ORIGINAL ARTICLE

Harnessing Nanoemulsion Technology for Enhanced Delivery of Canagliflozin in Type 2 Diabetes Therapy

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Abstract

Introduction: Canagliflozin, a selective sodium-glucose cotransporter-2 inhibitor indicated for the management of type 2 diabetes mellitus (T2DM), is limited by poor aqueous solubility and suboptimal bioavailability, which impede its therapeutic potential. This study aimed to develop and comprehensively characterize a nanoemulsion-based delivery system to enhance the solubility, stability, and bioavailability of Canagliflozin. Preformulation analyses confirmed the drug's high solubility in methanol and DMSO, contrasted by poor water solubility and unsatisfactory micromeritic properties, indicating the necessity for formulation intervention. **Materials and Methods:** Nanoemulsions were prepared using appropriate oil, surfactant, and cosurfactant systems, and subjected to sonication and high-pressure homogenization techniques to optimize droplet size and dispersion uniformity. **Results and Discussion:** Among the various formulations, F5 emerged as the most promising, exhibiting a droplet size of 68.1 nm and superior homogeneity. Differential scanning calorimetry of F5 revealed a marked reduction in the drug's melting point, suggesting enhanced dispersion and possible conversion to an amorphous state. Fourier-transform infrared spectroscopy indicated no significant chemical degradation, though minor spectral shifts suggested non-covalent interactions between the drug and excipients. Collectively, the results support the successful development of a stable nanoemulsion formulation capable of enhancing Canagliflozin's physicochemical and biopharmaceutical properties. **Conclusion:** This work underscores the potential of nanoemulsion technology as a strategic platform for improving the delivery of poorly soluble antidiabetic agents, thereby contributing to more effective and reliable therapeutic outcomes in the management of T2DM.

Key words: Bioavailability, canagliflozin, diabetes mellitus, nanoemulsion, sodium-glucose cotransporter-2 inhibitors, solubility enhancement

INTRODUCTION

Diabetes mellitus (DM) is a prevalent endocrine disorder affecting approximately 60% of the global population. It results from inadequate or ineffective insulin production by the pancreas, leading to dysregulated blood glucose levels. Insulin, an anabolic hormone, plays a crucial role in carbohydrate, protein, and lipid metabolism. Prolonged hyperglycemia can damage various organs, including the cardiovascular system, kidneys, blood vessels, eyes, and nervous system. DM is categorized into three primary types: Type 1 D (T1D), an autoimmune condition characterized by insulin deficiency; type 2 diabetes (T2D), marked by glucose intolerance and insulin resistance; and gestational DM, occurring during pregnancy in women without prior diabetes history.[1,2] T2DM is associated with microvascular complications (nephropathy, neuropathy, and retinopathy) and macrovascular diseases (cardiovascular, cerebrovascular,

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and peripheral artery disease). While glycemic control primarily benefits microvascular outcomes,[3] sodium-glucose cotransporter-2 (SGLT-2) inhibitors, such as canagliflozin, show additional promise in reducing macrovascular risks.[4] Canagliflozin significantly lowers hemoglobin A1C, blood pressure, and weight, and reduces the risk of end-stage renal disease, cardiovascular mortality, heart failure hospitalization, and proteinuria in diabetic nephropathy, as well as major cardiovascular events in those with T2DM and cardiovascular disease. However, its therapeutic efficacy is limited by poor solubility, low permeability, and suboptimal bioavailability.[5,6] In our study, we developed and evaluated a nanoemulsion-based formulation of canagliflozin using methanol (as solubilizer), castor oil (as the oil phase to improve drug loading), PEG 400 (as co-surfactant to reduce interfacial tension), Tween 80 (as surfactant to stabilize droplets), and water (as aqueous dispersion medium). These excipients were selected to enhance the solubility, stability, and permeability of canagliflozin, classified as a Biopharmaceutics Classification system Class IV compound.[7] Canagliflozin, marketed under Invokana, Invokamet, and Vokanamet, is indicated for type 2 diabetes management in combination with diet and exercise and is not recommended for type 1 diabetes. It acts by inhibiting sodium-glucose co-transporter 2 (SGLT2) in renal proximal tubules, decreasing glucose reabsorption and increasing urinary glucose excretion, thus improving glycemic control.[8] Nanoemulsion delivery systems enhance the pharmacokinetic profile of poorly soluble drugs by promoting solubility, absorption, and controlled release. This novel formulation provides improved bioavailability, mitigates adverse effects, reduces the dosing frequency, and improves compliance and outcomes.[9,10] The nanoemulsion developed in this research surmounts the limitations of conventional delivery and represents a more effective, patient-centric approach to managing T2DM.

MATERIALS AND METHODS

Materials

Canagliflozin was obtained as a gift sample from TCI, Hyderabad. Castor oil, PEG 400, Tween 80, methanol, and distilled water were sourced from National scientific laboratory suppliers and used without further purification. All excipients were of analytical grade. The selection of ingredients was based on their established roles in enhancing drug solubility, emulsification efficiency, and formulation stability. Castor oil served as the oil phase, whereas PEG 400 and Tween 80 were employed as the cosurfactant and surfactant, respectively, to facilitate nanoemulsion formation and stabilization. Methanol was utilized to dissolve Canagliflozin to ensure uniform drug distribution and distilled water was incorporated as the aqueous phase in the formulation.[11]

Preformulation studies

Preformulation studies were conducted to evaluate the physicochemical properties of Canagliflozin and assess its suitability for incorporation into a nanoemulsion formulation. Solubility tests in various solvents were performed to identify an appropriate medium for drug dissolution. Bulk density and tapped density were determined using a fixed amount of powder in a graduated cylinder, enabling the calculation of Carr's Index and Hausner's Ratio to assess the compressibility and flow properties of the powder. The angle of repose was also measured to evaluate the powder's flow behavior.[12] A calibration curve for Canagliflozin was established by preparing a primary stock solution in methanol, followed by serial dilutions to generate a range of concentrations. Absorbance measurements were recorded at 290 nm using a ultraviolet-visible (UV-Vis) spectrophotometer, and linear regression was applied to construct the calibration curve for quantitative analysis.[13,14]

Preparation of nanoemulsion

The nanoemulsion was prepared using a high-energy emulsification method to achieve a stable and uniform dispersion. A 100 mg quantity of Canagliflozin was dissolved in 10 mL of methanol to ensure homogeneous distribution. The oil phase was prepared by blending castor oil and PEG 400, while the aqueous phase consisted of Tween 80 and distilled water. The oil phase was gradually introduced into the surfactant mixture under continuous magnetic stirring, followed by the addition of the drug solution. The resulting pre-emulsion was homogenized at 10,000 rpm for 30 min using a high-speed homogenizer to reduce droplet size. Sonication was then performed for 6 min using a probe sonicator to further refine the droplet size and enhance the stability of the nanoemulsion.[15,16]

Formulation optimization

To optimize the nanoemulsion formulation, seven different batches (F1–F7) were prepared by varying the concentrations of castor oil, PEG 400, Tween 80, and distilled water while maintaining a constant amount of Canagliflozin (1 mg) and methanol (10 mL) in each formulation. The surfactant-to-co-surfactant (S: Co) ratio was adjusted in each formulation to evaluate its influence on the stability and physicochemical characteristics of the nanoemulsion.[17,18] The optimization process aimed to identify the formulation with the most suitable combination of ingredients for achieving a stable and effective nanoemulsion. The composition of the formulations is summarized in Table 1.

Characterization of nanoemulsion

Physicochemical characterization of the nanoemulsion formulations was performed to assess the particle size,

thermal behavior, and potential chemical interactions. Particle size and polydispersity index were measured using dynamic light scattering to determine droplet size distribution and uniformity.[19,20] Differential scanning calorimetry (DSC) was employed to analyze the physical state of Canagliflozin in the nanoemulsion, particularly focusing on any changes in the drug's thermal properties.[21] Fourier-transform infrared (FTIR) spectroscopy was utilized to examine any potential interactions between Canagliflozin and the excipients by comparing the characteristic functional group peaks of the pure drug and the nanoemulsion.[22,23]

RESULTS

Preformulation studies

Solubility studies revealed that Canagliflozin was highly soluble in methanol and DMSO, with methanol being the most suitable solvent for drug dissolution. The drug showed poor solubility in water and partial solubility in solvents such as acetonitrile, ethanol, and isopropanol.

The bulk density of Canagliflozin was found to be 0.237 g/cm³, indicating a relatively low value, which could affect the flowability and handling of the powder. The tapped density was measured at 0.349 g/cm³, suggesting a moderate degree of compressibility. The Carr's Index, calculated at 37.28%, indicated poor compressibility, which may present challenges in the formulation process. Similarly, the Hausner's ratio was determined to be 1.52, confirming poor compressibility and potential issues with flowability. The angle of repose was found to be between 30° and 35°, indicating moderately cohesive powder behavior that could also contribute to poor flow properties.

A calibration curve for Canagliflozin was constructed by preparing serial dilutions of the drug in methanol, with concentrations ranging from 10 µg/mL to 100 µg/mL. The absorbance of these solutions was measured at 242 nm using a UV-Vis spectrophotometer [Table 2]. Linear regression analysis of the calibration data yielded the following equation:

Absorbance = 0.021 × Concentration + 0.013, with a correlation coefficient (R^2) of 0.999, indicating excellent linearity between absorbance and concentration [Figure 1].

Characterization of nanoemulsion

Particle size analysis

Particle size analysis was conducted using a ZetaSizer to evaluate the droplet size of the Canagliflozin nanoemulsion formulations. The analysis revealed that the particle size varied across the formulations, with formulation F5 exhibiting the smallest particle size. The results indicated that homogenization had a significant impact on the particle size, with the size reduction process leading to improved uniformity in droplet distribution. The particle size distributions for each formulation are depicted in Figures 2-8 and Table 3 depicting all the formulations and its particle sizes.

DSC and FTIR analyses were conducted exclusively for formulation F5, as it exhibited the smallest particle size among all batches, indicating optimal nanoemulsion characteristics. The superior droplet size and stability suggested enhanced drug dispersion and entrapment efficiency. Therefore, F5 was selected as the representative formulation for detailed physicochemical characterization. This targeted approach ensured resource efficiency while focusing on the most promising candidate for further development.

Table 1: Composition of canagliflozin nanoemulsion formulations (F1–F7)

Ingredients	F1	F2	F3	F4	F5	F6	F7
Canagliflozin (mg)	1	1	1	1	1	1	1
Methanol (mL)	10	10	10	10	10	10	10
Castor oil (mL)	15	20	10	15	20	10	10
PEG 400 (mL)	20	20	20	25	10	30	20
Tween 80 (mL)	50	40	50	40	10	30	40
Water (mL)	15	20	20	20	60	30	30
S: Co	2.5:1	2:1	2.5:1	1.6:1	1:1	1:1	2:1

Table 2: Ultraviolet absorbance of canagliflozin

Concentration (µg/mL)	Absorbance
20	0.095
30	0.209
40	0.308
50	0.406
60	0.507

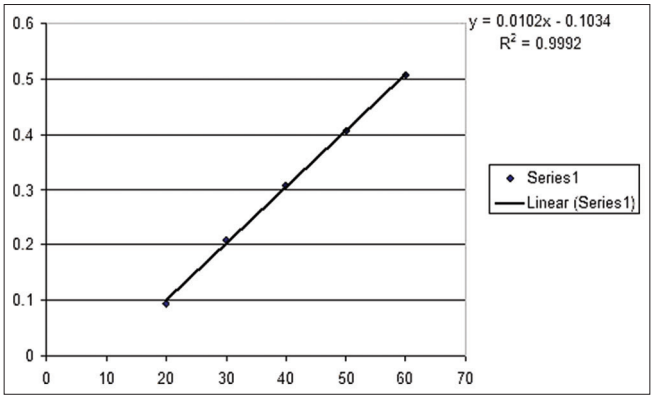

Figure 1: Linearity curve of CFZ

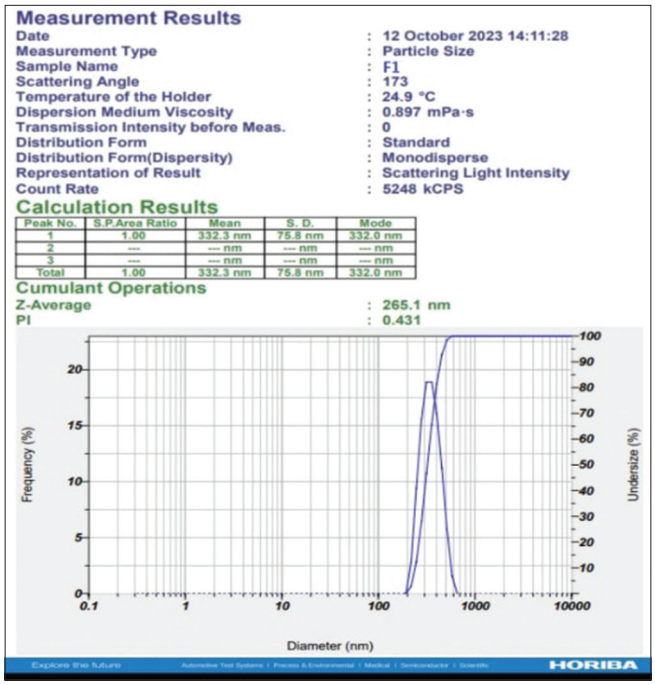

Figure 2: Particle size of F1

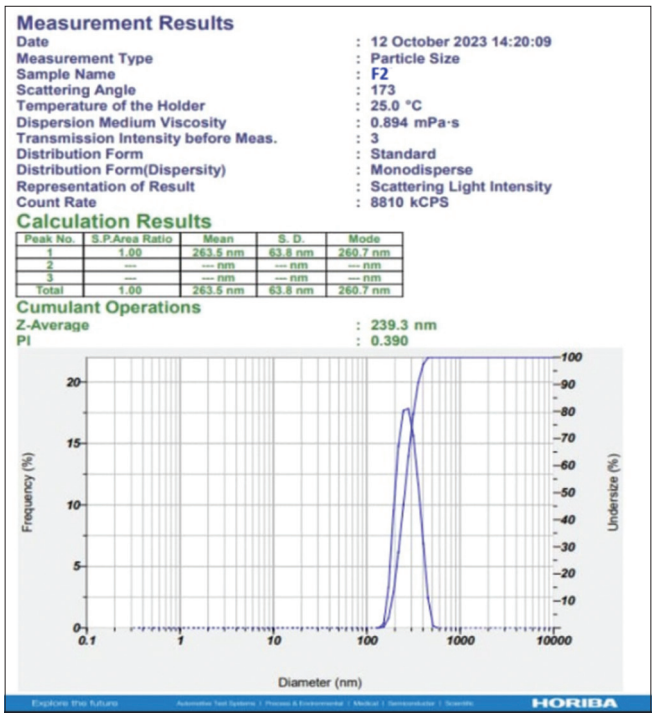

Figure 3: Particle size of F2

DSC

The thermal characteristics of Canagliflozin in the nanoemulsion were analyzed using DSC. The DSC thermogram for the nanoemulsion of Canagliflozin, represented in Figure 9, showed a broader endothermic peak at 220°C, indicating a decrease in the melting point of the drug. The observed shift in the melting temperature (Tm) suggests that the nanoemulsion formulation has

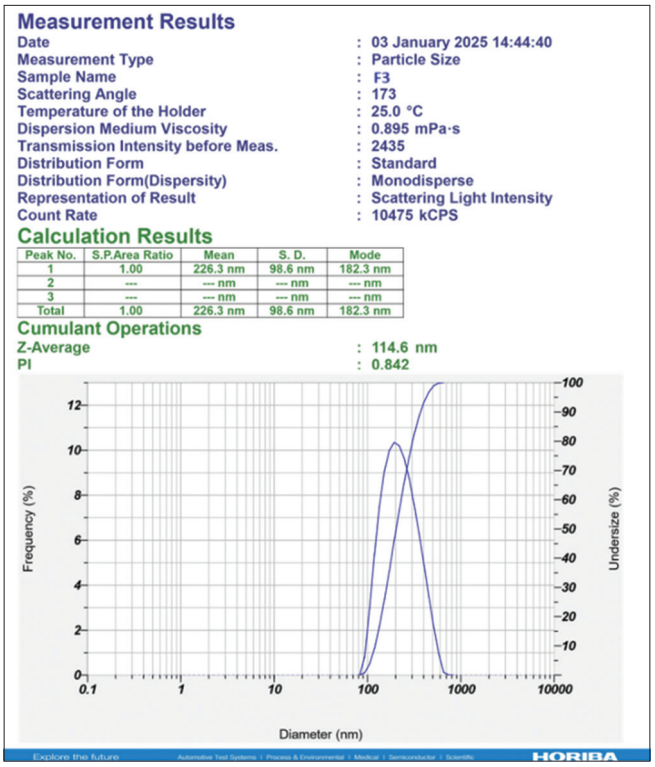

Figure 4: Particle size of F3

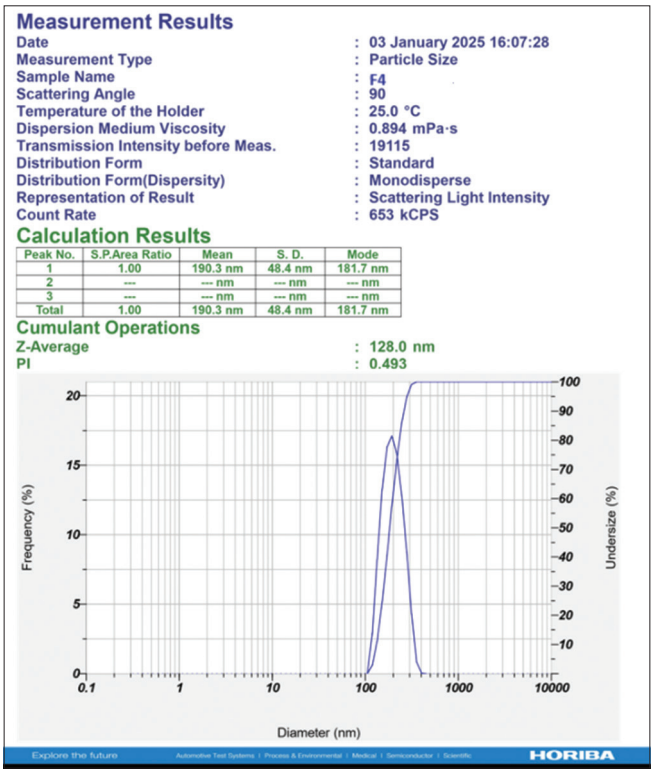

Figure 5: Particle size of F4

altered the thermal behavior of Canagliflozin. In addition, the exothermic peak seen in the pure drug was absent in the nanoemulsion formulation, further supporting the alteration of the drug's thermal properties. These results suggest that the formulation may enhance the solubility and

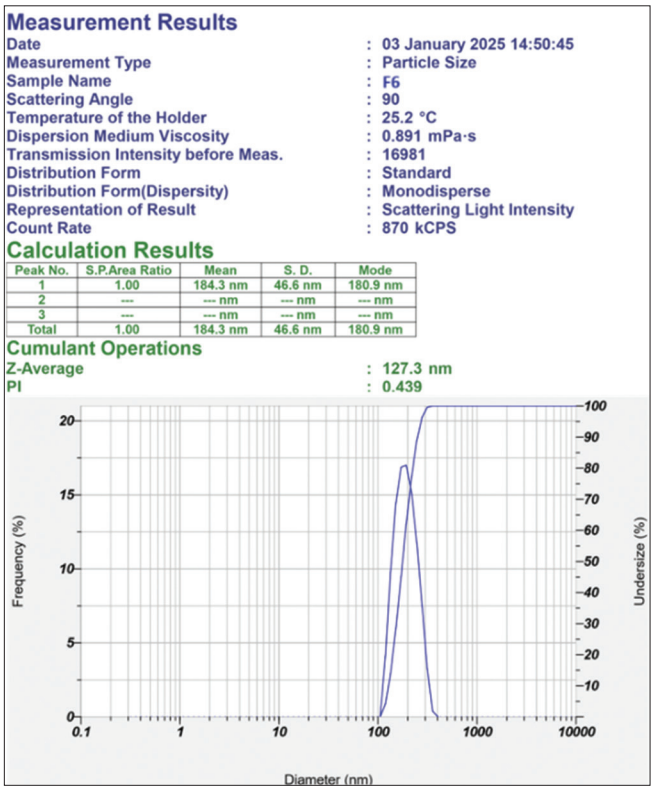

Figure 6: Particle size of F5

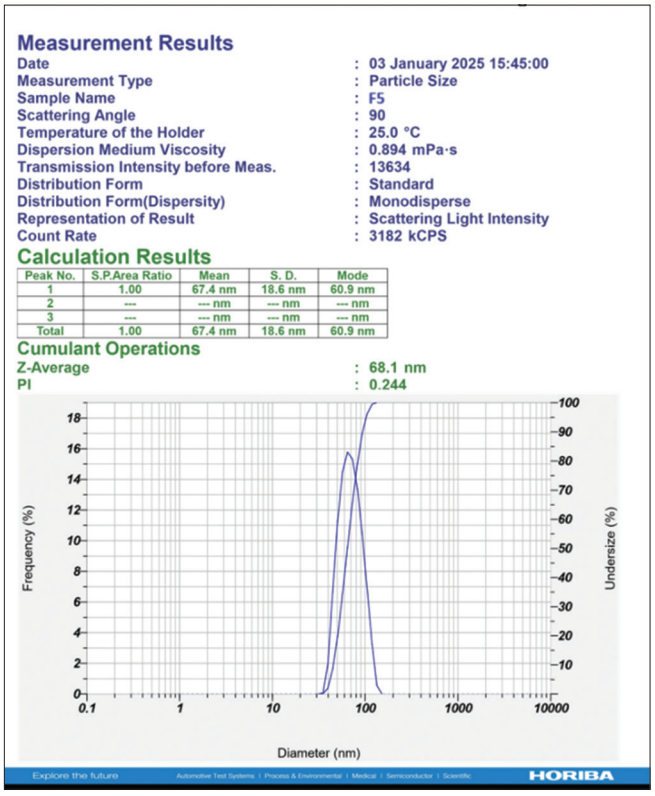

Figure 7: Particle size of F6

bioavailability of Canagliflozin by modifying its thermal behavior.

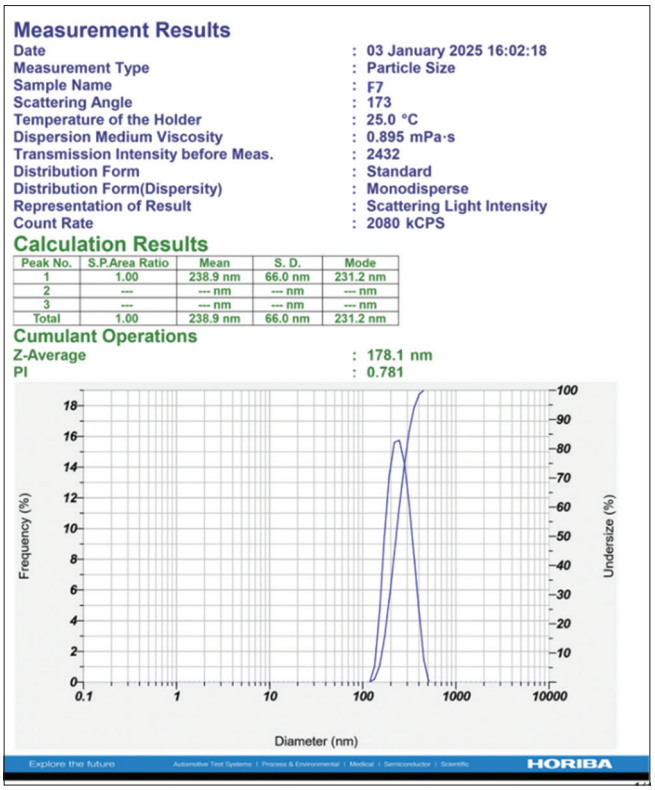

Figure 8: Particle size of F7

Table 3: Formulation and particle size

Formulation	Particle size
F1	265.1 nm
F2	239.3 nm
F3	114.6 nm
F4	128.0 nm
F5	68.1 nm
F6	127.3 nm
F7	178.1 nm

FTIR spectral analysis of pure canagliflozin and canagliflozin nanoemulsion

FTIR spectroscopy was performed to evaluate potential chemical interactions between Canagliflozin and the excipients used in the nanoemulsion formulation (F5). The FTIR spectra of pure Canagliflozin and the optimized nanoemulsion formulation are presented in Figures 10 and 11 respectively to detect any significant shifts or alterations indicative of chemical interactions. The comparative data are summarized in Table 4.

In the nanoemulsion formulation, the O–H stretching vibration exhibited a broadening and shift to a higher wavenumber range (3924.49–3282.24 cm^{-1}) compared to the pure drug (3335.90 cm^{-1}), indicating potential hydrogen bonding with excipients. The C–H stretching region showed a slight shift

from 2922.60–2857.09 cm^{-1} to 2928.03–2678.33 cm^{-1}, suggesting interaction without chemical modification. The C≡C or C≡N triple bond stretching vibrations also exhibited a marginal shift. Notably, the C=O stretching vibration peak observed at 1742.45 cm^{-1} in the pure drug shifted to 1643.08 cm^{-1} in the nanoemulsion, implying possible interaction with surfactant or co-surfactant components. The C–O and C–H bending peaks showed moderate changes in wavenumber, further supporting the possibility of physical interactions rather than chemical modifications. Overall, the FTIR results indicate that Canagliflozin remains chemically stable in the nanoemulsion, with minor spectral shifts suggestive of non-covalent interactions between the drug and formulation excipients.

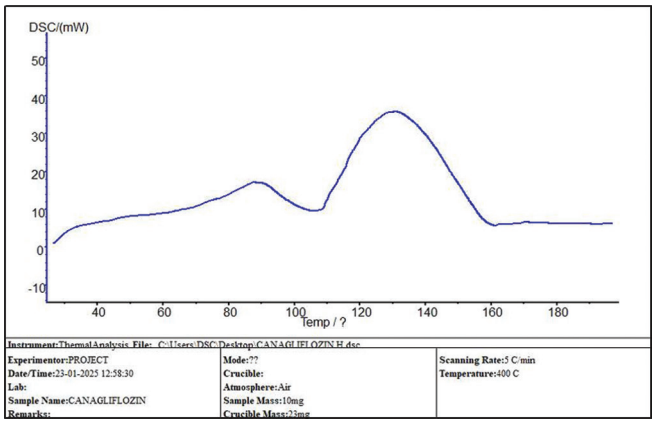

Figure 9: Differential scanning calorimetry curve of the F5 nanoemulsion

DISCUSSION

The pre-formulation studies of Canagliflozin revealed critical insights into its physicochemical characteristics, which are essential for designing an effective nanoemulsion-based delivery system. The solubility profile indicated that Canagliflozin is highly soluble in methanol and DMSO, with methanol being the most suitable solvent for drug dissolution. However, its poor aqueous solubility presents a significant challenge for oral bioavailability, underscoring the need for alternative formulation strategies such as nanoemulsions.

Powder flow and compressibility parameters including bulk density (0.237 g/cm^3), tapped density (0.349 g/cm^3), Carr's Index (37.28%), Hausner's ratio (1.52), and angle of repose (30°–35°) collectively suggest poor flowability and compressibility. These findings imply that direct compression of the drug into solid dosage forms may be problematic without the addition of suitable excipients or the use of an advanced drug delivery system.

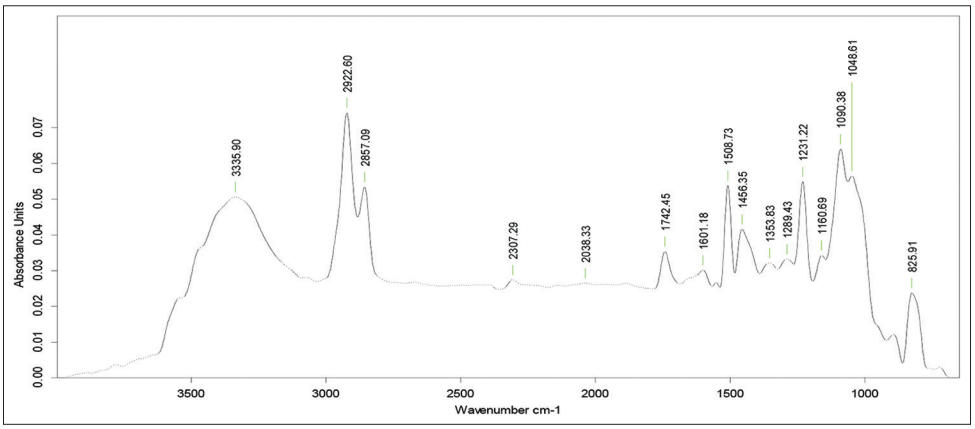

Figure 10: Fourier-transform infrared spectra of pure canagliflozin

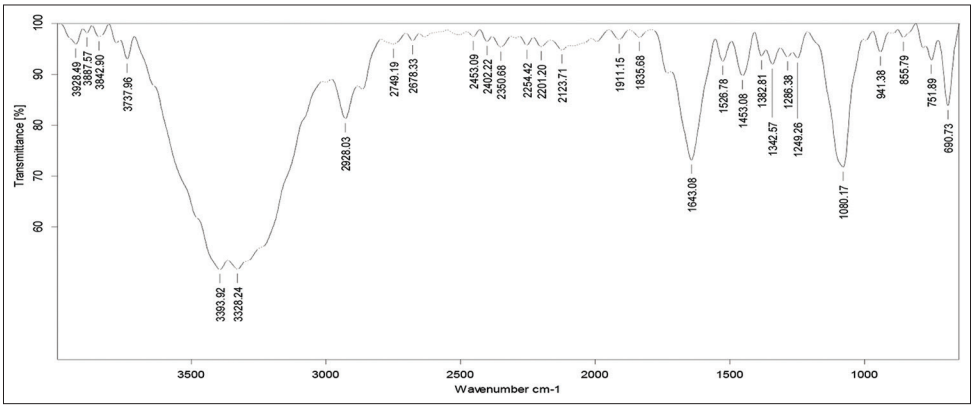

Figure 11: Fourier-transform infrared spectra of F5 nano formulation of canagliflozin

Table 4: FTIR spectral comparison of pure canagliflozin and F5 nanoemulsion formulation

Functional group	Pure drug (cm^{-1})	F5 nano formulation (cm^{-1})
O-H Stretching	3335.90	3924.49–3282.24
C-H Stretching	2922.60–2857.09	2928.03–2678.33
C≡C or C≡N Stretching	2307.29–2083.33	2453.09–2123.71
C=O Stretching	1742.45	1643.08
C-O Stretching	1601.18–1298.43	1526.78–1249.26
C-H Bending	1160.69–825.91	1090.17–690.73

FTIR: Fourier-transform infrared

The UV-Vis spectrophotometric calibration curve exhibited excellent linearity across the concentration range of 10–100 µg/mL with a correlation coefficient (R^2) of 0.999, validating the reliability of this method for quantitative analysis during formulation development.

Among the nanoemulsion formulations studied, F5 exhibited the smallest droplet size (68.1 nm), demonstrating the effectiveness of homogenization in reducing particle size and achieving uniformity. Smaller droplet size is typically associated with improved drug solubilization, enhanced absorption, and increased bioavailability due to larger surface area and better interaction with biological membranes.

DSC analysis of F5 showed a broader endothermic peak at 220°C, indicating a reduction in the melting point and a loss of the crystalline structure of Canagliflozin, likely due to encapsulation in the nanoemulsion matrix. The absence of the exothermic peak present in the pure drug further supports the hypothesis that the drug's thermal properties were altered during nanoformulation, which may contribute to improved solubility and stability.

FTIR spectral analysis revealed that the functional groups of Canagliflozin remained largely intact, with only slight shifts and broadenings in characteristic peaks. These spectral changes are indicative of physical interactions—such as hydrogen bonding—between the drug and the formulation excipients, rather than any chemical modifications. The stability of functional groups confirms the chemical integrity of Canagliflozin within the F5 nanoemulsion.

CONCLUSION

The results of the pre-formulation and characterization studies demonstrate the feasibility of a nanoemulsion-based delivery system for Canagliflozin. The selected formulation (F5) achieved optimal particle size and demonstrated favorable physicochemical properties, including altered thermal behavior and stable drug-excipient interactions. These modifications are expected to enhance the solubility and potentially improve the bioavailability of Canagliflozin.

Overall, the development of the F5 nanoemulsion represents a promising approach for overcoming the limitations associated with the poor aqueous solubility and compressibility of Canagliflozin. Future *in vivo* studies are warranted to validate the pharmacokinetic advantages and therapeutic efficacy of this optimized nanoformulation.

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