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Formulation And In Vitro Characterization Of Sotagliflozin Nanosuspension

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ABSTRACT

Introduction: Sotagliflozin is a dual sodium-glucose co-transporter 1 as well as 2 (SGLT1 and SGLT2) inhibitor. Sodium-dependent glucose transporter 2 (SGLT2) plays an important role in the regulation of blood glucose. It is indicated to treat type 2 diabetes mellitus. The absolute bioavailability of oral sotagliflozin was approximately 25%. It is classified as BCS class II drug and has limited bioavailability due to poor aqueous solubility.

Aim & Objective: The aim of this study was to develop and characterize Sotagliflozin nanosuspension and to compare with a coarse suspension for the enhancement of solubility and bioavailability.

Materials & methods: Sotagliflozin nanosuspension was developed by high pressure homogenization. DSC study was conducted to know the drug-excipient compatibility. All other physical characterization studies were conducted. Box Behnken design was employed for the optimization of the formulation.

Results & Discussion: The optimized nanoformulation (F6) showing the size, PDI, ZP and assay of 112 ± 1.10 nm, 0.211 ± 0.03, -29.64 ± 1.1 mV, 92.21 ± 0.13% respectively. The optimized formulation was stable for 3 months period at room temperature and refrigerated conditions.

Conclusion: Sotagliflozin nanosuspension was developed by using high pressure homogenization method. The optimized sotagliflozin nanosuspension (Run 6) showed smaller particle size, uniform particle size distribution and good zeta potential value

Keywords: *Box Behnken design. nanosuspension, sotagliflozin, particle size, zeta potential*

1. INTRODUCTION

Creating an enabling formulation that can make poorly water-soluble medications extremely soluble in order to address the issue of low bioavailability is one of the main issues facing pharmaceutical researchers. Nanotechnology is one of the most widely used approaches for targeted medication administration as well as for resolving the issue of inadequate solubility and, consequently, bioavailability (Sapavatu et al., 2020).An alternate and promising universal formulation method that improves the pharmacoeconomics and efficacy of the majority of medications is provided by nanosuspensions (Chettupalli et al., 2025). By altering a medicine's solubility and pharmacokinetics, nanosuspension technology increases drug safety and efficacy (Moschwitzer and Muller, 2007). Without a carrier system or delivery vehicle, nanosuspensions are composed entirely of pure medicine particles and are typically stabilized with surfactants or polymeric stearic stabilizers (Avula et al., 2023). Therefore, in contrast to polymeric drug delivery systems, they are a whole independent pharmaceutical technology with distinct manufacturing processes (Chettupalli et al., 2025). Because of its high drug content, nanosuspension technology can help maximize pharmacological effects, attain therapeutic concentrations that are high enough, and efficiently transport the medication entering the cells at a fast rate (Patravale et al., 2004; Hafner et al., 2014].

Sotagliflozin is a promising medication for the treatment of heart failure, which is a dual sodium-glucose co-transporter 1 as well as 2 (SGLT1 and SGLT2) inhibitor. Sodium-dependent glucose transporter 2 (SGLT2) plays an important role in the regulation of blood glucose. It is indicated to reduce the risk of cardiovascular death and heart failure in adults, type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors (Lamos *et al*., 2013; Tahara *et al.,* 2016]. The absolute bioavailability of oral sotagliflozin was approximately 25%.

2. MATERIALS AND METHODS

Materials

Sotagliflozin was received as gift sample from Dr. Reddy's Pvt Ltd, Hyderabad. Sodium carboxy methyl cellulose, PVP k30 and Tween 80 were purchased from S.D. Fine Chemicals Ltd. (Mumbai, India). All other chemicals used were of pharmaceutical grade. HPLC grade methanol was obtained from Merck. Triple distilled water was obtained from Milli-Q water purification system (Millipore).

Methods

Sotagliflozin nanosuspension was prepared by high-pressure homogenization method followed by lyophilization. Take the necessary amount of drug in a mortar and grind it. Next, mix Tween 80, PVP K30, and stabilizers in 20 mm of water. The dispersion was homogenized for a predetermined amount of time and at a predetermined speed. To obtain sotagliflozin nanosuspension, the resulted suspension was lyophilized using mannitol (1–4% w/v) as a cryoprotectant following the high pressure homogenization process (Hajare and Jadhav, 2012)

Preparation of Sotagliflozin coarse suspension

In order to formulate sotagliflozin coarse suspensions, 50 mg of sodium carboxymethyl cellulose was first triturated for three minutes in a mortar. Next, 200 mg of sotagliflozin was added, and the mixture was again triturated for three minutes. To obtain a coarse medication suspension, add 100 ml of water and triturate once more for five minutes.

Application of design of experiments

Using Design Expert software Version 13, the Box-Behnken design was used to maximize sotagliflozin nanosuspension (Patel and Patel, 2020; Chettupalli *et al.,* 2025). Based on some trials in this BBD approach, homogenization time (X1), stabilizer amount (X2), and homogenization speed (X3) were chosen as independent factors, while particle size (Y1) and zeta potential (PDI) (Y2) were chosen as dependent variables.

Characterization of Nanosuspensions

Differential Scanning Calorimetry (DSC)

Accurately weighed samples (5 mg) were heated in an aluminium pan at a heating rate of 5°C/min at the range of 200°C under nitrogen atmosphere. Drug-excipient interaction studies were conducted for pure drug, physical mixture and optimized nanosuspension. DSC calorimeter (DSC Shimadzu, DSC- 60, and Kyoto, Japan) was used for this purpose **(**Sharaff *et al.,* 2024; *Lapuerta et al*., 2015).

Particle Size, Polydispersity Index (PDI) and Zeta Potential

The average particle size (sown in fig. 1), polydispersity index (PDI) and zeta potential of the developed nanosuspensions were measured using dynamic light scattering using zeta sizer (Nano ZS; Malvern Instruments, UK). For the determination, take 100 µL of the developed formulation and which was diluted ten times with triple distilled water. All measurements were taken in triplicates (Eslavath *et al.,* 2019; Mujtaba *et al*., 2014). Zeta potential is the electric potential of a particle in a suspension. It is a parameter which is very useful for the assessment of the physical stability of colloidal dispersions.

Drug content

Take the required quantity, 10 mg of drug in 100 ml volumetric flask and diluted up to 100 ml with methanol. Then drug content was measured at 271 nm using UV-visible spectrophotometer (Kuchukuntla *et al.,* 2019).

Transmission electron microscopy

A drop of nanosuspension was applied on carbon coated grid with 2% phospho-tungestic acid and it was left for 30 sec. The dried coated grid was taken to a slide and after placing the cover slip, the sample was air dried in a vacuum dryer and observed under TEM operated at 60–80 KV (Geetha *et al.,* 2012; Jadi RK, Chinnala, 2016).

In vitro drug release

The dissolution test for was carried out to determine the drug release from the sotagliflozin nanosuspension and sotagliflozin

coarse suspension, by using USP type II dissolution tester (Electrolab, Hyderabad, India). For this, 900 ml of 0.1N HCl was used as the dissolution medium. The temperature maintained at 37.0 ± 0.5ºC and the rotating speed, 50 rpm, was used. At predetermined time intervals, about 5 ml samples were withdrawn and filtered through 0.45 µm filter. The samples were analyzed spectrophotometrically at 271 nm using UV-visible spectrophotometer. Repeat this experiment three times and recorded the average values (Akula *et al.,* 2021; Togaru *et al.,* 2017; Muller and Peters, 1998)

Physical stability study

The physical stability studies were conducted on the optimized sotagliflozin nanosuspension. The freshly prepared sotagliflozin nanosuspension was stored at different conditions i.e., room temperature and at 4°C for the period of three months (Narendar and Kishan, 2015). At the end of definite time interval (0, 30, 60 & 90 days), the average particle size, zeta potential and drug release was determined (Srinidhi *et al.,* 2016; Swapna *et al.,* 2018; Pandala *et al.,* 2019).

3. RESULTS AND DISCUSSION

Sotagliflozin nanosuspension was developed by high pressure homogenization method. Total 9 formulations were developed by using Box- Behnken design. The effect of homogenization time was studied on nanosuspension's particle size and exhibited a decrease in particle size with an increase in homogenization time. Later, the impact of different homogenization speed was evaluated on particle size of the formulation and it was observed that as the speed increases, particle size was found to be decreased. Further, the influence of the amount of stabilizer on the particle size of nanosuspension and it was demonstrated that an increase in particle size with an increase in the amount of stabilizer in nanosuspension (Zhang *et al.,* 2007].

Table 1: Factors & levels in the Box-Behnken design

Independent variable	**Level of variables**		
	Low (-1)	**Medium (0)**	**High (+1)**
Homogenization time (h) [X1]	1.5	2	2.5
Amount of stabilizer (%w/v) [X2]	1	1.5	2
Homogenization speed (rpm) [X3]	7500	10000	12500

Table 2: Runs designed for the trails

Runs	**Factor A**	**Factor B**	**Factor C**	**Response 1**	**Response 2**
	Homogenization time (h) [X1]	**Amount of stabilizer (%w/v) [X2]**	**Homogenization speed (rpm) [X3]**	**Particle size (nm) [Y1]**	**Zeta potential (mV) [Y2]**
1	-1	+1	-1	383±1.01	-23.16±0.1
2	-1	+1	-1	362±2.31	-24.12±1.5
3	-1	+1	-1	339±1.04	-25.13±0.1
4	+1	0	+1	162±2.21	-27.25±2.1
5	+1	0	+1	141±1.41	-28.17±1.4
6	+1	0	+1	112±1.10	-29.64±1.1
7	0	-1	0	251 ± 1.21	-24.12±1.6
8	0	-1	0	236±2.11	-26.23±1.2
9	0	-1	0	213±1.24	-27.10±0.2

DSC analysis

The DSC curves for pure drug, sotagliflozin exhibited its endotherm peak at 218.6ºC and PVP k30 showed endotherm peak at 74.15º C (Fig. 3). The study revealed that the drug is compatible with other excipients used in the study (Sapavatu and Jadi, 2020).

Particle size and ZP

All the developed nano formulations were subjected for particle size analysis and ZP value determination. The particle size of all the developed nanosuspension formulations ranged from 112 ± 1.10 nm to 383 ± 1.01 nm (Table 2). The difference in the size of all the formulations could be due to the variation in the homogenization time and homogenization speed. As the homogenization time and speed increases, the particle size was decreases (Patravale *et al.,* 2004). The ZP of all the formulations lies between -23.16 ± 0.1 to -29.64 ± 1.1 mV (Table 2).

Transmission electron microscopy (TEM)

The particle size of optimized sotagliflozin nanosuspensions formulation was found to be less than 112 nm by TEM. TEM (fig. 4) results were in good correlation with the results obtained by Zetasizer (Malvern Instruments Ltd) which was found to be 115 nm. The TEM micrographs revealed that nanosuspensions were spherical in shape with size below 390 nm in diameter. The reduced particle size allowed for an increase in the absorption and solubility of the medicine (Thakkar *et al.,* 2011). The increased surface area and quicker drug release kinetics of the nanosuspension further improved its high bioavailability and therapeutic efficacy.

***In vitro* release studies**

The drug release studies were conducted for both sotagliflozin coarse suspension and optimized nanosuspension. sotagliflozin nanosuspension showed 89.13 ± 0.11% of drug release in first ten min. Whereas coarse suspension releases its drug 47.12 ± 1.0%. Complete drug release was observed within 10 min. There was a significant difference between the dissolution rate of the plain drug and the nanosuspension (Fig. 5). The nanosuspension showed enhanced release because of reduction in particle size and higher surface area, which allowed for faster rate of drug release. This drastic increase in the dissolution rate was due to the increased surface area of the drug as a follow up of smaller particle size, increased saturation solubility and also due to presence of the stabilizers (Janagam *et al.,* 2024; Pardeike *et al.,* 2011).

Based on particle size, zeta potential and rate of drug release, Run 6 was considered as the optimized formulation. Because this formulation showing highest zeta potential, smaller particle size compared to the all the formulations.

Stability study of optimized sotagliflozin nanosuspension

The accelerated stability studies were conducted on optimized formulation (Run 6) by maintaining the temperature and RH conditions at 25±2ºC/60% ± 5% RH respectively for 3 months period. It was observed that there was no significant change was observed in particle size, zetapotential and drug release upto 3 months. Hence, it was concluded that the optimized formulation (Run 6) remained stable at both room and refrigerated temperature for 3 months anc shown in fig.2.

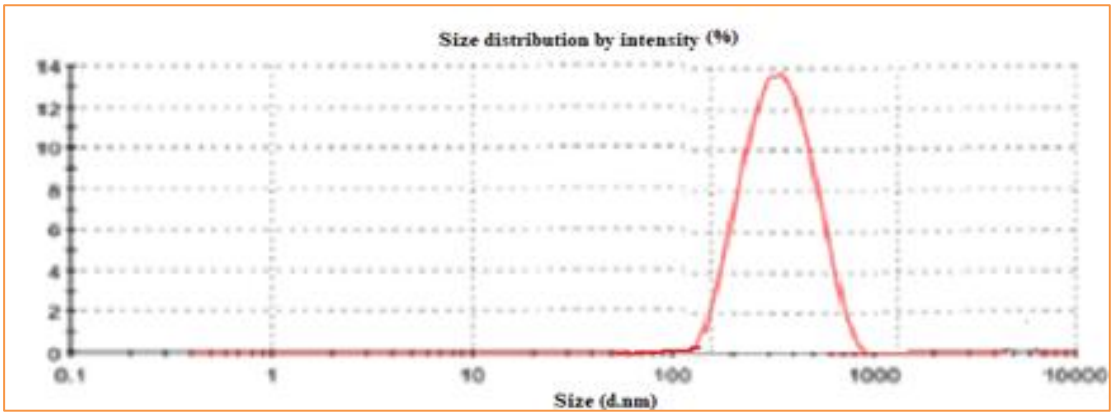

Fig. 1: Particle size of sotagliflozin nanosuspension

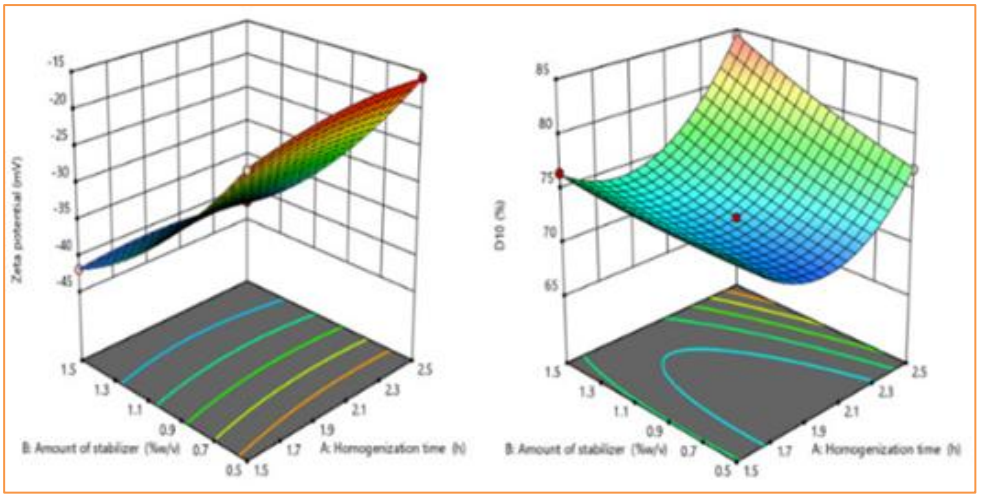

Fig. 2: Contour plots of amount of stabilizer versus homogenization time

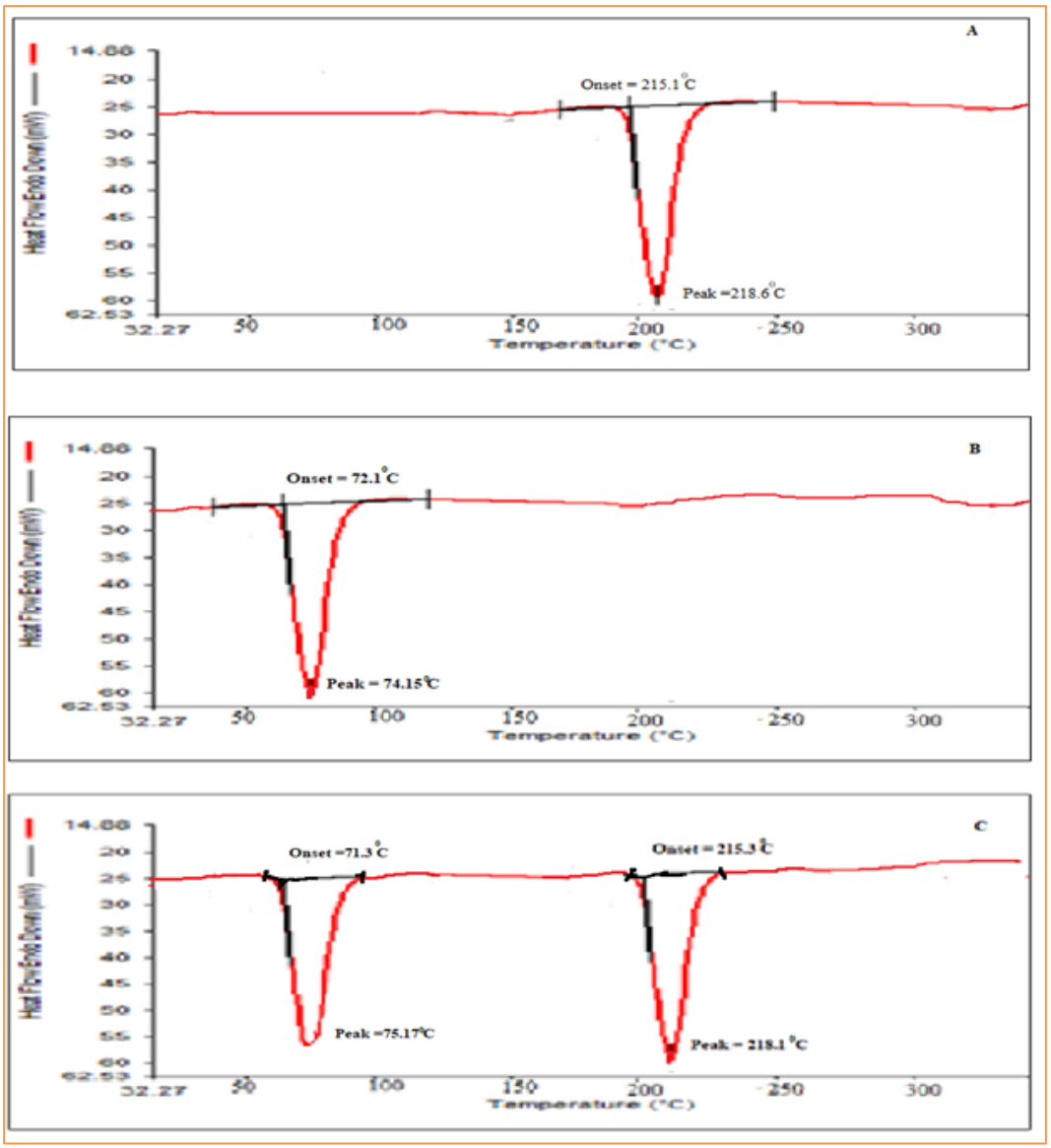

Fig 3: DSC thermograms of A) Pure drug B) PVP k-30 C) Physical mixture

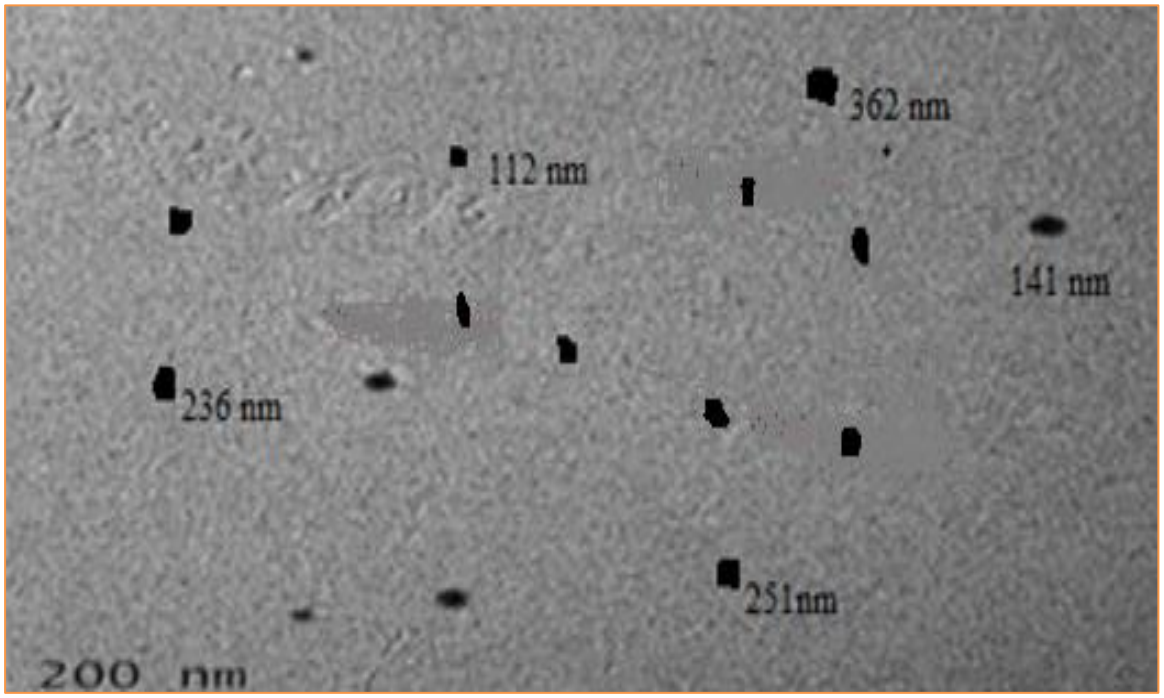

Fig. 4: TEM micrograph of sotagliflozin nanosuspensions

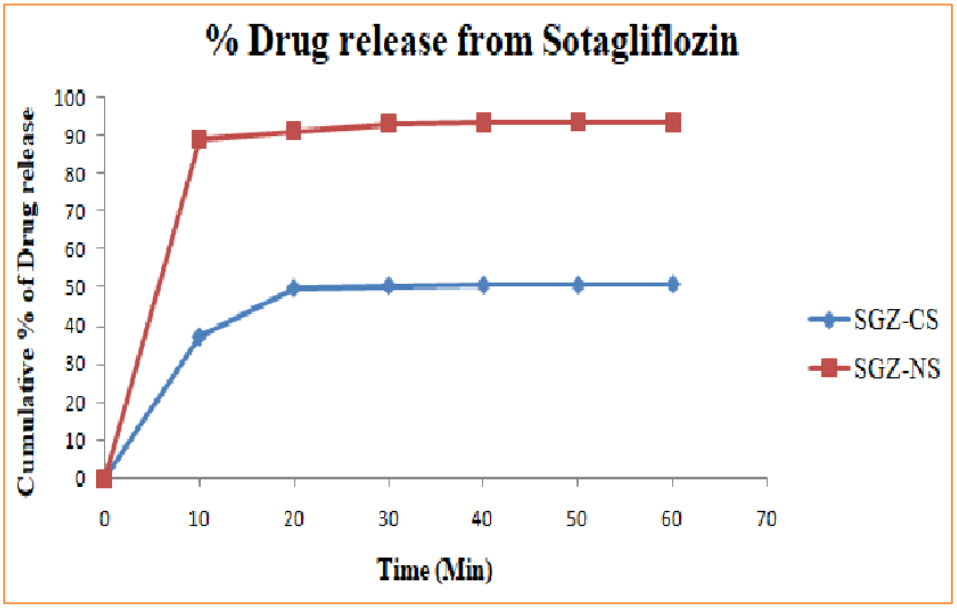

Fig. 4: Comparison of drug release profile of sotagliflozin nanosuspensions & coarse suspension

Table 3: Accelerated stability studies of optimized formulation

Time (Months)	Particle size (nm) (Mean±SD)	Zeta potential (mV) (Mean±SD)	% Drug release (Mean±SD)
0	112±1.2	-29.23±0.1	89.13 ± 0.11
1	112±2.3	-30.15±0.2	89.01 ± 0.23
3	112±4.1	-29.67±0.4	89.03 ± 0.14

4. CONCLUSION

Sotagliflozin nanosuspension was developed by using high pressure homogenization method. Box Behnken design was employed for the optimization of the formulation. The optimized sotagliflozin nanosuspension (Run 6) showed smaller particle size, uniform particle size distribution and good zeta potential value. It also showed higher drug release rate compared to the coarse suspension due to small particle size and large surface area. Accelerated stability studies were concluded that formulation 6 was stable for a period of 3 months.

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CONFLIT OF INTEREST: There is no conflict of interest.

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