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DEVELOPMENT & EVALUATION OF NAPROXEN LOADED TRANSFEROSOME TO IMPROVE TRANSDERMAL DELIVERY

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ABSTRACT
The present study focuses on the development and evaluation of Naproxen-loaded transferosomes to enhance transdermal drug delivery. Transferosomes were prepared using the thin-film hydration method by varying concentrations of soy lecithin, cholesterol, and Tween 80. The prepared formulations were evaluated for vesicle size, zeta potential, and entrapment efficiency. The vesicle size was found to be in the nanometer range, with the optimized formulation exhibiting the smallest size and highest stability as indicated by a high negative zeta potential. The entrapment efficiency of the formulations was satisfactory, with the optimized formulation showing maximum drug loading due to an optimal lipid composition. The optimized transferosomal formulation was further incorporated into a Carbopol gel base to improve ease of application and patient compliance. The prepared gel formulations were evaluated for viscosity, spreadability, extrudability, and drug content, and showed acceptable physicochemical properties. The in-vitro drug release study of the optimized gel demonstrated a sustained and controlled release pattern over an extended period, in contrast to the rapid release of the conventional formulation. Release kinetics studies revealed that the drug release followed first-order kinetics with a diffusion-controlled mechanism. The overall findings suggest that transferosomes are a promising vesicular carrier system for enhancing the transdermal delivery of Naproxen by improving drug permeation, stability, and therapeutic efficacy while reducing dosing frequency and side effects.

KEYWORDS: Naproxen, Transferosomes, Transdermal drug delivery, Thin-film hydration method, Entrapment efficiency, Vesicle size, Zeta potential, Carbopol gel, Sustained release, Release kinetics.

I. INTRODUCTION

Transdermal drug delivery systems (TDDS) have gained significant attention in recent years due to their ability to deliver drugs through the skin in a controlled and non-invasive manner. This route offers several advantages over conventional oral and parenteral delivery, including avoidance of first-pass metabolism, improved patient compliance, reduced dosing frequency, and minimized systemic side effects (Alkilani et al., 2022). However, the major limitation of transdermal delivery is the barrier function of the stratum corneum, which restricts the permeation of many drugs, especially those with high

molecular weight or poor lipophilicity (Prausnitz et al., 2012).

To overcome these limitations, novel vesicular carriers such as transferosomes have been developed. Transferosomes are ultra-deformable, elastic lipid vesicles composed of phospholipids and edge activators (surfactants), which impart high flexibility to the vesicle membran. Due to their unique structure, transferosomes can squeeze through narrow intercellular spaces of the skin, even when their size is larger than the pores, enabling efficient drug delivery across the skin barrier. This exceptional deformability allows them to penetrate deeper layers of the skin and even reach systemic circulation (Simrah et al., 2024).

Transferosomes possess several advantages over conventional liposomes and other vesicular systems, including enhanced skin penetration, higher drug entrapment efficiency, controlled drug release, and improved bioavailability. Additionally, they can encapsulate both hydrophilic and lipophilic drugs, making them versatile carriers for a wide range of therapeutic agents. Their biocompatibility and biodegradability further make them suitable for pharmaceutical applications (Jain and Kumar; 2017).

Naproxen, a widely used non-steroidal anti-inflammatory drug (NSAID), is commonly prescribed for the treatment of pain and inflammation. However, its oral administration is associated with several limitations such as gastrointestinal irritation, ulceration, and first-pass metabolism, which can reduce therapeutic efficiency and patient compliance. Therefore, delivering Naproxen through the transdermal route using transferosomes can be a promising strategy to enhance its therapeutic efficacy while minimizing systemic side effects (Stoev et al., 2021).

Incorporation of Naproxen into transferosomal vesicles can improve its skin permeation, provide sustained drug release, and enhance bioavailability. The elastic nature of transferosomes enables better penetration through the stratum corneum, overcoming the limitations of conventional formulations and making them an ideal carrier for transdermal delivery of NSAIDs.

Hence, the present study focuses on the development and evaluation of Naproxen-loaded transferosomes with the aim of improving transdermal drug delivery, enhancing therapeutic effectiveness, and reducing adverse effects associated with conventional dosage forms.

II. MATERIAL AND METHODS

Material

Naproxen was used as the active pharmaceutical ingredient. Soy lecithin and cholesterol were employed as lipid components for the preparation of transferosomes, while Tween 80 served as an edge activator to enhance vesicle deformability. Dichloromethane was used as an organic solvent for film formation. Carbopol 934 was utilized as a gelling agent for the preparation of gel base, and propylene glycol was added as a permeation enhancer and viscosity modifier. Double distilled water was used throughout the study, and suitable pH adjusters such as sodium hydroxide or citric acid were used to maintain the desired pH of the formulation.

Methods

Preparation of Naproxen-Loaded Transfersomes

Transfersomes were prepared using the thin-film hydration (rotary film evaporation) method. Accurately weighed quantities of Naproxen (50 mg), lecithin (250–750 mg), and cholesterol (50–150 mg) were dissolved in 0.25–0.75% Tween 80 and dichloromethane. The mixture was transferred into a round-bottom flask and rotated at 45°C to evaporate the solvent completely, forming a thin lipid film at the bottom. Hydration of the film was performed with 20 mL phosphate buffer (pH 6.8) for 90 min at 70°C. The resulting vesicular suspension was sonicated for 5 min to reduce vesicle size.

Table 1: Optimization of Transfersomes formulation.

Ingredients	F1	F2	F3	F4	F5	F6
Drug (API) (mg)	100	100	100	100	100	100
Soy Lecithin	250	500	750	250	500	750
Cholesterol	50	100	150	-	-	-
Tween 80 (%)	0.25	0.50	0.75	0.25	0.50	0.75
Dichloromethane (ml)	5	5	5	5	5	5

Preparation of Gel Base

The gel base was prepared by dispersing Carbopol 934 (0.5–1.5% w/v) in 80 mL of double distilled water under continuous stirring at 800 rpm for 1 hour to obtain a uniform dispersion. To enhance the viscosity and consistency of the gel, 10 mL of propylene glycol was added and mixed thoroughly. The final volume of the gel was adjusted to 100 mL using double distilled water. The prepared gel was then subjected to sonication for 10 minutes to remove any entrapped air bubbles and to obtain a clear, homogeneous gel. The pH of the formulation was adjusted to 6.8 using suitable pH modifiers such as sodium hydroxide or citric acid to ensure compatibility with the skin. Finally, Naproxen-loaded transferosomal preparation (3% w/w) was incorporated into the gel base under gentle stirring to achieve a uniform dispersion, resulting in the formation of transferosomal gel (Ghanbarzadeh *et al.*, 2013).

Characterization of Naproxen loaded Transfersomes
Surface charge and vesicle size
The vesicles size and size distribution and surface charge were determined by Dynamic Light Scattering method (DLS) (Malvern Zetamaster, ZEM 5002, Malvern, UK). Zeta potential measurement of the Transfersomes was based on the zeta potential that was calculated according to Helmholtz–Smoluchowsky from their electrophoretic mobility (Shiuan *et al.*, 2019). For measurement of zeta potential, a Zetasizer was used with field strength of 20 V/cm on a large bore measures cell. Samples were diluted with 0.9 % NaCl adjusted to a conductivity of 50 lS/cm.

Entrapment efficiency
One milliliter of Transfersomes suspension was centrifuged at 15.000 rpm for 1 h to allow the separation the entrapped drug from the un-entrapped drug. After removal of the supernatant, the sediment was lysed using methanol and then analyzed spectrophotometrically at 264 nm using a UV spectrophotometer (Labindia 3000+). The EE% of MIC in the prepared Transfersomes was calculated applying the following equation:

$$\%\ Entrapment\ Efficiency = \frac{Terotical\ drug\ content - Practical\ drug\ content}{\text{Therotical drug content}} \times 100$$

Characterization of Transfersomes containing gel
Measurement of Viscosity
Viscosity measurements of prepared topical Transfersomes based gel were measured by Brookfield viscometer using spindle no. 63 with the optimum speed of 10rpm; viscosity (Qushawy *et al.*, 2018).

pH measurements
pH of selected optimized formulations was determined with the help of digital pH meter. Before each measurement of pH, pH meter should be calibrated with the help of buffer solution of pH 4, pH 7 and pH 9.2. After calibration, the electrode was dipped into the vesicles as long as covered by the vesicles (Gupta *et al.*, 2012). Then pH of selected formulation was measured and readings shown on display were noted.

Drug content
Accurately weighed equivalent to 100 mg of topical transfersomal gel was taken in beaker and added 20 ml of methanol. This solution was mixed thoroughly and filtered using Whatman filter paper no.1. Then 1.0 mL of filtered solution was taken in 10 mL capacity of volumetric flask and volume was made upto 10 mL with methanol (Hanpramukkun *et al.*, 2009). This solution was analyzed using UV-Spectroscope at λ_{max} 264 nm.

Extrudability study
Extrudability was based upon the quantity of the gel extruded from collapsible tube on application of certain load. More the quantity of gel extruded shows better extrudability (Jivrani and Patel, 2014). It was determine by applying the weight on gel filled collapsible tube and recorded the weight on which gel was extruded from tube.

Spreadibility
Spreadibility of formulation is necessary to provide sufficient dose available to absorb from skin to get good therapeutic response. An apparatus in which a slide fixed on wooded block and upper slide has movable and one end of movable slide tied with weight pan (Mishra and Biswal, 2012). To determine spreadibility, placing 2-5 g of gel between two slide and gradually weight was increased by adding it on the weight pan and time required by the top plate to cover a distance of 6cm upon adding 20g of weight was noted. Good spreadibility show lesser time to spread.

$$Spreadibility\ (g.cm/\sec) = \frac{Weight\ tide\ to\ Upper\ Slide \times Lenth\ moved\ on\ the\ glass\ slide}{Time\ take\ nto\ slide}$$

***In vitro* drug diffusion study**
The *In-vitro* diffusion study is carried by using Franz Diffusion Cell. Egg membrane is taken as semi permeable membrane for diffusion (Nimker *et al.*, 2017). The Franz diffusion cell has receptor compartment with an effective volume approximately 60 mL and effective surface area of permeation 3.14sq.cms. The egg membrane is mounted between the donor and the receptor compartment. A two cm^2 size patch taken and weighed then placed on one side of membrane facing donor compartment. The receptor medium is phosphate buffer pH 7.4. The receptor compartment is surrounded by water jacket so as to maintain the temperature at 32 ± 0.5°C. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the diffusion cell.

During each sampling interval, samples are withdrawn and replaced by equal volumes of fresh receptor fluid on each sampling. The samples withdrawn are analyzed spectrophotometrically at wavelength of drug 264 nm.

RESULTS AND DISCUSSION
The prepared transferosomal formulations (F1–F6) were evaluated for vesicle size and zeta potential, which are critical parameters influencing stability and skin permeation. The vesicle size was found to range between 142.18 nm and 210.45 nm (Table 2), indicating successful formation of nanosized vesicles suitable for transdermal delivery. Among all formulations, F3 exhibited the smallest vesicle size (142.18 nm), which is advantageous for enhanced penetration through the stratum corneum. The zeta potential values ranged from −26.42 mV to −38.72 mV, confirming good stability of the vesicular system due to sufficient electrostatic repulsion. The optimized formulation F3 showed the highest negative zeta potential (−38.72 mV), indicating superior stability and reduced aggregation tendency.

The entrapment efficiency of the formulations was found to be in the range of 72.65% to 88.95% (Table 3), demonstrating effective incorporation of Naproxen into

the transferosomal vesicles. Among all formulations, F3 showed the highest entrapment efficiency (88.95 ± 0.61%), which can be attributed to the optimal ratio of lipid components that facilitated better drug encapsulation. In contrast, lower entrapment efficiency observed in formulations F4–F6 may be due to inadequate lipid composition or absence of stabilizing components, leading to drug leakage during preparation.

Based on vesicle size, zeta potential, and entrapment efficiency, F3 was selected as the optimized formulation. The characterization of F3 confirmed its desirable properties, including nanoscale vesicle size, high drug loading, and excellent stability (Table 4), making it suitable for transdermal drug delivery applications.

The optimized transferosomal formulation was further incorporated into a Carbopol gel base and evaluated for physicochemical properties (Table 5). All gel formulations exhibited acceptable viscosity, assay, extrudability, and spreadability. Among them, GF2 showed the most balanced properties, with appropriate viscosity, high drug content, good extrudability, and adequate spreadability, indicating ease of application and uniform drug distribution.

The in-vitro drug release study of the optimized gel formulation (GF2) demonstrated a controlled and sustained release pattern (Table 6). The formulation showed an initial release of 18.45% at 0.5 hours, followed by a gradual increase to 44.25% at 2 hours and 62.40% at 4 hours, eventually reaching 94.85% at 12 hours. This sustained release behavior can be attributed to the encapsulation of the drug within transferosomal vesicles and its subsequent diffusion through the gel matrix, which acts as a barrier and prolongs drug release.

The study indicates that transferosomes significantly enhance the performance of Naproxen by improving drug entrapment, stability, and providing sustained release. The optimized formulation (F3) and its gel form (GF2) demonstrated promising characteristics, making them suitable candidates for effective transdermal drug delivery.

Table 2: Results of average vesicle size and zeta potential.

S. No.	F. Code	Vesicle Size (nm)	Zeta Potential (mV)
1	F1	210.45	−33.28
2	F2	198.62	−35.14
3	F3	142.18	−38.72
4	F4	168.35	−26.42
5	F5	155.74	−29.86
6	F6	162.90	−31.25

Table 3: Results of percentage entrapment efficiency.

S. No.	F. Code	Entrapment Efficiency (%)
1	F1	78.42 ± 0.58
2	F2	82.36 ± 0.67
3	F3	88.95 ± 0.61
4	F4	74.18 ± 0.34
5	F5	72.65 ± 0.39
6	F6	73.24 ± 0.28

Table 4: Characterization of Optimized formulation F3 of Transfersomes.

F. Code	Average Vesicle Size (nm)	% Entrapment Efficiency	Zeta Potential (mV)
F3	142.18	88.95 ± 0.61	−38.72

Table 5: Characterization of gel based formulation.

Formulation	Viscosity (cps)*	Assay (%)*	Extrudability (g)*	Spreadability (g·cm/sec)*
GF1	3320 ± 14	98.45 ± 0.18	178 ± 6	11.42 ± 0.28
GF2	3190 ± 11	99.28 ± 0.24	184 ± 5	10.68 ± 0.30
GF3	2985 ± 13	98.10 ± 0.21	190 ± 6	9.92 ± 0.22

***Average of three determinations**

Table 6: *In vitro* drug release study of prepared gel formulation GF2.

S. No.	Time (hr)	% Cumulative Drug Release
1	0.5	18.45
2	1	32.80
3	2	44.25
4	4	62.40
5	6	72.15

6	8	86.60
7	12	94.85

Table 7: Release Kinetics of optimized gel of transferosomal gel.

Formulation	Zero Order (R^2)	First Order (R^2)	Higuchi (R^2)	Korsmeyer–Peppas (R^2)
GF3	0.9070	0.9890	0.9330	0.9810

CONCLUSION

The study successfully developed Naproxen-loaded transferosomes and incorporated them into a gel for enhanced transdermal delivery. The optimized formulation showed nanoscale vesicle size, high entrapment efficiency, good stability, and sustained drug release. The transferosomal gel proved to be a promising system for improving therapeutic efficacy and patient compliance.

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