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Formulation and Evaluation of Canagliflozin Self-nanomicellizing Solid Dispersion Based on Rebaudioside A for Dissolution and Solubility Improvement

Nizar Awish Jassem[1] and Shaimaa Nazar Abd Alhammid [*, 2]

[1] Department of pharmaceutics, College of Pharmacy, Al-Farahidi University, Baghdad, Iraq.
[2] Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq
***Corresponding Author.**
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Abstract.

Self-nanomicellizing solid dispersion is a new formulation that combines the advantages of solid dispersion and nanomicelles strategies to increase drug oral bioavailability. The strategy involves utilizing a suitable carrier to create a solid dispersion that could self-assemble into nanomicelles when it comes into contact with gastrointestinal fluids. Rebaudioside A is a steviol glycoside reported to possess nanocarrier-like characteristics by being self-assembled into nanomicelles in aqueous solutions. Canagliflozin is a novel sodium-glucose cotransporter-2 inhibitor approved for treating patients with type 2 diabetes. Its oral administration is associated with variable and poor absorption, owing primarily to insolubility in aqueous media. This work aimed to develop canagliflozin self-nanomicellizing solid dispersion systems to overcome its pharmaceutical limitation and potentially improve oral bioavailability. The solvent evaporation method was selected to prepare a self-nanomicellizing solid dispersion system of canagliflozin. Rebaudioside A was chosen as a nanocarrier after screening several polymers for their ability to improve the solubility of canagliflozin by phase solubility study. The optimized formula containing a 1:4 drug to Rebaudioside A was characterized by solid-state analysis, dissolution studies, particle size distribution, and transmission electron microscopy. The study demonstrated that the self-nanomicellizing solid dispersion of canagliflozin, based on Rebaudioside A (FR5), had spherical particle with size of 69.7 nm, stable distribution upon 20-fold dilution, and improved aqueous solubility by over 753.5-fold due to nanomicellization. Moreover, there is a significant enhancement of dissolution rate compared with the physical mixture (PM) and pure drug, as indicated by higher values of the difference factor (f_1) and lower values of similarity factor (f_2), which are obtained. The optimized formula of canagliflozin self-nanomicellizing solid dispersion (FR5) dissolved well after 30 minutes and demonstrated higher dissolution efficiency (DE) than the intact canagliflozin and physical mixture. The DE% parameter confirms these findings (DE_{30}, FR5 = 70.34%, DE_{30}, PM = 21.91%, and DE_{30}, pure drug = 18.28%. Fourier transform infrared spectroscopy revealed mild interactions between the drug and the excipient due to hydrogen bonding, favoring the formation of a stable solid dispersion system with negligible chemical interactions. The study indicated that optimized canagliflozin self-nanomicellizing solid dispersion systems using Rebaudioside A is a promising method for improving oral bioavailability.

Keywords: Amphiphilic, Canagliflozin, Nano micelles, Phase solubility, Rebaudioside

Introduction

Self-nanomicellizing solid dispersion SNMSD has become a viable approach to address the issues of low bioavailability and poor dissolution. Typically, SNMSDs are composed of the active pharmaceutical ingredient and a carrier. Selecting the appropriate carrier is crucial to achieving optimal drug release and therapeutic outcomes. Natural nanomaterials are safe for drug delivery systems because of their low toxicity and ability to come from various sources [(1,2)].

Rebaudioside A (RA) is a popular sweetener that is 240 times sweeter than sugar. However , because RA also possesses biological activities such as antihyperlipidemic, anti-lipid peroxidative, and antioxidant qualities, its uses go beyond those of a sugar substitute and sweetener. RA is composed of diterpenes with a steviol backbone and mono- and trisaccharide carbohydrate residues at C13 and C19. Figure 1A shows the chemical structure of Rebaudioside A [(3)].

RA can form micelles in aqueous solutions because of the combination of hydrophilic sugar side chain and hydrophobic diterpene in its structure. Therefore, RA is promising in clinical interest due to its importance in nanotechnology.

Li, Q. et al. (2022) studied the formulation of a novel SNMSD of Empagliflozin (EMP) with RA as the nanocarrier.

RA-EMP was fabricated to address the limitations of EMP's water-solubility and low bioavailability in treating acute pancreatitis (AP). RA-EMP improved EMP's oral bioavailability and therapeutic efficacy, demonstrating its potential for improved treatment [4].

When RA self-assembles into micelles in aqueous solutions, it creates a nanocarrier system that encapsulates hydrophobic drugs, enhancing solubility and bioavailability [5,6].

Canagliflozin CFZ is a novel Sodium-glucose cotransporter-2 inhibitor that reduces glucose reabsorption and increases urinary glucose excretion. It was initially approved by the FDA in 2013 for the management of type 2 diabetes patients and later approved in 2018 for the second indication, which is reducing the risk of cardiovascular disease in patients having type 2 diabetes mellitus. CFZ is soluble in many organic solvents (methanol, ethanol, Dimethyl sulfoxide) but is practically insoluble in aqueous media from pH 1.1 to 12. Pharmaceutically, CFZ oral administration is associated with variable and poor absorption, owing primarily to insolubility in aqueous media and a low intrinsic dissolution rate. The chemical structure of canagliflozin is shown in Figure 1 B [7,8].

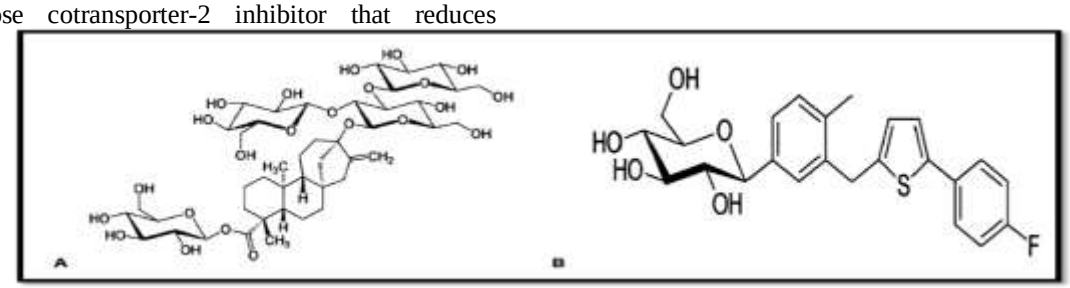


Figure 1. Chemical structure of A- Rebaudioside A B- Canagliflozin

Several attempts to increase the bioavailability of CFZ have been published, one of these introduced by Lotfy et al., 2022 who developed an amphiphilic self-assembly into nanostructured liquid crystals for CFZ transdermal delivery to improve its therapeutic efficiency. Results indicate that Poloxamer was superior for stabilizing and maximizing the formulations [9].

Another attempt conducted by Fathy E et al. 2023 is the development of CFZ nanocrystals sublingual tablets using sodium caprate as a wetting agent and permeability enhancer using the sono-homo-assisted precipitation ion technique. The optimized formula using PVP-K30 demonstrated the smallest particle and later created into a sublingual tablet containing Pharma Burst-V® that had a quicker disintegration time (51s). The results imply that CFZ nanocrystal-sublingual tablets can effectively treat diabetes [10].

Improvement in the solubility and dissolution of CFZ is the primary area of focus in improving oral bioavailability. Therefore, SNMSD of CFZ can play a crucial role in overcoming the solubility challenges of the drug. This study aimed to explore CFZ formulation based on a SNMSD strategy to improve solubility and dissolution rate. The selection of polymer based on solubility and miscibility study of CFZ using natural and synthetic polymers.

Materials and Methods

Materials

Canagliflozin was purchased from Wuhan Senwayer Century Chemical. Co. Ltd, China. Rebaudioside A from Hangzhou, Hyperchem, China; Sodium lauryl sulfate (SLS) was purchased from Sd Fine-Chem Limited Mumbai, India; Ethanol 99 % (HPLC grade) was purchased from Merck, USA; Poloxamer ٤٠٧ purchased from SIGMA, Germany; and Polyethylene glycol 8000 (PEG 8000) from Glentham, UK. All other reagents in this research were of analytical grade**.**

Phase solubility StudyTo select an appropriate carrier for preparing SNMSD, the apparent solubility of CFZ in polymer solutions was assessed using a proven method established by Higuchi and Connors.

An excess CFZ was added to the aqueous solutions of RA, poloxamer 407, and PEG 8000 at a polymer concentration of 2, 4,6, 8, and 10 mg/ml. The tubes were sealed and shaken for 48 hours at 75 rpm at 25±0.5 ºC in a thermostatically controlled water bath; the obtained dispersion was centrifuged for 10 minutes at 5000 rpm; the resultant supernatants were then filtered, appropriately diluted, and analyzed at 290 nm using a UV-vis spectrophotometer to determine the CFZ content [11].

Preparation of self-nanomicellizing solid dispersions SNMSD of CFZ were prepared in different drug-to-carrier ratios (1:2,1:3, 1:4,1:5,1:6,1:7 and 1:9) by a solvent evaporation method, ethanol as a solvent and rotary evaporator device. Briefly, the amounts of selected carriers from the phase solubility study and CFZ were dissolved in 10 ml of ethanol in a 100 ml round-bottom flask in a bath sonicator at 25±0.5 º C for 10 minutes. The ethanol was evaporated at 40 °C under reduced pressure in a rotary evaporator (BUCHI, Turkey) revolving at 220 rpm until a thin, dry film formed on the flask's inner wall. The film was crushed by a spatula and collected, making every

effort to prevent loss. It was then screened through sieve number 80 to obtain a solid system and stored until subsequent analysis ([12]). The contents of the formulations are shown in Table 1.

Table 1. Composition of Canagliflozin Self-Nanomicellizing Solid Dispersions

Substance	FR1	FR2	FR3	FR4	FR5	FR6	FR7
Drug: carrier ratio	1:2	1:3	1:4	1:5	1:6	1:7	1:9
Canagliflozin (mg)	100	100	100	100	100	100	100
Rebaudioside A	200	300	400	500	600	700	900
Ethanol (ml)	10	10	10	10	10	10	10

Drug content and percentage yield (PY %)

The drug content of CFZ was determined by dissolving 10 mg of accurately weighed solid dispersion systems in 10 ml ethanol using a 10 ml volumetric flask, followed by sonication for 15 min. The solutions were filtered by a 0.45 µm syringe filter and diluted appropriately, and then the concentration of the samples was measured spectrophotometrically at 290 nm ([13]).

The percentage of drug content in the obtained solid dispersion was determined by using Equation 1

$$\textbf{drug content}\ \% = \frac{\textbf{actual weight of canagliflozin}}{\textbf{theoretical weight of canagliflozin}} * \mathbf{100} \quad \ldots\ldots \quad \textbf{Eq (1)}$$

The practical percentage yield (PY%) was calculated by dividing the actual mass of the SNMSD formula obtained by the theoretical mass of the same formula using Equation 2 below ([14]).

$$\%\ \textbf{yield} = \frac{\textbf{Practical Weight of SD.}}{\textbf{Theoretical Weight of SD}}\ \mathbf{x\ 100} \quad \ldots\ldots \quad \textbf{Eq (2)}$$

Determination of particle size, polydispersity index, and zeta potential

Amounts of solid dispersion equivalent to 10 mg of CFZ were dispersed in 20 mL of deionized water and stirred at 300 rpm with a magnetic stirrer for one hour and then analyzed for particle size (PS) and polydispersity index (PDI) by using a Malvern Panalytical Ltd Zetasizer. The particle size stability of the CFZ-SNMSD formulas to potential dilution with the GIT fluid, which usually occurs after oral administration, was assessed by evaluating the PS and PDI of the CFZ-SNMSD dispersion diluted with water in a ratio of 1:20 of the original volume of formula ([15]). Zeta potential ZP determined for stable formulas after dilution by 1:20

Differential scanning calorimetry (DSC)

The thermal behavior of pure CFZ samples and optimized SNMSD formula were studied using a differential scanning calorimeter (DSC 60, Shimadzu, Japan). The samples of canagliflozin and optimized formulations were heated to temperatures ranging from 10° to 300° C at 10° C min^{-1} in a nitrogen atmosphere at a flow rate of about 100 ml min^{-1}. As a reference, an empty aluminum pan was used ([16]).

X-ray diffraction (XRD)

The purpose of the X-ray diffraction study was to describe the physical structure of CFZ in its pure state, physical mixture PM, and samples of optimized SNMSD. The X-ray diffractometer recorded the XRD pattern. Samples were scanned using diffraction angles (2θ) between 4° to 40° at 0.01° sampling width at the scanning speed of 4° per minute. The operational parameters were as follows: generator tension of 45 kV, generator current of 40 mA, scan time of 9 $s^{-1,}$ and scan speed of 0.008 ([17]).

Drug- excipients compatibility study

Fourier-Transform Infrared Spectroscopy (FTIR) was carried out for CFZ, PM, and optimized SNMSD formula using an FTIR spectrophotometer (Shimadzu Europe FTIR- 8400S). The spectra were generated using the KBr pellet method. The sample was mixed with dry KBr, and the spectra were scanned over a wave number range of 4,000–200 cm^{-1} using a resolution of 4 cm^{-1} ([18]).

Morphological studies

The morphological features of the optimized formula were determined by Transmission electron microscopy TEM (Tecnai 12, Philips Company, Holland). One drop of the nanomicellar solution was placed onto a copper grid. Then, 5 µl of 2 % (w/v) phosphotungstic acid was added for 60 s, and 5 µl of deionized water was added for 60 s. The samples were dried and observed at an acceleration voltage of 120 kV ([19]).

In-vitro dissolution rate studies

The dissolution for CFZ was performed using USP dissolution apparatus II. The paddle speed has been set to 75 rpm. The dissolution medium is 900 ml of freshly prepared 0.75% w/v SLS solution in distilled water maintained at 37 ±0.5 °C. Dissolution studies were carried out with 100 mg of pure drug, an equivalent amount of selected optimized SNMSD, and a PM. Before dissolution studies, each formulation of solid dispersion (equivalent to 100 mg CFZ) was filled in a size "000" hard gelatin capsule. A sinker was attached to each capsule to prevent it from floating ([20]).

Five mL samples were withdrawn at 5, 10, 15, 20, 30, 45, 60,90, and 120-minute intervals and replaced with fresh media to keep the volume and sink conditions constant. The samples were filtered with syringe filters and analyzed spectrophotometrically at 290 nm. Dissolution tests were performed in triplicate ([21]).

The dissolution profiles of pure CFZ and optimized SNMSD formula will be compared using a model-independent, mathematical approach proposed by Moore and Flanner and recommended in guidelines for the industry for dissolution testing of immediate-release solid oral dosage form. This

method calculates the difference factor (f_1) and similarity factor (f_2) between two dissolution profiles, as shown by equations 3 and 4 [22].

$$f_1 = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} * 100 \qquad \text{Eq (3)}$$

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{j=1}^{n} (R_j - T_j)^2\right]^{-0.5} * 100\right\} \qquad \text{Eq (4)}$$

Where *n* is the number of sample points, T and R are the percentages dissolved of the test and product reference at each time point j, respectively. The two dissolution profiles are similar if the values of f1 are between 0 and 15 and the values of f2 are greater than 50.

Dissolution efficiency (DE) is another parameter for evaluating in vitro dissolution data. The DE (%) was calculated as the area under the dissolution curve (AUC, y) up to time *t* compared to the area of the rectangle described as 100% dissolution at the same time, as expressed by equation 5 [23].

$$DE\% = \left(\frac{\int_0^t y * dt}{y_t^{100}}\right) \times 100 \qquad \text{……. Eq (5)}$$

, where y represents the y–axis in the dissolution test

Statistical analysis

The Student's t-test was used to analyze the data, presented as mean ± standard deviation (sd). The difference is considered significant at $p < 0.05$ and very significant at $p < 0.01$ [24,25]**.**

Results and Discussion

Selection of a suitable Polymer for canagliflozin SNMSD based on phase solubility study

A critical step in improving the biopharmaceutical properties of poorly water-soluble drugs in the SNMSD system is the selection of appropriate carriers. Several carriers, including PEG 8000 and poloxamer 407, were chosen in the phase solubility study for their ability to overcome the challenges of developing an oral delivery system. In addition, the natural polymer Rebaudioside A was investigated due to its demonstrated ability to improve the solubility and dissolution of several drugs [26].

The equilibrium aqueous solubility of CFZ in water at 25±0.5 ° C was 36.2 µg/ml. As shown in Figure 2, the phase solubility of canagliflozin was evaluated in distilled water in the presence of pre-dissolved polymers (Rebaudioside A, PEG 8000, and poloxamer 407) with varying concentrations ranging from 2-10mg/ml. When the concentration of polymers (w/v) increased, RA exhibited a significantly higher phase solubility of CFZ (p<0.05)

In the presence of 10 mg/mL pre-dissolved polymer, RA showed 102.9-fold improvement in the aqueous solubility of CFZ, whereas with the same concentration of PEG 8000, and Poloxamer 407 solutions presented 5.5 -, and 30.6-fold enhancement, respectively. The solubility enhancement of CFZ with RA is statistically more significant than that of other polymers, which justified the selection of RA for the development of SNMSD of CFZ. There are several reasons based on the literature and experiments that might explain its superior performance over other carriers due to its nanocarrier characteristics that allow it to self-assemble into micelles in an aqueous solution; this property of RA enables the formation of SNMSD, which has high stability and high drug encapsulating capacity. If desired, the fabrication and preparation protocol is also easily adaptable to large-scale preparation [25].

Drug content and percentage yield (PY %)

The content of CFZ in SNMSD formulations was measured by standard calibration curves of ethanol. The results indicate excellent homogenous distribution and effective formulation of the dispersion system with a high percentage of drug contents. The percent drug content in SNMSD based on RA formulation was from 96% ±2.4 to 99 % ±0.8, as shown in Table 2. A high percentage yield was obtained from 89.88 to 96.91% (Table 2). This result indicated that this method was suitable and efficient when using RA as a carrier. These observations suggested that the preparation process resulted in minimal loss of CFZ with uniform dispersion within SNMSD formulas.

Particle size, polydispersity index, and zeta potential study

Particle size analysis of the SNMSD during dissolution in water was analyzed using a zeta sizer, and the results of PS distribution and PDI are shown in Table 3. The results showed that at a low RA ratio (1:2), a larger PS was obtained (1368 nm); with increasing RA ratio, the PS decreased, and homogenous dispersion was obtained, and the best results were at drug: Rebaudioside A ratio 1:6 give a PS of 69.76 nm and PDI be = 0.048, indicating good formulation stability upon dilution in GIT. Figure 3 represents the particle size of the smallest formula FR5 by Malvern zeta seizer. The drug-to-carrier ratio could contribute to amorphization and maintain a supersaturated state, thus dramatically improving solubility. The optimum amount of carrier could also reduce the particle size of undissolved drug crystals to enhance the saturation solubility [27].

Also, the results showed that only formulations with the drug: carrier ratio of 1:6 and 1:7 retained their PS within the nanoscale after 20-fold dilution with water. In contrast, the others increase in PS and PDI. It was apparent from the

obtained data after dilution that the PDI values were less than 0.3 in the stable formulations; this indicates a homogenous particle size distribution in these formulas [28]. Zeta potential is the primary parameter that defines the physical stability of the dispersion; it is determined for stable formulas after dilution 1:20 with water (FR5 and FR6). The ZP value was –11.74 mV for formula FR5 and -30.1 mV for formula FR6. Figure 4 represents the ZP distribution and intensity of the optimum formula FR5.

Selection of the optimum CFZ-SNMSD formula according to the in vitro evaluation studies (PS, PDI, drug content, and % yield and stability upon 20-fold dilution), according to the above results, the best SNMSD formula chosen is FR5. This formulation will be further investigated**.**

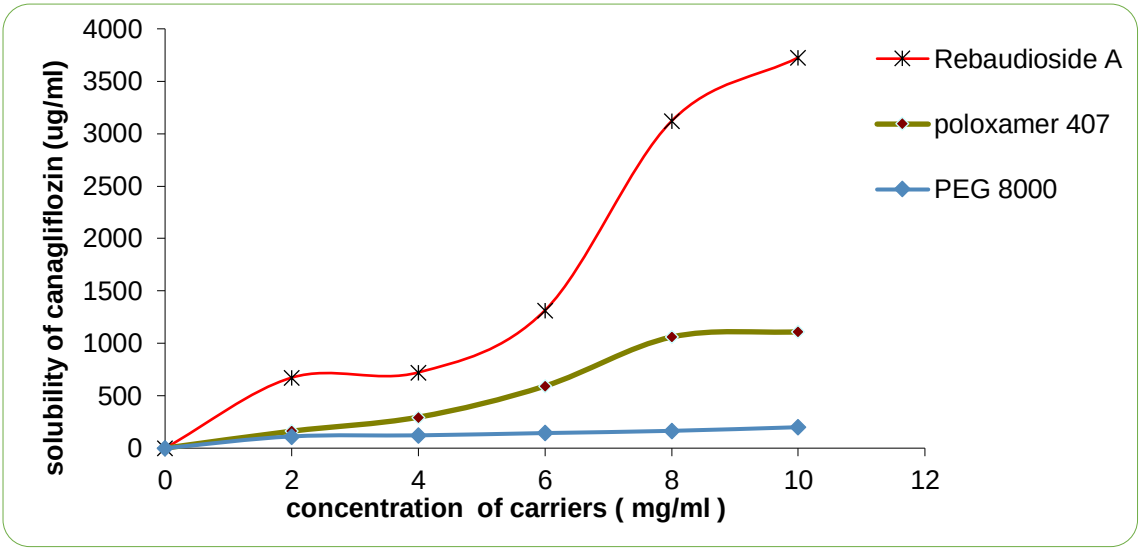


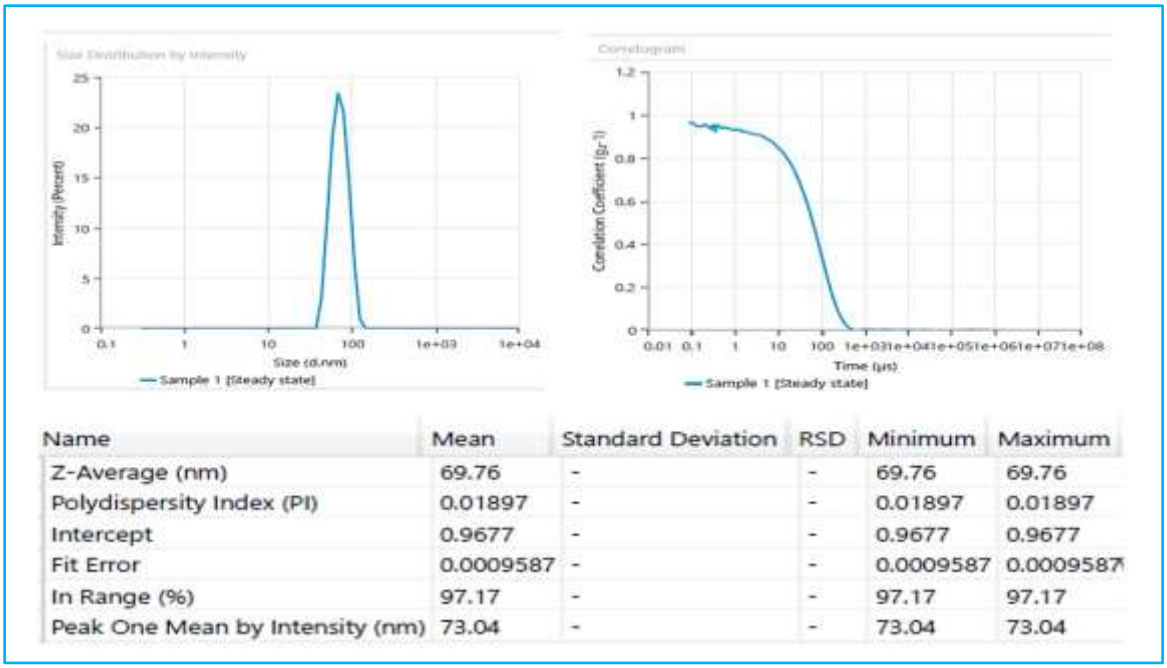
Figure 2. Phase solubility diagram of canagliflozin in water in the presence of various polymerswith various concentrations at 25 ± 0.5 °C (data represented as mean, n=3).

Table 2. Drug Content and Percent of Yield for Canagliflozin Self-nanomicellizing Solid Dispersion (mean ±sd, n-3)

Formula code	Drug contents % (Mean±sd) n=3	% yield (Mean±sd) n=3
FR1	96±2.4	89.82±1.9
FR2	98±2.0	91.64±1.1
FR3	98±2.1	94.0±1.0
FR4	99±2.4	94.2±2.0
FR5	99±0.8	96.91±1.1
FR6	98±2.0	96.5±1.3
FR7	98±1.4	96.9±1.7

Table 3. Measured Parameters of the Prepared Canagliflozin Solid Dispersion (mean±sd, n=3)

Formula code	Particle size	PDI Text	After 20-fold dilution		Stability after dilution
			Particle size nm	PD1	
FR1	1368±4.4	1.048±0.01	4937±5	1.92±0.0	Unstable
FR2	370.4±0.0	0.3923±0.0	2922 ±0.0	0.416±0.0	Unstable
FR3	186.5±0.0	0.4229±0.0	1043±0.0	0.757±0.0	Unstable
FR4	131.4±0.0	0.2052±0.0	2054±0.0	1.198±0.0	Unstable
FR5	69.76±2.3	0.0189±0.001	176.7±0.1.2	0.048±0.0	Stable
FR6	150.7±2.2	0.305±0.01	196.7±0.9	0.134±0.0	Stable
FR7	82.55±0.0	0.759±0.0	38.51±0.0	1.28±0.0	Unstable



Name	Mean	Standard Deviation	RSD	Minimum	Maximum
Z-Average (nm)	69.76	-	-	69.76	69.76
Polydispersity Index (PI)	0.01897	-	-	0.01897	0.01897
Intercept	0.9677	-	-	0.9677	0.9677
Fit Error	0.0009587	-	-	0.0009587	0.0009587
In Range (%)	97.17	-	-	97.17	97.17
Peak One Mean by Intensity (nm)	73.04	-	-	73.04	73.04

Figure 3. Average particle size for formula FR5 by Malvern zeta seizer.

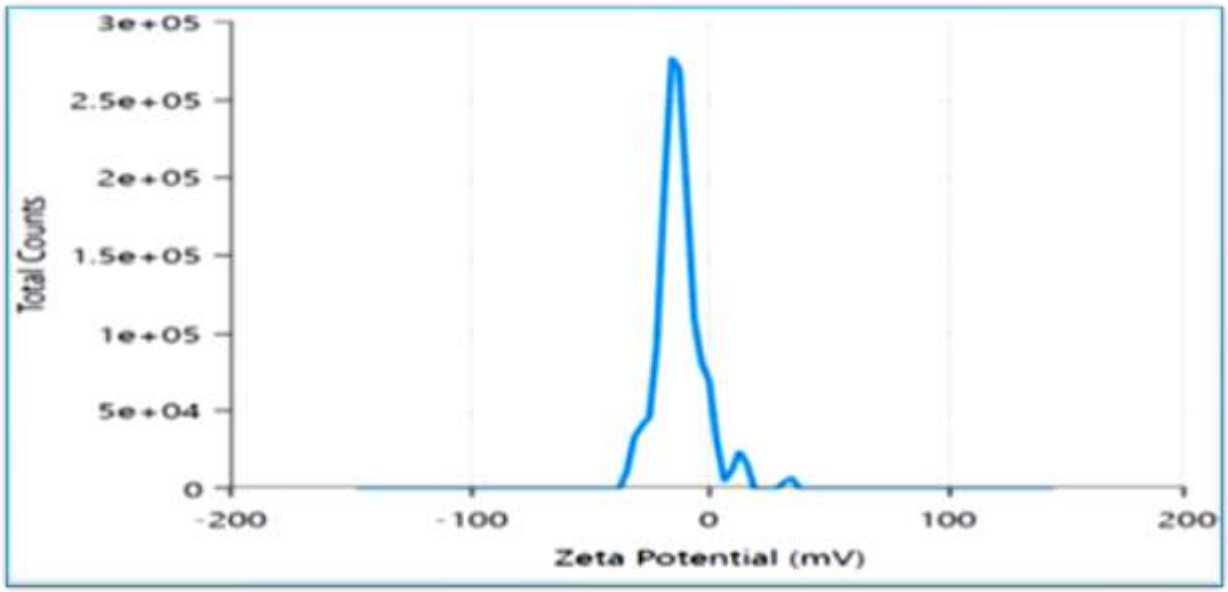


Figure 4. Zeta potential distribution of optimized formulation FR5

X-ray diffraction

X-ray diffractogram of CFZ typically consists of a random distribution of crystalline solids, which showed intense sharp diffraction peaks at various 2θ degrees of 15.621°, 18.897° 20.359°, and 23.45°, respectively, as shown in Figure 5A.

PM of CFZ with RA at a ratio of optimized formulation 1:6 was detected with partial amorphization, as shown in Figure 5B. In contrast, the optimized FR5 formula (Figure 5C) was observed with a reduction in the crystallinity index to a degree less than that in PM, indicating changes in the overall geometry of crystalline to amorphous form, suggesting effective encapsulation of CFZ in SNMSD [25].

In our previous study, we utilized soluplus for enhancing the dissolution rate of CFZ as amorphous nanodispersion; results showed enhancement in dissolution rate due to amorphization and nano-size particles of CFZ nanodispersion [29].

Differential scanning calorimetry (DSC)

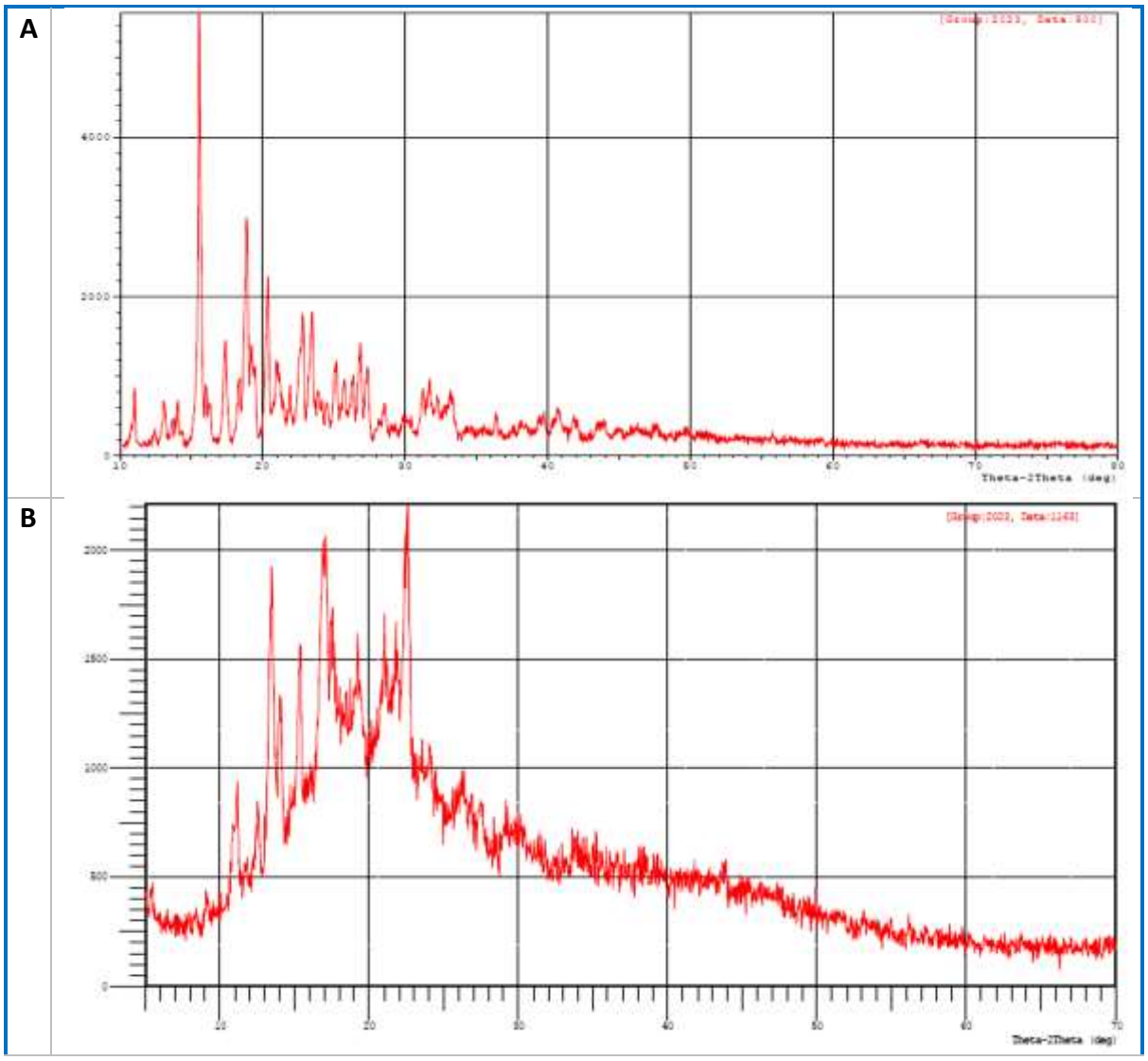
In DSC, the endothermic peak of pure CFZ exhibited 107.55 ºC, as shown in Figure 6A. At the same time, Figure 6B shows the DSC of PM of CFZ and carrier in a ratio as in the optimal formula. After solvent evaporation of SNMSD formula FR5, the intensity of the CFZ peak disappeared as in Figure 6C, certifying that CFZ had converted to an amorphous state by this method and RA as a carrier.

The broad endothermic peak in the optimal formula graph appeared at 39.5 °C, which was the Tg of the solid dispersion sample, and the peak related to the melting point of the CFZ was not observed [30].

Fourier-transform infrared spectroscopy (FTIR)

The FTIR spectrum of the optimal SNMSD formula FR5 was compared to the pure CFZ to identify the chemical stability and the interactions with added excipients. The FTIR graph of pure CFZ, as in Figure 7A, displayed the characteristic peaks at 2970.3 cm^{-1} for –OH stretching mode, 1627.9 cm^{-1} for aromatic C-C=C symmetric stretching, 1508 cm^{-1} for C-C=C asymmetric stretching, 1234 cm^{-1} for C-O stretching, 810.1 cm^{-1} for C-S stretching, 1346.3 cm^{-1} for C-F stretching. The peaks of CFZ were observed as sharp peaks in the PM of CFZ and RA at a ratio of 1:6 as in the optimized formula, as in Figure 7B.

No inherent interaction was seen in the PM of CFZ and RA. In the case of the optimal SNMSD FR5 formula (Figure 7C), Although the peak of CFZ has weakened, the peaks of the drug for its specified functional groups were observed to slightly shift from its original values in the optimal formula compared to the pure sample due to the hydrogen bonding and hydrophobic interactions caused by the presence of RA during the formation of the solid dispersion. The most likely reason for the weakening of characteristic peaks is that the CFZ in SNMSD has fewer components of CFZ and high amounts of the carrier [21].



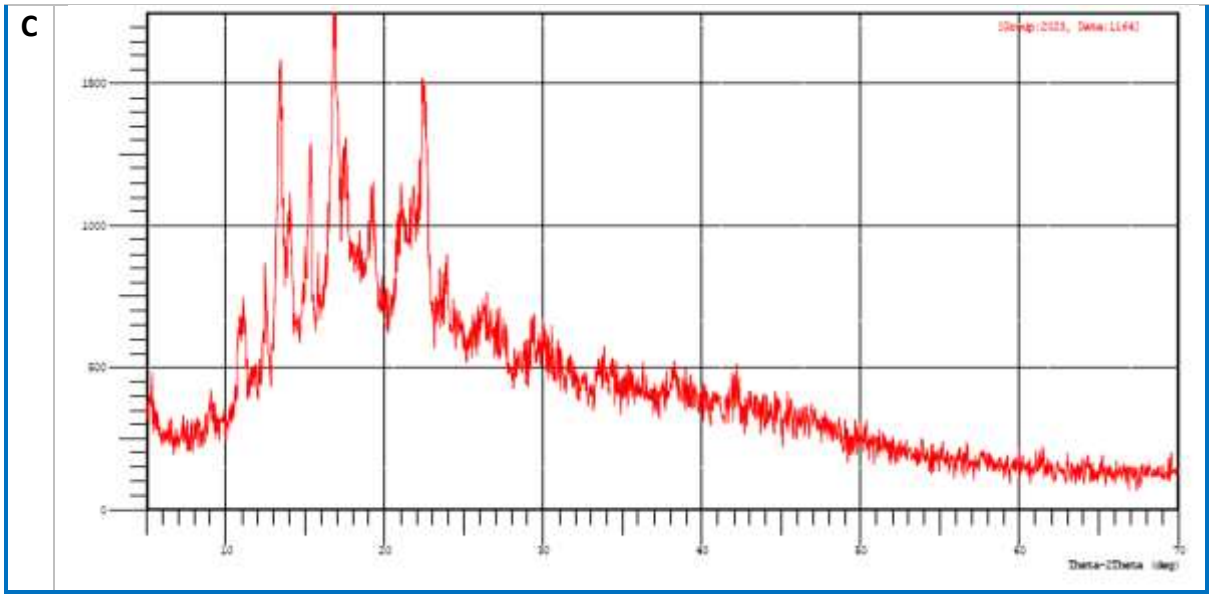
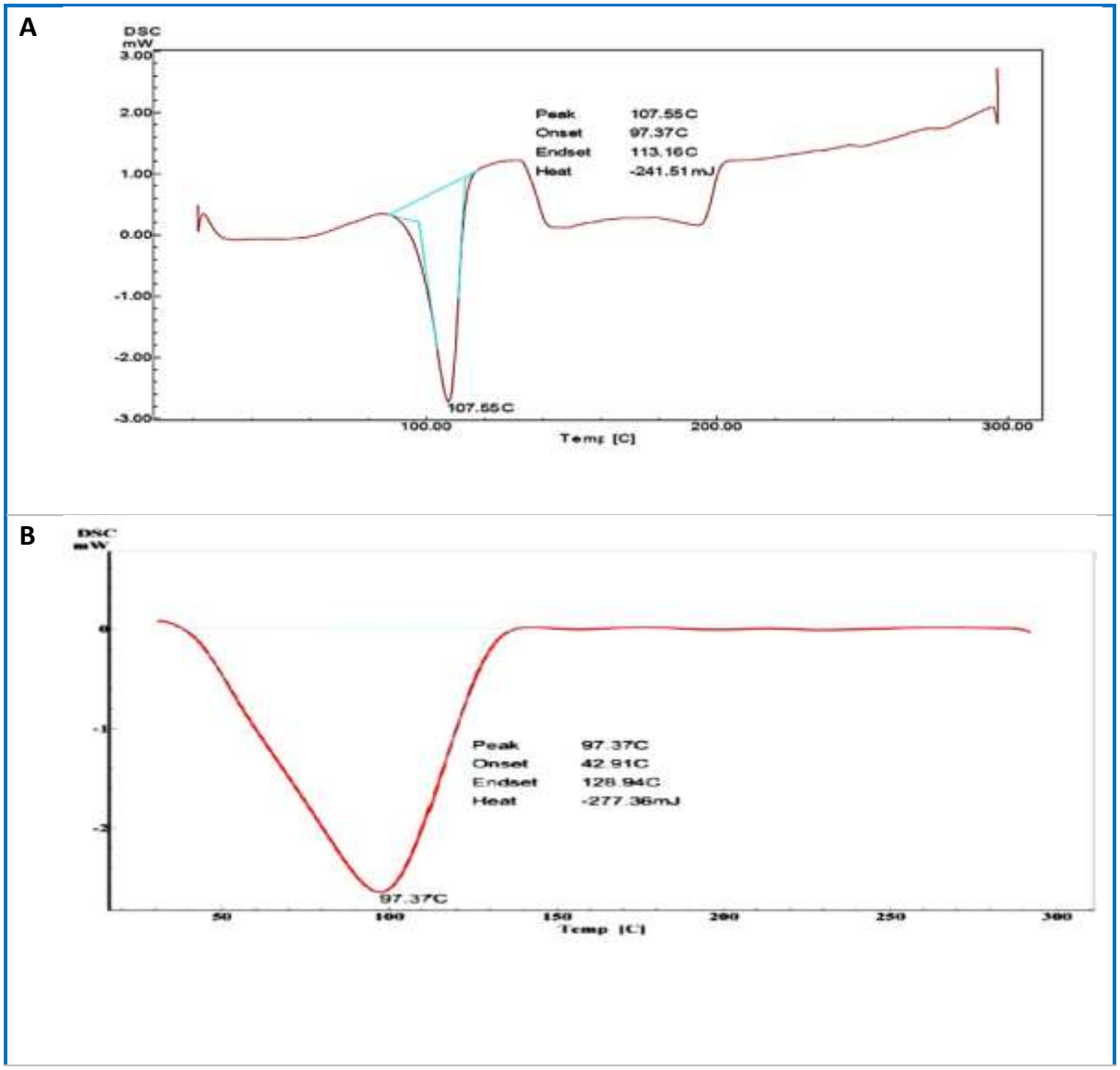


Figure 5. X-ray powder diffraction of A- pure canagliflozin; B- PM of CFZ and RA in a 1:6 drug-to-carrier ratio; C- optimized SNMSD formula FR5.



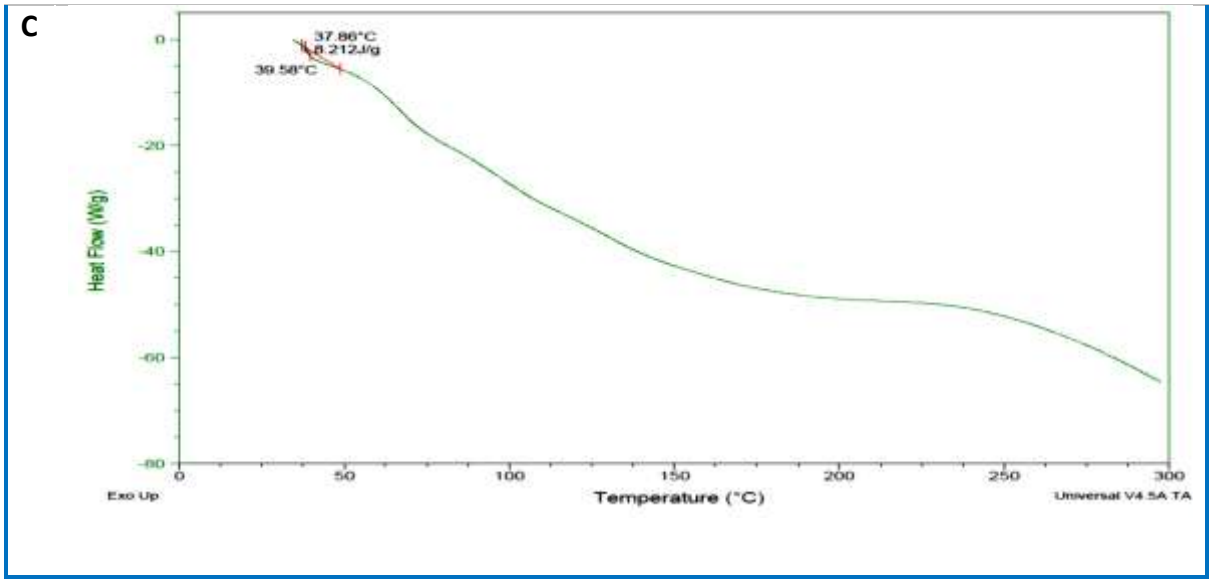
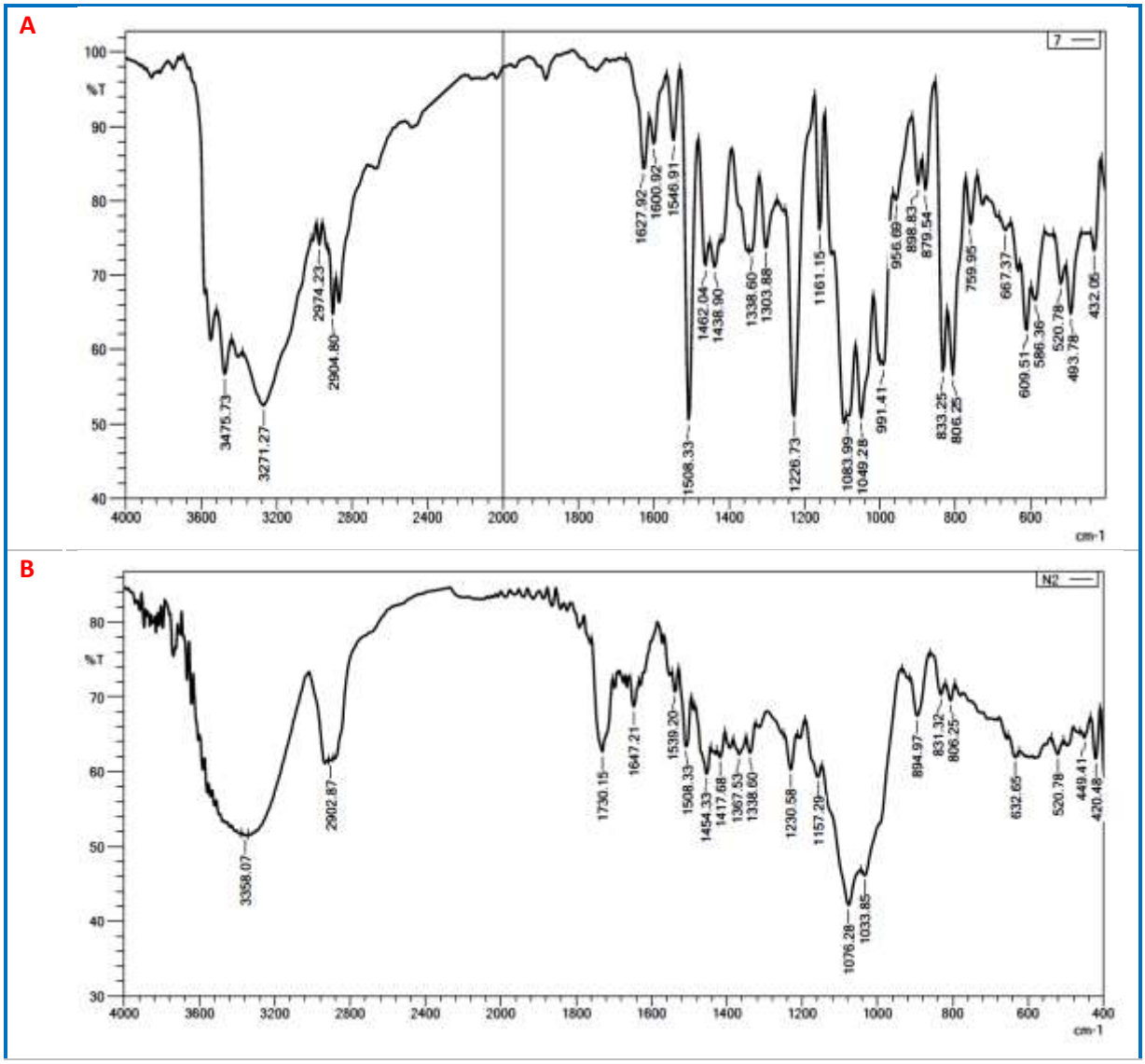


Figure 6. Differential Scanning Calorimetry of A- pure canagliflozin; B- PM of CFZ and Rebaudioside A at 1:6 ratios; C-optimal SNMSD formula FR5.



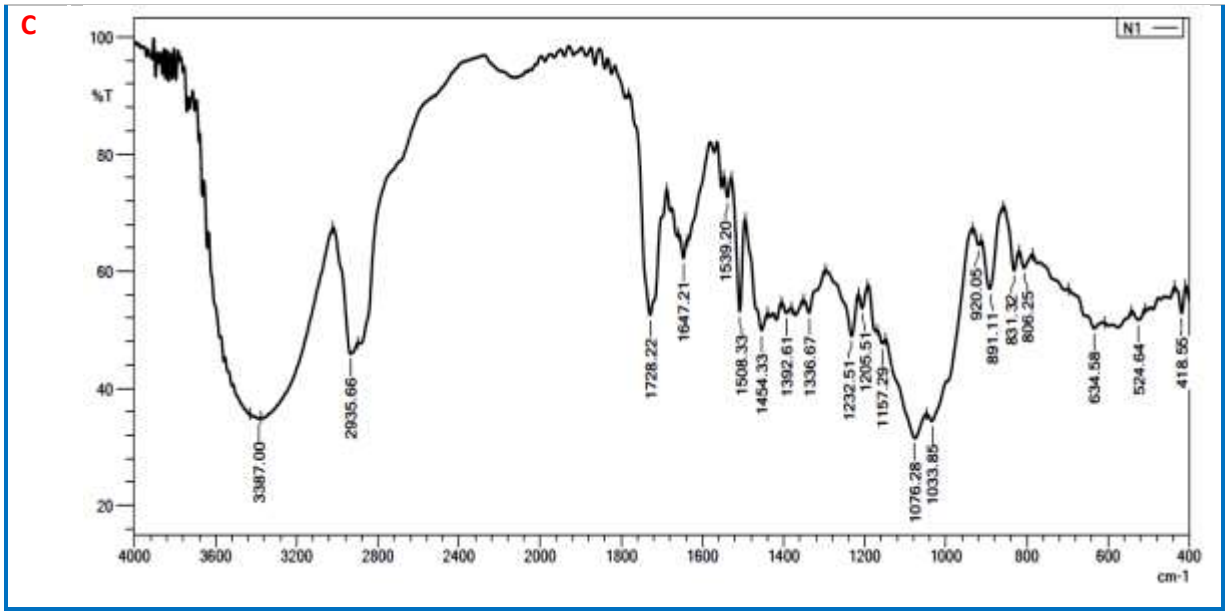


Figure 7. FTIR of A- pure canagliflozin; B- PM of CFZ and RA at a ratio of 1:6 C- optimized SNMSD formula FR5

Morphology of nanomicelles observed with TEM

TEM analysis of optimized formula FR5 showed that the nanomicelles were spherical, quasi-circular, and homogenous with good dispensability, consistent with the Zetasizer instrument's measurement results. Furthermore, the micrograph of CFZ in SNMSD demonstrated particles with relatively rough surfaces, which specified the amorphous nature of CFZ in optimized formula FR5 without any traces of crystalline CFZ, as shown in Figure 8 [19,31].

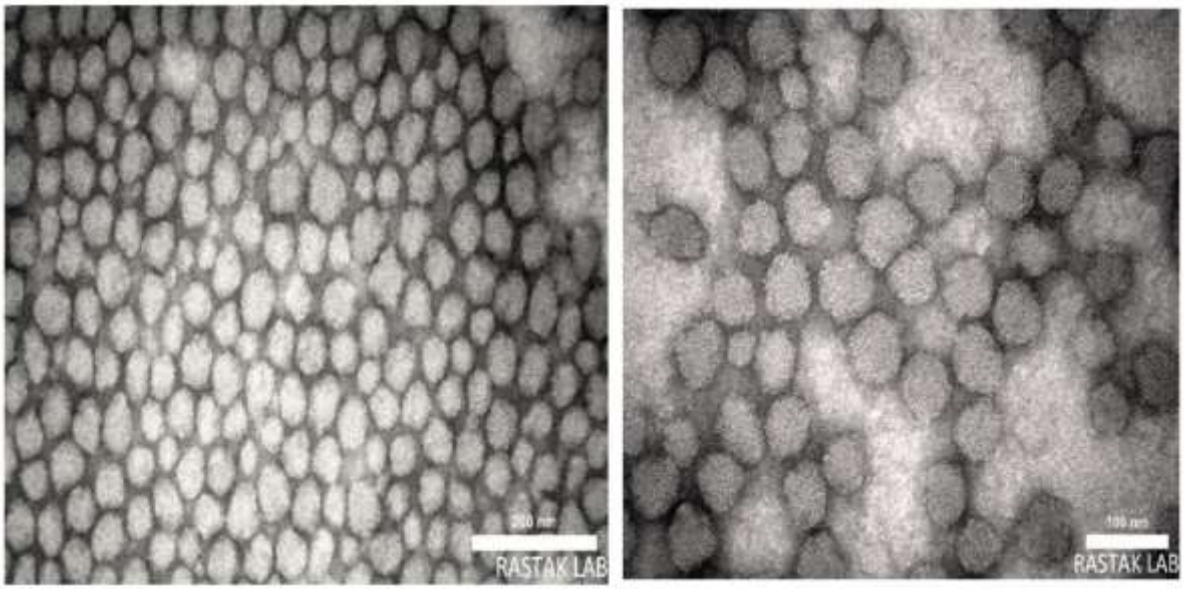


Figure 8. Transmission electron micrograph of optimal SNMSD formula FR5 with different magnification

In vitro dissolution study

Figure 9 illustrates dissolution patterns of optimized SNMSD formula FR5 and pure CFZ in water containing 0.75% SLS. It showed 93.4 % of the encapsulated CFZ in nanomicelles of optimized formula FR5 was dissolved in 0.75% SLS solution after 30 minutes, Compared to 32% and 36% for pure CFZ and PM, respectively.

The highest dissolution level was observed in RA-based SNMSD; according to the Noyes-Whitney equation, increasing the surface area in contact with the dissolution medium can improve drug wettability and reduce particle agglomeration. Furthermore, changing the physical state of the drug substance to a high free energy state (an amorphous state) can reduce the required energy to break the

crystal lattice, potentially leading to rapid drug dissolution in the medium [32,33].

Also, during the preparation process, CFZ and the carrier polymer (RA) were entirely dissolved in an organic solvent, which may have resulted in the dissemination of CFZ at a molecular level inside the SNMSD system, leading to fast dissolution and dispersion of CFZ molecules in the dissolution media [11]

The dissolution profile of the optimized formula was paired with pure CFZ and PM and compared by calculating values of f_1 and f_2 factors, and the results are summarized in Table 4. While comparing the dissolution profiles of PM and pure drugs, the f_2 value was 56, indicating that PM and pure drugs are moderately similar in dissolution profile. Meanwhile, the f_1 value of 22 indicates that the relative error between the two curves is high at any given time.

Relatively, higher values of f_1 and lower values of f_2 were obtained while comparing dissolution curves of optimized formula FR5 with pure drug and PM as a reference., indicating dissimilarity between the test (FR5) and reference (pure CFZ and PM) dissolution release profile.

The optimized SNMSD formula (FR5) dissolved well after 30 min and showed higher dissolution efficiency than the pure CFZ and PM. The DE% parameter confirms this results (DE_{30}, FR5 = 70.34% and DE_{30}, PM = 21.91% and DE_{30}, pure CFZ = 18.28%. This is due to the increasing solubility of canagliflozin by the nanomicellization and amorphous carrier presence surrounding the drug particles [34].

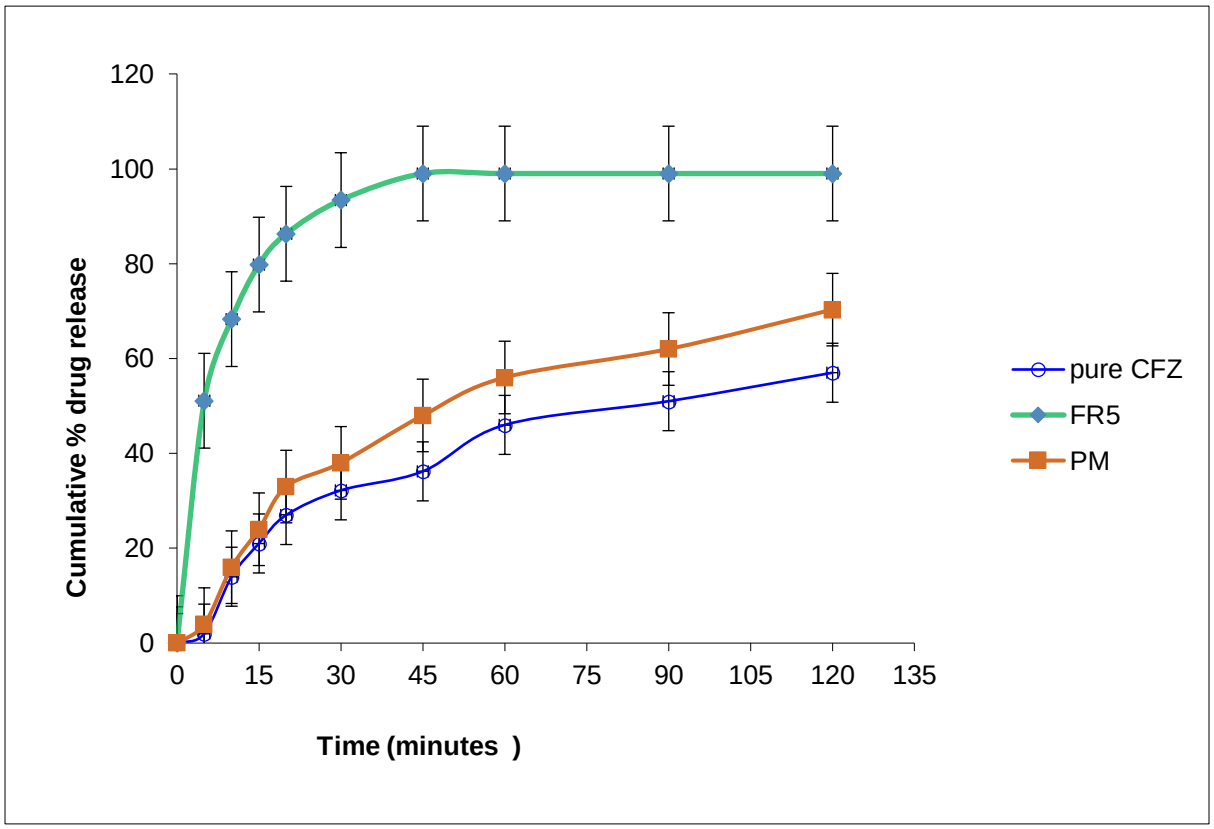


Figure 9. Release profile of optimized canagliflozin formulation FR5 according to dissolution test (mean, n=3) in 900 ml water containing 0.75% SLS at 37.0 ± 0.5 °C and 75 rpm.

Table 4. Difference factor f_1 and similarity factor f_2 comparing dissolution of optimized SNMSD formula FR5 with pure CFZ and PM

Reference	Test	f_1	f_2	Inference about dissolution profiles
Pure CFZ	FR5	189	13	Dissimilar
Pure CFZ	PM	22	56	Similar
PM	FR5	142	15	Dissimilar

Conclusion

Preliminary screening revealed that RA is the best carrier. The solvent evaporation technique improved the amorphous formulation, enhanced solubility and dissolution properties of CFZ, and made it affordable and easy to prepare, benefiting industrial production.

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Conflicts of Interest

Regarding this work, the authors declare no conflicts of interest.

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Ethics Statements

According to the research integrity rules in our country, the study does not require ethical approval from an ethics committee as it is an in-vitro study.

Author Contribution

All authors have actively participated in the research process and have reviewed the results. Additionally, they have approved the final version of the manuscript before submission.

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تصييغ وتقييم الكناجليفلوزين كتشتت صلب ذاتي التكون للمذيلات النانوية المستنده على ريبوديوسيد أ لتحسين التحلل والذوبان

نزار عويش جاسم[١]، شيماء نزار عبد الحميد [٢]

[١] فرع الصيدلانيات ،كلية الصيدله ،جامعة الفراهيدي ، بغداد ، العراق

[٢] فرع الصيدلانيات ،كلية الصيدلة ، جامعة بغداد ، بغداد ، العراق

الخلاصة

التشتت الصلب ذاتي تكوين المذيلات النانويه هو صيغة جديدة تجمع بين مزايا التشتت الصلب واستراتيجيات المذيلات النانوية لزيادة التوافر الأحيائي للادويه عن طريق الفم . وتنطوي الاستراتيجية على استخدام ناقل مناسب لخلق تشتت صلب يتم تجميعه ذاتياً في جزيئات نانوية عندما يتلامس مع السوائل المعوية . كاناجليفلوزين هو مثبط جديد لناقل الصوديوم والجلوكوز اقر لعلاج المرضى الذين يعانون من مرض السكري من النوع الثاني . ويرتبط تناوله عن طريق الفم بامتصاص متغير وقليل ويرجع ذلك إلى قلة ذوبانه في الوسائط المائيه. تم تطوير تركيبة جديدة من كاناجليفلوزين باستخدام استراتيجية التشتت الصلبة الذاتية التكون للمذيلات النانوية للتغلب على هذه المشاكل وتعزيز التوافر البيولوجي عن طريق الفم. تم اختيار ريبوديوسيد أ كناقل بعد فحص عدة بوليمرات لقدرتها على تحسين قابلية ذوبان واستقرار كاناجليفلوزين من خلال دراسة قابلية الذوبان في الطور. تم اختيار طريقة تبخير المذيب لتحضير المستحضرات .

تم تميز التركيبه المحسنة بتحليل الحالة الصلبة، ودراسات الذوبان، وتوزيع حجم الجسيمات، والمجهر الإلكتروني النافذ . يُظهر التشتت الصلب الذاتي تكوين المذيلات النانويه الأمثل للكاناجليفلوزين المستند الى ريبيديوسايد ا حجم جسيم يبلغ ٦٩,٧ نانومتر كروي الشكل مع توزيع مستقر عند التخفيف إلى ٢٠ ضعفًا بالماء وأظهر تحسنًا يزيد عن ٧٥٣,٥ ضعفًا في الذوبان المائي نتيجة لعدم التبلور والحجم النانوي الذي اثبت باستخدام قياس السعرات المسح التفاضلي، وحيود الأشعة السينية، وتشتت الضوء الديناميكي، والمجهر الإلكتروني النافذ. علاوة على ذلك، هناك تحسن كبير في معدل الذوبان مقارنة بالخليط الفيزيائي والدواء الخام كما يتضح من القيم الأعلى لـ f1 والقيم المنخفضة لـ f2 التي تم الحصول عليها. تم ذوبان التركيبة المثلى لـ كاناجليفلوزين FR5 جيدًا بعد ٣٠ دقيقة وأظهرت كفاءة ذوبان أعلى من كاناجليفلوزين الخام والخليط الفيزيائي. حيث كانت كفاءة الذوبان DE% النتائج (DE30FR5 = 70.34%، DE30PM = 21.91%، وDE30لعقار الخام = ١٨,٢٨٪). و كشف التحليل الطيفي بالأشعة تحت الحمراء كشف عن تفاعلات خفيفة بين الدواء والناقل بسبب الرابطة الهيدروجينية، مما يفضل تكوين نظام تشتت صلب مستقر بدون تداخل كيميائي. تشير هذه النتائج إلى أن هذه التركيبه لكاناجليفلوزين هي طريقة واعدة لتعزيز التوافر البيولوجي عن طريق الفم للكاناجليفلوزين.

الكلمات المفتاحية: أمفيفيليك ، كاناجليفلوزين، النانويلات ، مرحلة الذوبان، ريبوديوسيد أ.