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RESEARCH ARTICLE

Ex vivo permeability study and *in vitro* solubility characterization of oral Canagliflozin self-nanomicellizing solid dispersion using Soluplus® as a nanocarrier

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Background and objective: Self-nanomicellizing solid dispersion SNMSD is a new formulation that combines solid dispersion and nanomicelle strategies; the strategy involves utilizing a suitable carrier that self-assembles into nanomicelles when interacting with gastrointestinal fluids. Canagliflozin, a sodium-glucose cotransporter-2 inhibitor for treating type 2 diabetes, has been linked to poor absorption due to its insolubility in aqueous media. The study aimed to create self-nanomicellizing solid dispersion systems for canagliflozin to overcome its pharmaceutical limitations and improve oral bioavailability.
Materials and Methods: Soluplus® was chosen as a nanocarrier to improve canagliflozin solubility after screening several polymers using a phase solubility study. The solvent evaporation method was selected for preparing the solid dispersion. The optimal formula was characterized through ex vivo permeability and in vitro studies.
Results: The CFZ-SNMSD formula, with a particle size PS of 60.77±1.00 nm and polydispersity index PDI of 0.06±0.02, has a stable distribution upon dilution to 20-fold with water. The apparent solubility of canagliflozin in the optimized CFZ-SNMSD formula was enhanced by 904.40±4 folds due to amorphization and nanomicellization, as demonstrated by transmission electron microscopy. CFZ-SNMSD formula showed a significant enhancement in dissolution rate compared to the physical mixture and pure drugs. The dissolution efficiency parameter confirms these findings (DE30, CFZ-SNMSD = 77.20% compared to DE30, pure drug = 18.28%). Studies show that canagliflozin's permeability increases exponentially over time due to Soluplus® dispersibility, solubilization, and glycoprotein inhibitory effect, enhancing bioavailability and overcoming GIT membrane barriers. Conclusions: The study indicates that canagliflozin self-nanomicellizing solid dispersion systems are promising methods for improving the oral bioavailability of canagliflozin medication.

Keywords: self-nanomicellizing, bioavailability, phase solubility, canagliflozin, Soluplus

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Introduction

The oral route of administration is the most preferred by patients due to its compliance and comfort. Amphiphilic polymers, with their hydrophilic and hydrophobic components, have gained popularity for enhancing drug dissolution and absorption; they tend to self-micellize into nano- or micro-sized micelles [1].

Soluplus® is a polyvinyl caprolactam-polyvinyl acetate polyethylene glycol graft copolymer with hydrophilic and lipophilic moiety, forming micelles in aqueous solutions above its the critical micellar concentration (CMC) (7.6 mg/L), reducing free energy and acting as precipitation inhibitors [2].

Self-nanomicellizing solid dispersion (SNMSD) is a hybrid of well-proven solid dispersions and nanomicelles techniques for increasing the oral bioavailability of challenging drugs. It is a unique method that combines the advantages of solid dispersion with nanotechnology by forming nanomicelles when in contact with aqueous media. It enhances the physicochemical characteristics of drug substances, such as solubility and dissolution rate, by nanosizing, increasing wettability, and changing to an amorphous state. Moreover, it offers stability, simple manufacturing technology, scale-up process, economics, and potential of transformation into the conventional oral solid dosage form like tablets and capsules over other technologies [3-4].

Typically, SNMSDs consist of active pharmaceutical ingredients and suitable nanocarrier. Choosing a suitable carrier is critical for optimal SNMSD [5].

Canagliflozin (CFZ) is a novel sodium-glucose cotransporter 2 inhibitor for treating type II diabetes. Pharmaceutically, CFZ is practically insoluble in aqueous media from pH 1.1 to 12, but it is also soluble in many organic solvents. The adult dose is 100 mg once daily, increased if tolerated to 300 mg once daily if required, and preferably taken before breakfast. CFZ oral administration is associated with erratic and poor absorption because of its insolubility in aqueous media and a low intrinsic dissolution rate [6-7].

Several studies were done to increase the solubility and bioavailability of canagliflozin, one of which was done by *Patel NC*, *Patel HA,* 2022 to improve the dissolution characteristics of Canagliflozin by converting nanosuspension formulation into solidified forms as immediate-release pellets. Poloxamer 407 was used to stabilize canagliflozin nanosuspension. The optimized nanosuspension (NS1) was solidified into immediate-release pellets using microcrystalline cellulose as a binder. Results have shown the optimized nanosuspension, with an average particle size of

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120.50 nm and an *in vitro* release rate of 89.59% in 10 minutes in 0.75% w/v SLS [8].

Enhancing CFZ solubility and dissolution is the central area of emphasis for increasing oral bioavailability. Thus, canagliflozin self-nanomicellization may be essential for resolving the medication's solubility issues. In our previous study on canagliflozin as nanodispersion, we examined the factor's effect on particle size (PS) and polydispersity index (PDI) analysis and drug carrier interaction using FTIR, XRD, and DSC methods [9].

This study aimed to formulate a canagliflozin self-nanomicellizing solid dispersion system and choose the nanocarriers based on drug miscibility by phase solubility study and how the self-nanomicellizing solid dispersion optimized formula will improve the in-vitro solubility and *ex-vivo* permeability in rat's intestine.

Methods

Materials

Canagliflozin (CFZ) was purchased from Wuhan Senwayer Century Chemical. Co. Ltd, China; Soluplus® was gifted from BASF pharma, Germany; Sodium lauryl sulfate (SLS) was purchased from Sd Fine-Chem Limited Mumbai, India; Ethanol 99 % (HPLC grade) purchased from Merck, USA; Poloxamer 338 purchased from SIGMA, Germany; and Polyethylene glycol 8000 (PEG 8000) from Glentham, UK. All other reagents in this research were of analytical grade.

Saturation solubility study

The saturation solubility of canagliflozin was determined in different media: water, ethanol, and 0.75% w/v SLS solutions. After preparing each medium, an excess of canagliflozin was added, and it was maintained for 48 hours at 25±0.5 °C in an incubator shaker bath (GFL, Karl Kolb, Germany). Then, dispersions were centrifuged (Hermle Z 216 MK centrifuge, Germany) at 5000 rpm for 10 min. Supernatants were diluted with the specific solution after filtering through a 0.45 µm syringe filter. Then, solubility was measured by determining the CFZ concentration using a UV spectrophotometer (UV1100 model, EMC-LAB, Germany) at 290 nm [1].

Phase solubility study

The apparent solubility of canagliflozin in polymer solutions was evaluated using a well-proven technique developed by Higuchi and Connors to choose a suitable carrier for self-nanomicellizing solid dispersion [10].

Soluplus®, poloxzmer 338, and PEG 8000 were mixed with CFZ in aqueous solutions at 2, 4,6, 8, and 10 mg/ml polymer concentrations. The suspension was shaken for 48 hours in a water bath at 75 rpm and 25±0.5 °C, centrifuged (Hermle Z 216 MK, Germany), and filtered. The canagliflozin content was measured using a UV-VIS spectrophotometer (UV1100 model, EMC-LAB, Germany). The stability constant (Ks) was estimated from the phase solubility graph using equation 1 below [11].

$$Ks = \frac{\text{slope}}{So\,(1-\text{slope})} \qquad \ldots\ldots \text{ EQ 1}$$

Preparation of self-nanomicellizing solid dispersions

The solvent evaporation method was chosen for canagliflozin self-nanomicellizing solid dispersion after conducting a phase solubility study to determine the carrier that improves canagliflozin solubility. The CFZ-SNMSD was prepared through the solvent evaporation method by dissolving canagliflozin and nanocarrier in10 ml ethanol at a drug: carriers 1:4 ratio in 100 ml round-bottom flask in a bath sonicator at 25±0.5 °C. The ethanol was evaporated at 40 °C under reduced pressure in a rotary evaporator (Buchi, Turkey), rotating at 220 rpm until a thin, detached film was produced on the flask's inner wall, and the film was crushed and collected [12].

Characterization of CFZ- Soluplus® SNMSD (optimal formula)

Particle size analysis

The particle size (PS), polydispersity index (PDI), and zeta potential (ZP) of the developed canagliflozin-loaded nanomicelles were determined by using a Malvern Panalytical Ltd Zetasizer. Briefly, 40 mg of CFZ-SNMSD was dispersed in 20 ml deionized water, stirring at 300 rpm for 1 hour using a magnetic stirrer (Witeg labortechnik GMBH, Germany), filtering by 0.45 µm syringe filter and analyzed [13].

The particle size stability of the CFZ-SNMSD formula to an eventual dilution with the gastrointestinal tract (GIT) fluid, a process that usually occurs after oral administration, was estimated by analyzing the PS and PSI of the CFZ-SNMSD dispersion diluted with water in a ratio of 1:20 [14]

Transmission electron microscopy (TEM)

The nanomicelles' size and morphology were studied by transmission electron microscopy (TEM), using Tecnai 12, TEM apparatus, Philips Company, Holland, where a drop of the solution was applied to a copper grid, followed by phosphotungstic acid and deionized water, dried and mounted on a grid holder. Their morphology was studied at an acceleration voltage of 120 kV [15].

Determination of the apparent solubility of canagliflozin in SNMSD formula

The solubility of canagliflozin in optimal formula, physical mixture PM, and pure drug was determined by dissolving excess samples in water in vials, shaking for 24 hours at 37 ± 1.0°C in a bath shaker, centrifuging, filtering, and measuring concentration spectrophotometrically at 290 nm [16]. Equation 2 was utilized to understand the solubility properties of the carriers used.

$$\Delta G^{\circ} = -2.303RT \log \frac{S}{S_{\circ}} \quad \text{..... EQ2}$$

The equation S/S_o represents the solubility ratio of canagliflozin from CFZ-SNMSD nanodispersion (S) and CFZ pure powder (S_0) in water at 37 °C. In contrast, R represents the molar gas constant, T absolute temperature, and ΔG° represents the Gibbs free energy

In vitro dissolution test and dissolution efficiency

The study used 900 ml of 0.75% w/v SLS solution in distilled water, set to 75 rpm at 37.0±0.5 °C on the USP apparatus II (Copley Dissolution 8000, Copley Scientific, UK) for dissolution. The dissolution involved 100 mg of pure drug, equivalent amounts of self-nanomicellizing solid dispersion formula, and PM. The formulations were placed in a "000" hard gelatin capsule with a sinker to prevent floating before dissolution studies. A 5 mL sample was withdrawn at specified times of 5, 10, 15, 20, 30, 45, 60, and 90 minutes, replaced with fresh media, filtered, and analyzed for canagliflozin concentration spectrophotometrically (UV1100 model, EMC-LAB, Germany) at 290 nm. 0.75% w/v SLS solution was used as a dissolution medium to maintain the sink condition. Dissolution tests were performed in triplicate to validate reproducibility [17]

Dissolution efficiency (DE) was used to evaluate the *in vitro* dissolution curves. The % DE was determined by calculating the area under the dissolution curve (AUC, y) up to time t compared to the rectangle area representing 100% dissolution, as depicted by equation 3 [18].

$$DE\% = \left(\frac{\int_0^t y * dt}{y_t^{100}}\right) \times 100 \quad \text{..... EQ 3}$$

Ex vivo permeation studies

Ex vivo permeation investigations were performed using the non-everted intestinal sac method. Six Wistar rats (male) weighing approximately 250±12 g were obtained 12 h before the study from the animal house at the College of Pharmacy, Baghdad University (Approval No: RECAUBCP932023F). The Search Ethics Committee confirmed the experimental procedure to guarantee adherence to ethical guidelines. The study involved rats who underwent humane care following the US National Institutes of Health's Guideline for the Care and Use of Laboratory Animals. The study procedure included fasting Wistar rats overnight but allowing them free access to water, anesthetizing them, and sacrificially, a segment of about 10 cm from jejunum was erased and placed in a physiological salt solution (PSS). The tissue was prepared and cleaned using a syringe and cannula. The jejunum sac was filled with 1 ml containing 2 mg of canagliflozin dispersion or an equivalent amount of optimal CFZ-SNMSD formula, then ligated to a Dissolution test apparatus (using Copley Dissolution 8000, Copley Scientific, UK) and was immersed in 200 ml of the permeation media (phosphate buffer pH 6.8) at 37.0±0.5 °C, Samples of 5 ml were withdrawn at various intervals up to 120 minutes, replace with same volume of fresh phosphate buffer pH 6.8 medium. Samples were filtered by a 0.45-µm cellulose acetate syringe filter and analyzed using UV spectrophotometry at 290 nm. The sink condition was maintained during this experiment.

The cumulative amount of canagliflozin permeated was computed and plotted against time. The experimentation was constructed in triplicate [19].

The surface area SA of the jejunum sac was determined using Equation 4, which calculates the lateral surface area of the cylinder [20].

$$SA = 2\pi rL \quad \text{..... EQ 4}$$

Where SA (cm^2) is the area of the jejunum sac, r (cm) is the jejunum radius, and L is the length (cm) of the sac.

The steady-state Flux (J) of canagliflozin across a permeation barrier (intestine) in sink conditions can be determined by plotting the cumulative permeated amount vs. time following standardization by the permeation area, as explained in Equation 5 below [21].

$$J = \frac{1}{A} \cdot \frac{dQ}{dt} \quad \text{..... EQ5}$$

In which dQ/dt is the canagliflozin permeation rate from the tissue (µg/ml) obtained from the slope of the linear curve, A is the cross-sectional area of the tissue chamber in cm^2, J is the Flux (µg/min/cm^2). Fick's first law of diffusion states that Flux depends on the canagliflozin concentration gradient, normalized by initial drug concentration and described as apparent permeability (P_{app}) for comparison. P_{app} is calculated in equation 6 [22].

$$P_{app} = \frac{J}{C_O} \quad \text{..... EQ 6}$$

Where: P_{app} is The apparent permeability coefficient, and Co is the canagliflozin initial concentration in the donor compartment at t = 0.

The enhancement ratio (ER) of the canagliflozin self-nanomicellizing solid dispersion was calculated using Equation 7 [23].

$$ER \equiv \frac{P_{app} \text{ of CFZ from CFZ-SNMSD}}{P_{app} \text{ of CFZ from CFZ pure powder}} \quad \text{..... EQ 7}$$

Statistical analysis

The study utilized one-way ANOVA to compare results parameters, determining statistically significant differences between groups at p values of $P < 0.05$ and non-significant at $P > 0.05$ using Microsoft excel 2016. DDSolver software

for release test, version 1.0. The experimental results were presented as the mean of triplicate samples along with the standard deviation [24].

Results

Saturation solubility of CFZ in different relevant conditions

The saturation solubility of canagliflozin from CFZ-pure powder in different media solutions at 25±0.5 °C was found to be 36.2±2.3 µg/ml in water, 32.815±2.1 mg/ml in ethanol and 9.3 ±1.14 mg/ml in 0.75% w/v SLS solution.

Phase solubility study.

The equilibrium aqueous solubility of canagliflozin at 25±0.5 °C was 36.2 µg/ml. Figure 1 shows the canagliflozin's phase solubility in the three studied carrier solutions (Soluplus®, Poloxamer 338, and PEG 8000) with varying concentrations from 2-10 mg/ml. The results show an increase in saturation solubility of canagliflozin as the carrier's solution concentration increases.

The stability constant (KS) between canagliflozin and the three studied carrier polymers was determined from the slope of the linear regression of the solubility curve experimentally determined in the phase solubility study using equation (1) and was found to be 49.410 in CFZ - Soluplus® solutions; 3.910 in CFZ - Poloxamer 338 solutions; and 0.307 in CFZ - PEG 8000 solutions.

Preparation of self-nanomicellizing solid dispersion

According to the phase solubility study, Soluplus® was selected as a nanocarrier. The canagliflozin to Soluplus® ratio was chosen according to our previous survey on canagliflozin nanodispersion [9]. The ratio of CFZ: Soluplus® was 1:4. The resulting formula, CFZ-SNMSD in dry powders, was stored at 25 °C until further characterized.

Characteristics of the CFZ-Soluplus®-SNMSD product

Particle size analysis

The results of particle size distribution, PDI, and Zeta potential are summarized in Table 1. In addition, the stability of nanomicelles to maintain their particle size upon 20-fold dilution with water is also represented in the table1

Morphology of the nanomicelles

The surface morphology of the optimal CFZ-SNMSD formula was investigated using TEM, as shown in Figure 2.

Solubility study of canagliflozin in the optimized formula

The apparent solubility of CFZ in water at 37.0±0.5 oC was determined after 24 hours as being 51734.4 µg/ml from the optimal CFZ-SNMSD; 18009.0 µg/ml from the physical mixture (PM) of CFZ- Soluplus®; and 57.2 µg/ml from the CFZ-pure powder.

The enhancement ratio of apparent solubility of canagliflozin in optimal CFZ-SNMSD formula at 37 ± 0.5 °C after 24 hours is 904.40±4, while that for PM of canagliflozin: Soluplus®1:4 ratios was 314.2±2. Accordingly, Gibbs free energy of transfer (ΔG) for CFZ-SNMSD was found to be -17.539 kJ/mol, while for the CFZ- Soluplus® physical mixture, it has the value of -14.815 kJ/mol.

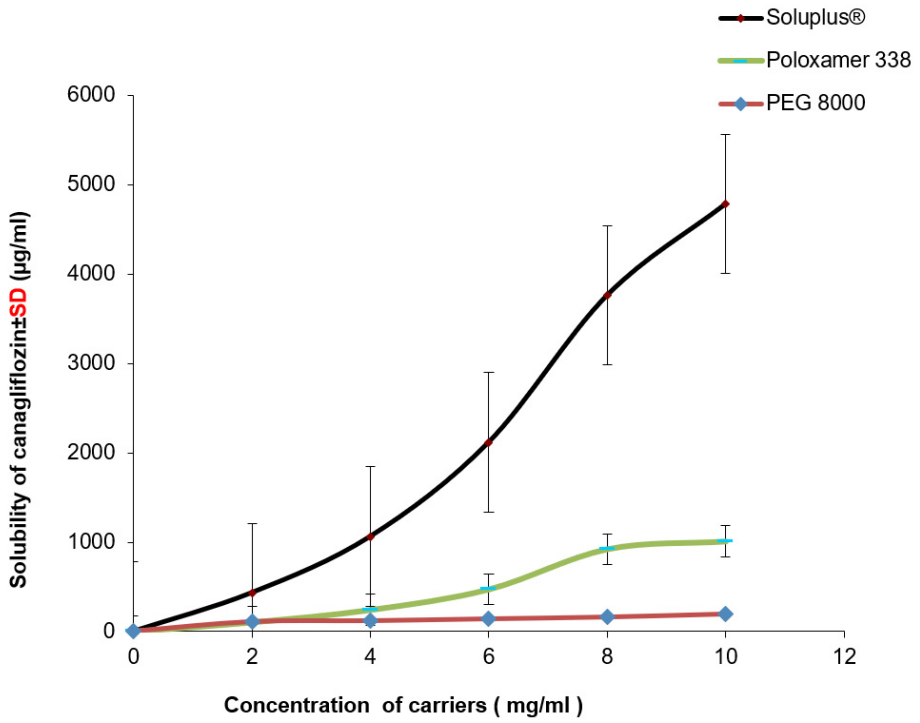

Fig. 1. Phase solubility graphic of canagliflozin in three different carrier solutions (Soluplus®, Poloxamer 338, and PEG 8000) with various concentrations at 25±0.5 °C

Table I. Particle size analysis of CFZ-SNMSD (mean ±SD, n-3)

Aqueous solution 0.5% of CFZ-SNMSD			After dilution with water 1:20	
PS ± SD (nm)	PDI ± SD	ZP ± SD (mV)	PS ± SD (nm)	PDI ± SD
60.770 ± 1.00	0.068 ± 0.020	- 3.4 ± 0.31	71.220 ± 1.30	0.048 ± 0.01

PS = particle size: PDI = particle dispersion index; ZP = Zeta potential; SD: standard deviation

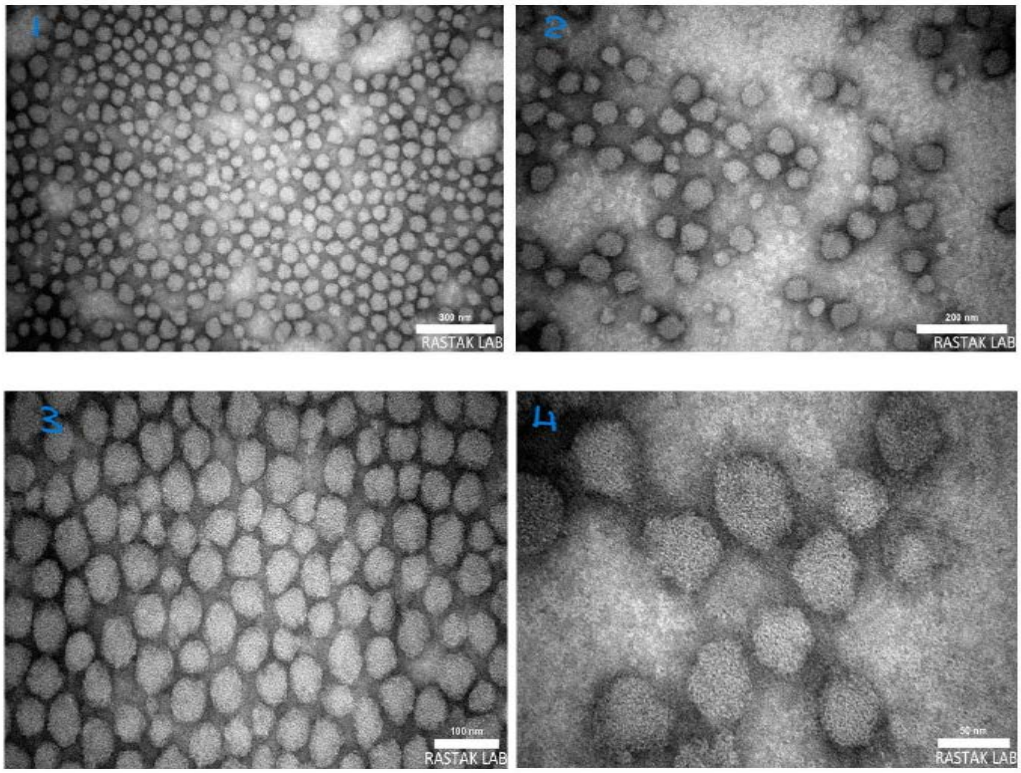

Fig. 2. Transmission electron micrograph of optimized CFZ-SNMSD with different magnification [(1) magnification scale 300 nm (2) magnification scale 200 nm (3) magnification scale 100 nm (4) magnification scale 50 nm]

In vitro dissolution study

Figure 3 shows the dissolution rate of the optimal CFZ-SNMSD formula, PM, and pure canagliflozin in water containing 0.75% w/v SLS. The optimal one showed a faster dissolution rate of 98% after 30 minutes, compared to 32% and 42% for pure drugs and PM, respectively.

Dissolution efficiency % was calculated up to 30 minutes of drug release for the optimal CFZ-SNMSD formula

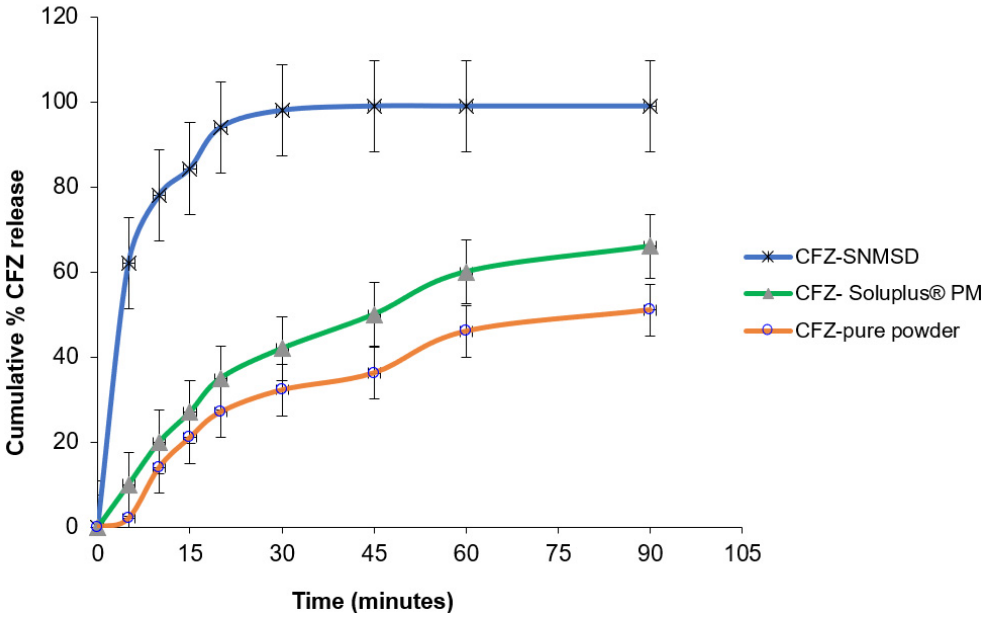

Fig. 3. *In vitro* dissolution curves (in 900 ml of 0.75% w/v SLS solution, at 37.0±0.5 °C and 75 rpm) of: CFZ-SNMSD (optimal formula), PM (physical mixture) at CFZ/Soluplus® ratio of 1:4 and CFZ pure powder

and found to be 77.21%, compared to 18.28% for the pure drug.

Permeability of CFZ through the biological membrane by ex vivo study

The present study applied the non-everted rat intestinal sac model to predict in-vivo human absorption kinetics and bioavailability. *Ex vivo* study, the cross-sectional area of the jejunum sac (S) was equal to 15.38 cm^2. The amount of canagliflozin permeated amongst intestinal mucosa over 120 minutes is shown in Figure 4. The steady-state Flux (J) for CFZ-SNMSD was determined to be 1.487±0.05 $\mu g/min/cm^2$; the permeation rate and cumulative amount of canagliflozin permeated from optimal CFZ-SNMSD in 120 minutes were 1803±8.60 µg; they were significantly higher ($p < 0.05$) than pure canagliflozin dispersion. Table 2 summarizes the determined diffusion parameters.

Discussions

The equilibrium solubility of canagliflozin pure powder in water shows poor solubility, suggesting the need to enhance its aqueous solubility. However, CFZ was soluble in ethanol and 0.75% w/v SLS solution.

Selecting suitable polymers as carriers is crucial in enhancing the biopharmaceutical properties of poorly water-soluble drugs in the SNMSD system. Amphiphilic polymers, with hydrophilic and lipophilic units, are popular pharmaceutical excipients. The phase solubility study results show that increased polymer concentration enhances canagliflozin solubility. Soluplus® highly enhances canagliflozin solubility more than the other carriers (poloxamer 407 and PEG 8000), justifying its use for a self-nanomicellizing solid dispersion system [25].

Soluplus® showed higher Ks than other polymers, suggesting canagliflozin could better interact with it, enhancing solubility in the hydrophobic core of nanomicelle. The optimal CFZ-SNMSD formula containing Soluplus®exhibits small particle size, 61.790±1.06 nm, and PDI of 0.058±0.02, indicating good PS formulation stability [26].

Soluplus®-based nanomicelle formulas can regain nanomicelle size after dilution with water 1:20 due to their low CMC (7.6 mg/L) and preserved canagliflozin encapsulation within nanomicelles. Polymers with low CMC values allow for the easy formation of colloidal nanomicelles with excellent solubilization ability and stability *in vitro* and *in vivo* [27-28].

The optimal formula CFZ-SNMSD showed a slightly negative surface charge in ZP value; since pure Soluplus® micelles have a slight negative surface charge, this will

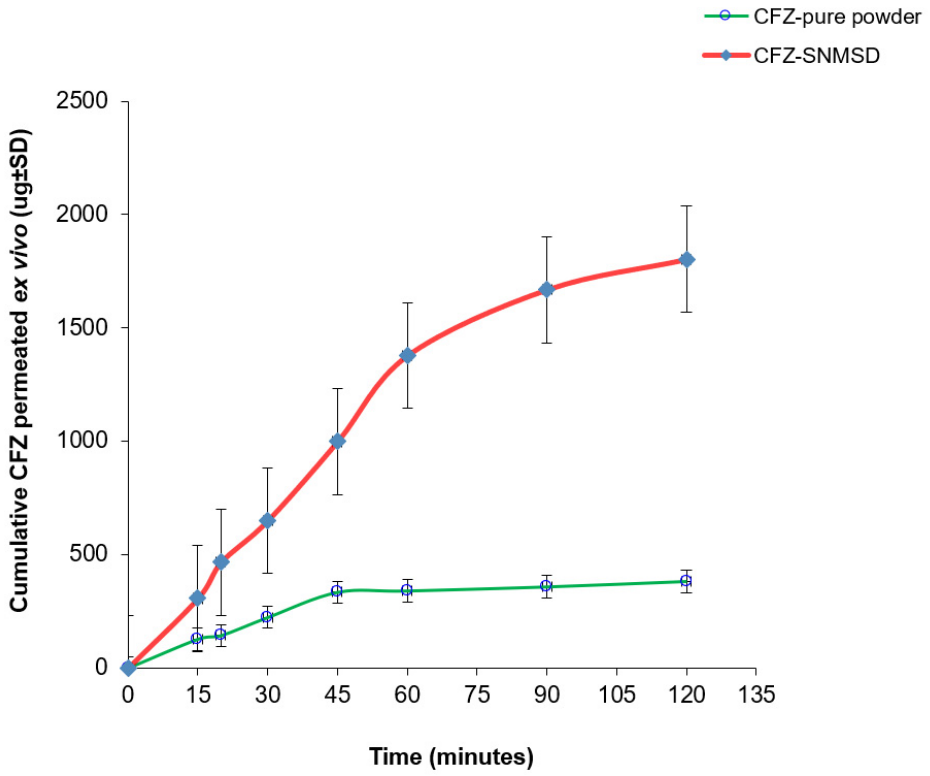

Fig. 4. *Ex vivo* permeation profiles (non-everted rat intestinal membrane, at 37.0±0.5 °C) of: CFZ-SNMSD (optimal formula) and CFZ (pure powder)

Table 2. *Ex vivo* diffusion parameters of permeability study of canagliflozin from CFZ-SNMSD and pure CFZ using non-everted rat intestinal sac model

Sample	Amount diffused within 120 min±SD ($Q_{120\ min}$ (µg)	Flux±SD (µg/min/cm^2)	P_{app} *10 $^{-5}$ ±SD (cm/min)	ER±SD
Pure canagliflozin	383±4.08	0.1928 ±0.01	9.64±0.00	-
CFZ-SNMSD formula	1803±8.60	1.487±0.05	74.35±0.00	7.712±0.03

SD: standard deviation; ER: enhancement ratio; P_{app}: apparent permeability coefficient

make upon loading canagliflozin would imply their complete allocation within the nanomicelles' core rather than on their surface [27].

TEM analysis of the optimal CFZ-SNMSD formula showed spherical or quasi-circular and homogenous nanomicelles with good dispensability, rough surfaces, and disordered shape, indicating the amorphous nature of canagliflozin without crystalline traces.

The optimal CFZ-SNMSD formula enhances canagliflozin solubility compared to pure drug and PM, possibly due to the hydrophilic nature of the carriers used. Soluplus® significantly enhances canagliflozin solubility in the CFZ-SNMSD formula, with a 904.40-fold increase compared to pure drugs, making it the best carrier for self-nanomicellizing formulation. The study found that canagliflozin's solubilization process is more intuitive and favorable for Soluplus® solutions, as indicated by its negative values of the Gibbs free energy (ΔG°) [29].

Soluplus® is an optimal amorphous polymer for improving the canagliflozin dissolution rate in dissolution media. Its increased surface area reduces particle agglomeration and reduces the energy required to break the crystal lattice. The optimized CFZ-SNMSD dissolved well in a dissolution medium water containing 0.75% w/v SLS and showed a higher % DE_{30} than pure drug due to its nanosize and quick self-nanomicellizing rate [30].

Intestinal permeation studies reveal an exponential increase in canagliflozin permeability over time, possibly due to Soluplus® ready dispersibility, solubilization effect, and glycoprotein inhibitory effect, enhancing its bioavailability. The higher P_{app} value for canagliflozin from SNMSD indicates its potential to overcome GIT membrane barriers and facilitate absorption [31].

Conclusions

The study developed a self-nanomicellizing solid dispersion drug delivery system for canagliflozin.

Soluplus® was selected as the best nanocarrier for developing one formulation informed of CFZ-SNMSD based on its potential to improve solubility according to the phase solubility study that includes three nanocarriers (Soluplus®, poloxamer 407, and PEG 8000). Moreover, the optimal CFZ-SNMSD formula performed better in the ex vivo permeability study than pure canagliflozin. The enhancement could be due to an improvement in the solubility and dissolution rate of canagliflozin due to nanomicellization.

Authors' contribution

NAJ (Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, writing – original draft, Writing – review editing)

SNA (Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, writing – original draft, Writing – review & editing, Supervision, Validation)

Conflict of interest

None to declare.

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