Rev. Colomb. Cienc. Quím. Farm., **54**(1), 272–285 (2025)

Technological research article

In-vivo pharmacokinetics evaluation of canagliflozin self-nanomicellizing solid dispersion as oral capsules dosage forms

Nizar Awish Jassem

Department of Pharmaceutics, College of Pharmacy, Al-Farahidi University, Baghdad, Iraq

ORCID ID: https://orcid.org/0000-0002-0338-8296
E-mail: nazar.jassem@uoalfarahidi.edu.iq

Received: November 5, 2024
Corrected: February 4, 2025
Accepted: February 11, 2025

https://doi.org/10.15446/rcciquifa.v54n1.117438

SUMMARY

Background: Self-nanomicellizing solid dispersion (SNMSD) is a method that integrates the advantages of solid dispersion with nanomicelles, enhancing the oral bioavailability of poorly water-soluble pharmaceuticals. This solid drug delivery system, when it comes into contact with GIT fluids, it forms nanomicelles. Canagliflozin (CFZ), a sodium-glucose co-transporter inhibitor, has become popular for managing type 2 diabetes. CFZ faces biopharmaceutical challenges such as poor water solubility, poor permeation, and susceptibility to P-glycoprotein mediated efflux, posing challenges for its pharmaceutical development. This study aims to compare the in-vivo pharmacokinetic parameters of CFZ in rats when prepared as SNMSD versus CFZ-suspension. ***Methods****:* The SNMSD formula was prepared using a solvent evaporation method using soluplus as a nanocarrier in a drug-to-carrier ratio of 1:4. The *in-vivo* studies were conducted on twelve male Wister rats with an average weight of 230±9.3 g. The rats were divided into two groups. In Group 1, the rats were orally administered pure CFZ in 0.1% w/v carboxymethylcellulose 2 mg/mL suspension. In Group 2, the rats were administered the identical dosage of the CFZ-SNMSD formula dissolved in water given orally. ***Results****:* The pharmacokinetics parameters in rats were obtained from plasma concentration/time data of the prepared CFZ-SNMSD formula, and these parameters were significantly higher ($p < 0.05$) when compared with CFZ-suspension. C_{max} for the CFZ-SNMSD formula was 4109 ng/ml, and T_{max} was 2 hours compared to the CFZ-suspension C_{max} value of 1401 ng/mL and 4 hours. The relative bioavailability of canagliflozin for oral SNMSD capsule to oral suspension was equal to 204.7%. This is due to soluplus® dispersibility, solubilization, and p-glycoprotein inhibitory effect, overcoming GIT membrane barriers. ***Conclusions:*** The utilization of SNMSD demonstrated great promise as an oral delivery system to enhance the oral bioavailability of canagliflozin.

Keywords: Self-nanomicellizing; pharmacokinetics; bioavailability; canagliflozin

RESUMEN

Evaluación de la farmacocinética *in vivo* de la dispersión sólida auto-nanomicelizante de canagliflozina en cápsulas orales

Antecedentes: La dispersión sólida auto-nanomicelizante (SNMSD) es un método que combina las ventajas de la dispersión sólida con nanomicelas, mejorando la biodisponibilidad oral de fármacos poco solubles en agua. Este sistema de liberación de medicamentos sólidos forma nanomicelas al entrar en

contacto con los fluidos del tracto gastrointestinal (GIT). La canagliflozina (CFZ), un inhibidor del cotransportador de sodio-glucosa, ha ganado popularidad para el tratamiento de la diabetes tipo 2. Sin embargo, CFZ enfrenta desafíos biofarmacéuticos, como baja solubilidad en agua, baja permeación y susceptibilidad a la expulsión mediada por la glicoproteína P, lo cual representa un reto para su desarrollo farmacéutico. Este estudio tiene como objetivo comparar los parámetros farmacocinéticos in vivo de CFZ en ratas cuando se prepara como SNMSD en comparación con una suspensión de CFZ. **Métodos:** La fórmula SNMSD se preparó mediante un método de evaporación de solvente utilizando soluplus como nanotransportador en una relación fármaco-transportador de 1:4. Los estudios in vivo se realizaron en doce ratas Wister machos con un peso promedio de 230 ± 9,3 g. Las ratas se dividieron en dos grupos: en el Grupo 1, las ratas recibieron oralmente CFZ puro en una suspensión de 2 mg/mL en carboximetilcelulosa al 0,1% p/v. En el Grupo 2, las ratas recibieron la misma dosis de la fórmula CFZ-SNMSD disuelta en agua por vía oral. **Resultados:** Los parámetros farmacocinéticos en ratas se obtuvieron a partir de datos de concentración plasmática/tiempo de la fórmula CFZ-SNMSD, y estos parámetros fueron significativamente más altos ($p < 0,05$) en comparación con la suspensión de CFZ. El valor de Cmax para la fórmula CFZ-SNMSD fue de 4109 ng/ml, y el T_{max} fue de 2 horas en comparación con el valor de C_{max} de 1401 ng/mL y T_{max} de 4 horas de la suspensión de CFZ. La biodisponibilidad relativa de la canagliflozina para la cápsula oral de SNMSD en comparación con la suspensión oral fue del 204,7%. Esto se debe a la capacidad de dispersión, solubilización y el efecto inhibidor de la glicoproteína P de Soluplus®, superando las barreras de la membrana del GIT. **Conclusiones:** El uso de SNMSD demostró un gran potencial como sistema de liberación oral para mejorar la biodisponibilidad de la canagliflozina.

Palabras clave: Auto-nanomicelizante; farmacocinética; biodisponibilidad; canagliflozina

RESUMO

Avaliação farmacocinética *in vivo* da dispersão sólida autonanomicelizante de canagliflozina como formas de dosagem de cápsulas orais

Contexto: A dispersão sólida autonanomicelizante (SNMSD) é um método que integra as vantagens da dispersão sólida com nanomicelas, aumentando a biodisponibilidade oral de produtos farmacêuticos pouco solúveis em água. Este sistema de administração de medicamentos sólidos, quando entra em contato com fluidos do TGI, forma nanomicelas. A canagliflozina (CFZ), um inibidor do cotransportador de sódio-glicose, tornou-se popular no tratamento do diabetes tipo 2. A CFZ enfrenta desafios biofarmacêuticos, como baixa solubilidade em água, baixa permeação e suscetibilidade ao efluxo mediado pela glicoproteína P, o que representa desafios para seu desenvolvimento farmacêutico. Este estudo tem como objetivo comparar os parâmetros farmacocinéticos in vivo da CFZ em ratos quando preparada como SNMSD versus suspensão de CFZ. **Métodos:** A fórmula SNMSD foi preparada usando um método de evaporação de solvente usando Soluplus como nanocarreador em uma proporção de fármaco para carreador de 1:4. Os estudos in vivo foram conduzidos em doze ratos Wister machos com peso médio de 230 ± 9,3 g. Os ratos foram divididos em dois grupos. No Grupo 1, os ratos receberam CFZ puro por via oral em suspensão de carboximetilcelulose 0,1% p/v 2 mg/mL. No Grupo 2, os ratos receberam a dosagem idêntica da fórmula CFZ-SNMSD dissolvida em água administrada por via oral. **Resultados:** Os parâmetros farmacocinéticos em ratos foram obtidos a partir de dados de concentração plasmática/tempo da fórmula CFZ-SNMSD preparada, e esses parâmetros foram significativamente maiores ($p < 0,05$) quando comparados com a suspensão CFZ. C_{max} para a fórmula CFZ-SNMSD foi de 4109 ng/ml, e T_{max} foi de 2 horas em comparação com o valor C_{max} da suspensão CFZ de 1401 ng/mL e 4 horas. A biodisponibilidade relativa da canagliflozina para cápsula oral de SNMSD para suspensão oral foi igual a 204,7%. Isso se deve à dispersibilidade, solubilização e efeito inibitório da glicoproteína P do Soluplus®, superando as barreiras da membrana do TGI. **Conclusões:** A utilização de SNMSD demonstrou grande promessa como um sistema de administração oral para aumentar a biodisponibilidade oral da canagliflozina.

Palavras-chave: Autonanomicelização; farmacocinética; biodisponibilidade; canagliflozina

1. INTRODUCTION

Self-nanomicellizing solid dispersion combines widely accepted solid dispersions and nanomicelles strategies to improve the oral bioavailability of challenging drugs. This novel strategy offers the advantage of solid dispersion and nanotechnology-based approaches as it forms nanosized micelles upon contact with an aqueous media. It combines an active pharmaceutical ingredient with a single or multiple amphiphilic block copolymer. It can achieve high dissolution characteristics of poorly water-soluble compounds by its self-nanomicellizing potency [1, 2].

Canagliflozin (CFZ) is a new orally active sodium-glucose co-transporter (SGLT II) inhibitor that diminishes renal tubular glucose reabsorption and is extensively utilized for the management of type 2 diabetes mellitus (T2DM) via insulin-independent mechanisms [3].

CFZ has an absolute oral bioavailability of about 60-65%, with plasma protein binding of 99%. After a single oral dosage, CFZ terminal half-life was 10.6-13.1 hrs. It is practically insoluble in aqueous media with a significant volume of distribution of 119 L [4]

Despite its promising anti-diabetic activity, CFZ faces biopharmaceutical challenges such as 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 [5].

Soluplus® is an amphiphilic copolymer utilized to improve the stability and bioavailability of hydrophobic substances. It forms a micelle with the drug through interactions between its hydrophilic and hydrophobic regions [6].

Patil *et al.* 2023 studied and evaluated *in-vitro, in-vivo,* and *in-silico* molecular docking canagliflozin hemihydrate-loaded bilosomes using the solvent evaporation method. The optimized formulation was tested for *in-vitro* drug release, *in-vivo* pharmacokinetic evaluation, and *in-silico* molecular docking to determine sodium deoxycholate's ability to lower blood sugar levels. The optimized CFZ-blossoms showed a 92.60% w/w EE and 177.40 nm vesicle size, significantly increasing CFZ release compared to CFZ in aqueous dispersion. CFZ-Bilosomes increased C_{max} by 1.5 times, increased bioavailability by 1.6-fold when formulated as Bilosomes, and *in-silico* molecular docking demonstrated hypoglycemic potential when combined with SDC, suggesting potential synergistic treatment for diabetes mellitus [7].

Singh *et al.* in 2021 focus on optimizing and evaluating a polymeric precipitation inhibitor-based supersaturable self-microemulsifying drug delivery system for the biopharmaceutical classification system (BCS) class IV drug CFZ. The selected formula (OSS 1), containing 781.1 mg supersaturable self-microemulsifying drug delivery system (SS SMEDDS) and 2.24% w/w Poloxamer 188, showed negligible aggregation and physical stability under various stress conditions. The formulation had an elevated solubility rate of CFZ compared to pure CFZ, and its permeability across different excised regions of the rat intestine was much greater, exhibiting a higher C_{max} and AUC $_{0\text{-}48}$ h following oral treatment to Wistar rats. The research indicated that the considerable absorption of CFZ in SS SMEDDS was due to its affinity for P-glycoprotein substrates and considerable lymphatic absorption [8].

This study compares the *in-vivo* oral bioavailability pharmacokinetic parameters of CFZ when applied as SNMSD versus CFZ-suspension.

2. METHODS

2.1. Materials

CFZ was purchased from Wuhan Senwayer Century Chemical. Co. Ltd, China. Soluplus® from gifted BASF pharma. Dapagliflozin was gifted from Pioneer, Iraq. Ethanol 99 % (HPLC grade) was purchased from Merck, USA; Acetonitrile-HPLC grade purchased from Biosolve B V, France; and carboxymethyl cellulose and Magnesium stearate from Glentham, UK. All other reagents in this research were of analytical grade.

2.2. Preparation of self-nanomicellizing solid dispersion capsules

A solvent evaporation method was selected to prepare CFZ-SNMSD. Briefly, 100 mg of CFZ and 400 mg of soluplus were dissolved in 10 mL of ethanol using a 100 mL round-bottom flask in a bath sonicator at 25.0 ±0.5 °C. The ethanol was evaporated at 40 °C under reduced pressure in a rotating evaporator (Buchi, turkey) revolving at 220 rpm until a thin, dry film formed on the flask's inner wall. The film was crushed and collected by spatula and screened through an 80-dimension mesh to obtain a solid system named CFZ-SNMSD and stored [9, 10]. Figure 1 shows the preparation method of CFZ-SNMSD using the solvent evaporation method.

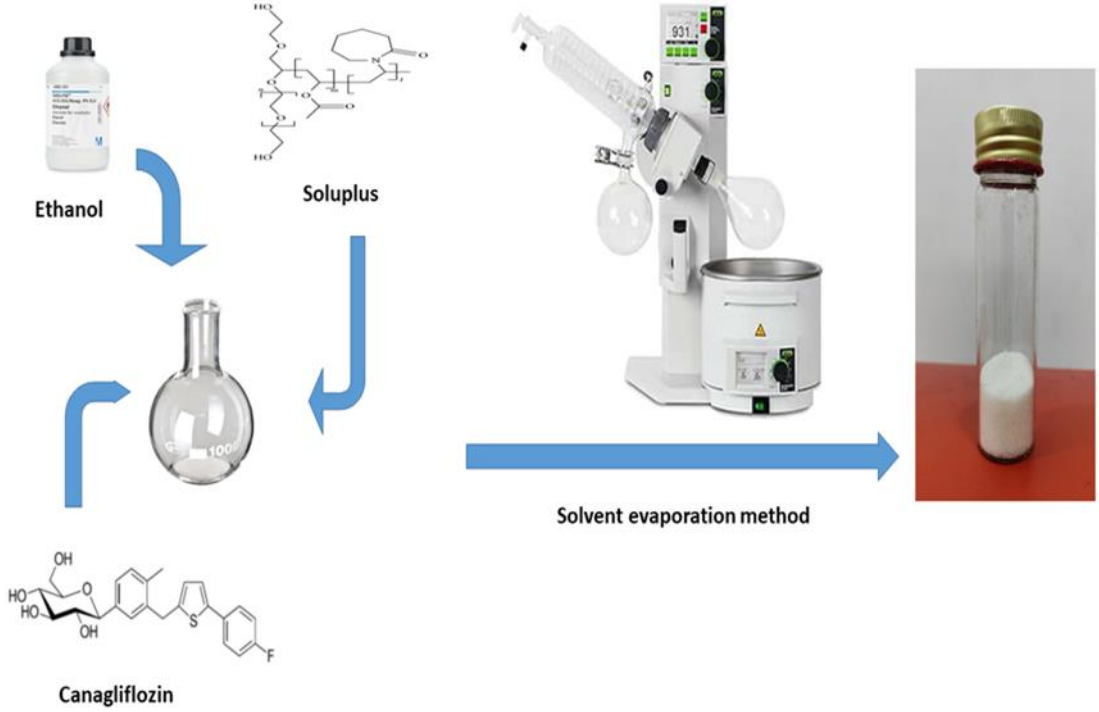

Figure 1. Solvent evaporation method of preparation of CFZ-SNMSD system

For the formulation of capsules, the capsule filler powder was prepared by mixing selected CFZ-SNMSD formula powder with an excipient. The capsules were prepared using the manual capsule-filling machine (Capsuline, Davie, FL, USA). The compositions of the CFZ - capsules are described in Table 1

Table 1. Compositions of the CFZ-Capsules Formula

Materials	**Amounts**
Powder equivalent to 100 mg CFZ-SNMSD	515.5 mg powder of CFZ-SNMSD
Avicel PH102	229.5 mg
Magnesium stearate	5 mg
Total weight	750 mg

2.3. Characterization of selected CFZ solid dispersion

2.3.1. Particle size and zeta potential analysis

Amounts of solid dispersion equivalent to 10 mg of CFZ were dispersed in 10 mL of deionized water and stirred at 300 rpm with a magnetic stirrer for up to one hour, filtered by a 0.45-µm cellulose acetate syringe. The particle size (PS) and polydispersity index (PDI) of the developed CFZ-loaded nanomicelles were determined using a Malvern Panalytical Ltd Zetasizer. The electrophoretic mobility of the selected formula was assessed and converted to zeta potential. The zeta potential value indicates the charge on the nanomicelles [11].

2.4. *In-vivo* pharmacokinetic study

2.4.1. Animals

The *in-vivo* studies were conducted on male Wister rats (n=12) with an average weight of approximately 230±9.3 g. Upon procurement, the rats could acclimate for at least one week under standard room temperature conditions (25 ±3 °C). This acclimatization period guarantees that the rats adjust to their new surroundings before the commencement of the study.

2.4.2. Dose calculation

The dose of CFZ for rats was estimated based on the body weight of the rats and the surface area ratio. The animal dose can be calculated using equation 1 [12].

$$\text{Animal dose } \left(\frac{\text{mg}}{\text{kg}}\right) = \text{human dose } \left(\frac{\text{mg}}{\text{kg}}\right) \text{x conversion factor} \quad \text{…..... Eq. (1)}$$

The correction factor for rats weighing 0.080 - 0.250 kg is 6.17
When a typical rat weighs 230 g, the human weight is 70 kg, and the average human oral dose of CFZ is 100 mg, converted to mg /kg by dividing it by human weight (70 kg), equal to 1.4285 mg/kg.
The oral dose of rats = 1.428 ×6.17
Oral dose of rats = 8.81 mg /kg
The oral dose for each rat = 2 mg

2.4.3. Study design

The rats were partitioned into two groups, each including six rats. In Group 1, the rats were orally administered 8.8 mg/kg of pure CFZ in 0.1% w/v carboxymethylcellulose (CMC) suspension to give 2 mg/mL. In Group 2, the rats were administered the same dose of the CFZ-capsule dissolved in water to obtain 2 mg/mL, also given orally. Before the administration, the rats were fasted overnight but had free access to water throughout the study. The formulation was administered to the rats using a gavage tube. This method of administration ensures precise dosing of the drugs to the rats. Blood samples were obtained from the retro-orbital venous

plexus before dosage administration to acquire a baseline measurement (time point zero) and after administration at different time intervals at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hrs, in EDTA vacuum glass tubes. The plasma was separated by centrifugation in the centrifuge (Hettich, Germany) at 6000 rpm for 10 min and kept at −25 °C until analysis [13].

2.4.4. HPLC determination of canagliflozin

The Shimadzu HPLC system was used for this study. HPLC system with a UV detector, micro-volume double plunger pump along 4.6 *150mm C-18 analytical column maintained at room temperature. HPLC analysis was performed under the following conditions: The mobile phase consists of HPLC grade of acetonitrile: 0.1% w/v orthophosphoric acid at a ratio of 50:50 % v/v at ambient temperature. The mobile phase was filtered by a 0.45 μm filter before use, and the injection volume was 20 μL. The mobile phase was kept at a 1.0 mL/min flow rate. The UV detector was employed to detect the substance at a wavelength of 290 nm, and the running time was 10 minutes. The column was equilibrated for a minimum of 25 minutes before the injection of the drug solution, with the mobile phase flowing through the system. The method was validated using canagliflozin by ICH and FDA criteria regarding specificity/selectivity, linearity, LOD, LOQ, accuracy, and precision [14].

2.4.5. Sample preparation

A simple liquid-liquid extraction technique was used to extract analyte and IS from plasma. The plasma samples (stored at −20 °C) were allowed to be thawed before sample preparation. An aliquot of 200 μL of plasma sample and 20 μL of IS solution (10 μg/mL of dapagliflozin) was added into the tube and vortex-mixed for 30 seconds, followed by the addition of 2 mL of acetone into each tube. The vortex mixing was conducted for 1 minute, subsequently followed by centrifugation at 5000 rpm for 4 minutes. After centrifugation, the organic portion was transferred to an acrylic tube, evaporated to dryness, and reconstituted with 200 μL of mobile phase; from this, 20 μL was injected into the HPLC for analysis. The unknown concentration of CFZ was calculated using the equation obtained from the spiked calibration curve [15].

2.4.6. Pharmacokinetic evaluation

Pharmacokinetic (PK) parameters were evaluated using conventional noncompartmental methods with the aid of PK solver software. The plasma concentration-time data determined essential pharmacokinetic parameters, including C_{max}, T_{max}, $t_{1/2}$, and AUC_{0-48} of CFZ [16].
Relative bioavailability (F) is calculated by equation 2: [17].

$$F\ relative = \frac{AUC\ standard * dose\ test}{AUC\ test * dose\ standard} \times 100 \quad \ldots\ldots\ldots\ldots\ldots Q(2)$$

2.4.7. Statistical analysis

The study employed one-way ANOVA to analyze results parameters, identifying statistically significant differences between groups at p values of $P < 0.05$ and non-significant at $P > 0.05$ using Microsoft Excel 2016. The experimental results were presented as the mean samples ± Sd. The PK parameters, such as C_{max}, T_{max}, and AUC_{0-48}, underwent statistical examination by a Student's t-test [18].

3. RESULTS

3.1. Particle size and zeta potential analysis

In the selected CFZ- solid dispersion formula at a ratio of CFZ: Soluplus® 1:4, which gives PS of 61.79±1.06 nm with PDI of 0.058±0.002, indicating good formulation stability upon dilution in GIT. Figure 2 shows the average particle size for the selected CFZ- SNMSD formula. Zeta potential determined for selected CFZ-solid dispersion. The result indicates a value of –9.4 mV ±0.2 of the Zeta potential d for selected CFZ- SNMSD as shown in Figure 2 which revealed the intensity and position of the zeta peak for the selected formula.

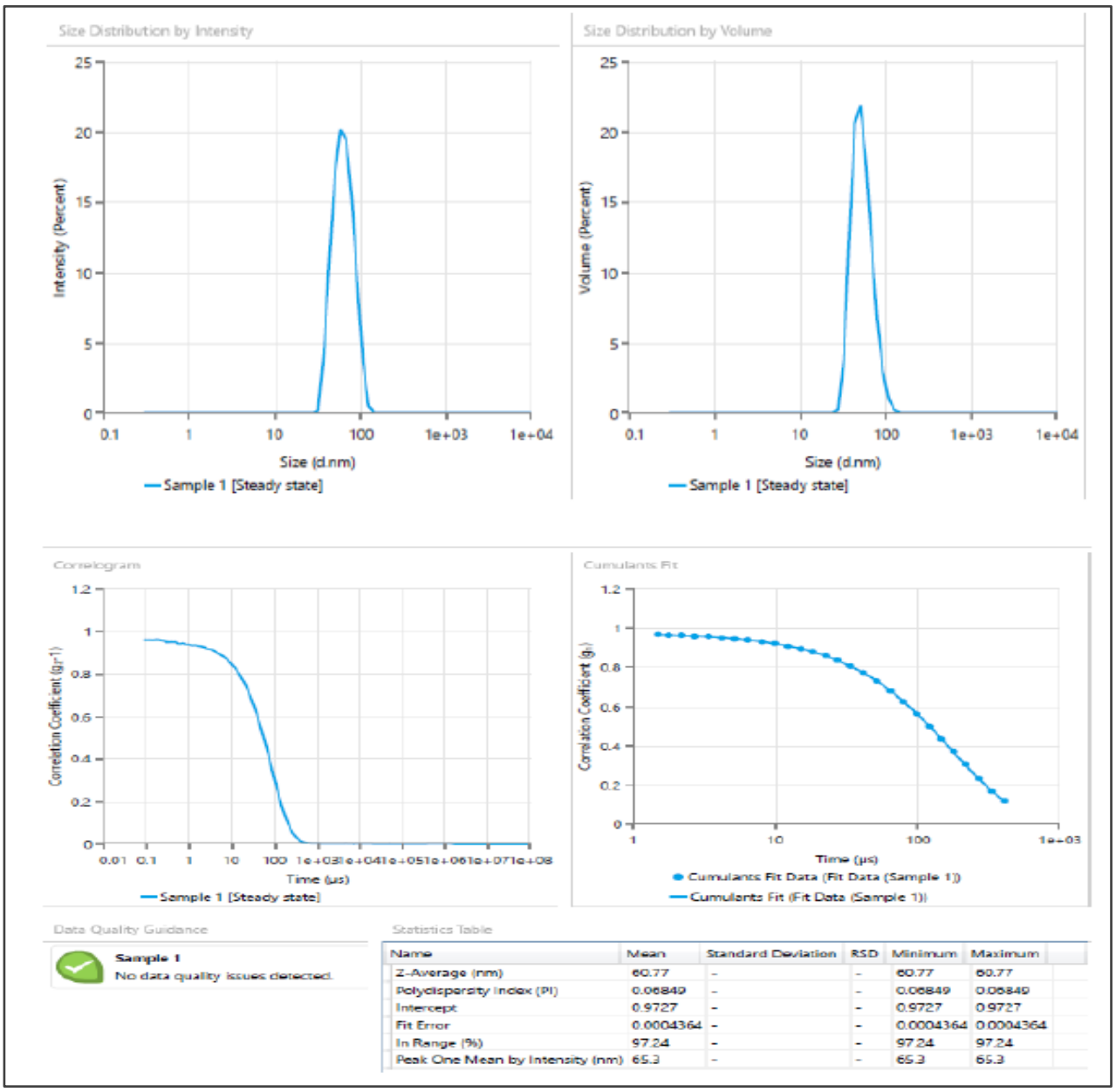

Figure 2. Average particle size for selected CFZ- SNMSD formula by Malvern zeta seizer represents the intensity of particle size and the cumulative data

3.2. Preparation of CFZ-SNMSD capsules

Hard gelatin capsules of 000 size were used in filling CFZ-capsule since they are the most suitable size for the contents of dose encapsulation, according to calculation, depending on the tapped density of the blending power for capsules obtained.

3.3. Validation of the HPLC method

The plasma sample demonstrated symmetric peaks with retention times of about 4.79 min for CFZ and 2.92 min for dapagliflozin (IS), as illustrated in Figures 3A and B, respectively. In contrast, Figure 3C is HPLC Chromatograms of CFZ in plasma spiked with IS (dapagliflozin).

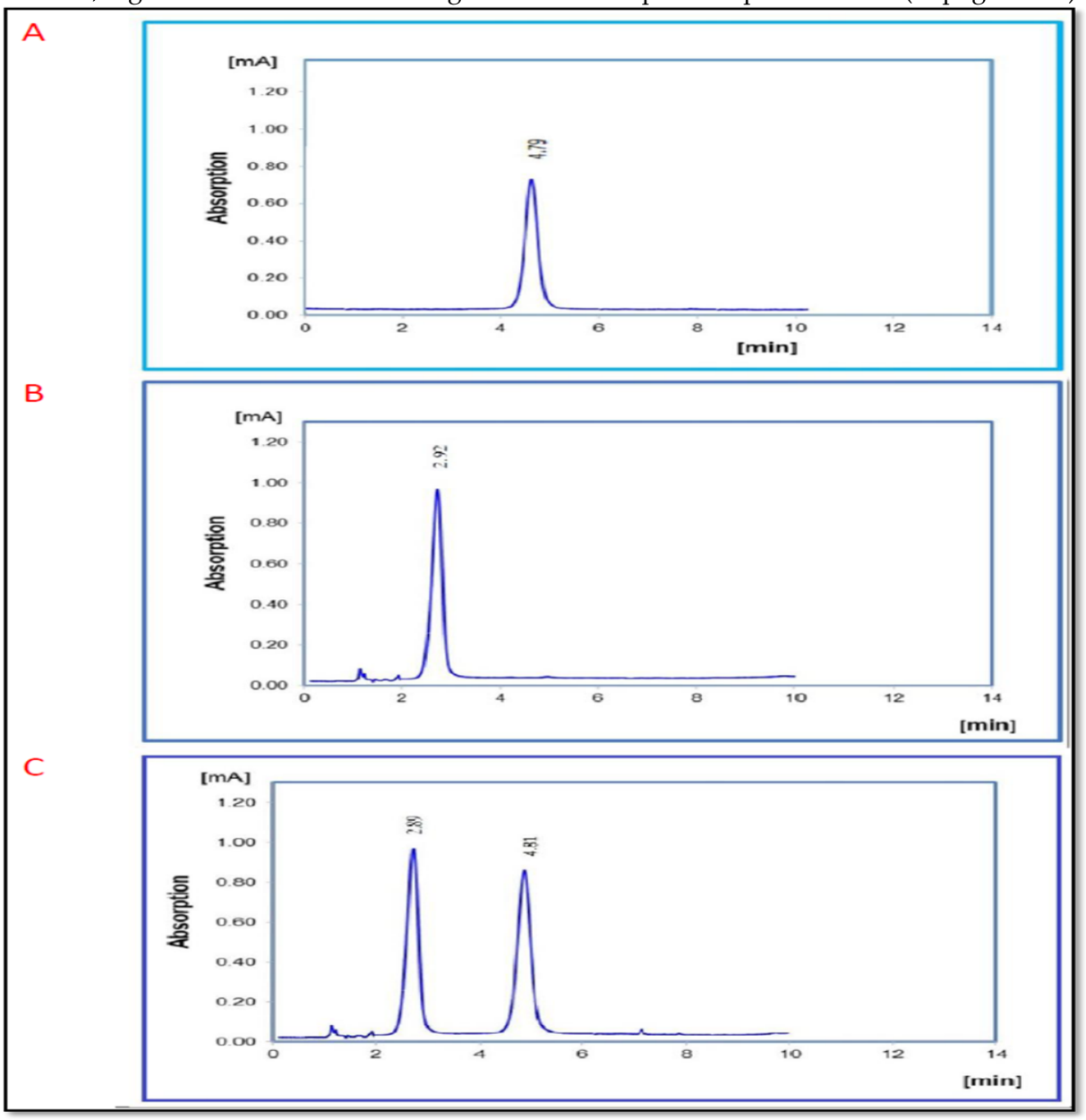

Figure 3. HPLC Chromatograms HPLC of A- canagliflozin in the mobile phase B- plasma spiked with IS (dapagliflozin) C- canagliflozin in plasma spiked with IS (dapagliflozin)

Figure 4 displays the calibration curves of CFZ by the HPLC method, obtained by plotting the ratio of the peak area of the canagliflozin to the area of IS (dapagliflozin) against CFZ concentration. These curves exhibit a straight line and a high correlation coefficient of 0.9999; the regression equation was (Y= 0.1046X+0.0072).
LOD of canagliflozin = 3.3 X 0.002625/0.1046 = 0.0828 µg/mL
LOQ of canagliflozin = 10 X 0.002625/0.1046 = 0.25 µg/mL

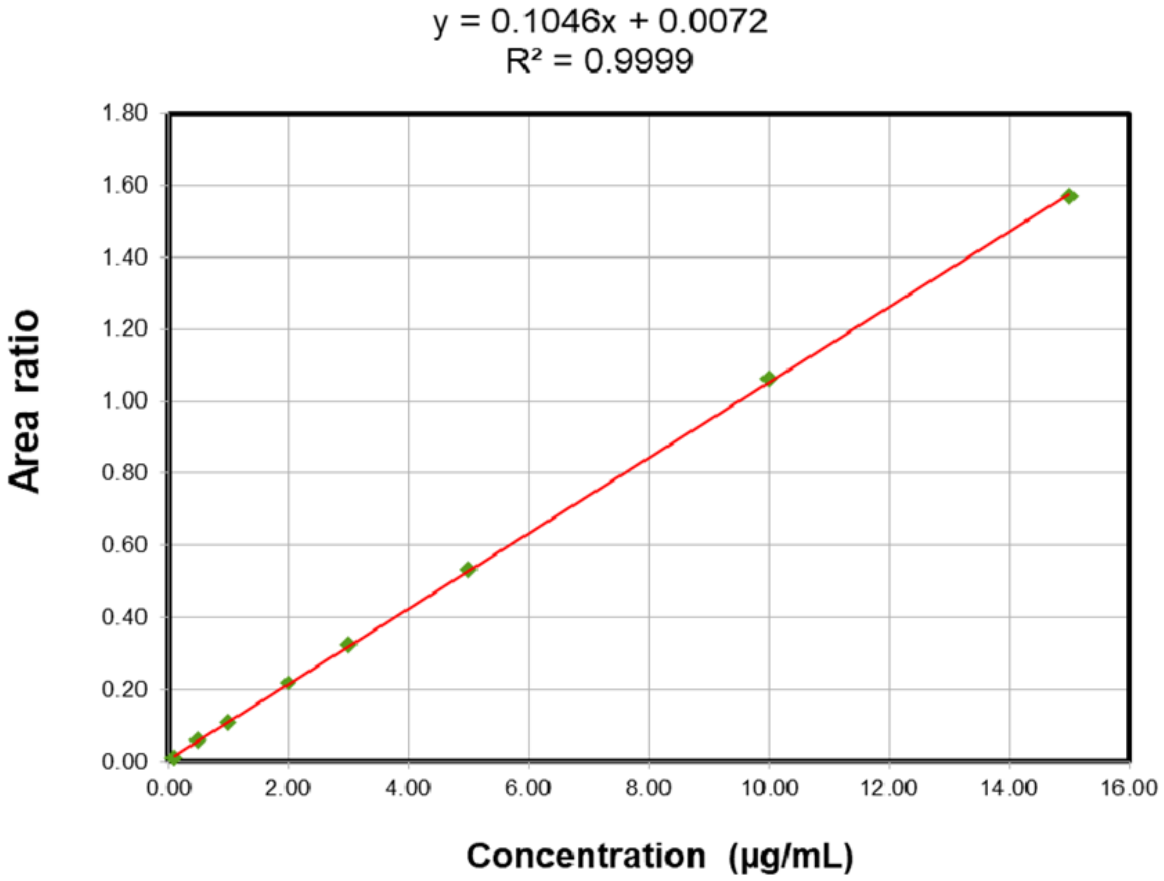

Figure 4. Calibration curve of spiked plasma with canagliflozin and dapagliflozin as internal standard

3.4. Determination of pharmacokinetic parameters

The *in-vivo* pharmacokinetics parameters of the selected CFZ-SNMSD formula were conducted after oral administration in rats and compared with the oral suspension of the pure drug. Figure 5 shows oral CFZ suspension's mean plasma concentration-time profiles versus the CFZ –SNMSD oral capsule formula. The pharmacokinetic parameters of the oral CFZ-suspension and selected CFZ-SNMSD formula were also presented in Table 2.

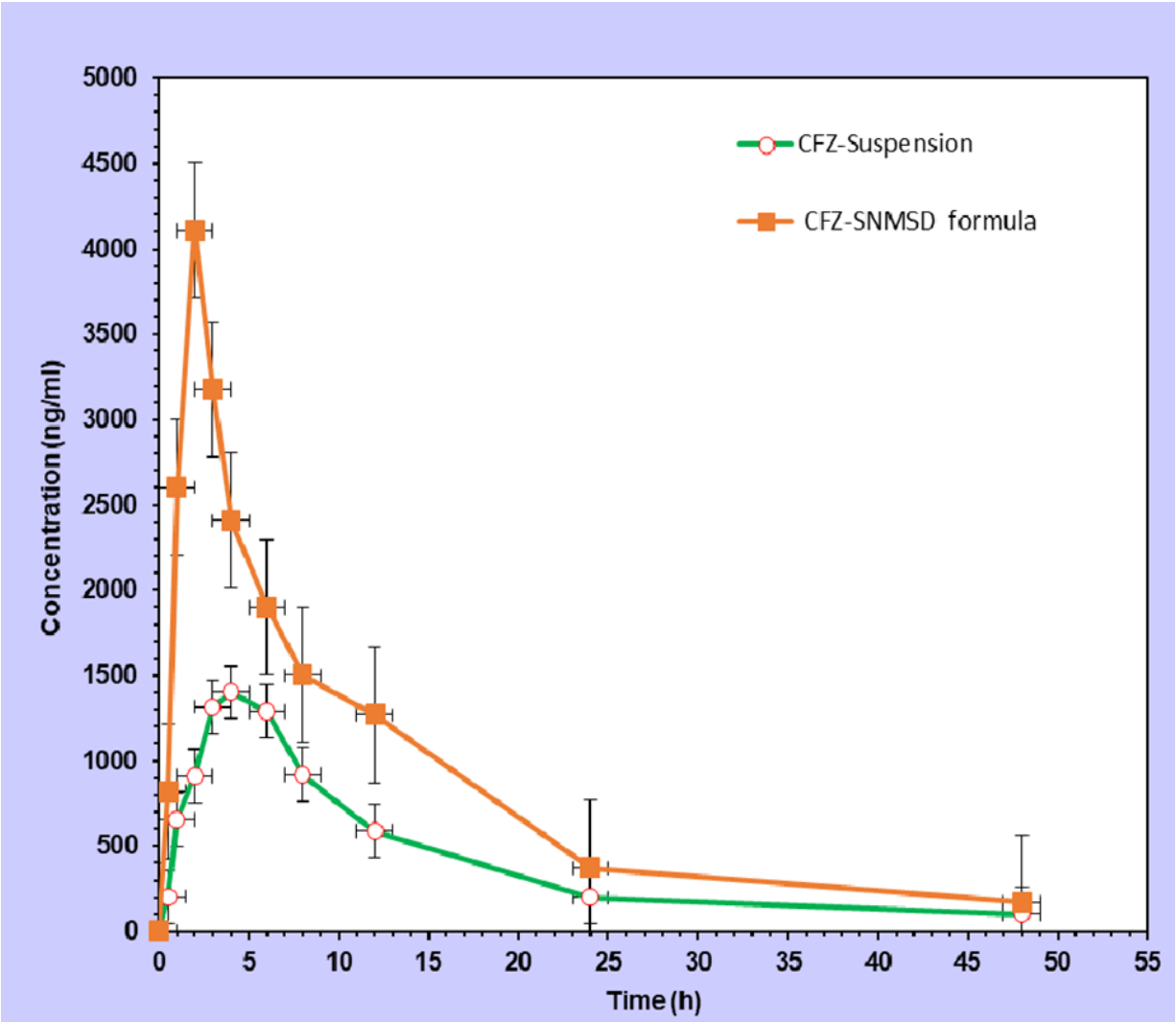

Figure 5. Plasma concentration of CFZ-SNMSD capsules versus CFZ-suspension

Table 2: Pharmacokinetics Parameters of CFZ-SNMSD Formula versus CFZ-Suspension in rats

Parameter	Unit	CFZ suspension	CFZ - SNMSD
C_{max}	ng/mL	1401	4109
T_{max}	hr	4	2
AUC 0-48	ng/mL×hr	19758.75	40440.75
Estimated $t_{1/2}$	hr	11.28	11.44

4. DISCUSSION

In the selected CFZ- solid dispersion formula at a ratio of CFZ: Soluplus® 1:4, the results show better results in terms of PS and PDI due to the low CMC of Soluplus®. The CMC is an essential parameter influencing the stability of the nanomicelles in vitro and *in vivo*. Soluplus® is a hydrophilic graft copolymer that can quickly form colloidal micelles with excellent solubilization ability and stability due to its low value of CMC (0.0076 mg/mL). The low CMC value ensures the CFZ self-nanomicellizing formula has high stability upon extreme dilution in GIT [19].

Optimized CFZ-SNMSD containing soluplus® formulation showed a slightly negative surface charge; since pure Soluplus® micelles themselves reported have a slightly negative surface charge, the absence of charge in this parameter upon loading CFZ would imply their complete allocation within the core of the nanomicelles and not on their surface [20].

Good micrometric properties of the particles are obtained for the CFZ- capsules blend powder, which may be due to the physical properties of the diluent. Avicel®PH102 is micro-crystalline cellulose that possesses good flow properties [21].

The specificity of the HPLC method was verified by examining the chromatogram of blank rat plasma spiked with the CFZ, plasma spiked with the internal standard (IS) (dapagliflozin), and plasma spiked with CFZ and IS (dapagliflozin). No interference was observed at the retention time of the canagliflozin peak, confirming the method's specificity for accurately quantifying CFZ in the presence of other components in the plasma samples. Dapagliflozin was chosen as an internal standard due to its chemical structure similar to that of CFZ, its consistent behavioral characteristics, and its physical and chemical properties, which align with the chemical requirement for HPLC. Its commercial availability and high purity ensure stability and avoid reactions with samples or mobile phases. While studying linear regression analysis shows a linear relationship between peak areas and concentrations of CFZ in the range of 0.1-15 μg/mL. The respective linear equation gives a high correlation coefficient (0.9999). The study determined the LOD of CFZ was 0.0828 μg/mL, and the LOQ of CFZ was 0.25 μg/mL. The LOD and LOQ represent the lowest concentrations that yield a signal-to-noise ratio of at least 3:1 and 10:1, respectively.

The C_{max} of CFZ is (1401± 5.7 ng/mL), and (4109±0.11 ng/mL) in oral suspension and oral SNMSD capsule formula, respectively. The low C_{max} of CFZ suspension indicates poor delivery of the pure drug from the oral route, while the C_{max} of CFZ-SNMSD was much higher. In other words, the C_{max} of CFZ- SNMSD capsule was significantly ($p < 0.05$) superior over oral CFZ suspension. In addition, the T_{max} value of CFZ- SNMSD was significantly less than that of oral CFZ suspension; this may be attributed to the higher and rapid absorption of the SNMSD. Furthermore, AUC_{0-48} value of CFZ- SNMSD oral capsules was estimated to be (40440.75±21.2 ng/ml*h) which was significant ($p < 0.05$) compared to AUC_{0-48} values of CFZ suspension (19758.75 ±12.3 ng /ml*h). The relative bioavailability (F) of canagliflozin (AUC_{0-48} oral SNMSD capsule / AUC_{0-48} oral suspension) was equal to 204.7%. A high C_{max} and a low T_{max} in the CFZ-SNMSD capsule indicated an enhancement in the bioavailability of the CFZ [22].

The results obtained in our study are higher in terms of pharmacokinetic parameters than that obtained by Patil *et al.* (2023) who conducted a study on CFZ-loaded bilosomes, prepared by solvent-evaporation method in which the optimized formula showed a 1.5-fold increase in C_{max} and 1.6-fold increase in relative bioavailability when formulated as bilosomes compare to the pure drug [7].

The reasons for increased CFZ bioavailability in the SNMSD formula compared to pure drugs in suspension are due to solubility enhancement by the presence of soluplus, which increased the solubility of CFZ in water. The permeability and solubility of CFZ are enhanced by soluplus due to nanomicelles formation, leading to increased drug absorption. Also, soluplus inhibits CFZ precipitation and crystallization, keeping drug supersaturation in the GIT. Additionally, it improves drug wettability and stability, which is vital for improving drug dissolution and absorption [23, 24].

The study found that nanomicelle formulation significantly enhances intestinal permeation by presenting CFZ in a solubilized form at its absorption sites, compared to the crystalline

state of a pure CFZ. The nanomicelles provide a large surface area for penetration, and nanosized particles can internalize cells through the endocytosis pathway [25].

Soluplus® is commonly studied for its solubilizing properties and ability to improve the bioavailability of drugs with poor aqueous solubility. There have been several studies that explore the use of Soluplus® as a nanocarrier to enhance the bioavailability of poorly soluble drugs, including canagliflozin, and that investigate its potential effect on P-glycoprotein (P-gp) inhibition. One study that supports the claim of solubilization and P-gp inhibition by Rehman *et al.* (2017) examined the role of Soluplus® in the inhibition of P-gp activity. They found that Soluplus® reduced the efflux of certain drugs mediated by P-gp, which could potentially increase drug (Darunavir) absorption and bioavailability. This was assessed by transport studies across Caco-2 cell monolayers, which are commonly used as a model for intestinal absorption [26].

Another study by Jassem & Abd (2024) explored the development of nanodispersion formulations of canagliflozin, using surfactants like poloxamers and Soluplus®. They found that formulations with Soluplus® had a significantly enhanced dissolution rate and bioavailability compared to the free drug [27].

5. CONCLUSIONS

The study concludes that the subsequent in-vivo pharmacokinetic study (C_{max}, T_{max}, and AUC_{0-48}) indicated valuable improvement in the oral bioavailability parameters of CFZ-SNMSD oral capsules in rats as compared with pure CFZ in 0.1% w/v carboxymethylcellulose suspension. This study was a suitable strategy for enhancing canagliflozin's dissolution and oral bioavailability.

DECLARATION

Ethical approval: All experimental methods were reviewed and authorized by the Institutional Animal Ethical Committee at the College of Pharmacy, University of Baghdad (Approval No: RECAUBCP1420245).

Conflict of Interest: The authors report no conflict of interest.

Funding: This research received no external funding.

Author contributions: the author contributed to the development, analysis, writing, and review of this article.

REFERENCES

1. S. Onoue, H. Suzuki, Y. Kojo, S. Matsunaga, H. Sato, T. Mizumoto, *et al.* Self-micellizing solid dispersion of cyclosporine A with improved dissolution and oral bioavailability. *European Journal of Pharmaceutical Sciences*, **62**, 16–22 (2014). Doi: https://doi.org/10.1016/j.ejps.2014.05.006
2. H. Suzuki, Y. Kojo, K. Yakushiji, K. Yuminoki, N. Hashimoto & S. Onoue. Strategic application of self-micellizing solid dispersion technology to respirable powder formulation of tranilast for improved therapeutic potential. *International Journal of Pharmaceutics*, **499**(1–2), 255–262 (2016). Doi: https://doi.org/10.1016/j.ijpharm.2015.12.065
3. D. Singh, A.K. Tiwary & N. Bedi. Canagliflozin loaded SMEDDS: formulation optimization for improved solubility, permeability, and pharmacokinetic performance. *Journal of Pharmaceutical Investigation*, **49**, 67–85 (2019). Doi: https://doi.org/10.1007/s40005-018-0385-5

4. R. Lajara. The potential role of sodium-glucose co-transporter 2 inhibitors in combination therapy for type 2 diabetes mellitus. *Expert Opinion on Pharmacotherapy*, **15**(17), 2565–2585 (2014). Doi: https://doi.org/10.1517/14656566.2014.968551
5. D. Singh, A.P. Singh, D. Singh, A.K. Kesavan, S. Arora, A.K. Tiwary, *et al.* Enhanced oral bioavailability and anti-diabetic activity of canagliflozin through a spray dried lipid-based oral delivery: a novel paradigm. *DARU Journal of Pharmaceutical Sciences*, **28**(1), 191–208 (2020). Doi: https://doi.org/10.1007/s40199-020-00330-3
6. J.Y. Lee, W.S. Kang, J. Piao, I.S. Yoon, D.D. Kim & H.J. Cho. Soluplus®/TPGS-based solid dispersions prepared by hot-melt extrusion equipped with twin-screw systems for enhancing oral bioavailability of valsartan. *Drug Design, Development and Therapy*, **9**, 2745–2756 (2015). Doi: https://doi.org/10.2147/DDDT.S84070
7. S. Patil, S. Bahadure & S. Patil. Formulation of canagliflozin hemihydrate-loaded bilosomes for the treatment of Type-2 diabetes mellitus: *in vitro*, *in vivo* and *in silico* molecular docking studies. *Journal of Drug Delivery Science and Technology*, **86**, 104630 (2023). Doi: https://doi.org/10.1016/j.jddst.2023.104630
8. D. Singh, A.K. Tiwary, T.S. Kang & N. Bedi. Polymeric precipitation inhibitor based supersaturable self-microemulsifying drug delivery system of canagliflozin: Optimization and evaluation. *Current Drug Delivery*, **18**(9), 1352–1367 (2021). Doi: https://doi.org/10.2174/1567201818666210217155909
9. H. Wang, Y. He, Y. Hou, Y. Geng & X. Wu. Novel self-nanomicellizing formulation based on Rebaudioside A: A potential nanoplatform for oral delivery of naringenin. *Materials Science and Engineering: C*, **112**, 110926 (2020). Doi: https://doi.org/10.1016/j.msec.2020.110926
10. N.A. Jassem & S.N.A. Alhammid. *Ex vivo* permeability study and *in vitro* solubility characterization of oral canagliflozin self-nanomicellizing solid dispersion using Soluplus® as a nanocarrier. *Acta Marisiensis - Seria Medica*, **70**(2), 42–49 (2024). Doi: https://doi.org/10.2478/amma-2024-0011
11. U. Varia, V. Soni, H. Katariya, K. Detholia, M. Jadeja & D. Joshi. *Development and evaluation of rizatriptan benzoate-loaded nanostructured lipid carriers for the treatment of migraine*. Research Square Preprints, 2022; 23 p. Doi: https://doi.org/10.21203/rs.3.rs-1893437/v1
12. S. Jacob, A.B. Nair & M.A. Morsy. Dose conversion between animals and humans: A practical solution. *Indian Journal of Pharmaceutical Education and Research*, **56**(3), 600–607 (2022). URL: https://archives.ijper.org/sites/default/files/IndJPhaEdRes-56-3-600.pdf
13. O.S. Salih & E.J. Al-Akkam. Pharmacokinetic parameters of ondansetron in rats after oral solution and transdermal invasomes gel: A comparison study. *Journal of Advanced Pharmacy Education & Research*, **13**(1), 116–121 (2023). Doi: https://doi.org/10.51847/hs5a27ei6o
14. K.R. Gupta, S. Shelke, A.V. Ganorkar, N. Patel & M.J. Umekar. Analysis of canagliflozin in rat plasma after oral administration by liquid chromatographic as (pharmacokinetic study). *Asian Journal of Applied Chemistry Research*, **9**(2), 22–30 (2021). Doi: https://doi.org/10.9734/ajacr/2021/v9i230210
15. H. Li, T. Bigwarfe, M. Myzithras, E. Waltz & J. Ahlberg. Application of Mitra® microsampling for pharmacokinetic bioanalysis of monoclonal antibodies in rats. *Bioanalysis*, **11**(1), 13–20 (2019). Doi: https://doi.org/10.4155/bio-2018-0228
16. S. Satyavert, S. Gupta, A.B. Nair & M. Attimarad. Development and validation of a bioanalytical method for the determination of hydrazinocurcumin in rat plasma and organs by HPLC-UV. *Journal of Chromatography B*, **1156**, 122310 (2020). Doi: https://doi.org/10.1016/j.jchromb.2020.122310
17. B. Davit, D. Conner & L. Shargel. Drug product performance, *in vivo*: Bioavailability and bioequivalence. In: L. Shargel & A.B.C. Yu (editors). *Applied Biopharmaceutics & Pharmacokinetics*, 7th ed. McGraw-Hill, Inc., New Yorl (NY), 2016; chapter 16, pp. 469–528. URL: https://accesspharmacy.mhmedical.com/content.aspx?bookid=1592&sectionid=100673388
18. S.H. Jaber & N.A. Rajab. Preparation, *in vitro*, *ex vivo*, and pharmacokinetic study of lasmiditan as intranasal nanoemulsion-based *in situ* gel. *Pharmaceutical Nanotechnology*, **13**(1), 239–253 (2024). Doi: https://doi.org/10.2174/0122117385285009231222072303
19. M.C. Bergonzi, M. Vasarri, G. Marroncini, E. Barletta & D. Degl'Innocenti. Thymoquinone-loaded Soluplus®-Solutol® HS15 mixed micelles: Preparation, *in vitro* characterization, and effect on the

SH-SY5Y cell migration. *Molecules*, **25**(20), 4707 (2020). Doi: https://doi.org/10.3390/molecules25204707

20. F. Alvarez-Rivera, D. Fernández-Villanueva, A. Concheiro & C. Alvarez-Lorenzo. A-Lipoic acid in Soluplus(®) polymeric nanomicelles for ocular treatment of diabetes-associated corneal diseases. *Journal of Pharmaceutical Sciences*, 105(9), 2855–2863 (2016). Doi: https://doi.org/10.1016/j.xphs.2016.03.006
21. D.A. Gaber, M.A. Alnwiser, N.L. Alotaibi, R.A. Almutairi, S.S. Alsaeed, S.A. Abdoun, *et al.* Design and optimization of ganciclovir solid dispersion for improving its bioavailability. *Drug Delivery*, **29**(1), 1836–1847 (2022). Doi: https://doi.org/10.1080/10717544.2022.2083723
22. W. Xu, P. Ling & T. Zhang. Polymeric micelles, a promising drug delivery system to enhance bioavailability of poorly water-soluble drugs. *Journal of Drug Delivery*, **2013**, 340315 (2013). Doi: https://doi.org/10.1155/2013/340315
23. R.N. Shamma & M. Basha. Soluplus®: A novel polymeric solubilizer for optimization of carvedilol solid dispersions: formulation design and effect of method of preparation. *Powder Technology*, **237**, 406–414 (2013). Doi: https://doi.org/10.1016/j.powtec.2012.12.038
24. V. Nekkanti, Z. Wang & G.V. Betageri. Pharmacokinetic evaluation of improved oral bioavailability of valsartan: Proliposomes versus self-nanoemulsifying drug delivery system. *AAPS PharmSciTech*, **17**(4), 851–862 (2016). Doi: https://doi.org/10.1208/s12249-015-0388-8
25. M. Linn, E.M. Collnot, D. Djuric, K. Hempel, E. Fabian, K. Kolter, *et al.* Soluplus® as an effective absorption enhancer of poorly soluble drugs *in vitro* and *in vivo*. *European Journal of Pharmaceutical Sciences*, **45**(3), 336–343 (2012). Doi: https://doi.org/10.1016/j.ejps.2011.11.025
26. S. Rehman, B. Nabi, M. Fazil, S. Khan, N.K. Bari, R. Singh, S. Ahmad, V. Kumar, S. Baboota & J. Ali. Role of P-glycoprotein inhibitors in the bioavailability enhancement of solid dispersion of Darunavir. *BioMed. Res. Int*., **2017**, 8274927 (2017). Doi: http://doi.org/10.1155/2017/8274927 .
27. NA. Jassem & S.N. Abd Alhammid. Enhancement of the dissolution and solubility of canagliflozin using nanodispersion systems. *Al-Rafidain J. Med. Sci.*, **6**(1), 222–231 (2024). Available from: Doi : http://doi.org/10.54133/ajms.v6i1.639

HOW TO CITE THIS ARTICLE

N.A. Jassem. *In-vivo* pharmacokinetics evaluation of canagliflozin self-nanomicellizing solid dispersion as oral capsules dosage forms. *Rev. Colomb. Cienc. Quim. Farm.*, **54**(1), 272–285 (2025). Doi: https://doi.org/10.15446/rcciquifa.v54n1.117438