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Development and Characterization of Minocycline Loaded Elastic Liposomal Gel for Effective Treatment of Skin Disease

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ABSTRACT

The study aimed to develop and evaluate elastic liposomal gel formulations for the effective delivery of therapeutic agents to treat skin diseases. Various formulations of elastic liposomes were prepared, and their vesicle size, entrapment efficiency, and stability were assessed. The optimized formulation (F4) exhibited the smallest vesicle size (135.25 nm) and the highest entrapment efficiency (76.65%). Additionally, the corresponding elastic liposomal gel formulation (ELG2) was evaluated for drug content, pH, spreadability, and viscosity. ELG2 exhibited good drug content (98.85%), skin-friendly pH (6.82), and desirable spreadability (12.65 gm.cm/sec.). In-vitro drug release studies revealed that ELG2 demonstrated a sustained release profile, with 96.65% of the drug released at 10 hours. The release kinetics followed zero-order and Korsmeyer-Peppas models, indicating a controlled release mechanism. Stability studies confirmed the long-term stability of ELG2, with minimal changes in drug content and viscosity at both 4°C and 28°C. These results highlight the potential of the developed elastic liposomal gel for effective and stable drug delivery, making it a promising formulation for the treatment of dermatological conditions.

Keywords: Elastic liposomes, liposomal gel, drug delivery, vesicle size, entrapment efficiency, sustained release, skin disease treatment, stability, in-vitro drug release, transdermal delivery.

1. INTRODUCTION

Minocycline, a broad-spectrum antibiotic from the tetracycline class, is widely used to treat various bacterial infections, including skin diseases such as acne *vulgaris, rosacea*, and other dermatological conditions [1]. Traditionally, minocycline is administered orally, but systemic absorption often leads to adverse effects such as gastrointestinal disturbances, photosensitivity, and even hepatotoxicity in certain cases [2]. To minimize these systemic side effects and enhance therapeutic efficacy, the development of localized drug delivery systems has gained significant attention in recent years.
One promising approach to achieve localized delivery of minocycline is the use of liposomal formulations, particularly elastic liposomes. Elastic liposomes, also known as ultradeformable liposomes, are liposomal vesicles that possess the ability to deform and squeeze through the skin's tight junctions, allowing for enhanced permeation of the drug across the stratum corneum [3]. This makes them an ideal carrier for skin-targeted therapies. The encapsulation of minocycline in such liposomal systems can enhance its skin penetration and provide sustained release at the site of infection, thus improving therapeutic outcomes.
In addition to liposomes, the incorporation of the drug into gels offers several advantages, including ease of application, better retention on the skin, and a controlled release profile. The combination of elastic liposomes and gels can therefore significantly improve the pharmacokinetics of minocycline, providing prolonged release and enhanced therapeutic efficacy at the target site. Various polymers, such as carbopol, hydroxypropyl methylcellulose (HPMC), and chitosan, are commonly used to formulate gels for topical drug delivery, as they provide the desired consistency, stability, and skin adhesion [4]
The objective of this research is to develop and characterize minocycline-loaded elastic liposomal gel for effective topical delivery in the treatment of skin diseases. The study will focus on the optimization of liposomal formulations to enhance their skin penetration and encapsulation efficiency, as well as the preparation of a gel formulation that ensures sustained drug release, improved stability, and enhanced therapeutic efficacy. Furthermore, the in-vitro characterization of the

liposomal gel, including drug release, skin permeation, and physical stability, will be performed to assess the feasibility of this novel system for dermatological applications.

2. MATERIAL AND METHODS

Material

The materials used for the preparation of the elastic liposomal hydrogel include **Minocycline** (active ingredient, sourced from a pharmaceutical company), **Soya Phosphatidyl Choline** (lipid from Ash Chemie India), and **Carbopol 934P** (gelling agent from S.D. Fine Chem. Ltd.). Other excipients include **preservatives** (Methyl and Propyl Paraben), **salts** (Disodium Hydrogen Phosphate, Di-potassium Hydrogen Orthophosphate, and Sodium Chloride), and **solvents** (Methanol, Ethanol, Chloroform from Qualigens Fine Chemicals). **Propylene Glycol** was used as a humectant to improve skin hydration.

Methods

Formulation of Minocycline loaded elastic liposomes

Elastic liposomes were prepared by rotary evaporation method given by Touitou *et al.*, (2000) [5-6] with slight modification. The accurately weighed amounts of phospholipids and surfactant were taken in a clean, dry, round-bottom flask and this lipid mixture was dissolved in minimum quantity of ethanol (5ml) as per table 1. The round bottom flask was rotated at 45º angle using rotator evaporator at 40°C in order to make uniform lipid layer. The organic solvent was removed by rotary evaporation under reduced pressure at the same temperature (40°C). Final traces of solvents were removed under vacuum overnight. The prepared lipid film in the inner wall of round bottom was hydrated with 2% w/v of drug solution in distilled water, followed by rotating the flask containing mixture of drug by rotation at speed of 60 rev/min for 1 hr. After complete hydration of film, the prepared formulation of elastic liposomes was subjected to sonication at 4°C in 3 cycles of 10 minutes with 5 sec rest between the cycles. The prepared formulation was stored at 4°C in closed container till further use for analysis.

Table 1: Optimization of Minocycline loaded elastic liposomes

Formulation code	Soya PC (% w/v)	Span 80 (% w/v)	Drug (mg)	Ethanol (ml)
F1	4	2	50	5
F2	5	2	50	5
F3	6	2	50	5
F4	4	3	50	5
F5	5	3	50	5
F6	6	3	50	5

3. CHARACTERIZATION OF ELASTIC LIPOSOMES

Vesicle size

Microscopic analysis was performed to determine the average size of prepared elastic Liposomes. Formulation was diluted with distilled water and one drop was taken on a glass slide and covered with cover slip. The prepared slide was examined under trinocular microscopic at 400 X. The diameters of more than 150 vesicles were randomly measured using calibrated ocular and stage micrometer. The average diameter was calculated using the flowing formula [7].

$$Average\ Diameter = \frac{\Sigma n.d}{\Sigma\, n}$$

Where n = number of vesicles; d = diameter of the vesicles

Zeta potential

The size distribution and surface charge were determined by Dynamic Light Scattering method (DLS) (Malvern Zetamaster, ZEM 5002, Malvern, UK). Zeta potential measurement of the elastic liposomes was based on the zeta potential that was calculated according to Helmholtz–Smoluchowsky from their electrophoretic mobility. 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 [8].

Entrapment efficiency

Minocycline entrapped within the elastic liposomes was estimated after removing the unentrapped drug. The unentrapped drug was separated from the elastic liposomes by subjecting the dispersion to centrifugation in a cooling centrifuge (Remi Equipments, Mumbai) at 18000 rpm at a temperature of 4°C for 45 minutes, where upon the pellets of liposomes and the supernatant containing free drug were obtained. The elastic liposomes pellets were washed again with phosphate buffer to remove any unentrapped drug by centrifugation. The combined supernatant was analyzed for the drug content after suitable dilution with phosphate buffer solution by measuring absorbance at 284 nm using Labindia 3000+ spectrophotometer [9].

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

Preparation of gel base

Carbopol 934 (1-3%w/v) was accurately weighed and dispersed into double distilled water (80ml) in a beaker. This solution was stirred continuously at 800 rpm for 1 hour and then 10ml of propylene glycol was added to this solution. The obtained slightly acidic solution was neutralized by drop wise addition of 0.05 N sodium hydroxide solutions, and again mixing was continued until gel becomes transparent. Volume of gel was adjusted to 100 ml and then sonicated for 10 min on bath sonicator to remove air bubbles. Gel was also prepared with plain drug by adding 10 mg of drug and dispersed properly by following same procedure given above. The same procedure was used to formulate liposome containing gel, Elastic liposomes preparation corresponding to 0.75% w/w of drug was incorporated into the gel base to get the desired concentration of drug in gel base.

4. CHARACTERIZATION OF ELASTIC LIPOSOMES CONTAINING GEL

Measurement of viscosity

Viscosity measurements of prepared topical liposomes based gel were measured by Brookfield viscometer using spindle no. 63 with the optimum speed of 10rpm [10].

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. Then pH of selected formulation was measured and readings shown on display were noted [11].

Drug content

Accurately weighed equivalent to 100 mg of topical liposome gel was taken in 10 ml volumetric flask, add 5 ml of methanol and sonicate it for 10 min and after sonication volume was made upto 10 ml with methanol [12]. This solution was mixed thoroughly and filtered using Whatman filter paper no.1. Then 0.1mL of filtered solution was taken in 10 mL capacity of volumetric flask and volume was made upto 10 mL with methanol. This solution was analyzed using UV-Spectroscope at λ_{max} 284 nm. Drug content of topical liposome based gel is shown in table no 8.3.

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. 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. It was determined by method reported by Multimer *et al.,* (1956) [13]. 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. 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.

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

***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. 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 284nm of drug.

Stability Studies

Stability study was carried out for drug loaded elastic liposomes at two different temperatures i.e. refrigeration temperature (4.0 ±0.2°C) and at room temperature (25-28±2°C) for 3 weeks. The formulation subjected for stability study was stored in borosilicate container to avoid any interaction between the formulation and glass of container. The formulations were analyzed for any physical changes and drug content.

5. RESULTS AND DISCUSSION

The present study focused on the development and evaluation of elastic liposomal gels (ELG) for the delivery of drugs in dermatological applications. The formulations were evaluated for various properties, including vesicle size, entrapment efficiency, drug content, spreadability, viscosity, and in-vitro drug release, to establish the optimal formulation for effective drug delivery.

As shown in Table 2, the vesicle size of the elastic liposomes formulations varied significantly, ranging from 135.25 nm to 186.65 nm. Formulation F4 exhibited the smallest vesicle size of 135.25 nm, which is a desirable characteristic for efficient skin penetration and drug delivery. Smaller vesicles are typically more stable and exhibit enhanced skin permeability, which is crucial for local drug delivery. Additionally, the entrapment efficiency of the formulations was evaluated, and F4 demonstrated the highest entrapment efficiency of 76.65%, suggesting that this formulation was capable of retaining a substantial amount of the active drug, thereby increasing its potential therapeutic effect. This high entrapment efficiency is essential for achieving sustained drug release and effective treatment.

The zeta potential of formulation F4 was measured at -42.50 mV, as seen in Table 3 and Figure 2. A high negative zeta potential indicates good stability of the liposomes, preventing aggregation and ensuring the uniform distribution of the liposomes in the formulation. A zeta potential of this magnitude suggests that the optimized formulation (F4) would remain stable over time and would not aggregate, ensuring a consistent drug release profile.

The physical characteristics of the elastic liposomal gels (ELG1, ELG2, and ELG3) were also evaluated. Table 4 presents the drug content, pH, spreadability, and viscosity of each formulation. The drug content for all formulations was close to 97%, indicating good drug incorporation in the gel. The pH values of the gels were in the skin-friendly range, with values ranging from 6.82 to 6.92, which is suitable for topical applications. Formulation ELG2 exhibited the highest spreadability (12.65 gm.cm/sec.) and a viscosity of 2365 cps, which indicates that it has a good balance of consistency and ease of application on the skin.

Table 5 presents the in-vitro drug release profile of ELG2. The release of the drug over time indicated that a significant amount of the drug was released in the first few hours, with 96.65% of the drug released by 10 hours. The release data suggests that the drug release from the gel formulation follows a controlled release pattern. This is beneficial for sustained therapeutic action, especially in the treatment of chronic skin conditions where prolonged drug release is desired. The cumulative drug release data showed a steady release profile, which is indicative of the gel's potential as an effective drug delivery system.

The release kinetics were analyzed using various models, and the results, as presented in Table 6, revealed that the data best fitted the Zero Order and Korsmeyer's Peppas models, with R^2 values of 0.9897 and 0.991, respectively. This suggests that the drug release from the formulation follows a zero-order kinetics (constant release rate), which is ideal for sustained and controlled drug delivery. The Korsmeyer-Peppas model further indicated that the release mechanism was likely a combination of diffusion and erosion, typical for systems designed for prolonged release.

Stability studies, as shown in Table 7, were conducted at two different temperatures: 4°C and 28°C. The drug content and viscosity values remained relatively stable over 30 days at both temperatures, with minimal changes observed in drug content (ranging from 97.95% to 96.65%) and viscosity (ranging from 2345 cps to 2255 cps). These results indicate that the optimized formulation, ELG2, is stable under typical storage conditions, and it can maintain its integrity and performance for extended periods.

Table 2: Evaluations of elastic liposomes for vesicle size and entrapment efficiency

Formulation	Vesicle Size (nm)	Entrapment efficiency (%)
F1	182.23±0.45	66.58±0.33
F2	165.85±0.36	68.89±0.25
F3	155.65±0.22	70.23±0.15
F4	135.25±0.15	76.65±0.36
F5	186.65±0.65	62.23±0.22
F6	163.58±0.47	68.79±0.14

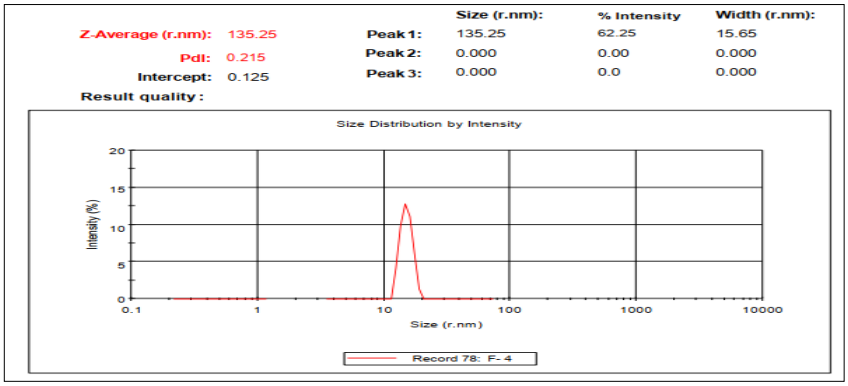

Figure 1: Graph of vesicle size and entrapment efficiency

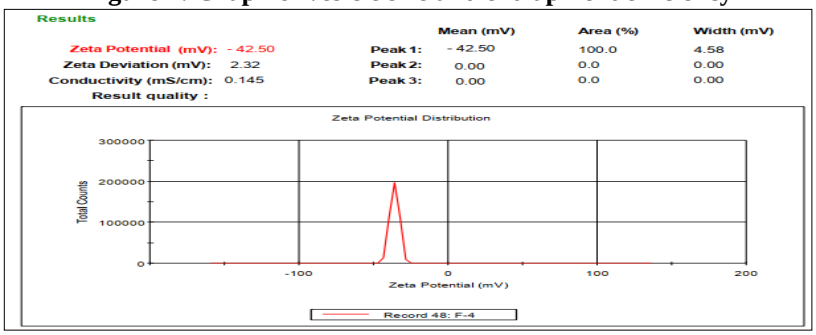

Figure 2: Zeta potential of optimized elastic liposomes formulation F4

Table 3: Vesicle size, Entrapment efficiency and Zeta potential of optimized formulation

Formulation Code	Vesicle Size (nm)	Entrapment Efficiency (%)	Zeta potential (mV)
F4	135.25±0.15	76.65±0.36	-42.50

Table 4: Results of elastic liposomes gel formulations

Code	Drug content (%)	pH	Spreadability (Gm.cm/sec.)	Viscosity (cps)
ELG1	96.65±0.25	6.85±0.15	13.45±0.65	2458±15
ELG2	98.85±0.32	6.82±0.32	12.65±0.45	2365±18
ELG3	95.65±0.65	6.92±0.33	11.85±0.32	2215±16

Table 5: *In-vitro* drug release data for ELG2

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative* % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	16.65	1.221	83.35	1.921
1	1	0	23.32	1.368	76.68	1.885
2	1.414	0.301	36.65	1.564	63.35	1.802
4	2	0.602	49.98	1.699	50.02	1.699
6	2.449	0.778	60.23	1.780	39.77	1.600
8	2.828	0.903	78.85	1.897	21.15	1.325
10	3.162	1	96.65	1.985	3.35	0.525

Table 6: Regression analysis data of elastic liposomes gel formulation

Batch	Zero Order	First Order	Higuchi's Model	Korsmeyers Peppas Equation
	R^2	R^2	R^2	R^2
ELG2	0.9897	0.8248	0.975	0.991

Table 7: Result of stability studies of optimized formulation ELG2

Parameters	4.0 ± 0.5°C		28 ± 0.5°C	
Days	**15**	**30**	**15**	**30**
Drug content (%)	97.95±0.32	97.45±0.32	97.02±0.32	96.65±0.32
Viscosity (cps)	2345±15	2315±10	2310±15	2255±25

6. CONCLUSION

The results of this study demonstrate that the developed elastic liposomal gel formulations, particularly ELG2, exhibit desirable characteristics for effective skin drug delivery. The small vesicle size, high entrapment efficiency, and stable zeta potential of formulation F4 provide an excellent foundation for its use in therapeutic applications. The in-vitro drug release data indicate that the formulation can provide sustained and controlled drug release, and the stability studies suggest that the formulation is reliable over time. The optimized elastic liposomal gel formulation (ELG2) appears to be a promising candidate for further development and clinical application in the treatment of skin diseases. The sustained release and stable formulation make it a valuable addition to transdermal drug delivery systems.

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