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Development, Optimization and Characterization of Quercetin-Loaded Nanoemulsion: A Pharmaceutical Formulation Approach

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ABSTRACT: Quercetin is a naturally occurring flavonoid with considerable pharmaceutical and biological importance. Despite its promising pharmacological properties, its formulation into conventional dosage forms is challenging because of its poor aqueous solubility and limited dissolution characteristics. The present study was undertaken to develop and optimize a quercetin-loaded nanoemulsion to improve its solubilization and provide a stable nanosized delivery system. Preformulation studies were performed to determine the solubility of quercetin in different oils, surfactants and co-surfactants. A pseudo-ternary phase diagram was constructed to identify a suitable nanoemulsion region. Capmul MCM was selected as the oil phase, Tween 80 as surfactant and Transcutol P as co-surfactant. Nanoemulsions were prepared by aqueous phase titration followed by probe sonication. A three-factor, three-level design was employed to optimize the formulation, with droplet size, polydispersity index, zeta potential and entrapment efficiency considered as critical quality attributes. The optimized formulation demonstrated a droplet size of 116.1 ± 1.22 nm, zeta potential of −28.6 ± 0.78 mV and entrapment efficiency of 93.8 ± 1.18%. Transmission electron microscopy showed predominantly spherical and smooth droplets. In-vitro release studies demonstrated controlled quercetin release up to 12 h, with 91.7 ± 1.56% cumulative release from the optimized formulation. The results demonstrate that nanoemulsion technology is an effective approach for formulating quercetin into a nanosized pharmaceutical delivery system with improved physicochemical characteristics and controlled drug release.

INTRODUCTION

Quercetin is a naturally occurring flavonoid belonging to the polyphenolic class of phytoconstituents. It is widely distributed in fruits, vegetables and medicinal plants and has been extensively investigated because of its antioxidant, anti-inflammatory and other biological activities. The pharmaceutical development of quercetin, however, is associated with several formulation-related challenges, particularly poor aqueous solubility and limited dissolution. Poor aqueous solubility is one of the major factors responsible for inadequate dissolution and variable bioavailability of many biologically active compounds. Conventional formulations of poorly water-soluble compounds may therefore exhibit slow dissolution, incomplete absorption and variable therapeutic performance. Consequently, pharmaceutical formulation approaches capable of increasing the apparent solubility and dissolution rate of poorly soluble compounds have received considerable attention. [1–3]

Nanotechnology-based drug delivery systems have emerged as promising approaches for addressing the limitations associated with poorly water-soluble compounds. Among these systems, nanoemulsions have gained considerable interest because of

their relatively simple composition, ease of preparation and ability to incorporate lipophilic compounds. [4–6] Nanoemulsions are colloidal dispersions consisting principally of an oil phase, aqueous phase, surfactant and, where appropriate, a co-surfactant. They generally possess nanoscale droplets and a high interfacial surface area. Reduction in droplet size can increase the surface area available for drug dissolution and may consequently improve the apparent solubility and dissolution behavior of poorly water-soluble compounds. [4,5,9–11].

The selection of appropriate formulation components is an important step in nanoemulsion development. The oil phase should possess adequate solubilization capacity for the drug, while the surfactant and co-surfactant should provide efficient interfacial stabilization. Pseudo-ternary phase diagrams are frequently employed to identify the concentration ranges that favor formation of stable nanoemulsion systems [9–11]. In addition to composition, processing variables can substantially influence the physicochemical properties of nanoemulsions. Droplet size, polydispersity index, surface charge and drug entrapment are important quality attributes that influence formulation performance and physical stability [9–11]. Therefore, systematic optimization using Design of Experiments (DoE) and Response Surface Methodology (RSM) provides an efficient approach for identifying optimized formulation conditions [9–11].

The present study was therefore designed to develop and optimize a quercetin-loaded nanoemulsion using suitable pharmaceutical excipients. Preformulation solubility studies were performed, followed by pseudo-ternary phase diagram construction, nanoemulsion preparation and systematic optimization. The optimized formulation was subsequently characterized for droplet size, PDI, zeta potential, morphology, entrapment efficiency and in-vitro drug release.

MATERIAL & METHODS

Materials

Quercetin (≥98% purity) was used as the model active pharmaceutical ingredient. Capmul MCM and Labrafac Lipophile WL 1349 were evaluated as oil phases. Tween 80 (Polysorbate 80) and Span 20 (Sorbitan monolaurate) were evaluated as surfactants. PEG 400 and Transcutol P were investigated as co-surfactants. Analytical-grade solvents and reagents were used throughout the study.

Solubility Study

The solubility of quercetin was determined in different oils, surfactants and co-surfactants. An excess quantity of quercetin was added to 2 mL of each vehicle in glass vials. The samples were vortexed and maintained in a thermostatically controlled water bath at 37 ± 1°C for 72 h with shaking. After equilibration, the samples were centrifuged at 10,000 rpm for 15 min. The supernatant was collected and filtered through a 0.45-µm membrane filter. The concentration of dissolved quercetin was determined using UV-visible spectrophotometry at 370 nm after appropriate dilution with methanol. The vehicles showing favorable quercetin solubilization were selected for further formulation studies. The reported solubility results were used to select Capmul MCM, Tween 80 and Transcutol P as the formulation components.

Construction of Pseudo-Ternary Phase Diagram

Pseudo-ternary phase diagrams were constructed using the water titration method. Oil, surfactant and co-surfactant were mixed at different surfactant/co-surfactant (Smix) ratios, including 1:1, 2:1 and 3:1. Distilled water was gradually added to the oil–Smix mixtures under continuous mixing. The resulting systems were visually evaluated for transparency, homogeneity, clarity and phase separation. The area demonstrating formation of clear and stable systems was identified as the nanoemulsion region [9–11].

Preparation of Quercetin Nanoemulsion

Capmul MCM was selected as the oil phase, Tween 80 as surfactant and Transcutol P as co-surfactant. Quercetin was accurately weighed and dissolved in the oil phase using gentle heating at approximately 40°C. The oil phase and Smix were mixed thoroughly to obtain a homogeneous mixture. Distilled water was subsequently added dropwise under continuous stirring at approximately 1,000 rpm to produce a coarse emulsion. The pre-emulsion was subjected to probe sonication at 20 kHz using 60% amplitude for 10 min. intermittent cooling was applied during sonication to minimize excessive temperature elevation. The resulting nanoemulsion was transferred into amber-colored glass containers and stored at room temperature until further evaluation.

Optimization Using Design of Experiments

A three-factor, three-level experimental design was used to investigate the influence of formulation and process variables on the quality attributes of the nanoemulsion.

The independent variables included:

- Oil concentration
- Surfactant/co-surfactant ratio
- Homogenization conditions

The selected dependent variables were:

- Droplet size
- Polydispersity index
- Zeta potential
- Entrapment efficiency

Response Surface Methodology was applied for formulation optimization. Regression analysis and ANOVA were used to evaluate the effects of independent variables and their interactions. Response surface and contour plots were generated to understand the relationship between formulation variables and responses. The optimized formulation was selected using a desirability function, with the objective of obtaining a low droplet size and PDI and high zeta potential and entrapment efficiency [9–11].

Droplet Size and Polydispersity Index

The average droplet size and PDI were determined by dynamic light scattering. The measurements were used to evaluate the nanoscale characteristics and uniformity of the prepared formulations. A droplet size below 200 nm and PDI below 0.30 were considered desirable characteristics for the developed nanoemulsion system [9–11].

Zeta Potential

Zeta potential was determined to evaluate the surface charge and potential colloidal stability of the prepared formulations. The optimized formulation was compared with the other experimental batches [9–11].

Transmission Electron Microscopy

The morphology of the optimized nanoemulsion was examined using transmission electron microscopy. The samples were observed for droplet morphology, shape and general surface characteristics [9–11].

Determination of Entrapment Efficiency

Entrapment efficiency was determined by ultracentrifugation. The formulation was centrifuged at 15,000 rpm for 30 min, and the concentration of free quercetin in the supernatant was determined spectrophotometrically at 370 nm.

Entrapment efficiency was calculated using:

$$\textbf{Entrapment efficiency (\%)} = [(\textbf{Total drug} - \textbf{Free drug}) / \textbf{Total drug}] \times 100$$

In-Vitro Drug Release Study

In-vitro release of quercetin from the nanoemulsion was investigated using the dialysis bag diffusion method. The dialysis membrane was soaked overnight before use. A quantity of nanoemulsion equivalent to 5 mg of quercetin was transferred into the dialysis bag. The bag was immersed in 100 mL of simulated nasal fluid maintained at 37 ± 0.5°C and stirred at 100 rpm. Samples were withdrawn at predetermined time intervals from 0.5 to 12 h and replaced with an equivalent volume of fresh release medium. The samples were analyzed spectrophotometrically for quercetin concentration.

Release Kinetic Analysis

The drug-release data were fitted to different mathematical models, including zero-order, first-order, Higuchi and Korsmeyer–Peppas models. The model providing the best fit was selected on the basis of the corresponding regression characteristics.

RESULT & DISCUSSION

Solubility of Quercetin in Different Vehicles

The solubility study demonstrated considerable variation in the ability of different formulation vehicles to solubilize quercetin. Among the tested vehicles, Transcutol P demonstrated the highest solubility of quercetin at 22.67 ± 0.67 mg/mL, followed by Tween 80 at 18.11 ± 0.78 mg/mL and PEG 400 at 15.89 ± 0.11 mg/mL. Capmul MCM showed a solubility of 12.40 ± 0.21 mg/mL, whereas Span 20 and Labrafac demonstrated comparatively lower solubility.

Vehicle	Quercetin solubility (mg/mL ± SEM)
Capmul MCM	12.40 ± 0.21
Labrafac	6.22 ± 0.44
Tween 80	18.11 ± 0.78
Span 20	10.78 ± 0.11
Transcutol P	22.67 ± 0.67
PEG 400	15.89 ± 0.11

The higher solubilization capacity of Transcutol P supported its selection as the co-surfactant. Capmul MCM was selected as the oil phase, while Tween 80 was selected as the surfactant based on their favorable formulation characteristics.

Pseudo-Ternary Phase Diagram

The pseudo-ternary phase diagram demonstrated a suitable nanoemulsion region for the Capmul MCM–Tween 80–Transcutol P system. The formation of clear and homogeneous regions indicated favorable interactions among the selected formulation components. The identification of a suitable nanoemulsion region is important because it enables selection of appropriate proportions of oil and Smix for subsequent formulation optimization. The phase behavior obtained in the present study supported further development of the selected formulation system.

Optimization of Formulation

The experimental formulations demonstrated considerable variation in droplet size, PDI and entrapment efficiency. F1 exhibited a droplet size of 183.4 ± 2.11 nm, whereas F3 showed the lowest droplet size of 116.6 ± 1.55 nm. The PDI of F3 was also the lowest among the formulations, indicating a relatively narrow droplet-size distribution. F3 additionally exhibited the highest entrapment efficiency of 94.2 ± 1.15%. Therefore, F3 was selected as the optimized formulation based on the overall desirability of the investigated responses.

Formulation	**Droplet size (nm)**	**PDI**	**Entrapment efficiency (%)**
F1	183.4 ± 2.11	0.29 ± 0.01	82.3 ± 1.21
F2	161.8 ± 1.93	0.27 ± 0.02	85.6 ± 1.43
F3	116.6 ± 1.55	0.19 ± 0.01	94.2 ± 1.15
F4	143.7 ± 2.11	0.21 ± 0.01	90.4 ± 1.32
F5	175.5 ± 1.87	0.28 ± 0.02	84.8 ± 1.58

The improved performance of F3 can be attributed to the optimized balance between the oil phase and Smix and the applied emulsification conditions. An appropriate surfactant/co-surfactant concentration can reduce interfacial tension and facilitate formation of smaller and more uniformly distributed droplets.

Droplet Size and PDI

The optimized F3 formulation demonstrated a droplet size of 116.1 ± 1.22 nm with a PDI of 0.19 ± 0.01.

The nanoscale droplet size indicates successful formation of the nanoemulsion. The relatively low PDI suggests a comparatively uniform droplet population. The reduction in droplet size increases the interfacial area of the dispersed phase and can favor improved interaction between the formulation and aqueous dissolution medium. The results demonstrate that appropriate selection of formulation composition and processing conditions was effective in producing a nanosized quercetin delivery system.

Zeta Potential

The optimized F3 formulation exhibited a zeta potential of −28.6 ± 0.78 mV. The negative surface charge can provide electrostatic repulsion among dispersed droplets and may contribute to the physical stability of the nanoemulsion. The other formulations showed zeta potential values ranging from −21.5 to −25.4 mV, whereas F3 demonstrated the highest magnitude of surface charge among the investigated formulations.

Entrapment Efficiency

F3 demonstrated an entrapment efficiency of 93.8 ± 1.18%, indicating efficient incorporation of quercetin into the nanoemulsion system. High entrapment efficiency is desirable because it indicates that a major proportion of the incorporated drug is associated with the dispersed formulation rather than remaining freely available in the external phase. The high entrapment observed may be attributed to the favorable solubilization capacity of the selected oil–surfactant–co-surfactant system. [13–14]

Formulation	Droplet size (nm)	Zeta potential (mV)	Entrapment efficiency (%)
F1	182.4 ± 2.11	−21.5 ± 0.84	83.4 ± 1.34
F2	160.6 ± 1.34	−24.2 ± 0.97	87.6 ± 1.25
F3	116.1 ± 1.22	−28.6 ± 0.78	93.8 ± 1.18
F4	140.6 ± 1.36	−25.4 ± 0.81	89.7 ± 1.49
F5	171.8 ± 2.78	−22.8 ± 0.93	85.2 ± 1.51

The characterization results confirmed that F3 provided the most favorable combination of nanoscale droplet size, surface charge and drug entrapment.

Morphological Characterization

Transmission electron microscopy demonstrated predominantly spherical droplets with smooth surfaces. The morphological observations were consistent with the nanoscale characteristics obtained by dynamic light scattering. The spherical morphology and uniform appearance support the successful formation of the nanoemulsion. The agreement between microscopic observation and dynamic light-scattering measurements further supports the successful development of the optimized formulation.

In-Vitro Drug Release

The nanoemulsion formulations demonstrated controlled quercetin release over the investigated 12-h period. F3 exhibited the highest cumulative release of 91.7 ± 1.56% at 12 h.

Formulation	Cumulative release at 12 h (%)	Best-fit model
F1	72.8 ± 1.63	Higuchi
F2	78.4 ± 1.11	Higuchi
F3	91.7 ± 1.56	Korsmeyer–Peppas
F4	85.8 ± 1.78	Higuchi
F5	76.4 ± 1.34	First-order

The release profile of F3 was best fitted by the Korsmeyer–Peppas model, suggesting that drug release involved diffusion and other formulation-associated mechanisms. The controlled release behavior can be attributed to the incorporation of quercetin within the oil/surfactant system and the resulting diffusion characteristics. The findings indicate that nanoemulsion formulation can provide a more controlled release pattern compared with an unformulated quercetin suspension.

DISCUSSION

The present investigation demonstrates the successful application of a systematic formulation-development approach for a poorly water-soluble flavonoid. Initial solubility screening enabled rational selection of formulation excipients, while pseudo-ternary phase diagram studies facilitated identification of the nanoemulsion region. The subsequent optimization study demonstrated that formulation composition and processing conditions markedly affected the critical quality attributes of the system. Among the tested formulations, F3 consistently demonstrated the most desirable characteristics.

The optimized formulation possessed a droplet size of approximately 116 nm, low PDI, favorable zeta potential and high entrapment efficiency. These properties are important characteristics of a well-developed nanoemulsion system. Furthermore, the optimized formulation provided controlled release of quercetin over 12 h. The findings are consistent with the general pharmaceutical application of nanoemulsions as delivery systems for poorly water-soluble compounds. Reduction in droplet size increases the surface area available for interaction with the surrounding aqueous phase, while appropriate surfactant and co-surfactant selection facilitates stabilization of the dispersed droplets.

Overall, the results demonstrate that the Capmul MCM–Tween 80–Transcutol P system is suitable for development of a quercetin nanoemulsion and that systematic optimization can substantially improve the formulation characteristics.

CONCLUSION

The present study successfully developed and optimized a quercetin-loaded nanoemulsion using Capmul MCM as the oil phase, Tween 80 as surfactant and Transcutol P as co-surfactant. Preformulation studies demonstrated favorable solubilization of quercetin in the selected formulation components. The pseudo-ternary phase diagram confirmed the suitability of the selected oil–surfactant–co-surfactant combination for nanoemulsion development. Among the investigated formulations, F3 was identified as the optimized formulation. It demonstrated a mean droplet size of 116.1 ± 1.22 nm, favorable zeta potential of −28.6 ± 0.78 mV and high entrapment efficiency of 93.8 ± 1.18%. The formulation exhibited predominantly spherical droplets and controlled drug release, reaching 91.7 ± 1.56% cumulative release after 12 h.

The overall findings indicate that nanoemulsion technology provides a promising pharmaceutical approach for improving the formulation characteristics of quercetin. The optimized formulation can serve as a suitable platform for further pharmaceutical development and stability evaluation. Future investigations should include accelerated and long-term stability studies, drug-content uniformity, thermodynamic stability, dilution robustness and, where applicable, ex-vivo permeation and in-vivo pharmacokinetic evaluation to establish the formulation's performance under biological conditions.

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