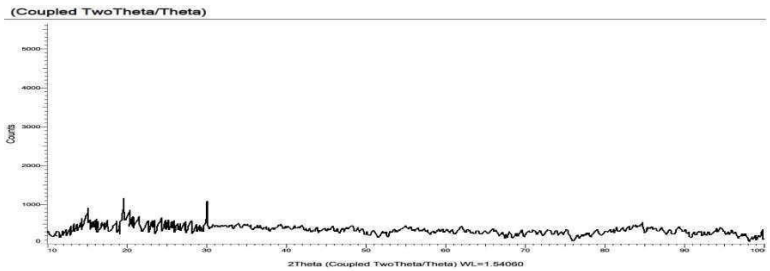


Figure 11: XRD of Optimized Formulation of Mupirocin (MF3)

3.8 In Vitro membrane permeation studies by Franz diffusion cell

In vitro drug release

Franz diffusion cells with an effective surface area of 3.14 cm2 and a volume of 15 ml were used to conduct in vitro drug release experiments from transfersomes.

3.9 Permeation Data Analysis

Testing the 12-hour in-vitro drug release of Transferosomal suspensions loaded with drugs was carried out. For the whole Mupirocin transferosomal suspension, the release profiles are shown in Figure 12. It was discovered that the absorption of the medication via the skin obeyed the Zero-order release curve, as the value of drug release of the MF3 transferosomal formulations was almost 1. The fact that MF3 stuck to zero-order release makes it a perfect candidate for transdermal administration, as it allows for the sustained release of the medicine.

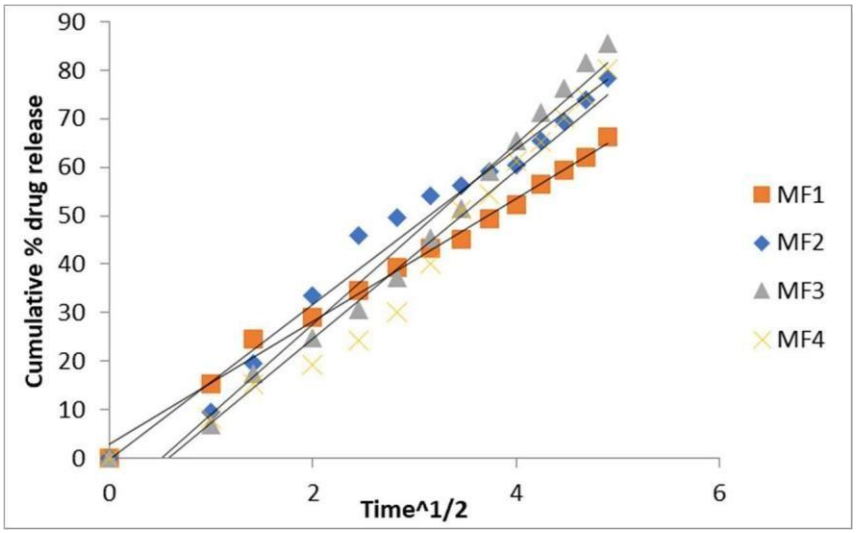


Figure 12: Drug Release Kinetic Models of MUPIROCIN from MF3 Showing Zero Order First Order, Higuchi and Peppas

Table 9: Correlation Coefficient (R^2) Values of Formulations MF1 – MF12 As Per Various Kinetic Models

Formulation	Correlation Coefficient (r^2) Values				
	Zero-order	First order	Higuchi's	Peppas's	n value
MF1	0.9741	0.8219	0.9640	0.9745	0.77
MF2	0.9801	0.8404	0.9690	0.9910	0.74
MF3	0.9823	0.7047	0.9507	0.9870	0.69
MF4	0.9898	0.7258	0.9593	0.9900	0.72
MF5	0.9747	0.8563	0.9735	0.9860	0.75

MF6	0.9651	0.8195	0.9450	0.9820	0.68
MF7	0.9989	0.8645	0.9579	0.9969	0.90
MF8	0.9968	0.7344	0.9425	0.9951	0.86
MF9	0.9741	0.8219	0.9745	0.9846	0.77
MF10	0.9904	0.7275	0.9550	0.9951	0.81
MF11	0.9843	0.8411	0.9699	0.9931	0.83
MF12	0.9789	0.8469	0.9710	0.9914	0.84

3.10 TEM analysis

Additionally, freeze-fractured transmission electron microscopy was used to investigate the transferosome shape. The microscopic MF3 vesicle was identifiable by its round form, smooth exterior, and diminutive size. (Fig. 13).

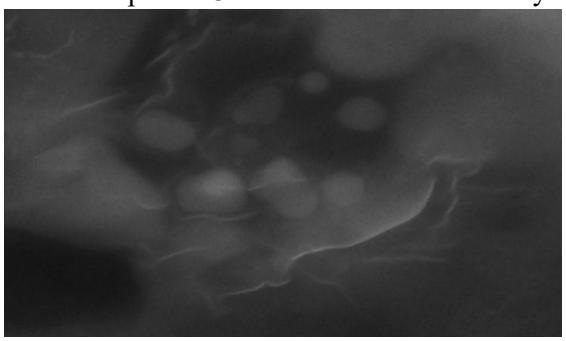


Figure13: TEM Image of Transferosomes of Mupirocin MF3 Using Cetomagragol as Edge Activator Studies on Optimized Transferosomal Gel

3.11 Optimisation of Transferosomal gel

Formulation MF3 (F4) was chosen as the best batch after considering several assessment criteria, including appearance, pH, spreadability, viscosity, and medication content. (Table 6) which shows.Further studies were performed on MF3 F4 and shown in Table 10 .

Table 10: Evaluation Properties of Transferosomal Gel of Mupirocin(MF3 M4)

Formulation	Color	Homogeneity	Texture	Viscosity (cps)	pH	Spreading Diameter (mm)	Drug content (%)	Extrudability	Skin Irritation test
MF3 F4 gel	Dull white	Homogeneous	Smooth	2000±0.15	6.2	55	93.2	Excellent	No irritation

- **Flux:** Mupirocin flux for Transferosomal gel formulations was determined to be 50.357, 52.30, 55.80, and 63.85µg/cm^2/hr for MF3 F1, MF3 F2, MF3 F3, and MF3 F4, accordingly as depicted in (fig 14).

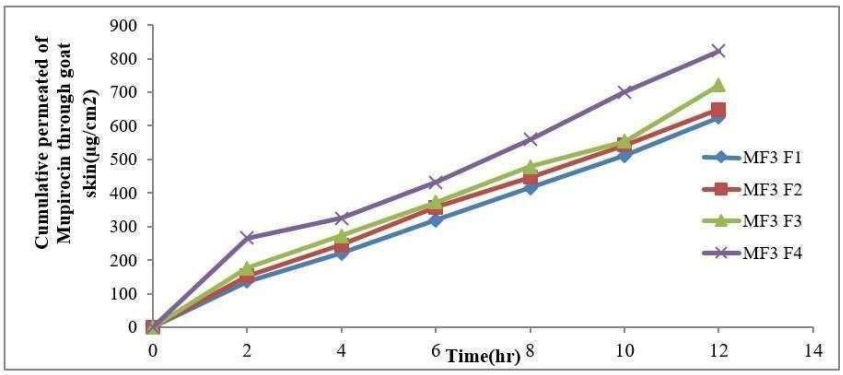


Figure 14: Comparison Flux between the Mupirocin Gel Formulations from MF3 F1, MF3 F2, MF3 F3 and MF3 F4

The permeation of transpersonal gel MF3 F4 was greater than that of MF3 F1, MF3 F2, and MF3 F3gels as illustrated in (Fig 15).

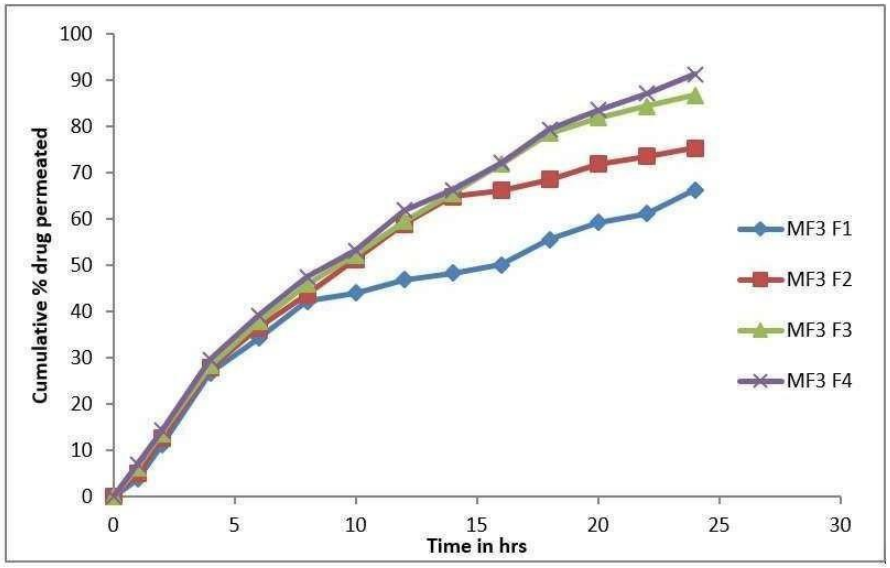


Figure 15: Cumulative % Of Mupirocin Permeated

- **Rheological Studies:** Rheograms of the gel can be seen in Figs (16, 17, 18)

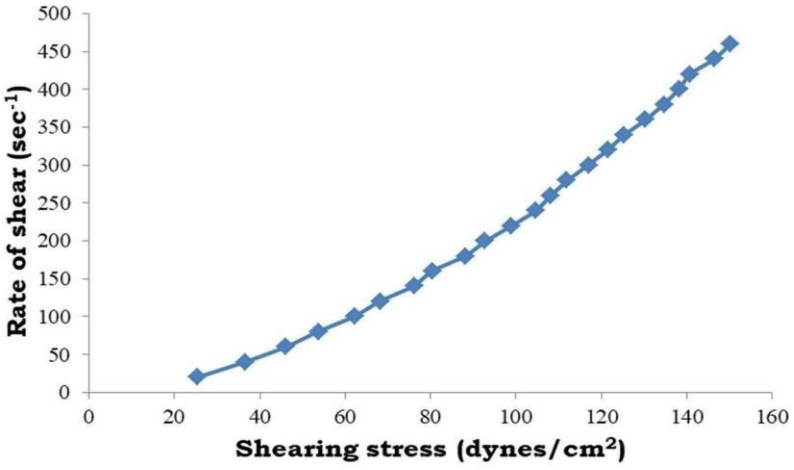


Figure 16: Rheogram Plotted Showing Flow Property of Gel

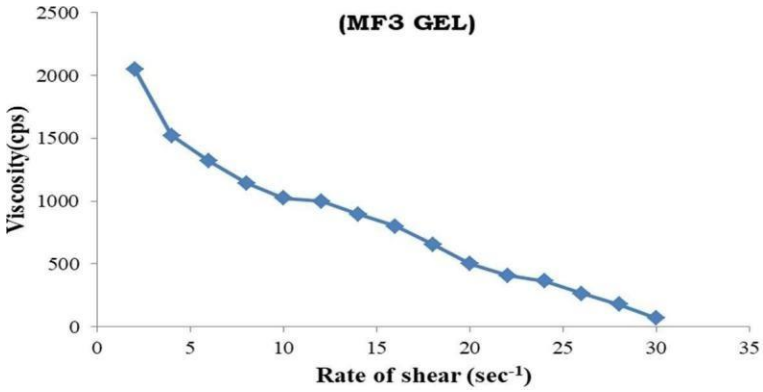


Figure 17: Rheological Behaviour of Transferosomal Gel Formulation (MF3 F4) At Different Shear Rate (N=3).

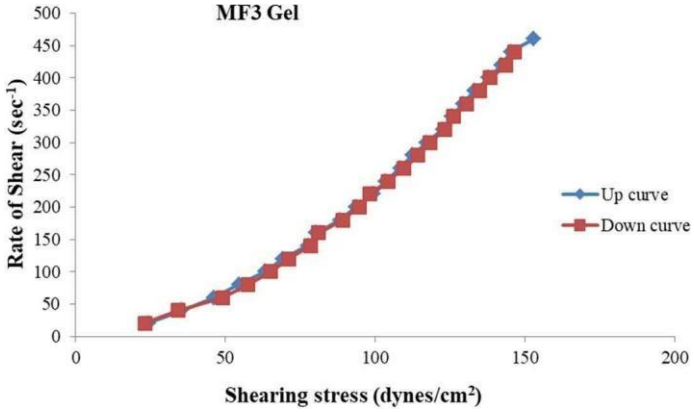


Figure 18: Thixotropic Behaviour for (MF3 F4) Gel

- **CLSM Studies:** From the studies as shown in (Fig 19), the produced gel exhibited a significant degree of permeability.

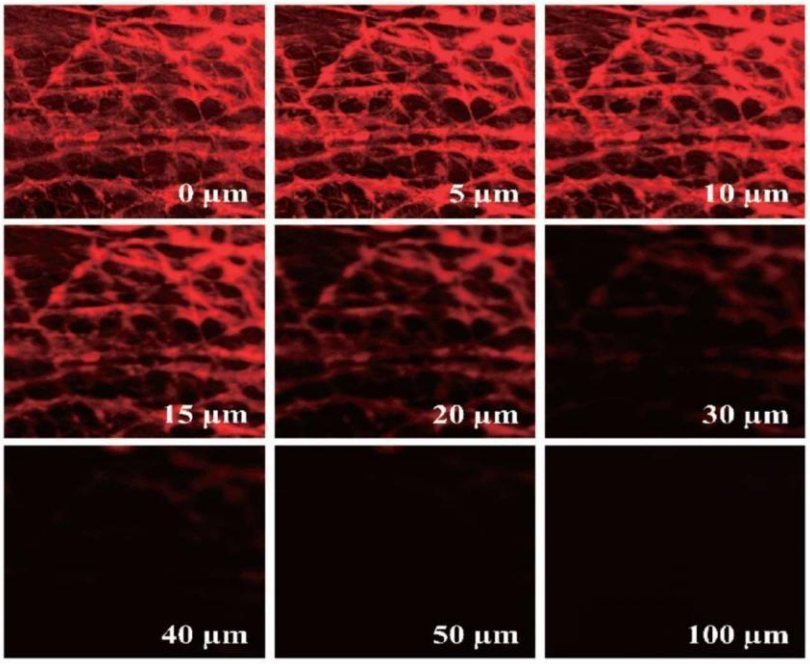


Figure19: CLSM studies Following 12 Hours of Transferosome Permeation

3.12 Conclusion

An optimised topical transferosomal gel formulation of Mupirocin was prepared successfully developed which is characterized by a submicron size of 295 nm, spherical shape and adequate loading capacity. The rationale behind this study is to enhance the delivery of drug and its efficacy. Transferosomes, due to their flexible and deformable nature, have the ability to reach deeper into the skin layers compared to traditional formulations, leading to improved permeation. This enhanced permeation results in a higher percentage of the drug being released at the intended site, thereby increasing the therapeutic effectiveness of Mupirocin. Hence, this topical delivery system for Mupirocin offers superior performance in terms of drug permeation and release, making it an attractive choice for addressing skin infections like Impetigo and Furnuncles etc.,

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