RESEARCH PAPER

Formulation, Characterization and Ex-Vivo Evaluation of a Clindamycin Hydrochloride-Loaded Liposomal Hydrogel Patch for Topical Acne Therapy

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Abstract
Background: Acne vulgaris is a common inflammatory disorder of the pilosebaceous unit, predominantly affecting adolescents and young adults. Although topical clindamycin is widely used for inflammatory acne, conventional topical formulations may be limited by inadequate drug retention, restricted penetration through the stratum corneum and the need for repeated application. Liposomal hydrogel patches may provide a suitable platform for improving topical drug localization while sustaining drug release.
Objective: To develop and evaluate a clindamycin hydrochloride-loaded liposomal hydrogel patch (LHP) and to compare its physicochemical and drug-delivery characteristics with those of a conventional clindamycin hydrochloride hydrogel patch (CHP).
Methods: Clindamycin hydrochloride-loaded liposomes were prepared by thin-film hydration. Nine formulations (F1–F9) were prepared in a 3 × 3 layout by varying the lipid-to-cholesterol ratio and rotational speed. The formulation with the best drug content, entrapment efficiency and drug loading were incorporated into a sodium alginate/HPMC hydrogel, which was converted into a patch by solvent casting. The optimized liposomes were characterized for particle size, polydispersity index (PDI) and zeta potential. The patch was evaluated for thickness, weight, folding endurance, swelling index, surface pH, ex-vivo adhesion time, drug content and stability, and for in-vitro release and ex-vivo permeation using Franz diffusion cells (goat skin). The LHP was compared with the CHP under the same conditions.
Results: Formulation F8 (9:1 lipid-to-cholesterol ratio, 100 rpm) showed the highest drug content (84.05 ± 0.25%), entrapment efficiency (81.67 ± 0.23%) and drug loading (7.55 ± 0.12%) among F1–F9. Its mean hydrodynamic diameter was 663.5 nm (multimodal size distribution), PDI 0.278 and zeta potential −25.4 ± 1.0 mV. The LHP showed a surface pH of 5.63 ± 0.06, folding endurance of 245.33 ± 3.51 folds, swelling index of 96.76 ± 0.72%, ex-vivo adhesion time of 12.16 ± 0.17 h and drug content of 88.63 ± 1.45% (CHP: 78.33 ± 1.45%). Release from the LHP was best fitted by the Korsmeyer–Peppas model (R^2 = 0.9917; zero-order R^2 = 0.9883), whereas ex-vivo permeation followed zero-order kinetics (R^2 = 0.9933). Cumulative permeation at 7 h was 92.71% for the LHP and 56.24% for the CHP. After 60 days, the LHP retained a larger fraction of its drug content than the CHP at both 4 °C and 25 °C.
Conclusion: The clindamycin hydrochloride-loaded liposomal hydrogel patch showed favorable physicochemical characteristics, sustained in-vitro release and greater ex-vivo permeation than the conventional hydrogel patch under the conditions tested. It is a promising platform for topical clindamycin delivery; microbiological, skin-retention, in-vivo and clinical studies are required to establish therapeutic efficacy and safety.
Keywords: Acne vulgaris; Clindamycin hydrochloride; Liposomes; Hydrogel patch; Topical drug delivery; Ex-vivo permeation; Sustained release.
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1. Introduction

Acne vulgaris is a common chronic inflammatory disorder of the pilosebaceous unit that predominantly affects adolescents and young adults. Clinically, it is characterized by comedones, papules, pustules, nodules and, in more severe cases, cystic lesions, with the face, chest and back being the most frequently affected sites. Although acne is not generally life-threatening, persistent or inadequately treated disease may result in post-inflammatory hyperpigmentation and permanent scarring, with considerable psychological and social consequences. [1,2]

The pathogenesis of acne is multifactorial and involves abnormal follicular keratinization, increased sebaceous gland activity, microbial colonization and inflammation. *Cutibacterium acnes* (formerly *Propionibacterium acnes*) has an important role in the inflammatory process within the pilosebaceous follicle; the organism and its associated inflammatory mediators can contribute to follicular inflammation

and the development of acne lesions. [1,2] Consequently, antimicrobial and anti-inflammatory approaches remain important components of topical treatment, particularly for inflammatory acne.

Clindamycin is a lincosamide antibiotic that is used as a topical treatment for inflammatory acne. [1] Its antibacterial activity is primarily associated with inhibition of bacterial protein synthesis through binding to the 50S ribosomal subunit. The topical route offers the advantage of delivering the drug directly to the site of application while potentially limiting systemic exposure. However, the effectiveness of topical drug delivery is influenced by the physicochemical properties of the drug, the formulation vehicle, skin-barrier characteristics and residence time at the application site. [9–11,25]

The stratum corneum represents the principal barrier to dermal and transdermal drug transport. Conventional topical formulations such as creams, gels and ointments may therefore show limitations in maintaining adequate drug concentrations at the target site and may require repeated application, which can affect treatment convenience and adherence. [9–11,25] Development of topical delivery systems capable of improving drug retention, controlling release and facilitating transport across the skin barrier is consequently of considerable interest.

Liposomes are vesicular drug-delivery systems composed primarily of lipid bilayers that can encapsulate therapeutic agents and modify their release and interaction with biological membranes. Their application in dermal drug delivery has attracted considerable attention because liposomal systems may improve drug localization, protect incorporated drugs and facilitate interaction with the skin barrier. [3–5,12] Previous investigations have also demonstrated the potential of liposomal systems containing clindamycin and other antimicrobial agents for the topical treatment of skin infections and acne. [7,16,19]

Hydrogels provide another useful platform for topical drug delivery because their hydrated polymeric networks can maintain moisture, provide a suitable vehicle for drug incorporation and facilitate prolonged contact with the skin. [6,13] Combining liposomes with a hydrogel matrix can therefore provide complementary advantages: liposomes can act as the drug-encapsulating carrier, while the hydrogel provides structural support, hydration and prolonged residence at the application site. Recent studies have explored liposome-in-hydrogel systems and liposomal hydrogels for topical delivery, supporting the potential of this combined platform for sustained dermal drug delivery. [6,8,14,15,17]

A patch-based hydrogel system may further improve application convenience by providing a defined dose, prolonged contact with the skin and reduced drug loss from the application site. In the present study, clindamycin hydrochloride-loaded liposomes were prepared by the thin-film hydration method and incorporated into a hydrogel matrix consisting of sodium alginate and hydroxypropyl methylcellulose (HPMC). The optimized liposomal hydrogel was fabricated as a patch by solvent casting. Nine liposomal formulations were initially investigated by varying the lipid-to-cholesterol ratio and rotational speed, after which the optimized formulation was selected for incorporation into the hydrogel. The resulting patch was evaluated for its physicochemical properties, swelling behavior, surface pH, adhesion, drug content, stability, in-vitro drug release and ex-vivo skin permeation.

The primary objective of this study was therefore to develop and characterize a clindamycin hydrochloride-loaded liposomal hydrogel patch as a topical drug-delivery system for acne. A secondary objective was to compare its physicochemical and drug-delivery performance with that of a conventional clindamycin hydrochloride hydrogel patch under the same experimental conditions, in order to determine whether incorporation of the drug into liposomes could provide controlled drug release and improved ex-vivo skin permeation.

2. Materials and Methods

2.1 Materials

Clindamycin hydrochloride was obtained from Yarrow Chem, India. Soya lecithin was procured from Sisco Research Laboratories (SRL), India. Cholesterol, mannitol, sodium alginate and polyethylene glycol 400 (PEG 400) were obtained from Loba Chemie Pvt. Ltd., India. Hydroxypropyl methylcellulose (HPMC K-15) and glycerol were obtained from Research Lab, India. Ethanol, methanol and distilled water were of laboratory grade, while analytical-grade chloroform was obtained from Qualikems, India.

2.2 Preformulation: UV spectrum and calibration curve

A solution of clindamycin hydrochloride in phosphate buffer (pH 5.1) was scanned between 200 and 800 nm to determine the wavelength of maximum absorption (λmax). Standard solutions of 5–25 µg/mL were prepared in the same buffer, and their absorbance was measured at λmax to construct the calibration curve (absorbance versus concentration) [18].

2.3 Preparation of clindamycin hydrochloride-loaded liposomes

Liposomes were prepared by the thin-film hydration method [19]. The lipid components were dissolved in an organic solvent in a round-bottom flask, and mannitol was added. The flask was attached to a rotary evaporator and rotated under reduced pressure until removal of the solvent produced a uniform thin lipid

film on the flask wall. The flask was then refrigerated for 24 h. An aqueous solution of clindamycin hydrochloride in distilled water was used to hydrate the lipid film, and the dispersion was sonicated to obtain the liposomal suspension.

2.4 Formulation design

Nine liposomal formulations (F1–F9) were prepared in a 3 × 3 layout by varying two variables: lipid-to-cholesterol ratio (5:5, 7:3 and 9:1) and rotational speed (80, 100 and 120 rpm) Formulation F8 (9:1, 100 rpm) was selected as the optimized formulation on the basis of its drug content, entrapment efficiency and drug loading.

2.5 Preparation of liposome-loaded hydrogel

The optimized liposomal formulation was incorporated into a hydrogel by a solution-mixing (sol–gel) method. The hydrogel comprised sodium alginate and HPMC K-15 (2:1), glycerol and PEG 400 (1:1) as plasticizers, 20 mL of water and 5 mL of the optimized liposomal suspension. The gel-forming and film-forming polymer solutions were prepared separately under continuous magnetic stirring. The plasticizer was added to the gel-forming polymer solution with continued stirring to achieve uniform plasticization. The film-forming polymer solution was then added and mixed gently until homogeneous, the liposomal suspension was added and mixed uniformly, and the pH of the formulation was adjusted.

2.6 Preparation of liposomal hydrogel patch

The liposomal hydrogel was converted into a patch by solvent casting. The hydrogel was poured into a Petri dish, spread evenly to the desired thickness and dried at room temperature to remove solvent/water. The dried film was peeled from the surface and cut to the required size to obtain the liposomal hydrogel patch (LHP).

2.7 Characterization of liposomal formulations

Formulations F1–F9 were evaluated for physical appearance, morphology, drug content, entrapment efficiency and drug loading; the optimized formulation was additionally characterized for particle size, PDI and zeta potential.

Physical appearance and morphology. Appearance (color, turbidity and sedimentation) was assessed visually against white and black backgrounds in daylight. Morphology was examined preliminarily using a trinocular microscope at 40× magnification.

Drug content. An accurately measured volume of liposomal dispersion was lysed with a suitable solvent to release the entrapped drug, suitably diluted and analyzed by UV spectrophotometry at 201 nm using the calibration curve [19]. Drug content (%) = (actual amount of drug present/theoretical amount of drug) × 100.

Entrapment efficiency and drug loading. Unentrapped drug was separated from the vesicles by centrifugation, and free drug in the supernatant was quantified at 201 nm [19]. Entrapment efficiency (%) = [(total drug − unentrapped drug)/total drug] × 100. Drug loading (%) = (amount of entrapped drug/total weight of liposomes, i.e. drug plus lipids) × 100.

Particle size, PDI and zeta potential. The liposomal dispersion was diluted with distilled water, and particle size and PDI were measured by dynamic light scattering and zeta potential by electrophoretic light scattering using a Litesizer 500 at room temperature [20,21]. Measurements were made in triplicate.

2.8 Evaluation of the optimized liposomal hydrogel

Physical appearance (color, clarity, homogeneity, texture, phase separation, grittiness and consistency) was assessed visually. The pH of 1 g of hydrogel dispersed in 10 mL of distilled water was measured with a digital pH meter calibrated with pH 4.0, 7.0 and 9.2 buffers. Spreadability was determined by the glass-slide method: about 1 g of hydrogel was placed between two glass slides under a 500 g weight for about 5 min, and the time taken for the upper slide to travel 5 cm under an applied weight was recorded; spreadability S = (M × L)/T, where M is the applied weight (g), L the distance travelled (cm) and T the time (min). Viscosity was measured with a Brookfield viscometer at 25 ± 1 °C and expressed in mPa·s.

2.9 Evaluation of the liposomal hydrogel patch

The LHP was evaluated for physical appearance (color, surface texture, homogeneity, transparency, air bubbles and stickiness), thickness, weight, folding endurance, swelling index, surface pH, ex-vivo adhesion time and drug content. Thickness was measured at five randomly selected points with a feeler gauge [22]. Weight was determined for three individually weighed patches [22]. Folding endurance was determined by repeatedly folding the patch at the same place until visible cracking or breakage occurred [23]. For the swelling index, three pre-weighed dry patches were immersed in distilled water at 37 ± 0.5 °C and weighed at 0, 5 and 10 min; swelling index (%) = $[(W_t - W_0)/W_0] \times 100$, where W0 is the initial dry weight and W_t the weight at time t [22]. Surface pH was measured at three positions on the patch surface after swelling in distilled water for 1 h at room temperature [23].

Ex-vivo adhesion time was determined using freshly excised goat skin obtained from a local slaughterhouse and washed with normal saline. The skin was mounted on a glass plate with the stratum corneum facing upward, and the patch was pressed onto it for a few seconds. The assembly was placed in phosphate buffer (pH 5.1) at 37 ± 0.5 °C under static conditions, and the time for complete detachment of the patch was recorded (n = 3). For drug content, an accurately weighed portion of the patch was cut into small pieces, extracted in a suitable solvent by sonication and

shaking to disrupt the vesicles, filtered, diluted and analyzed at 201 nm.

2.10 Stability study

The optimized LHP and the CHP were individually packed in aluminium foil and stored at 4 ± 2 °C and at 25 ± 2 °C/60 ± 5% relative humidity. Samples were evaluated at 0, 7, 15, 30 and 60 days for physical appearance, thickness, weight, folding endurance, swelling index, surface pH and drug content.

2.11 In-vitro drug-release study

In-vitro release was studied using a Franz diffusion cell. A cellophane membrane pre-soaked in phosphate buffer (pH 5.1) for about 24 h was mounted between the donor and receptor compartments. The receptor compartment contained phosphate buffer (pH 5.1) maintained at 37 ± 0.5 °C and stirred magnetically at 500 rpm. An accurately weighed quantity of patch containing a known amount of drug was placed on the membrane in the donor compartment. Samples were withdrawn at 0.5 h intervals from 0 to 7 h and replaced with an equal volume of fresh buffer to maintain sink conditions. Samples were diluted as required and analyzed at 201 nm [24]. Cumulative drug release (%) = (amount of drug released/total amount of drug loaded) × 100. Experiments were performed in triplicate. Release data were fitted to zero-order, first-order, Higuchi, Korsmeyer–Peppas and Hixson–Crowell models, and the model with the highest coefficient of determination (R^2) was considered the best fit.

2.12 Ex-vivo skin permeation study

Ex-vivo permeation was studied in a Franz diffusion cell with excised goat skin mounted with the stratum corneum facing the donor compartment. Phosphate buffer (pH 5.1) at 37 ± 0.5 °C with continuous stirring was used as the receptor medium. The LHP was applied to the skin surface; samples were withdrawn from the receptor compartment at predetermined intervals, replaced with fresh medium and analyzed at 201 nm. Cumulative drug permeation (%) = (amount of drug permeated/total amount of drug loaded) × 100. Data were fitted to the same five kinetic models. Flux (J) was calculated as $J = (dQ/dt)/A$, where Q is the cumulative amount permeated, t is time and A is the diffusion area, and the permeability coefficient as $Kp = J/C_0$, where C_0 is the initial drug concentration in the donor [25]. Experiments were performed in triplicate.

2.13 Comparative evaluation and data presentation

The LHP was compared with a conventional clindamycin hydrochloride hydrogel patch (CHP) prepared without liposomes. Both patches were evaluated under identical conditions for physical appearance, thickness, weight, folding endurance, swelling index, surface pH, ex-vivo adhesion time, drug content, stability, in-vitro release and ex-vivo permeation. Results are expressed as mean ± standard deviation (n = 3).

3. Results

3.1 Preformulation study

The UV absorption maximum of clindamycin hydrochloride in phosphate buffer (pH 5.1) was observed at 201 nm. The calibration curve over 5–25 µg/mL was linear ($A = 0.0068C + 0.0007$; $R^2 = 0.9936$; Figure 1).

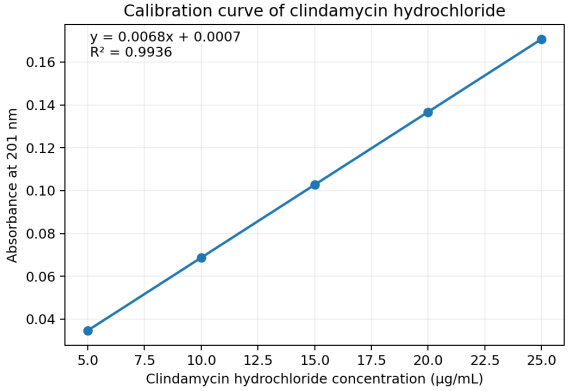


Figure 1. Calibration curve of clindamycin hydrochloride in phosphate buffer (pH 5.1). Absorbance was measured at 201 nm for standard solutions of 5–25 µg/mL; the line shows the linear regression ($y = 0.0068x + 0.0007$, $R^2 = 0.9936$).

3.2 Optimization of liposomal formulation

Nine formulations (F1–F9) were prepared at three lipid-to-cholesterol ratios and three rotational speeds (Table 1; Figure 2). Drug content ranged from 70.05 ± 0.37% to 84.05 ± 0.25%, entrapment efficiency from 66.35 ± 0.22% to 81.67 ± 0.23%, and drug loading from 6.22 ± 0.15% to 7.55 ± 0.12%. At every speed, the 9:1 ratio gave the highest values, and at every ratio, 100 rpm gave higher values than 80 or 120 rpm.

Formulation F8 (9:1, 100 rpm) showed the highest drug content (84.05 ± 0.25%), entrapment efficiency (81.67 ± 0.23%) and drug loading (7.55 ± 0.12%). On visual inspection, F8 was an off-white, slightly milky dispersion with low-to-moderate turbidity that appeared comparatively clear; sedimentation was present in all formulations. F8 was therefore selected as the optimized formulation.

Table 1. Optimization of clindamycin hydrochloride-loaded liposomal formulations

Formulation	Lipid:Cholesterol	Rotational speed (rpm)	Drug content (%)	Entrapment efficiency (%)	Drug loading (%)
F1	5:5	80	70.05 ± 0.37	66.35 ± 0.22	6.22 ± 0.15
F2	5:5	100	77.40	75.23	6.99
F3	5:5	120	74.45	72.19	6.73
F4	7:3	80	78.15	76.07	7.06
F5	7:3	100	82.57	80.78	7.47
F6	7:3	120	78.85	77.27	7.17
F7	9:1	80	79.60	78.29	7.26
F8	**9:1**	**100**	**84.05 ± 0.25**	**81.67 ± 0.23**	**7.55 ± 0.12**
F9	9:1	120	81.10	79.83	7.39

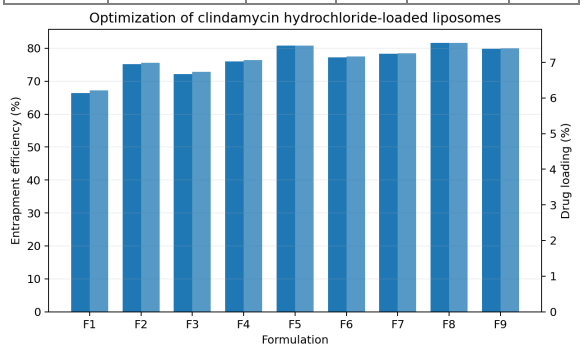


Figure 2. Entrapment efficiency (%, left axis, dark bars) and drug loading (%, right axis, light bars) of clindamycin hydrochloride-loaded liposomal formulations F1–F9, prepared at lipid-to-cholesterol ratios of 5:5 (F1–F3), 7:3 (F4–F6) and 9:1 (F7–F9) and rotational speeds of 80, 100 and 120 rpm within each ratio. Both parameters were highest for F8 (9:1, 100 rpm). Bars show mean values from Table 1.

3.3 Characterization of optimized liposomes

The optimized F8 dispersion showed a mean hydrodynamic diameter of 663.5 nm and a PDI of 0.278. The intensity-weighted size distribution was multimodal, with populations at 235.6 nm (56.82%), 1930.4 nm (42.32%) and 32.98 nm (0.86%) (Figure 3). The mean zeta potential was −25.4 ± 1.0 mV, with a predominant peak at −21.4 mV (Figure 4).

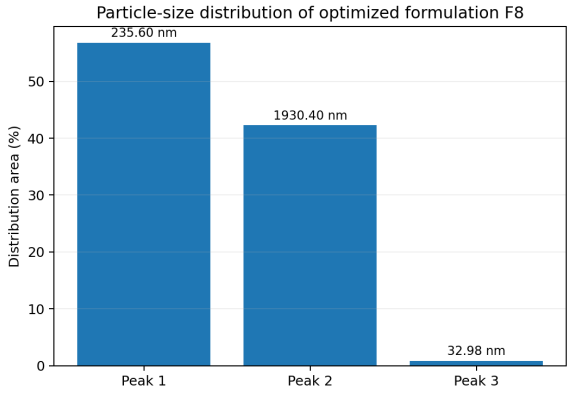


Figure 3. Particle-size populations of the optimized liposomal formulation F8 measured by dynamic light scattering. Bars show the contribution (% of distribution area) of each of the three size populations; the size of each population is labeled above its bar (peak 1, 235.60 nm, 56.82%; peak 2, 1930.40 nm, 42.32%; peak 3, 32.98 nm, 0.86%). The mean hydrodynamic diameter was 663.5 nm and the PDI was 0.278.

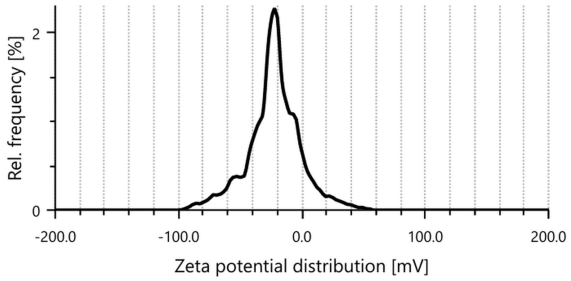


Figure 4. Zeta potential distribution of the optimized liposomal formulation F8 measured by electrophoretic light scattering (Litesizer 500). The distribution is centered in the negative range with a predominant peak at −21.4 mV; the mean zeta potential was −25.4 ± 1.0 mV.

3.4 Evaluation of the optimized liposomal hydrogel

The liposomal hydrogel was a light-cream, opaque, smooth, moderately viscous gel with no visible phase separation, coarse particles or grittiness. Its pH was 5.67 ± 0.12, spreadability was 21.0 ± 3.50 g·cm/min and viscosity were 9733.33 ± 251.66 mPa·s.

3.5 Evaluation of the optimized liposomal hydrogel patch

The LHP was light cream, smooth, uniform and semi-transparent, without major air bubbles. Thickness was 0.29 ± 0.01 mm, mean weight 115.00 ± 3.61 mg, folding endurance 245.33 ± 3.51 folds, swelling index 96.76 ± 0.72%, surface pH 5.63 ± 0.06, ex-vivo adhesion time 12.16 ± 0.17 h and drug content 88.63 ± 1.45% (Table 2).

3.6 Comparative evaluation of the patches

Compared with the CHP, the LHP showed greater folding endurance, longer ex-vivo adhesion time and higher drug content (Table 2; Figure 5). The LHP was also thicker and heavier, and its swelling index was slightly lower; surface pH was similar for both patches.

Table 2. Comparative physicochemical characteristics of the liposomal hydrogel patch (LHP) and the conventional hydrogel patch (CHP)

Parameter	LHP	CHP
Thickness (mm)	0.29 ± 0.01	0.20 ± 0.02
Weight (mg)	115.00 ± 3.61	98.00 ± 3.61
Folding endurance (folds)	245.33 ± 3.51	205.33 ± 2.52
Swelling index (%)	96.76 ± 0.72	99.30 ± 2.00
Surface pH	5.63 ± 0.06	5.70 ± 0.10
Ex-vivo adhesion time	12.16 ± 0.17 h	6 h 35 min (≈6.58 h) ± 0.22
Drug content (%)	88.63 ± 1.45	78.33 ± 1.45

Using the reported mean values, the LHP showed an adhesion time roughly 1.9-fold that of the CHP (≈12.2 h versus ≈6.6 h) and a drug content 10.3 percentage points (13.2% relative) higher.

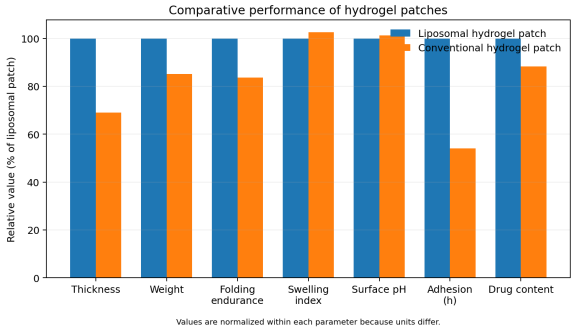


Figure 5. Comparison of the liposomal hydrogel patch (LHP, blue) and the conventional hydrogel patch (CHP, orange) for thickness, weight, folding endurance, swelling index, surface pH, ex-vivo adhesion time and drug content. Because the parameters have different units, each value is expressed as a percentage of the corresponding LHP value (LHP = 100%). Data are derived from the mean values in Table 2.

3.7 Stability

Both patches were stored at 4 ± 2 °C and 25 ± 2 °C/60 ± 5% RH for 60 days. The LHP remained clear, smooth and uniform up to 30 days at 4 °C, with slight moisture loss at 60 days; at 25 °C slight dullness (day 15), dryness (day 30) and reduced flexibility (day 60) were observed. Over 60 days, thickness decreased from 0.29 to 0.27 mm, weight from 115 to 113 mg (4 °C) or 112 mg (25 °C), folding endurance from 245 to 242, swelling index from 96.7% to 94.8% (4 °C) or 93.2% (25 °C), and surface pH remained between 5.6 and 5.8 (Table 3). Drug content of the LHP fell from 81.3% to 80.2% at 4 °C and to 78.6% at 25 °C (Figure 6), corresponding to retention of 98.6% and 96.7% of the initial value, compared with 94.6% and 92.6% for the CHP (Table 4).

Table 3. Stability of the liposomal hydrogel patch at 4 ± 2 °C and 25 ± 2 °C/60 ± 5% RH

Day	Drug content (%)		Folding endurance		Swelling index (%)		Surface pH	
	4 °C	25 °C	4 °C	25 °C	4 °C	25 °C	4 °C	25 °C
0	81.3	81.3	245	245	96.7	96.7	5.6	5.6
7	81.1	80.8	244	244	96.7	96.7	5.6	5.6
15	80.9	80.1	244	243	95.9	95.9	5.6	5.7
30	80.6	79.4	243	243	95.5	94.8	5.7	5.7
60	80.2	78.6	242	242	94.8	93.2	5.7	5.8

Values are means. Thickness, weight and appearance changes are described in the text.

Table 4. Drug content of the LHP and CHP after 60 days of storage

Condition	LHP			CHP		
	Day 0 (%)	Day 60 (%)	Retention (%)	Day 0 (%)	Day 60 (%)	Retention (%)
4 ± 2 °C	81.3	80.2	98.6	78.3	74.1	94.6
25 ± 2 °C/60 ± 5% RH	81.3	78.6	96.7	78.3	72.5	92.6

Retention = (day-60 drug content/day-0 drug content) × 100, calculated from the mean values.

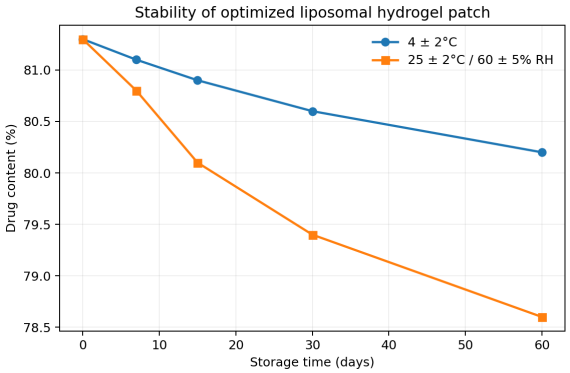


Figure 6. Drug content of the optimized liposomal hydrogel patch during 60 days of storage at 4 ± 2 °C (circles) and at 25 ± 2 °C/60 ± 5% RH (squares), measured at 0, 7, 15, 30 and 60 days. Note the truncated y-axis (78.5–81.5%).

3.8 In-vitro drug release and release kinetics

The CHP released its drug rapidly, with nearly complete release within about 3.5–4 h (burst release), whereas release from the LHP was slower and continued over the 7 h study. For the LHP, the Korsmeyer–Peppas model gave the highest R^2 (0.9917; release exponent n = 1.1693), followed by the zero-order (0.9883), Higuchi (0.9226), first-order (0.5912) and Hixson–Crowell (0.0617) models (Figure 7). For the CHP, the Korsmeyer–Peppas R^2 was 0.7814 (Table 5); the zero-order R^2 was 0.9883 for the LHP and 0.7469 / 0.6807 for the CHP.

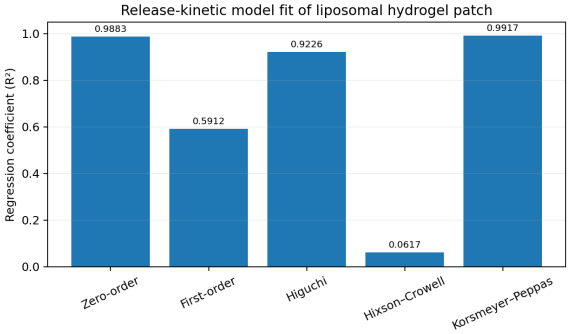


Figure 7. Goodness of fit (R^2) of five kinetic models to the in-vitro release data of the liposomal hydrogel patch: zero-order (0.9883), first-order (0.5912), Higuchi (0.9226), Hixson–Crowell (0.0617) and Korsmeyer–Peppas (0.9917). The Korsmeyer–Peppas model gave the highest R^2.

Table 5. Comparative Korsmeyer–Peppas release kinetics

Parameter	LHP	CHP
R^2	0.9917	0.7814
Slope (n)	1.1693	0.9326
Intercept	0.0856	0.3768

These findings indicate a slower, more sustained release from the LHP than from the CHP under the conditions used.

3.9 Ex-vivo skin permeation

Cumulative permeation from the LHP increased progressively and reached 92.71% at 7 h, compared with 56.24% for the CHP. For the LHP, permeation was best described by the zero-order model (R^2 = 0.9933; slope 1.3723 mg/h), followed by Korsmeyer–Peppas (R^2 = 0.9873; n = 1.0492), Higuchi (0.9417), first-order (0.3928) and Hixson–Crowell (0.0775) models. The CHP also followed zero-order kinetics (R^2 = 0.9924; slope 0.8363 mg/h) (Table 6; Figure 8). The permeation rate of the LHP was therefore about 1.6-fold that of the CHP (1.3723/0.8363), and cumulative permeation at 7 h was 64.8% greater (Figure 9).

Table 6. Comparative ex-vivo permeation kinetics (zero-order model)

Parameter	LHP	CHP
Cumulative permeation at 7 h (%)	92.71	56.24
Zero-order R^2	0.9933	0.9924
Zero-order slope (mg/h)	1.3723	0.8363
Zero-order intercept (mg)	0.1804	0.0757

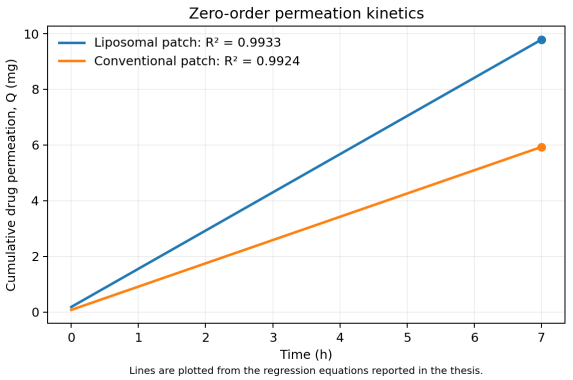


Figure 8. Zero-order permeation plots of the liposomal (blue) and conventional (orange) hydrogel patches across excised goat skin. Lines were drawn from the fitted regression equations (LHP: y = 1.3723x + 0.1804, R^2 = 0.9933; CHP: y = 0.8363x + 0.0757, R^2 = 0.9924); Q is the cumulative amount of drug permeated (mg) and markers indicate the values at 7 h.

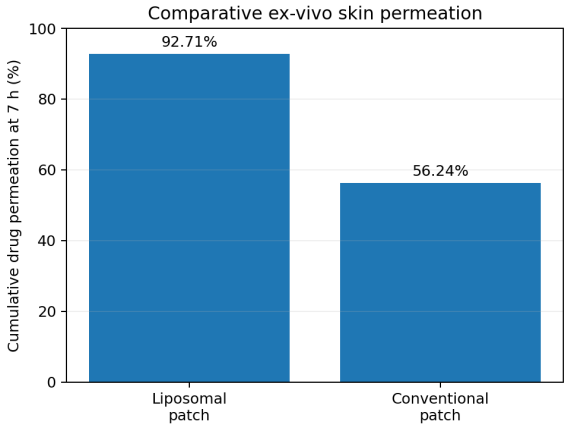


Figure 9. Cumulative ex-vivo drug permeation at 7 h across excised goat skin from the liposomal hydrogel patch (92.71%) and the conventional hydrogel patch (56.24%).

4. Discussion

Acne vulgaris is a common inflammatory disorder of the pilosebaceous unit for which topical therapy remains an important component of management, particularly for localized disease. [1,2] The effectiveness of topical treatment can, however, be influenced by the physicochemical properties of the drug, the skin barrier, formulation residence time and drug-release characteristics. [9–11,25] Clindamycin hydrochloride is an established topical antibacterial agent used in acne management, but conventional topical preparations may not provide sustained drug residence at the intended site. The present study therefore investigated a liposomal hydrogel patch as an alternative topical delivery platform for clindamycin hydrochloride.

The formulation variables influenced drug entrapment and loading. Among the nine formulations, F8 (9:1 lipid-to-cholesterol ratio, 100 rpm) showed the highest drug content (84.05 ± 0.25%), entrapment efficiency (81.67 ± 0.23%) and drug loading (7.55 ± 0.12%). Within each lipid-to-cholesterol ratio the intermediate speed (100 rpm) gave the best values, and within each speed the 9:1 ratio did, which may reflect more bilayer space for drug incorporation at higher lipid content; the reason for the effect of rotational speed was not investigated. The differences between F8 and the next-best formulation (F5) were small (about 1–2 percentage points) and were not tested statistically, so F8 should be regarded as the best-performing of the nine batches rather than a statistically distinct optimum. Lipid composition and vesicle characteristics are important determinants of liposomal drug incorporation and release. [3–5]

The F8 liposomes had a mean hydrodynamic diameter of 663.5 nm and a PDI of 0.278. A single mean and PDI, however, do not describe this dispersion well: the intensity distribution was multimodal, with about 57% of the signal near 236 nm and about 42% near 1.9 µm. The larger population may represent aggregates or large or multilamellar vesicles, and the formulation should be regarded as a heterogeneous, micron-range liposomal dispersion rather than a nanosized vesicular system. Size reduction (for example, extrusion or probe sonication) and direct imaging (TEM or cryo-TEM) would be needed to characterize the vesicles; the 40× optical microscopy used here cannot resolve vesicles of this size range. The negative zeta potential (−25.4 ± 1.0 mV) may contribute to electrostatic repulsion and reduce aggregation, but zeta potential alone cannot establish physical stability, and the stability study was performed on the patch rather than on the liposomal dispersion. [3,4]

Incorporation of the liposomes into the hydrogel produced a light-cream, smooth, homogeneous preparation with a pH of 5.67 ± 0.12, a spreadability of 21.0 ± 3.50 g·cm/min and a viscosity of 9733.33 ± 251.66 mPa·s. The mildly acidic pH is close to that of the skin surface and is appropriate for topical use. Recent studies have highlighted the potential of liposome-in-hydrogel systems to combine vesicular drug delivery with the mechanical and handling properties of hydrogels. [6]

The LHP had a thickness of 0.29 ± 0.01 mm, a weight of 115.00 ± 3.61 mg and a folding endurance of 245.33 ± 3.51 folds, indicating adequate flexibility for handling. Its ex-vivo adhesion time (about 12 h) was longer than that of the CHP (about 6.6 h), suggesting greater residence under the conditions of the adhesion test. Two points limit interpretation: the LHP was thicker (0.29 versus 0.20 mm) and heavier than the CHP, and film thickness can itself affect adhesion, mechanical properties and the diffusion path length, so the differences between patches cannot be attributed to liposomes alone; and no statistical comparison was made. The LHP also had a higher drug content (88.63 ± 1.45% versus 78.33 ± 1.45%), suggesting more efficient incorporation or retention of clindamycin hydrochloride in the liposomal patch. Drug content reflects formulation uniformity and recovery rather than therapeutic efficacy and should not be interpreted as evidence of clinical superiority.

The in-vitro release study showed sustained release from the LHP, whereas the CHP released its drug within about 3.5–4 h. For the LHP, the Korsmeyer–Peppas model gave the highest R^2 (0.9917), but the zero-order model (R^2 = 0.9883) fitted almost as well, so R^2 alone does not strongly discriminate between the models. The release exponent (n = 1.1693) exceeds 0.89, the value for Super Case II transport in thin films (Fickian diffusion corresponds to 0.5), which is consistent with non-Fickian, swelling- or relaxation-controlled release rather than simple diffusion. Because the CHP released its drug within about 4 h, its

poorer fit ($R^2 = 0.7814$) may partly reflect the plateau of the profile; the Korsmeyer–Peppas model is intended for the early part of release (roughly the first 60%), and the two R^2 values should therefore be compared with caution. Similar non-Fickian behavior has been reported for liposome-in-hydrogel systems. [6]

Ex-vivo permeation was greater from the LHP than from the CHP: cumulative permeation at 7 h was 92.71% versus 56.24%, and the zero-order permeation rate was about 1.6-fold higher (1.3723 versus 0.8363 mg/h). Zero-order behavior was best for both patches ($R^2 = 0.9933$ and 0.9924), and the Korsmeyer–Peppas exponent for the LHP ($n = 1.0492$) is also close to 1, consistent with constant-rate transport. Previous work has shown that liposomes can modify topical delivery and enhance drug localization or permeation. [3,7] The earlier study of Škalko et al. investigated clindamycin hydrochloride-loaded liposomes for acne therapy, providing a direct precedent for this approach. [7] Two cautions apply. First, permeation of more than 90% of the applied dose across the skin within 7 h is high for intact skin; skin integrity and mass balance (drug in the skin, on the surface and in the receptor) should be confirmed. Second, for acne the therapeutic target is the pilosebaceous unit within the skin, not the receptor compartment: high transdermal permeation may increase systemic exposure, and skin retention and follicular delivery should be measured.

Stability data showed limited changes during 60 days of storage. Drug content of the LHP fell from 81.3% to 80.2% at 4 °C and to 78.6% at 25 °C, whereas the CHP fell from 78.3% to 74.1% and 72.5%, respectively. The LHP therefore retained more of its drug content at both temperatures, and refrigerated storage preserved drug content better than room-temperature storage. Thickness, weight, folding endurance, swelling index and surface pH changed only gradually, although slight moisture loss at 4 °C and dryness with reduced flexibility at 25 °C were noted. These data suggest acceptable short-term stability under the tested conditions, but they do not constitute a complete regulatory stability programmed, and the day-0 drug content of the LHP in the stability study differs from that in Table 2 (see note to Table 4). The study did not test whether the liposomes protected the drug from degradation.

The study evaluated the formulation through several stages: liposome optimization, physicochemical characterization, hydrogel incorporation, patch evaluation, release, permeation and short-term stability. The comparison with a conventional patch provided a reference for interpreting release, adhesion and permeation. The findings are consistent with the broader literature indicating that liposomes can serve as versatile carriers for topical and dermal delivery. [3–5,8]

Several limitations should be acknowledged. The study was a formulation and ex-vivo investigation without clinical evaluation, so the findings cannot be translated directly into clinical efficacy, lesion reduction, tolerability or adherence. Goat skin does not fully reproduce the barrier of human skin. Results come from a single batch with $n = 3$ and no statistical testing; the CHP and LHP differed in thickness; the liposomal dispersion was heterogeneous in size; and UV detection at 201 nm, in the far-UV region, is susceptible to interference from excipients and requires confirmation of specificity (for example, by HPLC). Antibacterial activity against *C. acnes*, skin irritation, pharmacodynamic efficacy and long-term stability were not evaluated. Future studies should include microbiological assessment, skin-retention and follicular-localization studies, human-skin permeation, irritation and tolerability testing, and ultimately controlled clinical evaluation.

Overall, the optimized clindamycin hydrochloride-loaded liposomal hydrogel patch showed favorable physicochemical characteristics, longer experimental adhesion, sustained in-vitro release and greater ex-vivo permeation than the conventional hydrogel patch. It therefore represents a promising experimental platform for topical clindamycin delivery, while further biological and clinical studies are required to establish its therapeutic value.

5. Conclusion

A clindamycin hydrochloride-loaded liposomal hydrogel patch was developed and evaluated for topical delivery. Among nine liposomal formulations, F8 (lipid:cholesterol 9:1, 100 rpm) showed the highest drug content, entrapment efficiency and drug loading and was selected as the optimized formulation; it had a mean hydrodynamic diameter of 663.5 nm (multimodal distribution), a PDI of 0.278 and a zeta potential of -25.4 ± 1.0 mV.

After incorporation into a hydrogel and conversion into a patch, the formulation showed acceptable physicochemical characteristics, good flexibility and longer experimental adhesion than the conventional hydrogel patch. The liposomal patch also showed sustained in-vitro release and higher ex-vivo permeation (92.71% at 7 h versus 56.24% for the conventional patch) and retained more of its drug content during 60 days of storage.

These findings support the potential of the liposomal hydrogel patch as a topical delivery platform capable of modifying the release and permeation of clindamycin hydrochloride. Because the work was limited to formulation, in-vitro and ex-vivo evaluation, the results do not demonstrate clinical efficacy. Further microbiological, skin-retention, safety,

human-skin and clinical studies are required before therapeutic application in acne can be considered.

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