

DEVELOPMENT AND EVALUATION OF GRAS-DERIVED QUERCETIN-LOADED NANOSTRUCTURED LIPID CARRIERS FOR POTENTIAL INTRANASAL DELIVERY

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Abstract : The present study was undertaken to develop and evaluate GRAS-derived Quercetin-loaded nanostructured lipid carriers (NLCs) for potential intranasal delivery. Quercetin is a poorly water-soluble flavonoid, and its low aqueous solubility presents a formulation challenge. A screening-based experimental approach was used to investigate suitable solid and liquid lipid combinations and surfactant concentrations. Glyceryl monostearate, Compritol 888 ATO and stearic acid were evaluated as solid lipids, while medium-chain triglycerides (MCT) and oleic acid were investigated as liquid lipids. Tween 80 showed suitable emulsification behaviour during preliminary screening. Ten Quercetin-loaded NLC formulations (F1–F10) were prepared by hot homogenization followed by probe ultrasonication and evaluated for particle size, polydispersity index (PDI), zeta potential, encapsulation efficiency and drug loading. Particle size ranged from 142 ± 2.6 to 210 ± 5.8 nm, PDI from 0.21 to 0.38, zeta potential from -19.6 to -30.2 mV, encapsulation efficiency from $70.5 \pm 1.6\%$ to $91.5 \pm 0.8\%$, and drug loading from $5.3 \pm 0.2\%$ to $8.5 \pm 0.2\%$. F10, containing 80 mg Compritol 888 ATO and 30 mg MCT, with Tween 80 and Poloxamer 188, showed the most desirable comparative physicochemical characteristics and was selected for further evaluation. In-vitro release was studied by dialysis membrane diffusion in simulated nasal fluid and showed an initial burst followed by sustained release up to 8 h. F10 showed $84.2 \pm 3.1\%$ cumulative release at 8 h. Release-model analysis indicated that F10 followed the first-order model most closely ($R^2 = 0.9944$). Three-month stability evaluation showed only moderate changes in particle size, PDI, zeta potential and drug content. The findings provide preliminary formulation and in-vitro evidence supporting further investigation of the selected Quercetin NLC as a potential intranasal delivery system; however, brain targeting, enhanced bioavailability and therapeutic efficacy were not established in the present study.

Index Terms— Quercetin, nanostructured lipid carriers, GRAS excipients, intranasal delivery, lipid nanoparticles, in-vitro drug release, stability.

IndexTerms - Component,formatting,style,styling,insert.

I. INTRODUCTION

Diabetic neuropathy is a common chronic complication of diabetes mellitus associated with progressive structural and functional abnormalities of peripheral nerves. Hyperglycaemia, oxidative stress, inflammatory processes, microvascular dysfunction and altered cellular energetics contribute to its progression. Existing pharmacological approaches are mainly directed towards symptom control, creating interest in formulation strategies that can improve the delivery characteristics of bioactive compounds.

Quercetin is a naturally occurring flavonoid found in several fruits, vegetables and medicinal plants. It has been investigated for antioxidant and anti-inflammatory activities and has also been studied in relation to neurodegenerative and metabolic disorders. However, its poor aqueous solubility and associated formulation limitations can restrict its pharmaceutical use. A lipid-based nanocarrier can provide an approach for incorporating poorly water-soluble compounds and evaluating their dispersion and release characteristics.

Intranasal administration is a non-invasive route that provides rapid contact with the nasal mucosa and avoids gastrointestinal degradation and hepatic first-pass metabolism associated with oral administration. The nasal cavity is anatomically associated with olfactory and trigeminal regions; nevertheless, direct nose-to-brain delivery should be demonstrated experimentally rather than inferred solely from intranasal administration.

Nanostructured lipid carriers are second-generation lipid nanocarriers composed of solid and liquid lipids. Incorporation of a liquid lipid into a solid lipid matrix can create structural imperfections that influence drug incorporation and release. Important NLC quality attributes include particle size, PDI, zeta potential, encapsulation efficiency, drug loading and physical stability. In the present work, GRAS-derived lipid excipients were investigated to develop Quercetin-loaded NLCs and to compare their physicochemical and in-vitro release characteristics.

The study was therefore designed with emphasis on formulation development and screening, physicochemical characterization, in-vitro drug release, release kinetics and short-term stability. The work does not aim to establish brain targeting, systemic or brain bioavailability, or therapeutic efficacy against diabetic neuropathy.

1.1 RATIONALE AND SIGNIFICANCE OF THE STUDY

The rationale of the present study is based on the intersection of three formulation considerations: the low aqueous solubility of Quercetin, the potential utility of lipid-based nanocarriers for poorly water-soluble compounds, and the practical interest in intranasal dosage forms. Rather than attempting to establish therapeutic efficacy at the formulation stage, the study concentrates on measurable pharmaceutical quality attributes. These include particle size, PDI, zeta potential, encapsulation efficiency, drug loading, in-vitro release and short-term stability.

Use of GRAS-derived excipients provides a formulation-development perspective in which commonly used lipid and surfactant materials are screened for compatibility and performance. The designation “GRAS-derived” should not be interpreted as proof that the final NLC product is automatically safe for intranasal administration. Route-specific safety, excipient concentration, impurity profile, tolerability and final-product quality require separate evaluation. The present work therefore provides a formulation-screening basis rather than a completed safety assessment.

The study is also significant because it compares ten formulations rather than reporting only one selected composition. The F1–F10 series provides a practical basis for observing how the use of different solid lipids and the incorporation of MCT as a liquid lipid correspond with changes in particle size, PDI, surface charge, encapsulation efficiency and drug loading. The comparative results are used to select F10 for subsequent release and stability evaluation.

1.2 OBJECTIVES

- Develop Quercetin-loaded nanostructured lipid carriers using selected GRAS-derived solid and liquid lipid excipients.
- Perform preliminary screening of solid lipids, liquid lipids and surfactants for formulation suitability.
- Prepare ten experimental NLC formulations (F1–F10) using hot homogenization followed by probe ultrasonication.
- Characterize the prepared formulations for particle size, PDI, zeta potential, encapsulation efficiency and drug loading.
- Compare the physicochemical characteristics of F1–F10 and select a formulation for further evaluation.
- Evaluate in-vitro Quercetin release from the formulations in simulated nasal fluid using a dialysis membrane method.
- Fit the release data to zero-order, first-order, Higuchi and Korsmeyer–Peppas models.
- Evaluate short-term stability of the selected formulation for three months under the conditions used in the study.
- Identify the limitations and future experimental requirements for assessing intranasal performance, safety, pharmacokinetics and therapeutic relevance.

II. LITERATURE AND SCIENTIFIC BACKGROUND

2.1 Quercetin as a formulation candidate

Quercetin is a plant-derived flavonoid that has attracted extensive pharmaceutical and biomedical research interest. Its chemical structure contains multiple hydroxyl groups and an aromatic flavonoid framework. These structural features are relevant to its antioxidant behaviour but also influence its physicochemical properties. In formulation development, the most immediate challenge addressed in the present study is its limited aqueous solubility. A poorly water-soluble compound may exhibit dissolution-limited behaviour, making the selection of a suitable carrier particularly important.

The biological literature on Quercetin includes experimental investigations involving oxidative stress, inflammation, metabolic processes and neurological models. Such literature provides a broad scientific rationale for investigating delivery approaches, but the formulation study should not be interpreted as confirmation of those biological effects. The present experimental endpoints are pharmaceutical and in-vitro rather than therapeutic.

2.2 Lipid-based nanocarriers

Lipid-based nanocarriers can improve the dispersion of lipophilic or poorly water-soluble molecules in an aqueous environment. Depending on composition, these systems may include solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions and related lipid dispersions. NLCs differ from systems containing only solid lipid by including a liquid lipid component. The liquid lipid can disrupt the ordered crystalline structure of the solid matrix, potentially creating additional accommodation space for the drug and altering release behaviour.

2.3 Nanostructured lipid carriers

The performance of an NLC is not determined by particle size alone. A formulation may show a small mean particle size but still exhibit broad size distribution, inadequate drug loading or physical instability. PDI provides an estimate of distribution width, while zeta potential provides information about interfacial electrical characteristics. Encapsulation efficiency reflects the fraction of the initial drug associated with the carrier, whereas drug loading relates the amount of drug to the carrier system. Together these attributes provide a more complete formulation profile.

2.4 Intranasal delivery

The nasal route provides a mucosal surface with relatively direct access to the external environment. It can avoid gastrointestinal conditions and hepatic first-pass metabolism associated with oral administration. At the same time, nasal delivery presents challenges including limited dose volume, mucociliary clearance, enzymatic activity, irritation potential and variability in mucosal conditions. Therefore, a nanosystem intended for intranasal administration must ultimately be evaluated not only for particle characteristics and release, but also for nasal tolerability, retention and in-vivo exposure.

2.5 Nose-to-brain concept and evidentiary requirements

The nose-to-brain concept is based on the anatomical relationships between the nasal cavity and neural pathways. However, evidence for direct transport to the brain cannot be inferred simply from intranasal dosing. Demonstration may require

comparative pharmacokinetic studies, brain-to-plasma exposure ratios, tissue distribution, imaging or other appropriately designed biodistribution experiments. The current work does not contain these experiments and therefore appropriately limits its conclusion to potential intranasal delivery.

III. MATERIALS AND METHODS

3.1 MATERIALS

Quercetin was used as the model flavonoid. GRAS-derived excipients evaluated during screening included glyceryl monostearate (GMS), Compritol 888 ATO (glyceryl behenate), stearic acid, medium-chain triglycerides (MCT oil), oleic acid, Tween 80 and Poloxamer 188. Methanol and other analytical reagents were used as required for UV-visible analysis and formulation evaluation.

3.2 PREFORMULATION STUDIES

Quercetin was evaluated for colour, appearance, odour and physical characteristics. Identification was performed by UV-visible spectroscopy and FTIR spectroscopy. The melting point was determined by the capillary method. Solubility screening was carried out in candidate solid and liquid lipids, surfactants and relevant solvents to identify suitable components for NLC development.

The experimentally determined melting point of Quercetin was 316.4°C. The calibration curve was prepared at 5–25 µg/mL using methanol as solvent and measurement at 370 nm. The calibration data showed a linear relationship with the displayed regression coefficient $R^2 = 0.9964$.

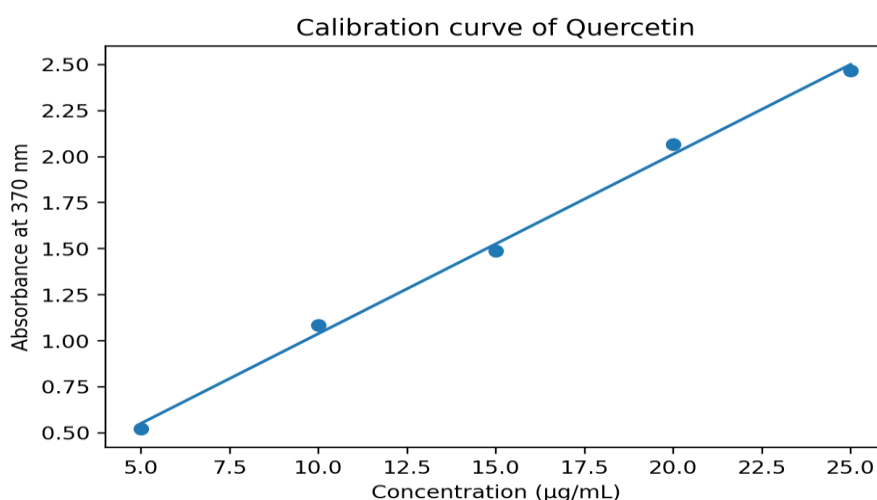


Figure 1. calibration curve of Quercetin at 370 nm.

3.3 PRELIMINARY LIPID AND SURFACTANT SCREENING

Candidate solid and liquid lipids were screened on the basis of Quercetin solubility and visual miscibility. Solid-to-liquid lipid ratios including 70:30, 72.7:27.3 and 50:50 were investigated during preliminary formulation screening. Tween 80 and Poloxamer 188 were evaluated for emulsification behaviour. Tween 80 provided favourable emulsification characteristics and was therefore used in the final formulation screening batches.

3.4 PREPARATION OF QUERCETIN-LOADED NLCS

The NLCs were prepared using a hot homogenization followed by probe ultrasonication approach. The lipid phase containing Quercetin was heated above the melting point of the selected solid lipid. An aqueous surfactant phase was prepared separately and maintained at a comparable temperature. The molten lipid phase was incorporated into the aqueous phase with high-shear homogenization to form a pre-emulsion, followed by probe ultrasonication to reduce particle size. The dispersion was subsequently cooled to obtain the NLC formulation.

3.5 FORMULATION COMPOSITION

Table 1. composition of Quercetin-loaded NLC formulations.

Formulation	Solid lipid (mg)	Liquid lipid (mg)	Tween 80 (% w/v)	Poloxamer 188 (% w/v)
F1	GMS 100	—	1.0	0.5
F2	GMS 110	—	1.0	1.0
F3	Compritol 100	—	1.5	0.5
F4	Compritol 110	—	1.5	1.0
F5	Stearic acid 100	—	1.0	0.5
F6	Stearic acid 110	—	1.5	1.0
F7	GMS 80	MCT 20	1.5	0.5
F8	GMS 80	MCT 30	1.5	1.0
F9	Compritol 80	MCT 20	1.5	0.5
F10	Compritol 80	MCT 30	1.5	1.0

3.6 PHYSICOCHEMICAL CHARACTERIZATION

Particle size, PDI and zeta potential were measured by dynamic light scattering. Encapsulation efficiency and drug loading were determined using the established analytical procedure. FTIR analysis was used to assess drug–excipient compatibility. The formulation showing the most desirable comparative physicochemical characteristics was selected for further in-vitro release and stability evaluation.

3.7 IN-VITRO DRUG RELEASE

In-vitro release was evaluated using a regenerated cellulose dialysis membrane with a molecular weight cut-off of 12,000–14,000 Da in simulated nasal fluid at approximately pH 6.4 and $37 \pm 0.5^\circ\text{C}$. Samples were withdrawn at predetermined intervals up to 8 h and analysed spectrophotometrically. Cumulative percentage drug release was calculated from the measured Quercetin concentration.

3.8 RELEASE KINETIC ANALYSIS

The release data were fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas models. The model with the highest coefficient of determination (R^2) was considered the closest mathematical fit to the experimental release data. The release mechanism was interpreted from the model-fitting results without extending the interpretation beyond the in-vitro experiment.

3.9 SHORT-TERM STABILITY STUDY

The selected formulation was stored in airtight amber glass vials under the evaluated storage conditions for three months. Particle size, PDI, zeta potential, drug content and visual appearance were assessed at initial, 1-, 2- and 3-month intervals. The observed changes were used to assess short-term physical and chemical stability.

IV. RESULTS AND DISCUSSION

4.1 PREFORMULATION FINDINGS

Quercetin was observed as a yellow crystalline powder. The experimental melting point was 316.4°C , consistent with the literature value reported in the thesis drug profile. The calibration curve prepared over 5–25 $\mu\text{g/mL}$ showed a strong linear relationship between concentration and absorbance at 370 nm, with $R^2 = 0.9964$. The low aqueous solubility observed during preformulation supported investigation of lipid-based formulation components.

4.2 LIPID AND SURFACTANT SCREENING

Quercetin showed greater solubility in the investigated liquid lipids than in the solid lipids. Compritol 888 ATO and GMS were selected as the principal solid lipids, while MCT oil and oleic acid were selected as liquid lipid candidates. Preliminary emulsification showed that Tween 80 provided favourable emulsification behaviour compared with Poloxamer 188. During formulation screening, the 72.7:27.3 solid-to-liquid lipid ratio was identified as a suitable ratio for the selected composition; it was not derived from a formal statistical DoE optimization.

4.3 PHYSICOCHEMICAL CHARACTERISTICS OF F1–F10

Table 2. physicochemical characterization of Quercetin-loaded NLC formulations.

Formulation	Particle size (nm)	PDI	Zeta potential (mV)	EE (%)	Drug loading (%)
F1	198 ± 5.2	0.36	–20.5	72.8 ± 1.4	5.6 ± 0.2
F2	185 ± 4.6	0.33	–22.3	75.4 ± 1.2	5.9 ± 0.3
F3	176 ± 4.1	0.31	–24.1	78.9 ± 1.3	6.3 ± 0.2
F4	168 ± 3.7	0.29	–25.6	81.2 ± 1.1	6.8 ± 0.3
F5	210 ± 5.8	0.38	–19.6	70.5 ± 1.6	5.3 ± 0.2
F6	194 ± 4.9	0.34	–21.7	74.1 ± 1.4	5.7 ± 0.2
F7	160 ± 3.2	0.26	–27.8	85.6 ± 1.1	7.5 ± 0.2
F8	148 ± 2.8	0.23	–29.4	88.9 ± 0.9	8.1 ± 0.2
F9	152 ± 3.0	0.24	–28.6	87.4 ± 1.0	7.8 ± 0.3
F10	142 ± 2.6	0.21	–30.2	91.5 ± 0.8	8.5 ± 0.2

Particle size ranged from 142 to 210 nm. F10 showed the smallest mean particle size (142 ± 2.6 nm), followed by F8 and F9. PDI values ranged from 0.21 to 0.38, with F10 showing the lowest PDI. Zeta potential values ranged from –19.6 to –30.2 mV, with F10 showing the most negative value. Encapsulation efficiency ranged from $70.5 \pm 1.6\%$ to $91.5 \pm 0.8\%$, while drug loading ranged from $5.3 \pm 0.2\%$ to $8.5 \pm 0.2\%$. F10 showed the highest encapsulation efficiency and drug loading among the tested batches. On comparative evaluation of these attributes, F10 was selected for further studies

4.4 IN-VITRO DRUG RELEASE

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	10.8	12.1	13.2	14.3	10.2	11.4	15.8	16.9	16.3	17.8
2	19.6	21.3	22.8	24.2	18.7	20.6	26.5	27.8	27.1	28.9
3	28.9	30.8	32.6	34.4	27.6	29.8	37.6	39.8	39.0	41.2
4	39.5	41.7	44.1	46.0	38.3	40.8	51.2	53.9	52.4	56.1
5	48.2	50.6	53.4	55.8	47.1	49.8	60.0	63.5	61.7	65.9
6	56.0	58.4	61.3	63.7	54.5	57.3	67.9	71.2	69.5	74.3
7	61.5	64.0	66.9	69.2	60.1	62.8	73.0	76.4	74.7	79.2
8	66.8	69.2	72.1	74.5	65.4	68.0	77.6	81.0	79.3	84.2

Table 3. cumulative in-vitro drug release (%) of Quercetin-loaded NLC formulations.

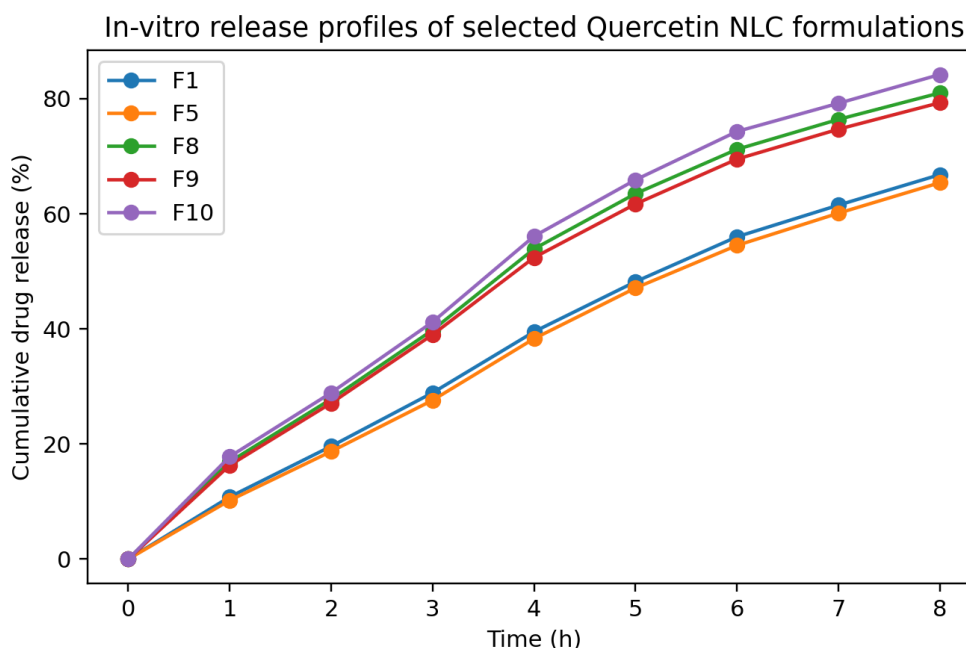


Figure 2. in-vitro release profiles of selected Quercetin NLC formulations.

All formulations demonstrated an initial burst release during the first hour followed by a gradual increase in cumulative release up to 8 h. At 8 h, cumulative release ranged from 65.4% to 84.2%. F10 exhibited the highest cumulative release ($84.2 \pm 3.1\%$), followed by F8 ($81.0 \pm 3.0\%$) and F9 ($79.3 \pm 2.9\%$). The higher release observed for F8–F10 may be associated with their smaller particle sizes and the presence of liquid lipid, which can introduce imperfections into the lipid matrix and facilitate drug mobility. These interpretations are limited to the observed in-vitro release behaviour.

4.5 RELEASE KINETICS

Table 4. release kinetic model fitting of Quercetin NLC formulations.

Formulation	Zero order R ²	First order R ²	Higuchi R ²	Peppas R ²	n	Best fit
F1	0.9883	0.9971	0.9928	0.9987	0.933	Peppas
F2	0.9870	0.9971	0.9933	0.9984	0.893	Peppas
F3	0.9852	0.9966	0.9931	0.9973	0.874	Peppas
F4	0.9839	0.9962	0.9932	0.9969	0.850	Peppas
F5	0.9887	0.9970	0.9919	0.9983	0.952	Peppas
F6	0.9865	0.9972	0.9930	0.9986	0.916	Peppas
F7	0.9734	0.9967	0.9922	0.9960	0.842	First order
F8	0.9706	0.9962	0.9911	0.9929	0.827	First order
F9	0.9723	0.9968	0.9922	0.9943	0.835	First order
F10	0.9704	0.9944	0.9904	0.9912	0.817	First order

For F10, the first-order model gave the highest R² value (0.9944) among the evaluated models, indicating that the experimental release profile was mathematically described most closely by the first-order model. The Korsmeyer–Peppas n value for F10 was 0.817. The data therefore support a concentration-dependent release fit for F10, while the Peppas model suggests anomalous transport behaviour within the limitations of the model and the in-vitro experiment. A mechanistic conclusion beyond these model-fitting observations was not made.

4.6 SHORT-TERM STABILITY

Table 5. short-term stability data of selected formulation F10.

Time	Particle size (nm)	PDI	Zeta potential (mV)	Drug content (%)	Physical appearance
Initial	142 ± 2.6	0.21	−30.2	98.5 ± 0.7	Clear, homogeneous
1 Month	150 ± 3.8	0.25	−28.7	96.5 ± 1.0	Slight turbidity
2 Months	158 ± 4.4	0.28	−27.3	94.8 ± 1.2	Slight aggregation
3 Months	165 ± 4.9	0.31	−26.1	93.2 ± 1.5	Mild aggregation

During three months of storage, particle size increased from 142 ± 2.6 to 165 ± 4.9 nm and PDI increased from 0.21 to 0.31. Zeta potential changed from -30.2 to -26.1 mV, while drug content decreased from $98.5 \pm 0.7\%$ to $93.2 \pm 1.5\%$. Visual examination showed slight turbidity at one month and slight to mild aggregation at two and three months. No phase separation was reported. These findings indicate relatively limited changes during the three-month observation period, supporting short-term stability under the evaluated conditions.

V. CONCLUSION

The present study developed and comparatively evaluated ten GRAS-derived Quercetin-loaded NLC formulations using a screening-based experimental approach. Preliminary studies supported the selection of suitable lipid and surfactant components, while physicochemical characterization demonstrated nanoscale particle sizes, acceptable PDI values, negative zeta potential, and measurable Quercetin encapsulation and loading. Formulation F10, comprising 80 mg Compritol 888

ATO and 30 mg MCT with Tween 80 and Poloxamer 188, showed the most desirable comparative physicochemical characteristics and was selected for further evaluation.

F10 provided $84.2 \pm 3.1\%$ cumulative Quercetin release at 8 h, and the release data were best fitted by the first-order model among the evaluated models. Three-month stability testing showed relatively limited changes in the measured quality attributes. Overall, the study provides preliminary formulation, physicochemical, in-vitro release and short-term stability evidence for the potential use of GRAS-derived Quercetin NLCs as an intranasal delivery platform. Direct brain targeting, improved systemic or brain bioavailability, and therapeutic efficacy in diabetic neuropathy were not experimentally established and require future pharmacokinetic, biodistribution, safety and efficacy studies.

VI. QUALITY-BY-DESIGN PERSPECTIVE

Although the present study used a screening-based approach rather than a formal statistical design of experiments, its formulation variables can be organized using a quality-by-design perspective. Critical material attributes may include solid lipid type, liquid lipid type and ratio, surfactant concentration and drug-to-lipid ratio. Potential critical process parameters include heating temperature, homogenization intensity, sonication energy and cooling rate. Critical quality attributes include particle size, PDI, zeta potential, encapsulation efficiency, drug loading, release profile and stability.

A future statistically designed study could evaluate the independent and interaction effects of these factors and define a design space for the selected NLC. Such an approach would reduce reliance on one-factor-at-a-time interpretation and could identify robust formulation ranges. The present F1–F10 screen should therefore be viewed as a preliminary selection step that identifies F10 for deeper optimization rather than as a statistically optimized final formulation.

VII. POTENTIAL INTRANASAL PRODUCT DEVELOPMENT CONSIDERATIONS

If F10 is developed further for intranasal administration, formulation design would need to consider nasal residence time, dose volume, viscosity, pH, osmolality, mucociliary clearance, microbial quality and local tolerability. The current study evaluates physicochemical properties and in-vitro release but does not report these nasal-product attributes. Consequently, the phrase “potential intranasal delivery” appropriately describes a development direction rather than a completed intranasal product.

Nasal safety studies would be important before animal or human administration. Histopathological evaluation of nasal tissues, irritation scoring and appropriate repeated-dose studies could help establish local tolerability. In addition, the final excipient concentrations should be justified for the intended route and formulation type rather than relying solely on the fact that individual materials have GRAS histories in particular contexts.

The formulation should also be evaluated for its behaviour after contact with simulated or actual nasal secretions. Changes in particle size, aggregation, viscosity and drug release in the presence of mucin or relevant biological media could provide a more realistic estimate of formulation performance. These experiments are beyond the current study but represent logical next steps.

VIII. NOSE-TO-BRAIN DEVELOPMENT STRATEGY

The present study should not be interpreted as proof of brain delivery. If the ultimate research objective is nose-to-brain delivery, a staged experimental strategy would be appropriate. First, the formulation should be shown to be physically stable and locally tolerated. Second, pharmacokinetic studies could compare intranasal administration with an appropriate control route. Third, tissue distribution studies could determine whether Quercetin or a validated marker associated with the NLC reaches brain tissue to a measurable extent.

Brain-to-plasma concentration relationships may provide supportive information, but tissue distribution can be influenced by systemic exposure. Therefore, evidence for direct transport should be interpreted using appropriate experimental controls. Imaging or tracer-based studies may provide additional evidence concerning localization. The choice of method should be based on the scientific question and validated analytical capability.

If the formulation is ultimately intended for diabetic neuropathy, efficacy studies would need to use an established experimental model with prespecified endpoints. Behavioural, biochemical, histological and molecular outcomes could then be considered as appropriate. However, such efficacy experiments should not be inferred from the current in-vitro release and stability results.

IX. LIMITATIONS OF THE PRESENT STUDY

- The study uses a screening-based formulation approach rather than a formal statistical design of experiments.
- The selected 72.7:27.3 solid-to-liquid ratio was identified during screening and was not statistically optimized.
- The release study is an in-vitro dialysis experiment and cannot directly predict nasal or brain exposure.
- No direct brain-targeting, brain-bioavailability or nose-to-brain transport study was performed.
- No therapeutic efficacy study for diabetic neuropathy was performed.
- No dedicated nasal irritation or histopathological safety study was reported.
- The stability assessment covered three months and therefore does not establish long-term shelf life.
- The supplied reference list contains descriptive placeholders for several sources; complete bibliographic verification is required before journal submission.
- Full analytical-validation parameters for the UV-visible method are not reported in the supplied manuscript.

X. FUTURE SCOPE

- Apply statistical design-of-experiments methodology to optimize solid lipid, liquid lipid and surfactant levels.
- Characterize the internal lipid state using complementary solid-state and thermal techniques.
- Investigate nasal mucosal compatibility, residence and retention characteristics.
- Conduct extended stability studies under multiple storage conditions.
- Perform pharmacokinetic and biodistribution studies following intranasal administration.
- Evaluate brain exposure only through appropriately controlled experimental studies rather than assuming direct transport.
- Investigate efficacy in a validated diabetic-neuropathy model after formulation safety and exposure have been established.
- Assess scalability, batch-to-batch reproducibility and critical process parameters.
- Complete analytical method validation and establish a suitable quality-control specification for the selected formulation.

XI. CONCLUSION

The present study developed and comparatively evaluated ten GRAS-derived Quercetin-loaded NLC formulations using a screening-based experimental approach. Preliminary studies supported selection of suitable lipid and surfactant components, while physicochemical characterization demonstrated nanoscale particle sizes, measurable encapsulation and drug loading, and differences in PDI and zeta potential across the formulation series.

Formulation F10, comprising 80 mg Compritol 888 ATO and 30 mg MCT with Tween 80 and Poloxamer 188, showed the most desirable comparative physicochemical characteristics among the tested batches. It exhibited a particle size of 142 ± 2.6 nm, PDI of 0.21, zeta potential of -30.2 mV, encapsulation efficiency of $91.5 \pm 0.8\%$ and drug loading of $8.5 \pm 0.2\%$. F10 also demonstrated $84.2 \pm 3.1\%$ cumulative Quercetin release at 8 h in the reported dialysis-membrane experiment, with the first-order model providing the closest mathematical fit among the evaluated models.

Three-month stability testing showed moderate changes in particle size, PDI, zeta potential and drug content, with no reported phase separation. Overall, the work provides preliminary formulation, physicochemical, in-vitro release and short-term stability evidence supporting further investigation of GRAS-derived Quercetin NLCs as a potential intranasal delivery platform. Direct brain targeting, improved systemic or brain bioavailability, nasal safety and therapeutic efficacy in diabetic neuropathy were not established and require dedicated future studies.

ACKNOWLEDGMENT

The author acknowledges the support of the Department of Pharmacy, Geetanjali University, Udaipur, Rajasthan, for providing academic and laboratory facilities required for the present work.

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