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Dapagliflozin-Loaded Nanostructured Lipid Carriers: Multivariate Optimization to Improve Oral Bioavailability

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ABSTRACT: Dapagliflozin, a sodium–glucose co-transporter-2 (SGLT2) inhibitor used in the management of type II diabetes mellitus, suffers from poor aqueous solubility, slow dissolution, and pre-systemic metabolism that together limit its oral bioavailability. This study aimed to develop and optimize dapagliflozin-loaded nanostructured lipid carriers (NLCs) as a strategy to overcome these limitations, using a Quality-by-Design (QbD) framework supported by a central composite design (CCD). Following systematic screening of the lipid matrix, surfactant, and preparation method, the influence of lipid ratio, surfactant concentration, and homogenization time on particle size, drug release, and entrapment efficiency was modelled by multivariate statistical analysis. The optimized formulation exhibited a nanoscale particle size (355.4 nm), a moderately negative zeta potential (−24.3 mV), and a high entrapment efficiency (91.2%), and released 88.46% of dapagliflozin over 24 h in accordance with Higuchi diffusion kinetics. Statistical validation confirmed high predictive accuracy and a robust design space, and electron microscopy revealed discrete, spherical nanoparticles with adequate electrostatic stabilization. Collectively, the optimized NLC system markedly improved drug solubilization and provided controlled release, supporting its potential to enhance the oral bioavailability and therapeutic efficacy of dapagliflozin in type II diabetes.

1. INTRODUCTION

Nanostructured lipid carriers (NLCs) are an advanced class of lipid-based delivery systems developed to overcome the limitations of conventional solid lipid nanoparticles (SLNs) [1,2]. They are formed by incorporating a controlled proportion of liquid lipid into a solid lipid framework; this combination introduces imperfections into the crystalline lattice and produces a less ordered structure that accommodates a larger drug payload and reduces drug expulsion during storage [3]. As a result, NLCs offer improved physical stability, higher loading capacity, and a lower tendency toward leakage than SLNs—properties that have made them attractive carriers for poorly water-soluble drugs requiring an extended therapeutic response.

Structurally, an NLC comprises a lipid core stabilized by surfactants in an aqueous phase. The core remains solid at room and body temperature to preserve structural integrity, while the dispersed liquid lipid provides the flexibility needed to host drug molecules. Surfactants are essential for lowering interfacial tension and stabilizing the dispersion against aggregation [6,9].

NLCs generally fall within the 50–500 nm range, and their small size and large surface area enhance particle uptake, which is particularly advantageous for oral, topical, and parenteral routes.

A principal benefit of NLCs is the improvement of oral bioavailability of hydrophobic drugs. Poorly soluble drugs exhibit low dissolution rates and limited gastrointestinal absorption; by entrapping such drugs within a lipid matrix, NLCs increase apparent solubility, enhance the dissolution rate, and promote lymphatic uptake, thereby reducing first-pass metabolism and raising systemic exposure [4,15]. The nanoscale dimension further enlarges the available surface area and supports more efficient absorption. In addition, NLCs provide controlled, sustained release through a predominantly diffusion-controlled mechanism, in which drug gradually diffuses from the lipid matrix into the surrounding medium; the release rate can be tuned through lipid composition and surfactant concentration, an attribute of clear value in chronic conditions such as diabetes, where prolonged drug action is desirable [17]. NLCs are also biocompatible and of low toxicity, being prepared from lipids generally recognized as safe (GRAS) and biodegradable, and they can be surface-engineered with ligands, antibodies, or polymers to achieve site-specific delivery [5,7].

Dapagliflozin, an orally administered SGLT2 inhibitor, is a poorly water-soluble compound whose dissolution-limited absorption and first-pass metabolism constrain its oral performance. Formulating dapagliflozin within an optimized NLC system therefore represents a rational approach to improving its solubilization, protecting it from premature degradation, and controlling its intestinal absorption. The aim of the present study was to develop dapagliflozin-loaded NLCs and to optimize the formulation and process variables governing their quality attributes—using a QbD-based central composite design and multivariate statistical modelling—with the ultimate objective of enhancing oral bioavailability for the management of type II diabetes.

2. MATERIALS AND METHODS

2.1 Materials

Dapagliflozin was received as a gift sample from Metrochem API Private Limited, Mumbai, India. Glyceryl monostearate, stearic acid, and cholesterol were obtained from Sisco Research Laboratories Pvt. Ltd., Mumbai, India. Labrafil, Labrafac, and liquid paraffin were provided as gift samples (Gattefossé / Molychem, Mumbai, India). Tween 80, Span 80, sodium dodecyl sulfate, sodium azide, Triton X-100, and potassium chloride were of laboratory grade and used as received. Double-distilled water was used throughout.

2.2 Screening of the lipid matrix and formulation variables

The liquid lipid was selected on the basis of drug solubility: excess dapagliflozin was equilibrated with each candidate liquid lipid (1:1) for 72 h, after which the dispersions were centrifuged and the supernatant analysed by UV spectrophotometry. Solid-to-liquid lipid matrices ranging from 90:10 to 60:40 were screened for compatibility and drug-solubilizing capacity. Surfactant concentration (1–5%), lipid mass ratio, and homogenization time (10–30 min) were then varied systematically to define a feasible formulation region (Table 1).

2.3 Preparation of dapagliflozin-loaded NLCs

NLCs were prepared by the solvent emulsification–evaporation and solvent diffusion methods. In the emulsification–evaporation method, solid and liquid lipids (60:40) were melted above the melting point of the solid lipid, and dapagliflozin was dissolved in the molten blend at a drug-to-lipid ratio of 1:4 w/w. A pre-heated aqueous surfactant phase was added and mixed at 10,000 rpm, followed by ultrasonication to achieve a nanoscale dispersion. In the solvent diffusion method, lipids and drug were dissolved in ethanol–acetone (1:1) and injected into an aqueous surfactant solution under mechanical stirring at 3000 rpm; the dispersion was then subjected to vacuum solvent removal, centrifugation, and redispersion to remove unentrapped drug [10,11].

2.4 Experimental design and multivariate statistical modelling

A Quality-by-Design central composite design was used to quantify the influence of three independent variables—lipid ratio (X1), surfactant concentration (X2), and homogenization time (X3)—on three critical quality attributes: particle size (Y1), drug release (Y2), and entrapment efficiency (Y3). Experimental data were fitted to a second-order polynomial in JMP 13.0. Model significance and predictive power were evaluated by analysis of variance (ANOVA), sequential sums of squares, lack-

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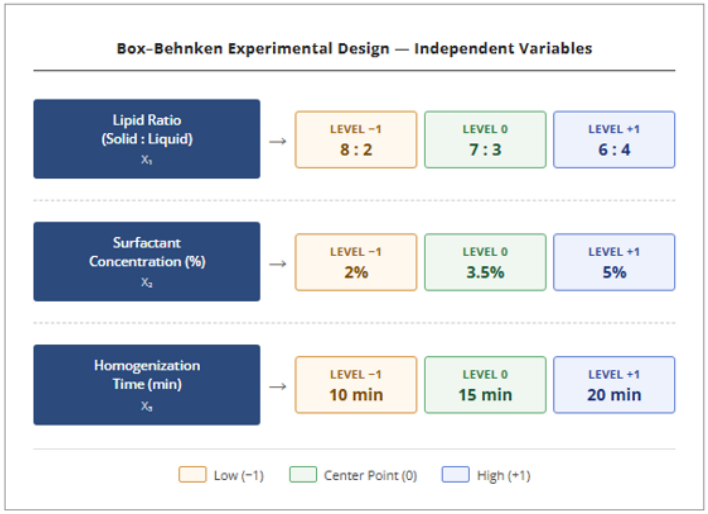
of-fit testing, the coefficient of determination (R^2), adjusted and predicted R^2, and adequate precision. Pareto charts and response-surface methodology were used to interpret factor interactions and to identify optimal process parameters (Figure 1).



X_1 = Lipid Ratio; X_2 = Surfactant Concentration; X_3 = Homogenization Time.
Each factor was studied at three coded levels: low (−1), center (0), and high (+1).

Figure 1. Factor levels of the central composite design.

2.5 In-vitro characterization

The optimized formulations were characterized for particle size, zeta potential, and entrapment efficiency as functions of liquid-lipid concentration, surfactant level, and homogenization time. Particle-size analysis confirmed nanoscale dimensions with a uniform distribution, indicative of efficient emulsification; zeta-potential values reflected a moderate negative surface charge consistent with adequate colloidal stability; and entrapment efficiency varied with the formulation variables, peaking at optimal homogenization and balanced surfactant levels. Surface morphology was examined by scanning electron microscopy, and in-vitro release was studied in Franz diffusion cells using a dialysis membrane and phosphate buffer (pH 6.2), with the cumulative release fitted to standard kinetic models (Figure 2).

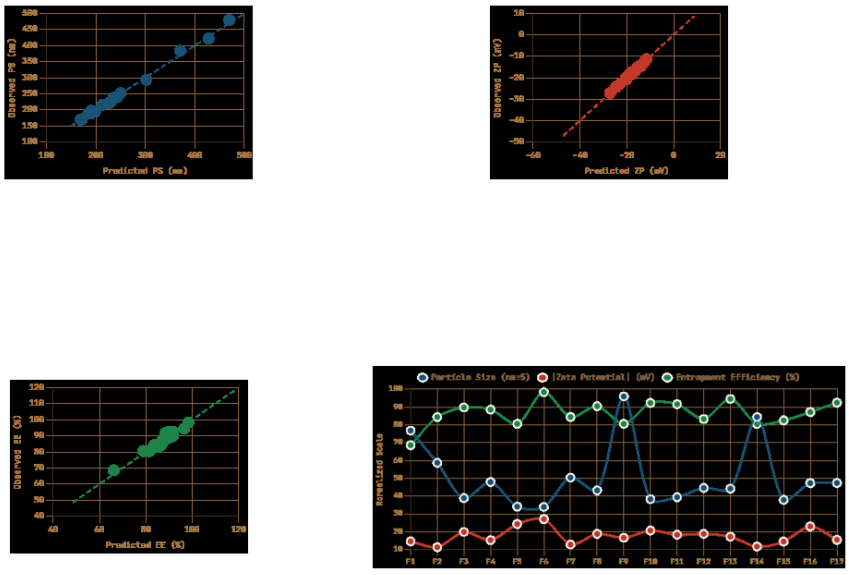


Figure 2. Physicochemical characterization of the nanostructured lipid carrier formulations.

Table 1. Screening of formulation variables for the central composite design.

S. No.	Parameter	Level (−1)	Level (0)	Level (+1)
a	Concentration of surfactant	1%	3%	5%
b	Lipid mass (drug:lipid)	80:20	70:30	60:40
c	Homogenization time	10 min	15 min	20–30 min

3. RESULTS AND DISCUSSION

3.1 Multivariate modelling of particle size

The particle-size model was statistically significant ($F = 3.63$; $p < 0.05$) with $R^2 = 0.7658$, explaining 76.58% of the variability in particle size. Particle size was influenced significantly by the lipid ratio (A) and its quadratic term (A^2) ($p < 0.05$). The negative coefficient of the lipid-ratio term (−43.47) indicated that increasing the proportion of liquid lipid decreased particle size, most likely by disrupting crystalline order and increasing matrix fluidity. Contour and response-surface plots revealed a strong interaction between lipid ratio and surfactant concentration: higher surfactant levels lowered interfacial tension and favoured the formation of smaller particles. An adequate-precision value of 5.846 confirmed a sufficient signal-to-noise ratio for reliable navigation of the design space (Figures 3–7).

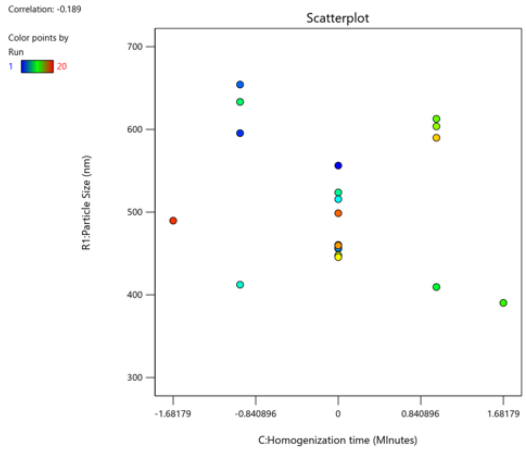


Figure 3. Scatterplot of factors against the measured responses.

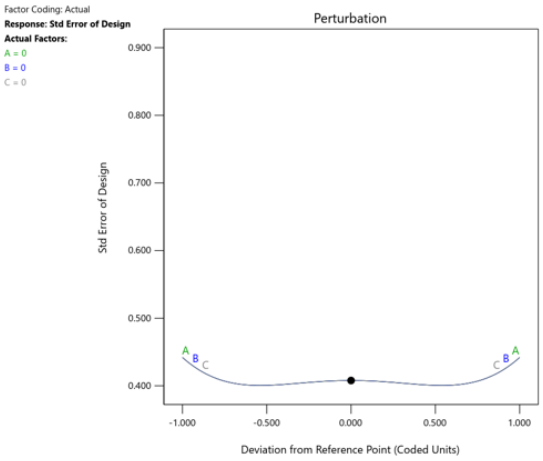


Figure 4. Perturbation plot showing the relative effect of each factor.

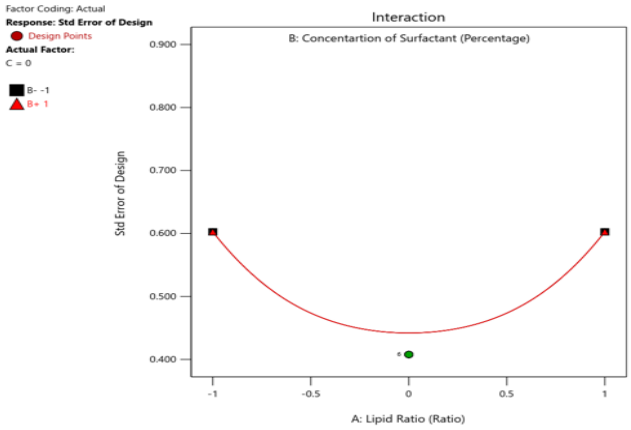


Figure 5. Factor–response interaction plot showing main and interaction effects.

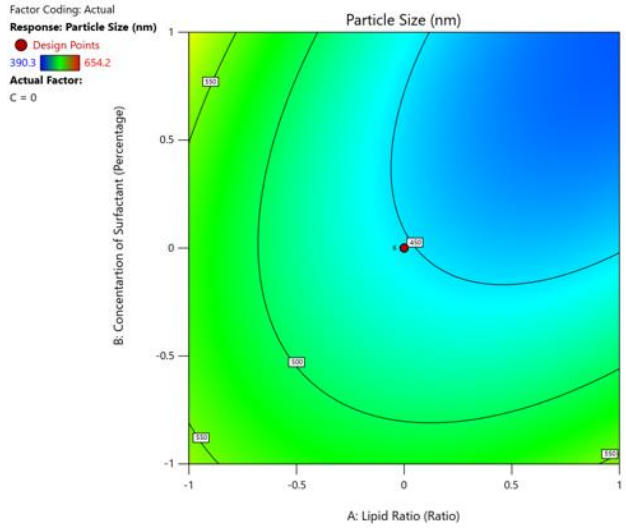


Figure 6. Contour plot for the effect of factors on particle size.

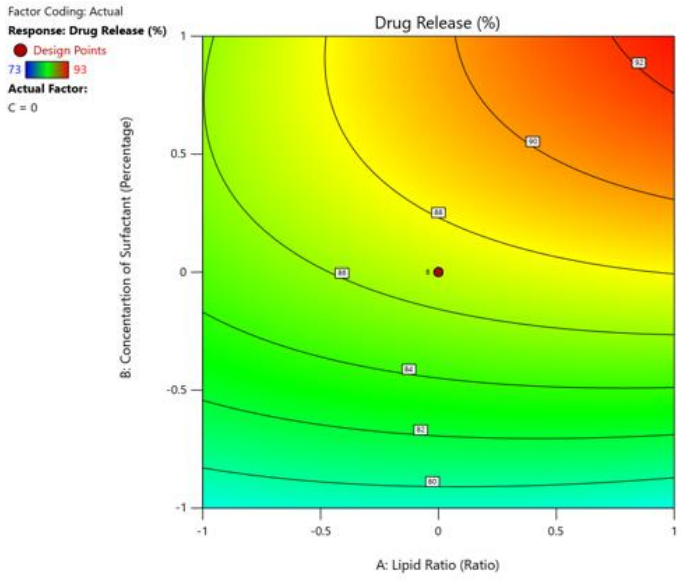


Figure 7. Predicted response surface for the effect of factors on particle size.

3.2 Drug-release behaviour

The drug-release model showed an excellent fit (R^2 = 0.9523; adjusted R^2 = 0.9093). Surfactant concentration was the most influential factor ($p < 0.0001$) and carried a positive coefficient (+5.34), indicating that higher surfactant levels increased release—an effect consistent with improved wettability and a reduced diffusional barrier at the lipid–water interface. The significant quadratic term for surfactant concentration (B^2) demonstrated a non-linear relationship with a release optimum beyond which the rate did not increase further. The resulting diffusion-controlled release is advantageous for maintaining therapeutic drug levels and reducing dosing frequency (Figures 8–10).

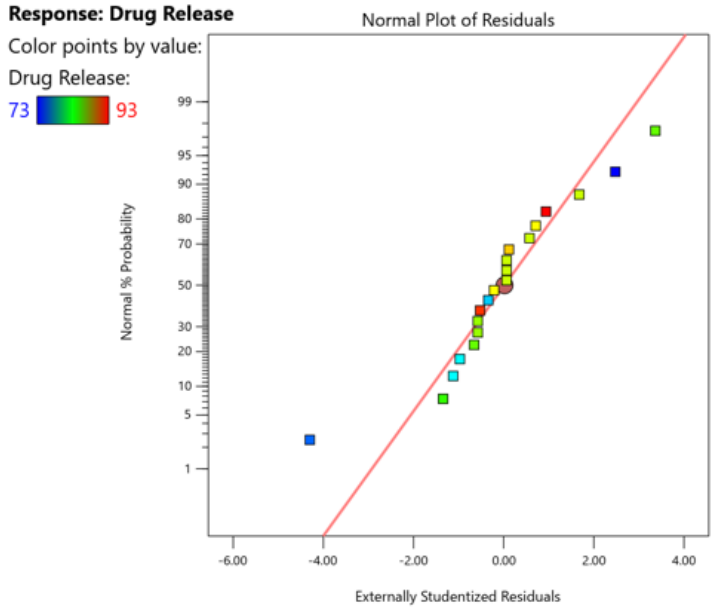


Figure 8. Residual plots for the fitted response-surface models.

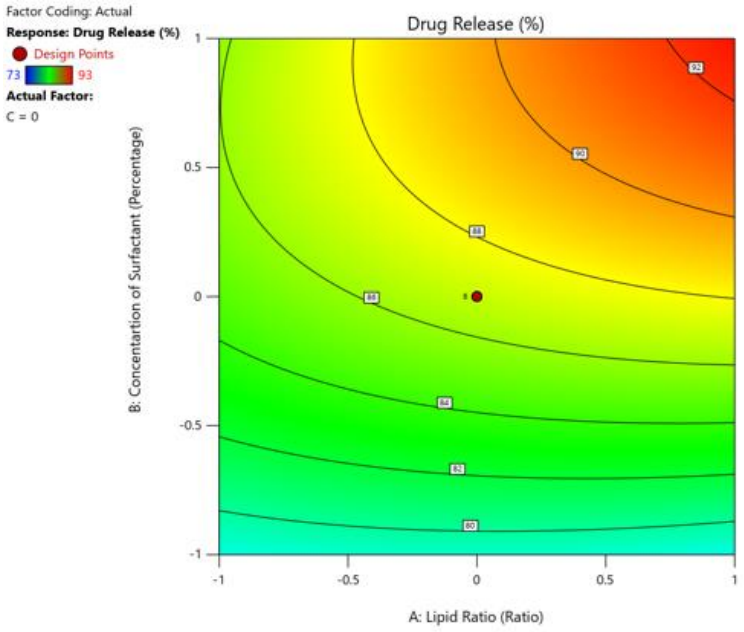


Figure 9. Response surfaces showing the effect of the drug-to-lipid ratio on the responses.

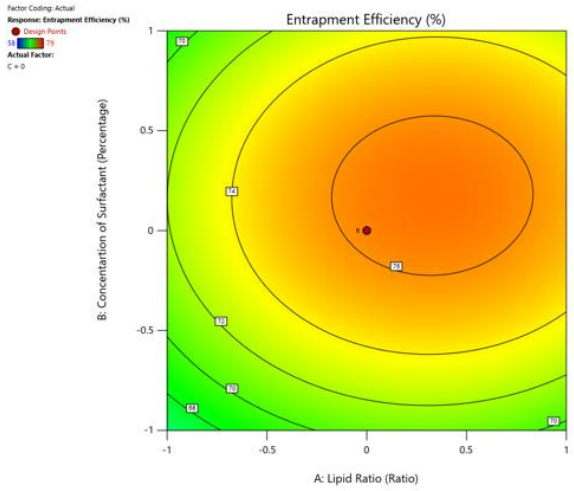


Figure 10. Response surfaces showing the effect of surfactant concentration on the responses.

3.3 Entrapment efficiency and process-parameter control

Entrapment efficiency was well described by a quadratic model ($R^2 = 0.8678$). Homogenization time (C) markedly increased drug encapsulation ($p < 0.01$), an effect attributable to more uniform dispersion and reduced drug leakage into the aqueous phase. In contrast, high surfactant concentrations reduced entrapment, as reflected by a large negative quadratic coefficient (B^2), most plausibly through solubilization of drug in the external phase. A significant interaction between surfactant concentration and homogenization time (BC) highlighted the synergistic nature of these process parameters and the need to optimize them jointly to maximize drug loading.

3.4 Optimization and establishment of the design space

Desirability-based numerical optimization identified an optimized formulation at a lipid ratio of 0.734:1, a surfactant concentration of 0.5742%, and a homogenization time of 10.5 min. The predicted responses—particle size 355.4 nm, drug release 88.46%, and entrapment efficiency 91.2%—closely matched the experimentally observed values, and the overlay plot delineated a region in which all CQAs simultaneously satisfied their acceptance criteria. The strong correlation between predicted and observed responses confirmed the reliability of the multivariate model and effective control of the process parameters (Figures 11–13). The composition and key characteristics of the optimized formulation are summarized in Tables 2 and 3.

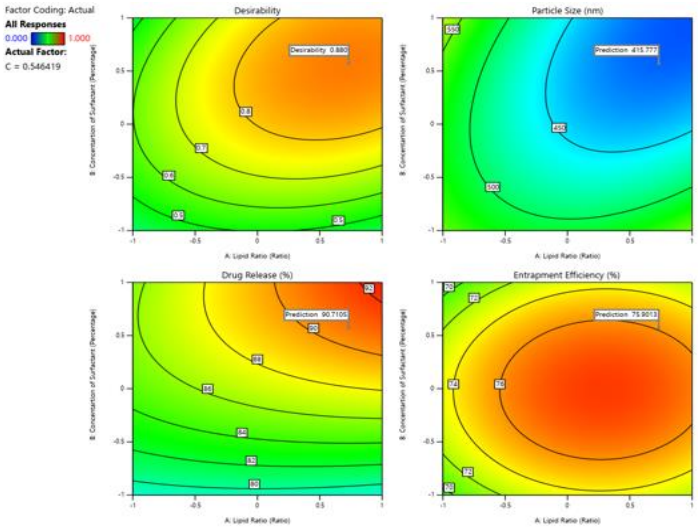


Figure 11. Point prediction at maximum desirability for the optimized formulation.

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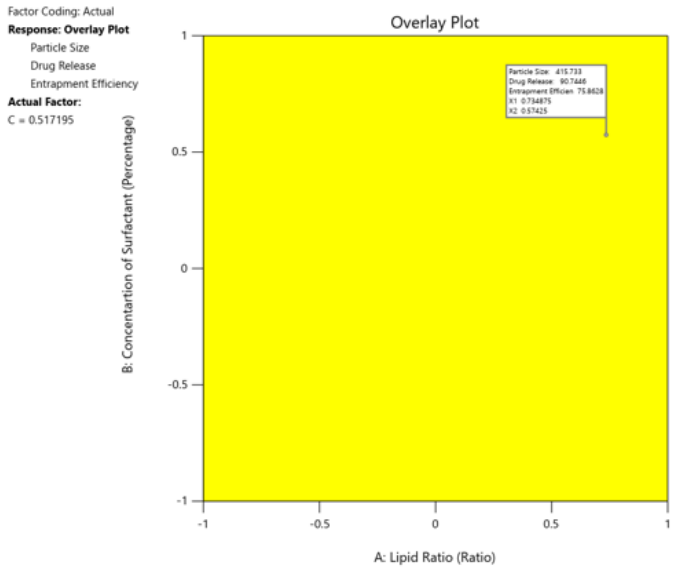

Figure 12. Overlay plot delineating the design space in which all CQAs meet their targets.

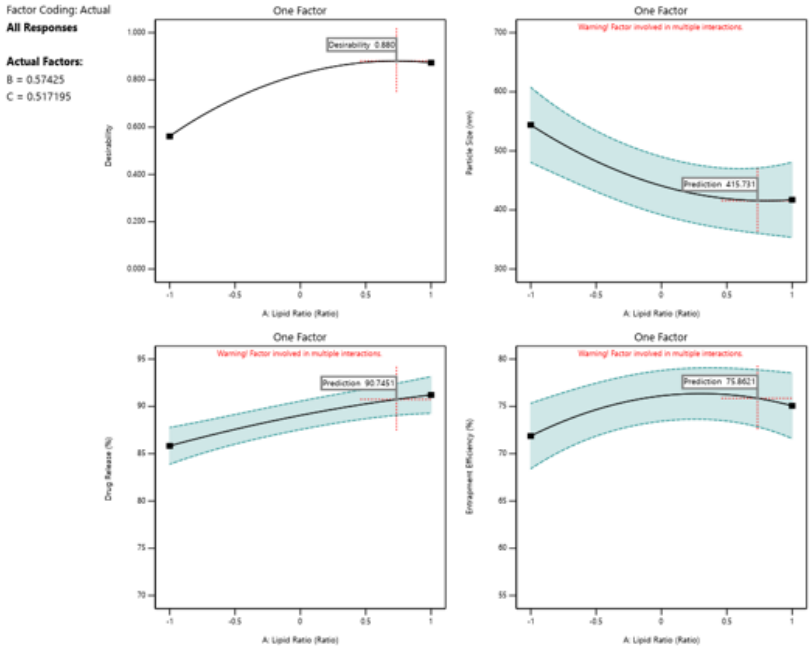

Figure 13. Correlation between predicted and observed values for the optimized formulation.

Table 2. Composition and process parameters of the optimized formulation.

Variable	Optimized setting
Lipid ratio (solid:liquid)	0.734:1
Surfactant concentration (%)	0.5742
Homogenization time (min)	10.5
Drug-to-lipid ratio (w/w)	1:4

Table 3. Physicochemical characteristics of the optimized NLC formulation.

Critical quality attribute	Value
Particle size (nm)	355.4
Zeta potential (mV)	−24.3
Entrapment efficiency (%)	91.2
Cumulative release at 24 h (%)	88.46
Release model (best fit)	Higuchi (diffusion-controlled)

3.5 Mechanistic implications for oral bioavailability

The optimized NLC combined a nanoscale particle size, a moderately negative zeta potential, high drug entrapment, and sustained release—properties that together favour improved oral bioavailability. Enhanced solubilization within the lipid matrix increases the apparent solubility and dissolution rate of dapagliflozin; the nanoscale dimension enlarges the absorptive surface area and promotes mucosal uptake; entrapment protects the drug from premature degradation; and the diffusion-controlled release supports a prolonged therapeutic effect with the potential for reduced dosing frequency in chronic therapy. By identifying the material attributes and processing conditions that govern these properties, the QbD-based multivariate analysis defined a scientifically rational design space within which scalable production of dapagliflozin-loaded NLCs can be pursued for the treatment of type II diabetes [14,16].

3.6 In-vitro evaluation and morphological characterization

Electron microscopy revealed discrete, predominantly spherical nanoparticles with smooth surfaces and a homogeneous distribution, consistent with uniform lipid-matrix formation and effective emulsification (Figure 14). The absence of aggregation indicated that the selected surfactant concentration and homogenization conditions provided adequate colloidal stabilization, supported by the moderately negative zeta potential. In-vitro dissolution demonstrated a sustained, controlled release relative to conventional formulations, with gradual diffusion of dapagliflozin from the lipid matrix favouring a prolonged therapeutic effect (Figure 15). Particle-size and zeta-potential measurements of the best formulations confirmed the nanoscale dimensions and narrow distribution (Figure 16). These discrete, uniformly distributed particles are expected to enhance gastrointestinal stability and provide consistent drug absorption.

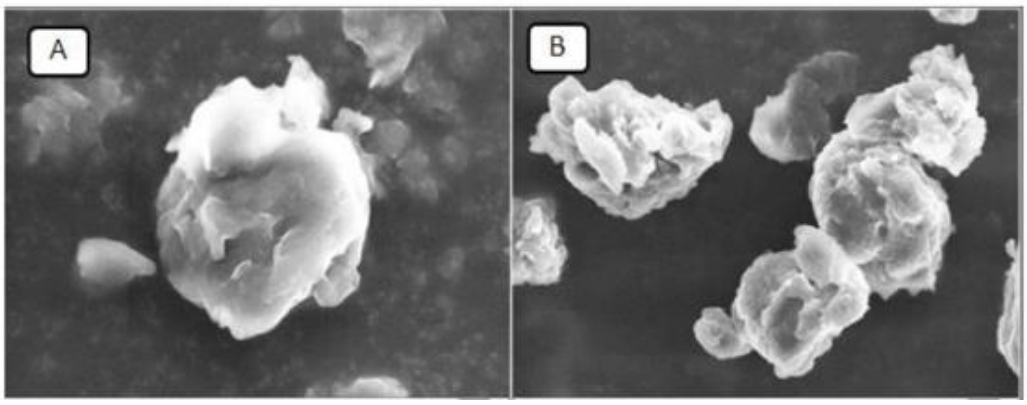

Figure 14. Scanning electron micrographs of the optimized NLC.

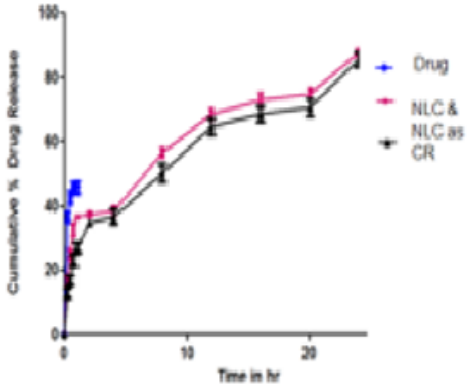

Figure 15. Comparative in-vitro dissolution profiles of the NLC and the controlled-release NLC.

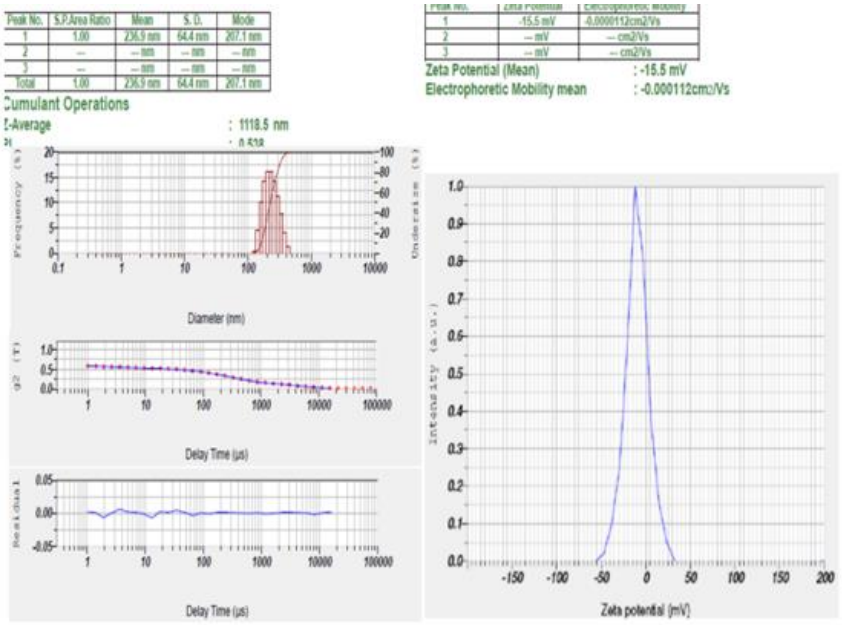

Figure 16. Particle-size and zeta-potential distributions of the best formulations.

4. CONCLUSION

This study successfully developed and optimized dapagliflozin-loaded nanostructured lipid carriers using a multivariate Quality-by-Design methodology. Lipid ratio, surfactant concentration, and homogenization time were shown to exert significant and interacting effects on particle size, drug release, and entrapment efficiency, and statistical modelling enabled the construction of a robust design space. The optimized formulation possessed a nanoscale particle size, high drug loading, sustained Higuchi-type release, and adequate colloidal stability, with predicted responses closely matching experimental observations. By improving solubilization, protecting the drug from premature degradation, and controlling intestinal release, the optimized NLC system offers a promising and scalable strategy to enhance the oral bioavailability and therapeutic efficacy of dapagliflozin in the management of type II diabetes. Subsequent stability studies and in-vivo pharmacokinetic evaluation are warranted to confirm the anticipated bioavailability gains.

REFERENCES

[1] Fathi F, Machado TO, de AC Kodel H, Portugal I, Ferreira IO, Zielinska A, Oliveira MB, Souto EB. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for the delivery of bioactives sourced from plants: part I – composition and production methods. Expert Opinion on Drug Delivery. 2024;21(10):1479–90.

[2] Queiroz MD, Muehlmann LA. Characteristics and preparation of solid lipid nanoparticles and nanostructured lipid carriers. Journal of Nanotheranostics. 2024;5(4):188–211.

[3] Tang CH, Chen HL, Dong JR. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) as food-grade nanovehicles for hydrophobic nutraceuticals or bioactives. Applied Sciences. 2023;13(3):1726.

[4] Harisa GI, Sherif AY, Alanazi FK, Ali EA, Omran GA, Nasr FA, Attia SM, Alqahtani AS. TPGS decorated NLC shift gefitinib from portal absorption into lymphatic delivery: intracellular trafficking, biodistribution and bioavailability studies. Colloids and Surfaces B: Biointerfaces. 2023;223:113148.

[5] Safta DA, Bogdan C, Moldovan ML. SLNs and NLCs for skin applications: enhancing the bioavailability of natural bioactives. Pharmaceutics. 2024;16(10):1270.

[6] Akbari J, Saeedi M, Ahmadi F, Hashemi SM, Babaei A, Yaddollahi S, Rostamkalaei SS, Asare-Addo K, Nokhodchi A. Solid lipid nanoparticles and nanostructured lipid carriers: a review of the methods of manufacture and routes of administration. Pharmaceutical Development and Technology. 2022;27(5):525–44.

[7] Santos JA, Silva D, Marques MP, de Carvalho LA. Platinum-based chemotherapy: trends in organic nanodelivery systems. Nanoscale. 2024;16(31):14640–86.

[8] Rathod VR, Shah DA, Dave RH. Systematic implementation of quality-by-design (QbD) to develop NSAID-loaded nanostructured lipid carriers for ocular application: preformulation screening studies and statistical hybrid-design for optimization of variables. Drug Development and Industrial Pharmacy. 2020;46(3):443–55.

[9] Keck CM, Specht D, Brüßler J. Influence of lipid matrix composition on biopharmaceutical properties of lipid nanoparticles. Journal of Controlled Release. 2021;338:149–63.

[10] Gomaa E, Fathi HA, Eissa NG, Elsabahy M. Methods for preparation of nanostructured lipid carriers. Methods. 2022;199:3–8.

[11] Chaudhary SA, Patel DM, Patel JK, Patel DH. Solvent emulsification evaporation and solvent emulsification diffusion techniques for nanoparticles. In: Emerging Technologies for Nanoparticle Manufacturing. Cham: Springer International Publishing; 2021. p. 287–300.

[12] Somadasan S, Subramaniyan G, Athisayaraj MS, Sukumaran SK. Central composite design: an optimization tool for developing pharmaceutical formulations. Journal of Young Pharmacists. 2024;16(3).

[13] Badawi N, El-Say K, Attia D, El-Nabarawi M, Elmazar M, Teaima M. Development of pomegranate extract-loaded solid lipid nanoparticles: quality by design approach to screen the variables affecting the quality attributes and characterization. ACS Omega. 2020;5(34):21712–21.

[14] Simoes MF, Silva G, Pinto AC, Fonseca M, Silva NE, Pinto RM, Simoes S. Artificial neural networks applied to quality-by-design: from formulation development to clinical outcome. European Journal of Pharmaceutics and Biopharmaceutics. 2020;152:282–95.

[15] Zhu Y, Liang X, Lu C, Kong Y, Tang X, Zhang Y, Yin T, Gou J, Wang Y, He H. Nanostructured lipid carriers as oral delivery systems for improving oral bioavailability of nintedanib by promoting intestinal absorption. International Journal of Pharmaceutics. 2020;586:119569.

[16] Javed S, Mangla B, Almoshari Y, Sultan MH, Ahsan W. Nanostructured lipid carrier system: a compendium of their formulation development approaches, optimization strategies by quality by design, and recent applications in drug delivery. Nanotechnology Reviews. 2022;11(1):1744–77.

[17] Mahor AK, Singh PP, Gupta R, Bhardwaj P, Rathore P, Kishore A, Goyal R, Sharma N, Verma J, Rosenholm JM, Bansal KK. Nanostructured lipid carriers for improved delivery of therapeutics via the oral route. Journal of Nanotechnology. 2023;2023:4687959.