"Development and Quality-By-Design Optimization of *Swertia Chirayita* Extract-Loaded Nanoemulsion for Topical Drug Delivery"

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ABSTRACT

The present study aimed to formulate, optimize, and characterize a nanoemulsion containing *Swertia chirayita* extract for topical drug delivery. *Swertia chirayita* is a medicinal plant traditionally used for various therapeutic purposes and contains several phytoconstituents of pharmacological interest. In the present investigation, different oils, surfactants, and co-surfactants were screened for their suitability in nanoemulsion development. Nanoemulsions were prepared using the aqueous titration method, and pseudo-ternary phase diagrams were constructed to identify suitable formulation regions. Seven formulations (NE1–NE7) were developed and subjected to preliminary stress stability screening. Based on the screening results, NE3, NE6, and NE7 were selected for further evaluation. Among these, NE6 exhibited the lowest polydispersity index (0.270 ± 0.015) and a zeta potential of −26.8 ± 1.4 mV. The in-vitro drug release study demonstrated 97.9% cumulative release from NE6 at 720 minutes. The release data showed the highest correlation coefficient for the Higuchi model (R^2 = 0.9818), indicating that this model provided the best fit among the evaluated kinetic models. Temperature-dependent stability assessment showed a gradual decrease in drug content with increasing storage temperature. Overall, the findings indicate that the developed nanoemulsion, particularly NE6, demonstrated promising physicochemical characteristics and in-vitro release performance for further investigation as a topical delivery system. Further studies involving extract standardization, formulation safety, skin permeation and retention, and pharmacological evaluation are required before establishing its therapeutic efficacy.

Keywords: *Swertia chirayita*; herbal extract; nanoemulsion; topical drug delivery; aqueous titration; pseudo-ternary phase diagram; in-vitro release; stability.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycaemia resulting from impaired insulin secretion, insulin action or both. Long-term hyperglycaemia is associated with complications affecting the cardiovascular system, kidneys, eyes, peripheral nerves and other organs. The International Diabetes Federation estimated that 536.6 million adults aged 20–79 years were living with diabetes in 2021, with the number projected to increase to 783.2 million by 2045 [1]. In India, the ICMR–INDIAB study estimated that approximately 101 million people were living with diabetes and 136 million had prediabetes in 2021 [2]. These estimates highlight the continuing need for effective prevention, treatment and pharmaceutical research.

Conventional diabetes management includes lifestyle modification and pharmacological interventions selected according to disease type, glycaemic status and individual clinical requirements. In parallel, medicinal plants and their phytoconstituents have attracted research interest because of their chemical diversity and reported biological activities. However, traditional use and preliminary experimental findings should not be interpreted as proof of clinical efficacy.

Swertia chirayita (Roxb.) H. Karst., belonging to the family Gentianaceae, is a medicinal plant traditionally used in South Asian systems of medicine. Its phytochemical profile includes several classes of constituents, including

secoiridoids and xanthones. Published studies have investigated its pharmacological properties, including antioxidant and glucose-related activities [3,4]. Nevertheless, botanical extracts are chemically complex, and their composition may vary according to plant source, extraction procedure, storage and processing. Standardization and appropriate pharmaceutical formulation are therefore important considerations.

The topical route offers an accessible approach for local drug delivery, although the stratum corneum acts as a major barrier to the penetration of many substances. Skin permeation is influenced by molecular size, lipophilicity, ionization, vehicle composition, skin condition and contact time [5,6]. Importantly, topical delivery and transdermal delivery are not interchangeable terms. Topical formulations are generally intended for local application, whereas transdermal systems are designed to deliver an active substance across the skin into systemic circulation.

Nanoemulsions are dispersions of oil and water stabilized by surfactants, often in combination with co-surfactants. Their small dispersed droplets and relatively large interfacial area may support the incorporation and delivery of compounds with limited aqueous solubility. However, nanoemulsions are kinetically stabilized systems and may undergo physical changes such as creaming, flocculation, coalescence or Ostwald ripening during storage [7–9]. Their identity and quality must therefore be established using suitable instrumental characterization and stability testing rather than visual clarity alone.

The selection of oil, surfactant and co-surfactant is a key step in nanoemulsion development. Aqueous titration and pseudo-ternary phase diagrams can be used to investigate the influence of component ratios on the formation of clear, translucent or turbid dispersions. Subsequent evaluation of droplet size, polydispersity index, surface charge, pH, viscosity and drug release is required to assess formulation performance [8–10].

Considering the phytochemical diversity of *S. chirayita* and the potential application of nanoemulsion systems in topical delivery, the present study focused on the formulation screening and preliminary evaluation of *S. chirayita* extract-loaded nanoemulsions. The investigation included component screening, aqueous titration, pseudo-ternary phase-diagram assessment, preliminary stress stability, in-vitro release and release-kinetic analysis.

MATERIALS AND METHODS

Materials

The dried *Swertia chirayita* extract was procured from Yekka Enterprises, Mumbai, Maharashtra, India. Candidate oil phases, surfactants and co-surfactants were considered during preliminary screening. The formulation-development records included oleic acid, medium-chain triglycerides, isopropyl myristate, sesame oil, castor oil, soybean oil and olive oil as candidate oil phases; Tween 80, Labrasol, Tween 20, Kolliphor RH 40 and Kolliphor HS 15 as candidate surfactants; and Transcutol P, PEG 200, PEG 400 and propylene glycol as candidate co-surfactants or co-solvents.

Preliminary characterization of the extract

The dried extract was examined for colour, odour, physical appearance, texture and homogeneity. Its apparent dispersibility in water and visible sediment formation were also recorded. These preliminary observations were used to assess the physical characteristics of the extract before formulation development.

Screening of formulation components

Candidate oil phases, surfactants and co-surfactants were screened for their ability to accommodate the extract. The recorded screening dataset included solubility values expressed as mean ± standard deviation. The candidate excipients were compared to identify suitable components for further formulation screening.

Preparation of surfactant–co-surfactant mixture (Smix)

The surfactant and co-surfactant were considered in different proportions to investigate their influence on emulsification behaviour. The evaluated surfactant-to-co-surfactant ratios included 1:0, 1:1, 1:2, 2:1 and 3:1. The selected Smix compositions were subsequently assessed during aqueous titration.

Construction of pseudo-ternary phase diagrams

Pseudo-ternary phase diagrams were constructed using oil, Smix and water as the three formulation components. Different oil-to-Smix proportions were evaluated, and water was added incrementally during aqueous titration. The resulting mixtures were visually classified as clear, translucent, turbid or white/opaque. The observations were used to identify compositions suitable for further formulation development.

The percentage of each component was calculated using:

Component (%) = (Volume of individual component / Total volume of mixture) × 100

The number of clear and translucent observations was compared across the evaluated Smix ratios.

Preparation of extract-loaded nanoemulsions

Seven candidate formulations (NE1–NE7) were considered using the selected oil-to-Smix proportions and aqueous phase quantities. The extract loading was specified as 1% w/w, equivalent to 10 mg of extract per gram of final formulation. The final batch mass was adjusted according to the intended formulation quantity.

Preliminary stress-stability screening

The candidate formulations were subjected to preliminary stress-stability screening. The documented results identified NE3, NE6 and NE7 as the formulations shortlisted for further evaluation. The assessment included visual observations and the reported outcomes of applicable stress tests.

Physicochemical characterization

The comparative dataset available for formulations 3, 6 and 7 included polydispersity index (PDI), zeta potential, pH and apparent viscosity. These parameters were considered to compare the reported physical characteristics of the shortlisted formulations.

In-vitro drug-release study

The in-vitro release profile of NE6 was recorded at predetermined time intervals up to 720 min. Cumulative percentage release was plotted against time to assess the release behaviour of the formulation.

Release-kinetic modelling

The release data were evaluated using zero-order, first-order, Higuchi and Korsmeyer–Peppas models. The coefficient of determination (R^2) was used to compare the reported model fits. The model with the highest R^2 was considered to provide the best mathematical fit among the evaluated models. Model fitting alone was not considered sufficient to establish the precise release mechanism.

Stability assessment

The drug-content data were recorded at 0, 30, 60 and 90 days at 30 ± 0.5°C, 40 ± 0.5°C, 50 ± 0.5°C and 60 ± 0.5°C. The percentage of drug remaining was used to examine the temperature-associated change in content.

An exploratory first-order kinetic and Arrhenius approach was used to estimate temperature-dependent degradation rates and a theoretical t90 value. This estimate was treated as preliminary and not as an experimentally confirmed shelf life.

RESULTS AND DISCUSSION

Physical and organoleptic characterization of the extract

The dried *S. chirayita* extract showed a yellowish-brown to dark-brown colour and characteristic herbal odour. The material was observed as a solid with a powdery to slightly granular texture and a relatively uniform appearance. Partial dispersibility in water and slight sediment formation on standing were recorded.

Table 1. Preliminary physical and organoleptic characteristics of *S. chirayita* extract

Parameter	**Observation**
Colour	Yellowish-brown to dark brown
Odour	Characteristic herbal odour
Physical appearance	Dried solid extract
Texture	Powdery to slightly granular
Homogeneity	Relatively uniform
Water dispersibility	Partial dispersibility
Sedimentation	Slight sediment formation on standing

These observations provide preliminary information about the physical characteristics of the extract. However, organoleptic evaluation alone cannot establish botanical identity, phytochemical composition or the concentration of pharmacologically relevant constituents. A validated chemical fingerprint or marker assay is required for extract standardization.

Screening of formulation components

The recorded component-screening data indicated differences in the apparent solubility of the extract among the tested excipients.

Table 2. Recorded screening results for candidate formulation components

Component category	**Candidate**	**Solubility (mg/mL), mean ± SD**
Oil	Oleic acid	8.00 ± 0.24
Oil	Castor oil	7.00 ± 0.28
Oil	MCT	5.00 ± 0.18
Oil	Isopropyl myristate	3.00 ± 0.12
Oil	Olive oil	3.00 ± 0.10
Oil	Sesame oil	2.00 ± 0.08
Oil	Soybean oil	2.00 ± 0.06
Surfactant	Tween 80	29.68 ± 1.12

Surfactant	Labrasol	20.31 ± 0.76
Surfactant	Tween 20	19.22 ± 0.69
Surfactant	Kolliphor RH 40	15.42 ± 0.58
Surfactant	Kolliphor HS 15	13.18 ± 0.47
Co-surfactant	Transcutol P	33.84 ± 1.28
Co-surfactant	PEG 200	24.91 ± 0.91
Co-surfactant	Propylene glycol	20.73 ± 0.78
Co-surfactant	PEG 400	17.26 ± 0.63

MCT: medium-chain triglycerides.

Among the tested oils, oleic acid showed the highest recorded solubility value, followed by castor oil. Tween 80 showed the highest recorded solubility among the tested surfactants, while Transcutol P showed the highest value among the evaluated co-surfactants. These findings provide a preliminary basis for component selection. However, final selection must also consider emulsification behaviour, extract compatibility, topical suitability and the possibility of precipitation after dilution.

Pseudo-ternary phase-diagram screening

The different surfactant-to-co-surfactant ratios showed variation in the number of clear and translucent observations. The 1:2 ratio produced the highest number of clear and translucent observations among the evaluated ratios.

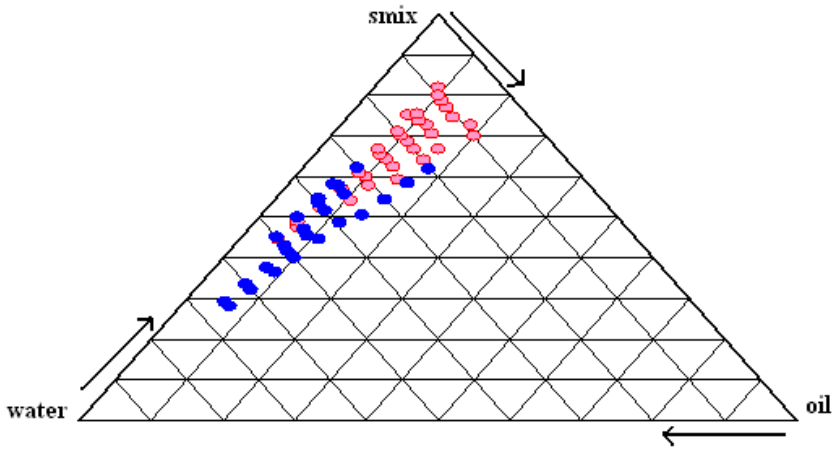


Figure 1. Nanoemulsion area of Smix Ratio: 1:2

Table 3. Comparative screening of Smix ratios

Surfactant ratio	**Clear + translucent observations**	**Percentage (%)**
1:0	67	39.9
1:1	96	57.1
1:2	101	60.1

2:1	80	47.6
3:1	73	43.5

The 1:2 ratio showed the highest proportion of clear and translucent observations (60.1%), followed by 1:1 (57.1%). The 1:0 ratio showed the lowest proportion (39.9%). These findings suggest that the relative proportion of surfactant and co-surfactant influenced the visual emulsification behaviour of the tested compositions.

The 1:2 ratio may therefore be considered a candidate for further investigation. Nevertheless, clear or translucent appearance does not independently confirm Nanoemulsion formation. Instrumental droplet-size measurement, PDI assessment and physical-stability testing are required to establish the suitability of the selected system.

Composition of extract-loaded Nanoemulsions

Seven candidate formulations were considered using different oil-to-Smix ratios and aqueous-phase volumes. The extract loading was specified as 1% w/w.

Table 4. Composition of *S. chirayita* extract-loaded Nanoemulsion formulations

Formulation	Smix ratio	Oil ratio	Oil (µL)	Smix (µL)	Water (µL)	Extract loading
NE1	1:1	2:8	20	80	75	1% w/w
NE2	1:1	1:7	20	140	95	1% w/w
NE3	1:1	1:6	20	120	95	1% w/w
NE4	1:2	3:7	30	70	180	1% w/w
NE5	1:2	4:6	40	60	180	1% w/w
NE6	2:1	3:7	30	70	145	1% w/w
NE7	3:1	5:5	50	50	180	1% w/w

The specified extract loading corresponds to 10 mg of extract per gram of final formulation. The final mass should be adjusted to the intended batch size, because the listed oil, Smix and water quantities are volume-based and do not automatically represent a final mass of 1 g.

Preliminary stress-stability screening

Seven candidate formulations were considered for preliminary stress-stability assessment. Based on the documented screening outcome, NE3, NE6 and NE7 were shortlisted for further evaluation.

Table 5. Preliminary stress-stability screening outcome

Formulation	Screening outcome
NE1	Not shortlisted
NE2	Not shortlisted
NE3	Shortlisted
NE4	Not shortlisted

NE5	Not shortlisted
NE6	Shortlisted
NE7	Shortlisted

The screening results identified NE3, NE6 and NE7 as candidates for subsequent comparative evaluation. The exact conditions and individual observations for each stress test should be reported from the laboratory record. The outcome of preliminary stress screening should not be interpreted as proof of long-term stability.

Comparative physicochemical characteristics

The available comparative dataset for formulations 3, 6 and 7 included PDI, zeta potential, pH and apparent viscosity.

Table 6. Reported comparative physicochemical characteristics

Parameter	**Formulation 3**	**Formulation 6**	**Formulation 7**
PDI	0.342 ± 0.018	0.270 ± 0.015	0.315 ± 0.016
Zeta potential (mV)	−22.6 ± 1.2	−26.8 ± 1.4	−14.2 ± 1.3
pH	5.82 ± 0.08	5.94 ± 0.06	5.89 ± 0.07
Apparent viscosity (cP)	55.2 ± 2.4	48.6 ± 1.8	51.4 ± 2.1

In-vitro release profile of NE6

The cumulative release of the measured material from NE6 increased progressively during the 720-min study period.

Table 7. In-vitro cumulative release profile of NE6

Time (min)	**Cumulative release (%)**	**Drug remaining (%)**
0	0.0	100.0
10	10.9	89.1
20	19.1	80.9
30	27.3	72.7
60	39.9	60.1
120	49.9	50.1
240	60.1	39.9
360	78.9	21.1
480	86.5	13.5
720	97.9	2.1

The release profile showed an increase from 10.9% at 10 min to 27.3% at 30 min. Release continued throughout the study period, reaching 60.1% at 240 min and 97.9% at 720 min. This indicates substantial release of the measured material under the reported in-vitro test conditions.

The progressive release profile may be relevant to further investigation of the formulation as a topical delivery vehicle. However, in-vitro release does not establish skin permeation, systemic absorption or glucose-lowering efficacy. Interpretation also depends on the analytical method used to quantify the released material and the experimental release conditions.

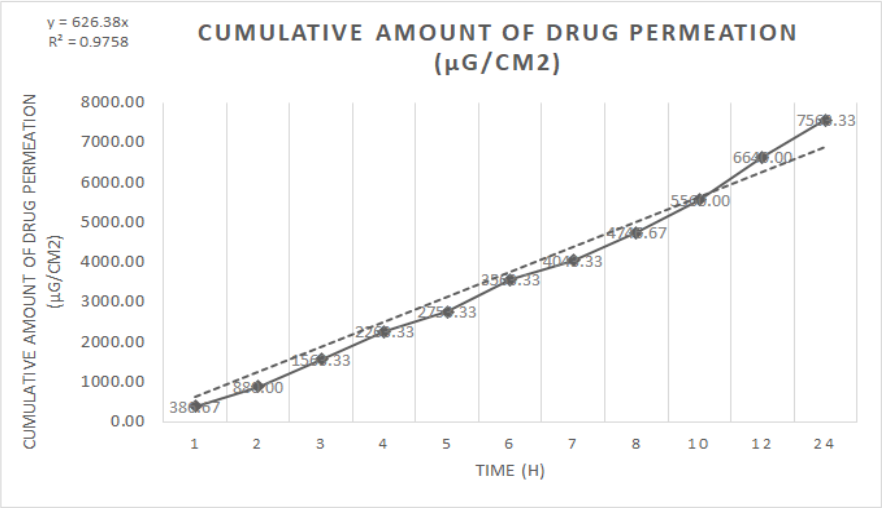


Figure 2: In Vitro Membrane Permeation Study Using a Franz Diffusion Cell

Release-kinetic modelling

The release data were evaluated using different mathematical models. The reported coefficients of determination are presented in Table 8.

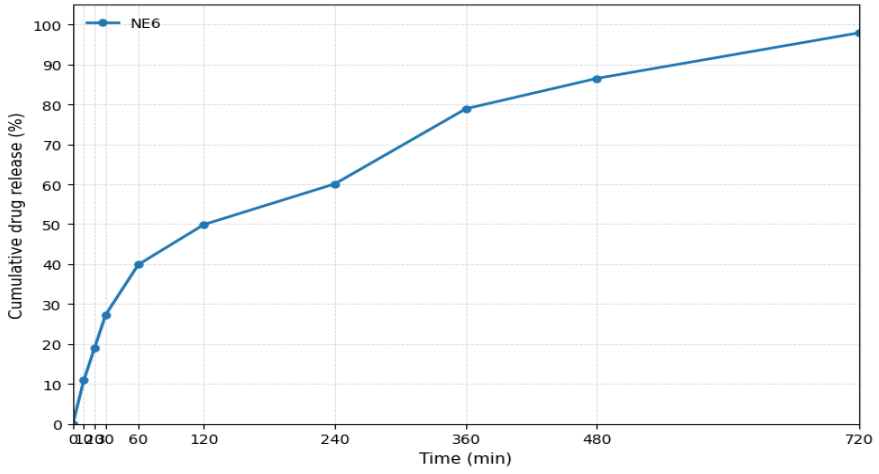


Figure 3: In-vitro drug release profile of Swertia chirayita extract-loaded NE6.

Table 8. Comparative release-kinetic model fitting for NE6

Release model	**Coefficient of determination (R^2)**
Zero-order	0.8776
First-order	0.7771

Higuchi	0.9818
Korsmeyer–Peppas	0.7446

Among the evaluated models, the Higuchi model showed the highest reported R^2 value (0.9818), followed by the zero-order model (0.8776). The first-order and Korsmeyer–Peppas models showed lower reported R^2 values.

The comparatively higher Higuchi R^2 suggests that the release profile was more closely described by a square-root-of-time relationship within the evaluated dataset. This may indicate a contribution from diffusion-associated release. Nevertheless, a high R^2 value alone does not prove a specific release mechanism. The assumptions of the Higuchi model, the suitability of the model for the formulation geometry and the validity of the analytical data should be considered before mechanistic conclusions are made.

Temperature-dependent stability assessment

The drug-content data showed a progressive decrease over the 90-day observation period at all tested temperatures. The reduction was greater at higher temperatures.

Table 9. Temperature-dependent drug-content profile over 90 days

Temperature	**Day 0 (%)**	**Day 30 (%)**	**Day 60 (%)**	**Day 90 (%)**
30 ± 0.5°C	100.000	99.470	98.900	98.400
40 ± 0.5°C	100.000	99.129	98.447	97.882
50 ± 0.5°C	100.000	98.992	98.198	96.895
60 ± 0.5°C	100.000	98.440	97.400	95.440

At day 90, the remaining drug content was highest at 30°C (98.40%) and lowest at 60°C (95.44%). The observed pattern indicates a temperature-associated decline in the reported content measurements. The difference between the temperature groups suggests that elevated storage temperatures may accelerate the loss of the measured material.

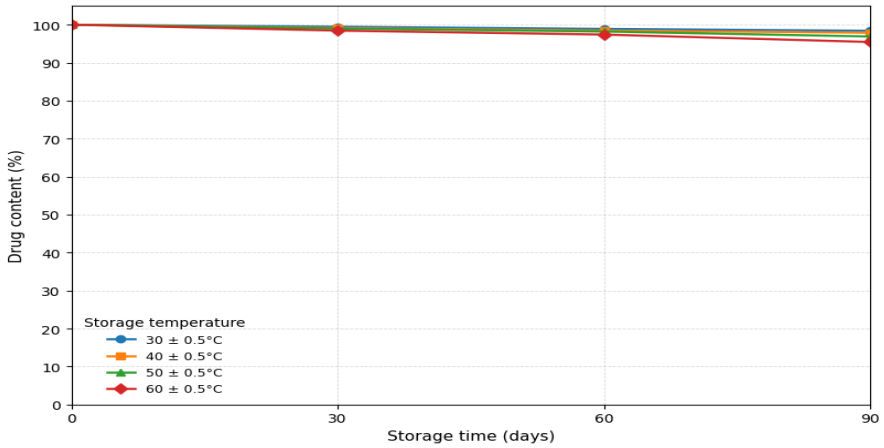


Figure 4: Temperature-dependent drug-content profile of the formulation during 90 days of storage.

Preliminary shelf-life estimation

An exploratory first-order kinetic and Arrhenius approach was applied to the temperature-dependent drug-content dataset. The reported apparent degradation-rate constants and calculated t90 values are summarized below.

Table 10. Exploratory degradation-rate and t90 estimates

Storage temperature	Apparent rate constant, k (day^{-1})	Calculated t90 (days)
30 ± 0.5°C	0.000180	583.9
40 ± 0.5°C	0.000237	444.4
50 ± 0.5°C	0.000342	307.8
60 ± 0.5°C	0.000502	209.8

The Arrhenius extrapolation produced a theoretical t90 estimate of approximately 737 days (about 2.02 years) at 25°C. This value is a model-derived estimate based on the available 90-day dataset and should not be interpreted as a confirmed shelf life or used to assign an expiry date. Confirmation requires appropriately designed real-time and accelerated stability studies, a validated stability-indicating assay and evaluation of relevant physical, chemical and microbiological quality attributes.

CONCLUSION

The present study investigated the preliminary formulation development and evaluation of *Swertia chirayita* extract-loaded nanoemulsions intended for topical drug delivery. The work included preliminary characterization of the dried extract, screening of candidate formulation components, aqueous titration, pseudo-ternary phase-diagram assessment and the preparation of seven candidate formulations.

Among the evaluated surfactant-to-co-surfactant ratios, the 1:2 ratio showed the highest number of clear and translucent observations (60.1%). Based on the documented preliminary stress-screening outcome, formulations NE3, NE6 and NE7 were shortlisted for further evaluation. The reported comparative physicochemical dataset showed that formulation 6 had the lowest PDI and the most negative zeta-potential value among the three compared formulations; however, the provenance of these measurements must be verified before they are accepted as primary results of the present study.

NE6 showed a progressive in-vitro release profile, reaching 97.9% cumulative release at 720 min. Among the evaluated mathematical models, the Higuchi model showed the highest reported R^2 value (0.9818), suggesting a diffusion-associated contribution to the observed release pattern. The temperature-dependent stability data showed a reduction in drug content with increasing storage temperature. The theoretical t90 estimate of approximately 737 days at 25°C remains exploratory and requires confirmation through real-time stability studies.

Overall, the findings provide a preliminary formulation-development framework for S. chirayita extract-loaded nanoemulsions. Further studies involving extract standardization, validated skin-permeation and skin-retention studies, formulation safety assessment and relevant pharmacological investigations are necessary before therapeutic claims relating to diabetes management can be made.

Limitations of the Study

The interpretation of the present findings is subject to certain limitations. The exact composition and processing conditions of the final formulations require confirmation from the original laboratory records. The provenance of the comparative PDI, zeta-potential, pH and viscosity measurements must be verified. Complete analytical and instrumental details for the release and stability studies are required for reproducibility. In-vitro release data do not establish ex-vivo skin permeation or systemic delivery, and no conclusion regarding antidiabetic efficacy can be drawn without appropriate pharmacological evaluation.

Conflict of Interest

The authors declare no conflict of interest.

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