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Research Article

DESIGN-BASED DEVELOPMENT OF CANAGLIFLOZIN TABLETS: FORMULATION AND CHARACTERIZATION STUDIES

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ABSTRACT

Objectives: The study aimed to convert liquid self-microemulsifying drug delivery systems (SMEDDS) of canagliflozin into solid SMEDDS to enhance stability and develop a tablet formulation. The key goal was to improve disintegration time and *in vitro* drug release.

Methods: Solidification of SMEDDS was achieved using two approaches: Adsorption onto carriers and lyophilization with mannitol. An I-optimal design was used to optimize the tablet formulation. Key variables included concentrations of super-disintegrants and adsorbents, while responses evaluated were disintegration time (R1) and *in vitro* drug release (R2). Aerosil 200 was used as the primary adsorbent, and croscarmellose as the super-disintegrant. Pre-compression parameters, such as flow properties, were analyzed based on different ratios of lactose and Aerosil 200. In addition, lyophilized formulations (L1-L4) were prepared and compared to adsorbed SMEDDS.

Results: Disintegration time was significantly influenced by the concentration of the super-disintegrant, with croscarmellose promoting faster disintegration. Among the formulations, S6 demonstrated optimal characteristics, including a rapid disintegration time of 40 s and a high dissolution rate of 97.3%. Lyophilized formulation L4 showed the highest drug release (at 25 min), though adsorption onto Avicel proved superior in enhancing overall dissolution. Pre-compression evaluations confirmed improved flow properties with optimized ratios.

Conclusion: Adsorption of SMEDDS onto solid carriers, particularly using Avicel, was more effective than lyophilization in improving dissolution and tablet performance. The optimized formulation (S6) exhibited robust characteristics suitable for long-term storage and use, demonstrating the potential of this approach for enhancing the bioavailability of poorly water-soluble drugs such as canagliflozin.

Keywords: Self-microemulsifying drug delivery system, Canagliflozin, Tablets, Adsorption, Lyophilization, Drug dissolution.

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INTRODUCTION

Oral drug delivery remains the most widely accepted and convenient route for medication administration, offering simplicity, non-invasiveness, and enhanced patient compliance. However, significant challenges exist for drugs with poor aqueous solubility, as the low dissolution rate in the gastrointestinal tract (GIT) often restricts their bioavailability [1]. In recent years, numerous strategies, including solid dispersions, salt formation, and lipid-based formulations, have been investigated to overcome these barriers. Among these, lipid-based systems, particularly self-emulsifying drug delivery systems (SEDDS) and self-micro-emulsifying drug delivery systems (SMEDDS) have demonstrated great potential to enhance the solubility and absorption of poorly water-soluble drugs [2].

SMEDDS are isotropic mixtures of oils, surfactants, and co-solvents capable of forming fine oil-in-water microemulsions upon mild agitation in aqueous media, such as GIT fluids. Their ability to self-emulsify without external energy facilitates improved drug dissolution and uniform absorption. Unlike conventional SEDDS, SMEDDS form transparent microemulsions with droplet sizes below 50 nm, allowing for rapid drug absorption and minimizing issues related to poor solubility [3-6]. In addition to enhancing bioavailability, SMEDDS-based formulations can be incorporated into Tablets to further improve patient compliance and provide rapid onset of action [5].

The current study explores the development and evaluation of a canagliflozin-loaded tablet using an optimized SMEDDS formulation. By combining the advantages of SMEDDS for enhancing solubility and the patient-centered benefits of tablets, this approach aims to create a novel delivery system that provides rapid drug release and improved bioavailability. The factorial design methodology was employed to optimize the formulation parameters, ensuring efficient drug loading, stability, and desirable disintegration properties. This innovative formulation offers a promising alternative for enhancing the therapeutic performance of poorly water-soluble drugs administered orally, whereas also addressing common challenges in bioavailability and patient adherence.

MATERIALS AND METHODS

Materials

In this study, canagliflozin was provided as a complimentary sample by Aurobindo Pharma Limited in Hyderabad. A range of excipients was utilized to formulate an effective SMEDDS, which included lipids such as castor oil, cetyl alcohol, and polysorbate 80; surfactants such as Tween 20 and Span 60; the co-surfactant propylene glycol; solubilizers such as ethanol, polyethylene glycol 400, and Transcutol HP; and preservatives including sodium benzoate and potassium sorbate. All chemicals used were of laboratory grade and sourced from standard deviation Fine Chemicals Ltd, located in Chennai, Tamil Nadu.

Methods

Preparation of liquid SMEDDS

In our previous study, by screening different compositions of the oil, surfactant, and cosurfactant, an optimized formulation (F7) with 100 mg canagliflozin, 45% peceol, 31% tween 80, and 24%

Table 1: Optimization factors and their respective levels

Factor	Name	Units	Type	Subtype	Minimum	Maximum	Coded low	Coded high	Mean	SD
A	Super disintegrants	%	Numeric	Continuous	2.00	10.00	−1−2.00	+1−10.00	6.11	2.45
B	Bulking agents	%	Numeric	Continuous	10.00	30.00	−1−2.00	+1−30.00	19.49	5.90

SD: Standard deviation

transcutol was prepared. Canagliflozin was mixed in peceol oil using a vortex mixer. Specific quantities of peceol, and surfactants, are combined and subjected to high shear mixing to achieve a uniform dispersion [7].

The optimized formulation exhibited the drug release in 30 min, along with advantages such as minimal particle size, rapid emulsification capability, and enhanced stability. Consequently, this chapter proposes converting the liquid SMEDDS to a solid SMEDDS through lyophilization and adsorption techniques. Subsequently formulating tablets for easier administration for adsorbed SMEDDS. The preparation of canagliflozin oro-dispersible tablets utilizing a 2^2-factorial design is discussed in detail, along with the evaluation of the tablet's performance and properties.

Conversion of liquid SMEDDS to solid SMEDDS through adsorption and preparation of canagliflozin ODT

Initially, all the ingredients are passed through #100 (150 μm aperture size as per Bureau of Indian Standard) to remove agglomerates. Liquid SMEDDS (F7) is gradually mixed by adding drop by drop to the adsorbent, aerosol 200 in the ratio specified in Table 1, and thoroughly mixed for 10 min allowing effective adsorption of SMEDDS and dried in a hot air oven. Later, croscarmellose sodium and lactose are added to the mixture followed by talc, and vanillin. All the ingredients were mixed to get a homogenous blend. Blend equivalent to 10 mg of the SMEDDS was directly compressed to a tablet with optimal compression force to get a hardness range of 4–5 kg/cm^2 using the 8 mm punch in an automated tablet punching machine 2 (Karnavati Minipress-II automated compression machine).

Optimization of preparation parameters of Tablets using 2^2-factorial design

In the preparation of tablets, the concentration of the adsorbent and the super disintegrant agent were varied at two levels to study their influence on the disintegration time and dissolution time of the canagliflozin tablets (Tables 1 and 2). 2^2-factorial design was employed to understand the influence of variables on the dependent responses and 12 different formulations were prepared based on the model and evaluated (Table 3) [8].

Evaluation of canagliflozin Tablets prepared by adsorption

Based on the factorial design, 12 different formulations were prepared with varying quantities of Aerosil 200, croscarmellose, and lactose. The blend prepared for each formulation was evaluated for pre-compression parameters.

Pre-compression parameters [9-11]

To determine bulk and tapped densities, a pre-weighed amount of powder was placed in a 25 mL graduated cylinder, and the bulk volume was measured without any compression. The cylinder was then tapped by dropping it from a height of 2.5 cm onto a hard surface every 2 s, until the volume remained constant. Bulk density was calculated as the ratio of the powder's weight to its initial volume, while tapped density used the volume after tapping. Hausner's ratio, indicating the powder blend's flow characteristics, was calculated by dividing tapped density by bulk density. In addition, Carr's index, which reflects flowability, was determined as the percentage difference between the two densities, divided by the tapped density. The angle of repose (θ), calculated from the height and radius of the powder pile, was also measured to assess internal friction and flow properties.

Table 2: Design of experiments for the process parameters in preparation of canagliflozin ODT

Run	Factor 1 A: Super disintegrating %	Factor 2 B: Bulking agents %
1	6	20
2	6	20
3	4.8	13
4	6	20
5	6	20
6	3.52	22.3
7	2	27.8
8	7.92	15.7315
9	6	20
10	2	16.7
11	10	19.416
12	6	20
13	9.04	10
14	6	20
15	9.04	10
16	6	20
17	2	10
18	10	30
19	8.08	24.8
20	5.8	30

Post-compression parameters

The compressed tablets were subjected to evaluation for various parameters, including general appearance, hardness [12], thickness, weight uniformity [13], friability [14], drug content [15], disintegration time [16], and *in vitro* dissolution studies [17] using the standard pharmacopeia procedures. The dissolution studies were conducted using a USP Type II paddle method with the Electrolab dissolution apparatus (Inspire 8 Basic), operated at 50 rpm in 900 mL of dissolution medium maintained at 37°C±0.5°C in 0.1 N HCl. Samples were taken at specific intervals, and the drug release was quantified using a UV-Visible S164, Elico Ltd. at 290 nm, with cumulative drug release calculated accordingly.

Conversion of liquid SMEDDS to solid SMEDDS through lyophilization

The optimized liquid SMEDDS F7 was combined with cryoprotectants, at concentrations of 10%, 15%, and 20% (Table 4). These mixtures were then subjected to lyophilization, a freeze-drying process, conducted at temperatures ranging from −40°C to −80°C. Sucrose and mannitol were studied as cryoprotectants. This approach was undertaken to convert the liquid formulation into a solid state, thereby enhancing the stability and handling of the SMEDDS [18].

Evaluation of lyophilized canagliflozin solid SMEDDS

For the purpose of large-scale production, the micrometric properties of powder blends play a significant role. Hence, the lyophilized sample is also evaluated for Hausner's ratio, Carr's index, and angle of repose according to the procedure specified in as above. The lyophilized solid SMEDDS with an equivalent quantity of 10 mg canagliflozin is crushed using a mortar and pestle and dispersed in 100 mL of 0.1 N HCl. The dispersion is allowed to rest for 24 h and the drug present is estimated at 290 nm. The dissolution process parameters employed and the drug estimation process are as specified in above. However, to study the drug release profile of solid SMEDDS, initially, lyophilized powder equivalent to 10 mg of canagliflozin is punched through an 8 mm punch to convert it into a tablet. The tablet obtained is introduced into a dissolution medium.

Table 3: Formulation of canagliflozin tablets prepared by adsorption

Materials	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12
L-SMEDDS 10 mg/10 mL	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Aerosil 200	20	14	22.3	27.8	16.7	19	15.73	10	10	30	24.8	30
Croscarmellose	6	4.8	3.52	2	2	10	7.92	9.04	2	10	8.08	5.8
Lactose	60	67.2	60.2	56.2	67.3	57	62.35	66.96	74	56	57.12	54.2
Vanillin	1	1	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Total (mg)	100	100	100	100	100	100	100	100	100	100	100	100

SMEDDS: Self-microemulsifying drug delivery systems

Table 4: Formulation L1-L6 with varied cryopreservatives

Ingredients	L1 (%)	L2 (%)	L3 (%)	L4 (%)	L5 (%)	L6 (%)
L-SMEDDS (1 mg/1 mL)	10 mL	10 mL	10 mL	10 mL	10 mL	10 mL
Sucrose	10	15	20	-	-	-
Mannitol	-	-	-	10	15	20

SMEDDS: Self-microemulsifying drug delivery systems

Table 5: Details of DOE model used in the canagliflozin tablets design

Build information				
File version	13.0.5.0			
Study types	Response surface		Subtype	Randomized
Design type	l-optimal	Coordinate exchange	Runs	20.00
Design model	Quadratic		Blocks	No blocks
Build time	30.00			

Stability Studies of the optimized tablets formulation

To further assess the formulation's stability, the optimized formulation underwent both accelerated and long-term stability studies. Stability studies are conducted to evaluate and confirm a formulation's ability to retain its physical, chemical, and therapeutic properties throughout its storage period [19].

RESULTS AND DISCUSSION

Two dependent factors, or responses, were selected for this study: R1, disintegration time, and R2, *in vitro* drug release. From the literature, it is observed that the disintegration time (R1) was substantially affected by the concentration of the super-disintegrant, while the *in vitro* drug release (R2) was influenced by the concentration of the adsorbent. Both of these parameters were optimized to achieve the ideal formulation for the tablets.

In the study model, both R1 and R2 responses followed a quadratic model. An I-optimal design was employed, which optimizes model parameter estimates and improves prediction accuracy given a specific number of experimental runs. The general quadratic model, suggested by the study, was used to evaluate the responses. This model incorporates linear, quadratic, and interaction effects of the factors, allowing for a more accurate capture of curvature in the response surface. Quadratic designs are commonly used when the response surface is expected to exhibit curvature, making them well-suited for this formulation study.

Pre-compression parameters of canagliflozin tablets prepared by adsorption

The pre-compression evaluation results of the powder blend of different formulations are presented in Table 6. The carr's index values ranged from 16.37±0.01 to 26.03±0.05, indicating good to poor flow. The Hausner's values were between 1.19±0.005 and 1.34±0.01 which indicated fair to poor flow. The results of the angle of repose are also in agreement with the other two parameters. Among all the formulations, the S9 blend showed poor flowability and the S10 blend has good flowability. While S6 showed fair flow. The micrometric properties of the formulation blend are found to be influenced by the diluent ratios, and ratio of lactose to the Aerosil 200. An increase in the Aerosil 200 quantity with a parallel decrease in the lactose weight improved the flow from poor to good.

Evaluation parameters of canagliflozin tablets post-compression

The tablets compressed were round without any signs of crevices. The thickness is uniform throughout the tablet and ranges from 2.2 to 2.46 (Table 7) depending on the constituents. The tablets S1-S10 were hard enough to endure the mechanical stress, with hardness between 4.0 and 4.45 kg/cm^2 (Table 7). S9 and S11 tablets were identified to have more weight variation with average weight values of 113.2 and 112.2 respectively. The high weight variations might be due to the poor flow of the powder blend resulting in inefficient and non-uniform filling of die. The remaining formulations showed less variation (Table 7) in compliance with the standards, resulting in a weight between 99.8 and 103 mg. The friability of the compressed canagliflozin tablets remained within the standard limits of <1% (Table 7). The drug content of the different tablets compressed is presented in Table 8. The percentage of drugs present in each tablet is above 85%, the acceptance limit. However, more variations in drug content are observed between the formulations, which could be due to the low dose of the drug (accounting for only 10% of the total weight of the tablet).

The disintegration time taken for each formulation is presented in Table 8. All the formulations were able to disintegrate to fine particles in <1 min. However, within a minute the number of seconds varied with the composition. The influence of different formulation parameters on disintegration time was interpreted through the design of experiments in further sections.

On observing the cumulative percentage drug release from S1 to S10 (Tables 9 and 10), it is evident that tableting the liquid SMEDDS has increased the dissolution time to more than 30 min, in spite of the fact that liquid SMEDDS F7 used in the tablet showed complete drug release. In the S5 formulation, only 57% of the drug is released at the time point of 25 min. The dissolution profiles are represented as Figs. 1 and 2. Formulation or conversion of liquid SMEDDS to solid SMEDDS is advantageous in terms of handling and stability but however, but retaining the dissolution enhancement attained through liquid SMEDDS in solid form is also a necessity. S6 showed 97.3% cumulative drug release in 20 min while S11 showed 98.3% drug dissolution in 25 min. The reason for these results in terms of factors influencing was established through the design of experiments using different statistical methods.

Influence of preparation parameters on disintegration and dissolution of canagliflozin tablets

The trial responses obtained in the study were input into the design table as suggested by the software according to the formulation as

Table 6: Pre-compression parameters of canagliflozin tablets prepared by adsorption

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	CI (%)	Hausner's ratio	Angle of repose(°)
S1	0.50±0.005	0.64±0.007	22.67±0.02	1.28±0.001	30.15±0.002
S2	0.50±0.001	0.63±0.05	20.37±0.06	1.24±0.02	29.20±0.005
S3	0.49±0.005	0.65±0.005	24.7±0.01	1.32±0.004	28.78±0.012
S4	0.52±0.002	0.65±0.002	19.55±0.005	1.23±0.005	27.65±0.01
S5	0.49±0.005	0.65±0.01	24.54±0.004	1.32±0.007	28.03±0.03
S6	0.51±0.03	0.63±0.0004	18.89±0.002	1.22±0.006	26.28±0.07
S7	0.46±0.05	0.56±0.005	22.3±0.007	1.21±0.01	32.01±0.06
S8	0.44±0.001	0.66±0.001	25.01±0.06	1.3±0.002	30.2±0.002
S9	0.49±0.005	0.59±0.005	26.03±0.05	1.34±0.01	32.24±0.005
S10	0.51±0.06	0.62±0.006	16.37±0.01	1.19±0.005	29.31±0.06
S11	0.42±0.001	0.65±0.002	25.03±0.001	1.33±0.005	30.00±0.01
S12	0.51±0.01	0.64±0.001	20.24±0.01	1.25±0.007	28.45±0.02

Table 7: Evaluation parameters of canagliflozin tablets prepared by adsorption

Formulation code	Thickness[a] (mm)	Hardness[a] (kg/cm^2)	Friability[c] (%)	Weight variation[b] (mg)
S1	2.43±0.01	4.56±0.02	0.68±0.02	100.2±1.05
S2	2.34±0.01	4.40±0.021	0.71±0.01	100.2±0.98
S3	2.40±0.03	4.20±0.03	0.79±0.009	99.7±0.85
S4	2.46±0.06	4.41±0.01	0.77±0.02	100.5±1.01
S5	2.2±0.002	4.51±0.01	0.49±0.1	100.2±0.76
S6	2.23±0.01	4.53±0.009	0.57±0.002	100.2±0.58
S7	2.34±0.009	4.23±0.04	0.78±0.02	99.8±0.43
S8	2.22±0.01	4.32±0.05	0.69±0.009	100.6±0.21
S9	2.43±0.001	4.24±0.01	0.98±0.02	113.2±1.52
S10	2.45±0.02	4.45±0.002	0.78±0.005	103.0±0.91
S11	2.23±0.01	4.33±0.007	0.58±0.051	112.2±1.73
S12	2.24±0.04	4.25±0.01	062±0.019	100.5±0.59

a: Mean±s.d, n=5; b: Tablets equivalent 6.5 g i.e., 65 tablets; c: Mean±% deviation, n=20

Table 8: Drug content and disintegration time of canagliflozin tablets prepared by adsorption

Formulation code	Drug content[a] (%)	Disintegration time[b] (seconds)
S1	94.08±0.01	39±0.02
S2	94.07±0.06	35±0.05
S3	95.6±0.04	53±0.01
S4	87.1±0.07	44±0.06
S5	95.56±0.03	52±0.03
S6	98.2±0.01	52±0.05
S7	90.2±0.02	40±0.05
S8	89.1±0.01	16±0.03
S9	93.01±0.05	28±0.05
S10	92.08±0.05	24±0.04
S11	98.87±0.01	20±0.05
S12	89.9±0.03	32±0.01

a: Mean±s.d., n=3; b: Mean±s.d., n=5

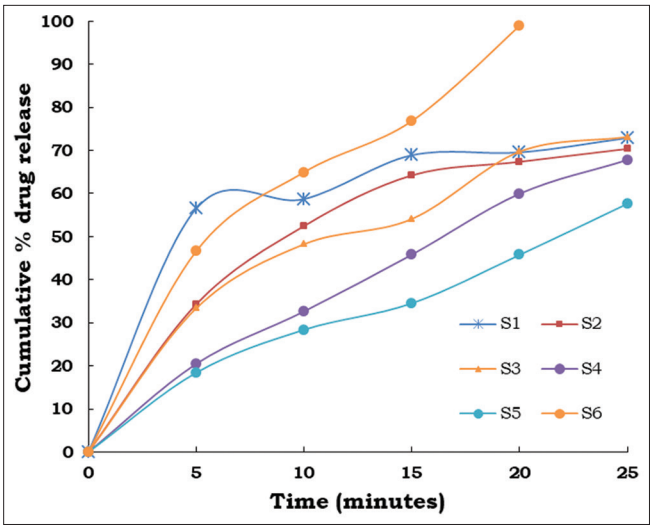

Fig. 1: Cumulative % drug release of canagliflozin tablets S1-S6

depicted in Table 11. Disintegration time and cumulative percentage drug release from the dissolution study were selected as two responses to establish the process parameters to attain study objectives. The design fitting for each response is calculated to validate the results obtained from the optimization study. As improper model fitting leads to wrong interpretations, the statistical significance of each factor's influence on the two responses was calculated using the analysis of variance to know the relation between the actual and predicted mean.

The ANOVA for 2FI showed significant model fitting with a p=0.0196 for response 1, disintegration time (Table 12). The super disintegrant concentration showed a significant influence on the disintegration time of the formulation (p=0.0078), and the bulking agent used, Aerosil 200 did not influence the disintegration time of the formulations (p>0.05). However, the interaction effect of the two variables (AB) showed a significant influence on the disintegration process and time. It indicated that Aerosil 200 alone may not affect or improve the disintegration but if used along with the super disintegrants such as croscarmellose, it can facilitate the disintegration process, reducing the time for disintegration.

Response 2, the cumulative percentage of drug dissolved in 20 min also showed significant model fitting with p=0.080 (Table 13). Crosscarmelose not only improved the disintegration but also showed significant influence on the percentage of drugs released. Croscarmellose, a commonly used super-disintegrant, can enhance drug dissolution by promoting rapid tablet disintegration into finer particles, increasing the surface area available for drug dissolution. Its cross-linked polymer structure also allows for significant water uptake, leading to rapid swelling and subsequent disintegration of the tablet.

Table 9: Cumulative percentage of drug released versus time of canagliflozin SMEDDS (S1-F5)

Time (min)	Percentage cumulative drug release (mean±s.d., n=3)					
	S1	S2	S3	S4	S5	S6
5	56.50±1.03	34.29±1.36	33.36±1.06	20.48±1.51	18.43±1.10	46.61±2.01
10	58.72±1.21	52.47±1.29	48.25±1.57	32.65±1.20	28.39±1.21	64.95±1.18
15	68.90±1.09	64.22±1.41	54.10±1.26	45.82±1.31	34.53±1.03	76.83±1.26
20	69.56±1.17	67.38±1.20	69.74±1.61	59.96±1.22	45.77±1.31	98.94±1.75
25	72.90±1.31	70.40±1.21	73.15±1.23	67.81±1.17	57.64±1.21	

SMEDDS: Self-microemulsifying drug delivery systems

Table 10: Cumulative percentage of drug released versus time of canagliflozin SMEDDS (S6-S10)

Time (min)	Percentage cumulative drug release (mean±s.d., n=3)					
	S7	S8	S9	S10	S11	S12
5	29.51±1.09	36.42±1.17	34.35±1.24	22.32±1.33	54.17±1.29	25.14±1.36
10	41.60±1.12	54.83±1.24	54.69±1.20	45.84±1.26	66.30±1.34	46.39±1.42
15	53.79±1.21	60.79±1.37	65.81±1.31	45.27±1.20	73.56±1.43	53.02±1.51
20	73.65±1.19	74.66±1.29	78.36±1.47	58.19±1.41	89.22±1.49	64.33±1.61
25	87.55±1.31	88.05±1.33	89.51±1.28	69.88±1.52	98.37±1.51	72.69±1.49

SMEDDS: Self-microemulsifying drug delivery systems

Table 11: Optimization table of canagliflozin tablets with factors and responses

Run	Factor 1: A: Superdisntegrating %	Factor 2: B: Bulking agents %	Response 1: Disintegration time (min)	Response 2: Dissolution time (min)
1	6	20	39	82.1
2	6	20	39	82.1
3	4.8	13	35	72
4	6	20	39	82.1
5	6	20	39	82.1
6	3.52	22.3	53	69.2
7	2	27.8	44	87.2
8	7.92	15.7315	52	84.3
9	6	20	39	82.1
10	2	16.7	40	97.3
11	10	19.416	16	87
12	6	20	39	82.1
13	9.04	10	28	74
14	6	20	39	82.1
15	9.04	10	28	74
16	6	20	39	82.1
17	2	10	24	65
18	10	30	20	69
19	8.08	24.8	32	98.3
20	5.8	30	58	72

Table 12: Analysis of variance of response 1: Disintegration time

Source	Sum of square	Df	Mean of square	F-value	p-value	
Model	0.0010	3	0.0003	4.38	0.0196	Significant
A: Susperdisintegrants	0.0007	1	0.0007	9.26	0.0078	
B: Bulking agent	0.0001	1	0.0001	1.35	0.2621	
AB	0.0004	1	0.0004	4.81	0.0434	
Residual	0.0013	16	0.0001			
Lack of fit	0.0013	8	0.0002			
Pure error	0.0000	8	0.0000			
Cor total	0.0023	19				

Factor coding is coded
Sum of squares is type III Partial

This swelling action facilitates the breakup of the tablet matrix, reducing particle size and allowing greater interaction between the drug particles and the dissolution medium. As a result, croscarmellose helps accelerate the dissolution process. Such observations are also reported by earlier researchers, where different super disintegrants improved the drug dissolution enhancing the drug bioavailability [13-17].

The bulking agent showed an insignificant effect on the drug dissolution process. Even the combination factor AB showed p>0.05. Hence, alteration of Aerosil 200 alone or in combination with super disintegrant may not alter the dissolution process significantly. However, the B2 variable indicating the squaring of the bulking agent concentration showed p=0.0005. It suggests that Aerosil 200 in high

Table 13: Analysis of variance of response 2: Cumulative percentage of drug released in the dissolution

Source	Sum of square	Df	Mean of square	F-value	p-value	
Model	1197.03	9	133.00	5.27	0.0080	Significant
A: Susperdisintegrants	407.33	1	407.33	16.13	0.0025	
B: Bulking agent	0.1308	1	0.1308	0.0052	0.9440	
AB	15.21	1	15.21	0.6021	0.4557	
A^2	111.02	1	111.02	4.40	0.0624	
B^2	655.03	1	655.03	25.94	0.0005	
A^2B	2.80	1	2.80	0.1108	0.7461	
AB^2	3.02	1	3.02	0.1197	0.7365	
A^3	454.37	1	454.37	17.99	0.0017	
B^3	22.39	1	22.39	0.8867	0.3686	
Residual	252.54	10	25.25			
Lack of fit	252.54	2	126.27			
Pure error	0.000	8	0.0000			
Cor total	1449.57	19				

Table 14: Point prediction for the responses of the optimized formulation (S6)

Run 10 response	Predicted mean	Predicted median	Observed	SD	n	SE prediction	95% PI low	95% PI high
Disintegration time	48.4399	42.4336	40	18.0838	1	N/A	22.5314	363.633
Dissolution time	92.891	92.8291	97.3	5.02537	1	6.96375	77.3129	108.345

SD: Standard deviation, SE: Standard error

Table 15: Micromeritic properties of canagliflozin lyophilized solid SMEDDS

Formulations	Carr's index	Hausner's ratio	Angle of repose
L4	19.2±0.002	1.22±0.05	27.23±0.003
L5	20.96±0.01	1.34±0.001	30.01±0.006
L6	24.23±0.01	1.42±0.002	30.9±0.01

SMEDDS: Self-microemulsifying drug delivery systems

Table 16: Drug content of canagliflozin lyophilized solid SMEDDS

Formulation code	Drug content (%)*
L4	98.7±0.002
L5	97.2±0.01
L6	98.1±0.006

*Mean±s.d, n=3. SMEDDS: Self-microemulsifying drug delivery systems

Table 17: Cumulative percentage of drug released versus time of canagliflozin lyophilized solid SMEDDS (S1-F5)

Time (min)	Percentage cumulative drug release (mean±s.d., n=3)		
	L4	L5	L6
5	32.15±1.11	22.46±1.16	27.36±1.09
10	37.06±1.19	34.18±1.29	33.51±1.14
15	65.25±1.23	43.59±1.34	49.82±1.20
20	87.59±1.21	57.63±1.31	64.80±1.31
25	96.16±1.13	78.06±1.29	80.94±1.23

SMEDDS: Self-microemulsifying drug delivery systems

concentration can influence the cumulative amount of drug released in the dissolution process [18,19]. It was observed from the contour plots that both disintegration and dissolution of canagliflozin from tablets were dependent on the super disintegrant concentration. A linear increase in drug dissolution is clearly observed in the Fig. 3.

The predicted versus actual plot is commonly used in regression analysis to assess the accuracy of a statistical or mathematical model. It compares the values predicted by the model to the actual, observed data. In Fig. 4, the Closer alignment of points along the diagonal line

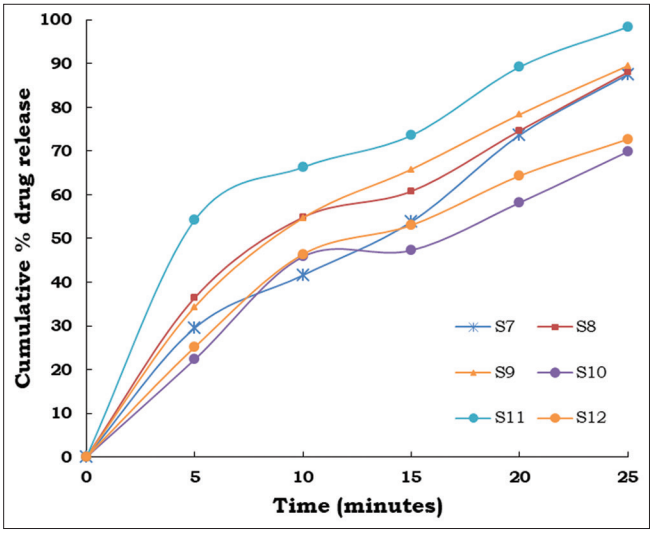

Fig. 2: Cumulative % drug release of canagliflozin tablets (S7-S12)

indicates that the model's predictions are accurate and the model fits the data well [20].

An overlay plot is frequently used in response surface methodology to visualize multiple response variables or factors on a single graph, making it easier to identify regions where the desired outcomes for all responses coincide. In Fig. 5, the feasible region is highlighted in yellow colour, where all response variables meet the target criteria of disintegration and dissolution. This Specifies the different possible optimal experimental conditions. The overlay plots served as multi-criteria optimization, allowing for a balanced decision between attaining required outcomes with more practical and effective formulation parameters possible [21,22].

The most desirable solution among the provided alternatives was taken into consideration. Here, in this model, one of the experimental formulations (S6) also met the desirability level and was shown in the list of solutions. Hence, the formulation S6 was chosen as an optimized formulation based on the factorial design and resynthesized. The confirmation parameters along with the confidence intervals are provided in Table 14. The observed responses for the disintegration time and cumulative percentage of drug

Table 18: Stability data of canagliflozin tablets (S6)

Test	Initial	Storage conditions			
		30°C±2°C/70°C±5% RH		40±2°C/75±5% RH	
		3 months	6 months	3 months	6 months
Physical appearance	White and round	White and round	White and round	White and round	White and round
Hardness[a] (kg/cm^2)	4.53±0.009	4.35±0.03	4.30±0.03	4.30±0.05	4.29±0.10
Friability[c] (%)	0.57±0.002	0.57±0.02	0.58±0.04	0.58±0.04	0.60±0.07
Uniformity of weight[b] (mg)	100.2±0.58	100.2±0.62	100.2±0.75	100.2±0.69	100.5±1.13
Drug content[d] (%)	98.2±0.01	98.2±0.08	98.2±0.11	98.2±0.06	98.2±0.14
Dintegration time[a] (s)	52±0.05	52±0.03	52±0.06	52±0.15	54±0.24

a: Mean±s.d, n=5; b: Mean±% deviation, n=20; c: Tablets equivalent 6.5 g i.e., 65 tablets; d: Mean±s.d., n=10

Table 19: Cumulative percent of drug released from canagliflozin SMEDDS (S6), before and after storage

Time (h)	Cumulative percent drug released (mean±s.d.,) (n=3)				
	Initial	30°C±2°C/70±5% RH		40°C±2°C/75±5% RH	
		3 months	6 months	3 months	6 months
5	46.61±2.01	47.07±1.98	47.54±1.45	48.12±1.46	48.73±1.49
10	64.95±1.18	65.13±1.70	65.87±1.57	66.35±1.51	66.40±1.39
15	76.83±1.26	77.09±1.65	78.43±1.61	77.58±1.61	78.21±1.59
20	98.94±1.75	98.96±1.74	99.25±1.83	99.14±1.71	99.37±1.42

SMEDDS: Self-microemulsifying drug delivery systems

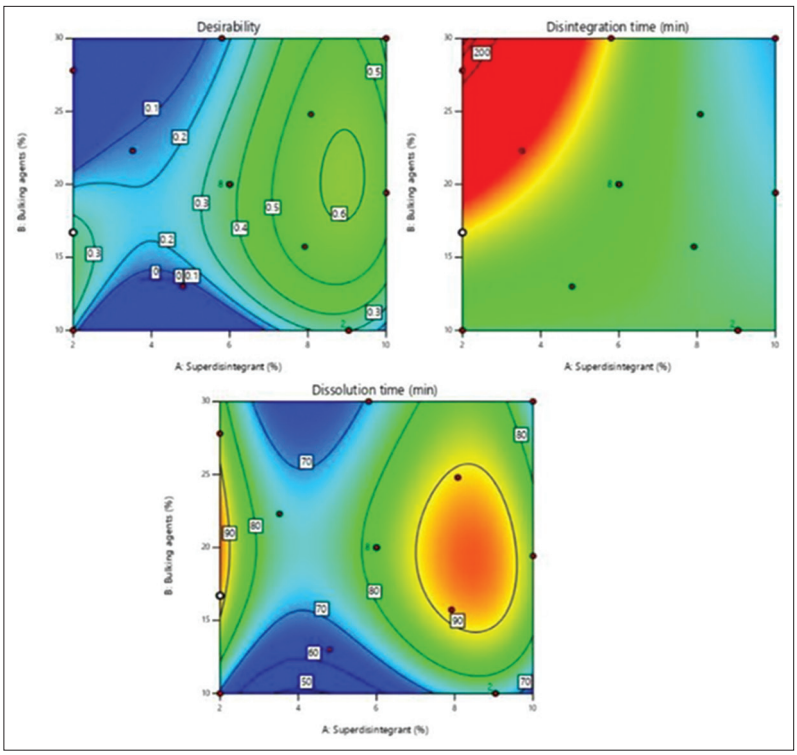

Fig. 3: Contour plots of responses versus factors studied

dissolved were observed to be 40 s, and 97.3%, respectively, whereas the predicted mean values were 48 s and 92%, respectively [23,24].

Evaluation of lyophilized canagliflozin solid SMEDDS

The six possible lyophilized products were prepared with varying concentrations of sucrose and mannitol. Products with sucrose as cryoprotectants were not converted into a fine powder, instead, it remained sticky even after lyophilization for a long period of time. Hence, sucrose-based products were not further evaluated and the products L4-L6 with mannitol were only evaluated for micromeritic properties, drug content, and *in vitro* drug release.

Micromeritic properties

The Carr's index, Hausner's ratio, and angle of repose of the lyophilized solid SMEDDS are given in Table 15. L4 with 10% mannitol showed fair flow, and an increase in further concentration in mannitol caused a decreased flowability resulting in poor [25].

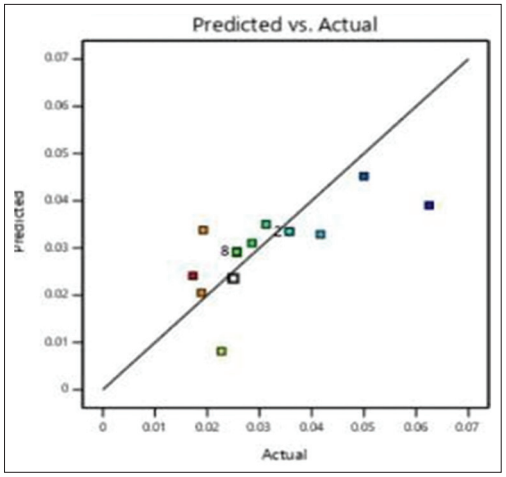

Fig. 4: Predicted versus actual response plot of canagliflozin tablet

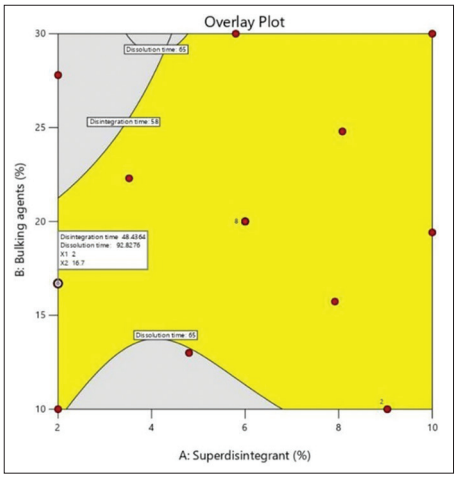

Fig. 5: Overlay plot of canagliflozin tablet

Drug content

All the products lyophilized showed drug content of 97–98.7% as shown in Table 16.

***In vitro* dissolution studies**

The *in vitro* dissolution study was performed for 25 min and product L4 with 10% mannitol released a higher percentage drug compared to L5 and L6 (Table 17 and Fig. 6). The cumulative canagliflozin released at 25 min from L4, L5, and L6 was 96.16%, 78.06%, 80.94%, respectively. The percentage of mannitol used for lyophilization showed a negative influence on the canagliflozin dissolution. The cumulative percentage of drug released decreased with the increase in mannitol concentration used for lyophilization.

Although LH4 performed better among the three lyophilized products, the drug dissolution was better in S6 ODT tablets, which released 98.94% drug in 20 min. The presence of super disintegrants and other excipients might have resulted in improved canagliflozin dissolution. Hence, liquid SMEDDS conversion to solid SMEDDS through adsorption method using avicel is selected over the lyophilization method and S6 was selected as optimized formulation for further stability studies [27].

Stability studies of the optimized formulation

These studies help determine the formulation's shelf life or the retest period, ensuring the product remains effective and safe for use over time. A new S6 batch with 500 tablets was prepared and excess tablets than the quantity needed for evaluation were stored. The results are presented in Tables 18 and 19; Figs 7 and 8.

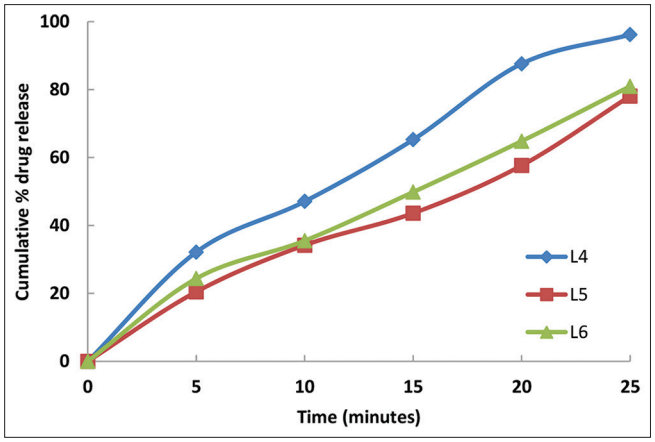

Fig. 6: Cumulative percentage of drug released by lyophilized solid self-microemulsifying drug delivery systems (L4-L6)

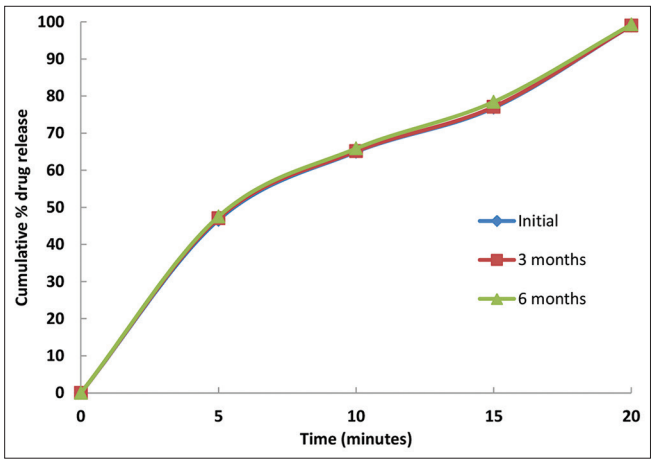

Fig. 7: Dissolution profile of canagliflozin from S6 tablet during long-term stability studies

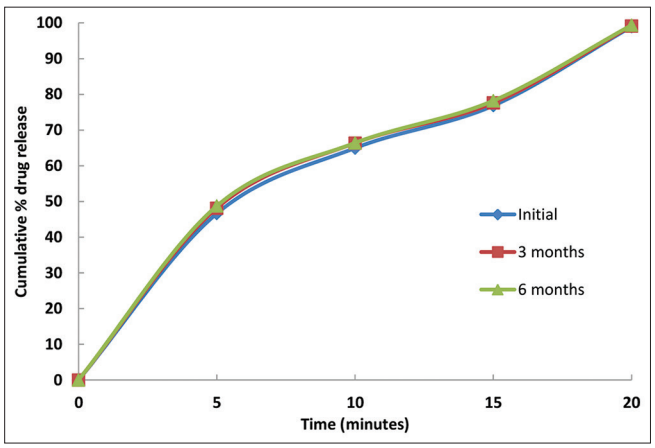

Fig. 8: Dissolution profile of canagliflozin from S6 orally disintegrating tablet during accelerated stability studies

No significant differences were observed in the post-compression parameters when comparing long-term and accelerated storage conditions to the initial conditions. The *in vitro* dissolution profiles were consistent and overlapped across these conditions, leading to the conclusion that a 6-month stability study was sufficient. Based on these results, the formulation was deemed suitable for *in vivo* pharmacodynamic evaluation.

CONCLUSION

The canagliflozin liquid SMEDDS optimized were converted to solid SMEDDS adopting two different methods, adsorption on carrier aerosol followed by tablet preparation, later prepared by lyophilization with cryoprotectants (sucrose and mannitol). Mannitol is selected over sucrose for lyophilization as sucrose results in sticky products. The canagliflozin tablets was optimized for super disintegrant concentration and bulking agent, Aerosil 200 concentration with respect to disintegration time and dissolution profile. The super disintegrant, croscarmellose concentration showed a decrease in disintegration time with concentration and it also significantly influenced the canagliflozin dissolution. Aerosil 200 as a bulking agent has not shown any significant improvement in terms of drug dissolution, but in combination with super disintegrant, it showed a significant impact on disintegration time. Overall, S6 tablet formulation released the complete drug in 20 min meeting the standards of immediate-release tablets with a disintegration time of 52 s, it was also stable during the accelerated and long-term study.

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Not declared.

AUTHOR CONTRIBUTIONS

All authors are contributed equally.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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