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RESEARCH ARTICLE

Preparation and evaluation of self-assembling mixed polymeric nanomicelles drug delivery system for canagliflozin

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Background and objective: Mixed polymeric nanomicelles are nanoscale structures produced by the self-assembly of two or more amphiphilic polymers in an aqueous solution. These nanomicelles are of great interest in a variety of fields, including medication delivery, due to their capacity to encapsulate both hydrophobic and hydrophilic drugs, as well as their stability and capacity to enhance the solubility and bioavailability of poorly water-soluble medications. Our study focuses on preparing and evaluating mixed polymeric self-nanomicellizing solid dispersions (MP-SNMSD) of Canagliflozin (CFZ), a sodium-glucose co-transporter-2 inhibitor used in managing Type 2 Diabetes Mellitus (T2DM). Its poor aqueous solubility and bioavailability remain significant challenges.

Materials and methods: The solvent evaporation technique was employed to create CFZ-MP-SNMSDs using Soluplus® as a main carrier and Solutol® HS15 or D-α-tocopherol polyethylene glycol succinate (TPGS) as the second carrier.

Results: Ten formulations with high drug loading and stability are prepared. Optimized CFZ-MP-SNMSD formula, consisting of 1:1:4 of CFZ: Solutol® HS15: Soluplus®, exhibited reduced particle size (68.44 nm) and improved dissolution rates under non-sink conditions in phosphate buffer pH 6.8, with a 58% release in 60 minutes compared to 18% for the pure drug. X-ray diffraction revealed a transition of CFZ to an amorphous state in an optimized CFZ-MP-SNMSD formula, enhancing solubility. The MP-SNMSD formulations demonstrated significant enhancements in solubility and dissolution efficiency, which will improve the oral bioavailability of CFZ.

Conclusion: These findings suggest that MP- SNMSD formulations represent a promising approach to overcoming the limitations of CFZ, providing a foundation for more effective oral drug delivery systems of hydrophobic drugs and improving therapeutic outcomes.

Keywords: canagliflozin, amphiphilic, nanomicelles, polymeric

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Introduction

Nanomicelles, self-assembling nanosized colloidal dispersions with a hydrophobic core and hydrophilic shell, make for multifunctional applications in biomedical and other fields due to their unique characteristics, such as solubility and customized surface. nanomicelles are formed by amphiphilic molecules at critical temperatures and concentrations [1].

Nanomicelles are thermodynamically and kinetically stable as a result of polymer chains being entangled in their inner core. Kinetic stability becomes significant when drug delivery conditions are not at equilibrium. Amphiphilic polymers have benefits over typical polymers for enhancing the dissolution and absorption of medicines given as amorphous solid dispersion forms. The amphiphilic nature of these newer polymers tends to generate nano- or microscaled micelles via a self-nanomicellization process after dispersal in aqueous media [2-3].

Self-nanomicellizing solid dispersion is a novel formulation approach that combines the beneficial properties of solid dispersion and self-assembling nanomicelles. It improves drugs' solubility, stability, and bioavailability [4-5].

Canagliflozin (CFZ) is a novel orally acting class of sodium-glucose co-transporter inhibitors that reduces the renal tubular reabsorption of glucose into the blood and has been widely used for managing T2DM through insulin-independent mechanisms. CFZ was the first oral anti-diabetic medicine authorized by the FDA in 2018 to prevent cardiovascular disease in people with T2DM. It has a positive effect on lowering serious cardiac events and hospitalization for heart failure. In clinical trials, the drug's half-life was 10.6 hours for a dose of 100 mg and 13.1 hours for 300 mg. It is practically insoluble in solutions from pH 1.1 to 12. However, it is soluble in several organic solvents such as methanol, ethanol, and dimethyl sulfoxide [6-8].

CFZ exhibits potential anti-diabetic activity; however, it encounters biopharmaceutical challenges, notably poor water solubility, poor permeation, and susceptibility to P-glycoprotein (P-gp) mediated efflux. These challenges can lead to erratic bioavailability, which poses a significant obstacle to developing a successful oral drug product [9].

The enhancement of solubility and dissolution of CFZ is the main focus for increasing oral bioavailability. Therefore, the self-nanomicellization of canagliflozin can play a crucial role in overcoming the solubility challenges of the CFZ.

Singh et al.'s 2022 study on natural bio-functional lipids and a solid self-microemulsifying drug delivery system for

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synergistic prevention of Type 2 Diabetes (T2DM) demonstrated the enhanced efficacy of CFZ, a drug combining Trigonelline (TGL) in fenugreek oil. The solid formulation (NADF-SD) was optimized for enhanced surface area, negligible chemical incompatibility, and uniform drug content. Confocal microscopy validated the permeability of the jejunum intestinal segment, showing a significant increase in Cmax and AUC relative to the pure drug and commercial formulations [10].

Fathy Elhabal et al. (2023 have developed CFZ nanocrystal sublingual tablets using sodium caprate permeability enhancers. The nanocrystal-based formulations, suitable for children and adults, improve solubility and avoid enterohepatic circulation through sublingual mucosa absorption. The optimized formula, formulated using PVP-K30, produces the smallest particle size. In an in-vivo investigation, the optimized formula was converted into a sublingual tablet containing Pharma burst-V®, which disintegrated in 51 seconds. The selected tablet improved histological and biochemical markers in diabetic rabbits, including blood glucose, kidney and liver function, and AMP-activated protein kinase pathway. It also increased CFZ's anti-diabetic potency, boosted bioavailability, and produced faster action, suggesting successful diabetes treatment [11].

Soluplus® is soluble in water and organic solvents such as ethanol, methanol, and acetone. It was once utilized to improve the stability and bioavailability of hydrophobic substances. Soluplus® produces smaller spherical micelles in comparison to other surfactants. These Soluplus® characteristics can help improve the dissolving behavior and bioavailability of drugs loaded in SNMSD [12-13].

Solutol® HS15 (polyoxyethylene esters of 12-hydroxystearic acid) is a well-known non-ionic surfactant that has excellent solubility, stability, and negligible toxicity *in-vivo*. Solutol® HS15 has a CMC of 0.005–0.02% in distilled water and a reported HLB value to be 16. It dissolves in water, ethanol, and 2-propanol, forming transparent solutions [14].

D-a-tocopherol polyethylene glycol succinate (TPGS), a derivative of vitamin E (a-tocopherol) and polyethylene glycol 1000. TPGS is frequently used in formulations to increase the solubility and bioavailability of hydrophobic drugs by incorporating them into TPGS nanomicelles. The HLB value of TPGS is approximately 13.2, and it is a non-ionic surfactant. However, TPGS has a reasonably large CMC (0.02%w/w), making its micellar formulation prone to significant dilution. Therefore, TPGS is typically combined with other materials to generate mixed micelle systems [15-16].

Bernabeu et al. (2016) conducted a study for improving paclitaxel (PTX) solubility and anti-tumor activity using Soluplus® and TPGS mixed micelles. The solubility of PTX increased 60000 and 38000 times when formulated in these micelles. The in-vitro PTX release profile from mixed micelles was compared to pure soluplus® micelles, and the drug was accessible in all cell lines. Mixed micelles showed better anti-tumor activity than pure soluplus® micelles against human cancer cell lines, indicating potential as a nano-drug delivery system for cancer chemotherapy [17].

Methods

Materials

CFZ has been bought from Wuhan Senwayer Century Chemical. Co. Ltd, China. Soluplus ® TM was gifted from BASF Pharma. Ethanol 99 % (HPLC grade) was purchased from Merck, USA; Solutol® HS15 and Tocopherol polyethylene glycol1000 succinate (TPGS) from Hangzhou, Hyperchem, China.

Saturation solubility study of CFZ as pure powders

The saturation solubility of pure canagliflozin (CFZ) powder was investigated in various media, including distilled water, 0.1 N hydrochloric acid (HCl), ethanol, and phosphate buffer (pH 6.8). An excess amount of CFZ pure powder was added to 10 mL of each medium in screw-capped glass vials to ensure saturation. The vials were placed in an incubator shaker bath (Model: G.F.L, Karl Kolb, Germany) maintained at 25 ± 0.5 °C and agitated at a constant speed (100 rpm) for 48 hours to reach equilibrium. After incubation, the suspensions were centrifuged at 5000 rpm for 10 minutes (using a Hettich automated centrifuge, Germany). The supernatants were carefully collected and filtered through 0.45 µm syringe filters (China) to remove undissolved particles. The filtered samples were appropriately diluted with their respective media and analyzed spectrophotometrically at λmax = 290 nm using a UV–Visible spectrophotometer (Model: Shimadzu, Japan). All measurements were performed in triplicate, and the solubility of CFZ in each medium was reported as the mean ± standard deviation (SD) [18].

Preparation of CFZ mixed polymeric self-nanomicellizing solid dispersions

A solvent evaporation technique was selected to prepare canagliflozin mixed polymeric self-nanomicellizing solid dispersion CFZ-MP-SNMSD. CFZ-MP-SNMSD was prepared using 100 mg of canagliflozin with different ratios of soluplus and 100 mg of solutol SH15 or TPGS 1000 as a second carrier, as in Table 2. CFZ, the soluplus, and the second carriers (solutol HS15 or TPGS) were dissolved in 10 mL of ethanol using a round-bottom flask of 100 mL in a bath sonicator at 25±0.5 °C. Under reduced pressure, the solvent ethanol was evaporated at 40 °C in a Buchi rotating evaporator revolving at 220 rpm until a thin, dry film formed on the inner surface of the round-bottom flask. The film was crushed and collected by spatula and screened through an 80-dimension mesh to obtain a solid system and stored until used [19].

Mixed polymeric self-nanomicellizing solid dispersions of canagliflozin were prepared in different drug-to-carrier ratios, as shown in Table 1.

Table 1. Composition of canagliflozin mixed polymeric self-nanomicellizing solid dispersions

Formula code	Drug: carrier ratio	Substance			
		Canagliflozin (mg)	Soluplus® (mg)	Solutol SH 15 (mg)	TPGS 1000 (mg)
CFZ-MP-SNMSD 1	1:1:2	100	200	100	
CFZ-MP-SNMSD 2	1:1:3	100	300	100	
CFZ-MP-SNMSD 3	1:1:4	100	400	100	
CFZ-MP-SNMSD 4	1:1:5	100	500	100	
CFZ-MP-SNMSD 5	1:1:6	100	600	100	
CFZ-MP-SNMSD 6	1:1:2	100	200		100
CFZ-MP-SNMSD 7	1:1:3	100	300		100
CFZ-MP-SNMSD 8	1:1:4	100	400		100
CFZ-MP-SNMSD 9	1:1:5	100	500		100
CFZ-MP-SNMSD 10	1:1:6	100	600		100

Characterization

Drug content, drug loading, and percentage yield (PY %)

The CFZ content was determined by dissolving 10 mg of precisely weighed solid dispersion in 10 mL ethanol using a 10 mL volumetric flask, followed by sonication for 10 min. The solutions were filtered by a syringe filter of 0.45 µm and properly diluted, and the concentration of the samples was measured spectrophotometrically [20].

The percentage of CFZ content in the obtained SD was determined by using Equation (1) (See Box 1).

The CFZ loading was calculated from Equations (2) below [21] (See Box 1).

The PY% of CFZ formulas was calculated by dividing the actual mass of the SD formula obtained by the theoretical mass of the same formula using Equation (3) below [22] (see Box 1)

Particle size analysis

Amounts of solid dispersion containing 10 mg of CFZ were dispersed in 10 mL of deionized water and stirred at 300 rpm using a magnetic stirrer for up to one hour. The particle size (PS) and polydispersity index (PDI) of the developed CFZ-loaded polymeric nanomicelles were determined using a Malvern Panalytical Ltd Zetasizer [23].

To ensure nanomicelles particle size stability against dilution with GIT fluid without drug precipitation after being administered, aliquots (1 mL) of each MP-SNMSD were placed into a cell and diluted with deionized water to a total volume of 20 mL and kept at 37 °C. The dispersion was shaken at 50 rpm for 30 min and analyzed to measure any change in nanomicelle mean PS and PDI, which was to be compared with the initial one determined. Each experiment was performed in triplicate [24-25].

Selection of the optimized CFZ formulas

The optimum formula was selected based on numerous parameters of in-vitro evaluation studies: PS, PDI, drug content, % Yield, and stability of PS upon 20-fold dilution. The formula that exhibited the best results in these parameters detailed above was chosen as the optimized formula and kept for further characterization.

Characterization of optimized CFZ-PM-SNMSD formula

Particle size analysis of CFZ-PM-SNMSD in GIT media

The same technique to determine particle size for MP-SNMSD in deionized water was used to measure PS and PDI values of the optimized formula in SGF, pH 1.2, and SIF, pH 6.8, for 3 hours [24].

Determination of the CFZ apparent solubility in the optimized formulation

The CFZ apparent solubility in the optimized MP-SNMSD formula and their corresponding physical mixture (PM) was determined by dispersing excess samples in water in a vial. Sealed vials were shaken at 37 ± 0.5°C for 24 hrs in a water bath shaker that is thermostatically controlled. Samples were centrifuged at 5000 rpm for 10 minutes and filtered using a 0.45µm cellulose acetate syringe filter. The filtrates were diluted, and the CFZ concentration in the solutions was measured by a UV spectrophotometer [26].

X-ray diffraction

The X-ray diffraction (XRD) study aimed to describe the physical structure of CFZ in its pure state, PM, and samples of the optimized MP-SNMSD formula. Samples were scanned using diffraction angles (2θ) between 4° to 40° at

Box 1. Equations

$$\text{CFZ content \%} = \frac{\text{actual weight of canagliflozin}}{\text{theoretical weight of canagliflozin}} * 100 \qquad \text{.....Q (1)}$$

$$\text{CFZ loading \%} = \frac{\text{weight of canagliflozin in MP-SNMSD}}{\text{weight of MP- SNMSD}} * 100 \qquad \text{.....Q (2)}$$

$$\text{\% yield} = \frac{\text{Practical Weight of SD.}}{\text{Theoretical Weight of SD}} \text{x } 100 \qquad \text{.....Q (3)}$$

0.01° sampling width at the scanning speed of 4° per minute. The operational parameters were as follows: generator tension (voltage) of 45 kV, generator current of 40 mA, scan step time of 9 s-1, and scan step size of 0.008 [27].

In-vitro dissolution rate studies

The dissolution conditions for CFZ were carried out in 900 mL dissolution media at 37± 0.5 °C for 120 min in non-sink conditions using USP Apparatus II; phosphate buffer solutions of pH 6.8 were recommended as non-sink dissolution media. Non-sink conditions may better represent the in-vivo situation, where the gastrointestinal fluids are limited to dissolving drugs, particularly for low-solubility compounds. Non-sink conditions can impact concentration gradients on the drug release rate [28].

Dissolution tests were performed using 100 mg of pure CFZ and an equivalent amount from the selected optimized CFZ-MP-SNMSD formula. Before dissolution studies, each formulation was filled in a size "000" hard gelatin capsule. A sinker was attached to each capsule to prevent it from floating. An aliquot of 5 mL was withdrawn at an interval of 5, 10, 15, 20, 30, 45, 60, 90, and 120 min and replaced with a fresh medium to maintain the volume constant. The samples were filtered with syringe filters, and the CFZ concentration was analyzed spectrophotometrically. The dissolution tests were performed in triplicate to validate the reproducibility of the results [29].

Dissolution efficiency (DE) is a parameter for evaluating *in-vitro* dissolution data. The DE (%) was computed by comparing the area under the dissolution curve (AUC, y) up to time t to the area of the rectangle specified as 100% dissolution at the same time as defined by equation 4 (see Box 2) [30], where y represents the y–axis in the dissolution test

Statistical analysis

The study used one-way ANOVA in Microsoft Excel 2016 to compare outcome parameters, identifying statistically significant differences between groups at $P < 0.05$ and non-significant differences at $P > 0.05$. The DDSolver program is for the release test, version 1.0. The experimental data were reported as mean samples ± SD [31].

Results

Canagliflozin saturation solubility in different media

The equilibrium solubility of canagliflozin pure powder in different media is shown in Table 2.

Characterization

Drug content, percentage yield (PY %), and drug loading %

The content, PY %, and drug loading of CFZ in the PM-SNMSD formulations were measured, and the results were represented as mean ±Sd in Table 3.

Particle size analysis

Particle size analysis of PM-SNMSD after dispersion in water was analyzed using a zeta sizer, and the results of PS distribution and PDI are shown in Table 4.

Table 4 further shows the stability of polymeric nanomicelles in preserving their PS upon 20-fold dilution with water. Particle size analysis of solid dispersion during dissolution in water was analyzed using a zeta sizer.

Selection of the optimized CFZ-PM-SNMSD formula

The optimum CFZ-PM-SNMSD formula was selected according to the in-vitro evaluation results (PS measurement (<100nm), PDI, drug content, and % Yield), and the best choice is CFZ-MP-SNMSD 3.

Box 2. Equation

$$DE\% = \left(\frac{\int_0^t y*dt}{y^{100}.t}\right) \times 100 \qquad \ldots\ldots \qquad Q\,(4)$$

Table 2. Saturation solubility of canagliflozin in different media at 25±0.5 °C

Solvent		0.1N HCl	Phosphate buffer (pH 6.8)	ethanol	Water
Solubility of canagliflozin	(mean ±SD)	45.9±3.2 µg/mL	70.6±3 µg/mL	32.815±2.1 mg/mL	36.2±2.3 µg/mL

*SD: The standard deviation from the mean of the triple sample.

Table 3. Drug content, percent of yield, and drug loading % for CFZ-MP-SNMSD formulas (mean ±Sd, n=3)

Formula code	Drug contents %	% yield	Drug loading %
CFZ-MP-SNMSD 1	93±2	Sticky mass	23.25±0.4
CFZ-MP-SNMSD 2	93±2	Sticky mass	18.6±0.32
CFZ-MP-SNMSD 3	96.5±2.1	88.9±1	16±0.3
CFZ-MP-SNMSD 4	95±2	86.3±1	13.57±0.2
CFZ-MP-SNMSD 5	95±2	85.6±1	11.87±0.2
CFZ-MP-SNMSD 6	94±2.5	82.2±2	23.5±0.3
CFZ-MP-SNMSD 7	95±2	84±2.3	19±0.4
CFZ-MP-SNMSD 8	96±2.1	84.4±1	16±0.25
CFZ-MP-SNMSD 9	96±2.2	86.7±1.2	13.71±0.2
CFZ-MP-SNMSD 10	96±2	88.5±1.4	12±0.2

Table 4. Particle size and PDI measurement before and after 20-fold dilution of the prepared CFZ-MP-SNMSD formulas (mean±Sd, n=3)

Formula code	Z-Ave (nm)±Sd	PDI± Sd	Diluted 20-fold		Commentary
			Z-Ave (nm)±Sd	PDI± Sd	
CFZ-MP-SNMSD 1	82.33±2	0.193±0.01	117.5±1	0.244±0.1	Stable
CFZ-MP-SNMSD 2	75.2±1.0	0.0133±0.002	84.72±1.1	0.0266±0.01	Stable
CFZ-MP-SNMSD 3	68.44±1.2	0.032±0.01	68.74±1	0.0367±0.01	Stable
CFZ-MP-SNMSD 4	70.32±2.1	0.002±0.0	105.5±2	0.151±0.02	Stable
CFZ-MP-SNMSD 5	79.76±2	0.17±0.01	129±2	0.249±0.03	Stable
CFZ-MP-SNMSD 6	246.9±4	0.431±0.2	828±5	0.8±0.2	Unstable
CFZ-MP-SNMSD 7	120.7±5	0.128±0.01	188.4±2	0.26±0.0	Stable
CFZ-MP-SNMSD 8	99.24±3	0.17±0.01	100.1±1	0.3016±0.1	Stable
CFZ-MP-SNMSD 9	77.08±2	0.0268±0.01	122±2	0.32±0.13	Stable
CFZ-MP-SNMSD 10	83.39±2	0.237±0.01	165±2	0.41±0.11	Stable

Particle size analysis of CFZ- SNMSD in GIT media

The PS and PDI values of the optimized formula CFZ-MP-SNMSD 3 in SGF, pH 1.2, are found to be 71.15 nm and 0.073, respectively. In SIF, pH 6.8, the PS and PDI values were 73.36 nm and 0.035, respectively.

Apparent solubility study of CFZ-PM-SNMSD optimized formula

The apparent solubility of CFZ in the optimized PM-SNMSD formula and corresponding physical mixture in water at 37 ± 0.5 oC after 24 hr is shown in Table 5

The optimized CFZ-PM-SNMSD 3 formula shows a remarkable solubility improvement in CFZ relative to pure CFZ and PMs of each formula.

Table 5. The apparent solubility of CFZ from the optimized formula and corresponding physical mixture in water at 37 ± 0.5 °C after 24 hours (mean, n=3)

code	apparent solubility ug/ml
Pure drug	57.2
PM	16011
CFZ-MP-SNMSD 3	46674

X-ray diffraction

The X-ray diffractogram of CFZ is shown in Figure 1A. The XRD of the PM of canagliflozin with the carriers as the ratio in the optimized formula is represented in Figure 1B. Whereas the optimized CFZ-MP-SNMSD 3 formula is represented in Figure 1C.

In-vitro dissolution study

Figure 2 illustrates the dissolution rate of optimized formulations in phosphate buffer pH 6.8 compared to pure CFZ.

DE % was measured for up to 30 min of drug release for the optimized CFZ-PM-SNMSD formula and pure CFZ in phosphate buffer pH 6.8 dissolution media, and found to be 32.16 % compared to 11% of pure drug.

Discussions

The equilibrium solubility of CFZ pure powder in water, 0.1N HCl, and phosphate buffer pH 6.8 was low, indicating the need to enhance its aqueous solubility. However, canagliflozin was found to be soluble in ethanol solution [29].

The results indicate excellent miscibility and effective formulation of the dispersion system with a high percentage of drug content. The percent CFZ content in PM-SNMSD formulations was from 93% to 96.5 %w/w ± Sd. These data indicate that the preparation technique resulted in low loss of canagliflozin and uniform solid dispersion. The practical percentage yields were calculated to determine the efficiency of the preparation methods, and it help select appropriate production methods. All formulations showed good percentage yield ranging from 82.2% to 88.9%±Sd (except for CFZ-MP-SNMSD 1 and CFZ-MP-SNMSD 2 formulas, which resulted in sticky mass that was unable to sieve due to the high content of Solutol® HS15 compared to other formulas). It was found that as the drug: polymer ratio increased, the % yield was found to increase. This may be because increasing the drug: polymer ratio increases the bulk of solid dispersion and decreases the product's stickiness, which aids in collecting material from the round-bottom flask. This result indicates that this method was suitable and efficient for preparing CFZ-MP-SNMSD.

At present, most nanoparticle systems have relatively low drug loading (<10 wt%), making it challenging to find techniques to improve drug loading. In our study, drug loading was 11.87±0.2 to 23.5±0.3 %w/w, which is (>10 wt%), indicating good drug loading % [32].

In CFZ-PM-SNMSD formulations, the results indicated that the formulations containing Solutol® HS15 as a second carrier with Soluplus® (CFZ-MP-SNMSD 1-CFZ-MP-SNMSD 5) showed better results in terms of PS and PDI than those containing TPGS (CFZ-MP-SNMSD 6 - CFZ-MP-SNMSD 10); these results were due to the low CMC of Solutol® HS15 (0.005-0.02% in water) compared to TPGS, which imparted high physical stability and preserved canagliflozin encapsulation [33].

Also, to ensure the stability of the nanomicelles particle size upon dilution with a large volume of fluids in the GIT, the PS was analyzed after a 20-fold dilution with water. The capacity of mixed polymeric nanomicelles to retain their initial PS after dilution in water was assessed as a means for evaluating their stability following systemic administration, where contact with physiological fluids can induce a de-aggregation of nanomicellar assembly and a rapid leakage of the entrapped active substance.

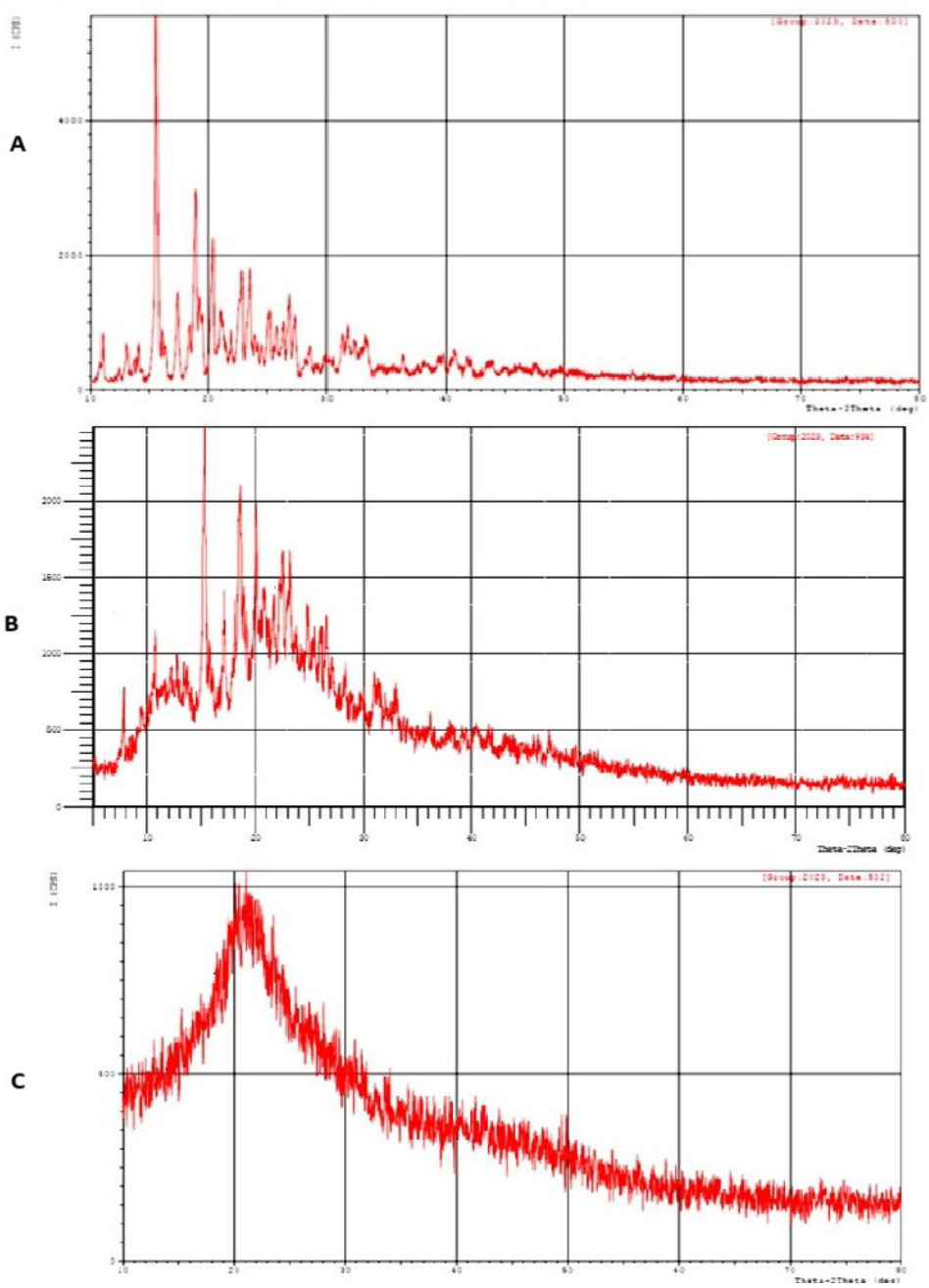

Fig. 1. A. X-ray powder diffraction of pure canagliflozin; B. X-ray powder diffraction of a physical mixture of canagliflozin: solutol SH15: soluplus at a ratio of 1:1:4; C. X-ray powder diffraction of optimized formula CFZ-MP-SNMSD

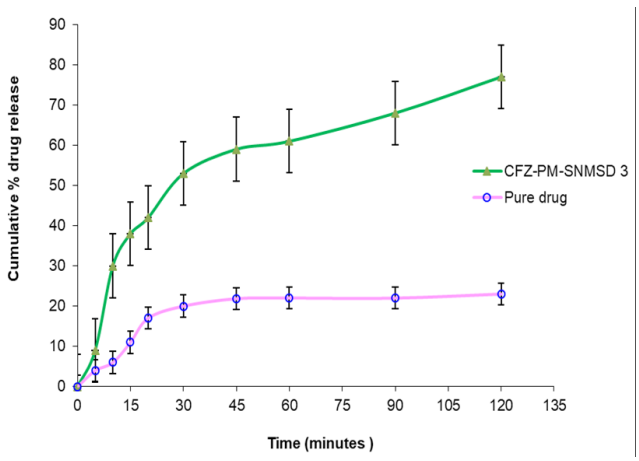

Fig. 2. Release profile of optimized canagliflozin formulations and pure drug according to dissolution test (mean, n=3) in 900 ml phosphate buffer pH 6.8 at 37.0 ± 0.5 °C at 75 rpm

The nanomicelles PS were stable for mixed polymeric nanomicelles, maintaining a mean size close to the initial one. Soluplus® is a hydrophilic graft copolymer that can quickly produce colloidal nanomicelles with excellent solubilization capability and stability due to its extremely low value of CMC (0.0076 mg/mL). Solutol® HS15 has a CMC of 0.05-0.2 mg/mL in distilled water [34-35].

Changes in pH can induce conformational changes in the copolymer molecules, altering their overall structure and interactions. This might result in a shift in the equilibrium between different conformations, which could contribute to changes in particle size [36].

A slight increase in particle size was seen in gastric pH in the optimized CFZ-PM -SNMSD 3. In an acidic medium, the ionization of functional groups on the polymer can affect the overall electrostatic interactions between the polymer and the surrounding solvent molecules. This can influence the degree of solvation and hydration of the polymer chains. The polymer chains within Soluplus nanomicelles can undergo conformational changes in response to pH variations [37].

When the formulas are incubated in SIF pH 6.8, the PS and PDI are slightly increased in the optimized formula; this could weaken the hydrophilic interactions that stabilize the nanomicelles, leading to swelling and partial disruption of the micelle structure. Swelling of nanomicelles could occur if the disruption of hydrophilic interactions causes the copolymer chains to expand, increasing particle size. On the other hand, aggregation could result from stronger hydrophobic interactions, causing individual nanomicelles to cluster together [38].

The huge increase in CFZ solubility can be attributed to the fact that CFZ inside self-nanomicellizing solid dispersion is in the amorphous state with higher Gibbs free energy than in the crystalline state, and the molecular crystal lattice at the amorphous state can be broken freely [19].

X-ray diffractogram of CFZ, as shown in Figure 1A, shows a random distribution of crystalline solids with intense, sharp diffraction peaks at various 2θ degrees of 15.621°, 18.897°, 20.359°, and 23.45°, respectively. As shown in Figure 1B, a PM of CFZ with carriers at a ratio as optimized formula (CFZ-PM-SNMSD 3) was detected with partial amorphization. The crystallinity was absent in the optimized formula CFZ-PM-SNMSD 3, as in Figure 1C, indicating changes in the overall geometry from crystalline to amorphous form, revealing an excellent molecular dispersion of CFZ in mixed polymeric self-nanomicellizing solid dispersion [39].

Sink conditions are desirable but not mandatory for an *In-vitro* dissolution study. To test their dissolution, non-sink conditions were investigated for drugs with low water solubility prepared as self-nanomicellizing solid dispersion [40].

Non-sink conditions can simulate drug release in vivo, where the drug concentration in the gastrointestinal fluids is not constant and may influence the absorption rate and extent.

In phosphate buffer solution pH 6.8, the Pure drug showed both poor and fair release characteristics, possibly owing to low CFZ aqueous solubility in this media, resulting in hindered dissolution. In-vitro release assay of CFZ-PM-SNMSD 3 formula revealed that about 58 % of the drug was released in 60 min compared to 18% for pure drugs. Experimental observations indicated that the carrier used for the CFZ-PM-SNMSD 3 formula eliminates the influence of the low solubility of CFZ in non-sink dissolution conditions. The formula has a smaller PS and narrower size distribution, which also contributes to producing a higher dissolution rate compared to the pure drug formula [9].

The enhancement in release behavior of CFZ from the CFZ-PM-SNMSD 3 formula in the dissolution media was found to be statistically significant ($p < 0.05$) than pure CFZ. It might be attributed to the size of the CFZ-PM-SNMSD 3 formula and quick self-nanomicellizing rate, which leads to immediate solubilization of the drug and causes a profound dissolution rate.

DE is another parameter suitable for evaluating *in-vitro* dissolution, which has been suggested by Khan and Rhodes (1972) [41].

The optimized formula CFZ-PM-SNMSD 3 dissolved well after 30 min in the dissolution medium. They showed DE30 more than 30 %, which is higher than the pure drug (DE30, pure CFZ = 11%). This is due to the increasing solubility of CFZ by the nanomicellization and amorphous carrier presence surrounding the drug particles [42].

Conclusion

Based on the results, Canagliflozin can efficiently be formulated as a PM-SNMSD using solvent evaporation techniques. The carrier selected (soluplus and solutol SH15) was appropriately and successfully competent to produce nanomicelles with the acceptance size and in vitro stability. XRD studies indicate the transformation of CFZ to an amorphous state in the optimized formula

Authors' contributions

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

Conflict of interest

None to declare.

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