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Research Paper

Formulation And In Vitro Evaluation of Hesperidin Phytosomal Gel for Its Anti-Inflammatory Potential

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ABSTRACT

The present study aimed to develop and evaluate a hesperidin-loaded phytosomal gel for topical delivery and anti-inflammatory potential. Preformulation studies confirmed the physicochemical characteristics of hesperidin, including a λmax of 286 nm and a reported melting range of 252–255°C. Compatibility studies using FTIR, DSC and XRD indicated no significant drug–excipient interaction. A 3^2 factorial design was used with soya lecithin (X_1) and cholesterol (X_2) as independent variables, while particle size and entrapment efficiency were selected as responses. The optimized formulation F9 showed a particle size of 133.8 nm, zeta potential of −22.6 mV and entrapment efficiency of 88.35%. Drug content was 97.23%. The resulting phytosomal gel showed a pH of 6.90, acceptable spreadability and suitable viscosity for topical application. In the protein denaturation assay, the gel produced an IC_{50} of 94.81 µg/mL and showed greater inhibition at higher tested concentrations than pure hesperidin. In-vitro drug release reached 92.31% over 8 h and was reported to fit zero-order and Korsmeyer–Peppas models ($R^2 = 0.999$). The formulation remained stable over the reported 30-day stability period. These findings support the potential of hesperidin phytosomal gel as a topical delivery system with sustained release and anti-inflammatory activity.

INTRODUCTION

Novel drug delivery systems are designed to improve drug administration, therapeutic performance and delivery to the intended site. Vesicular and lipid-based systems such as liposomes, niosomes, transferosomes, ethosomes and phytosomes have been investigated to overcome limitations associated with conventional dosage forms. Phytosomes are lipid-compatible molecular complexes in which plant-derived bioactives are associated with phospholipids, commonly phosphatidylcholine. This approach can improve interaction with biological

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membranes and enhance delivery of phytoconstituents.

Hesperidin is a flavanone glycoside and a naturally occurring citrus bioactive. The dissertation describes hesperidin as having antioxidant, anti-inflammatory and vascular-protective properties, while its limited aqueous solubility can restrict formulation and delivery. A topical phytosomal system was therefore selected to combine phospholipid complexation with a gel vehicle and to facilitate local skin delivery.

The skin is a major barrier to topical drug delivery, with the stratum corneum representing the principal barrier. Drug movement may occur through intercellular, transcellular and appendageal pathways. Factors including molecular size, lipophilicity, solubility, pH, vehicle, hydration and drug concentration can influence penetration. Phytosomes and topical gels are consequently relevant approaches for improving delivery of poorly soluble phytoconstituents.

The present work focused on preparation of hesperidin phytosomes using a solvent-evaporation approach, incorporation of the optimized phytosomes into a Carbopol 934 gel and evaluation of the resulting formulation for physicochemical properties, anti-inflammatory activity, drug release, permeation and stability.

2. MATERIALS AND METHODS

2.1 Materials

Hesperidin was used as the active phytoconstituent. Soya lecithin and cholesterol were used for phytosome formation. Carbopol 934 was used as the gel-forming polymer. The study also used methanol and other solvents/excipients described in the dissertation, together with phosphate-buffered saline for release and protein denaturation studies.

2.2 Preformulation studies

Preformulation evaluation included organoleptic examination, melting point determination, solubility assessment, UV spectrophotometric analysis, FTIR, DSC and XRD. The analytical method for hesperidin was established by determining the wavelength of maximum absorption and preparing a calibration curve. The reported λmax was 286 nm.

2.3 Preparation and optimization of phytosomes

Hesperidin-loaded phytosomes were prepared by solvent evaporation. Soya lecithin and cholesterol were selected as formulation variables and a 3^2 factorial design was used. Particle size and entrapment efficiency were selected as response variables. Nine formulations (F1–F9) were evaluated and the optimized formulation was selected on the basis of the observed response profile.

Formulation	Particle size / response	Entrapment efficiency (%)
F1	Evaluated	77.15
F2	Evaluated	79.62
F3	Evaluated	82.40
F4	Evaluated	77.43
F5	Evaluated	79.33
F6	Evaluated	82.57
F7	Evaluated	82.40
F8	Evaluated	84.70
F9	133.8 nm	88.35

2.4 Preparation of phytosomal gel

The optimized phytosomal dispersion was incorporated into a topical gel base containing Carbopol 934. The prepared gel was evaluated for pH, viscosity and spreadability and subsequently investigated for morphology, anti-inflammatory activity, in-vitro drug release, release kinetics, permeation and stability.

3. EVALUATION METHODS

Particle size and zeta potential were determined for the optimized phytosomes. Entrapment efficiency and drug content were evaluated to assess incorporation of hesperidin into the phytosomal system. FTIR was used to assess compatibility and DSC/XRD were used as physicochemical characterization tools.

For anti-inflammatory evaluation, the protein denaturation method was used. A reaction mixture containing egg albumin and phosphate-buffered saline was treated with test samples at different concentrations. Following incubation and heating, absorbance was measured at 660 nm and percentage inhibition of protein denaturation was calculated.

In-vitro drug release was studied using a dialysis technique in phosphate-buffered saline at controlled temperature with continuous stirring. Samples were withdrawn at predetermined time points and analyzed spectrophotometrically. Release data were fitted to zero-order, first-order, Higuchi, Korsmeyer–Peppas and Hixson–Crowell models as described in the dissertation.

4. RESULTS AND DISCUSSION

4.1 Characterization and optimization

The optimized F9 phytosome exhibited a particle size of 133.8 nm and a zeta potential of −22.6 mV. The dissertation reports zeta-potential values from −22.6 to −10.6 mV across the formulations, with F9 showing the most negative value. Entrapment efficiency ranged from 77.15% to 88.35%, and F9 showed the highest value, indicating efficient incorporation of hesperidin in the selected formulation composition.

Parameter	Optimized F9 result
Particle size	133.8 nm
Zeta potential	−22.6 mV
Entrapment efficiency	88.35%
Drug content	97.23%
Gel pH	6.90

The F9 phytosomes were described as predominantly spherical under projection microscopy, with moderate dispersion and slight aggregation. TEM was also used for morphology assessment. The physicochemical characterization supported formation of the intended lipid-based delivery system.

4.2 Anti-inflammatory activity

Concentration (µg/mL)	Hesperidin % inhibition	Hesperidin gel % inhibition
20	12.98	1.94
40	22.07	20.77
60	27.27	32.46
80	40.25	41.55
100	43.50	55.19

At 20 µg/mL, pure hesperidin showed higher inhibition than the gel. At higher concentrations, the phytosomal gel showed greater inhibition, reaching 55.19% at 100 µg/mL compared with 43.50% for hesperidin. The reported IC_{50} for the phytosomal gel was 94.81 µg/mL, whereas pure hesperidin was reported as not effective within the tested concentration range for IC_{50} determination.

4.3 In-vitro drug release and kinetics

The phytosomal gel demonstrated progressive drug release, with cumulative release reported up to 92.31% over 8 h. The release profile indicated

sustained delivery from the formulation. The dissertation reports the best fit with zero-order and Korsmeyer–Peppas models, with $R^2 = 0.999$, and interprets the release as controlled and non-Fickian diffusion.

Release characteristic	Reported result
Maximum cumulative drug release	92.31%
Study duration	8 h
Best-fit models	Zero-order and Korsmeyer–Peppas
Reported R^2	0.999
Release interpretation	Controlled, non-Fickian diffusion

4.4 Stability

Stability evaluation was conducted over 30 days. The dissertation reports that the formulation remained stable over this period based on the evaluated physicochemical parameters. Longer-term and accelerated stability studies were identified as future requirements.

CONCLUSION

The study developed and evaluated a hesperidin-loaded phytosomal gel for topical delivery. The optimized F9 phytosomes showed a particle size of 133.8 nm, zeta potential of −22.6 mV, entrapment efficiency of 88.35% and drug content of 97.23%. The gel showed an acceptable pH of 6.90 and suitable topical characteristics. The protein denaturation assay demonstrated measurable anti-inflammatory activity, with an IC_{50} of 94.81 µg/mL for the phytosomal gel. Drug release reached 92.31% over 8 h and the formulation showed the reported zero-order and Korsmeyer–Peppas release behavior. Overall, the results indicate that phytosomal incorporation followed by gel formulation can provide a useful approach for topical delivery of hesperidin.

FUTURE SCOPE

Further work should include in-vivo pharmacokinetic and pharmacodynamic studies, long-term and accelerated stability studies, scale-up studies and clinical evaluation. Advanced morphology and surface-characterization techniques may also be used. Comparative studies with conventional hesperidin formulations could further characterize the delivery performance of the phytosomal gel.

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