



Received on 18 January 2018; received in revised form, 28 February 2019; accepted, 17 March 2019; published 01 June 2019

NOVEL AMORPHOUS SOLID DISPERSIONS OF CANAGLIFLOZIN HEMIHYDRATE IN EUDRAGIT® E PO

Ruchi Agrawal^{1,*2}, Nirav Patel¹ and Mihir Raval¹

Department of Pharmaceutical Sciences¹, Saurashtra University, Rajkot - 360005, Gujarat, India.

Krupanidhi College of Pharmacy², Carmelaram, Bengaluru - 560035, Karnataka, India.

Keywords:

Amorphous,
Canagliflozin, Dissolution rate,
Eudragit® E PO, Solid dispersion,
Solubility enhancement

Correspondence to Author:

Mrs. Ruchi Agrawal

Associate Professor,
Department of Pharmaceutics,
Krupanidhi College of Pharmacy,
Carmelaram, Bengaluru - 560035,
Karnataka, India.

E-mail: ruchi.kcp@gmail.com

ABSTRACT: The purpose of this research was to develop novel solid dispersions (SDs) of BCS class IV drug, canagliflozin hemihydrate (CFZ) using Eudragit® E PO (EE PO) as a carrier, to enhance its solubility and dissolution rate. Solvent evaporation technique was used to prepare SDs. The SDs were evaluated for saturated solubility, *in-vitro* dissolution study, solid-state characterization using FTIR, DSC, XRD and SEM, and flow properties. The solubility of CFZ in SDs increased manifold as compared with pure CFZ. Low values of angle of repose, Carr's index, and Hausner ratio indicated good flow properties. The difference factor (f_1) and similarity factor (f_2) values suggested that dissolution profiles of the SDs were dissimilar to market product and the comparative dissolution curves revealed that SDs released CFZ faster than the marketed product. XRD patterns and DSC thermographs suggested that the SDs were present in an amorphous form, unlike pure crystalline CFZ. SEM studies showed CFZ has discrete crystalline particles whereas SD2 has diffuse, irregular asymmetrical structure. The SDs was superior to pure CFZ as they showed substantial improvement in solubility and dissolution rate along with good flow properties. Hence, the amorphous form of CFZ was successfully achieved by formulating it into SDs using EE PO as the carrier, which has conferred an increase in solubility and dissolution rate.

INTRODUCTION: Diabetes mellitus (DM) is a chronic and progressive disease which is characterized by impaired glucose utilization, and increased hepatic glucose and free fatty acid production. Epidemiological data reveals that the prevalence of diabetes in adults aged 18-99 years was estimated to be 8.4% in 2017 and predicted to rise to 9.9% in 2045 and is known to have important social, financial and developmental implications in the society¹.

Diabetes is one of four priority non-communicable diseases (NCDs) targeted by world leaders in the 2011 Political Declaration on the Prevention and Control of NCDs² and remains a thrust area for healthcare scientist to explore and make further inventions to develop cost-effective and patient compliant remedies for diabetic patients. In the year 2009, sodium glucose -2 transporters (SGLT2) inhibitors were developed as novel antidiabetic agents with independent insulin mechanism of action for reducing plasma glucose levels, to overcome the limitations of current antihyperglycemic agents (AHAs)³. Canagliflozin (CFZ) ((1S)-1, 5- anhydro- 1- [3- [[5- (4- fluoro- phenyl)- 2- thienyl]- methyl]- 4-methylphenyl]-D- glucitol hemihydrate) is the first drug approved in this class of SGLT-2 inhibitors (also called as

	<p style="text-align: center;">DOI: 10.13040/IJPSR.0975-8232.10(6).2923-33</p>
	<p style="text-align: center;">The article can be accessed online on www.ijpsr.com</p>
<p>DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(6).2923-33</p>	

gliflozin class of drugs)^{4,5}. It is administered orally as a tablet in a dose of 100 or 300 mg once daily as an adjunct to diet and exercise for the treatment of type 2 diabetes mellitus (T2DM)^{6,7}. Based on low solubility and low permeability, canagliflozin is classified as a BCS 4 compound⁸. Pharmacokinetic studies reveal that canagliflozin shows peak plasma concentrations within 1 to 2 h following oral administration, and steady-state levels are reached in 4 to 5 days; it has a bioavailability of 65% and is highly protein bound (99%), mainly to albumin. Following single oral doses, the terminal half-life was 10.6 and 13.1 h for canagliflozin 100 mg and 300 mg, respectively⁹⁻¹¹. The FDA database of the patented product INVOKANA[®] mentions that CFZ shows dose-dependent adverse effects. Some of them are related to reduced volume-related events such as hypotension, postural dizziness, while others include an increase in low-density lipoprotein cholesterol (LDL-C) and a small reduction in bone mineral density (BMD)¹¹. Hence, the primary focus remains on exploring novel methods to enhance the bioavailability of CFZ and consequently, its dose reduction.

Solid dispersion (SD) technology has been explored by formulation scientists as one of the suitable approaches to formulate poorly water-soluble drugs to enhance their solubility and dissolution rate¹²⁻¹⁸. This technology was first introduced by Sekiguchi and Obi¹⁹, where they enhanced the solubility of poorly soluble sulfathiazole by using crystalline carriers like urea. Crystalline solid dispersions (SDs) have a major disadvantage of being thermodynamically unstable and hence being unable to release the drug quickly. The second generation solid dispersions were then introduced which used amorphous carriers like hydrophilic polymers leading to amorphous SDs as end product²⁰. Due to its amorphous state, the drug-polymer SD possess a larger enthalpy, entropy and free energy than its the crystalline form of active pharmaceutical ingredient (API), which results in higher solubility of API¹⁵. This may lead to significant improvement in bioavailability leading to dose-reduction possibilities. The objective of this research is to develop amorphous solid dispersions of novel antidiabetic drug CFZ, which is classified as BCS class IV drug for enhancing its aqueous solubility and dissolution rate.

In this study, Eudragit E[®] PO (EE PO) was examined as a carrier for preparation of SDs with the purpose to enhance solubility and dissolution rate of CFZ. EE PO is a cationic copolymer, also known as poly(butyl methacrylate, (2-dimethylamino ethyl) methacrylate, methyl methacrylate) 1: 2: 1. It is popularly used as a film coating and taste masking agent for tablets and capsules²¹⁻²³. Recently, it has been explored by formulation scientist as a carrier for preparation of solid dispersion to improve solubility and dissolution rate of API. Amorphous spray-dried solid dispersions of valsartan were prepared using EE PO as a carrier for enhancing its dissolution rate in a gastric environment²⁴. Similarly, amorphous solid dispersions of curcumin - EE PO resulted in a significant increase in aqueous solubility of curcumin²⁵.

MATERIALS AND METHODS:

Materials: The drug CFZ was generously donated by Cadila Health Care Limited, Sarkhej, Sanand, Gujarat, India. EE PO was donated by Cipla Limited, Vikhroli, Maharashtra, India. Sodium lauryl sulfate (SLS) was procured from Sigma-Aldrich, Bangalore, India; ethanol analytical grade (99.5%), methanol HPLC grade (99.9%), and acetonitrile HPLC grade (99.3%) were procured from SD Fine-Chem Limited, Bangalore, India. All the other chemicals and reagents were of analytical grade.

Preparation of CFZ- EE PO Solid Dispersions: Solid dispersions (SDs) of CFZ were prepared using EE PO as the carrier. The formulations containing drug and polymer in different ratios were prepared by using solvent evaporation method¹⁵. Details on the composition of SDs are given in **Table 1**. Ethanolic solutions of CFZ and EE PO were prepared by dissolving the calculated amount of CFZ and EE PO in a predetermined volume of ethanol. The ethanolic solution of CFZ was added to an ethanolic solution of EE PO, and the resulting mixture was stirred using magnetic stirrer at 300 rpm for 10 min. The clear solution containing CFZ and EE PO was subjected to evaporation, overnight at room temperature. This was followed by vacuum drying at room temperature for 4 h for terminal drying. The powder mass obtained was pulverized using mortar and pestle, passed through a 710 µm sieve and retained on 250 µm sieve and finally

stored in a desiccator until use. The method for preparation of SDs is also depicted in Fig. 1.

TABLE 1: FORMULATION CHART OF CANAGLIFLOZIN-EUDRAGIT® E PO SOLID DISPERSIONS

Formulation code	CFZ: EE PO (w:w)	Amount of CFZ (g)	Amount of EE PO (g)
SD1	1:1	5	5
SD2	1:2	5	10
SD3	1:3	5	15

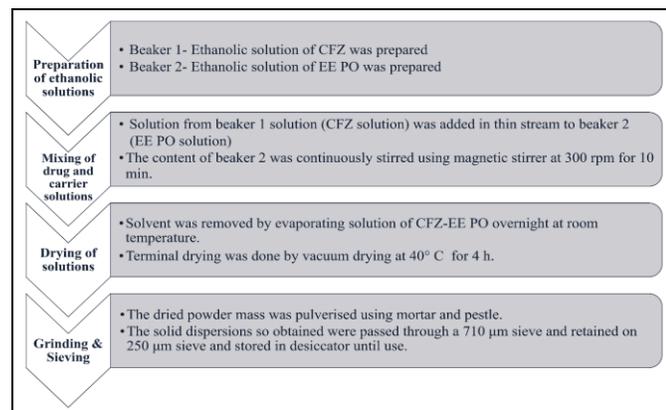


FIG. 1: SCHEMATIC REPRESENTATION OF METHOD OF PREPARATION OF CANAGLIFLOZIN-EUDRAGIT® E PO SOLID DISPERSIONS

Evaluation of CFZ- EE PO Solid Dispersions:

Determination of Saturated Solubility of CFZ and SDs: Solubility of CFZ and the SDs was determined in distilled water and 0.75% w/v solution of SLS at room temperature (RT) (25 ± 2 °C). For this purpose, excess of CFZ or SDs was added to vehicle and vortex mixed (SPINIX-Vortex Shaker) for 48 h at room temperature (25 ± 2 °C). The dispersion saturated with CFZ was centrifuged using microcentrifuge (Remi-RMI) at 3000 rpm for 30 min. The supernatant was decanted and filtered through a 0.22 µm syringe filter. The filtrate was then suitably diluted with methanol, and the concentration of CFZ was determined by measuring absorbance through UV-Visible spectroscopy (UV-1800, Shimadzu, Japan) at λ_{\max} 290 nm. The procedure for solubility determination is summarised in Fig. 2.

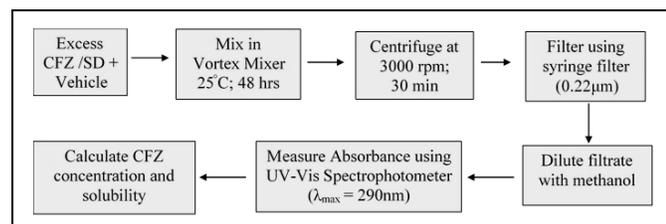


FIG. 2: SCHEMATIC REPRESENTATION OF METHOD OF SOLUBILITY DETERMINATION OF CANAGLIFLOZIN IN PURE STATE AND IN SOLID DISPERSIONS

Solid State Characterisation: Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) was performed for pure CFZ, EE PO, physical mixture of CFZ and EE PO (1:1) (PM) and the SDs. X-ray powder diffraction (XRD) was carried out for CFZ, EE PO, and the SDs. Finally, surface morphology was studied and compared for CFZ and the best SD formulation.

Fourier-Transform Infrared Spectroscopy (FTIR): Fourier-transform infrared (FTIR) spectroscopy is powerful for identifying types of chemical bonds in a molecule by producing an infrared (IR) absorption spectrum that is similar to a molecular "fingerprint." The IR spectroscopy was performed using an FTIR spectrophotometer (Shimadzu Europe FTIR- 8400S) and software IR solutions 30. The spectra were generated by using the potassium bromide (KBr) pellet method. A little quantity of the previously dried sample was intimately mixed with dried KBr. The mixture was pressed using a die set for 2 min. The transparent sample-KBr pellet so obtained was put in the sample holder of FTIR and the spectrum recorded in the range of $4000-500 \text{ cm}^{-1}$ using a resolution of 4 cm^{-1} .

Differential Scanning Calorimetry (DSC): The DSC thermographs help to measure the heat flow associated with transitions in materials as a function of temperature and time. They provide information on physical and chemical changes that include endothermic/exothermic processes or changes in heat capacity²⁶. Differential Scanning calorimeter (DSC 60, Shimadzu, Tokyo, Japan) was used to study the thermal behavior of the samples of CFZ, EE PO, PM, and SDs¹⁸. The samples were subjected to the temperature range of $25^{\circ}-200^{\circ} \text{ C}$ at a heating rate of $10^{\circ} \text{ C min}^{-1}$ under nitrogen atmosphere at a flow rate of 100 ml min^{-1} . Empty aluminum pan was used as a reference.

X-ray Diffraction (XRD): The X-ray diffraction study was carried out to characterize the physical form of CFZ in its pure state and samples of solid dispersion¹⁸. The X-ray diffractometer (Rigaku SmartLab) recorded the XRD pattern using Cu K α line at a voltage of 40k V and current 30mA. Samples were scanned using diffraction angles (2θ) between 4° to 40° at 0.01° sampling width at the scanning speed of 4° per min.

Field Emission Scanning Electron Microscopy (FESEM): The surface characteristics of pure CFZ and the best SD formulation were studied by field emission scanning electron microscopy (FESEM) (TESCAN-MIRA 3 LMH, Kohoutovice, Czech Republic). The samples were mounted onto the aluminum stage using double-sided carbon tape and sputter-coated, using an electron microscopy sputter coater equipped with a gold (Au) source. Samples were exposed to Au for 2.5 min and then examined using FESEM for morphological characterization.

In-vitro Dissolution Rate Studies: Comparative dissolution studies were performed between marketed product (MKT) (available as a film-coated tablet containing 100 mg CFZ) and different SD formulations. Before dissolution studies, each formulation of SD (equivalent to 100 mg CFZ) was filled in size “000” hard gelatine capsule. A sinker was attached to each capsule to prevent it from floating. The dissolution conditions were maintained as recommended in the FDA database for CFZ 27. USP dissolution apparatus II (paddle apparatus) was used, and the paddle speed was set at 75 rpm. The dissolution medium in each bowl consisted of 600 ml of freshly prepared 0.75% w/v solution of SLS in distilled water, which was maintained at 37 ± 0.5 °C. The dissolution conditions are summarised in **Fig. 3**.

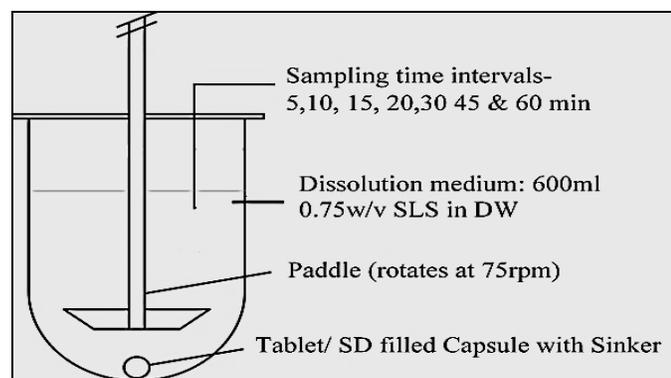


FIG. 3: EXPERIMENTAL CONDITIONS FOR IN-VITRO DISSOLUTION STUDIES FOR MARKETED TABLET AND SOLID DISPERSION FILLED CAPSULES

Aliquots (2 ml) from the dissolution medium were withdrawn at different time intervals (5, 10, 15, 20, 30, 45 and 60 min). The withdrawn samples were replaced by equal volumes of dissolution medium to maintain the volume and sink conditions constant. The samples were filtered through a membrane filter (0.2 μ m, Whatman), and drug

concentration was analyzed via validated HPLC method 28. The HPLC (Agilent 1200 HPLC, Agilent Technologies, USA) conditions comprised use of C18 reversed phase column (250 mm \times 4.6 mm, 5 μ); mixture of 0.1% orthophosphoric buffer and ACN in the ratio 55:45 (isocratic mode) as mobile phase and the injection volume of 10 μ l with a flow rate of 1.1 ml/min. The elution was monitored at 290 nm, and the chromatographic data were acquired and processed with the Agilent Infinity Lab solutions software. All measurements were done in triplicate.

Difference Factor (f_1) and Similarity Factor (f_2): The dissolution profiles of MKT and SDs were compared by using a model-independent, the mathematical approach proposed by Moore and Flanner and recommended in guidelines for the industry for dissolution testing of immediate release solid oral dosage form^{29, 30}. This approach involves calculating the difference factor (f_1) and the similarity factor (f_2) between two dissolution profiles and is given by equations (1) and (2) respectively^{27, 29}.

$$f_1 = \left\{ \frac{[\sum_{t=1}^n |R_t - T_t|]}{\sum_{t=1}^n R_t} \right\} \times 100 \quad \dots(1)$$

$$f_2 = 50 \times \log \{ [1 + (1/n) \sum_{t=1}^n (R_t - T_t)^2]^{-0.5} \times 100 \} \dots(2)$$

Where ‘n’ is the sampling number, ‘T’ and ‘R’ is the percent dissolved of the test and product reference at each time point ‘t.’ Two dissolution profiles are similar if the value of f_1 is between 0 and 15, and value of f_2 is greater than 50.

Evaluation of Flow Properties: Flow properties of pure CFZ and the SDs were evaluated by measuring the angle of repose (θ), bulk density (ρ_b) and tapped density (ρ_t) and calculating Carr’s index (C) and Hausner ratio (H).

Angle of Repose: The angle of repose of pure CFZ and the SDs was determined by fixed funnel method³¹. Height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of SD powder. The powder was allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured, and the angle of repose was calculated using equation (3), given below

$$\tan \theta = h/r \quad \dots(3)$$

Where; h = height of the heap, r = radius of the heap

Bulk Density (ρ_b) and Tapped Density (ρ_t): Bulk density (ρ_b) and tapped density (ρ_t) were calculated by measuring bulk volume (V_b) and tapped volume (V_t) for the predetermined weight (W) of CFZ and SDs. The sample was introduced into a 10 ml cylinder in quantity sufficient to fill the cylinder to 10 ml mark. The initial volume was noted, and the cylinder was allowed to fall under its weight onto a hard surface from a height of 2.5 cm at 2 s intervals. The tapping was continued until no further change in volume was observed (minimum 500 taps). Bulk density and tapped density were calculated using equations 4 and 5, respectively³¹.

$$\rho_b = W / v_b \quad \dots(4)$$

$$\rho_t = W / v_t \quad \dots(5)$$

Carr's Compressibility Index (C): The Carr's compressibility index (C) was calculated for CFZ and SDs using equation (6) shown below³¹:

$$C (\%) = \left[\left(\frac{\rho_t - \rho_b}{\rho_t} \right) \right] \times 100 \quad \dots(6)$$

Hausner ratio (H): Hausner ratio (H) is the ratio of tapped density to bulk density. It gave an insight

into the flow characters of powder particles and was calculated for CFZ and the SDs using equation (7) as shown below³¹:

$$H = \rho_t / \rho_b \quad \dots(7)$$

RESULTS:

Evaluation of CFZ- EE PO Solid Dispersions:

Determination of Saturated Solubility of CFZ and SDs:

The values obtained by saturated solubility determination of CFZ and the SDs are shown in **Table 2**. **Fig. 4A** and **4B** present the solubility results in distilled water and 0.75% solution of SLS, respectively. In distilled water, pure CFZ showed solubility of 0.104 ± 0.005 mg/ml, which increased nearly twice when formulated as SD1 (0.214 ± 0.005 mg/ml) and nearly 20 times when formulated as SD2 (2.084 ± 0.044 mg/ml). Further increase in the proportion of EE PO (SD3) showed decreased solubility of CFZ (0.058 ± 0.005 mg/ml). Similar results were obtained when the solubility was determined in 0.75% w/v solution of SLS. Pure CFZ showed solubility of 10.08 ± 0.51 mg/ml in 0.75% SLS solution, which increased marginally in SD1 (12.95 ± 0.198 mg/ml) but significantly in SD2 (20.79 ± 3.08 mg/ml). A higher proportion of EE PO in SD3 led to the lower solubility of CFZ (15.93 ± 2.09 mg/ml) than in SD2.

TABLE 2: SATURATED SOLUBILITY DETERMINATION OF CANAGLIFLOZIN AND CANAGLIFLOZIN-EUDRAGIT® E PO SOLID DISPERSIONS IN DISTILLED WATER AND 0.75% SLS SOLUTION AT ROOM TEMPERATURE (25 ± 2 °C)

Formulation code	Solubility in distilled water (mg/ml) (n=3)	Solubility in 0.75% SLS solution (mg/ml) (n=3)
CFZ	0.10 ± 0.005	10.08 ± 0.506
SD1	0.21 ± 0.044	12.95 ± 0.198
SD2	2.08 ± 0.005	20.79 ± 3.08
SD3	0.06 ± 0.005	15.92 ± 2.09

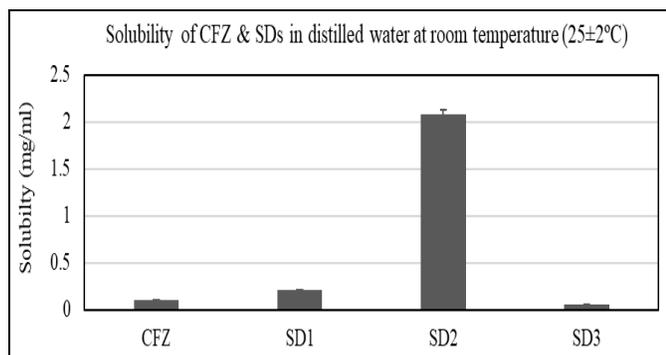


FIG. 4A: SATURATED SOLUBILITY DETERMINATION OF CANAGLIFLOZIN AND CANAGLIFLOZIN-EUDRAGIT® E PO SOLID DISPERSIONS IN DISTILLED WATER AT ROOM TEMPERATURE (25 ± 2 °C)

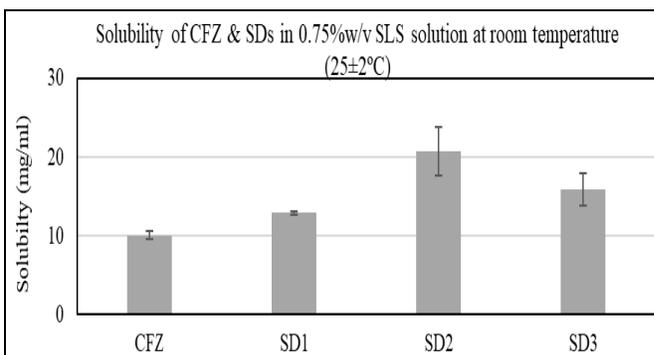


FIG. 4B: SATURATED SOLUBILITY DETERMINATION OF CANAGLIFLOZIN AND CANAGLIFLOZIN-EUDRAGIT® E PO SOLID DISPERSIONS IN 0.75% SLS SOLUTION AT ROOM TEMPERATURE (25 ± 2 °C)

Solid State Characterisation:

Fourier-Transform Infrared Spectroscopy (FTIR): Fig. 5 depicts the IR spectra of CFZ, EE PO, PM and the SDs. The spectrum of CFZ showed bands: 3477 cm^{-1} , 3372 cm^{-1} , 2914 cm^{-1} , 1626 cm^{-1} , 1600 cm^{-1} , 1549 cm^{-1} , 1509 cm^{-1} , 1438 cm^{-1} , 1233 cm^{-1} , 1161 cm^{-1} , 1086 cm^{-1} , 1054 cm^{-1} , 1022 cm^{-1} and 831 cm^{-1} . IR spectrum of EE PO showed characteristic bands at 2958 cm^{-1} , 1730 cm^{-1} , 1458 cm^{-1} and 1149 cm^{-1} .

The PM retained characteristic peaks of CFZ (3275 cm^{-1} , 1626.05 cm^{-1} , 1600 cm^{-1} , 1556 cm^{-1} , 1509 cm^{-1} , 1232 cm^{-1} , 1151 cm^{-1} , 1087 cm^{-1} , 1057 cm^{-1} , and 819 cm^{-1}) and EE PO (2956 cm^{-1} , 1732 cm^{-1} , 1456 cm^{-1} and 1151 cm^{-1}). The IR spectrum of SD1, SD2 and SD3 formulations displayed broadening of band at 3412.19 cm^{-1} , 3429.55 cm^{-1} and 3433.41 cm^{-1} respectively, while retaining other characteristic peaks of CFZ and EE PO.

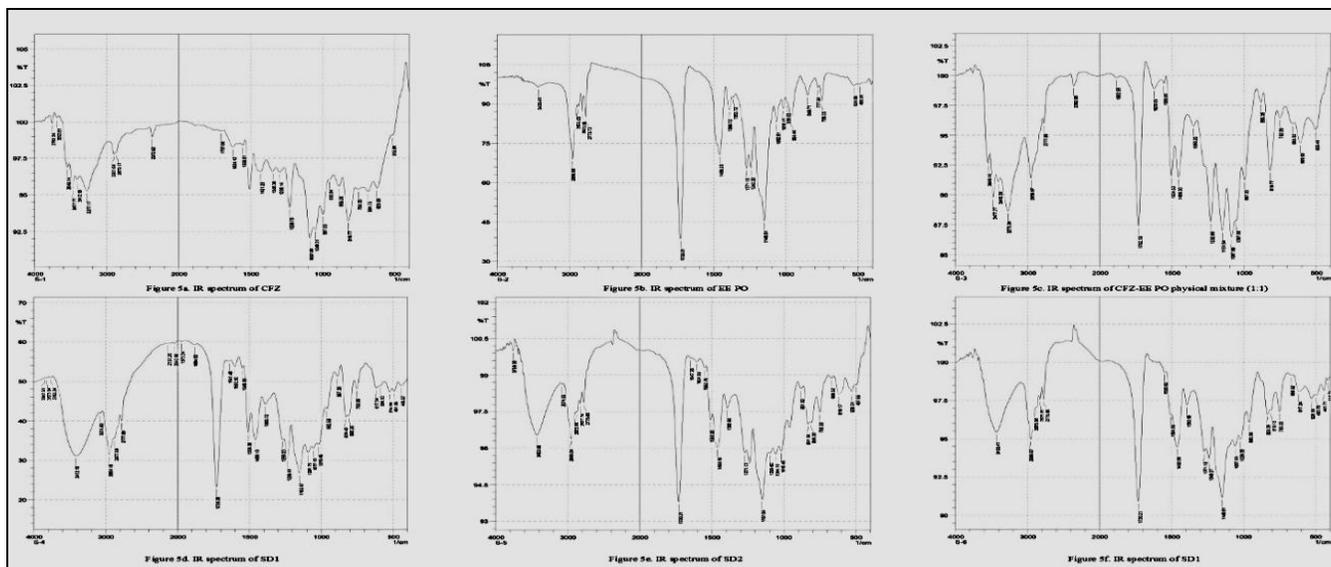


FIG. 5: FTIR SPECTRA OF CANAGLIFLOZIN, EUDRAGIT[®] E PO, CANAGLIFLOZIN-EUDRAGIT[®] E PO PHYSICAL MIXTURE AND CANAGLIFLOZIN-EUDRAGIT[®] E PO SOLID DISPERSIONS

Differential Scanning Calorimetry (DSC): The DSC curves obtained for pure CFZ, EE PO, PM, and SDs are displayed in figure 6. DSC curve for CFZ showed an endothermic peak at $98\text{ }^{\circ}\text{C}$. No

distinct peaks were observed for the polymer EE PO. The PM retained the endothermic peak of CFZ while it disappeared completely in SD1 and SD2. SD3 showed a broad endothermic peak at $71.7\text{ }^{\circ}\text{C}$.

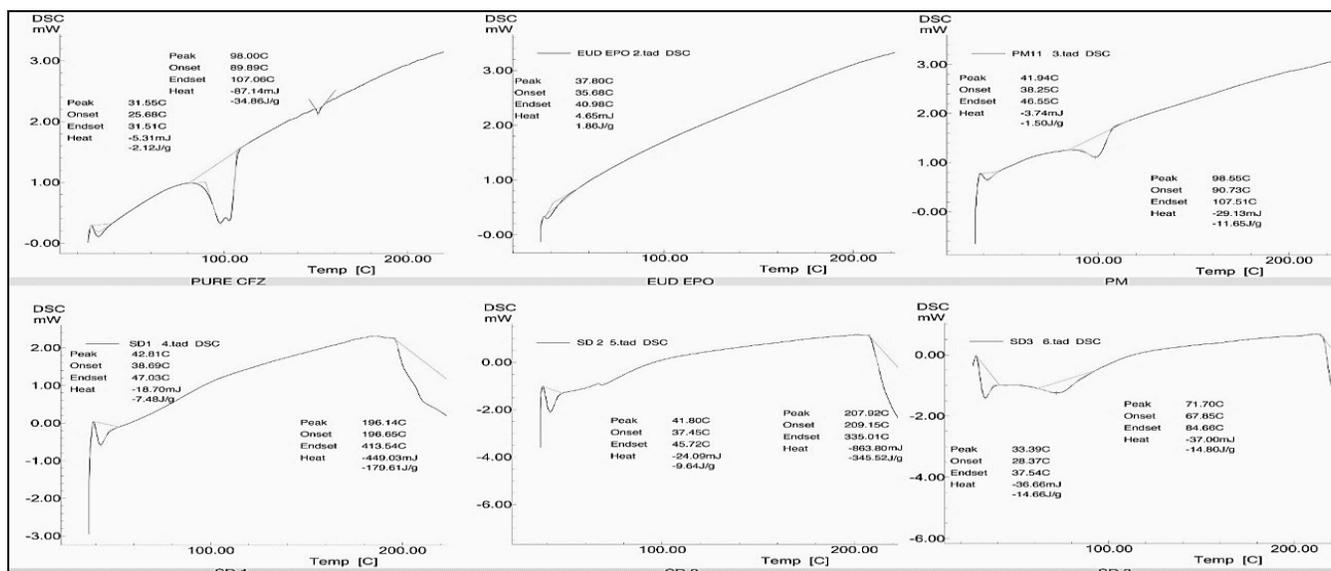


FIG. 6: DSC THERMOGRAPHS OF CANAGLIFLOZIN, EUDRAGIT[®] E PO, CANAGLIFLOZIN-EUDRAGIT[®] E PO PHYSICAL MIXTURE AND CANAGLIFLOZIN-EUDRAGIT[®] E PO SOLID DISPERSIONS

X-ray Powder Diffraction (XRD): The XRD patterns of CFZ, EE PO, and the SDs are shown in Fig. 7. The XRD scan of pure CFZ illustrates high-intensity sharp peaks at $4.75 \pm 0.2^\circ$, $13.02 \pm 0.2^\circ$, $16.2 \pm 0.2^\circ$, $18.76 \pm 0.2^\circ$, $19.09 \pm 0.2^\circ$, and $20.24 \pm 0.2^\circ$ which are consistent with the canagliflozin

hemihydrate intrinsic peaks at diffraction angles $4.36 \pm 0.2^\circ$, $13.54 \pm 0.2^\circ$, $16.00 \pm 0.2^\circ$, $19.32 \pm 0.2^\circ$, and $20.80 \pm 0.2^\circ$ as disclosed in the patent document U.S. Pat. No. 7,943,582B2³². No intrinsic peaks were observed in the case of EE PO, SD1, SD2, and SD3.

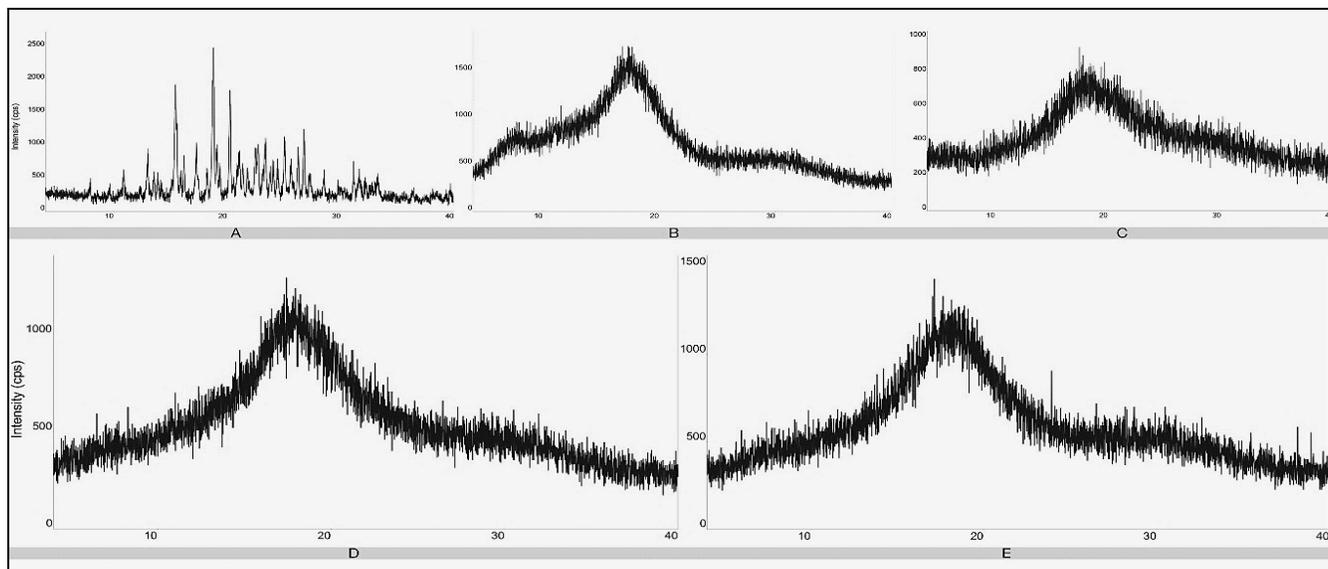


FIG. 7: XRD SPECTRUM OF A) CANAGLIFLOZIN, B) EUDRAGIT® E PO, C) SD1, D) SD2, E) SD3

Field Emission Scanning Electron Microscopy (FESEM): FESEM micrographs of pure CFZ and SD2 are shown in Fig. 8A and 8B, respectively.

Fig. 8A displays crystalline morphology of pure CFZ while Fig. 8B displays diffuse, irregular particles in SD2.

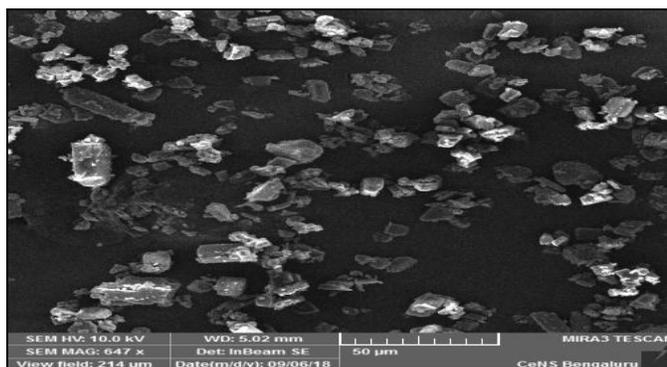


FIG. 8A: FESEM OF CANAGLIFLOZIN

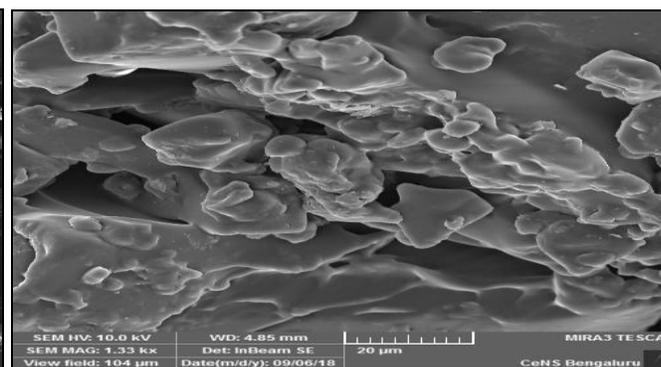


FIG. 8B: FESEM OF SD2

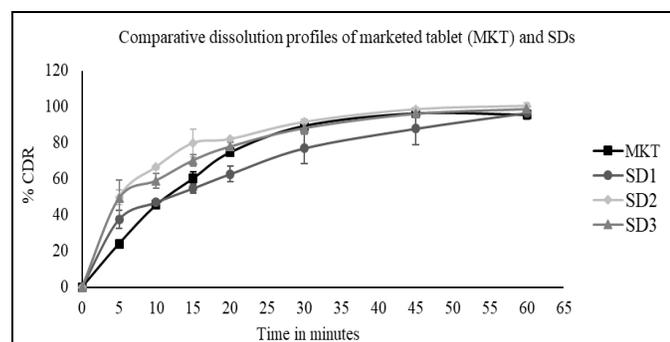


FIG. 9: COMPARATIVE DISSOLUTION PROFILES OF MARKETED TABLET AND CANAGLIFLOZIN-EUDRAGIT® E PO SOLID DISPERSIONS

In-vitro Dissolution Study: The comparative *in-vitro* dissolution profiles of MKT and SDs are presented in Fig. 9. The dissolution curves reveal that at the end of 5 min, MKT, SD1, SD2 and SD3 exhibit % cumulative drug release (% CDR) of 24%, 38%, 50% and 49% CFZ respectively. The % CDR at the end of 15 min was found to be 60%, 55%, 80% and 70% for MKT, SD1, SD2, and SD3 respectively.

Difference Factor (f_1) and Similarity Factor (f_2): Each dissolution profile was paired with another

and compared by calculating values of f_1 and f_2 factors which are summarised in **Table 3**. While comparing the dissolution profiles of MKT and SD1, the f_1 value was found to be below 15 (11.21), and the f_2 value was found to be above 50 (51.67). Relatively, higher values of f_1 and lower values of f_2 were obtained while comparing

dissolution curves of MKT and SD2 ($f_1=19.72$, $f_2=39.69$) and that of MKT and SD3 ($f_1=17.5$, $f_2=45.23$). The f_1 value was found to be well below 15 ($f_1=5.88$) and f_2 value much above 50 ($f_2=62.63$), while comparing dissolution profiles of SD2 and SD3.

TABLE 3: DIFFERENCE FACTOR (F_1) AND SIMILARITY (F_2) FACTOR FOR COMPARING DISSOLUTION PROFILES OF MARKETED TABLET (MKT) AND SOLID DISPERSIONS (SDS)

Reference	Test	f_1	f_2	Inference about dissolution profiles
MKT	SD1	11.21	51.67	Similar
MKT	SD2	19.72	39.69	Dissimilar
MKT	SD3	17.50	45.23	Dissimilar
SD1	SD2	27.51	37.71	Dissimilar
SD1	SD3	20.02	36.83	Dissimilar
SD2	SD3	5.88	62.63	Similar

Evaluation of Flow Properties: Flow properties of pure CFZ and SDs were evaluated in terms of bulk density (ρ_b), tapped density (ρ_t), Carr's compressibility index (C), Hausner ratio (H) and angle of repose (θ), are displayed in **Table 4**. The SDs showed C value ranging from 19.83 ± 0.76 to 12.5 ± 0.55 , which are much lower than C value of

CFZ (37.6 ± 1.5). The H values for SDs (1.25 ± 0.01 to 1.14 ± 0.01) were also found to be lower than CFZ (1.59 ± 0.04). Similar observations were recorded for θ values, which were in the range of $30.15 \pm 0.4^\circ$ to $27.59 \pm 0.37^\circ$ for SDs and $37 \pm 0.6^\circ$ for CFZ.

TABLE 4: FLOW PROPERTY CHARACTERISATION OF CANAGLIFLOZIN AND CANAGLIFLOZIN-EUDRAGIT® E PO SOLID DISPERSIONS

Formulation code	Bulk density (ρ_b) g/cc	Tapped density (ρ_t) g/cc	Carr's index (C)	Hausner ratio (H)	Angle of repose (θ)	Flow property
CFZ	0.236 ± 0.002	0.38 ± 0.014	37.6 ± 1.5	1.59 ± 0.04	$37 \pm 0.6^\circ$	Fair
SD1	0.47 ± 0.005	0.58 ± 0.006	19.83 ± 0.76	1.25 ± 0.01	$30.15 \pm 0.4^\circ$	Good
SD2	0.48 ± 0.01	0.58 ± 0.011	14.67 ± 0.29	1.17 ± 0.003	$25.43 \pm 0.37^\circ$	Excellent
SD3	0.56 ± 0.005	0.65 ± 0.004	12.5 ± 0.55	1.14 ± 0.01	$27.59 \pm 0.37^\circ$	Excellent

DISCUSSION: Canagliflozin is a poorly water-soluble (~ 0.558 mg/L at 25° C), BCS IV compound which is practically insoluble in aqueous media from pH 1.1 to pH 12.9^{4, 8, 11, 33}. The insolubility of CFZ in aqueous media throughout the pH range makes buffers unsuitable as the dissolution medium.

In such cases, the addition of surfactants helps to obtain sink conditions, by enabling the drug release process at the solid-liquid interface and micelle solubilization in bulk³⁴ and is recommended for performing *in-vitro* dissolution studies^{35, 36}.

For CFZ, 0.75% w/v SLS solution in water is recommended as dissolution media²⁷. Hence, the solubility determination of CFZ and the solid dispersions was done in distilled water as well as 0.75% SLS solution. The solubility studies indicate that solubility of CFZ in water and SLS solution,

increases initially on increasing the proportion of EE PO in SD formulations, (solubility of SD2 > SD1 > CFZ). The solubility decreases when proportion of EE PO is raised further (as in SD3).

The initial increase in solubility might be attributed molecular dispersion of CFZ in an amorphous matrix of EE PO, which leads to the transformation of the crystalline state of CFZ to an amorphous or partially amorphous state. The amorphous state is a highly disordered and high-energy state which results in augmented solubility. Decreased solubility of CFZ upon increasing proportion EE PO (SD3) might be attributed to the formation of a viscous matrix, which decreases the drug diffusion across the thick polymeric matrix and hence decreased solubility. The results indicate that the highest increase in solubility is seen when CFZ and EE PO are present in a ratio of 1:2 (SD2).

The conversion of crystalline CFZ to amorphous form when formulated as SDs was established by solid-state characterization of CFZ and the SDs. The endothermic peak of CFZ at 98 °C observed in DSC corresponds to its melting point range (95 °C-105 °C)^{37, 38}. The endothermic peak height and heat of fusion were reduced in PM and completely disappeared in solid dispersions SD1 and SD2. These findings suggest that the physical state of CFZ transformed from crystalline to amorphous in SD1 and SD2. A broad endothermic peak in case of SD3 indicates an interaction between the drug and the polymer. The small peaks at the beginning of all thermographs are supposed to be endothermic startup hooks, which appeared due to differences in the heat capacity of the sample and reference, and were therefore ignored.

The powder X-ray diffractometry patterns supported results obtained in DSC. XRD pattern of CFZ showed intrinsic peaks at the diffraction angles, showing a typical crystalline pattern, while, the XRD pattern of EE PO shows broad, amorphous peak characteristic of a polymer. The solid dispersions of CFZ and EE PO depicts XRD spectrum which is diffuse and represents low-frequency halo, characteristic of 'amorphous halo'³¹. This confirmed the transformation of CFZ from crystalline form to amorphous form when formulated as solid dispersions. The absence of crystallinity contributes to the enhancement of dissolution of CFZ when formulated as SDs.

FESEM micrographs of SD2 show rough and diffuse structure of particles in contrast to FESEM micrograph of CFZ where particles appeared to be regular and crystalline. This morphological visualization further confirmed the presence of CFZ in the amorphous form in SD2.

IR spectra of CFZ, EE PO, PM, and SDs were studied to detect any complexation or chemical interaction between CFZ and EEPO. The IR spectrum of CFZ displayed characteristic peaks in confirmation with literature³⁷. The band at 3477 cm⁻¹ indicates O-H stretch of water molecule (hemihydrate composition of CFZ), 3277 cm⁻¹ signifies O-H stretch of alcohol, several bands at 1626.05 cm⁻¹, 1600 cm⁻¹, 1556 cm⁻¹, 1509 cm⁻¹ relate to C=C stretch in aromatic ring, medium peak at 1431 cm⁻¹ is due to CH₂ bend, strong peak

at 1087 cm⁻¹ indicates C-F stretch, several strong peaks from 1232 cm⁻¹, 1151 cm⁻¹, 1087 cm⁻¹, 1057 cm⁻¹ are due to dialkyl C-O-C stretch; peak at 1232 cm⁻¹ may also be due to C-O stretch of alcohol, and peak at 819 cm⁻¹ is due to aromatic C-H bend (para). EE PO shows peaks at 2956 cm⁻¹, 1732 cm⁻¹, 1456 cm⁻¹ and 1151 cm⁻¹, characteristic of C-H stretch of alkanes, C=O stretch of esters, CH₂ bend of alkanes, C-C(O)-C stretch of esters. The IR spectra of a physical mixture retain the peak of the CFZ and EE PO, indicating that the drug and the polymer are compatible with each other. The formulations SD1, SD2 and SD3 show broadening of the band at 3400-3300 cm⁻¹ which suggests hydrogen bonding at hydroxyl groups. Other peaks and bands of CFZ and EE PO remain unchanged in all SD formulations.

The *in-vitro* dissolution studies reflect that highest dissolution is achieved by SD2 followed by SD3, SD1, and MKT, which is in confirmation with solubility order of SDs in dissolution medium (SD2>SD3>SD1>CFZ). The calculation of the difference factor and the similarity factor revealed that MKT and SD1 illustrated similar dissolution profiles ($f_1 < 15$ and $f_2 > 50$). SD2 and SD3 dissolution curves are dissimilar to MKT dissolution curve ($f_1 > 15$ and $f_2 < 50$ for SD2- MKT and SD3-MKT) but similar to each other ($f_1 < 15$ and $f_2 > 50$ for SD2-SD3). The results also show that nearly 50% of the % CDR took place in the first 5 min by SD2 and SD3 as compared to 25% CDR by MKT.

Hence, there was a significant increase in dissolution rate when CFZ was formulated as SD2 and SD3. This may be attributed to the conversion of crystalline CFZ into an amorphous system when it is molecularly dispersed into amorphous carrier EE PO. This may be due to the lack of energy requirements during the dissolution process to break up the disordered amorphous structure unlike the organized crystalline state¹⁵. The lower values of C, H, and θ for SDs than CFZ indicate that flow property of CFZ was improved when formulated as SDs. The value of C for SD2 in range of 11 - 15, H in range of 1.12 - 1.18 and θ value $\sim 25^\circ$ suggest good flow property of SD2, which makes it suitable to attain weight uniformity when filling in capsules³⁹.

CONCLUSION: Amorphous form of CFZ is successfully achieved by formulating it into SDs, which has conferred an increase in solubility and dissolution rate. SD2 shows the best performance in this regard as the further increase in the proportion of EE PO in SDs is detrimental to solubility and dissolution rate of CFZ. SD2 also exhibits good flow properties and is expected to show good performance in the uniform filling of the capsule. The CFZ- EE PO SDs are novel and fill the knowledge gap as they are not being investigated earlier.

ACKNOWLEDGEMENT: Authors express their sincere thanks to Shrideep Labs Pvt. Ltd., Bangalore for supporting this research work.

CONFLICT OF INTEREST: All the authors declare no conflict of interest.

REFERENCES:

1. Cho NH, Shaw JE, Karuranga S, Huang Y, Rocha JD and Ohlrogge AW: IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Research and Clinical Practice* 2018; 138: 271-81.
2. Political declaration of the high-level meeting of the general assembly on the prevention and control of non-communicable diseases. Resolution adopted by the General Assembly. United Nations 2012; A/RES/66/2.
3. Sessa R: Novel SGLT2 inhibitor dosage forms. WIPO Patent; WO2010/045656A2.
4. Compounds S: Canagliflozin Compound Summary for CID 24812758. PubChem open chemistry database 2016; 2.
5. Haas B, Eckstein N, Pfeifer V, Mayer P and Hass MD: Efficacy, safety and regulatory status of SGLT2 inhibitors: Focus on canagliflozin. *Nutrition and Diabetes* 2014; 4(11): 1-8.
6. Lamos EM, Younk LM and Davis SN: Canagliflozin, an inhibitor of sodium-glucose cotransporter 2, for the treatment of type 2 diabetes mellitus. *Expert Opinion on Drug Metabolism & Toxicology* 2013; 9(6): 763-75.
7. Coelln-Hough J: Canagliflozin Advisory Committee Meeting. Janssen Pharm 2013.
8. European Medicines Agency: Assessment Report Vokanamet. Committee for Medicinal Products for Human Use 2014; EMA/179391/2014.
9. Tahara A, Takasu T, Yokono M, Imamura M and Kurosaki E: Characterization and comparison of sodium-glucose cotransporter 2 inhibitors in pharmacokinetics, pharmacodynamics, and pharmacologic effects. *Journal of Pharmacological Science* 2016; 130(3): 159-69.
10. Dietrich E, Powell J and Taylor JR: Canagliflozin: A novel treatment option for type 2 diabetes. *Drug Design, Development and Therapy* 2013; 7: 1399-08.
11. European Medicines Agency: Assessment Report Canagliflozin. Committee for Medicinal Products for Human Use 2013; EMA/374133/2013.
12. Newman A, Hastedt JE and Yazdani M: New directions in pharmaceutical amorphous materials and amorphous solid dispersions, a tribute to Professor George Zografi – Proceedings of the June 2016 Land O'Lakes Conference. *AAPS Open* 2017; 3(1): 7.
13. Younis MA: Solid dispersion technology, a contemporary overview on a well-established technique. *Universal Journal of Pharmaceutical Research* 2017; 2(3): 15-9.
14. Vasconcelos T, Marques S, das Neves J and Sarmiento B: Amorphous solid dispersions: Rational selection of a manufacturing process. *Advanced Drug Delivery Reviews* 2016; 100: 85-01.
15. Baghel S, Cathcart H and 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. *Journal of Pharmaceutical Sciences* 2016; 105(9): 2527-44.
16. Ellenberger, Daniel J, Miller DA and Williams RO: Expanding the application and formulation space of amorphous solid dispersions with KinetiSol®: A review. *AAPS PharmSciTech* 2018; 19(5): 1933-56.
17. Teófilo V, Marques S, Neves JD and Sarmiento B: Amorphous solid dispersions: a rational selection of a manufacturing process. *Advanced Drug Delivery Reviews* 2016; 100: 85-01.
18. Bhatnagar P, Dhote V, Mahajan S, Mishra P and Mishra D: Solid dispersion in pharmaceutical drug development: from basics to clinical applications. *Current Drug Delivery* 2014; 11(2): 155-71.
19. Sekiguchi K and Obi N: Studies on absorption of the eutectic mixture. I. a comparison of the behavior of a eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. *Chemical & Pharmaceutical Bulletin* 1961; 9(11): 866-72.
20. Gupta R, Mishra AK and Pathak AK: A critical review on different pharmaceutical aspects of solid dispersion technique for solubility enhancement. *International Journal of Pharmacy and Biological Sciences* 2015; 5(3): 119-28.
21. Drašković M, Medarević D, Aleksić I and Parojčić J: *In-vitro* and *in-vivo* investigation of taste-masking effectiveness of Eudragit E PO as drug particle coating agent in orally disintegrating tablets. *Drug Development and Industrial Pharmacy* 2017; 43(5): 723-31.
22. Klimkowsky D: Moisture protection and taste-masking with polymethacrylate coatings. Evonik Industries 2015; Available from <http://www.phexcom.cn/uploadfiles/200899112713336.pdf>.
23. Evonik. EUDRAGIT® E 100, EUDRAGIT® E PO and EUDRAGIT® E 12,5. Evonik Technical Information 2015; 1-6.
24. Pradhan R, Kim SY, Yong CS and Kim JO: Preparation and characterization of spray-dried valsartan-loaded Eudragit® E PO solid dispersion microparticles. *Asian Journal of Pharmaceutical Sciences* 2016; 11(6): 744-50.
25. Li J, Lee IW, Shin GH, Chen X and Park HJ: Curcumin-Eudragit® E PO solid dispersion: A simple and potent method to solve the problems of curcumin. *European Journal of Pharmaceutics and Biopharmaceutics* 2015; 94: 322-32.
26. Thomas LC: Interpreting unexpected events and transitions in DSC results. *Government Information Quarterly* 2010; 27(4): 423-30.
27. USFDA. Dissolution Methods Drug Database 2016 [cited 2018 Sep 10]. Available from: <https://www.accessdata.fda.gov/scripts/cder/dissolution>.
28. Suneetha A and Sharmila D: Research Journal of Pharmaceutical, Biological and Chemical Sciences A Validated Stability Indicating RP-HPLC Method for

- Estimation of Canagliflozin in Dosage Form .Research Journal of Pharmaceutical, Biological and Chemical Sciences 2015; 6: 1186-94.
29. Moore WJ: Mathematical Comparison of Dissolution Profiles. Pharmaceutical Technology 1996; 20: 64-75.
 30. Stevens RE, Gray V and Dorantes A: Scientific and regulatory standards for assessing product performance using the similarity factor, f2. AAPS Journal 2015; 17: 301.
 31. Bates S. Amorphous Materials: A Structural Perspective. Proceedings of Pharmaceutical Powder X-ray Diffraction Symposium; 2012; 15-18; FL, USA.
 32. 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.
 33. Wang: Chongqing Medical and Industrial Research Institute Co., Ltd., assignee. Crystalline forms i and a method of manufacturing canagliflozin. JP Patent; JP2018500368A, 2015.
 34. Qureshi S: Drug dissolution testing: selecting a dissolution medium for solid oral products dissolution. American Pharmaceutical Review 2009; 12(1): 2-5.
 35. Sciences P: *In-vitro* dissolution testing for solid oral dosage forms. Particle Sciences 2010; 5: 2.
 36. Hassan HA, Charoo NA, Ali AA and Alkhatem SS: Establishment of a bioequivalence- indicating dissolution specification for candesartan scilexetil tablets using a convolution model. Dissolution Technologies 2015; 22(1): 36-43.
 37. Nomura S, Sakamaki S, Hongu M, Kawanishi E, Koga Y and Sakamoto T: Discovery of Canagliflozin, a Novel C - Glucoside with Thiophene Ring, as Sodium-Dependent Glucose Cotransporter 2 Inhibitor for the Treatment of Type 2 Diabetes Mellitus(1). Journal of Medicinal Chemistry 2010; 53(17): 6355-60.
 38. Kaur I, Wakode S and Singh HP: Development and validation of UV Spectroscopic Method for Determination of Canagliflozin in Bulk and Pharmaceutical Dosage Form 2015; 6(2): 82-6.
 39. Osorio JG and Muzzio FJ: Effects of powder flow properties on capsule filling weight uniformity. Drug Development and Industrial Pharmacy 2013; 39(9): 1464-75.

How to cite this article:

Agrawal R, Patel N and Raval M: Novel amorphous solid dispersions of canagliflozin hemihydrate in Eudragit® E PO. Int J Pharm Sci & Res 2019; 10(6): 2923-33. doi: 10.13040/IJPSR.0975-8232.10(6).2923-33.

All © 2013 are reserved by International Journal of Pharmaceutical Sciences and Research. This Journal licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License.

This article can be downloaded to **Android OS** based mobile. Scan QR Code using Code/Bar Scanner from your mobile. (Scanners are available on Google Play store)