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Research Article

Design And Assessment Of Transfersomal Vesicles For Enhanced Transdermal Delivery Of 5-Fluorouracil

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ABSTRACT

Transfersomes, ultra-deformable lipid vesicles, have emerged as promising carriers for transdermal drug delivery. These vesicles, comprising phospholipids and surfactants, facilitate the penetration of therapeutic agents through the skin barrier. This study focuses on formulating transfersomes loaded with 5-Fluorouracil (5-FU) and evaluating their physicochemical properties such as particle size, entrapment efficiency, zeta potential, and drug release behavior to enhance its dermal absorption.

Keywords: Transfersomes, 5-Fluorouracil, Nanocarriers, Skin Cancer, Entrapment Efficiency, Transdermal Delivery

Introduction

5-Fluorouracil (5-FU) is a widely utilized chemotherapeutic agent effective against a broad spectrum of malignant conditions. It is particularly indicated for the treatment of both internal (visceral) and skin-related (dermatologic) cancers. Its mechanism of action involves the inhibition of DNA synthesis in rapidly dividing cancer cells, making it a valuable option in oncologic therapies.

Topical application of 5-FU has demonstrated promising results in the treatment of squamous cell carcinoma lesions. However, the recurrence of nonmelanoma skin cancers, such as basal and squamous cell carcinoma, is common, often necessitating repeated interventions. One of the key limitations of 5-FU in topical formulations is its poor skin permeation, which significantly reduces its therapeutic efficacy. To overcome this challenge, the present study aims to develop and evaluate 5-FU-loaded transfersomal nanocarriers, designed to enhance transdermal drug delivery. These formulations were further assessed for their permeability characteristics and in-vitro release profile.

Materials and methods

5-FU was procured from S.K. Traders, Indore. Soya lecithin (30%), Rhodamine, Tween 80, and Span 80 were obtained from reputed suppliers. All other reagents were of analytical grade[2].

Preparation of transfersomes

Transfersomes containing 5-FU were formulated using the thin-film hydration technique, also known as the rotary evaporation method. In this process, 5-FU, 30% soya lecithin (SPL), and surfactants such as Tween 80 and Span 80 (serving as edge activators) were dissolved in ethanol within a round-bottom flask. The mixture was heated to 55°C to facilitate the complete evaporation of the organic solvent, resulting in the formation of a thin lipid film on the inner wall of the flask. The film was allowed to dry further for 12 hours to ensure complete solvent removal. Subsequently, the dry lipid film was hydrated with phosphate buffer (pH 7.4) under vigorous shaking at room temperature for 15–30 minutes. The obtained dispersion was then subjected to additional hydration in phosphate buffer at a controlled temperature of 2–8°C for 1 hour to yield the final transfersomal suspension[3].

Evaluation of transferosomes

1. Vesicle Size Analysis:

The particle size of the transfersomal vesicles was determined using dynamic light scattering (DLS) with the Malvern Zetasizer 3000 HSA. This technique provides both the average vesicle diameter and the polydispersity index (PDI), which reflects the uniformity of the size distribution. All measurements were carried out in triplicate to ensure accuracy and reproducibility. [4]

2. Zeta Potential Measurement:

Zeta potential, indicative of the surface charge and colloidal stability of vesicular systems, was assessed by measuring the electrophoretic mobility of the transfersomes using a Malvern Zetasizer 3000 HSA. Higher absolute zeta potential values suggest better physical stability due to electrostatic repulsion between vesicles[5].

3. Morphological Analysis:

The surface morphology of the prepared transfersomal vesicles was examined through transmission electron microscopy (TEM). A drop of the vesicular dispersion was placed on carbon-coated copper grids and negatively stained with a 1% aqueous solution of phosphotungstic acid. The samples were observed under the TEM at an accelerating voltage of 100 kV to visualize the vesicle structure and lamellarity[6].

3. Fourier Transform Infrared Spectroscopy (FTIR):

FTIR analysis was performed using a Shimadzu 8400S spectrophotometer to investigate potential interactions between 5-FU and excipients. Samples including pure drug, phospholipids, and the optimized formulation were analyzed using the potassium bromide (KBr) pellet method. Spectra were recorded in the range of 4000–400 cm^{-1} in transmission mode[7].

5. Entrapment Efficiency (%EE):

The amount of 5-FU encapsulated within the transfersomal vesicles was quantified by ultracentrifugation. The entrapment efficiency was calculated using the following formula:

%EE = (Qt – Qs/ Qt) X 100

Where EE is the entrapment efficacy, Qt is the amount of apigenin added, and Qs is the amount of 5-FU detected in the supernatant. [8]

6. In Vitro Drug Release Study:

The in vitro release profile of 5-FU from the optimized transfersomal formulation was evaluated using a Franz diffusion cell setup equipped with a cellophane membrane. The membrane, with a diffusion area of 2.5 cm^2, separated the donor and receptor compartments. The receptor chamber was filled with 22.5 mL of phosphate buffer (pH 5.5), stirred at 100 rpm, and maintained at 37 ± 0.5°C. A measured amount of the transfersomal formulation was placed in the donor compartment. At predetermined intervals, 2 mL of sample was withdrawn and replaced with fresh buffer to maintain sink conditions. The cumulative drug permeation was calculated and plotted as a function of time.[9]

7. Stability of Formulated Transferosome

To evaluate the stability of the transferosome, studies were conducted under various stress conditions to assess its resistance to physical, chemical, microbial, toxicological, and environmental degradation. The optimized formulation was stored under different ICH-recommended conditions, including long-term (25 ± 2°C and 60 ± 5% RH), intermediate (30 ± 2°C and 65 ± 5% RH), and accelerated (40 ± 2°C and 75 ± 5% RH) environments. The samples were analyzed at predetermined intervals of 0, 3, 6, 9, and 12 months[10]. After each storage period, the formulations were evaluated for key physical parameters such as particle size, polydispersity index (PDI), and drug content to determine their stability profile[11].

Results and discussion

An optimal ratio of phospholipid (SLP) to edge activator (EA) plays a critical role in enhancing both vesicle deformability and drug entrapment efficiency. The entrapment efficiency of 5-FU is influenced by several factors, including the drug–lipid bilayer interactions, lipid concentration, and processing parameters such as the number of extrusion cycles. Various weight-to-weight (w/w) ratios of SLP and EA were employed to formulate different batches of transfersomes, as outlined in Table 1.

Among the prepared formulations, P3—comprising an 85:15 (SLP:EA) ratio—produced vesicles with a mean particle size of 153.2 ± 10.3 nm and demonstrated the highest drug entrapment efficiency of 86.06 ± 0.076%. This same ratio also led to the formation of uniformly sized vesicles using the hydration technique. TEM analysis confirmed the vesicles to be predominantly unilamellar in nature. Additionally, zeta potential measurements indicated superior colloidal stability in transfersomes (–39.6 ± 0.2 mV) compared to liposomes (–36.9 ± 0.1 mV) and niosomes (–33.4 ± 0.4 mV), suggesting enhanced electrostatic repulsion and system stability (Table 2).

FTIR spectroscopy provided further insight into the successful encapsulation of 5-FU. The pure drug exhibited prominent peaks in the range of 3550–3200 cm^{-1} due to O–H stretching, along with C–H stretching signals above 3000 cm^{-1} and strong C=O bands between 1750–1735 cm^{-1}. Characteristic peaks at 1651, 1500, 1354, and 1245 cm^{-1} associated with aromatic ring vibrations were significantly diminished or absent in the spectra of the transfersomal formulation. Instead, new peaks appeared at 1559 cm^{-1} (C–C stretching) and 1607 cm^{-1} (aromatic C–H bending), indicating possible interactions between 5-FU and lipid constituents—thus confirming successful drug incorporation within the nanocarrier matrix (refer to Fig. 3).

Zeta potential values across the formulations ranged from 9.24 to 13.46 mV, which is indicative of reasonable physical stability. All formulations exhibited a net negative surface charge. However, no strong correlation was observed between the zeta potential and the phospholipid-to-surfactant ratio. Additionally, the polydispersity index (PDI) values tended to increase with higher ratios of phospholipids to surfactants, suggesting a broader size distribution under these conditions.

The stability evaluation of the optimized transfersomal formulation revealed a minimal increase in particle size over the six-month storage period. At both 4°C and 25°C, particle size exhibited a slight change from 35.45 ± 0.58 nm to 36.85 ± 3.43 nm. The initial entrapment efficiency (%EE) was recorded at 84.54 ± 0.52%. After six months, %EE declined marginally to 81.52 ± 0.65% at 4°C and 78.88 ± 0.46% at 25°C. These findings suggest that the formulation maintained its physical and chemical integrity under both storage conditions, with no statistically significant variation observed in entrapment efficiency during the study period. The detailed stability data are summarized in Table 3.

Formulation P3, composed of 30% soya lecithin (SL) and edge activator (EA) in an 85:15 ratio, demonstrated the highest drug release, achieving 69.65 ± 0.52% over a 10-hour period.

Table 1: Composition, particle size, and encapsulation efficiency of various formulations of 5-fluorouracil-loaded transfersomes

S.No.	Preparation code	SL(30%) phospholip id: EA ratio	5-FU drug	Vesicle Size (nm)	EE (%)	Zeta Potential
1.	F1	95:5	10mg	240.11± 1.21	86.79±0.091	9.24±0.20
2.	F2	90:10	10mg	230.53±2.23	87.08±0.986	8.08 ± 0.2
3.	F3	85:15	10mg	225.54±1.52	89.86±0.073	9.54 ± 0.43
4.	P1	95:5	10mg	150.25±2.52	84.71±0.073	13.46 ± 0.5
5.	P2	90:10	10mg	145.58±1.84	85.46±0.040	10.64 ± 0.3
6.	P3	85:15	10mg	140.52±1.24	86.06±0.076	8.12 ± 0.5

Mean values was be find out ordinary of triple reading then ± shown as standard deviance
SL (30%) so that Soya Lecithin (30%), **5-FU:** 5- Florouracil and EA that show as edge activator, (Tween 80 inF1-F3 & Span 80 in P1-P3) and EE (%) Entrapment efficiency (%)

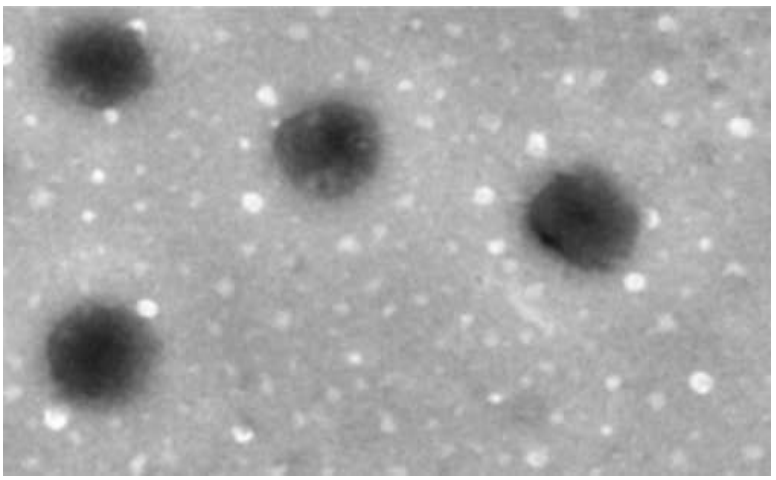

Figure 1: Transmission electron micrograph of optimized Transferosome

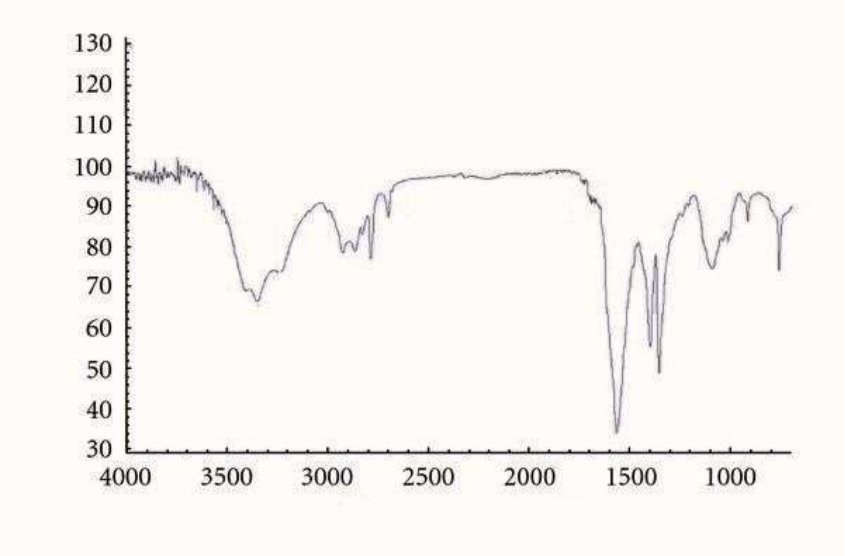

Figure 2: FTIR of 5-FU

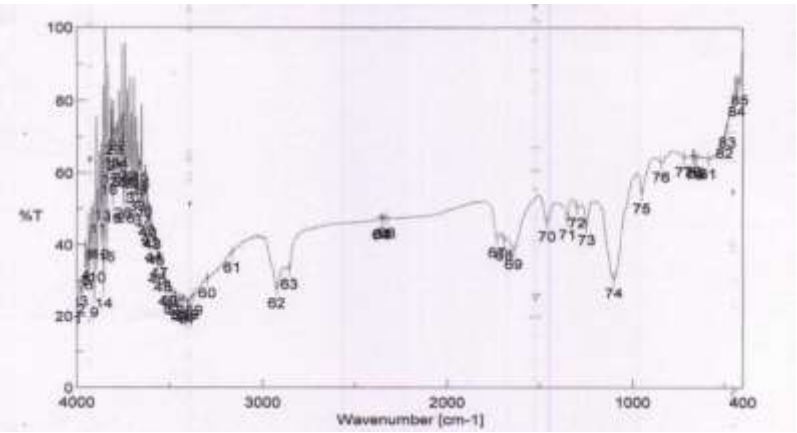

Figure 3: FTIR of optimized transferosome

Table 2: *In-vitro* drug release

Formulation	*In-vitro* drug release (time in hr)				
	2	**4**	**6**	**8**	**10**
F1	15.26±22	25.28±24	39.34±24	52.22±24	64.28±24
F2	16.18±52	26.42±54	40.26±52	53.46±56	65.16±56
F3	17.12±40	27.10±40	41.76±24	53.12±42	66.14±42
P1	14.18±38	23.16±38	38.48±48	51.20±36	62.19±36
P2	16.20±26	26.18±38	40.22±72	53.28±28	66.23±28
P3	18.68±54	29.76±48	42.42±52	54.62±52	69.65±52

Table 3: Drug Stability Study of Optimized Transferosome Stored at Different Temperatures (4°C and 25°C) Over Six Months

Para meters	Initial Values (0 month)	One month		Three month		Six month	
		(4°±2°C, 75±5 %RH)	(25±2°C, 60±5 % RH)	(4°±2°C, 75±5 %RH)	(25±2°C, 60±5 % RH)	(4°±2°C, 75±5 %RH)	(25±2°C, 60±5 % RH)
Mean particles size (nm)	35.45±0.58	35.52±0.33	35.65±0.46	35.85±0.73	35.55±1.4	35.41±242	36.85±3.43
% Entrapment Efficiency	84.54 ± 0.52%	83.23±0.14%	82.12±0.43 %	82.63±0.73%	80.22±0.76 %	81.52±0.65 %	78.88±0.46 %

*All values expressed as mean ± SD, (n=3).

Conclusion

Transfersomes offer several advantages, including low toxicity, excellent biocompatibility, and enhanced skin penetration capabilities. They are versatile carriers capable of encapsulating both hydrophilic and lipophilic drugs. In this study, the optimized formulation achieved a sustained drug release of up to 69.65%, indicating its potential for prolonged therapeutic action. Such a delivery system is promising for improving the efficacy of topical treatments, particularly in managing skin cancer.

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