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Development, Optimization and Evaluation of a Salicylic Acid-Loaded Transferosomal Gel for Enhanced Topical Management of *Acne Vulgaris*

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ABSTRACT

Background: Acne vulgaris is a common chronic inflammatory disorder of the pilosebaceous unit, and salicylic acid is one of the most widely used topical keratolytic agents for its management. However, conventional topical formulations of salicylic acid show limited penetration across the stratum corneum, restricted follicular residence time, and require frequent application. Objective: The present study aimed to develop, optimize and evaluate a salicylic acid-loaded transferosomal gel as an ultra-deformable vesicular carrier for improved skin penetration and sustained topical delivery of the drug.

Methods: Preformulation studies (organoleptic evaluation, solubility, melting point, UV calibration and FTIR) were performed on salicylic acid. Transferosomal vesicles were prepared by the ethanol injection method using soya lecithin, cholesterol and Tween 80, and eight batches (F1–F8) were evaluated for appearance, pH, vesicle size, polydispersity index (PDI), entrapment efficiency, deformability index and drug content. The optimized suspension was incorporated into Carbopol 934 gel bases (G1–G5) and evaluated for appearance, homogeneity, pH, viscosity, spreadability, gel consistency, drug content, in vitro drug release, FTIR drug–excipient compatibility, zeta potential and SEM morphology. Release data were fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas kinetic models.

Results: Formulation F6 emerged as the optimized transferosomal suspension, with a mean vesicle size of 158 nm, PDI of 0.108, entrapment efficiency of 93.00 ± 0.72%, deformability index of 92.41 ± 0.86%, and drug content of 96.8%. Among the gel batches, G5 (1.5% w/w Carbopol 934) was optimized, showing a smooth, homogeneous, translucent appearance, pH of 5.66, spreadability of 133.93 g·cm/s, homogeneity index of 99.89%, and drug content of 97.5%. FTIR spectra confirmed retention of all characteristic salicylic acid peaks in the optimized gel with only minor shifts (≤ 7 cm^{-1}), indicating drug–excipient compatibility. In vitro release from G5 was sustained, reaching 97.34% at 12 h, and best fitted the Korsmeyer–Peppas model (R^2 = 0.9945), indicating a diffusion-controlled, non-Fickian release mechanism. Conclusion: A salicylic acid-loaded transferosomal gel with desirable physicochemical, rheological and sustained drug-release properties was successfully developed, representing a promising patient-compliant alternative to conventional topical formulations for acne management.

Introduction

Acne vulgaris is one of the most prevalent chronic inflammatory disorders of the skin, primarily affecting the pilosebaceous unit of the face, chest and back, where sebaceous activity is highest. It is clinically characterised by comedones, papules, pustules and, in severe cases, nodulocystic lesions that can progress to permanent scarring. Its pathogenesis is multifactorial, involving follicular hyperkeratinisation, excess sebum production, colonisation by Cutibacterium acnes, and a resulting inflammatory response.

Salicylic acid, a lipophilic beta-hydroxy acid, is a well-established keratolytic agent used extensively in topical acne therapy. It promotes desquamation of the stratum corneum and comedolysis, thereby helping to clear existing lesions and reduce the formation of new ones. Being applied topically, it allows drug action to be localised to the affected pilosebaceous unit while minimising systemic exposure. However, the stratum corneum remains a formidable barrier to drug penetration, and conventional salicylic acid gels and lotions typically show limited retention within hair follicles, a short duration of action, and the need for frequent reapplication to maintain efficacy, all of which can compromise patient compliance.

To address these limitations, vesicular carrier systems have been explored as a means of enhancing the cutaneous delivery of topically applied drugs. Among

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these, transferosomes — ultra-deformable lipid vesicles composed of a phospholipid bilayer destabilised by an "edge activator" such as a single-chain surfactant — are of particular interest. The edge activator imparts high flexibility to the vesicle membrane, allowing transferosomes to squeeze through channels considerably narrower than their own diameter and to traverse the densely packed lipid matrix of the stratum corneum without significant loss of vesicle integrity. This unique deformability differentiates transferosomes from conventional liposomes, which tend to remain confined to the upper skin layers, and makes transferosomes an attractive platform for improving both the penetration and the follicular deposition of drugs such as salicylic acid.

The present study was therefore designed to develop and systematically optimize a salicylic acid-loaded transferosomal suspension using the ethanol injection technique, to incorporate the optimized vesicles into a Carbopol 934 gel base for practical topical application, and to comprehensively characterise the resulting transferosomal gel with respect to its physicochemical properties, drug–excipient compatibility, surface morphology, and in vitro drug release behaviour, with the overall aim of offering a more effective and patient-compliant topical option for the management of acne vulgaris.

Materials and Methods

Materials

Salicylic acid was obtained as a gift sample. Soya lecithin, cholesterol, Tween 80, Carbopol 934, propylene glycol, glycerol, triethanolamine, methyl paraben, propyl paraben and ethanol (all of laboratory/analytical grade) were procured from standard laboratory chemical suppliers. Double-distilled water was used throughout the study.

Preformulation Studies of Salicylic Acid

Preformulation characterisation of the drug was carried out prior to formulation development. Organoleptic properties (colour, odour, appearance and physical state) were noted by visual and sensory examination. Solubility was determined by the shake-flask method in distilled water, ethanol, methanol, acetone and phosphate buffer (pH 7.4), with quantification by UV–visible spectrophotometry at 303 nm after 24 h of equilibration. The melting point was determined using the capillary method. A standard calibration curve of salicylic acid in ethanol was constructed at 303 nm over the concentration range of 2–10 µg/mL, and Fourier Transform Infrared (FTIR) spectroscopy (4000–400 cm^{-1}) was performed to confirm drug identity through its characteristic functional-group peaks.

Preparation of Salicylic Acid-Loaded Transferosomes

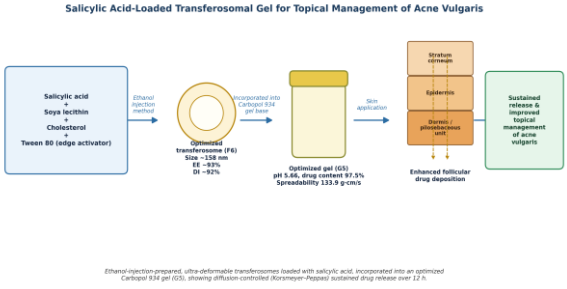
Transferosomal vesicles were prepared by the ethanol injection method. Salicylic acid, soya lecithin and cholesterol were dissolved in ethanol to form the organic (lipid) phase, while Tween 80 served as the edge activator. The organic phase was injected slowly, using a syringe at a controlled rate, into an aqueous phase maintained under continuous magnetic stirring. Stirring was continued to allow spontaneous formation of vesicles, and the resulting dispersion was probe-sonicated to yield a homogeneous transferosomal suspension. Eight formulations (F1–F8) were prepared by systematically varying the phospholipid, cholesterol and edge-activator proportions in order to identify the combination giving the most favourable vesicular characteristics.

Evaluation of Transferosomal Suspensions

Each transferosomal suspension (F1–F8) was evaluated for: (i) appearance, colour, homogeneity and phase stability by visual inspection; (ii) pH, using a calibrated digital pH meter; (iii) mean vesicle size and polydispersity index (PDI), by dynamic light scattering; (iv) entrapment efficiency, calculated from the difference between total and free (unentrapped) drug after separation of the vesicles; (v) deformability index, determined from the change in vesicle diameter before and after extrusion through a defined membrane pore size under fixed pressure; and (vi) drug content, by UV–visible spectrophotometry after disruption of the vesicles.

Preparation of the Transferosomal Gel

Carbopol 934 was dispersed in distilled water under continuous stirring and allowed to hydrate fully. Propylene glycol (as humectant) and the preservative system (methyl paraben/propyl paraben) were incorporated, after which the optimized transferosomal suspension was added gradually with gentle stirring to preserve vesicle integrity. The gel was neutralised with triethanolamine to a skin-compatible pH. Five gel formulations (G1–G5) were prepared by varying the Carbopol 934 concentration (0.5–1.5% w/w) to optimise gel consistency and drug release.



Evaluation of the Transferosomal Gel

The gel formulations were evaluated for appearance and homogeneity (visual/microscopic inspection), pH (digital pH meter), viscosity and spreadability (parallel-plate method, using a fixed weight, plate diameter and time interval), gel consistency, and drug content (UV–visible spectrophotometry at 303 nm). In vitro drug release was studied using a Franz diffusion cell over 12 h, with samples withdrawn at fixed intervals, replenished with fresh medium, and analysed spectrophotometrically; cumulative percentage drug release was plotted against time.

FTIR Compatibility, Zeta Potential and SEM Analysis

Drug–excipient compatibility of the optimized gel (G5) was assessed by comparing its FTIR spectrum with that of pure salicylic acid, examining the retention or shift of characteristic functional-group peaks. The surface charge of the optimized formulation was determined by zeta potential analysis using a Zetasizer, and vesicle/gel morphology was examined by scanning electron microscopy (SEM).

Drug Release Kinetics

In vitro release data from the optimized gel (G5) were fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas kinetic models, and the model giving the highest coefficient of determination (R^2) was taken to best represent the drug release mechanism.

RESULTS AND DISCUSSION

Preformulation Studies

Salicylic acid was obtained as a fine, white to almost white, odourless crystalline powder, consistent with its pharmacopoeial description. It was found to be freely soluble in ethanol, methanol and acetone (100 mg/mL each), moderately soluble in phosphate buffer pH 7.4 (8.5 mg/mL), and slightly soluble in distilled water (2.0 mg/mL), confirming its lipophilic character and supporting the choice of ethanol as the organic solvent for vesicle preparation. The observed melting point was 158–160°C, in agreement with the reported reference range, confirming drug purity. The UV calibration curve constructed at 303 nm was linear across 2–10 µg/mL ($y = 0.0605x - 0.0006$, $R^2 = 0.9994$), confirming its suitability for subsequent drug-content and release estimations.

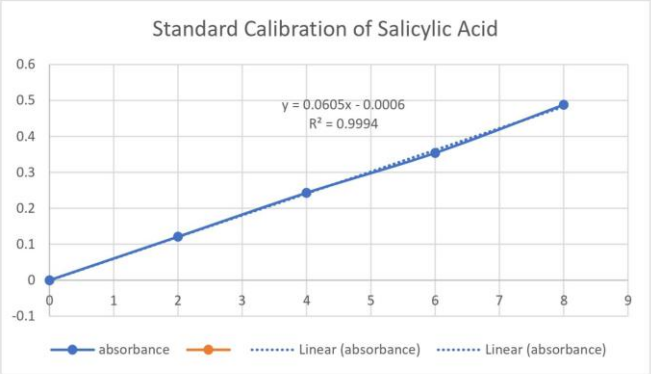


Figure 1. Standard calibration curve of salicylic acid at 303 nm (2–10 µg/mL).

FTIR spectroscopy of the pure drug (Figure 2) showed all diagnostic peaks expected for salicylic acid: O–H stretching at 3461 cm^{-1}, aromatic C–H stretching at 3061 cm^{-1}, carbonyl (C=O) stretching at 1686 cm^{-1}, aromatic C=C stretching at 1602 cm^{-1}, O–H/C–H bending at 1462 cm^{-1}, and C–O stretching at 1283 and 1211 cm^{-1}, confirming the identity and purity of the procured drug sample.

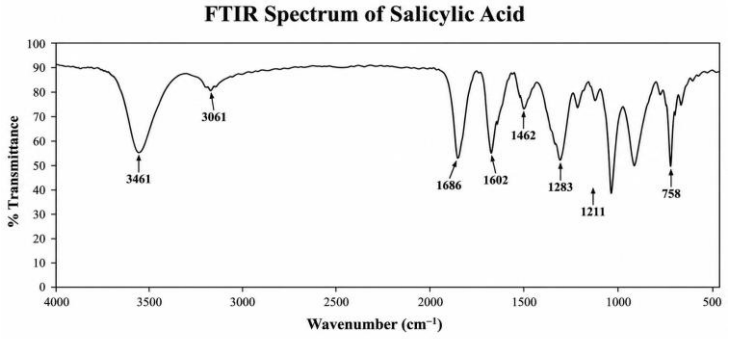


Figure 2. FTIR spectrum of pure salicylic acid.

Optimization of the Transferosomal Suspension (F1–F8)

Among the eight transferosomal formulations prepared, F6 was selected as the optimized suspension based on its superior overall performance profile. It exhibited a clear, uniform appearance with no phase separation, the smallest mean vesicle size (158 nm) with the lowest polydispersity index (0.108, indicating a highly uniform vesicle population), the highest entrapment efficiency (93.00 ± 0.72%), the greatest deformability index (92.41 ± 0.86%), and the highest drug content (96.8%) of all eight batches. A summary of the key evaluation parameters for all formulations is given in Table 1.

Table 1. Evaluation of transferosomal suspension formulations (F1–F8).

Formulation	pH	Vesicle size (nm)	PDI	Entrapment efficiency (%)	Deformability index (%)	Drug content (%)
F1	5.21	172	0.298	79.00 ± 1.25	75.00 ± 1.42	89.2
F2	5.36	162	0.268	81.50 ± 1.18	78.57 ± 1.28	92.3
F3	5.21	168	0.232	84.50 ± 1.12	81.48 ± 1.15	94.4
F4	5.42	170	0.238	83.00 ± 1.20	82.94 ± 1.20	90.1
F5	5.48	155	0.160	88.00 ± 0.96	86.45 ± 1.08	95.4
F6 (optimized)	5.52	158	0.108	93.00 ± 0.72	92.41 ± 0.86	96.8
F7	5.33	182	0.235	86.00 ± 1.08	82.97 ± 1.34	88.7
F8	5.21	190	0.342	80.50 ± 1.30	76.84 ± 1.46	90.2

The improved performance of F6 is consistent with the recognised effect of phospholipid-to-edge-activator ratio on vesicle behaviour: an optimal proportion of Tween 80 relative to soya lecithin and cholesterol appears to have imparted adequate membrane flexibility for high deformability, without excessive surfactant content that would otherwise increase membrane permeability and reduce drug entrapment, as reflected in the comparatively lower entrapment efficiencies of the more surfactant-rich batches (e.g., F8).

Optimization of the Transferosomal Gel (G1–G5)

Incorporation of the optimized F6 transferosomal suspension into Carbopol 934 gel bases of increasing polymer concentration (G1–G5) showed a clear trend of improving gel quality with increasing Carbopol content, up to an optimum at 1.5% w/w (G5). G5 was smooth, homogeneous and clear to slightly translucent, free from lumps, grittiness, air bubbles and phase separation, and showed the highest homogeneity index (99.89%), a skin-compatible pH (5.66), the best spreadability (133.93 g·cm/s) and the highest drug content (97.5%) among the five gel batches (Table 2).

Table 2. Evaluation of transferosomal gel formulations (G1–G5).

Formulation	Carbopol 934 (% w/w)	Appearance	pH	Homogeneity index (%)	Spreadability (g·cm/s)	Drug content (%)
G1	0.50	Clear, smooth gel	5.40	99.54	107.19	91.0
G2	0.75	Clear and smooth gel	5.50	99.68	117.23	94.3
G3	1.00	Slightly thin gel	5.34	99.52	129.27	92.2
G4	1.25	Smooth, homogeneous gel	5.60	99.73	113.04	96.0
G5 (optimized)	1.50	Smooth, translucent gel	5.66	99.89	133.93	97.5

The final optimized gel (G5) is shown in Figure 3. It presented as a smooth, homogeneous, pale, translucent semi-solid, free from grittiness or phase separation, and cosmetically acceptable for topical application.

Figure 3. Photograph of the final optimized salicylic acid-loaded transferosomal gel (G5).

FTIR Drug–Excipient Compatibility Study

The FTIR spectrum of the optimized gel (G5) retained all the principal functional-group peaks of salicylic acid — O–H (3468 cm^{-1}), aromatic C–H (3056 cm^{-1}), C=O (1682 cm^{-1}), aromatic C=C (1605 cm^{-1}) and C–O (1286 and 1215 cm^{-1}) — with only minor shifts of ≤ 7 cm^{-1} relative to the pure drug (Table 3, Figure 4). An additional band at 1078 cm^{-1} was attributed to the C–O stretching contribution of the gel/vesicle excipients. The absence of any new peak, peak disappearance, or major wavenumber shift indicates that no significant chemical interaction occurred between salicylic acid and the formulation excipients (soya lecithin, cholesterol, Tween 80 and Carbopol 934), confirming drug–excipient compatibility in the optimized formulation.

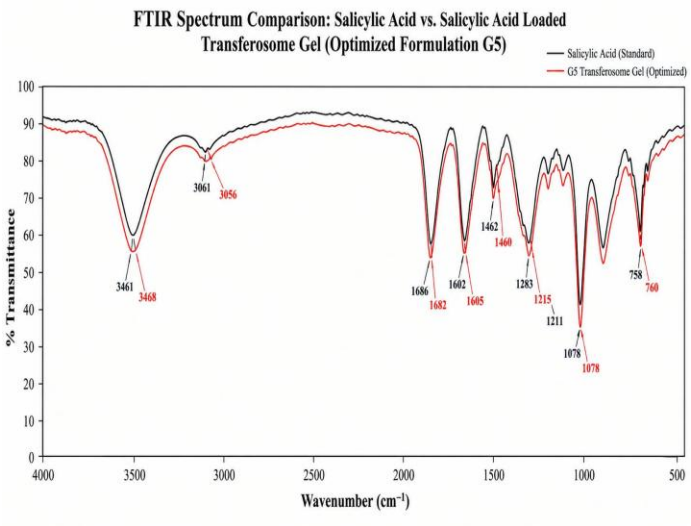


Figure 4. Comparative (overlaid) FTIR spectra of salicylic acid (API) and the optimized transferosomal gel, G5.

Table 3. Comparative FTIR peak assignment of salicylic acid and the optimized G5 gel.

Functional group	Salicylic acid (cm^{-1})	Optimized G5 gel (cm^{-1})	Shift (cm^{-1})
O–H	3461	3468	+7
Aromatic C–H	3061	3056	−5
C=O	1686	1682	−4
Aromatic C=C	1602	1605	+3
Aromatic C–H	1462	1460	−2
C–O	1283	1286	+3
C–O	1211	1215	+4
Aromatic C–H	758	756	+2

Zeta Potential and Surface Morphology

Zeta potential analysis of the optimized formulation was performed to assess colloidal stability, and scanning electron microscopy (SEM) was used to examine vesicle/gel surface morphology. Together, these analyses supported the physical stability and expected vesicular architecture of the optimized transferosomal system, complementing the particle-size and deformability data discussed in Section 3.2.

In Vitro Drug Release and Release Kinetics

The in vitro release profiles of the gel formulations (G1–G5) over 12 h are shown in Figure 5. Release rate decreased progressively with increasing Carbopol concentration, consistent with the higher gel viscosity restricting drug diffusion. The optimized gel, G5, showed the slowest and most sustained release among the five batches, with cumulative drug release increasing gradually from 8.00% at 1 h to 97.34% at 12 h, indicating that the transferosomal gel matrix was able to sustain salicylic acid release over an extended period rather than releasing the drug as an immediate burst.

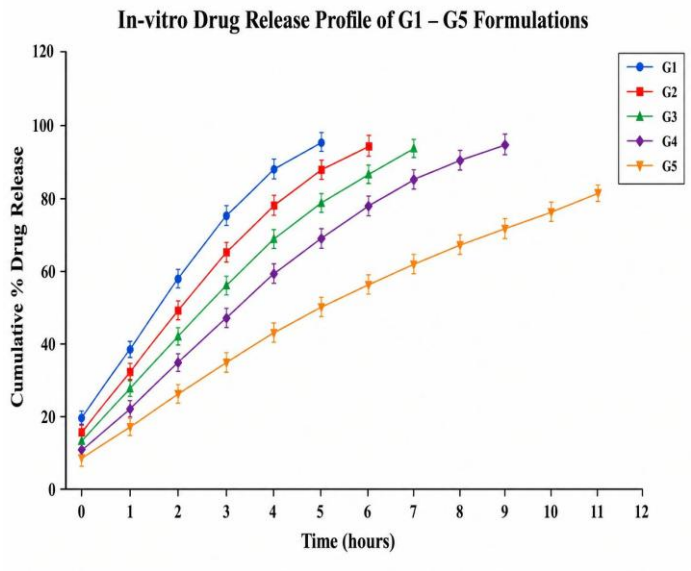


Figure 5. In vitro cumulative percentage drug release profiles of gel formulations G1–G5 over 12 h.

When the release data for the optimized G5 formulation were fitted to different kinetic models (Table 4), the Korsmeyer–Peppas model gave the best fit (R^2 = 0.9945), followed by the zero-order model (R^2 = 0.9894) and the Higuchi model (R^2 = 0.9774), while the first-order model showed a comparatively poorer fit (R^2 = 0.7580). This indicates that drug release from the optimized transferosomal gel was predominantly diffusion-controlled, consistent with a non-Fickian (anomalous) transport mechanism combining diffusion through the vesicular/gel matrix with polymer relaxation, rather than simple concentration-dependent release.

Table 4. Release kinetic model fitting for the optimized transferosomal gel (G5).

Kinetic model	Plot	R^2 value	Interpretation
Zero-order	Cumulative % release vs. time	0.9894	Good linearity
First-order	log (100 – % release) vs. time	0.7580	Poorer fit
Higuchi	Cumulative % release vs. √time	0.9774	Good diffusion-related fit
Korsmeyer–Peppas	log cumulative % release vs. log time	0.9945	Best fit among models tested

Table 4. Release kinetic model fitting for the optimized transferosomal gel (G5).

Conclusion

A salicylic acid-loaded transferosomal gel was successfully developed and optimized using a systematic formulation approach. The optimized transferosomal vesicles (F6) exhibited a small, uniform vesicle size, high entrapment efficiency and excellent deformability, properties expected to facilitate enhanced penetration of salicylic acid across the stratum corneum and into the pilosebaceous unit. Incorporation of these vesicles into a Carbopol 934 gel base (G5) yielded a formulation with desirable physicochemical, rheological and sustained drug-release characteristics, together with confirmed compatibility between the drug and the formulation excipients. The optimized transferosomal gel therefore represents a promising, patient-compliant alternative to conventional topical salicylic acid formulations for the management of acne vulgaris, offering the potential for reduced application frequency and improved localized therapeutic action. Further ex vivo skin permeation studies, long-term stability studies under ICH conditions, and in vivo/clinical evaluation are recommended to fully establish the therapeutic potential of the optimized formulation.

Future Scope

Future work may include evaluation of the pharmacological (anti-acne) activity of the optimized gel, ex vivo and in vivo permeation studies, pharmacokinetic and biodistribution assessment, dosage-regimen determination, and clinical/bioequivalence evaluation in human volunteers.

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