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Research

Formulation And Evaluation Of Neomycin Sulfate Loaded Transferosomes Gel For Topical Use

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Abstract

Neomycin Sulfate is an aminoglycoside antibiotic used to treat bacterial skin infections. Neomycin Sulfate transferosomes were prepared using the thin lipid film hydration technique. The prepared transferosomes demonstrated high drug entrapment efficiency (EE), ranging from 39.07% to 85.03%, with small particle sizes between 445 nm and 592 nm. The optimized Neomycin Sulfate transferosomes formulation was incorporated into a Carbopol 940 gel base and evaluated for appearance, clarity, pH, drug content, and *in vitro* activity. The *in vitro* release study indicated an inverse relationship between entrapment efficiency and drug releases. Over 12 hours of studies, the drug release ranged from 69.74% to 83.68%. Kinetic analysis of the optimized formulation's release profiles followed the Korsmeyer-Peppas model, with the highest correlation coefficient ($R^2 = 0.9983$) for the optimized TF3 formulation. The value of "n" was calculated as 0.9683 which indicates that the drug release from the polymeric matrix followed a non-Fickian transport mechanism. These findings underscore the promise of Neomycin Sulfate-loaded transferosomes gel as an innovative drug delivery system for treating skin conditions.

Keywords: Carbopol 940, Entrapment Efficiency, Neomycin Sulfate, Transferosomes.

INTRODUCTION

Traditional drug delivery methods often face limitations, particularly in transdermal applications due to the skin's robust barrier, the stratum corneum (SC). This layer, composed of keratinized skin cell remnants, is impermeable to water and acts as a resilient shield, making effective drug delivery challenging. Challenges include

systemic metabolism, side effects, invasive procedures, and poor patient adherence [1-5]. To overcome these barriers, advanced drug delivery systems such as transferosomes have been developed, offering significant therapeutic advantages for established and novel drugs as shown in Fig. 1. Transferosomes, introduced by Gregor Cevc in 1991 and patented by the German company IDEA AG, are highly deformable lipid vesicles designed for transdermal delivery. The term "transferosome" is derived from Latin and Greek, meaning "carrier body"[6,7]. These vesicles mimic natural cell structures involved in exocytosis and are engineered to enhance drug delivery across the skin. Their unique composition allows them to penetrate the skin barrier efficiently, even though pores are up to 1,500 times smaller than their size, without losing their payload [8,9]. Structurally, transferosomes consist of an aqueous core surrounded by a lipid bilayer embedded with edge activators, such as sodium cholate, sodium deoxycholate, Span 80, and Tween 80. These edge activators enhance the flexibility of the lipid bilayer, enabling the vesicles to navigate through narrow intercellular pathways within the subcutaneous tissue [10]. The inclusion of phospholipids like soya phosphatidylcholine, dipalmityl phosphatidylcholine, and surfactants (10–25%) ensures structural integrity, while alcohol (3–10%) acts as a solvent. A hydrating medium, such as saline phosphate buffer (pH 6.5–7.5), maintains the system's stability [11]. The deformability of transferosomes is a key advantage, allowing them to transport both low and high-molecular-weight drugs effectively. Unlike liposomal and niosomal systems, which suffer from issues like poor skin permeability, drug leakage, and vesicle instability, transferosomes deliver drugs in a controlled and targeted manner. They can be applied in semi-dilute suspensions without causing blockages or aggregation. Transferosomes have demonstrated practical applications in modern medicine. For instance, ketoprofen formulated in transferosomes (Diractin) was approved by Swiss Medic in 2007 for transdermal application, targeting peripheral subcutaneous tissues. Similarly, cationic transferosomes have been explored for topical immunization with DNA vaccines, combining the benefits of DNA vaccines with non-invasive delivery methods. Overall, transferosomes represent a revolutionary approach to overcoming the limitations of traditional transdermal delivery systems. Their deformable structure, enhanced permeability, and ability to deliver a wide range of drugs make them a promising solution for targeted and efficient therapeutic interventions. This innovative technology opens new possibilities for treating various skin conditions and advancing non-invasive drug delivery [12,13]. Neomycin Sulfate (NS) is a bactericidal aminoglycoside antibiotic (or antibacterial agent) that is categorized as a BCS class-III i.e. high solubility and poor permeability, and generally, it is used as a topical agent in skin infection. Physicochemical properties of NS like highly polar nature and high molecular weight (908.87D). Poor skin permeability (<3%) of Neomycin sulphate reduces its deeper skin penetration [14]. That aminoglycoside antibiotic works by binding to the bacterial 30S ribosomal subunit, causing misreading of t-RNA, leaving the bacterium unable to synthesize proteins vital to its growth [15,16]. In the present investigation transferosomes gel of NS was prepared by using Soya Lecithin, Cholesterol, span 80 and tween 80 to increase the skin penetration.

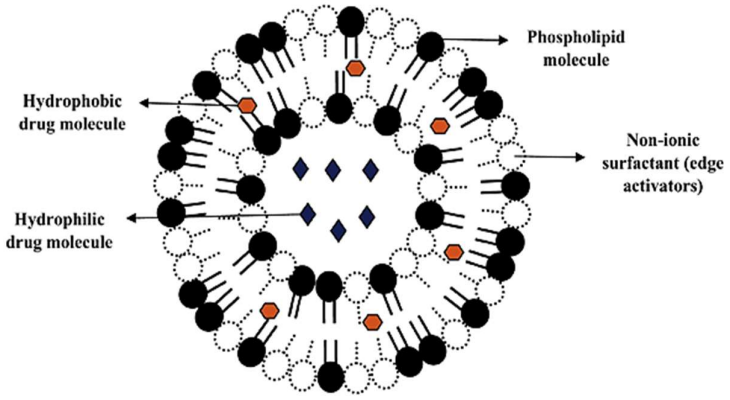

Fig 1: Diagrammatic Representation of transferosomes

MATERIALS AND METHODS

Materials

Neomycin sulfate was received as a gift sample from Safetab Pharma Company in Puducherry. Soya lecithin and cholesterol were purchased from SD Fine Chemicals Ltd in India, while ethanol and chloroform were acquired from Universal Scientific and Chemicals in Madurai. Span 80 and Tween 80 were obtained from Mohini Organics Pvt. Ltd. in Mumbai, India, and Carbopol 940 was procured from Sai Mirra Pharmaceuticals in Chennai.

Formulation of transfersomes

Preparation of Neomycin Sulfate Transferosomes by Thin Film Hydration Technique

The weighed amounts of the drug, soya lecithin, cholesterol, and surfactant were combined in a round-bottom flask and dissolved in a 2:1 mixture of chloroform and ethanol. Rotary evaporation was employed to create a thin film over 15 minutes at a temperature of 60°C, under a pressure of 600 mmHg, and at a speed of 100 rpm. After the evaporation process, the vacuum was applied until a film was formed. This film was then hydrated with a buffer at pH 7.4 and rotated for 45 minutes to create vesicles. Following this, the transferosome vesicles were examined using a projection microscope [17]. Finally, the transferosome vesicles were transferred into a 2% w/v carbopol gel as presented in Table 1.

Table 1: Formulation Table of Neomycin Sulfate Transferosomes

Formulation Code	Composition				
	Drug (mg)	Soya Lecithin +Cholesterol (mg)	Span 80 (mg)	Tween 80 (mg)	Phosphate Buffer (ml)
TF1	100	95	5	-	10
TF2	100	90	10	-	10
TF3	100	85	15	-	10
TF4	100	80	20	-	10
TF5	100	75	25	-	10
TF6	100	70	30	-	10
TF7	100	95	-	5	10
TF8	100	90	-	10	10
TF9	100	85	-	15	10
TF10	100	80	-	20	10
TF11	100	75	-	25	10
TF12	100	70	-	30	10

Preformulation studies

Calibration Curve for Neomycin Sulfate

A stock solution was prepared by dissolving 100 mg of Neomycin Sulfate in 100 ml of phosphate buffer (pH 7.4). This solution was diluted to obtain concentrations ranging from 10–50 µg/ml. Absorbance was measured at 205 nm using a UV spectrophotometer with phosphate buffer (pH 7.4) as the blank. A standard curve was plotted with concentration on the X-axis and absorbance on the Y-axis.

FT-IR Analysis of Drug-Polymer Interactions

Drug-polymer interactions were studied using FT-IR spectroscopy. FT-IR spectra of Neomycin Sulfate and its combination with soya phosphatidylcholine were recorded using a spectrometer. Samples were prepared as KBr pellets and scanned over a range of 4000–400 cm^{-1} with a resolution of 4 cm^{-1} [18].

Evaluation of Neomycin Sulfate transfersomes

Drug Content Analysis

The drug content was assessed using the microbial assay method as per the Indian Pharmacopoeia 2018[19]. Antibacterial activity was evaluated via the agar well diffusion method following NCCLS guidelines, using *Staphylococcus epidermidis* as the test organism. MHA agar plates were inoculated under aseptic conditions, and wells were filled with 50 µg and 100 µg of test samples. Plates were incubated at 37°C for 24 hours, and results were calculated using the following formula.

a = (U1 + U2) - (S1+S2)/ (U1-U2) + (S1-S2) % Potency = Antilog (2.0 + a log 4)

Percentage drug entrapment efficiency (%DEE)

Entrapment efficiency was determined by first separation of the unentrapped drug by centrifugation. The supernatant liquid was used for the determination of free drug. After centrifugation the supernatant liquid was diluted with buffer and absorbance was detected by UV Spectrophotometer at 205nm [20].

$$\% \textbf{ Entrapment Efficiency} = \frac{\textbf{Total amount og drug} - \textbf{UnentrapedDrug}}{\textbf{Total amount of Drug}} \textbf{X 100}$$

Unentrapped drug = Sample Absorbance / Standard Absorbance X100

Vesicle Size, Distribution, and Zeta Potential

The vesicle size, size distribution, and zeta potential of transferosomes were measured using a Lite Zetasizer. Transfersomes were dispersed in distilled water using a cyclo-mixer for homogeneity, and then placed in Zetasizer cuvettes. Measurements, including size and polydispersity index, were performed in triplicate [21].

***In-Vitro* Release Studies for Transferosomal Gel**

Drug release was evaluated using a Franz diffusion cell. A 1 g gel sample was applied to an egg membrane in the donor compartment, with phosphate buffer (pH 7.4) as the receptor medium. The setup was maintained at 37°C on a magnetic stirrer. Samples were collected at regular intervals, replacing the medium to maintain sink conditions. Drug concentration was analyzed at 205 nm using a UV spectrophotometer [22].

Kinetic model of *in- vitro* drug release studies

The *in vitro* release studies data were applied to numerous kinetic models like Zero order, first order, Higuchi plot, Hixson-Crowell cube root law model, and Korsemeyer Peppas plot to spot the model of drug release.

RESULTS AND DISCUSION

Calibration Curve for Neomycin Sulfate

Calibration Curve of Neomycin Sulfate was done in Phosphate buffer pH 7.4. The correlation coefficient was found to be 0.9988. Hence, Neomycin Sulfate obeys the Beer's law within the concentration range of 10-50µg/ml. Calibration curve of Neomycin Sulfate was drawn with Concentration on X axis and Absorbance on Y axis which is shown in Fig 2 and the results are given in the table 2.

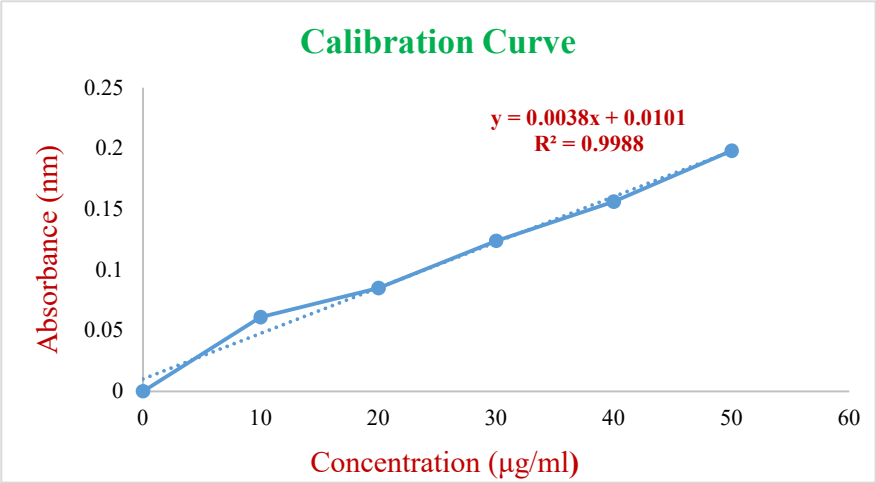

Fig 2: Standard Calibration Curve of Neomycin Sulfate

Table 2: Standard Calibration Curve of Neomycin Sulfate

S.No	Concentration (µg/ml)	Absorbance at 205 (nm)±SD
1	0	0.000
2	10	0.061±0.0016
3	20	0.085±0.0021
4	30	0.124±0.0016
5	40	0.162±0.0021
6	50	0.198±0.0355
7	Regression value (r^2)	0.9988

Fourier transforms infrared spectroscopy (FT- IR)

The spectra analyzed between 4000 cm^{-1} and 400 cm^{-1} are presented in Fig 3 to 5. It was observed from the spectra that there were no significant shifts or losses of functional peaks in the spectra of the drug and its physical mixture with the surfactant, soya phosphatidylcholine, cholesterol, and Carbopol 940. The results indicate that the selected surfactant, soya phosphatidylcholine, and cholesterol are compatible with the chosen drug.

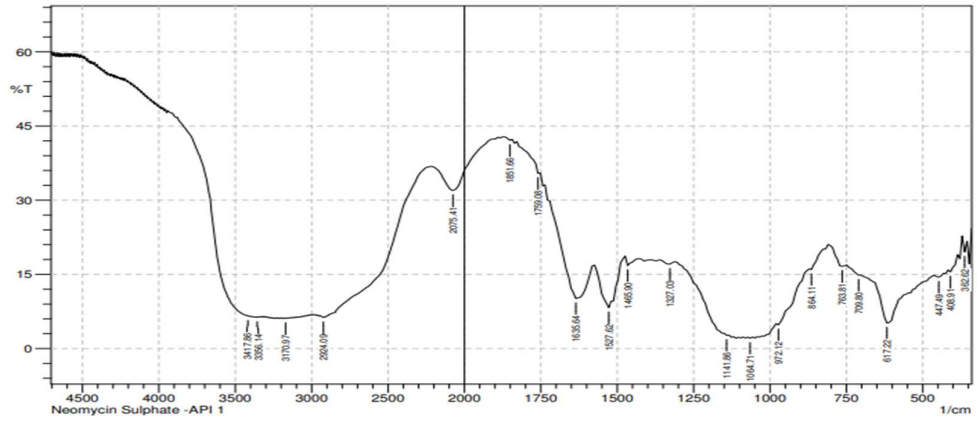

Fig 3: Infrared Spectrum of Neomycin Sulfate (API)

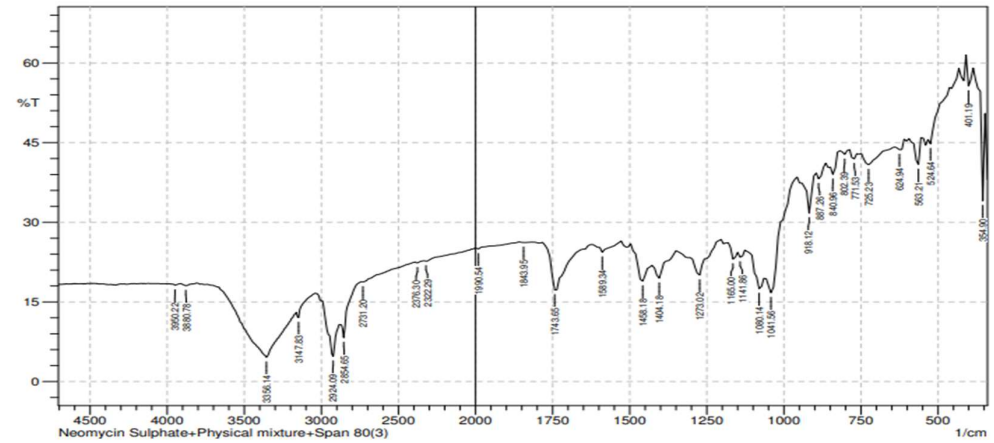

Fig 4: Infrared Spectrum of API + Physical Mixture + Span 80

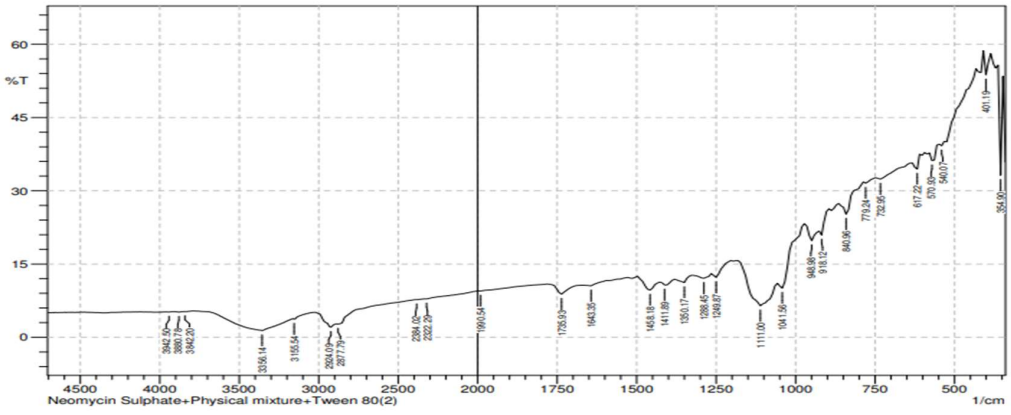

Fig 5: Infrared Spectrum of API+ Physical Mixture + Tween 80

Table 3: Characteristic Peaks of API and Physical Mixture

S.No	Functional group	Observed peak cm-1		
		API	API + Physical Mixture + Span 80	API+ Physical Mixture + Tween 80
1	NH stretching (aliphatic)	3417	3356	3356
2	CH stretching (aliphatic)	2924	2924	2924
3	CH stretching (aromatic)	3170	3147	3155
4	O-H stretching (alcohol)	3795	3880	3842

**API- Active Pharmaceutical Ingredients*

Evaluation of Neomycin Sulfate transfersomes

Determination of Drug Content

The drug content was found to range from 81.03% to 94.44%. These results indicate a uniform distribution of the drug in the prepared transferosomal formulations. The observed results are presented in Table 4, and the drug content of the formulated transferosomes (TF1 to TF12) is shown in Fig 6.

Estimation of Drug Entrapment Efficiency

The entrapment efficiency of twelve transferosomal formulations was observed to range from 39.07% to 85.03%. These results are presented in Table 4 and Fig 7. The highest entrapment efficiency was achieved with the formulation containing Neomycin Sulfate, lipid, and Span 80 (15%). The entrapment efficiency of transfersomes depends on the surfactant concentration in the bilayer. Initially, with increasing surfactant concentration, there was an increase in entrapment efficiency. This may be due to the fact that at a certain concentration, surfactant molecule gets associated with the phospholipid bilayer, resulting in better partitioning of drug. So above a 15% concentration of the surfactant, molecules may start forming micelles in a bilayer resulting in pore formation in vesicle membranes and complete conversion of vesicle membranes into mixed micelles. However, after a threshold level (above 15% w/w), a further increase in surfactant concentration lead to a decrease in entrapment efficiency.

Table 4: Drug Content and Entrapment Efficiency of Neomycin Sulfate Transferosomes Formulation

S.No	Formulation Code	Drug Content (%) (±S.D)	Entrapment Efficiency (%) (±SD)
1	TF1	91.93±0.02	53.93±0.13
2	TF2	92.47±0.07	73.50±0.20
3	TF3	94.44±0.03	85.03±0.20
4	TF4	83.98±0.34	58.91±0.15
5	TF5	92.07±0.04	48.69±0.35
6	TF6	82.99±0.10	41.04±0.08
7	TF7	81.03±0.02	43.99±0.39
8	TF8	82.72±0.31	57.10±0.20
9	TF9	88.39±0.19	76.94±0.15
10	TF10	87.67±0.31	67.16±0.08
11	TF11	84.33±0.21	50.77±0.08
12	TF12	81.44±0.09	39.07±0.20

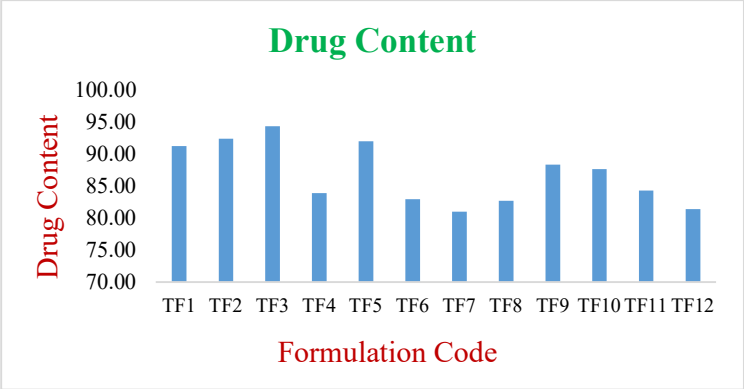

Fig 6: Drug Content of Neomycin Sulfate Transferosomes Formulation

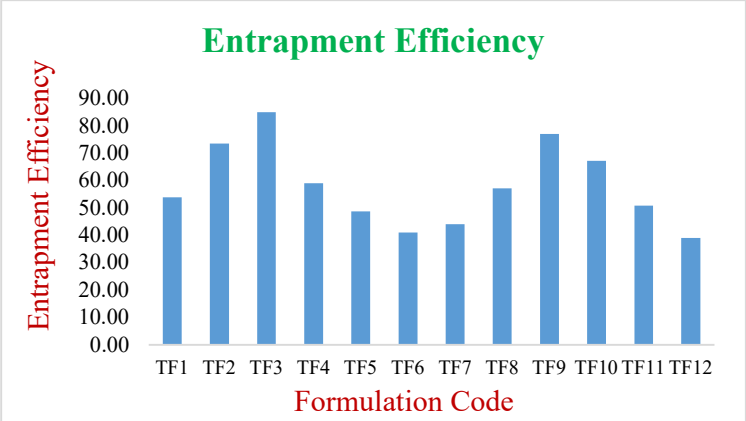

Fig 7: Drug Entrapment Efficiency of Neomycin Sulfate Transferosomes Formulation

Vesicle size and Zeta potential

The vesicle size and zeta potential of the optimized formulations (TF2, TF3, TF9) were measured using a Lite Sizer through light scattering techniques, with a focus on achieving high drug content and entrapment efficiency. The average vesicle diameter ranged from 445 to 592 nm, and the size distribution curve confirmed a normal distribution including Span 80 as an edge activator led to the formation of smaller vesicles. Zeta potential measurements, conducted with a Lite Zetasizer, revealed highly negative values, indicating strong electrical stabilization that helps prevent particle aggregation as shown in Table 5.

Table 5: Particle Size and Zeta Potential of TF2, TF3, TF9

S.No	Formulation code	Particle size	Zeta potential
1	TF2	592	-28.79
2	TF3	445	-32.38
3	TF9	480	-23.45

***In*-vitro release studies**

The *in vitro* drug release studies of Neomycin Sulfate from transferosome gel were conducted using the Franz diffusion method in phosphate buffer at pH 7.4. The results of these studies are presented in Table 6. The cumulative percentage of drug release for formulations TF1 to TF12 is illustrated in Fig 8 and 9. The in vitro release study was performed over 12 hours in the phosphate buffer at pH 7.4. The in vitro release study suggested that there was an inverse relationship between EE% and in vitro release. The results indicate that the TF3 formulation exhibits a controlled release of the drug for up to 12 hours compared to the other formulations. Based on the findings of the in vitro release study, the TF3 formulation was selected for further kinetic studies.

Kinetic analysis studies

The release data was modelled for Zero order, First order, Higuchi model, Hixson Crowell model, Korsemeyer-Peppas model.

Based on the findings, it was determined that the Korsmeyer-Peppas model had the highest correlation coefficient, R^2 (0.9983). and was therefore the model that best fit the optimized TF3 formulation. The fact that the value of "n" was calculated to be 0.9683 (0.5 to 1.00). Shows that the drug release from the polymeric matrix follows non-Fickian or anomalous transport. Diffusion and other processes such matrix swelling, erosion, or relaxation, are all Part of the release mechanism.

Table 6*: %*Cumulative *In-Vitro* Drug Release Studies of Transferosomes Gel

S.No	Time in Hours	Batch Code (Lipid: Surfactant Ratio)					
		TF1(95:5) Mean±SD	TF2(90:10) Mean±SD	TF3(85:15) Mean±SD	TF4(80:20) Mean±SD	TF5(75:25) Mean±SD	TF6(70:30) Mean±SD
1	0	0.00	0.00	0.00	0.00	0.00	0.00
2	1	8.16±0.02	8.68±0.48	9.74±0.09	7.42±0.25	7.89±0.12	8.68±0.15
3	2	11.05±0.22	10.53±0.25	12.11±0.31	11.05±0.31	13.42±0.25	11.11±0.18
4	3	16.05±0.35	16.84±0.43	16.05±0.26	18.42±0.16	21.32±0.19	16.32±0.26
5	4	22.11±0.02	22.11±0.38	22.11±0.06	21.58±0.09	27.37±0.24	21.84±0.33
6	5	28.68±0.12	27.63±0.27	26.32±0.09	27.37±0.13	34.21±0.35	30.00±0.28
7	6	36.84±0.28	34.21±0.36	33.42±0.35	32.89±0.38	39.47±0.29	38.16±0.39
8	7	42.63±0.24	43.16±0.25	39.74±0.24	42.89±0.46	47.37±0.31	43.16±0.45
9	8	48.68±0.32	51.32±0.34	45.26±0.29	48.42±0.24	56.32±0.19	50.79±0.42
10	9	56.58±0.15	55.53±0.09	51.05±0.32	57.37±0.50	64.47±0.41	54.47±0.46
11	10	61.84±0.27	61.58±0.19	58.05±0.45	65.00±0.19	69.47±0.22	61.84±0.49
12	11	69.74±0.02	68.68±0.48	63.32±0.25	73.95±0.21	75.79±0.46	73.16±0.25
13	12	76.58±0.35	74.47±0.32	69.74±0.30	78.95±0.32	80.03±0.25	81.84±0.34

S.No	Time in Hours	Batch Code (Lipid: Surfactant Ratio)					
		TF7(95:5) Mean±SD	TF8(90:10) Mean±SD	TF9(85:15) Mean±SD	TF10(80:20) Mean±SD	TF11(75:25) Mean±SD	TF12(70:30) Mean±SD
1	0	0.00	0.00	0.00	0.00	0.00	0.00
2	1	7.37±0.01	7.11±0.09	8.16±0.09	6.84±0.06	6.58±0.10	7.11±0.16
3	2	11.58±0.05	10.79±0.10	11.05±0.12	10.79±0.09	11.05±0.16	11.32±0.19
4	3	16.58±0.09	18.68±0.14	16.05±0.19	15.53±0.12	15.26±0.24	16.50±0.10
5	4	21.58±0.10	21.32±0.24	20.26±0.24	18.68±0.17	19.47±0.32	22.11±0.24
6	5	30.03±0.33	27.11±0.35	27.11±0.31	23.95±0.21	26.84±0.19	27.37±0.29
7	6	37.63±0.42	31.05±0.29	33.68±0.22	33.68±0.26	34.4±70.25	32.37±0.22
8	7	43.16±0.21	42.11±0.14	42.37±0.29	41.32±0.32	41.05±0.35	40.53±0.34
9	8	48.68±0.32	48.16±0.32	49.21±0.24	48.16±0.41	46.84±0.12	46.05±0.19
10	9	57.11±0.44	57.89±0.28	55.26±0.45	54.74±0.34	55.53±0.25	55.53±0.45
11	10	64.47±0.49	66.32±0.26	62.37±0.24	62.58±0.34	62.37±0.29	68.16±0.49
12	11	73.18±0.26	73.95±0.24	68.95±0.32	67.45±0.45	68.95±0.35	76.61±0.35
13	12	80.16±0.31	79.18±0.36	74.47±0.14	75.13±0.24	77.89±0.40	83.68±0.26

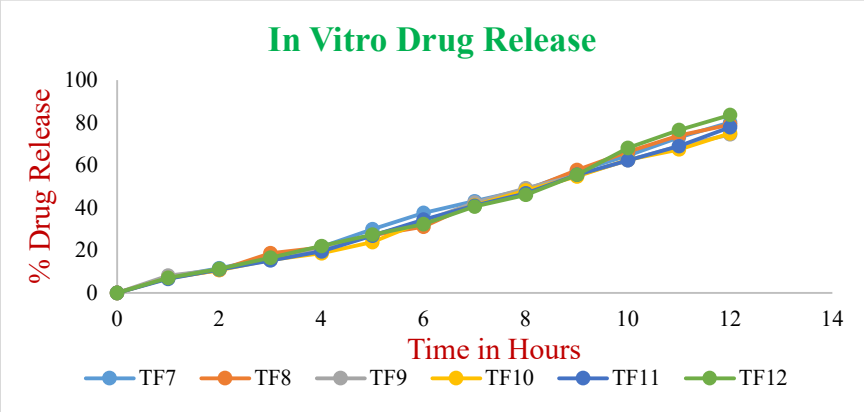

Fig 8: Comparison of *In-Vitro* drug release studies of Neomycin SulfateTransferosomes Gel Containing Span 80 at Different Ratio

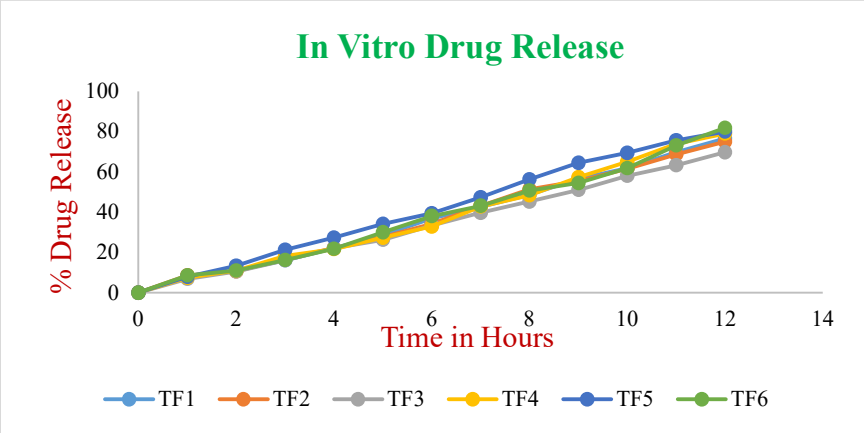

Fig 9: Comparison of *In-Vitro* drug release studies of Neomycin SulfateTransferosomes Gel Containing Tween 80 at Different Ratio

Selection and Evaluation of Best Formulation

Out of the twelve prepared formulations, TF3 was selected based on its entrapment efficiency, drug content, and in-vitro drug release. This formulation, TF3, was then subjected to further studies.

Morphological studies

The selected transferosome formulation, chosen based on entrapment efficiency, was analyzed using Scanning Electron Microscopy (SEM), revealing predominantly spherical vesicles.

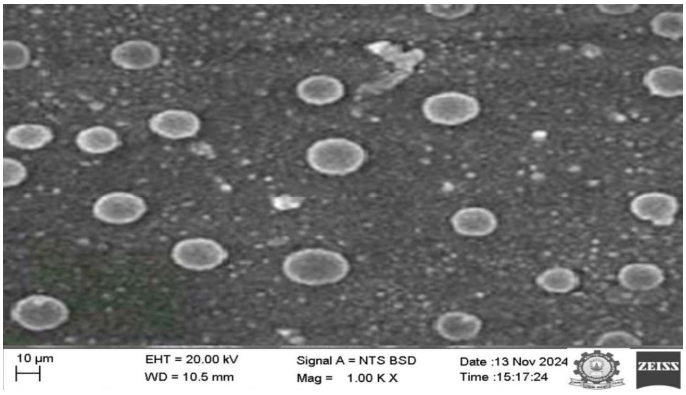

Fig 10: SEM Image of Best Formulation

Comparison of TF3 Transferosomal Gel with Plain Gel

Drug Content

The TF3 Neomycin Sulfate transferosomal gel showed the highest drug content at 94.44%, compared to 92.07% for the plain gel, as detailed in Table 7.

Table 7: Drug Content of Plain Gel and Transferosomes Gel

S.No	Formulation Code	Drug Content(%)(±SD)
1	Plain Gel	92.07±0.31
2	TF3	94.44±0.03

Fig 11: Drug Content through Microbial Assay of Plain Gel and Transferosomes Gel

***In-vitro* drug release studies**

At 12 hours, the cumulative drug release for the TF3 Neomycin Sulfate transferosomal gel was 69.74%, while the plain gel achieved 94.47% release at 8 hours. These results, shown in Table 8, indicate that the TF3 transferosomal gel provided prolonged drug release due to its higher entrapment efficiency compared to the plain gel.

Table 8: *In- Vitro* Cumulative %Drug Release Studies of Plain Gel and TF3 Transferosome Gel

S.No	Time in Hours	Plain Gel Mean±SD	TF3 Gel Mean±SD
1	0	0.0	0.00
2	1	13.38 ±0.24	9.74±0.09
3	2	25.79±0.31	12.11±0.31
4	3	37.11±0.22	16.05±0.26
5	4	49.47±0.18	22.11±0.06
6	5	61.32±0.42	26.32±0.09
7	6	73.95±0.09	33.42±0.35
8	7	85.26±0.29	39.74±0.24
9	8	94.47±0.34	45.26±0.29
10	9	-	51.05±0.32
11	10	-	58.05±0.45
12	11	-	63.32±0.25
13	12	-	69.74±0.30

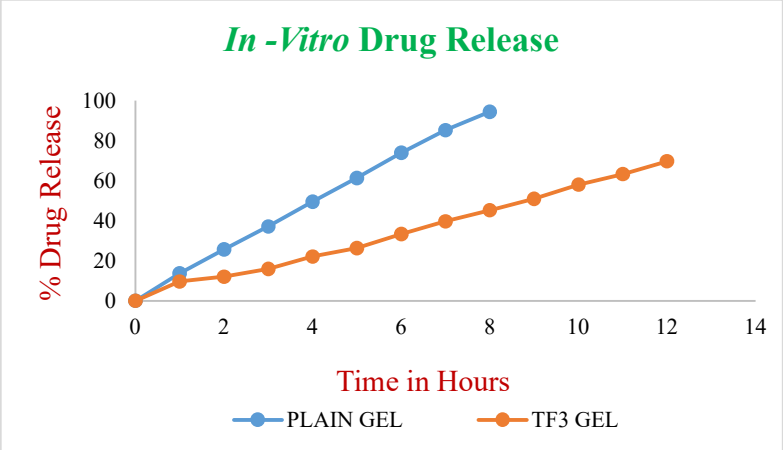

Fig 12: Comparison of *In-Vitro* Drug Release studies of Plain Gel and TF3 Gel

Table 9: Characteristics of Plain Gel and TF3 Transferosomes Gel

S.No	Characterisation	Plain Gel	TF3 Gel
1	Appearance	White	White
2	Clarity	Clear	Clear
3	pH	6.4	6.7
4	Drug content	92.07±0.31	94.44±0.03
5	Drug release	94.47±0.34	69.74±0.30

CONCLUSION

The study demonstrated the successful preparation of neomycin sulfate transferosomes using the thin-film hydration method, achieving optimal properties and improved *in vitro* drug release profiles. Among the tested formulations, TF3, incorporating Span 80 as a surfactant, exhibited the highest drug content, entrapment efficiency, and drug release rate, establishing it as the optimized formulation. The transferosomal gel, developed with Carbopol 940 as the gel base, was designed to enhance skin targeting. *In vitro* studies revealed that the transferosomal gel provided prolonged drug release compared to standard gel formulations, confirming its effectiveness as a controlled-release system for topical applications. These findings highlight the potential of neomycin sulfate-loaded transferosomal gel as a novel skin-targeted drug delivery system. This approach enhances drug permeability and absorption while ensuring sustained therapeutic effects, making it a promising candidate for clinical use in skin-targeted therapies.

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Conflicts of interest
There are no conflicts of interest regarding the publication of this article to disclose.

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