Al-Rafidain J Med Sci. 2024;6(1):222-231.
DOI: https://doi.org/10.54133/ajms.v6i1.639

Research Article

Enhancement of the Dissolution and Solubility of Canagliflozin Using Nanodispersion Systems

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

[1]*Department of Pharmaceutics, College of Pharmacy, Al-Ayen Iraqi University, Thi-Qar, Iraq;* [2]*Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq*

Received: 28 January 2024; Revised: 6 March 2024; Accepted: 12 March 2024

Abstract

Background: Self-nanomicellizing solid dispersion is a new formulation that combines the advantages of solid dispersion with nanomicelle methods to increase drug oral bioavailability. The technique employs an appropriate carrier to produce a solid dispersion that self-assembles into nanomicelles when in contact with gastrointestinal fluids, improving medication solubility and absorption. ***Objective***: The study aims to develop a self-nanomicellizing solid dispersion of canagliflozin and compare it to non-nanomicellizing formulations. ***Methods***: The solvent evaporation approach was chosen to create a solid dispersion system with soluplus and poloxamer 407 as carriers. Different canagliflozin-to-carrier ratios were investigated in order to develop nanomicellar systems with improved canagliflozin dissolving characteristics. Solid-state analysis was used to characterize the optimum self-nanomicellizing and non-self-nanomicellizing formulations. ***Results***: The physicochemical tests revealed that canagliflozin's crystalline structure transitioned to an amorphous state in the solid dispersion system of both carriers, as evidenced by powder X-ray diffraction and differential scanning calorimetry. Particle size analysis reveals that only soluplus, in all ratios tested, produces self-nanomicellizing solid dispersion of canagliflozin, whereas poloxamer 407 does not. Self-nanomicellizing systems incorporating soluplus had a faster dissolving profile than pure drug and non-self-nanomicellizing formulae. ***Conclusions***: Canagliflozin nanodispersion systems with Soluplus as a carrier may improve solubility, dissolving rate, and bioavailability.

Keywords: Canagliflozin, Self-nanomicellizing, Solid dispersion, Solubility.

تعزيز قابلية التحلل والذوبان لعقار كاناجليفلوزين بواسطة أنظمة التشتت النانوي غير المتبلور

الخلاصة

الخلفية: التشتت الصلب النانوي الذاتي هو عباره عن تركيبه تجمع فوائد التشتت الصلب واشتراتيجيات نانو المذيلات لتحسين التوافر الحيوي للأدوية عن طريق الفم . تستلزم الستراتيجيه استخدام حامل مناسب لإنشاء مشتت صلب يتجمع ذاتيًا في جزيئات نانوية عندما يتلامس مع سوائل الجهاز الهضمي، مما يؤدي إلى تحسين قابلية ذوبان الدواء وامتصاصه مما يؤدي إلى توفر بيولوجي أفضل عن طريق الفم. **الهدف**: يهدف هذا العمل الى تطوير مشتتات صلبه ذاتية تكوين نانو المذيلات لعقار كناجليفلوزين لتعزيز قابالية ذوبانه ومعدل التحلل للدواء ومقارنة النظام المحضر مع تريكيبات مشتت صلب غير ذاتي تكوين نانو المذيلات. **االطرائق**: تم اختيار طريقة التبخر بالمذيب لتحضير نظام تشتيت صلب باستخدام مادة سولبلس وبولوكسامر 407 كحاملات. تمت دراسة نسب مختلفة من الكاناجليفلوزين إلى الناقلات لإنشاء أنظمة نانوية مذيلة تعمل على تحسين خصائص الذوبان للكاناجليفلوزين. تميزت التركيبات المُحسّنة للتحليل النانوي الذاتي وغير النانوي الذاتي بتحليل الحالة الصلبة باستخدام حيود الأشعة السينية ، وقياس سعرات المسح التفاضلي، ودراسات الذوبان، وتوزيع حجم الجسيمات و المجهر الإلكتروني الماسح للانبعاث الميداني. **النتائج**: أظهرت الدراسات الفيزيائية والكيميائية انخفاضا في التركيب البلوري للكاناجليفلوزين إلى حالته غير المتبلورة في نظام التشتت الصلب في كلا الحاملين، كما يتضح من استخدام حيود الأشعة السينية وقياس السعرات الحرارية بالمسح التفاضلي. يُظهر تحليل حجم الجسيمات أن السولوبلوس فقط في جميع النسب المستخدمة هو الذي يمكن أن يعطي تشتيتًا صلبًا ذاتي النانو للكاناجليفلوزين، في حين أن البولوكسامير 407 لم يعطي جسيمات نانويه. وقد لوحظ ملف تعريف الذوبان والتشتت السريع في أنظمة نانو المذيلات ذاتية الانتشارمقارنةً بالتشتت الصلب غير النانوي و الدواء الخام . **الاستنتاجات**: تشير هذه الدراسة إلى أن أنظمة التشتت النانوي للكاناجليفلوزين التي تستخدم سولوبلص كحامل يمكن ان تعزز قابلية الذوبان والانحلال للدواء.

* ***Corresponding author***: Nizar A. Jassem, Department of Pharmaceutics, College of Pharmacy, Al-Ayen Iraqi University, Thi-Qar, Iraq; Email: nizar.awish@alayen.edu.iq

Article citation: Jassem NA, Abd Alhammid SN. Enhancement of the Dissolution and Solubility of Canagliflozin Using Nanodispersion Systems. *Al-Rafidain J Med Sci*. 2024;6(1):222-231. doi: https://doi.org/10.54133/ajms.v6i1.639

© 2024 The Author(s). Published by Al-Rafidain University College. This is an open access journal issued under the CC BY-NC-SA 4.0 license (https://creativecommons.org/licenses/by-nc-sa/4.0/).

INTRODUCTION

Solubility is critical for establishing the proper drug concentration in systemic circulation and eliciting a pharmacological response. When administered orally, poorly soluble medicines may require large doses to produce therapeutic plasma concentrations [1]. Recent breakthroughs in computer modeling, combinatorial chemistry, and high-throughput screening have aided the creation of numerous medications with low bioavailability. Furthermore, the biopharmaceutical classification system categorizes 50% of oral drugs as class II (poorly water soluble) [2]. Solid dispersion. SD is a well-known technique for tackling major pharmaceutical difficulties such as low oral medicine solubility and insufficient chemical or physical stability. A solid dispersion is made up of two components: a hydrophobic drug and a hydrophilic carrier. The hydrophobic drug is disseminated solidly within the hydrophilic carrier. The SD method has been widely studied to alleviate the constraints of several poorly soluble medicines [3]. Crystallinity is important for the water solubility of poorly soluble medicines. Crystalline states have lower energy and greater stability, resulting in low aqueous solubility. Reducing crystallinity with an amorphous form of the drug can provide a meta-stable form with a higher free energy state and, as a result, higher solubility. The shift of a solid from crystalline to metastable amorphous form during preparation can be attributed to a variety of drug delivery techniques, including solid dispersion (SD), which is currently generally advocated as a promising method of preparation due to its ease of production [4]. To manufacture the SD, the surfactant can be employed alone or in conjunction with other hydrophilic carriers. The adsorption of surfactant materials on a solid surface can alter the drug's hydrophobicity, reducing the surface tension between two liquids or between a fluid and solid. SD is made utilizing many surfactants, including poloxamer 407 and Compritol 888 ATO. [5]. Amphiphilic polymers, especially SD carriers, have lately gained popularity due to their ability to increase the dissolution rate and absorption of water-insoluble medicines. Because such polymers have both hydrophilic and hydrophobic components, when exposed to an aqueous solution, they tend to self-micellize into nano- or micro-sized micelles. To create self-nanomicellizing SDs, amphiphilic self-micellizing carriers with micellar structures generated during the release process are required. Soluplus® is a promising carrier for creating solid dispersions and other nanocarrier systems with better solubility and bioavailability. Furthermore, Soluplus® has a tendency to self-assemble into a micellar structure, reducing free energy and allowing precipitation to occur at lower critical solution temperatures. However, some obstacles must be solved before Soluplus® may be employed instead of standard polymers. For example, environmental variables in the gastrointestinal tract are expected to affect Soluplus® solubility, as have conventional non-ionic polymers with similar cloud points. [6]. Canagliflozin CFZ is a new inhibitor of sodium-glucose cotransporter 2 (SGLT2) in the renal proximal convoluted tubule, which reduces glucose reabsorption and increases urine glucose excretion. The recommended adult dose is 100 mg once daily, which can be increased to 300 mg once daily if tolerated, and should be taken before breakfast [7]. Pharmaceutically, CFZ oral administration is linked with variable and poor absorption, owing mostly to its insolubility in aqueous solutions and a slow intrinsic dissolution rate. Several attempts to boost canagliflozin bioavailability have been published, one of which was introduced by Singh D et al. (2020), which comprises the creation and evaluation of spray-dried lipid-based formulations for improving CFZ oral bioavailability and anti-diabetic effectiveness. [8]. Patel et al. (2022) have attempted to improve the stability and dissolving qualities of canagliflozin by creating a nanosuspension and solidifying it into immediate-release pellets [9]. These two approaches in nanosuspension make use of expensive and high-energy machines such as spry dryers, lyophilizers, and probe sonicators. The current study intends to create the anti-diabetic medication canagliflozin as a solid dispersion that can self-nanomicellize when in contact with an aqueous solution using an amphiphilic polymer, and then compare this formulation to a non-self-nanomicellizing solid dispersion formula.

METHODS

Materials

Canagliflozin was purchased from Wuhan Senwayer Century Chemical. Co. Ltd, China; Poloxamer 407 was purchased from SIGMA (Germany); Soluplus® was gifted from BASF Pharma. Ethanol 99 % (HPLC grade) was purchased from Merck, USA.

Calibration curves and λ_{max} determination

Determination of λ_{max} and standard curves preparation of canagliflozin in ethanol and water containing 0.5% sodium lauryl sulfate was performed using a UV-vis spectrophotometer (UV-1800, Shimadzu Corporation, Japan) [10-11].

Saturation solubility of canagliflozin as pure powders

The saturation solubility of canagliflozin powder was determined in water, ethanol, and water containing 0.75% SLS. All media were prepared, and an excess of canagliflozin was added to each of them and kept in an incubator shaker bath at 25 ± 0.5 °C. After 48 hours, the supersaturated solution was centrifuged at 5000 rpm for 10 min. The supernatants were filtered by a 0.45 u syringe filter and diluted with the corresponding

solution. Absorbance was measured at a wavelength specific to each medium using a UV spectrophotometer, and solubility was calculated according to the corresponding calibration curve [12].

Preparation of physical mixtures

Canagliflozin and carriers (poloxamer 407 or soluplus) were precisely weighed and thoroughly mixed in a glass mortar by triturating for five minutes at various drug-to-carrier weight ratios of optimized formulations [13].

Preparation of solid dispersions

A solvent evaporation method was used to generate self-nanomicellizing solid dispersion (SNMSD) and non-self-nanomicellizing solid dispersion (NSNMSD) of canagliflozin in (1:2), (1:3), (1:4), and (1:6) by weight (drug carrier) ratios. It was accomplished by dissolving the canagliflozin and carriers in 10 ml of ethanol in a round-bottom flask placed in a bath sonicator heated to 25 degrees Celsius. This resulted in canagliflozin solid dispersion. The ethanol was evaporated at 40°C under decreased pressure in a rotary evaporator (BUCHI, Turkey) that rotated at 220 rpm until a thin, dry layer formed on the flask's interior wall. The film was crushed and collected with a spatula, minimizing loss, then filtered through an 80-mesh mesh to obtain a solid system and stored until further investigation [14,15].

Determination of drug content and % yield

Drug content was determined by dissolving 10 mg of accurately weighed quantities of SD systems in 10 ml of ethanol using a 10 ml volumetric flask, followed by sonication for 15 min. The solutions were filtered and diluted appropriately, and then the concentration of the samples was measured spectrophotometrically at λ max [16].

The percentage of drug content was determined by using Equation (1):

$$\text{Content \%} = \frac{\text{actual weight of canagliflozin}}{\text{theoretical weight of canagliflozin}} \text{x}100 \quad \text{.... Eq. (1)}$$

The practical percentage yield (PY%) was determined for all the prepared SD formulations. The PY% was calculated by dividing the actual mass of the self-nanomicellizing SD formula obtained by the theoretical mass of the same formulae using Equation 2 [17]:

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

Particle size analysis

Amounts of solid dispersion equivalent to 10 mg of canagliflozin were dispersed in 10 mL of water and stirred at 500 rpm with a magnetic stirrer for up to 1 h. The solution obtained was filtered through a 0.45-µm polyvinyl difluoride syringe filter to get a homogeneous micellar solution [18]. The particle size (PS) and polydispersity index (PDI) of the developed canagliflozin formulations were determined using a Malvern Panalytical Ltd. Zetasizer. 1 mL of samples were directly placed into a disposable quartz cuvette to measure the hydrodynamic diameter of a particle undergoing Brownian motion within the dispersion at 25°C [19]. We chose the best formula from self-nanomicellizing SD and some other formulas from non-self-nanomicellizing SD to study and test further based on drug content, particle size, PDI, and percent yields.

Fourier-Transform Infrared Spectroscopy

The IR spectroscopy was carried out for Canagliflozin, physical mixture, and selected solid dispersion formulae (self-nanomicellizing and non-self-nanomicellizing) using an FTIR spectrophotometer (Shimadzu Europe FTIR- 8400S). The spectra were generated using the potassium bromide (KBr) pellet method. About 2–4 mg of the sample was mixed with dry KBr, and the spectra were scanned over a wave number range of 4,000–200 cm-1 using a resolution of 4 cm-1 [20].

Differential Scanning Calorimetry

DSC thermographs help measure the heat flow caused by material transitions as a function of temperature and time. They offer data on physical and chemical changes, such as endothermic and exothermic processes and changes in heat capacity. The thermal behavior of CFZ samples and refined SD formulations was investigated with a differential scanning calorimeter (DSC 60, Shimadzu, Tokyo, Japan). The canagliflozin and improved SD formulation samples were heated to temperatures ranging from 10 to 300 °C at 10 °C min-1 in a nitrogen environment at a flow rate of approximately 100 ml min-1. For reference, an empty aluminum pan was utilized [21].

X-ray Diffraction

The purpose of this X-ray diffraction (XRD) investigation was to describe the physical structure of CFZ in its pure form, as a physical combination, and as samples from two types of improved solid dispersion formulations. The X-ray diffractometer captured the XRD pattern. Samples were scanned with diffraction angles (2θ) ranging from 4° to 40°, a sample width of 0.01°, and a speed of 4° per minute. The operational parameters were as follows: 45 kV generator tension (voltage), 40 mA generator current, 9 s-1 scan time, and 0.008 scan step size [22].

In-vitro dissolution rate studies

The dissolving conditions for canagliflozin were maintained as indicated by the FDA database. The paddle speed on the USP dissolving equipment II (paddle apparatus) is adjusted to 75 rpm. To maintain a sink temperature of 37 ± 0.5°C, 900 cc of newly made 0.75% w/v SLS solution was used as the dissolution medium. Dissolution studies were conducted using 100 mg of pure medication and an equal quantity of selected optimum SD formulations. Before dissolution testing, each formulation of SD (equal to 100 mg CFZ) was placed in a "000" hard gelatin capsule. Each capsule had a sinker attached to prevent it from floating [23]. A 5 mL sample was taken at 5, 10, 15, 20, 30, 45, and 60 minute intervals and replaced with fresh media to keep the volume and sink conditions constant. The samples were filtered with syringe filters and examined spectrophotometrically. The quantity of canagliflozin was calculated at the λmax. The dissolution experiments were carried out in triplicate to ensure that the results were reproducible [8]. The dissolution profiles of pure canagliflozin and the SDs of improved formulations were compared using Moore and Flanner's model-independent, mathematical technique, which is recommended in industry standards for dissolution testing of immediate-release solid oral dosage forms. Equations 3 and 4 demonstrate how this method estimates the difference factor (f1) and similarity factor (f2) between two dissolution profiles.

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

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{j=1}^{n}(R_j - T_j)^2\right]^{-0.5} x100\right\} \quad \ldots \text{Eq. (4)}$$

Where *n* is the number of sample points, T and R are the percentages dissolved of the test and product reference at each time point j respectively. Two dissolution profiles are similar if the value of f_1 is between 0 and 15 and the value of f_2 is greater than 50.

Determination of zeta potential

The zeta potential of the selected canagliflozin self-nanomicellizing formula was determined using a Malvern Panalytical Ltd Zetasizer. The electrophoretic mobility of the optimized formula was assessed and converted to zeta potential. The zeta potential value indicates the charge on the nanomicelles [19].

Field emission scanning electron microscope

The morphology of the formulation of chosen canagliflozin self-nanomicellizing SD was studied using FeSEM (FESEM S-4160, Hitachi, Japan). The sample preparation process includes carefully collecting nanomicelles to avoid contamination or damage, sample fixation to protect the formula's structural integrity, and formula dehydration to eliminate water from the nanomicelles. Critical point drying is a technique for removing solvent from a formula while preserving the shape of the nanoparticles. The formula is then placed on a stub with conductive adhesive carbon tape coated in platinum to avoid charging and improve image quality. Finally, the nanomicelle formula is ready to be photographed using the FESEM. SEM micrographs of the samples were collected and stored digitally. The samples underwent different magnification scans at a voltage of 20 kV [26-27].

Statistical analysis

The data were analyzed using the Student's t-test, with results presented as the mean ± standard deviation (SD) at a significance level of $p<0.05$ [28].

RESULTS

Canagliflozin's λmax in water and ethanol was reported to be 290 nm. The calibration curves for canagliflozin in ethanol and water containing 0.5% sodium lauryl sulfate were created. Plotting absorbance versus concentration yielded a straight line with a high coefficient. The equilibrium saturation solubility of canagliflozin pure powder in water, ethanol, and water containing 0.75% SLS solution was 36.2±2.3 ug/ml, 32.815±2.1 mg/ml, and 9.3±1.14 mg/ml. Canagliflozin solid dispersions were made utilizing poloxamer 407 and soluplus as carriers in various drug ratios (1:2, 1:3, 1:4, and 1:6) using the solvent evaporation method, ethanol as a solvent, and a rotary evaporator apparatus, with the formulation composition provided in Table 1. The concentration of canagliflozin in the SD formulations was determined using conventional ethanol calibration curves.

Table 1: Composition of canagliflozin solid dispersions using different carriers

Substance	F1	F2	F3	F4	F5	F6	F7	F8
Drug: carrier ratio	1:2	1:3	1:4	1:6	1:2	1:3	1:4	1:6
Canagliflozin (mg)	100	100	100	100	100	100	100	100
Soluplus (mg)	200	300	400	600	-	-	-	-
Poloxamer 407 (mg)	-	-	-	-	200	300	400	600
Ethanol (ml)	10	10	10	10	10	10	10	10

Table 2 shows the results of medication content and percent yield. The total drug concentration in the solid dispersion was found to be greater than 91%. A zeta sizer was used to investigate particle size distribution of SD during dissolving in water, and the results of the polydispersity index are shown in Table 2.

Table 2: Measured Parameters of the Prepared Canagliflozin Solid Dispersion

Formula code	Drug contents (%)	% yield	Particle size (nm)	PDI
F1	92.2±1.1	86.7±3.1	142.7±3.1	0.325±0.04
F2	92±1.8	90.5±2.3	108.5±2.16	0.138±0.016
F3	97±1.2	93.9±1.2	61.793±1.06	0.058±0.02
F4	92±1.2	93.1±2	104±2.01	0.22±0.09
F5	91±2.0	95±2	1220±0.0	1.2±0.0
F6	96±1.4	96±2	576.5±0.0	0.482±0.0
F7	95±2.0	97±2.1	821.8±0.0	0.86±0.0
F8	91±2.2	98±3	1845±0.0	0.2±0.0

Values were expressed as mean±SD, *n*=3.

Formulations including soluplus exhibit nanoscale particle size, with all ratios used demonstrating that soluplus can provide canagliflozin with a self-nanomicellizing solid dispersion system. The optimal drug-carrier ratio for Soluplus is 1:4, resulting in a PS of 61.79±1.06 nm and a low PDI of 0.058±0.02, showing high formulation stability. Figure 1 shows the particle size distribution of the improved formulation F3.

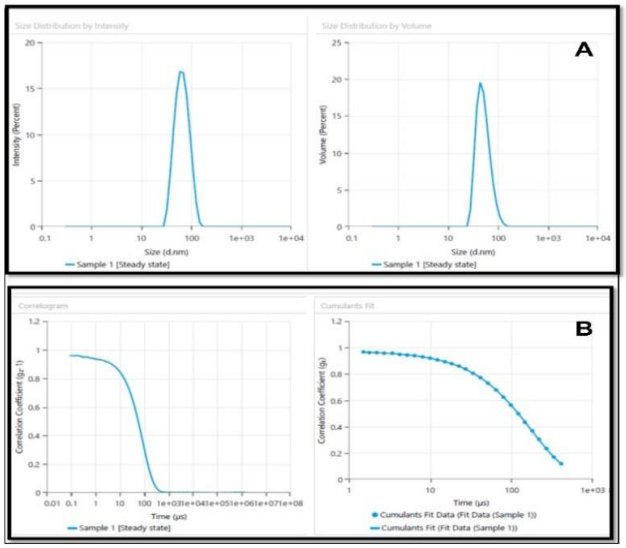

Figure 1: Average particle size for formula F3 by malven zeta seizer. A) intensity of particle size; B) cumulative data.

The polydispersity index measures particle size distribution. The monodisperse sample has PDI values close to zero, but those between 0.1 and 0.3 indicate a narrow size distribution. All self-nanomicellizing solid dispersion formulations met the PDI standards and are included in Table 2. The results with poloxamer 407 show that all formulations were microscale, showing that poloxamer 407 produces a non-self-nanomicellizing solid dispersion in which poloxamer 407 cannot self-assemble into nananomicelles in these formulae. At a 1:3 drug-to-carrier ratio, the optimal particle size in formulations containing poloxamer 407 was determined to be 576.2 nm with a PDI of 0.482. Figure 2 depicts the PS distribution for formula F6. The best canagliflozin self-nanomicellizing solid dispersion and non-self nanomicellizing formulae were selected based on in vitro evaluation studies (particle size measurement, PDI, drug content, and percent yield); the best formulations were F3 for self-nanomicellizing and F6 for non-self nanomicellizing solid dispersion. These compositions will be further studied.

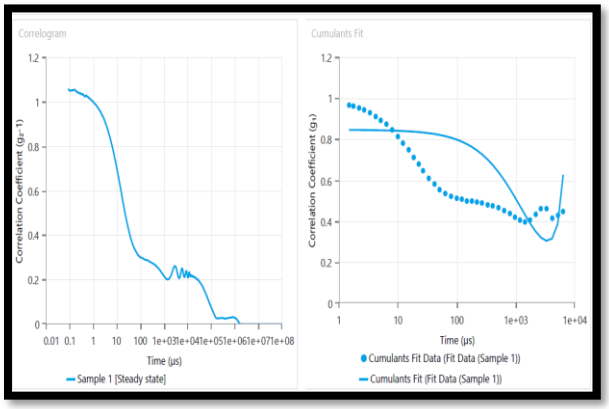

Figure 2: Average particle size for formula F6 by Malvern zeta seizer: cumulative data.

The FTIR spectra of the adjusted solid dispersion formulations was compared to that of the pure medication to determine their chemical stability and interactions with additional excipients. The FTIR graph of pure Canagliflozin, as shown in Figure 3A, displayed the characteristic peaks at 2974 cm-1 for OH stretching mode, 1627 cm-1 for aromatic C-C=C symmetric stretching, 1508 cm-1 for C-C=C asymmetric stretching, 1226 cm-1 for C-O stretching, 806 cm-1 for C-S stretching, 1338 cm-1 for C-F stretching, and 759.9, 840, and 806 cm-1 for C-H out of plane bending mode. These peaks were detected as sharp peaks in the physical mixtures of canagliflozin and poloxamer 407 (Figure 3B) and canagliflozin and soluplus (Figure 3C). There was no intrinsic interaction in the physical composition. The peak of canagliflozin has decreased in the solid dispersions formulation of optimal self-nanomicellizing SD F3 (Figure 3D) and optimized non-self-nanomicellizing SD F6 (Figure 3E). However, there was no change in the typical peaks. Drug peaks changed slightly from their initial values in SD when compared to pure samples. Shift mediated by surfactant-induced hydrogen bonding and hydrophobic interactions during SD formation. Figure 4A depicts a DSC thermogram from a solid sample of pure canagliflozin. The endothermic peak for pure canagliflozin was 107.55 oC. Even after adding poloxamer 407 and soluplus, the endothermic peak of crystalline canagliflozin remained in the physical mixture (Figure 4B) due to the diluting effect. After solvent evaporation of the solid dispersion preparation, the intensity of the canagliflozin peak completely disappeared in self-nanomicellizing SD F3 (Figure 4C) and non-self-nanomicellizing SD (F6), as shown in Figure 4D, indicating that canagliflozin had converted to an amorphous state via solvent evaporation.

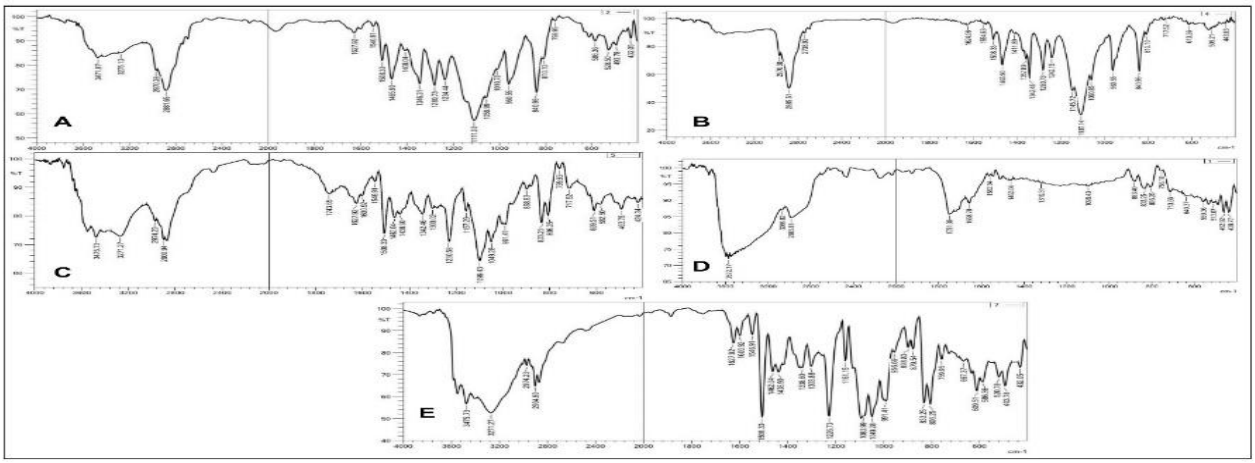

Figure 3: FTIR of A) pure canagliflozin, B) physical mixture of canagliflozin and poloxamer 407 at a ratio of 1:3, C) Physical mixture of canagliflozin and soluplus at a ratio of 1:4, D) optimized formula F3, and E) optimized SD formula F6

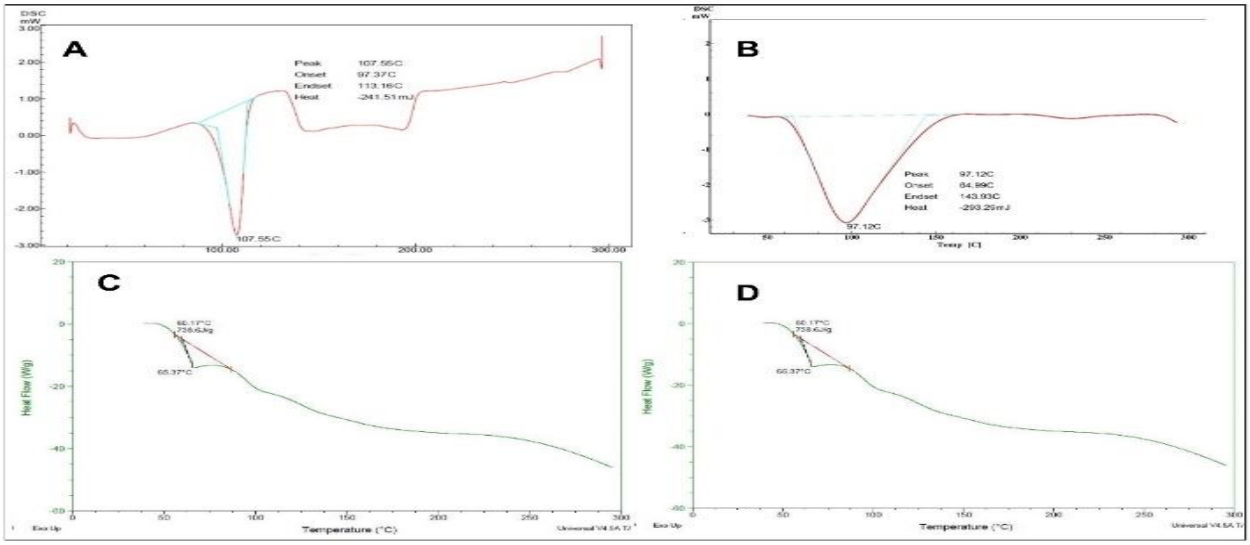

Figure 4: Differential Scanning Calorimetry of A) pure canagliflozin, B) Physical mixture of canagliflozin:soluplus at 1:4 drug-to-carrier ratio, C) selected self-nanomicellizing SD formula F3, and D) selected non- self-nanomicellizing SD formula F6.

The X-ray diffractogram (XRD) of canagliflozin typically consists of 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°, as illustrated in Figure 5A. A physical mixture of canagliflozin with soluplus at a ratio of optimized formulation 1:4 and the ratio of 1:3 as drug: poloxamer 407 was detected with partial amorphization as in Figure 5B, which shows that it contains poloxamer 407, whereas optimized self-nanomicellizing in Figure 5C and non-self nanomicellizing solid dispersion in Figure 5D were observed with a reduction in the crystallinity index indicating a change in overall geometry from crystalline to amorphous form. Figure 6 shows different dissolution patterns for self-nanomicellizing, non-self-nanomicellizing solid dispersion, and pure canagliflozin.

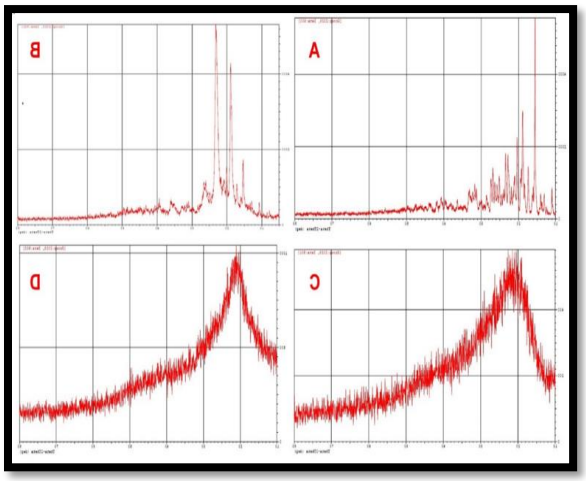

Figure 5: X-ray Powder Diffraction of A) pure canagliflozin, B) a physical mixture of canagliflozin and poloxamer 407 in 1:3 drug-to-carrier ratio, C) Selected formula F3, and D) selected formula F6.

After 30 minutes, 98% of the encapsulated canagliflozin in nanomicelles of optimal self-nanomicellizing solid dispersion F3 dissolved in water containing 0.75% SLS.In contrast, 67% of the non-self nanomicellizing solid dispersion F6 and 36% of the pure medication were dissolved in the same medium after 30 minutes. SNMSD or NSNMSD systems demonstrated significantly quicker dissolving rates than pure canagliflozin. The following sequence clearly demonstrated a change in dissolution rate for various SDs: Soluplus® SNMSD > >poloxamer p. 407 NSNMSD.

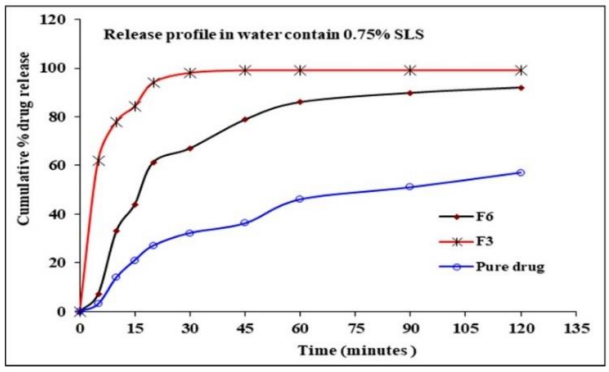

Figure 6: Release profile of optimized canagliflozin formulations according to dissolution test (mean±SD, n=3) In 900 ml water containing 0.75% sodium lauryl sulfate at 37.0 ± 0.5 °C at 75 rpm.

The drug release characteristics of the improved formulations containing pure canagliflozin were compared using similarity and dissimilarity variables. The in-vitro dissolution profiles showed similarities with f2 values of 11 and 26 for F3 and F6, respectively. F3 and F6 had Difference Factor f1 values of 196 and 95, respectively, demonstrating a significant difference in the in-vitro release profile of self-nanomicellizing and non-self-nanomicellizing solid dispersion of the optimized formulations vs that of pure medicines. In addition, when the similarity factors f2 of F3 and F6 were compared, the f2 value was 22, suggesting a significant difference in the release profile of self-nanomicellizing solid dispersion F3 and non-self-nanomicellizing solid dispersion F6. The zeta potential is the primary characteristic that defines the physical stability of the dispersion; because the soluplus is a neutral copolymer, a slightly negative surface charge was detected with a ZP value of -3.436 mV for the chosen formula F3 of the self-nanomicellizing SD, as shown in Figure 7. The FESEM images in Figure 8 depict the self-nanomicellizing SD of formula F3 at various magnifications. The results show that when a nanomicellizing solid dispersion of canagliflozin was created, the nanomicelles were spherical and nanosized.

DISCUSSION

Calibration curves of canagliflozin in ethanol and water containing 0.5% sodium lauryl sulfate were used to determine the drug concentration and saturated solubility of the compound.

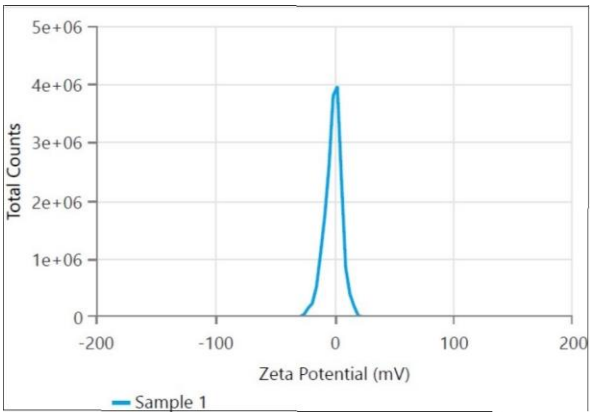

Figure 7: Zeta potential distribution of selected formulation F3.

The equilibrium solubility of canagliflozin in water is low, indicating the need to improve its aqueous solubility. However, canagliflozin is extremely soluble in a solution of 0.75% SLS and ethanol. Solvent evaporation was used to create eight canagliflozin solid dispersion formulations that contained both SNMSD and NSNMSD.

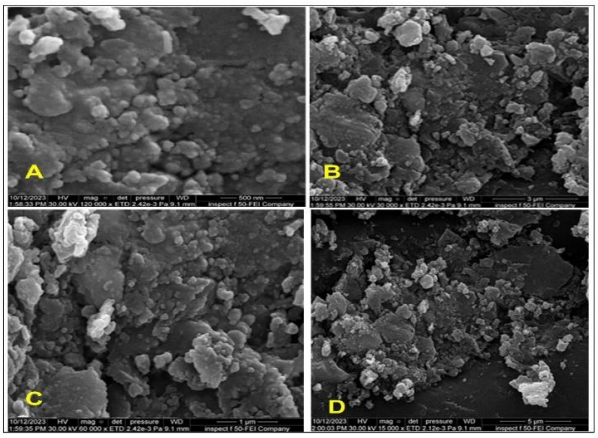

Figure 8: FeSEM images of optimized formulation self-nanomicellizing solid Dispersion F3.

The total elimination of pale yellowish tints of canagliflozin in solid dispersion at 1:4 canagliflozin:soluplus and 1:3 canagliflozin:polloxamer 407 ratios indicates outstanding miscibility and effective dispersion formulation. The practical percentage yields were determined to assess the efficiency of the preparation processes and to assist in selecting acceptable manufacturing practices. All formulations had high yields, ranging from 86.7% to 98%±sd. This result suggests that this approach was appropriate and efficient for producing canagliflozin SNMSD. Soluplus-based nanomicelles are stable, can maintain their initial nanomicelle size (PDI ranging from 0.05 to 0.3), and can be used to encapsulate a variety of medications, hence

increasing their therapeutic potential [29]. The drug-to-carrier ratio may lead to amorphization and maintain a supersaturated state, resulting in significantly increased solubility. The optimal proportion of carrier may also lower the particle size of undissolved drug crystals, increasing saturation solubility [30]. The results with poloxamer 407 differed from those with soluplus in terms of particle size and PDI, as all formulations were microscale, showing that poloxamer 407 produces non-self-nanomicellizing solid dispersion. The reason for the formulation of self-nanomicelles in soluplus formulations but not in poloxamer 407 formulations is that soluplus self-assembles into nanomicelles with mild shaking or agitation due to its low CMC and hydrogen bonding, whereas poloxamer 407 does not easily develop self-nanomicelles due to variations in its molecular structure and bonding capacities. The FTIR spectra of the optimized self-nanomicellizing solid dispersion formula F3 and non-self-nanomicellizing solid dispersion formula F6 were compared to those of pure canagliflozin and the physical mixture to determine their chemical stability and interactions with additional excipients. Some canagliflozin peaks have weakened, but the trademark peaks have not changed. However, certain peaks in the SD differed somewhat from those in the pure sample. This was due to the surfactant causing hydrogen bonding and hydrophobic interactions while the SD was being formed. The drug-excipient interactions were modest, allowing for the development of stable SD with little chemical interactions. The most plausible explanation for the weakening of distinctive peaks is that canagliflozin SD contains less canagliflozin than the polymer quantity (diluted). In DSC, pure canagliflozin exhibited a strong endothermic peak at 107.55°C. The physical mixing of canagliflozin and soluplus at a 1:4 ratio produced a broad melting peak with an onset temperature of 42.9°C and an endothermic peak of 97.3°C. However, in the thermogram of self-nanomicellizing solid dispersion formulae samples, F3, a broad endothermic peak appeared at 65.37 °C, which was the Tg of the SD sample, and the peak corresponding to the drug's melting point was not observed, indicating that canagliflozin had converted to an amorphous state via solvent evaporation. Figure 4D shows a prominent endothermic melting peak for the non-self-nanomicellating solid dispersion formula F6 at 66.03°C. This graph also demonstrates the absence of the canagliflozin melting endothermic peak. However, a complete amorphous transition occurs when the endothermic peak of canagliflozin disappears in the thermograms of SNMSD and NSNMSD, indicating that canagliflozin is molecularly dispersed in the formulation [22]. X-ray diffraction was utilized to investigate any changes in the inner structure of canagliflozin during formulation. Canagliflozin XRD normally shows powerful, crisp diffraction peaks, whereas the physical mixing of drug and carriers in a ratio as the corresponding selected formulae was discovered to have significant amorphization. Whereas optimized self-nanomicellizing formula F3 and non-self nanomicellizing solid dispersion formula F6 reduced the crystallinity index, indicating a change in the overall geometry of the crystalline to amorphous form and suggesting effective encapsulation of CFZ in solid dispersion [31]. The maximum dissolving rate was seen in Soluplus SNMSD; it is worth noting that Soluplus® is a more effective amorphous polymer for improving canagliflozin dissolution. The first dissolve rates revealed that self-nanomicellizing Soluplus® could significantly improve canagliflozin in vitro dissolution when compared to polymers that did not self-nanomicellize in SDs. The solid dispersion technique has the advantage of altering the drug's physical state while also lowering particle size. According to the Noyes-Whitney equation (equation 4), increasing the surface area in contact with the dissolving medium can improve medication wettability while decreasing particle aggregation. Furthermore, converting the drug substance's physical state to a high-free-energy state (an amorphous form) can lower the energy required to break the crystal lattice, potentially resulting in rapid drug breakdown in the medium [2,32].

$$\frac{dM}{dt} = AD(Cs - Ct)/h \quad \ldots\ldots \text{ Eq. (4)}$$

where dm/dt: The dissolution rate of a solid in solvent, Ct and Cs represent the concentration of the dissolved substance at a given time t and the solubility concentration of the substance, respectively. A surface area and D dissolution rate constant.

The formulations improved F3 and F6 release profiles by breaking the crystal lattice with minimal energy during dissolution. Furthermore, the reduction in particle size in self-nanomicellizing solid dispersion increases the surface area, which improves the dissolution rate of formulation F3 over F6. Similarity and dissimilarity factors show a considerable difference in the in-vitro release profile of the self-nanomicellizing SD formula F3, the non-self-nanomicellizing solid dispersion formula F6, and pure drug. The Zeta potential of the optimized formula F3 is -3.436 mV, demonstrating the stability of the nanocolloidal formulation other than surface charge. The FESEM confirmed that the nanomicelles were spherical in size, as Zeta Sizer had reported. The results showed that solvent evaporation procedures might reduce particle size and create amorphous structures in produced formulations.

CONCLUSIONS

In the current study, self-nanomicellizing and non-self-nanomicellizing SD of canagliflozin systems were prepared for oral administration using an amphiphilic self-micellizing Soluplus® polymer and poloxamer p

407 as non-self-micellizing polymers via solvent evaporation. We determined the physiochemical properties of the synthesized self-nanomicellizing and non-self-nanomicellizing SDs, including their solid-state and dissolving properties. We discovered that self-nanomicellizing SD has superior dissolving properties when compared to pure drug and non-self-nanomicellizing SD. This shows that novel self-nanomicellizing formulations based on canagliflozin and Soluplus could become an important technique for enhancing medication absorption and bioavailability.

ACKNOWLEDGEMENTS

The authors thank Wuhan Senwayer Century Chemical, China, for providing canagliflozin, BASF Pharma for supplying Soluplus®, and all the department staff for their support throughout the study.

Conflict of interests

No conflict of interests was declared by the authors.

Funding source

The authors did not receive any source of fund.

Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

REFERENCES

1. Hamed HE, Hussein AA. Preparation, in vitro, and ex-vivo evaluation of mirtazapine nanosuspension and nanoparticles incorporated in orodispersible tablets. *Iraqi J Pharm Sci*. 2020;29(1):62-75. doi: 10.31351/vol29iss1pp62-75
2. Althobaiti AA, Ashour EA, Almutairi M, Almotairy A, Al Yahya M, Repka MA. Formulation development of curcumin-piperine solid dispersion via hot-melt extrusion. *J Drug Deliv Sci Technol*. 2022;76(103753):103753. doi: 10.1016/j.jddst.2022.103753.
3. Tran PHL, Duan W, Lee BJ, Tran TTD. Current designs of polymer blends in solid dispersions for improving drug bioavailability. *Curr Drug Metab*. 2018;19(13):1111-1118. doi: 10.2174/1389200219666180628171100.
4. Halder S, Azad MAK, Iqbal H, Shuma ML, Kabir ER. Improved dissolution of albendazole from high drug loaded ternary solid dispersion: Formulation and characterization. *Dhaka Univ J Pharm Sci*. 2021;20(2):149-158. doi: 10.3329/dujps.v20i2.57165.
5. Karolewicz B, Gajda M, Pluta J, Górniak A. Dissolution study and thermal analysis of fenofibrate–Pluronic F127 solid dispersions. *J Therm Anal Calorim*. 2016;125(2):751-757. doi: 10.1007/s10973-015-5013-2.
6. Liu X, Zhou L, Zhang F. Reactive melt extrusion to improve the dissolution performance and physical stability of naproxen amorphous solid dispersions. *Mol Pharm*. 2017;14(3):658-673. doi: 10.1021/acs.molpharmaceut.6b00960.
7. BNF. Pharmaceutical Press is the publishing division of the Royal Pharmaceutical Society. 66-68 East Smithfield, London E1W1AW,UK; 83:2022;769-771.
8. Singh D, Singh AP, Singh D, Kesavan AK, Arora S, Tiwary AK, et al. Enhanced oral bioavailability and anti-diabetic activity of canagliflozin through a spray dried lipid based oral delivery: a novel paradigm. *Daru*. 2020;28(1):191-208. doi: 10.1007/s40199-020-00330-3.
9. Patel NC, Patel HA. A recent solidification approach for Nano suspension: formulation, optimization, and evaluation of canagliflozin immediate release pellets. *Folia Med (Plovdiv)*. 2022;64(3):488-500. doi: 10.3897/folmed.64.e68866.
10. Alatraqchi FI, AL Gawhri JF. Preparation and in-vitro evaluation as an oral microsponge tablet of baclofen. *Iraqi J Pharm Sci*. 2019;28(1):75-90. doi: 10.31351/vol28iss1pp75-90.
11. Kaur I, Wakode S, Pal Singh H. Development and validation of UV spectroscopic method for determination of canagliflozin in bulk and pharmaceutical dosage form. *Pharm Methods*. 2015;6(2):82-86. doi: 10.5530/phm.2015.6.11.
12. Shi NQ, Zhang Y, Li Y, Lai HW, Xiao X, Feng B, et al. Self-micellizing solid dispersions enhance the properties and therapeutic potential of fenofibrate: Advantages, profiles, and mechanisms. *Int J Pharm*. 2017;528(1–2):563-577. doi: 10.1016/j.ijpharm.2017.06.017.
13. M, Wei W, Xu W, Polyakov NE, Dushkin AV, Su W. Preparation of DNC solid dispersion by a mechanochemical method with glycyrrhizic acid and polyvinylpyrrolidone to enhance bioavailability and activity. *Polymers (Basel)*. 2022;14(10):2037. doi: 10.3390/polym14102037.
14. Abdulqader AA, Rajab NA. Bioavailability study of posaconazole in rats after oral poloxamer P188 Nano-micelles and oral posaconazole pure drug. *J Adv Pharm Edu Res*. 2023;13(2):140-143. doi: 10.51847/Q59uyvRmY.
15. Wang H, He Y, Hou Y, Geng Y, Wu X. Novel self-nanomicellizing formulation based on Rebaudioside A: A potential nanoplatforms for oral delivery of naringenin. *Mater Sci Eng C Mater Biol Appl*. 2020;112:110926. doi: 10.1016/j.msec.2020.110926.
16. AlKhalidi MM, Jawad JF. Enhancement of aqueous Solubility and dissolution rate of etoricoxib by solid dispersion technique. *Iraqi J Pharm Sci*. 2020;29(1):76-87. doi: 10.31351/vol29iss1pp76-87.
17. Chuah AM, Jacob B, Jie Z, Ramesh S, Mandal S, Puthan JK, et al. Enhanced bioavailability and bioefficacy of an amorphous solid dispersion of curcumin. *Food Chem*. 2014;156:227-233. doi: 10.1016/j.foodchem.2014.01.108.
18. Ponnusamy C, Sugumaran A, Krishnaswami V, Palanichamy R, Velayutham R, Natesan S. Development and evaluation of polyvinylpyrrolidone K90 and poloxamer 407 self-assembled nano micelles: Enhanced topical ocular delivery of artemisinin. *Polymers (Basel)*. 2021;13(18):3038. doi: 10.3390/polym13183038.
19. Muhammed SA, Al-Kinani KK. Formulation and in vitro evaluation of meloxicam as a self-micro emulsifying drug delivery system. *F1000Res*. 2023;12:315. doi: 10.12688/f1000research.130749.2.
20. Alkufi H, Kassab H, Hussein L. Use of factorial design in formulation and evaluation of intrarectal in situ gel of sumatriptan. *J Adv Pharm Technol Res*. 2023;14(2):119. doi: 10.4103/japtr.japtr_603_22.
21. Malik B, Bekir E. Formulation and in vitro /in vivo evaluation of silymarin solid dispersion- based topical gel for wound healing. *Iraqi J Pharm Sci*. 2023;32(Suppl.):42-53. doi: 10.31351/vol32isssuppl.pp42-53.
22. Baghel S, Cathcart H, O'Reilly NJ. Polymeric amorphous solid dispersions: A review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization of biopharmaceutical classification system class II drugs. *J Pharm Sci*. 2016;105(9):2527-2544. doi: 10.1016/j.xphs.2015.10.008.
23. Singh D, Tiwary AK, Bedi N. Canagliflozin loaded SMEDDS: formulation optimization for improved Solubility, permeability, and pharmacokinetic performance. *J Pharm Investig*. 2019;49(1):67-85. doi: 10.1007/s40005-018-0385-5.
24. Pourmohamad T, Ng HKT. Statistical modeling approaches for the comparison of dissolution profiles. *Pharm Stat*. 2023;22(2):328-348. doi: 10.1002/pst.2274.
25. Nokhodchi A, Chavan S, Ghafourian T. In vitro dissolution and permeability testing of inhalation products: Challenges and advances. *Pharmaceutics*. 2023;15(3). doi: 10.3390/pharmaceutics15030983.

26. Abdulqader AAE, Sultan NAR. Preparation and characterization of posaconazole as a nano-micelle using d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS). *Iraqi J Pharm Sci*. 2023;32(Suppl.):26-32. doi: 10.31351/vol32isssuppl.pp26-32.
27. Emad H, Nazar Abd-Alhammid S. Improvement of the solubility and dissolution characteristics of risperidone via nanosuspension formulations. *Iraqi J Pharm Sci*. 2022;31(1):43-56. doi: 10.31351/vol31iss1pp43-56.
28. Alkawak RSY, Rajab NA. Lornoxicam-loaded cubosomes: Preparation and in vitro characterization. *Iraqi J Pharm Sci*. 2022;31(1):144-153. doi: 10.31351/vol31iss1pp144-153.
29. Pignatello R, Corsaro R, Bonaccorso A, Zingale E, Carbone C, Musumeci T. Soluplus® polymeric nanomicelles improve Solubility of BCS-class II drugs. *Drug Deliv Transl Res*. 2022;12(8):1991-2006. doi: 10.1007/s13346-022-01182-x.
30. Hou Y, Wang H, Zhang F, Sun F, Xin M, Li M, et al. Novel self-nanomicellizing solid dispersion based on rebaudioside A: a potential nano platform for oral delivery of curcumin. *Int J Nanomed*. 2019;14:557-5571. doi: 10.2147/IJN.S191337.
31. Sheng: Hangzhou Pushai Pharmaceutical Technology Co., Ltd., assignee. Canagliflozin monohydrate and its crystalline forms, preparation methods, and uses thereof. US patent; US 2017/0145000 A1, 2017.
32. Nashat BI, Al-Kinani KK. Nanoemulsion formulation of leflunomide for transdermal delivery: Preparation and characterization. *Int J Drug Deliv Technol*. 2023;13(01):57-65. doi: 10.25258/ijddt.13.1.09.