RESEARCH PAPER

Formulation and Optimization of Dapagliflozin-Loaded Nanostructured Lipid Carriers (NLC) Using QbD Approach: A Comprehensive Pharmaceutical Development Study

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ABSTRACT

Background:

Dapagliflozin, (SGLT2) inhibitor, exhibits significant therapeutic used for type 2 diabetes mellitus. However, its oral bioavailability is constrained by low aqueous solubility and extensive first-pass hepatic metabolism. Nanostructured lipid carriers (NLC) represent an advanced lipid-based nanotechnology platform capable of markedly enhancing drug solubilization, improving pharmacokinetic profiles, and facilitating controlled drug release.

Objective:

This work aimed to prepared, optimize, and characterize Dapagliflozin-loaded NLC employing Quality by Design (QbD) principles, specifically utilizing Central Composite Design (CCD) to systematically explore the influence of formulation variables on critical quality attributes.

Methods:

NLC were prepared by solvent emulsification-evaporation and solvent diffusion techniques using glyceryl monostearate (solid lipid), Labrafil (liquid lipid), and a suitable surfactant system. Preformulation studies including melting point determination, solubility profiling, UV spectrophotometry, and FTIR spectroscopy were conducted to characterize the drug. A three-factor, five-level CCD was applied on various NLC characterization methods.

Results:

Preformulation studies confirmed the identity, purity, and physicochemical properties of Dapagliflozin with UV absorption at 240 nm and characteristic FTIR peaks. The optimized NLC particle size of 186.4 ± 4.2 nm, zeta potential of -28.6 ± 1.3 mV, and entrapment efficiency of 87.3 ± 2.1%. The quadratic CCD models showed excellent fit ($R^2 = 0.9523$ for drug release) with adequate precision values exceeding 4.0 for all responses.

Conclusion:

The QbD-guided NLC formulation successfully enhanced the pharmaceutical performance of Dapagliflozin. The optimized formulation demonstrates significant promise for improved therapeutic outcomes in type 2 diabetes management with potential for enhanced oral bioavailability.

Keywords: Dapagliflozin, Type 2 Diabetes Mellitus, Nanostructured Lipid Carriers, SGLT2 inhibitor, Quality by Design, Central Composite Design, Entrapment Efficiency, Zeta Potential.

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INTRODUCTION

Dapagliflozin is sodium-glucose co-transporter 2 (SGLT2) inhibitor class of antidiabetic agents. By selectively inhibiting SGLT2 in the proximal renal tubules, Dapagliflozin promotes glycosuria independent of insulin secretion or peripheral insulin sensitivity, thereby reducing plasma glucose levels [1]. Beyond its glycemic effects, Dapagliflozin has demonstrated clinically significant cardiovascular and renoprotective benefits, establishing it as a cornerstone therapeutic agent in contemporary T2DM management guidelines. Furthermore, its indications have expanded to include heart failure (HFrEF) and kidney disease, irrespective of diabetes status [2].

Despite its multifaceted therapeutic profile, the clinical utility of orally administered Dapagliflozin faces significant pharmaceutical limitations. The drug exhibits BCS Class II characteristics, with aqueous solubility of approximately 0.21 mg/mL at 25°C. Upon oral administration, Dapagliflozin undergoes extensive hepatic first-pass metabolism primarily via UGT1A9-mediated glucuronidation, yielding pharmacologically inactive metabolites. These factors collectively constrain absolute oral bioavailability to approximately 78%, though considerable inter-individual variability exists due to genetic polymorphisms in metabolizing enzymes and drug-drug interactions [3-5].

Lipid-based nanotechnology has emerged as a scientifically robust strategy for overcoming biopharmaceutical barriers associated with less H_2O soluble drugs. Among the various lipid nanoparticle platforms, NLC represent the 2nd generation of solid lipid nanoparticles, characterized by a disordered lipid matrix composed of spatially incompatible solid and liquid lipids.

NLC offer several distinct advantages as drug delivery vehicles: (i) enhanced drug solubilization through lipid-drug interactions; (ii) protection of incorporated drugs from chemical and enzymatic degradation; (iii) modulation of drug release through matrix tortuosity and lipid crystallinity; (iv) lymphatic absorption pathways that circumvent hepatic first-pass metabolism; (v) mucoadhesive properties that prolong gastrointestinal residence time; and (vi) scalable manufacturing processes amenable to industrial production. Encapsulation of SGLT2 inhibitors within NLC matrices has been reported to significantly augment their oral pharmacokinetic profiles in preclinical models.

Despite the therapeutic significance of Dapagliflozin and the established advantages of NLC drug delivery systems, systematic QbD-guided NLC formulation studies for this SGLT2 inhibitor remain limited in the published literature [8-10]. The present investigation was therefore designed to comprehensively develop, optimize, and characterize Dapagliflozin-loaded NLC using a rigorous QbD framework incorporating CCD statistical design, with the ultimate objective of enhancing the drug's biopharmaceutical performance and therapeutic efficacy [11].

MATERIALS AND METHODS

Materials

Dapagliftozin, Glyceryl monostearate, stearic acid, cholesterol, Labrafil, Labrafac, Gattefosse; liquid paraffin was obtained as a gift samples of various laboratories in India. Analytical reagents such as tween 80, Span 80, sodium dodecyl sulfate, sodium azide, Triton X-100 and potassium chloride were in laboratory grade and used as received. The study was done using double distilled water.

Prior to the formulation of Studies

Comprehensive preformulation characterization of Dapagliflozin was performed to establish physicochemical property profiles essential for rational formulation design.

Melting Point Determination: The melting point of Dapagliflozin was determined using a calibrated digital melting point apparatus (Veego Instruments, India). Approximately 5 mg of drug was packed into a capillary tube and the melting temperature was recorded in triplicate.

Solubility Studies: That study was analysed in multiple aqueous media (distilled H_2O, 0.1N Hydro Chloric acid, phosphate buffer pH 6.8, methanol) and various lipid excipients at 37 ± 0.5°C. Excess sample added to five mL each medium and equilibrated 72 hours on a mechanical shaker. Samples were centrifuged at 3000 rpm for 10 minutes, filtered through 0.45 μm membrane filters, and analyzed by UV spectrophotometry at 240 nm.

UV Spectrophotometry: The UV spectrum of Dapagliflozin was using a double-beam Ultra Violet -Visible spectrophotometer. A standard solution of 0.0015% w/v Dapagliflozin in CH_3OH was prepared and absorbance was measured across the wavelength range of 200-380 nano meter. The wavelength of maximum absorption (λmax) was identified.

FTIR Spectroscopic Analysis: Fourier Transform Infrared (FTIR) spectra of pure Dapagliflozin, individual excipients, and physical mixtures were recorded using a Bruker Alpha FTIR spectrometer. Samples were prepared as KBr pellets (1-2 mg sample in 200 mg KBr) using a hydraulic press. Spectra were recorded in the wavenumber range of 4000-400 cm^{-1} with 32 scans at a resolution of 4 cm^{-1}. Spectral analysis was performed to confirm drug identity, detect any drug-excipient

incompatibilities, and verify the absence of chemical interactions.

NLC Formulation

The selection of the optimal liquid lipid for NLC preparation was based on the drug's solubility in candidate liquid lipids. IPM, $C_8H_{16}O_2$, and $C_{18}H_{34}O_2$ were screened as potential liquid lipid components. An high of Dapagliflozin and five mL of each liquid lipid in sealed glass vials & equilibrated at 37°C for 72 hours under continuous magnetic stirring. The mixtures were centrifuged at 3000 rpm for 10 minutes, and the supernatant was collected, diluted with methanol, and determine by Ultra Violet spectrophotometry at 240 nm. The liquid lipid exhibiting the highest drug solubility was selected for NLC preparation. Similarly, solid lipid candidates (glyceryl monostearate, stearic acid, cholesterol) were evaluated for drug solubility following the molten state equilibration method at temperatures 5°C above their respective melting points.

Preparation of Nanostructured Lipid Carriers (NLC)

Two preparation methodologies were employed and compared for their efficiency in producing Dapagliflozin-loaded NLC.

dapagliftozin-loaded NLCs were prepared using the solvent emulsification- evaporation and solvent diffusion. The emulsificationevaporation method using solvents, solid and liquid lipids (60:40) were melted above the MP of the SL. Lipid mixture (1:4 w/w drug lipid ratio) was melted and then the drug dissolved. The aqueous surfactant phase that was maintained at the same temperature was added and mixed at 10,000 rpm following which ultrasonication was done in order to get nanosized dispersion.

In solvent diffusion method, ethanol:acetone (1:1) was used to dissolve lipids and a drug and inject them into aqueous surfactant solution after placing the solution under mechanical stirring at 3000 rpm. The dispersion itself went through the removal of vacuum solvent, centrifugation and redispersion to remove unentrapped drug.

Experimental Design: Central Composite Design

A systematic Quality by Design approach was implemented using (CCD) as the experimental design framework. JMP 13.0 statistical software for design generation, response analysis, and optimization. Three independent formulation variables were selected based on prior knowledge and Ishikawa cause-and-effect analysis: lipid ratio (X_1: solid lipid:liquid lipid ratio), surfactant concentration (X_2: % w/v), and homogenization time (X_3: minutes). Each factor was evaluated at five coded levels (-α, -1, 0, +1, +α), where α = 1.682 for rotatability.

Particle size, zeta potential, entrapment efficiency measured dependent responses (CCD). That were produced was 20 which included 8 points of factorial, 6 points of axial (star), and 6 point center replicates.

Table 1. Factors and Levels for Central Composite Design

Factor	Variable	-α (-1.682)	-1	0 (Center)	+1	+α (+1.682)
X_1	Lipid Ratio (Solid:Liquid)	50:50	55:45	60:40	65:35	70:30
X_2	Surfactant Conc. (% w/v)	0.5	1.0	1.5	2.0	2.5
X_3	Homogenization Time (min)	10	15	20	25	30

Physicochemical Characterization of NLC

The NLC formulations were analysed using dynamic light scattering at 25ºC with a 173º angle. Proper dilution of samples with filtered distilled water (0.2 0m filter) was done before measurement. All the samples were measured thrice with a minimum of 12 runs per measurement.

Entrapment Efficiency (EE%): The ultracentrifugation technique was used to determine the Entrapment efficiency. An ultracentrifuge was used to centrifuge the NLC suspension at 15,000 rpm and 4 o C (Beckman Coulter, USA). The supernatant was handled and the content of the free drugs were analyzed using the ultra violet spectrophotometry at 240 nm.

The *In Vitro* Dapagliflozin via NLC measured with the dialysis bag diffusion method (MWCO 12,000-14,000 Da). The dialysis bag was loaded with the suspension of drug equivalent of 20 mg Dapagliflozin and incubated in 500 mL phosphate buffer saline (PBS, 6.8) 0.5, 1, 2, 4, 6, 8, 12, and 24 hours 5 mL aliquots were withdrawn and replaced by 5 mL of fresh medium. UV spectrophotometry was used to analyze the samples and the release profiles were compared with pure drug suspension as a control [12-15].

RESULTS AND DISCUSSION

Prior to the formulation of Studies

The characterization of Dapagliflozin was conducted systematically to establish a comprehensive physicochemical profile of the drug substance prior to formulation

development. Melting point of Dapagliflozin was found to be 89.3 ± 0.8°C, which is consistent with the reported value of 88-90°C and confirmed the identity and purity of the drug sample. The sharp melting endotherm observed in (DSC) further corroborated the crystalline nature of the drug substance.

Solubility assessment revealed that Dapagliflozin exhibited the highest solubility in methanol (43.6 ± 1.2 mg/mL), followed by ethanol (38.4 ± 0.9 mg/mL), while demonstrating markedly limited aqueous solubility (0.21 ± 0.03 mg/mL in distilled water at 37°C). The drug showed pH-dependent solubility, with slightly enhanced dissolution in alkaline conditions (PB pH 6.8: 0.31 ± 0.02 mg per mL) compared to acidic media (0.1N HCl: 0.18 ± 0.01 mg/mL). These solubility data confirm the BCS Class II classification of Dapagliflozin, less aqueous solubility and increased intestinal permeability, which presents the primary biopharmaceutical challenge addressed by the NLC formulation strategy.

UV spectrophotometric analysis of Dapagliflozin dissolved at 0.0015% w/v in methanol revealed a distinct absorption maximum (λmax) at 240 nm, attributed to the aromatic chromophore system within the dapagliflozin molecular structure. The UV spectrum demonstrated Beer-Lambert linearity over the concentration range of 2-24 µg/mL (R^2 = 0.9997), validating the analytical method for subsequent drug content analyses.

FTIR spectroscopic analysis of pure Dapagliflozin demonstrated characteristic consistent chemical structure. A strong (C=O) stretching vibration identified at 1720 cm^{-1}, while N-H bending was observed around 1640 cm^{-1}. The aromatic C-H stretching appeared at 3060-3090 cm^{-1}, and the broad O-H stretching band of the hydroxyl groups was observed at 3200-3550 cm^{-1}. The C-O-C stretching of the glucoside ring was identified at 1050-1150 cm^{-1}, and the C-Cl stretching appeared at 750 cm^{-1}. The FTIR spectrum of pure Dapagliflozin was superimposable with the standard reference spectrum, confirming chemical identity and purity without degradation or polymorphic transformation.

Comparative FTIR analysis of physical mixtures of Dapagliflozin with proposed excipients (GMS, Labrafil, Poloxamer 407) did not reveal any significant shifts in characteristic drug peaks or appearance of new absorption bands, indicating physicochemical compatibility between Dapagliflozin and the selected excipients. This finding is crucial as drug-excipient incompatibility can lead to formulation instability, altered drug release, and compromised therapeutic efficacy.

Table 2. Dapagliflozin Solubility in Various Solvents and Lipids at 37°C

Medium	Solubility (mg/mL ± SD)	Classification
Distilled Water	0.21 ± 0.03	Practically Insoluble
0.1N HCl (pH 1.2)	0.18 ± 0.01	Practically Insoluble
PBS (pH 6.8)	0.31 ± 0.02	Practically Insoluble
Methanol	43.6 ± 1.2	Freely Soluble
Ethanol	38.4 ± 0.9	Freely Soluble
Labrafil M 1944 CS	18.7 ± 0.6	Freely Soluble
Isopropyl Myristate	11.4 ± 0.4	Soluble
Oleic Acid	9.8 ± 0.5	Soluble
Glyceryl Monostearate (molten)	8.3 ± 0.3	Soluble

3.2 Selection of Lipid Excipients

Lipid screening studies demonstrated that Labrafil M 1944 CS exhibited the highest solubilization capacity for Dapagliflozin among the liquid lipid candidates tested (18.7 ± 0.6 mg/mL), followed by isopropyl myristate (11.4 ± 0.4 mg/mL) and oleic acid (9.8 ± 0.5 mg/mL). The superior solubilizing ability of Labrafil M 1944 CS may be attributed to its amphiphilic character as a polyoxyethylated oleic glyceride, which enables both hydrophobic interaction with the drug molecule and self-emulsification properties that facilitate dispersion in aqueous media. Consequently, Labrafil M 1944 CS was selected as the liquid lipid component for NLC formulation.

Among solid lipid candidates, glyceryl monostearate (GMS) demonstrated the highest drug solubility in the molten state (8.3 ± 0.3 mg/mL) and was selected as the primary solid lipid matrix former. GMS possesses a medium melting point (approximately 57-60°C), appropriate lipophilicity (log P ≈ 4.2), biodegradability, and GRAS regulatory status, making it an ideal candidate for oral lipid nanoparticle formulations. The combination of GMS and Labrafil at a 60:40 ratio was

identified as the optimal baseline lipid blend for NLC development.

Preliminary Screening of NLC Formulations

Preliminary NLC formulations were prepared to compare the two preparation methodologies and screen the influence of formulation variables. Table 3 presents the results of initial screening experiments.

Table 3. Results of NLC Formulation Screening

Formulation	Preparation Method	Particle Size (nm)	PDI	Zeta Potential (mV)	EE %
F1	Emulsification-Evaporation	285.6 ± 12.3	0.386	-18.4 ± 2.1	71.2 ± 3.4
F2	Emulsification-Evaporation	243.8 ± 9.7	0.342	-22.6 ± 1.8	76.8 ± 2.9
F3	Emulsification-Evaporation	198.4 ± 7.2	0.287	-25.3 ± 1.5	82.1 ± 2.3
F4	Solvent Diffusion	312.7 ± 14.6	0.418	-15.7 ± 2.6	65.4 ± 4.1
F5	Solvent Diffusion	267.3 ± 11.8	0.375	-19.8 ± 2.2	70.3 ± 3.7
F6	Solvent Diffusion	221.6 ± 8.9	0.318	-23.4 ± 1.9	78.6 ± 2.8

Comparative evaluation revealed that the solvent emulsification-evaporation method consistently produced NLC with smaller particle sizes, lower PDI values, higher absolute zeta potential, and superior entrapment efficiency compared to the solvent diffusion method. These differences are attributed to the higher energy input from high-shear homogenization and probe sonication in the emulsification-evaporation approach, which provides more uniform lipid matrix formation and better drug encapsulation. The solvent emulsification-evaporation method was therefore selected for further optimization using CCD.

Optimization Using Central Composite Design (CCD)

The CCD experimental matrix comprised 20 formulation runs with measured responses for particle size, zeta potential, and entrapment efficiency. The experimentally obtained data were analyzed using JMP 13.0 software to fit quadratic polynomial equations for each response.

Table 4. CCD Experimental Matrix and Observed Responses

Run	X_1 (Lipid Ratio)	X_2 (Surf. Conc., %)	X_3 (Homog. Time, min)	Y_1 PS (nm)	Y_2 ZP (mV)	Y_3 EE %
1	-1 (55:45)	-1 (1.0)	-1 (15)	234.7	-21.4	79.3
2	+1 (65:35)	-1 (1.0)	-1 (15)	268.3	-18.6	83.4
3	-1 (55:45)	+1 (2.0)	-1 (15)	198.6	-26.8	81.7
4	+1 (65:35)	+1 (2.0)	-1 (15)	221.4	-23.7	85.9
5	-1 (55:45)	-1 (1.0)	+1 (25)	218.3	-23.1	81.4
6	+1 (65:35)	-1 (1.0)	+1 (25)	247.6	-20.4	84.8
7	-1 (55:45)	+1 (2.0)	+1 (25)	183.4	-28.7	84.2
8	+1 (65:35)	+1 (2.0)	+1 (25)	204.7	-26.1	87.6
9	-α (50:50)	0 (1.5)	0 (20)	176.8	-30.4	82.7
10	+α (70:30)	0 (1.5)	0 (20)	271.3	-17.8	86.4
11	0 (60:40)	-α (0.5)	0 (20)	267.8	-16.4	77.3
12	0 (60:40)	+α (2.5)	0 (20)	176.2	-31.6	85.8

13	0 (60:40)	0 (1.5)	-α (10)	224.6	-24.3	80.1
14	0 (60:40)	0 (1.5)	+α (30)	186.4	-28.6	87.3
15	0 (60:40)	0 (1.5)	0 (20)	196.3	-26.7	84.6
16	0 (60:40)	0 (1.5)	0 (20)	193.8	-27.1	85.1
17	0 (60:40)	0 (1.5)	0 (20)	198.7	-26.4	84.8
18	0 (60:40)	0 (1.5)	0 (20)	195.2	-27.8	85.3
19	0 (60:40)	0 (1.5)	0 (20)	197.6	-26.9	84.9
20	0 (60:40)	0 (1.5)	0 (20)	194.4	-27.3	85.2

Statistical Analysis and Model Evaluation

ANOVA analysis of the fitted quadratic models demonstrated statistical significance for all three response models. The adjusted R^2 values (0.7243, 0.9391, and 0.8387) were in close agreement with predicted R^2 values, confirming the absence of overfitting. Adequate Precision ratios exceeded the critical threshold of 4.0 for all responses (particle size: 8.47, zeta potential: 14.32, entrapment efficiency: 10.65), affirming adequate signal-to-noise ratios for reliable prediction within the design space.

Lack-of-fit tests were non-significant ($p > 0.05$) for all models, confirming that the quadratic polynomial equations adequately described the experimental data without systematic model error. The normal probability plots of residuals and residuals versus predicted values plots displayed random distributions without discernible patterns, validating model assumptions of normality, homoscedasticity, and independence of residuals.

Table 5. ANOVA Summary and Model Fit Statistics for CCD Responses

Response	R^2	Adjusted R^2	Predicted R^2	Adeq. Precision	F-value	p-value
Particle Size (Y_1)	0.7658	0.7243	0.6871	8.47	18.46	< 0.0001
Zeta Potential (Y_2)	0.9523	0.9391	0.9217	14.32	72.31	< 0.0001
Entrapment Efficiency (Y_3)	0.8678	0.8387	0.8124	10.65	29.84	< 0.0001

Effect analysis revealed that lipid ratio (X_1) exerted a statistically significant ($p < 0.001$) positive effect on particle size, with increasing proportions of solid lipid resulting in larger nanoparticle dimensions due to augmented lipid matrix crystallinity and reduced fluidity. Surfactant concentration (X_2) demonstrated a significant negative effect on particle size ($p < 0.001$), consistent with the mechanism of interfacial tension reduction and steric stabilization provided by Poloxamer 407 adsorption at the lipid-water interface. Homogenization time (X_3) also showed significant negative correlation with particle size ($p < 0.01$), as prolonged high-shear processing enables more complete lipid droplet disruption and size reduction.

For zeta potential, surfactant concentration was the most influential factor, with higher Poloxamer 407 concentrations generating more negative surface charge through the anionic character of the polyoxyethylene chains and electrostatic repulsion effects. Entrapment efficiency was positively influenced by both lipid ratio and homogenization time, reflecting enhanced drug incorporation within the disordered lipid matrix and improved physical stabilization of encapsulated drug molecules during NLC formation.

Optimization and Validation

Numerical optimization was performed using the desirability function approach in JMP 13.0, with simultaneous optimization criteria set as: minimize particle size (target: < 200 nm), maximize absolute zeta potential (target: > 25 mV), and maximize entrapment efficiency (target: > 85%). The optimized formulation was predicted at a lipid ratio of 60:40 (GMS:Labrafil), surfactant concentration of 1.5% w/v Poloxamer 407, and homogenization time of 30 minutes, yielding predicted values of 186.4 nm (particle size), -28.6 mV (zeta potential), and 87.3% (entrapment efficiency).

Triplicate preparation of the optimized formulation yielded experimental values of 188.2 ± 3.7 nm, -27.9 ± 1.2 mV, and 87.1 ± 1.8%, respectively. The excellent agreement between predicted and experimental values (percentage bias < 2.5% for all responses) validated the predictive capability of the CCD models and confirmed the robustness of the optimization process.

Table 6. Optimized NLC Formulation - Predicted vs. Experimental Values

Response	Predicted Value	Experimental Value (Mean ± SD)	% Bias
Particle Size (nm)	186.4	188.2 ± 3.7	0.97
Zeta Potential (mV)	-28.6	-27.9 ± 1.2	2.45
Entrapment Efficiency (%)	87.3	87.1 ± 1.8	0.23
PDI	< 0.300	0.268 ± 0.018	—

***In Vitro* Drug Release Studies**

The optimized Dapagliflozin-NLC formulation and pure drug suspension were evaluated in PBS (pH 6.8) at 37°C over 24 hours. The pure drug suspension exhibited relatively rapid initial release, with approximately 65.3 ± 4.2% of the drug released within the first 4 hours, attributed to the fine particle size of the drug suspension and its direct contact with the dissolution medium.

The optimized NLC formulation exhibited a biphasic release profile with an initial burst release profile and a sustained release profile. This is a good two-stage release design because the burst phase gives a rapid achievement of therapeutic drug concentrations, whereas the sustained release allows the drug concentration to remain in the therapeutic range over a long duration.

Release kinetic modeling demonstrated that the Dapagliflozin-NLC drug release data best fitted the Higuchi diffusion model ($R^2 = 0.9834$), suggesting that drug release is governed primarily by diffusion through the lipid matrix. The Korsmeyer-Peppas model yielded a release exponent n = 0.62, indicating anomalous (non-Fickian) transport, which implies a coupled mechanism of matrix erosion and diffusion controlling drug release from the NLC system.

DISCUSSION

The present investigation represents a comprehensive QbD-guided pharmaceutical development of Dapagliflozin-loaded NLC, addressing the critical biopharmaceutical limitations of this important SGLT2 inhibitor. The systematic approach encompassing preformulation characterization, rational excipient selection, statistical experimental design, and rigorous model validation is consistent with contemporary regulatory expectations for quality pharmaceutical product development.

The physicochemical characterization of Dapagliflozin confirmed its BCS Class II biopharmaceutical classification, establishing the scientific rationale for lipid nanocarrier-mediated drug delivery [16]. The extremely limited aqueous solubility (0.21 mg/mL) underscores the challenge in achieving adequate gastrointestinal dissolution, while the high lipophilicity (estimated log P ≈ 1.8) makes the drug amenable to lipid-based formulation approaches. The confirmed physicochemical compatibility between Dapagliflozin and the selected NLC excipients is a fundamental prerequisite for formulation stability and predictable drug release behavior.

The selection of Labrafil M 1944 CS as the liquid lipid component was scientifically justified by its superior drug solubilization capacity among tested candidates. The unique amphiphilic nature of Labrafil, as a lauroyl polyoxylglyceride, facilitates drug partitioning within the NLC matrix while also contributing to the self-emulsifying properties of the system [17]. The mixed of GMS and Labrafil creates a purposefully disordered lipid matrix that represents the fundamental architectural distinction of NLC from conventional SLN, providing enlarged drug accommodation space and improved encapsulation capacity.

The superiority of the solvent emulsification-evaporation method over solvent diffusion in producing smaller, more uniform NLC with higher entrapment efficiency can be rationalized by the higher energy imparted during high-shear homogenization and ultrasonication. The combination of 10,000 rpm homogenization and probe sonication disrupts the lipid phase into nanoscale droplets, maximizing interfacial area and enabling uniform drug distribution throughout the lipid matrix. The solvent diffusion method, while technically simpler, relies on organic solvent extraction as the primary driving force for nanoparticle formation, which is inherently less controllable and may lead to incomplete solvent removal affecting nanoparticle morphology and drug distribution.

The CCD optimization results provide quantitative insights into the complex multivariate relationships governing NLC quality attributes. The significant negative effect of lipid ratio on particle size aligns with established theory: higher solid lipid content increases matrix rigidity and crystallinity, impeding lipid droplet fragmentation during homogenization and yielding larger particles [18]. Conversely, reduced solid lipid content with concomitant increase in liquid lipid proportion maintains matrix fluidity, facilitating more efficient nanoemulsification. The critical influence of surfactant concentration on particle size and zeta potential reflects the fundamental role of Poloxamer 407 in both kinetic stabilization (reducing interfacial tension during homogenization) and thermodynamic stabilization (preventing aggregation and Ostwald ripening through steric repulsion).

The entrapment efficiency of 87.1 ± 1.8% achieved by the optimized NLC formulation represents a significant improvement over previously reported Dapagliflozin formulations. The high encapsulation reflects successful drug partitioning into the disordered lipid matrix, with the intentional structural imperfections of NLC providing additional drug accommodation sites compared to the highly ordered crystalline lattice of SLN. The positive influence of homogenization time on entrapment efficiency suggests that extended processing enables more complete drug incorporation into the NLC matrix while simultaneously reducing particle size through progressive lipid droplet fragmentation.

The biphasic *In Vitro* release profile observed for Dapagliflozin-NLC has significant therapeutic implications. The initial burst release component, while sometimes considered undesirable, may be beneficial for SGLT2 inhibitors by rapidly achieving therapeutic plasma concentrations following postprandial administration. The subsequent sustained release phase, governed by Higuchi diffusion kinetics, is expected to maintain drug concentrations within the therapeutic window, potentially enabling once-daily dosing with improved tolerability compared to conventional immediate-release formulations. The anomalous transport mechanism indicated by the Korsmeyer-Peppas n value of 0.62 suggests that both matrix erosion (as the lipid matrix undergoes lipolysis in the gastrointestinal environment) and molecular diffusion through the lipid phase contribute to the overall drug release process.

From a regulatory and clinical translation perspective, the QbD approach employed in this study establishes a robust design space within which the NLC formulation can be manufactured with predictable and reproducible quality [19]. The statistically validated mathematical models allow prospective prediction of formulation performance, risk assessment through Monte Carlo simulation, and process robustness evaluation capabilities that are increasingly valued by regulatory agencies including the USFDA and EMA in new drug applications.

CONCLUSION

This study successfully demonstrated the development, systematic optimization, and characterization of Dapagliflozin-loaded NLC using a Quality by Design framework incorporating Central Composite Design. Comprehensive preformulation studies confirmed the physicochemical identity and excipient compatibility of Dapagliflozin. The solvent emulsification-evaporation method, optimized using CCD with factors of lipid ratio, surfactant concentration, and homogenization time, yielded NLC formulations. The quadratic polynomial CCD models demonstrated excellent statistical validity with high R^2 values and adequate precision ratios exceeding 4.0 for all responses, validating their predictive utility within the defined design space. The optimized Dapagliflozin-NLC exhibited a characteristic biphasic *In Vitro* release profile governed by Higuchi diffusion and anomalous transport mechanisms, offering the dual advantage of rapid initial drug delivery and sustained therapeutic concentrations. The QbD approach adopted in this investigation provides a scientifically robust foundation for the rational development of Dapagliflozin lipid nanomedicine, meeting the rigorous quality standards expected for contemporary pharmaceutical development. The optimized NLC system demonstrates significant promise for improving the biopharmaceutical performance of Dapagliflozin. Future investigations should focus on in vivo pharmacokinetic evaluation in validated animal models, long-term stability assessment under ICH-specified storage conditions, and comprehensive safety profiling to support clinical translation of this NLC formulation.

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