RESEARCH ARTICLE

Development and Optimization of Canagliflozin-Loaded Self-Nanoemulsifying Drug Delivery System (SNEDDS) Using Box-Behnken Design: *In-vitro* and Stability Evaluation

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ABSTRACT
The goal of this work was to improve the solubility, permeability, and therapeutic effectiveness of canagliflozin, a weakly water-soluble antidiabetic medication, by creating and refining a transdermal patch based on a self-nanoemulsifying drug delivery system (SNEDDS). Transdermal administration guarantees continuous drug release, enhances patient compliance, and avoids first-pass metabolism. Tween 20, caprylic acid, and groundnut oil were shown to be the best excipients by solubility screening. The formulation variables were optimized using a Box-Behnken design and a pseudo-ternary phase diagram. With a globule size of 142.9 nm, a PDI of 0.420, and a zeta potential of −27.0 mV, the optimized SNEDDS, which included 1.68 g groundnut oil, 0.7663 g Tween 20, and 0.1573 g caprylic acid, had good physical stability and homogeneity. FTIR, DSC, and XRD confirmed drug-excipient compatibility and the amorphous nature of the formulation. The SNEDDS was successfully incorporated into a transdermal patch and demonstrated excellent emulsification efficiency. The developed system offers a promising non-invasive platform for sustained canagliflozin delivery, potentially improving its bioavailability and clinical effectiveness in managing type 2 diabetes mellitus.
Keywords: Canagliflozin; Self-nanoemulsifying drug delivery system (SNEDDS); Transdermal patch; Box-Behnken design; Nanoemulsion; Drug permeability; Diabetes mellitus; Optimization.
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INTRODUCTION

In pharmaceutical formulation, the efficient distribution of poorly water-soluble medications remains a major difficulty, particularly for treatments meant to address chronic illnesses like type 2 diabetes mellitus. A selective sodium-glucose co-transporter 2 (SGLT2) inhibitor, canagliflozin has become well-known for treating type 2 diabetes because of its distinct mode of action, which encourages glycosuria and aids in maintaining ideal glycemic control. The medication is categorized as a Biopharmaceutics Classification System (BCS) Class II compound, which is distinguished by high permeability but limited water solubility, notwithstanding its therapeutic advantages. This poor solubility hampers its dissolution rate and, consequently, its oral bioavailability, often resulting in suboptimal therapeutic responses, increased inter-patient variability, and the need for higher doses that may increase the risk of adverse effects[1].

To overcome these challenges, innovative drug delivery strategies are required to enhance solubility, improve absorption, and ensure sustained therapeutic levels. Creating self-nanoemulsifying drug delivery systems (SNEDDS), which are isotropic blends of oils, surfactants, and co-surfactants that spontaneously create fine oil-in-water nanoemulsions when they come into contact with aqueous fluids, is one such strategy. By providing a high surface area for absorption, SNEDDS can greatly enhance the solubility and rate of dissolution of lipophilic medications, enhancing their bioavailability and therapeutic effectiveness. Moreover, SNEDDS offer the advantage of protecting drugs from enzymatic degradation and minimizing first-pass metabolism[2-4].

A further non-invasive method of administration that avoids hepatic first-pass metabolism, provides regulated and prolonged drug release, and enhances patient adherence—particularly in the treatment of chronic diseases—is provided by transdermal drug delivery systems (TDDS)[5]. The skin, being a large and accessible organ, allows for systemic delivery of drugs, particularly when the formulation is optimized to penetrate the stratum corneum barrier. Combining SNEDDS with transdermal delivery technology could therefore present a synergistic strategy to address the bioavailability issues associated with poorly soluble drugs like Canagliflozin[4,6,7].

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MATERIALS AND METHODS

Materials

A local pharmaceutical manufacturer generously gave us a complimentary sample of canagliflozin. Analytical-grade commercial vendors provided the groundnut oil, Tween 20, and caprylic acid, which were utilized without further purification. Merck (India) supplied additional excipients and solvents, such as phosphate buffer salts, methanol, and ethanol. Every chemical and reagent utilized in this investigation was of analytical quality and complied with pharmacopoeial requirements. The studies were conducted using water that had been double distilled.

Solubility Study

Using the traditional shake flask method, the solubility of canagliflozin was assessed in a variety of oils (such as groundnut, coconut, and castor oils), surfactants (such as Tween 20, Tween 80, and sodium lauryl sulfate), and co-surfactants (such as propylene glycol, polyethylene glycol, and caprylic acid). In summary, 5 mL of each excipient was mixed with an excess of canagliflozin in hermetically sealed vials. The vials were vortexed for 10 minutes and allowed to sit in a thermostatically controlled shaking incubator set at 25 ± 1°C for 72 hours. Samples were centrifuged for 10 minutes at 10,000 rpm after reaching equilibrium, and the supernatants were filtered using a 0.45 µm membrane filter. A UV-Visible spectrophotometer set at 289 nm was used to examine the filtrates after they had been suitably diluted with methanol. For additional formulation experiments, the excipients with the highest solubility—caprylic acid (6.83 ± 1.23 mg/mL), Tween 20 (7.16 ± 1.25 mg/mL), and groundnut oil (9.82 ± 1.23 mg/mL)—were chosen[8-10].

Pseudo-Ternary Phase Diagram Construction

Using caprylic acid as the co-surfactant, Tween 20 as the surfactant, and groundnut oil as the oil phase, pseudo-ternary phase diagrams were created in order to identify the self-emulsifying area. The ratios of 1:1, 1:2, 2:1, and 3:1 (w/w) were used to produce the surfactant and co-surfactant mixes (Smix). To create 36 combinations, the oil was subsequently combined with Smix in different ratios (ranging from 1:9 to 9:1). Clearness, phase separation, and emulsification behavior were visually assessed after each combination was titrated with distilled water dropwise while being gently stirred. Transparent and homogeneous mixtures were considered to belong to the nanoemulsion region. The data were plotted to identify the optimal S:CS:Oil ratios for the development of a robust SNEDDS[11].

Table 1: Percentage drug release from Drug-SNEDDS using dialysis membrane

Time (h)	Pure drug (%)	Drug-SNEDDS (%)
0	0	0
0.5	11.23 ± 4.8	28.89 ± 1.9
1	14.26 ± 5.7	47.45 ± 5.2
2	19.67 ± 4.2	66.26 ± 6.9
4	20.31 ± 5.8	81.31 ± 5.1
6	26.05 ± 6.1	89.95 ± 6.2
8	33.18 ± 6.2	99.57 ± 5.7
10	39.41 ± 3.7	
12	41.86 ± 5.6	
14	50.09 ± 4.9	
16	52.74 ± 5.4	

Table 2: Transmittance (%) of SNEDDS-Drug (Drug in SNEDDS)

Formulation	Transmittance (%)
SNEDDS-Drug	97.18 ± 3.1

Table 3: Stability Study

Drug loading (%) at 40 ± 2°C/75% ± 5% RH			
0 Days	1 month	3 months	6 months
98.22 ± 4.6	94.85 ± 3.1	91.7 ± 2.8	89.35 ± 5.1

Box-Behnken Design Optimization

Design-Expert software (Version 12, Stat-Ease Inc., USA) was used to optimize the SNEDDS formulation utilizing a three-factor, three-level Box-Behnken statistical design. Tween 20 (B: 0.3–0.9 g), caprylic acid (C: 0.1–0.4 g), and groundnut oil (A: 1.0–2.0 g) were the independent variables chosen. Three dependent responses were used to evaluate the formulation: globule size (nm) to ascertain the properties of the nanoemulsion, polydispersity index (PDI) to examine droplet size distribution, and zeta potential (mV) to evaluate physical stability. The program produced a total of 17 trial runs. ANOVA was used to evaluate the resultant data, and response surface and contour plots were created to determine the best formulation conditions and understand the impact of the independent variables[12-15].

Characterization of Optimized SNEDDS

Fourier-Transform Infrared Spectroscopy (FTIR)

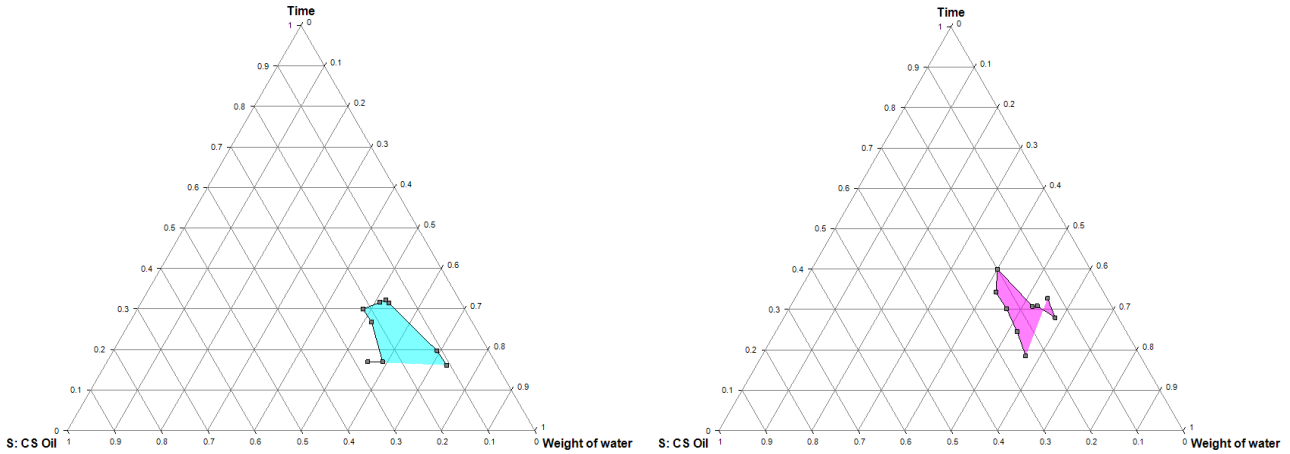

Figure 1: Ternary phase diagram data for surfactant and co-surfactant: A -3:1 B- 2:1

To assess drug-excipient interactions, FTIR analysis was carried out using an ATR-FTIR spectrophotometer (Bruker Opus 7.0, Germany). The range of 4000–400 cm^{-1} was used to examine pure canagliflozin, individual excipients, and the optimized formulation. The spectra were analyzed to look for any notable peak shifts, peak disappearances, or peak emergences that would point to a chemical interaction or incompatibility[16-18].

Differential Scanning Calorimetry (DSC)

A DSC-60 instrument (Shimadzu, USA) was used for DSC analysis in order to ascertain the thermal behaviour of canagliflozin and its formulations. Samples (2–5 mg) were placed in aluminium pans and heated in a nitrogen environment between 30 and 300 °C at a rate of 10 °C/min. To evaluate variations in melting point that could indicate a crystalline-to-amorphous transition or interaction with excipients, thermograms were examined[19].

X-ray Diffraction (XRD)

An ARL EQUINOX 100 (Thermo Scientific, India) was used for XRD analysis in order to ascertain the drug's crystallinity in the formulation. Diffractograms were captured at a scan rate of 2°/min spanning the 2θ range of 5–50°. To verify the amorphous nature of the improved SNEDDS, peak intensity and sharpness were compared between the formulation and the pure drug[20,21].

Zeta Potential and Polydispersity Index (PDI)

A Malvern Zetasizer Nano ZS (UK) was used to assess the SNEDDS's surface charge (zeta potential) and PDI. The formulation was diluted 100-fold in distilled water before analysis. Zeta potential values greater than ±20 mV indicated stable nanoemulsions, while PDI values below 0.5 reflected uniform droplet distribution[16,22].

Globule Size Analysis

Using a Horiba SZ-100 nanoparticle size analyzer, dynamic light scattering was used to measure the SNEDDS's globule size. Samples were diluted with water to appropriate concentrations before measurement. The average droplet size was expressed in nanometers, and the size distribution profile was recorded.

Partition Coefficient Determination

The partition coefficient (log P) of Canagliflozin was determined using a two-phase octanol-water system. Ten milligrams of Canagliflozin were combined with equal amounts (20 mL each) of pre-saturated octanol and water, and the mixture was agitated in a mechanical shaker at 30 ± 2 °C for a full day.

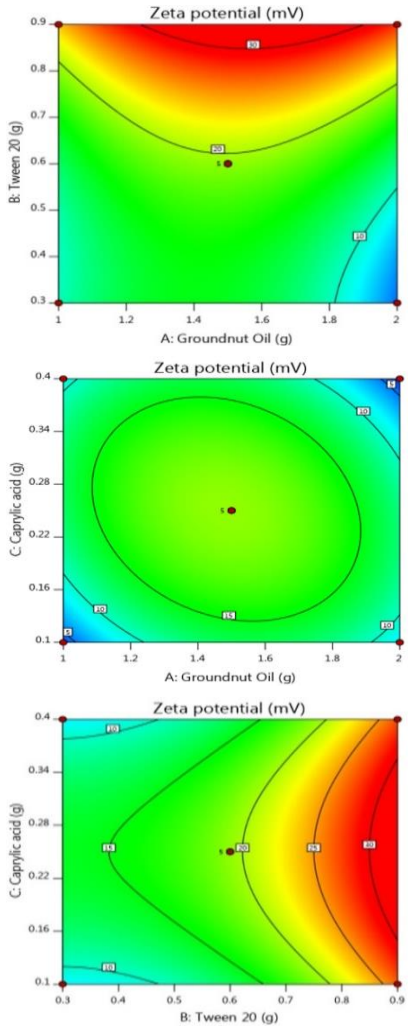

Figure 2: 2D Contour plot of Response 1(Zeta potential): Tween 20 Vs Oil; Caprylic acid Vs Oil; Caprylic acid Vs Tween 20

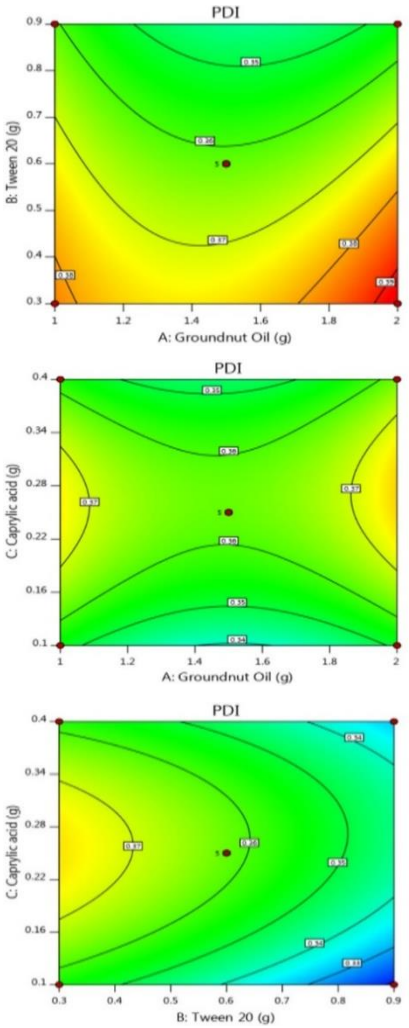

Figure 3: 2D Contour plot of Response 1(PDI): Tween 20 Vs Oil; Caprylic acid Vs Oil; Caprylic acid Vs Tween 20

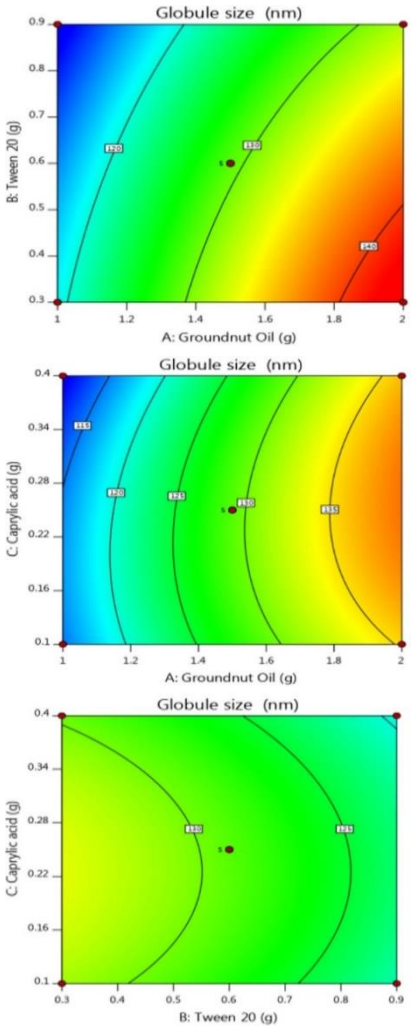

Figure 4: 2D Contour plot of Response 1(Globule size): Tween 20 Vs Oil; Caprylic acid Vs Oil; Caprylic acid Vs Tween 20

Table 4: Formulation of transdermal patch

	FSC1	FSC2	FSC3	FSC4	FSC5	FSC6	FSC7	FSC8
Optimized SNEDDS (Equivalent to 20 mg of Cana)	20	20	20	20	20	20	20	20
Chitosan (mg)	100	100	150	150	-	-	-	-
Pectin (mg)	-	-	-	-	100	100	150	150
Propylene glycol (%w/v)					2	2	2	2
Glycerol (% w/v)	2	2.5	2	2.5	-	-	-	
Tween 80 (% w/v)	1	1	-	1.0	1.5	-	2.0	2.5
Solvent (Water: Ethanol; 8 2)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 5: Evaluation parameters of the developed transdermal patch

Run / Formulation	Thickness (mm)	pH	Hygroscopicity (%)	Folding Endurance	Tensile Strength (MPa)	Mucoadhesive Strength (gF)
FSC1	0.22	4.8	2.8	217	5.69	14.57
FSC2	0.22	5.1	2.6	238	6.27	11.30
FSC3	0.21	5.2	2.5	198	5.19	12.50
FSC4	0.20	4.8	1.9	207	5.76	15.62
FSC5	0.23	5.2	2.3	187	3.98	10.31
FSC6	0.22	4.7	2.6	189	5.33	12.08
FSC7	0.21	5.2	2.8	203	4.26	9.15
FSC8	0.24	5.3	2.5	195	5.64	13.44

After equilibration, the aqueous phase was analyzed spectrophotometrically at 289 nm. The partition coefficient (P) was calculated.

Evaluation of Transdermal Patch

The patch thickness was measured using a screw gauge, and the mean ± SD was calculated. Folding endurance was tested by folding the patch repeatedly at the same point until it broke.

Tensile strength was determined using a texture analyzer. The surface pH was measured using a pH meter on the moistened patch. Hygroscopicity was calculated by measuring the weight gain after exposure to humidity. Mucoadhesive strength was evaluated using a modified balance with porcine buccal mucosa.

RESULTS AND DISCUSSION

Solubility Studies

Solubility screening of Canagliflozin in various excipients was the preliminary step in developing a SNEDDS formulation. Among the tested oils, groundnut oil exhibited the highest solubility (9.82 ± 1.23 mg/mL), followed by Tween 20 (7.16 ± 1.25 mg/mL) as a surfactant and caprylic acid (6.83 ± 1.23 mg/mL) as a co-surfactant. These excipients were selected for further formulation as they

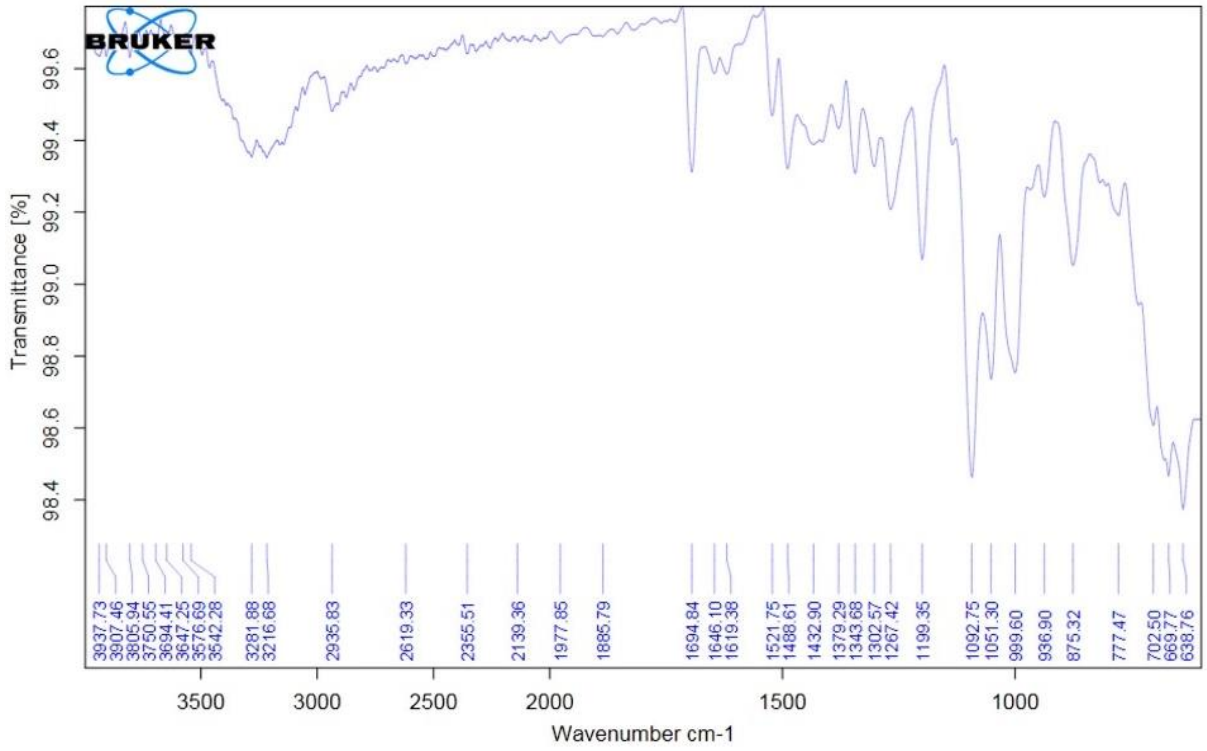

Figure 5: ATR-FTIR spectra of Canagliflozin

exhibited excellent solubilizing capacity for the lipophilic drug.

Pseudo-Ternary Phase Diagram

Pseudo-ternary phase diagrams were constructed to identify the nanoemulsion regions using various Smix ratios (1:1, 2:1, and 3:1). The diagrams revealed that higher Smix ratios (2:1 and 3:1) exhibited larger nanoemulsion zones, indicating improved emulsification capacity. In contrast, formulations with lower Smix ratios and high oil content showed cloudiness and phase separation, indicating instability. These results suggested that formulations with a higher surfactant concentration favored stable nanoemulsion formation, as in Figure 1.

Optimization using Box-Behnken Design

The quantities of groundnut oil (A), Tween 20 (B), and caprylic acid (C) were the three independent variables used in a Box-Behnken experimental design to optimize the SNEDDS. Zeta potential, globule size, and polydispersity index (PDI) were the measured responses. Significant ($P < 0.05$) polynomial correlations between the variables and responses were found by the model. 1.68 g of oil, 0.7663 g of Tween 20, and 0.1573 g of caprylic acid made up the ideal formulation shown in Figure 2,3 and 4. With a zeta potential of -27.0 mV, a PDI of 0.420, and a globule size of 142.9 nm, it demonstrated outstanding stability and homogeneous droplet dispersion. The stability of the nanoemulsion against aggregation was validated by the negative zeta potential.

Characterization Studies

FTIR Analysis

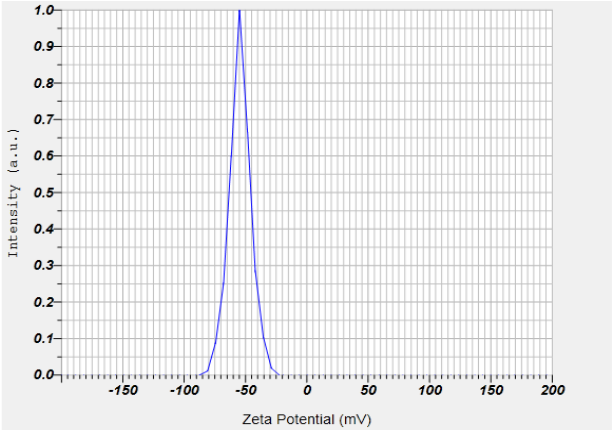

Figure 6: Zeta Potential

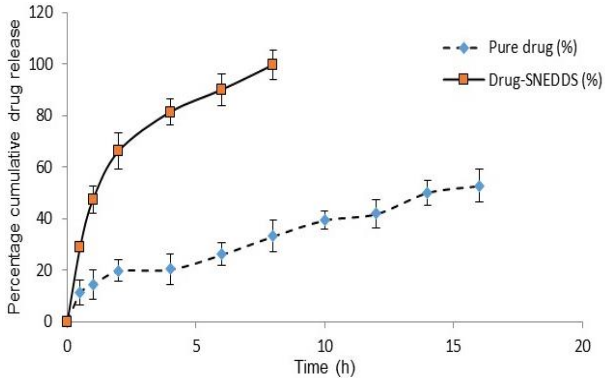

Figure 7: Percentage drug release from Drug-SNEDDS

The ATR-FTIR spectra of Canagliflozin, individual excipients, and the optimized SNEDDS formulation were recorded. No major shift or disappearance of functional peaks was observed, suggesting compatibility between the drug and excipients shown in Figure 5.

DSC and XRD Studies

Pure Canagliflozin's crystalline nature was demonstrated by the DSC thermogram, which showed a prominent endothermic peak at 214°C, corresponding to its melting point. The improved SNEDDS formulation, on the other hand, had a broad, decreased peak, indicating that the drug had changed into an amorphous form. The transformation was confirmed by XRD analysis, which showed that the improved formulation eliminated the strong crystalline peaks in the pure drug pattern.

Globule Size and PDI

The droplet size analysis showed a mean globule size of 142.9 nm with a PDI of 0.420. These values indicated that the formulation falls within the nanoscale range and has a uniform particle size distribution suitable for transdermal application.

Zeta Potential

The zeta potential of the optimized formulation was −27.0 mV, reflecting sufficient electrostatic repulsion between droplets, which helps prevent coalescence and indicates good physical stability, as in Figure 6.

Partition Coefficient

The calculated log P value of 3.5 confirmed the lipophilic nature of Canagliflozin, which is favorable for its permeation through the lipid-rich layers of the skin in transdermal drug delivery.

Entrapment Efficiency of Drug-SNEDDS

About 2 g of Drug-SNEDDS (containing 20 mg of drug) was dispersed in purified water and centrifuged for 10 min (Remi R-8C). The supernatant was filtered (0.45 µm) and analyzed using a UV spectrophotometer at 289 nm (Elico 210).

Total drug =20 mg, Drug in supernatant =6.26 mg

Drug Loading (DL) of Drug-SNEDDS

For Canagliflozin determination, 2 g of Drug-SNEDDS (20 mg drug) was diluted with ethanol in a 100 ml flask and shaken to ensure solubility. A UV spectrophotometer was used to produce, dilute, and measure the absorbance of three separate samples at 289 nm. The calibration curve was used to calculate the drug content.

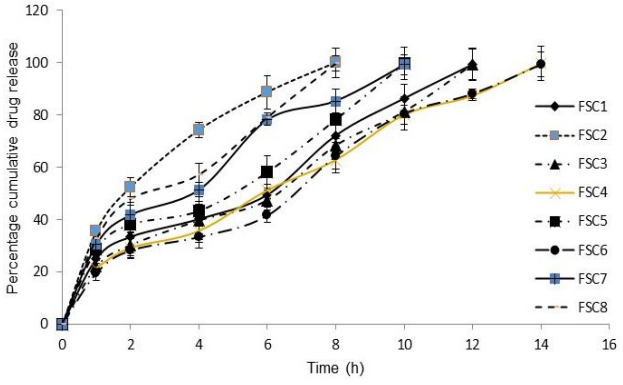

Figure 8: The figure shows *the In-vitro* percentage drug release from patches prepared from Optimized SNEDDS

Table 6: *In-vitro* percentage drug release from patches prepared for Optimized SNEDDS

Time (h)	FSC1	FSC2	FSC3	FSC4	FSC5	FSC6	FSC7	FSC8
0	0	0	0	0	0	0	0	0
1	25.17 ± 4.7	35.61 ± 1.1	22.11 ± 2.1	21.33 ± 2.1	28.66 ± 1.7	19.64 ± 2.8	30.61 ± 3.1	32.69 ± 1.8
2	33.47 ± 6.1	52.42 ± 3.7	30.25 ± 4.7	29.06 ± 3.8	38.18 ± 2.8	28.27 ± 1.9	41.82 ± 4.6	48.01 ± 2.6
4	40.28 ± 5.7	74.26 ± 2.8	39.69 ± 7.2	35.54 ± 4.2	43.39 ± 5.3	33.44 ± 4.3	51.44 ± 2.8	57.25 ± 4.3
6	49.55 ± 3.8	88.74 ± 6.3	47.42 ± 3.8	51.16 ± 5.1	58.27 ± 6.2	41.69 ± 2.9	78.15 ± 1.9	79.16 ± 1.8
8	72.21 ± 4.2	99.98 ± 5.7	68.34 ± 2.6	62.77 ± 4.8	78.41 ± 1.7	64.41 ± 5.2	85.37 ± 4.4	99.73 ± 2.9
10	86.37 ± 5.5		81.21 ± 4.9	80.05 ± 3.6	99.73 ± 6.3	80.64 ± 6.3	99.22 ± 3.7	
12	99.36 ± 6.2		99.25 ± 5.8	87.42 ± 1.9		88.25 ± 1.8		
14				99.74 ± 6.6		99.47 ± 4.7		

$$DL = \frac{Practical\ amount\ of\ drug}{Theoretical\ amount\ of\ drug}\ x\ 100$$

$$DL = 19.4/20\ x\ 100 = 97.00\ \%$$

Dissolution Study of Drug-SNEDDS

A 12 kDa dialysis membrane was dissolved in 200 mL of medium (0.1 N HCl for 1 hour, followed by pH 6.8 buffer) at 37°C. The bag containing 20 mg of SNEDDS was shaken at 50 rpm. To calculate cumulative drug release, 2 mL samples were periodically taken out, replaced with new medium, filtered, diluted, and measured at 289 nm Shown in Table 1 and Figure 7.

On a hot plate with a thermostat, optimized drug-SNEDDS was heated from 25°C to 80°C at a rate of 2°C per minute after being diluted 100 times with deionized water. The cloud point was defined as the temperature at which cloudiness first arose. The experiment was repeated for repeatability when the cloud point was determined to be 43°C.

Percentage Transmittance

100 mL of distilled water was used to dilute 2 g of SNEDDS-Drug, which was then filtered and further diluted. The transmittance was measured with a UV-visible spectrophotometer at 289 nm. The percentage transmittance of the sample was 97.18 ± 3.1%, indicating good optical clarity and confirming the absence of drug microprecipitation upon dilution Shown in Table 1.

Centrifugation Study

The formulation was centrifuged at 5000 rpm for 30 minutes. Visual examination showed sedimentation at the bottom of the test tube, indicating instability in the formulation.

Thermodynamic Stability (Heating and Cooling) Study

The formulations were subjected to six heating and cooling cycles at 4 to 40 °C for at least 48 h. The formulations were analyzed for phase separation, creaming, and cracking.

Thermodynamic Study of SNEDDS-Drug

Plain drug loaded in SNEDDS showed no significant changes in the first two cycles. However, from the third cycle onward, cloud formation occurred, indicating phase separation due to temperature variation.

Stability Study

The formulation was stored at accelerated conditions (40°C ± 2°C/75% ± 5% RH) for up to 6 months. No phase separation was observed. Drug loading was determined by UV spectrophotometry, showing minimal changes over time Shown in Table 3.

Formulation of Transdermal Patch with Optimized SNEDDS

Dissolve chitosan in 1% acetic acid and stir until clear. Add glycerol or propylene glycol as a plasticizer, followed by Tween 80 as a permeation enhancer. Incorporate the plant extract (dissolved in ethanol) into the polymer solution and stir until uniform. Pour the solution onto a Petri dish, spread evenly, and allow it to dry for 24-48 hours. Once dry, peel off the patch, cut it to the desired size, and proceed with further evaluation, as in Table 4.

Evaluation of Transdermal Patches

Chitosan-based patches (FSC1–FSC4) exhibited uniform thickness (0.20–0.24 mm), while pectin-based patches (FSC5–FSC8) were slightly thicker, with plasticizers having minimal impact. The pH ranged from 4.7 to 5.3, near skin pH, with chitosan patches being slightly more acidic. Hygroscopicity was comparable for both types (1.9–2.8%), supporting flexibility. Folding endurance was higher in chitosan patches (198–238 folds), indicating better flexibility, slightly enhanced by plasticizers. Tensile strength was superior in chitosan patches (up to 6.27 MPa), while pectin patches were lower (~3.98 MPa). Mucoadhesive strength was also better in chitosan formulations (9.15–15.62 gF). *In-vitro* drug release was evaluated via a Franz diffusion cell using phosphate buffer (pH 6.8) at 37 °C, with measurements taken at 289 nm Shown in Table 5.

In-vitro Drug Release Summary

FSC2 showed the highest drug release (35.61% at 1 hr; 99.98% at 8 hrs; 99.74% at 14 hrs), followed by FSC8 and FSC7. FSC5 and FSC3 had slower release rates. Faster release in FSC2 and FSC8 is attributed to optimized levels of Tween 80 and pectin, which enhance permeability. In contrast, chitosan-based formulations like FSC1 and FSC3 exhibited slower diffusion. Plasticizers had minimal impact on drug release but improved flexibility. Overall, FSC2 and FSC8 were optimal for sustained and efficient drug delivery Shown in Table 6.

CONCLUSION

This study developed and optimized a SNEDDS-based transdermal patch of Canagliflozin to overcome its poor solubility and bioavailability. The optimized formulation showed nanoscale globule size, good stability, and drug–excipient compatibility. Transdermal patches exhibited suitable mechanical properties, near-skin pH, and sustained drug release, with FSC2 and FSC8 showing the best performance. Overall, SNEDDS-based transdermal delivery offers a promising non-invasive strategy to enhance the therapeutic efficacy of canagliflozin in type 2

diabetes management. The system ensures improved patient compliance by avoiding first-pass metabolism and providing controlled drug release. Future *In vivo* studies and clinical evaluations are essential to confirm the long-term safety, efficacy, and patient acceptability of this novel delivery approach.

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