RESEARCH PAPER

Formulation and Evaluation of Dapagliflozin-Loaded Nanoemulsion using a Box–Behnken design for Antidiabetic Delivery

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Abstract

Dapagliflozin (DG), is Sodium-Glucose Cotransporter 2 inhibitor approved for the treatment of type 2 diabetes that Lowers blood glucose levels by helping the body expel excess sugar through urine. The drug faces clinical limitations like not recommended for patients with polycystic kidney disease and may cause hypoglycemia as a monotherapy. Formulating DG as a nanoemulsion is an advanced colloidal platform, lipid-based drug delivery system designed to overcome the drug's poor water solubility and limited oral bioavailability that ensure faster drug release and enhancing dissolution. The aim of the present work was developing Dapagliflozin-Loaded Nanoemulsion (DLN) for Diabetic Management. Pre-formulation studies established a melting point of 65°C and confirmed low aqueous solubility using a 3-factor, 3-level Box-Behnken design (Design-Expert v.13). FTIR analysis confirmed that the chemical structure of the drug remained intact, revealing no significant drug-excipient incompatibility. Nine formulations were prepared via spontaneous emulsification using Oleic acid (oil), Tween 80/PEG 400 (□□□□), and distilled water. Characterization included particle size, zeta potential, pH, viscosity, encapsulation efficiency (EE%), drug content, and *in vitro* drug release. ANOVA confirmed that the quadratic models for particle size (□ = 0.0364) and drug release (□ = 0.0409), and a linear model for drug content (□ = 0.0126), were statistically significant, confirming model adequacy. The □□□□ ratio demonstrated a highly significant impact on both drug content and release kinetics. As a result, Batch DE9 was optimized, exhibiting the smallest particle size 107.4 nm, optimal stability (zeta potential: −29.8 mV), near-neutral pH 6.22, maximum viscosity 67.41cps, high Entrapment efficacy 90.10%, maximum drug content 92.09%, and superior sustained drug release 94.58±0.66% at 12 hr. In conclusion, the optimized nanoemulsion formulation successfully overcomes the dissolution barriers of dapagliflozin, offering a highly stable and effective oral delivery platform for diabetes management.

Keywords: Dapagliflozin, SGLT2 Inhibitor, Antidiabetic Therapy, Nanoemulsion, ANOVA Analysis, *In-vitro* drug release etc.

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Introduction

Dapagliflozin (DG), is an oral antidiabetic agent classified as a sodium-glucose cotransporter-2 inhibitor and was the first drug of this class approved for the management of type 2 diabetes mellitus. Dapagliflozin acts by selectively inhibiting SGLT2 in the proximal renal tubules, thereby reducing glucose reabsorption and enhancing urinary glucose excretion, which leads to decreased blood glucose levels. The drug exhibits a bioavailability of approximately 78% and a half-life of 12.9 hours, with primary hepatic metabolism via the UGT1A9 enzyme.[1]

Dapagliflozin, a potent SGLT2 inhibitor, suffers from low aqueous solubility (-0.21 mg/ml, at 25°C) although possessing high permeability, limiting its oral bioavailability (-70%). Improving solubility and protecting the drug from degradation could improve Therapeutic outcomes, especially important given dapagliflozin's benefits for diabetes, cardio-renal complications, and heart Failure. Initially, FDA approved dapagliflozin on January 8, 2014 for improving glycemic control in adults with type-2 diabetes in combination with diet and exercise. In April 2021, its indications were expanded to include reduction of kidney function decline, kidney failure, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease.[2]

Nanoemulsions are sub-micron size (20-200 nm) oil-in-water dispersions stabilized by surfactants and co-surfactants, offering transparency and thermodynamic stability, they facilitate enhanced drug loading of lipophilic drugs and improve absorption by maximizing surface are for drug release, and potentially lymphatic transport to bypass hepatic first-pass metabolism.[3] 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]

In this study, aimed to develop the formulation using a Box–Behnken design that have gained prominence for systematic formulation optimization by evaluating the relationships between critical formulation variables and product performance attributes. The effects of oil, surfactant, and co-surfactant concentrations were systematically investigated on critical responses, including particle size, drug content, and percentage *in vitro* drug release [5]. The outcomes provide insights into formulation strategies that can potentially enhance the oral bioavailability and therapeutic efficacy of dapagliflozin.[6]

Materials And Methods

The active pharmaceutical ingredient, Dapagliflozin (purity greater than 99.0%) was obtained as s gift from a reputed pharmaceutical manufacturer. Oleic acid was used as the oil phase, Tween 80 as the surfactant, and PEG 400 as the co- surfactant. Methyl paraben, methanol and other analytical reagents used for drug estimation were procured from standard suppliers.[7]

Pre-formulation studies

Pre-formulation characterization of DG was performed to establish physicochemical properties, which are essential for formulation design based on visual observation.

1. Melting point: The melting point of DG was determined by Melting point apparatus.
2. Solubility Studies**:** The study was analyzed in multiple aqueous media such as methanol, dichloromethane, distilled water, phosphate buffer pH 7.4, phosphate buffer pH 6.8, and acidic buffer pH 1.2 using the shake flask method. Accurately weighed 25 mg of drug was added to 25 ml of each solvent in separate 100 ml conical flasks. The flasks were placed on a mechanical shaker and agitated at 150 RPM for 24 h to maintain equilibrium. samples were withdrawn, filtered through Whatman filter paper, suitably diluted and analyzed for drug concentration by UV spectroscopy.
3. Ultraviolet - Visible Spectroscopy (UV): A standard solution of drug in methanol (10 µg) was prepared, and scanned across the wavelength range of 200-400 nm showing the maximum absorbance at 231 nm against blank solvent. The absorbance vs concentration graph of working solution was plotted.
4. FTIR (Fourier Transform Infrared Spectroscopy): FTIR spectra of drug were obtained using FT/IR-4600 type A in the region of 4000–400 cm-1 with 32 scans at a resolution of 4 cm^{-1} and reported.[8]

Drug excipient compatibility study:
(Preparation of Physical Mixture: Dapagliflozin: Oleic acid: Tween 80: PEG 400)
Suitable amount of dapagliflozin, Tween-80 and PEG 400 were placed directly on the ATR crystal of the FTIR spectrophotometer. The sample was pressed gently to ensure proper contact with the crystal surface. A background spectrum was recorded before analysis. The FTIR spectrum was collected to check the interaction of drug with excipients over the range of 4000-400 cm^{-1} at a resolution of 4 cm^{-1} using 32 scans.

Experimental design
The response surface methodology (RSM) was employed to perform a Quality by Design approach for constructing and investigating the polynomial models, using fewer experimental runs. Box–Behnken Design, comprising 3 factors and 3 levels, was employed for optimization of DLN using Design-Expert software to examine the quadratic response surfaces by assessing the effect of independent variables on different response dependent variables Particle size (nm), Drug content (%) and In-vitro drug release (%).[9]

Preparation of Dapagliflozin-Loaded Nanoemulsion (DLN)
Dapagliflozin-Loaded Nanoemulsion was prepared by the high-energy emulsification method using Oleic acid as the oil phase, Tween 80 as the surfactant, and PEG 400 as the co-surfactant. Initially, the required quantity of DG was accurately weighed and dissolved in the measured quantity of Oleic acid under continuous magnetic stirring until a clear solution was obtained. Separately, Tween 80 and PEG 400 were mixed in the predetermined Smix ratio to obtain a homogeneous surfactant mixture. The prepared Smix was then added gradually to the drug-containing oil phase with continuous stirring at the optimized stirring speed 2000 rpm. The mixture was stirred for 15 min to obtain a clear and uniform preconcentrate. Subsequently, the required quantity of methyl paraben and distilled water was added dropwise to the oil–Smix mixture under continuous stirring using a high-pressure homogenizer at 900 bars for 5 cycles, resulting in the formation of a fine oil-in-water nanoemulsion. The resulting dispersion was then subjected to probe ultrasonication for 5 min to reduce the droplet size and obtain a stable nanoemulsion. Same procedure was adopted for all formulation batches DE1-DE9 (Table 1). The prepared formulation was allowed to equilibrate at room temperature and then stored in airtight amber-colored glass containers for further characterization [10,11].
Table 1: formulation composition of Dapagliflozin-Loaded Nanoemulsion

Formulation code	Dapagliflozin (gm)	Oleic acid (mL)	Tween 80 (mL)	PEG 400 (mL)	Water (mL)	Methyl paraben (gm)	Stirring Speed (RPM)
DE1	10	15	25	10	30	10	1000
DE2	10	5	25	10	40	10	2000
DE3	10	15	25	15	25	10	1500
DE4	10	15	25	10	30	10	2000
DE5	10	5	25	10	40	10	1000
DE6	10	10	20	10	40	10	1000
DE7	10	5	20	10	45	10	1500
DE8	10	5	25	15	35	10	1500
DE9	**10**	**10**	**25**	**15**	**30**	**10**	**2000**

Evaluation of Dapagliflozin-Loaded Nanoemulsion
1. Particle size and Zeta potential
The average particle size and zeta potential of all formulation were examined through the dynamic light scattering technique Initially, the all samples were diluted with distilled water (1:10) to revoke the multi-scattering effect, reduce the expected formulation viscosity, and provide a precise comparison between different formulations. The particle size data were reported as the Z-average mean diameter, and the Z-average particle diameter was obtained based on distribution by number, which was gathered by the software. All measurements were taken in triplicate at ambient temperature (25 ◦C±2 ◦C) and an angle of 90◦ to the incident beam [12].
2. pH
pH values were measured for all formulation using a calibrated digital pH meter at 25°C. Before the readings were observed, the pH meter was calibrated using pH 7.01, pH meter was calibrated using pH7.01,4.01, and 10.01 buffer solutions, respectively.
3. Viscosity
Viscosity was measured for all formulations using a Brookfield viscometer at 60 rpm, spindle s63, and the viscosity of the nanoemulsion was measured. [13]
4. Entrapment efficiency (%EE)

Accurately weighed 1 ml of the prepared nanoemulsion was dispersed in 9 ml of methanol. The dispersion was centrifuged at 10,000 rpm for 30 min, and the supernatant containing the free drug was collected and measured using a UV method at 231 nm.[14]

%EE was calculated using the following equation-

Encapsulation Efficiency (%) = Total drug−Free drug /Total drug ×100

5. Drug Content (%)

Drug content was determined to assess the uniformity and efficiency of drug incorporation in the formulation. An aliquot of 1 ml of the nanoemulsion (equivalent to a known amount of drug) was dissolved in 9 ml of phosphate buffer 6.8 to achieve complete dissolution. The solution was then filtered to remove any undissolved material. The clear filtrate was analyzed using a UV for all samples statistically at 231 nm.[15]

Drug content (%) was calculated using equation-

Drug Content (%) = Measured drug concentration/ Theoretical drug concentration ×100

6. *In-vitro* Drug Release Studies

In-vitro release tests of the formulations and drug solution were performed using dialysis membrane in phosphate buffer 6.8 (37±2ºC) for all formulation batches. The dialysis bag was pretreated by soaking it in the phosphate solution buffer 6.8 for 24 h prior to the release study. The apparatus was set at100 rpm and was maintained at37±2ºC. 5ml of samples was withdrawn at regular time intervals of 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 h, and the same amount of fresh phosphate buffer 6.8 was replaced every time to maintain sink condition. The samples were then analyzed in triplicate at 231 nm by UV after suitable dilution statistically [16].

7. Physical stability study

Stability studies of the optimized DLN were conducted as per ICH guidelines. The formulation was stored at 4 ± 2°C, 25 ± 2 °C/60 ± 5% RH, and 40 ± 2 °C/75 ± 5% RH for 3 months. After every month time interval, physical appearance was determined and reported.[17]

Results and discussion

Dapagliflozin was odorless, white powder. The observed melting point of 65°C, which indicates that the drug sample is pure, authentic, and free from major impurities, thereby confirming its identity and suitability for further formulation studies.

The solubility study revealed that DG exhibited the highest solubility in methanol (4.856 ± 0.85 mg/ml) and the lowest solubility in acidic buffer pH 1.2 (0.824 ± 0.43 mg/ml). The drug showed appreciable solubility in distilled water and phosphate buffer media (Table 2). These findings suggest that these solubility data confirm the BCS Class II classification of DG, less aqueous solubility, and increased intestinal permeability, which presents the primary biopharmaceutical challenge addressed by the nanoemulsion formulation strategy.

Table 2: Solubility of dapagliflozin in different Medium

Medium	**Solubility (mg/ml)**
Distilled Water	1.1243 ± 0.6245
Methanol	**4.8567 ± 0.8532**
Dichloromethane	2.6784 ± 0.7418
Phosphate Buffer pH 6.8	1.6489 ± 0.5824
Phosphate Buffer pH 7.4	1.3853 ± 0.6941
Acidic Buffer pH 1.2	0.8245 ± 0.4386

The UV spectrum of DG in methanol showed a λmax of 231 nm and the regression equation of y = 0.0653x- 0.0081 with a very high correlation coefficient (R^2 = 0.9994), indicating almost perfect correlation between concentration and absorbance. This confirms that methanol is a highly suitable solvent for the quantitative estimation of DG, showing strong adherence to Beer–Lambert's law as shown in Fig.1.

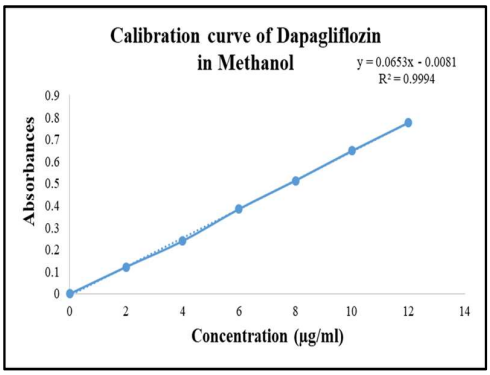

Fig.1: Calibration curve of dapagliflozin in methanol

The FTIR of pure drug and the drug excipient compatibility study by FTIR confirmed the presence of characteristic functional groups of DG and formulation excipients without any significant shift or disappearance of major peaks. The absence of additional peaks or major spectral changes suggested good compatibility between the drug and excipients (Fig.2).

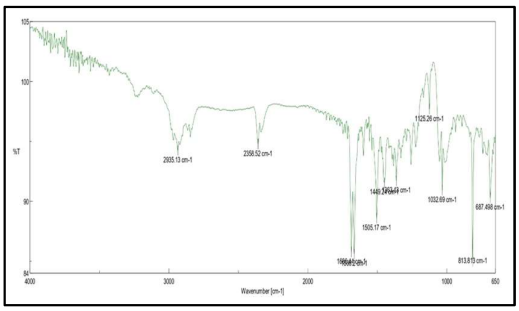

Fig.2: FTIR of Physical mixture of Dapagliflozin: Tween 80: PEG 400

Evaluation of DLN

The particle size was ranged from 107.4 nm to 145.8 nm in all batches. Among all formulations, DE9 exhibited the smallest particle size (107.4nm), which may contribute to improved drug release and bioavailability. Zeta potential values varied from −19.7 mV to -29.8 mV. DE9 showed the highest negative zeta potential (−29.8 mV), suggesting superior physical stability.

The pH evaluation of formulations DE1–DE9 showed values ranging from 5.11 to 6.22. DE9 showed the highest pH value of 6.22. Overall, the pH results confirmed the suitability of the developed formulations for oral delivery. The formulations exhibited near-neutral and slightly acidic pH, which may help maintain formulation stability and minimize irritation.

The viscosity values ranged from 36.95cps to 67.41cps, indicating good flow properties and formulation stability. Among all formulations, DE9 exhibited the highest viscosity (67.41cps), which may contribute to improved stability and sustained drug release behavior.

The %EE values ranged from 75.40±0.54% to 90.10±0.64%, indicating satisfactory drug entrapment in all formulations. Among all batches, DE9 exhibited the highest entrapment efficiency (90.10±0.64%), suggesting superior drug loading capacity and formulation stability.

The % drug content values ranged from 78.14±0.55% to 92.09±0.65%, indicating uniform distribution of drug within the nanoemulsion systems. Among all formulations, DE9 exhibited the highest drug content (92.09±0.65%), suggesting better drug entrapment and formulation efficiency.

The *in vitro* drug release study of formulation DE9 exhibited the highest cumulative %drug release (94.58±0.66%) at 12 h, indicating superior release characteristics. The study confirmed that the developed formulations provided effective sustained drug release, with DE9 identified as the optimized formulation as shown in Table 3.

Table 3: Evaluation results of DLN

Sr. No.	**Formulation batches**	**Particle size (nm)**	**Zeta potential (mV)**	**pH**	**Viscosity (cps)**	**Entrapment efficiency (%EE)**	**Drug Content (%)**	***In-vitro* Drug Release (%)**
1	DE1	142.4	-24.5	5.11	41.36	75.40 ± 0.54	87.47 ± 0.62	80.13 ± 0.56
2	DE2	118.6	-23.6	6.03	50.18	80.10 ± 0.57	84.33 ± 0.60	82.27 ± 0.57
3	DE3	115.9	-25.1	6.14	57.44	82.10 ± 0.59	88.66 ± 0.63	89.04 ± 0.62
4	DE4	122.5	-27.2	6.04	55.27	81.00 ± 0.58	87.05 ± 0.61	85.26 ± 0.56
5	DE5	121.1	-22.4	5.68	36.95	77.00 ± 0.04	84.75 ± 0.60	78.64 ± 0.55
6	DE6	119.7	-22.4	6.22	60.83	83.40 ± 0.63	83.71 ± 0.59	90.27 ± 0.63
7	DE7	118.2	-25.3	5.91	47.92	78.10 ± 0.59	78.14 ± 0.55	82.45 ± 0.57
8	DE8	145.8	-27.8	5.58	44.88	79.30 ± 0.02	85.94 ± 0.61	81.54 ± 0.57
9	**DE9**	**107.4**	**-29.8**	**6.22**	**67.41**	**90.10 ± 0.31**	**92.09 ± 0.65**	**94.58 ± 0.66**

ANOVA Analysis of Particle Size

The ANOVA results demonstrated that the quadratic model developed for particle size was statistically significant, with an F-value of 11.08 ($p = 0.0364$), indicating that the model adequately explained the variation in particle size. Among the model terms, the interaction between oil concentration (A) and Smix ratio (B) (AB), the quadratic effect of Smix ratio (B^2), and the quadratic effect of stirring speed (C^2) significantly influenced particle size ($p < 0.05$). However, the individual effects of oil concentration (A), Smix ratio (B), stirring speed (C), the interactions AC and BC, and the quadratic term A^2 were found to be statistically non-significant ($p > 0.05$). The quadratic model was considered suitable and adequate for predicting and optimizing the particle size of the nanoemulsion formulation.

ANOVA Analysis of Drug Content

It revealed that the linear model was statistically significant, with an F-value of 6.48 ($p = 0.0126$). The analysis indicated that oil concentration (A) and Smix ratio (B) significantly affected drug content, with p-values of 0.0392 and 0.0051, respectively. In contrast, stirring speed (C) did not show a

significant influence on drug content (p = 0.7328). Since the model was statistically significant, it was considered adequate for predicting drug content within the selected experimental range.

ANOVA Analysis of *In-Vitro* Drug Release-

The ANOVA results showed that the quadratic model for in-vitro drug release was statistically significant, with an F-value of 10.19 (p = 0.0409). Among the model terms, the Smix ratio (B), the interaction between Smix ratio and stirring speed (BC), and the quadratic effect of oil concentration (A^2) significantly influenced the drug release profile ($p < 0.05$). The individual effects of oil concentration (A) and stirring speed (C), the interactions AB and AC, and the quadratic terms B^2 and C^2 were statistically non-significant ($p > 0.05$). Hence, the quadratic model was considered adequate for predicting and optimizing the *in-vitro* drug release behavior of the nanoemulsion formulation and results presented in Table 4.

Table 4: ANOVA results of DLN

Response	**F-value**	**Significant Factors ($p < 0.05$)**	**Non-Significant Factors**	**Lack of Fits (p-value)**	**Model Adequacy**
Particle size	11.08	AB (Oil conc .X Smix ratio), B^2 (Smix ratio²), C^2 (Stirring speed²),	A (Oil conc.), B (Smix ratio), C (Stirring speed), AC, BC, A^2	0.0364	Adequate
Drug content	6.48	A (Oil conc.), B (Smix ratio), BC (Smix ratio X Stirring speed), A^2 (Oil conc.²)	C (Stirring speed)	0.0126	Adequate
In-vitro drug release	10.19	B (Smix ratio), BC (Smix ratio X Stirring speed), A^2 (Oil conc.²)	A (Oil conc.), C (Stirring speed), AB, AC, B^2, C^2	0.0409	Adequate

esponse Surface Plots

The response surface and contour plots presented in Figures 3–5 illustrated the influence of formulation variables on particle size, drug content, and in-vitro drug release of the dapagliflozin Nanoemulsion.

Figure-3 indicated that particle size was influenced by both oil concentration and Smix ratio. The optimized formulation indicates successful preparation of a nanoemulsion with nanosized droplets suitable for improved stability and drug delivery.

Figure-4 demonstrated that drug content increased with increasing oil concentration and Smix ratio. The optimized formulation indicates efficient drug incorporation and minimal drug loss during formulation.

Figure-5 showed maximum drug release at a higher Smix ratio and moderate oil concentration. The optimized formulation exhibited approximately 94% cumulative drug release, suggesting efficient release characteristics and enhanced availability of the drug.

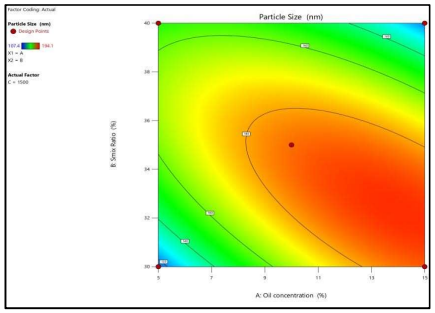

Fig.3: Response surface plot showing the effect on particle size

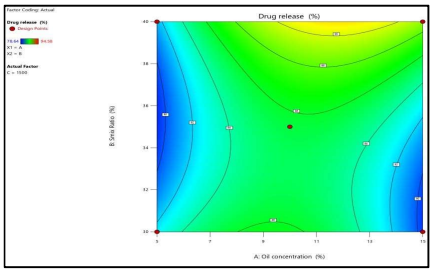

Fig.4: Response surface plot showing the effect on drug content

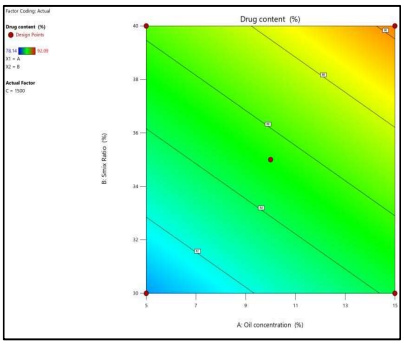

Fig.5: Response surface plot showing the effect on in-vitro drug release

Stability studies

The stability study of the optimized DE9 formulation was conducted at 4°C, 25°C, and 40°C for 3 months. The formulation remained homogeneous throughout the study period, with no visible phase separation, precipitation, or sedimentation. A slight color variation observed at 40°C but no phase separation was detected after prolonged storage. These indicates that the DE9 formulation remained physically stable during the 3-month storage period, with the best stability observed under refrigerated (4°C) and room temperature (25°C) conditions.

Conclusion

The present study successfully demonstrated the development and optimization of DLN for oral antidiabetic therapy using a systematic Box-Behnken design approach. Nanoemulsion formulations were successfully prepared using the spontaneous emulsification method and optimized using the Box–Behnken Design approach. Among all the developed formulations, DE9 was identified as the optimized formulation based on its superior performance. The prepared nanoemulsions were evaluated for particle size, zeta potential, viscosity, pH, %EE, drug content, and cumulative % *in-vitro* drug release. The optimized formulation DE9 exhibited excellent physicochemical properties with a particle size of 107.4 nm and zeta potential of −29.8 mV, indicating good stability and uniformity of the nanoemulsion system. The optimized formulation showed 92.09 ± 0.6584% drug content and 90.10 ± 0.6482% entrapment efficiency, confirming efficient incorporation of dapagliflozin within the nanoemulsion droplets. The in-vitro drug release study demonstrated a sustained and controlled release pattern of dapagliflozin from the nanoemulsion system. Statistical optimization and ANOVA analysis confirmed that formulation variables, particularly the Smix ratio, significantly influenced drug content and drug release behavior. FTIR analysis confirmed the absence of drug–excipient interactions, demonstrating good compatibility and stability of the formulation. It can be concluded that the developed dapagliflozin-loaded nanoemulsion successfully enhanced drug solubility, entrapment efficiency, and sustained drug release characteristics. The optimized formulation demonstrated excellent stability and performance, making it a promising oral drug delivery system for effective diabetic management.

CONFLICT OF INTEREST: Nil

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