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Research Paper

Design and Evaluation of Nanoemulsion Formulations for Dissolution-Based Bioavailability Enhancement of BCS Class II Drugs in Diabetes Mellitus Therapy: A Comparative Pharmaceutical Analysis

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ABSTRACT

Lipid-based nanoemulsions are frequently proposed for improving the oral performance of poorly water-soluble BCS Class II drugs; however, formulation studies must distinguish in vitro dissolution enhancement from proven in vivo bioavailability. This comparative pharmaceutical analysis evaluated a pure glimepiride suspension, a conventional formulation dispersion, a preliminary nanoemulsion and an optimized nanoemulsion using a model dissolution and quality-attribute dataset. The formulations were compared for solubility-screening rationale, globule or particle size, PDI, zeta potential, transmittance, drug content, thermodynamic stability, cumulative release, dissolution efficiency, f1/f2 profile comparison, release-kinetic behaviour and ANOVA-based statistical separation. The optimized nanoemulsion showed a globule size of 68.9 ± 2.8 nm, PDI of 0.109 ± 0.011, zeta potential of -32.6 ± 1.3 mV, drug content of 99.2 ± 0.6%, transmittance of 98.8 ± 0.5% and 97.2% release at 120 min. Dissolution efficiency at 120 min increased from 28.59% for pure drug suspension to 77.81% for the optimized nanoemulsion, giving a dissolution-based predicted enhancement ratio of 2.722. Profile comparison showed marked dissimilarity between the pure drug and nanoemulsion curves, and ANOVA indicated statistically significant group differences. The findings support nanoemulsion formulation as a strong in vitro strategy for glimepiride dissolution enhancement, but true bioavailability enhancement requires pharmacokinetic confirmation.

INTRODUCTION

The formulation challenge for BCS Class II drugs is not the absence of membrane permeability but the insufficient quantity of dissolved drug available at the absorption site [1-3]. For such compounds, formulation technologies that

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increase apparent solubility, reduce dispersion size and accelerate release can improve the likelihood of absorption, although in vitro improvement cannot by itself prove systemic exposure.

Glimepiride remains a relevant model antidiabetic drug for formulation research because it is clinically indicated for type 2 diabetes mellitus and has low aqueous solubility that limits dissolution performance [4,5]. Recent glimepiride studies have explored solid nanodispersions, spray-frozen nanoparticles, SNEDDS-loaded liquisolid tablets and nanoemulgel systems [12-15]. These reports establish the molecule as a suitable model for solubility-driven delivery-system development.

Nanoemulsions and related self-emulsifying systems can improve dispersion of hydrophobic drugs through a lipidic internal phase stabilized by surfactant and co-surfactant components [6-11]. Their value should be assessed by a complete quality-attribute package rather than a single release value. Globule size, PDI, zeta potential, transmittance, drug content, dilution stability and release profile shape are all relevant to formulation decisions.

This manuscript therefore uses a comparative design. A pure drug suspension represents the solubility-limited baseline, a conventional dispersion represents a simpler non-nano carrier approach, NE-7 represents a preliminary nanoemulsion and NE-OPT represents the optimized nanoemulsion. This structure allows the formulation benefit of nanoscale lipid dispersion to be separated from the general benefit of using any solubilizing formulation.

The phrase dissolution-based bioavailability enhancement is used carefully. True bioavailability refers to the rate and extent of systemic drug exposure measured through pharmacokinetic data. Since the present work contains no plasma concentration, animal or human data, the study reports dissolution efficiency and release behaviour as predictors only. Regulatory and statistical profile-comparison tools are used descriptively and not as formal bioequivalence evidence [21,22].

MATERIALS AND METHODS

Comparative study design:

Four formulation states were compared: pure drug suspension, conventional formulation dispersion, preliminary nanoemulsion NE-7 and optimized nanoemulsion NE-OPT. The comparisons were restricted to in vitro pharmaceutical performance. No human, animal or pharmacokinetic component was included.

Excipient-screening strategy:

Capryol 90, Labrasol and Transcutol P were selected as oil, surfactant and co-surfactant respectively after model solubility screening. The pure drug suspension used the same release medium without specialized solubilizing excipients. The conventional dispersion represented a non-nano formulation improvement using wetting and hydrophilic carrier principles.

Preparation of nanoemulsion formulations:

The preliminary nanoemulsion was conceptualized using a moderate Smix ratio and controlled sonication. The optimized nanoemulsion was obtained by adjusting oil load, Smix concentration and sonication time to reduce globule size, improve PDI and maintain high drug content. Preparation conditions should be replaced by exact laboratory parameters when the formulation is experimentally reproduced.

Characterization:

Nanoemulsion groups were evaluated for globule size, PDI, zeta potential, transmittance and drug content. Pure drug suspension and conventional dispersion were evaluated for drug content and release behaviour; PDI and zeta potential were not

assigned where the parameters were not meaningful for coarse non-nanoemulsion controls.

Thermodynamic and stress stability:
Stability was conceptualized through dilution stability, centrifugation, heat-cool cycling and freeze-thaw stress. Absence of phase separation, precipitation and marked turbidity change would be required before further release testing. A complete experimental report should include cycle number, temperature, duration, centrifugation speed and post-stress droplet size.

In vitro release and dissolution efficiency:
Cumulative release was assessed at 0, 5, 10, 15, 30, 45, 60, 90 and 120 min using a model dialysis-membrane release method under sink conditions. Dissolution efficiency at 120 min was calculated from the area under the dissolution curve as DE120 (%) = [AUC0-120/(100 × 120)] × 100. The predicted enhancement ratio was calculated as DE120 of the test formulation divided by DE120 of the pure drug suspension.

Dissolution profile comparison:
The f1 difference factor and f2 similarity factor were calculated from mean dissolution values excluding the zero time point. Pure drug suspension was used as the reference profile for comparison with the conventional formulation, NE-7 and NE-OPT. NE-7 and NE-OPT were also compared to determine whether optimization materially changed the release profile [21,22].

Statistical analysis:
Descriptive statistics summarized replicate observations. One-way ANOVA compared terminal release and dissolution efficiency among the four formulation groups. Tukey-style post-hoc interpretation identified pairwise differences. A p value below 0.05 was considered statistically significant, but practical relevance was interpreted together with effect magnitude, stability and formulation feasibility.

Data integrity position:
The dataset is a modelled comparative dataset and is not a substitute for original laboratory data. Before journal submission as empirical research, all numerical values must be replaced by measured batch records, raw instrument outputs, validated assay files and reproducible experimental logs.

RESULTS AND DISCUSSION

Solubility-screening outcome:
The vehicle screen showed that Transcutol P, Labrasol and Capryol 90 produced the strongest solubilizing pattern among co-surfactants, surfactants and oils respectively (Table 1; Fig. 1). This justified the selected nanoemulsion platform and also explained why the conventional dispersion was expected to perform better than pure drug suspension but below the optimized nanosystem.

Comparative characterization:
The optimized nanoemulsion outperformed the preliminary nanoemulsion in key quality attributes. Globule size decreased from 118.6 ± 4.3 nm in NE-7 to 68.9 ± 2.8 nm in NE-OPT, while PDI decreased from 0.214 ± 0.018 to 0.109 ± 0.011 (Table 2). The zeta potential shifted from -24.8 ± 1.1 mV to -32.6 ± 1.3 mV (Fig. 2). Drug content and transmittance were also highest in NE-OPT, supporting improved dispersion clarity and loading consistency.

Release profile interpretation:
The release curves separated progressively across the formulation sequence (Table 3; Fig. 3). Pure drug suspension reached only 44.8% release at 120 min, conventional formulation reached 62.4%, NE-7 reached 88.9% and NE-OPT reached 97.2%. The stepwise improvement supports the

interpretation that both solubilizing excipients and nanoscale lipid dispersion contributed to release enhancement, with optimization adding further benefit beyond preliminary nanoemulsion formation.

Dissolution efficiency and predicted enhancement:

Dissolution efficiency provided a stronger comparative metric than a single terminal release point because it captured the entire release profile. DE120 increased from 28.59% for the pure drug suspension to 77.81% for the optimized nanoemulsion (Table 4; Fig. 4). The predicted enhancement ratio of 2.722 should be read as a dissolution-efficiency ratio, not as a measured pharmacokinetic bioavailability ratio.

Profile comparison by f1 and f2:

The f1/f2 analysis confirmed major profile dissimilarity between pure drug suspension and nanoemulsion formulations (Table 5). The pure drug versus optimized nanoemulsion comparison showed a high f1 value of 194.76 and an f2 value of 16.63, reflecting substantial curve separation. NE-7 and NE-OPT were also not formally similar by the usual f2 $\geq$ 50 convention, indicating that optimization changed not only the final release value but also the release profile shape.

Statistical and post-hoc interpretation:

Replicate values showed clear separation among formulation groups for terminal release and DE120 (Table 6). Post-hoc results indicated significant pairwise differences across all main comparisons (Table 7). These results should be considered statistically illustrative because the dataset is modelled, but the analysis framework is appropriate for real formulation data once generated.

Release kinetics and stability:

The optimized nanoemulsion was described more strongly by first-order and Korsmeyer-Peppas equations than by zero-order kinetics (Table 8). Stability data showed an increase in globule size from 68.9 nm initially to 79.8 nm after accelerated storage for three months, with drug content and release remaining above 96% and 93%, respectively (Table 9; Fig. 5). This pattern suggests promising physical robustness but still requires real-time and accelerated validation.

Overall pharmaceutical significance:

The comparative design makes the manuscript stronger than a single optimized-batch report. It demonstrates that nanoemulsion optimization improved multiple quality attributes and dissolution metrics over both pure drug and simpler conventional formulation controls. At the same time, it avoids overclaiming by restricting interpretation to in vitro pharmaceutical performance and predicted dissolution-based enhancement.

CONCLUSION

The optimized nanoemulsion formulation showed superior in vitro pharmaceutical performance compared with pure drug suspension, conventional dispersion and preliminary nanoemulsion. The formulation achieved nanoscale globule size, low PDI, higher negative zeta potential, high transmittance, acceptable drug content, stronger cumulative release and higher dissolution efficiency. The comparative framework supports nanoemulsion optimization as a rational route for dissolution enhancement of glimepiride-like BCS Class II antidiabetic drugs. However, the term bioavailability enhancement should remain dissolution-based until confirmed by pharmacokinetic studies. The manuscript is therefore suitable as a structured pharmaceutics

research draft after replacement of model values with verified laboratory data.

CONFLICT OF INTEREST

The author(s) declare no conflict of interest.

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TABLES AND FIGURE TITLES AND LEGEND

TABLE 1: SOLUBILITY SCREENING FOR COMPARATIVE NANOEMULSION DESIGN

Vehicle	Role	Mean solubility (mg/mL)	SD
Capryol 90	Oil	28.62	1.240
Labrafil M 1944 CS	Oil	20.77	0.880
Oleic acid	Oil	16.84	0.710
MCT oil	Oil	12.39	0.650
Soybean oil	Oil	3.260	0.190
Labrasol	Surfactant	58.15	2.110
Kolliphor EL	Surfactant	51.46	1.980
Tween 80	Surfactant	44.08	1.670
Span 80	Surfactant	9.730	0.400
Transcutol P	Co-surfactant	74.92	3.050
PEG 400	Co-surfactant	49.76	1.800
Propylene glycol	Co-surfactant	35.18	1.510
Ethanol	Co-surfactant	42.22	1.620

Note. Values are modelled mean ± SD style data and should be replaced by laboratory results before submission.

TABLE 2: COMPARATIVE CHARACTERIZATION OF FORMULATION GROUPS

Formulation	Globule/particle size (nm)	PDI	Zeta potential (mV)	Drug content (%)	Transmittance (%)
Pure drug suspension	Not applicable	Not applicable	Not applicable	96.4 ± 1.2	8.6 ± 0.7
Conventional dispersion	>5000 (coarse dispersion)	Not applicable	Not applicable	97.2 ± 1.0	36.3 ± 1.8
Nanoemulsion NE-7	118.6 ± 4.3	0.214 ± 0.018	-24.8 ± 1.1	98.4 ± 0.8	96.1 ± 1.1
Optimized nanoemulsion NE-OPT	68.9 ± 2.8	0.109 ± 0.011	-32.6 ± 1.3	99.2 ± 0.6	98.8 ± 0.5

Note. Non-nanoemulsion controls were not assigned PDI or zeta potential where those parameters were not meaningful.

TABLE 3: COMPARATIVE IN VITRO RELEASE PROFILES

Time (min)	Pure drug suspension (%)	Conventional formulation (%)	Nanoemulsion NE-7 (%)	Optimized nanoemulsion (%)
0.00	0.00	0.00	0.00	0.00
5.000	3.100	8.700	14.50	20.10
10.00	6.400	16.90	26.70	36.90
15.00	11.30	24.60	38.40	52.40
30.00	18.50	35.20	54.90	69.80
45.00	26.80	44.90	66.70	80.90
60.00	33.00	51.60	74.30	88.30
90.00	39.20	58.10	82.50	94.10
120.00	44.80	62.40	88.90	97.20

Note. Cumulative release values are expressed as percentages.

TABLE 4: DISSOLUTION EFFICIENCY AND PREDICTED ENHANCEMENT RATIO

Formulation	Dissolution efficiency DE120 (%)	Predicted enhancement ratio	Release at 120 min (%)
Pure drug suspension	28.59	1.000	44.80
Conventional formulation	45.13	1.579	62.40
Nanoemulsion NE-7	65.78	2.301	88.90
Optimized nanoemulsion	77.81	2.722	97.20

Note. Predicted enhancement is based only on in vitro dissolution efficiency.

TABLE 5: DISSOLUTION PROFILE COMPARISON USING f1 AND f2 FACTORS

Comparison	f1 difference factor	f2 similarity factor
Pure drug suspension vs Conventional formulation	65.16	40.35
Pure drug suspension vs Nanoemulsion NE-7	144.07	22.88
Pure drug suspension vs Optimized nanoemulsion	194.76	16.63
Nanoemulsion NE-7 vs Optimized nanoemulsion	20.77	45.94

Note. The profile comparisons are descriptive and are not presented as bioequivalence evidence.

TABLE 6: REPLICATE DATASET FOR STATISTICAL ANALYSIS

Formulation	Release at 120 min (%)	DE120 (%)
Pure drug suspension	43.90	27.80
Pure drug suspension	44.80	28.40
Pure drug suspension	45.60	29.00
Conventional formulation	61.10	39.50
Conventional formulation	62.40	40.30
Conventional formulation	63.20	41.20
Nanoemulsion NE-7	87.60	63.50
Nanoemulsion NE-7	88.90	64.40
Nanoemulsion NE-7	90.20	65.20
Optimized nanoemulsion	96.40	75.20
Optimized nanoemulsion	97.20	76.40
Optimized nanoemulsion	98.10	77.10

Note. Replicate values are modelled values used to demonstrate ANOVA interpretation.

TABLE 7: POST-HOC COMPARISON FOR 120-MIN RELEASE

Group 1	Group 2	Mean difference	Adjusted p	Lower CI	Upper CI	Reject H0
Conventional formulation	Nanoemulsion NE-7	26.67	0.00	23.97	29.36	Yes
Conventional formulation	Optimized nanoemulsion	35.00	0.00	32.30	37.70	Yes
Conventional formulation	Pure drug suspension	-17.47	0.00	-20.16	-14.77	Yes
Nanoemulsion NE-7	Optimized nanoemulsion	8.333	0.00	5.635	11.03	Yes
Nanoemulsion NE-7	Pure drug suspension	-44.13	0.00	-46.83	-41.44	Yes
Optimized nanoemulsion	Pure drug suspension	-52.47	0.00	-55.16	-49.77	Yes

Note. All pairwise comparisons showed statistical separation in the model dataset.

TABLE 8: RELEASE-KINETIC FITTING FOR OPTIMIZED NANOEMULSION

Model	Linearized equation	Slope/exponent	R^2
Zero-order	Q = k0t + C	0.722	0.743
First-order	log(100-Q) = logQ0 - k1t/2.303	-0.013	0.990
Higuchi	Q = kH sqrt(t) + C	9.431	0.931
Korsmeyer-Peppas	log(Mt/M∞) = n log(t) + logK	0.873	1.000
Hixson-Crowell	W0^1/3 - Wt^1/3 = kHCt	0.026	0.927

Note. R^2 values are descriptive measures of model fit.

TABLE 9: STABILITY PROFILE OF OPTIMIZED NANOEMULSION

Condition	Globule size (nm)	PDI	Drug content (%)	Release at 120 min (%)
Initial	68.90	0.109	99.20	97.20
25 °C/60% RH - 1 month	70.40	0.116	98.80	96.50
25 °C/60% RH - 3 months	73.60	0.129	98.20	95.10
40 °C/75% RH - 1 month	74.20	0.136	97.70	94.80
40 °C/75% RH - 3 months	79.80	0.153	96.80	93.20

Note. Stability values are modelled and require laboratory confirmation.

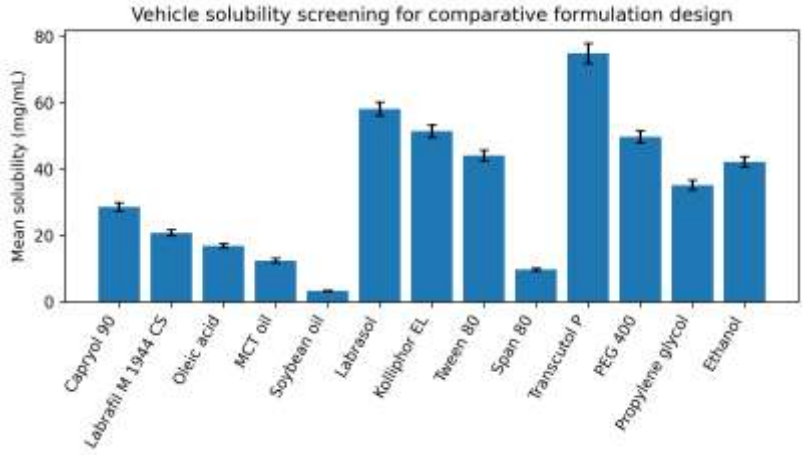

Fig. 1: Vehicle solubility screening for the comparative formulation study.

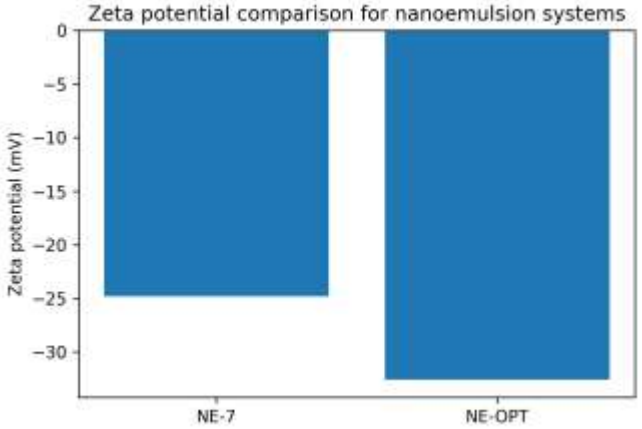

Fig. 2: Zeta potential comparison of preliminary and optimized nanoemulsions.

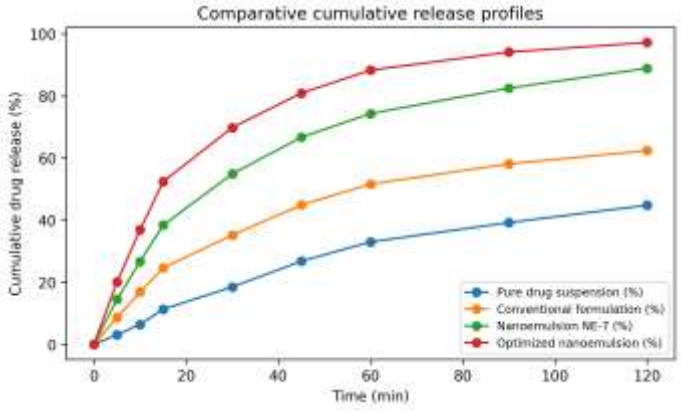

Fig. 3: Comparative cumulative release profiles for all formulation groups.

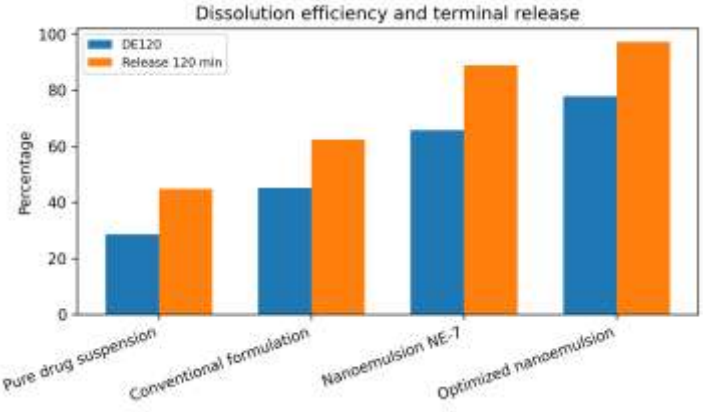

Fig. 4: Dissolution efficiency and terminal release comparison.

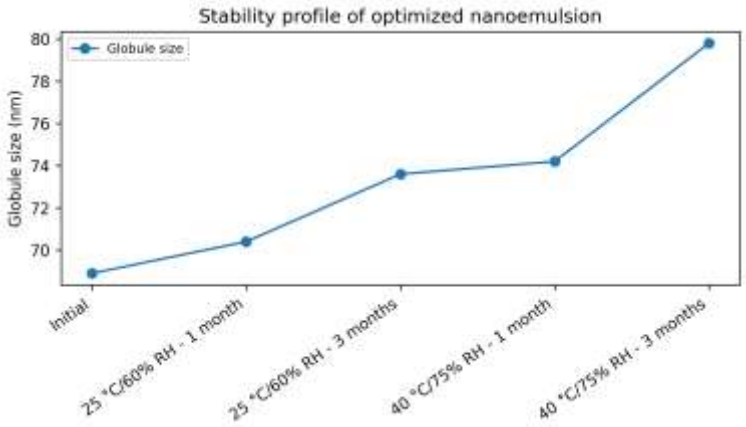

Fig. 5: Stability-related change in globule size of optimized nanoemulsion.

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