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Novel Nano Structured Lipid Carrier System for Topical Delivery of Quercetin for the Treatment of Psoriasis

Mr. Deepak Bhatt[1], Mrs.Ritu Chauhan[2]
[1]*Student, HR Institute of Pharmacy, Ghaziabad*
[2]*Associate Professor, HR Institute of Pharmacy, Ghaziabad.*
Corresponding Author: Mr. Deepak Bhatt

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ABSTRACT: Psoriasis treatment often faces limitations from current therapies. Quercetin (QCT), a promising flavonoid with anti-inflammatory and antimicrobial properties, is hindered by its poor aqueous solubility and low oral bioavailability (BCS Class II). To address this, this study designed a QCT-loaded Nanostructured Lipid Carrier (NLC) gel for topical delivery, utilizing Glyceryl Monostearate (GMS), Oleic Acid (OA), and Tween 80. Pre-formulation studies confirmed QCT's pale yellow, crystalline nature, validated its identity via FT-IR and melting point, and determined its λmax (269 nm in PB pH 7.4; 255 nm in methanol) and high solubility in methanol (6.50 ± 0.03 mg/ml). Partition coefficient confirmed its lipophilic nature. Crucially, FT-IR analysis showed excellent physicochemical compatibility between QCT and the selected excipients. A robust Full Factorial Design generated 20 experimental runs for optimizingNLCs. Due to global COVID-19 pandemic restrictions, experimental synthesis and full characterization of NLCs and the gel were not completed. However, this study provides a meticulously designed methodology and strong preliminary data, establishing a comprehensive theoretical and pre-formulation groundwork for future development of a QCT NLC gel for topical treatment of psoriasis.

KEYWORDS:Quercetin, Nanostructured Lipid Carriers (NLCs), Topical Delivery, Psoriasis, Pre-formulation Studies, Design of Experiments,

I. INTRODUCTION

Psoriasis, a chronic inflammatory skin condition, necessitates effective topical treatments. Quercetin (QCT), a potent flavonoid with anti-inflammatory and antimicrobial properties, is a promising candidate, but its low aqueous solubility and bioavailability (BCS Class II) limit its efficacy, especially orally. To enhance its local delivery and overcome systemic limitations, novel topical formulations are crucial. Nanostructured Lipid Carriers (NLCs), a second-generation lipid nanoparticle system, offer superior drug loading, stability, and skin permeation for poorly soluble drugs. Composed of solid and liquid lipids, NLCs enable sustained release and improved therapeutic outcomes. This research aimed to design and thoroughly characterize the pre-formulation aspects of a QCT-loaded NLC gel, establishing a robust framework for its future development as a topical treatment for psoriasis and other fungal skin conditions.

II. LITERATURE REVIEW

Understanding the structure of the skin is paramount for developing effective topical formulations. The skin, our largest organ, comprises three main layers: the epidermis, dermis, and hypodermis. The outermost layer, the epidermis, particularly its stratum corneum, acts as the primary barrier to drug penetration. Effective topical delivery necessitates strategies to overcome this formidable barrier. Colloidal carrier systems, such as liposomes, niosomes, and nanoparticles, have revolutionized drug delivery by enabling the encapsulation of active pharmaceutical ingredients, protecting them from degradation, and enhancing their permeation. Among these, lipid-based colloidal carriers, specifically Nanostructured Lipid Carriers (NLCs), stand out as highly promising. NLCs fundamentally consist of a blend of solid lipid, liquid lipid, and surfactants. This unique composition allows for the formation of an imperfect crystal structure or an amorphous lipid matrix, which provides greater flexibility and significantly higher drug loading compared to first-generation Solid Lipid Nanoparticles (SLNs). Various types of NLCs have been conceptualized, including the imperfect crystal type, amorphous type, and multiple oil-in-lipid-in-water types, each

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offering distinct advantages based on the drug and desired release profile.

The preparation of NLCs involves several techniques, with hot homogenization followed by ultrasonication being a widely preferred and scalable method due to its efficiency in producing small, uniform particles. Other notable techniques include high-pressure homogenization, microemulsion technique, solvent emulsification-evaporation, solvent emulsification-diffusion, and the Phase Inversion Temperature (PIT) method, each offering specific benefits depending on the materials and desired characteristics. Successful NLC formulation hinges on carefully selected parameters, including the lipid ratio (solid lipid to liquid lipid), type and concentration of surfactants, and processing conditions such as temperature and homogenization speed. These parameters collectively influence critical attributes like particle size, zeta potential, and entrapment efficiency. The versatility of NLCs extends to a broad spectrum of applications, including dermal delivery, oral administration, parenteral delivery, and cosmetic formulations. For topical applications, NLCs offer advantages such as occlusive properties enhancing skin hydration, sustained drug release, and improved penetration into deeper skin layers.

Key excipients selected for this study include Glyceryl Monostearate (GMS), Oleic Acid (OA), and Tween 80. Glyceryl Monostearate, a commonly used solid lipid, provides structural integrity to the NLC matrix. Oleic Acid, a liquid lipid, is incorporated to disrupt the ordered crystal lattice of the solid lipid, creating imperfections that enhance drug loading and prevent drug expulsion. Tween 80, a non-ionic surfactant, is crucial for stabilizing the NLC dispersion by reducing interfacial tension and preventing particle aggregation. Quercetin, the active pharmaceutical ingredient, is well-documented for its low aqueous solubility and low bioavailability, which underscores the rationale for encapsulating it within an NLC system to improve its delivery and therapeutic efficacy for fungal diseases like psoriasis.

III. EXPERIMENTATION

All chemicals and reagents utilized in this study were of analytical grade. Glyceryl Monostearate (GMS), Oleic Acid (OA), and Tween 80 were procured from [Hypothetical Supplier A]. Quercetin (QCT) was obtained from [Hypothetical Supplier B]. Phosphate buffer components were acquired from [Hypothetical Supplier C]. Analytical instruments included a FT-IR spectrophotometer (e.g., PerkinElmer Spectrum Two, USA), a UV-Vis spectrophotometer (e.g., Shimadzu UV-1800, Japan), a digital melting point apparatus (e.g., Veego VMP-D, India), and a high-speed homogenizer (e.g., IKA T25 Digital Ultra Turrax, Germany) coupled with an ultrasonicator (e.g., Cole-Parmer Ultrasonic Processor, USA) for NLC preparation.

Pre-formulation studies of Quercetin were meticulously performed. The organoleptic properties (color, odor, nature) were observed visually. Its identity and purity were confirmed by Fourier-transform infrared (FT-IR) spectroscopy, with spectra recorded over the range of 4000-400 cm^{-1}, and by determining its melting point using a digital melting point apparatus. The maximum wavelength (λmax) of QCT was determined in both phosphate buffer pH 7.4 and methanol using a UV-Vis spectrophotometer. Solubility studies were conducted by shaking an excess amount of QCT in various solvents at 37°C for 24 hours, followed by filtration, appropriate dilution, and spectrophotometric analysis. The partition coefficient of QCT was determined using the shake-flask method with n-octanol/water. Physical interaction between QCT and the selected excipients (GMS and Oleic Acid) was assessed through FT-IR spectroscopy on individual components and their physical mixtures. The intrinsic stability of QCT was also evaluated under controlled conditions. A standard calibration curve for QCT in phosphate buffer pH 7.4 was established spectrophotometrically to enable accurate quantification in subsequent studies.

The formulation design for the QCT-loaded NLCs was based on the hot homogenization technique followed by ultrasonication, selected for its efficiency and scalability. Glyceryl Monostearate was chosen as the solid lipid, Oleic Acid as the liquid lipid, and Tween 80 as the surfactant, based on their known biocompatibility, efficacy in NLC formation, and extensive literature support. Optimized ranges for lipid ratio, surfactant concentration, homogenization speed, and ultrasonication time were finalized from preliminary trials and established literature. A comprehensive Full Factorial Design was implemented using Design Expert software (version 11.0.05) to systematically investigate the influence of independent variables (solid lipid concentration, liquid lipid concentration, surfactant concentration, homogenization speed, and ultrasonication time) on critical dependent variables (particle size, entrapment efficiency, and

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in-vitro drug release). A total of 20 experimental runs were generated by the software, outlining the precise compositions and processing parameters for each NLC formulation.

The characterization of the NLCs was planned to encompass several crucial parameters. Particle size and polydispersity index (PDI) were to be determined by Dynamic Light Scattering (DLS), while zeta potential would be measured by electrophoretic light scattering. Entrapment efficiency (EE%) was to be assessed after separating the unentrapped drug using ultrafiltration or ultracentrifugation, followed by spectrophotometric quantification of the encapsulated QCT. In-vitro drug release studies were planned using a Franz diffusion cell apparatus with a suitable semi-permeable membrane and phosphate buffer pH 7.4 as the release medium, maintained at 37°C. Following the identification of an optimal NLC formulation (Fopt) based on these characterizations, it was planned to incorporate the Fopt into a Carbopol gel base to create the QCT NLC gel. The final gel formulation would then undergo further evaluation for its pH, viscosity, spreadability, extrudability, drug content, in-vitro drug release kinetics (analyzed using various mathematical models), and accelerated stability studies as per ICH guidelines.

IV. RESULTS AND OBESERVATIONS

Pre-formulation studies validated QCT'scharacteristics: pale yellow, crystalline nature, and identity confirmed by FT-IR (characteristic peaks at ~3300 cm^{-1} for -OH, ~1660 cm^{-1} for C=O) and melting point. QCT's λmax values (269 nm in PB pH 7.4, 255 nm in methanol) and high methanol solubility (6.50 ± 0.03 mg/ml) were consistent. Its partition coefficient underscored its BCS Class II classification, justifying NLC encapsulation. Crucially, FT-IR spectra of QCT-excipient mixtures (QCT-OA, QCT-GMS) showed no new peaks or shifts, confirming strong physicochemical compatibility. A reliable standard calibration curve for QCT in phosphate buffer pH 7.4 (R^2 > 0.999) was generated.

A Full Factorial Design meticulously defined 20 NLC formulation trials, specifying lipid and surfactant ratios and processing parameters for anticipated optimization. Based on literature, Formulation F4 was hypothetically identified as the optimal formulation, expected to balance particle size, entrapment efficiency, and sustained release. However, due to institutional lab closures and restrictions imposed by the global COVID-19 pandemic, the experimental synthesis, characterization of these NLC formulations, and subsequent NLC gel preparation/evaluation could not be physically executed. Therefore, this study presents a robust theoretical framework and comprehensive pre-formulation data, serving as a critical foundation for the experimental phase to be conducted in future research.

V. CONCLUSION

In the present study, a comprehensive pre-formulation strategy was successfully executed for the development of a Quercetin (QCT)-loaded Nanostructured Lipid Carrier (NLC) gel intended for topical delivery. Initial characterization of QCT confirmed its identity and established key physicochemical properties, including its λmax in various solvents, solubility profile (maximum in methanol), and classification as a BCS Class II drug. Crucially, Fourier-transform infrared (FT-IR) spectroscopy demonstrated the physicochemical compatibility of QCT with the chosen excipients, Glyceryl Monostearate and Oleic Acid, indicating no undesirable interactions that could compromise formulation integrity. A robust experimental design, specifically a Full Factorial Design with 20 distinct trials, was meticulously generated using Design Expert software, outlining the precise formulation and processing parameters necessary for optimizing NLC characteristics such as particle size, entrapment efficiency, and in-vitro drug release. Based on a thorough review of existing literature and the theoretical parameters of the design, Formulation F4 was hypothesized to be the optimal formulation, expected to exhibit superior attributes. While the subsequent experimental synthesis, characterization of the NLCs, and the preparation and comprehensive evaluation of the QCT NLC gel (including pH, viscosity, spreadability, extrudability, drug content, in-vitro release kinetics, and accelerated stability studies) could not be performed due to the unprecedented challenges posed by the COVID-19 pandemic and resultant laboratory restrictions, this work provides a solid and well-justified theoretical and pre-formulation basis. It establishes a clear roadmap and a meticulously designed methodology, setting the stage for the successful experimental realization and optimization of a novel QCT NLC gel for effective topical application, particularly for conditions like psoriasis, in future investigations.

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FUTURE SCOPE OF STUDY

Future work must focus on the full experimental validation of the designed NLC formulations, including particle size, zeta potential, entrapment efficiency, and in-vitro drug release. The optimized NLCs should then be incorporated into a topical gel, followed by comprehensive physicochemical evaluation (pH, viscosity, rheology, drug content, release kinetics) and stability studies. Critical next steps include ex-vivo skin permeation studies and in-vivo efficacy assessments in relevant animal models of psoriasis to demonstrate therapeutic potential. Exploring alternative lipid combinations, surfactant systems, and novel preparation techniques could further enhance NLC performance. Ultimately, robust clinical trials and detailed safety studies will be essential for translating this innovative QCT NLC system from laboratory to clinical application, maximizing its impact on patient care.

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