RESEARCH PAPER

Design and Optimization of a Novel Oral Drug Delivery System of Dapagliflozin for Antidiabetic Therapy

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ABSTRACT

Dapagliflozin is a poorly water-soluble antidiabetic drug with limited oral bioavailability, which can restrict its therapeutic performance. The present study aimed to develop and optimize an oral Nanoemulsion of dapagliflozin to enhance its physicochemical properties and in-vitro drug release. A Nanoemulsion was prepared using Capryol 90 as the oil phase, Tween 80 as the surfactant, and Transcutol P as the co-surfactant by the spontaneous emulsification method. Optimization was carried out using a Box–Behnken design to evaluate the effect of formulation variables on encapsulation efficiency, particle size, and in-vitro drug release. Statistical analysis revealed that oil concentration and surfactant concentration significantly influenced the responses. Numerical optimization using the desirability function identified an optimized formulation with high encapsulation efficiency (93.29%), reduced particle size (172.14 µm), and enhanced in-vitro drug release (80.30%), with an overall desirability of 0.935. Experimental validation of the optimized batch showed prediction errors within ±5%, confirming the robustness and predictive validity of the model. FTIR analysis demonstrated the absence of drug–excipient interactions, indicating good compatibility and stability of the optimized formulation. The results suggest that the developed dapagliflozin Nanoemulsion is a promising approach to improve oral drug delivery and bioavailability for effective antidiabetic therapy.

Keywords: Dapagliflozin, Nanoemulsion, Box–Behnken design, Desirability function, In-vitro drug release, Oral drug delivery

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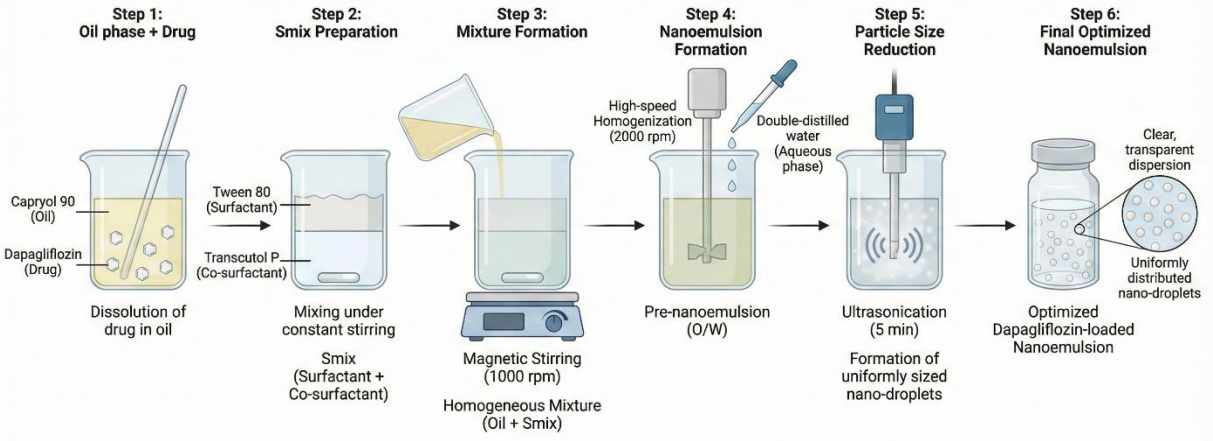

INTRODUCTION

Dapagliflozin, a selective sodium-glucose co-transporter-2 (SGLT2) inhibitor, has emerged as a potent antidiabetic

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agent due to its insulin-independent mechanism of enhancing urinary glucose excretion and improving glycaemic control in patients with type 2 diabetes mellitus (T2DM). Despite its clinical efficacy, the therapeutic performance of dapagliflozin is constrained by its poor aqueous solubility and variable oral bioavailability, categorizing it as a Biopharmaceutics Classification System (BCS) class II compound. Such biopharmaceutical limitations often result in suboptimal absorption, reduced onset of action, and compromised therapeutic outcomes, necessitating the development of advanced drug delivery systems to overcome these challenges [1,2].

Nanoemulsions are thermodynamically stable colloidal dispersions of oil and water stabilized by surfactants and co-surfactants, characterized by droplet sizes in the nanometer range. Owing to their high surface area, low interfacial tension, and enhanced solubilization capacity, nanoemulsions have attracted considerable interest for improving the oral delivery of poorly water-soluble drugs [3]. These systems can facilitate enhanced drug dissolution, improved intestinal permeability, and reduced first-pass metabolism, thereby offering a promising strategy to augment the bioavailability of lipophilic therapeutic agents. In recent years, Nanoemulsion-based formulations have been successfully explored for various therapeutic classes, demonstrating superior pharmacokinetic and pharmacodynamic profiles compared to conventional dosage forms [4].

Design of experiments (DoE) approaches, such as the Box–Behnken design, have gained prominence for systematic formulation optimization by evaluating the relationships between critical formulation variables and product performance attributes [5]. These statistical tools provide robust predictive models, reduce experimental trials, and ensure formulation reproducibility, making them indispensable in contemporary pharmaceutical development. Integrating Nanoemulsion technology with DoE-based optimization enables a rational and efficient pathway to achieve desirable quality attributes, including high drug encapsulation, controlled droplet size, and enhanced drug release [6].

In this study, we aimed to develop and optimize a dapagliflozin-loaded Nanoemulsion for oral antidiabetic therapy using a Box–Behnken design. The effects of oil, surfactant, and co-surfactant concentrations were systematically investigated on critical responses, including encapsulation efficiency, particle size, and in-vitro drug release [5]. The optimized formulation was validated experimentally and characterized for drug–excipient compatibility. The outcomes provide insights into formulation strategies that can potentially enhance the oral bioavailability and therapeutic efficacy of dapagliflozin [6].

Materials and Methods

Materials

Dapagliflozin was obtained as a gift sample from a reputed pharmaceutical manufacturer. Capryol 90 was used as the oil phase, Tween 80 as the surfactant, and Transcutol P as the co-surfactant. Methanol and other analytical-grade solvents used for drug estimation were procured from standard suppliers. Double-distilled water was used throughout the study.

Experimental Design

A three-factor, three-level Box–Behnken experimental design was employed for optimization of Dapagliflozin Nanoemulsion using Design-Expert software. The independent variables selected were oil concentration (Capryol 90, Factor A), surfactant concentration (Tween 80, Factor B), and co-surfactant concentration (Transcutol P, Factor C). The ranges of these variables were selected based on preliminary studies. The design matrix with corresponding factor levels for each experimental run is presented in Table 1. A total of fifteen experimental runs were generated to evaluate the effect of formulation variables on the selected responses [7].

Table 1. Formulation Composition of Dapagliflozin-Loaded Nanoemulsion

Batch	Capryol 90 (Oil) %	Tween 80 (Surfactant) %	Transcutol P (Co-surfactant) %	Water % (q.s.)
1	10	25	8	56
2	14	25	13	47
3	10	45	18	26
4	10	35	13	41
5	14	35	18	32
6	10	35	13	41
7	10	35	13	41
8	6	45	13	35
9	14	45	13	27
10	6	25	13	55
11	6	35	8	50
12	10	45	8	36
13	14	35	8	42
14	6	35	18	40
15	10	25	18	46

Preparation of Dapagliflozin-Loaded Nanoemulsion

Dapagliflozin-loaded Nanoemulsion was prepared using the spontaneous emulsification method. Initially,

dapagliflozin (1% w/w) was dissolved in the oil phase (Capryol 90). Tween 80 and Transcutol P were accurately weighed according to the experimental design (Table 1) and mixed to form the surfactant–co-surfactant (Smix) phase. The oil phase containing dapagliflozin was then added to the Smix phase under magnetic stirring at 1000 rpm until a clear and homogeneous mixture was obtained. Subsequently, double-distilled water was added dropwise to the oil–Smix mixture under continuous stirring using a high-speed homogenizer operated at 2000 rpm for 10–15 minutes, resulting in the formation of a fine oil-in-water nanoemulsion. The resulting dispersion was further subjected to ultrasonication for 5 minutes to reduce droplet size and improve stability. The prepared nanoemulsion was stored in airtight glass containers for further evaluation [8].

Evaluation of Formulation

Encapsulation Efficiency

Encapsulation efficiency was determined by separating the free drug from the Nanoemulsion using centrifugation. The supernatant was suitably diluted and analyzed spectrophotometrically. Encapsulation efficiency was calculated using the formula:

$$\text{Encapsulation Efficiency (\%)} = \frac{\text{Total drug} - \text{Free drug}}{\text{Total drug}} \times 100$$

Particle Size Analysis

Particle size of the Nanoemulsion was measured using dynamic light scattering technique after appropriate dilution with distilled water. The mean particle size was recorded in micrometres (μm) [8].

In-Vitro Drug Release Study

In-vitro drug release was carried out using the dialysis bag method. The Nanoemulsion equivalent to a known amount of dapagliflozin was placed in a dialysis membrane and immersed in dissolution medium maintained at 37 ± 0.5 °C with continuous stirring. Samples were withdrawn at predetermined time intervals, replaced with fresh medium, and analyzed spectrophotometrically to determine cumulative drug release [6].

Optimization and Statistical Analysis

The experimental data were analyzed using Design-Expert v-13 software. Polynomial equations were generated to study the effect of independent variables on responses. Numerical optimization was performed using desirability function to obtain an optimized formulation with maximum encapsulation efficiency, minimum particle size, and enhanced in-vitro drug release.

RESULTS AND DISCUSSION

Encapsulation Efficiency (EE%)

The encapsulation efficiency of dapagliflozin Nanoemulsion formulations ranged from 85.02% to 94.26%, as shown in Table 2. An increase in oil concentration resulted in improved drug encapsulation due to enhanced solubilization of dapagliflozin in the lipid phase. Higher surfactant and co-surfactant concentrations further contributed to improved encapsulation by stabilizing the oil droplets and reducing drug diffusion into the aqueous phase.

Particle Size Analysis

Particle size of the Nanoemulsion formulations varied from 171 to 221 μm (Table 2). Increasing surfactant concentration significantly reduced droplet size due to decreased interfacial tension and efficient emulsification. Formulations with lower surfactant levels showed comparatively larger particle sizes, indicating insufficient stabilization of oil droplets.

In-Vitro Drug Release (DR%)

The in-vitro drug release from the Nanoemulsion formulations ranged from 66.2% to 80.3%, as presented in Table 2. Formulations containing higher surfactant and co-surfactant concentrations exhibited enhanced drug release due to improved drug solubilization and increased surface area of Nano-sized droplets. Higher oil concentration slightly reduced drug release due to stronger drug retention within the oil phase.

Table 2. Response Values for Dapagliflozin-Loaded Nanoemulsion

Response 1 EE (%)	Response 2 Particle Size (μm)	Response 3 *In-Vitro* DR (%)
86.48	219	67.6
89.02	208	72.1
90.76	199	74.6
87.34	214	69.8
91.84	195	75.9
93.21	178	78
90.12	201	72
90.08	198	73.2
94.26	171	80.3
88.14	210	68.7
85.02	221	66.2
91.36	187	76.7
92.58	183	77.4

89.41	205	73.9
91.18	193	75.2

Effect on Encapsulation Efficiency

ANOVA for encapsulation efficiency showed that the linear model was statistically significant with an F-value of 5.02 and a p-value of 0.0197 ($p < 0.05$), as presented in Table 3. Oil concentration (Factor A) had a significant effect on encapsulation efficiency ($p = 0.0160$), whereas surfactant concentration (Factor B) and co-surfactant concentration (Factor C) were not significant. The lack-of-fit was not significant ($p = 0.9305$), indicating a good fit of the model to the experimental data.

Effect on Particle Size

For particle size, ANOVA revealed that the 2FI model was not statistically significant ($p = 0.0518$); however, oil concentration (Factor A) and surfactant concentration (Factor B) individually showed a significant effect on particle size ($p < 0.05$), as shown in Table 3. Co-surfactant concentration and all interaction terms were not significant. The non-significant lack-of-fit value ($p = 0.9920$) confirms the adequacy of the selected model.

Effect on In-Vitro Drug Release

ANOVA for in-vitro drug release indicated that the 2FI model was statistically significant with an F-value of 6.48 and a p-value of 0.0095, as shown in Table 3. Oil concentration (Factor A) and surfactant concentration (Factor B) showed a significant effect on drug release ($p < 0.05$), while co-surfactant concentration and interaction terms were not significant. The lack-of-fit was not significant ($p = 0.9994$), indicating good predictability of the model.

Table 3. Summary of ANOVA Results for Dapagliflozin Nanoemulsion Responses

Response	Model Type	Model F-value	Significant Factors ($p < 0.05$)	Non-Significant Factors	Lack of Fit (p-value)	Model Adequacy
Encapsulation Efficiency	Linear	5.02	A (Oil concentration)	B (Surfactant), C (Co-surfactant)	0.9305	Adequate
Particle Size	2FI	3.53	A (Oil concentration), B (Surfactant)	C, AB, AC, BC	0.9920	Adequate
In-Vitro Drug Release	2FI	6.48	A (Oil concentration), B (Surfactant)	C, AB, AC, BC	0.9994	Adequate

Response Surface Plots

The response surface and contour plots presented in Figures 1–3 illustrate the influence of formulation variables on encapsulation efficiency, particle size, and in-vitro drug release of the dapagliflozin Nanoemulsion. Figure 1 shows that encapsulation efficiency increases with increasing oil concentration due to enhanced solubilization of dapagliflozin within the oil phase. Figure 2 demonstrates that particle size decreases significantly with increasing surfactant concentration as a result of reduced interfacial tension, whereas higher oil concentration leads to larger droplet size. Figure 3 indicates that in-vitro drug release increases with increasing surfactant concentration, while higher oil concentration slightly reduces drug release. Overall, the plots confirm that oil concentration predominantly influences encapsulation efficiency, whereas surfactant concentration plays a major role in controlling particle size and drug release.

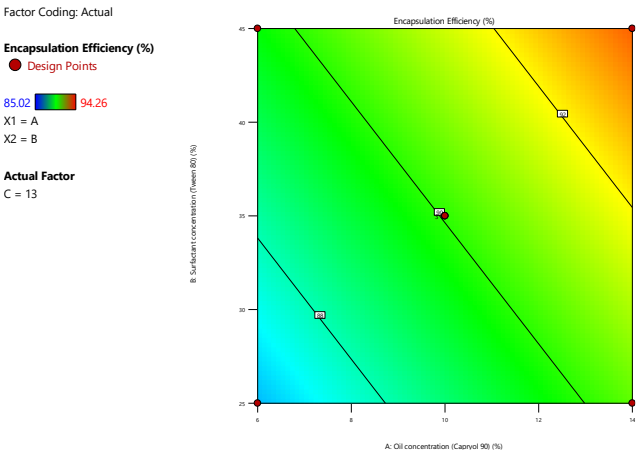

Figure 1. Response surface plot showing the effect on encapsulation efficiency

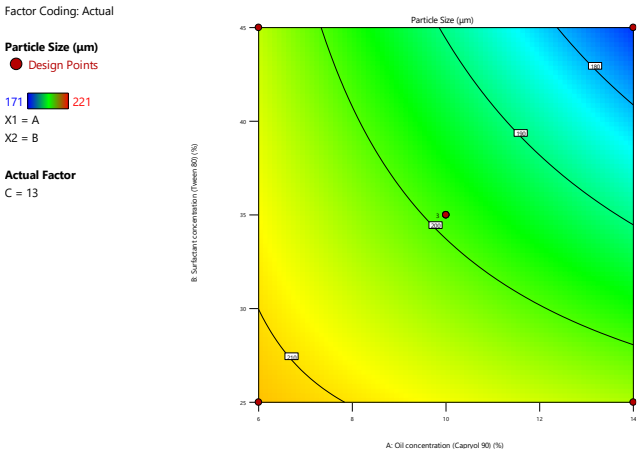

Figure 2. Response surface plot showing the effect of particle size

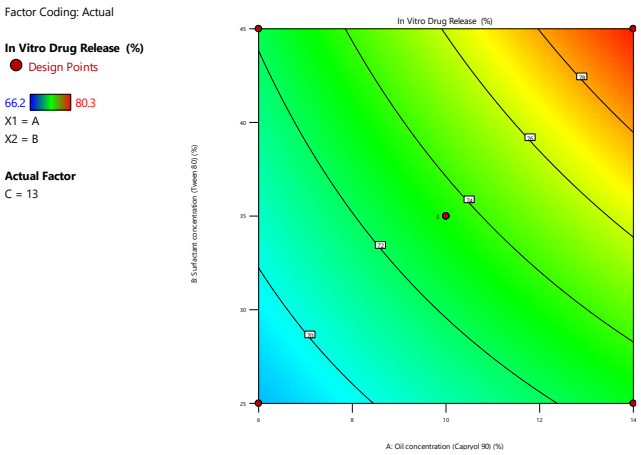

Figure 3. Response surface plot showing the effect of in-vitro drug release

Optimization of the Formulation Using Desirability Function

Numerical optimization was carried out using the desirability function approach in Design-Expert software with the objective of maximizing encapsulation efficiency and in-vitro drug release while minimizing particle size. The optimized formulation Batch F16 composition consisted of Capryol 90 (14.0%), Tween 80 (45.0%), and Transcutol P (12.506%), with an overall desirability value of 0.935. The predicted responses for the optimized formulation were 93.294% encapsulation efficiency, 172.141 µm particle size, and 80.30% in-vitro drug release.

Model Validation of the Optimized Batch

To validate the predictive capability of the developed model, the optimized formulation was prepared experimentally and evaluated for encapsulation efficiency, particle size, and in-vitro drug release. The observed responses were compared with the predicted values, and the percentage prediction error was calculated. The prediction error for all responses was found to be within **±5%,** Table 4confirming the robustness and reliability of the optimization model.

Table 4. Predicted and Observed Responses for Optimized Batch F-16

Response	Predicted Value	Observed Value	% Prediction Error
EE (%)	93.29	91.86	1.53
Particle Size (µm)	172.14	176.08	2.29
In-Vitro DR (%)	80.30	78.74	1.94

FTIR Analysis of Optimized Batch F-16

The FTIR spectrum of the optimized dapagliflozin nanoemulsion formulation is shown in Figure 7. The characteristic peaks of dapagliflozin were observed at 3468 cm^{-1} (O–H stretching), 2923 and 2853 cm^{-1} (C–H stretching), and 1680 cm^{-1} (C=O stretching). Additional peaks at 1579, 1522, 1456, 1344, and 1278 cm^{-1} correspond to functional groups associated with the drug and formulation components. The presence of all major characteristic peaks without significant shifts or disappearance indicates no chemical interaction between dapagliflozin and the excipients, confirming the compatibility and stability of the optimized formulation.

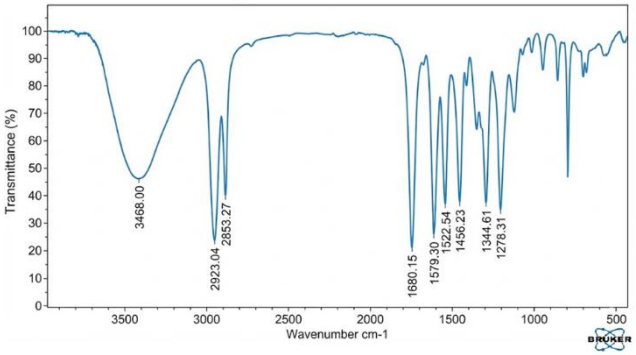

Figure 7. FTIR spectrum of Optimized Dapagliflozin-Loaded Nanoemulsion

Conclusion

The present study successfully demonstrated the development and optimization of a dapagliflozin-loaded nanoemulsion for oral antidiabetic therapy using a systematic Box–Behnken design approach. The selected formulation variables significantly influenced encapsulation efficiency, particle size, and in-vitro drug release, highlighting the importance of rational formulation optimization. Numerical optimization using the desirability function yielded an optimized nanoemulsion with high encapsulation efficiency, reduced particle size, and enhanced drug release, indicating its potential to improve the oral bioavailability of dapagliflozin. Experimental validation of the optimized batch showed close agreement between predicted and observed responses, with prediction errors within ±5%, confirming the robustness and reliability of the developed statistical model. Furthermore, FTIR analysis confirmed the absence of drug–excipient interactions, demonstrating good compatibility and stability of the formulation. Overall, the optimized dapagliflozin Nanoemulsion represents a promising oral drug delivery system for effective management of type 2 diabetes mellitus

and provides a scalable platform for improving the biopharmaceutical performance of poorly water-soluble drugs

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