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Enhancing the Solubility of Canagliflozin Using Self-Microemulsifying Drug Delivery Systems (SMEDDS): A Novel Approach for Improved Bioavailability

P. J. V. V. Naga Phani[1], Dr. K.V. Ratnamala,[2] Dr.K. V. Ramana Murthy[1]

[1]AU College of Pharmaceutical Sciences, Visakhapatnam, Andhra Pradesh, India-530003.

[2] RBVRR Women's college of Pharmacy, Barkatpura, Hyderabad.

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KEYWORDS

Canagliflozin, Peceol, Transcutol, microemulsions, SMEDDS

ABSTRACT:

The objective of this study was to create self-emulsifying microemulsion preconcentrates that could enhance the solubility and oral bioavailability of canagliflozin, a drug used to treat Type II diabetes mellitus. Canagliflozin belongs to BCS class IV due to its poor solubility and permeability. The oils, surfactants, and co-surfactants were selected for the pre-concentrates based on solubility studies and the range of concentrations that could impact the development of microemulsions was determined. The prepared formulations are then evaluated for the in vitro behaviour to determine the drug's dissolution rate, and found that the formulation containing peceol, Tween 80, and Transcutol was effective. 15 formulations of microemulsions were prepared using these lipid excipients with varying agitation times and water quantities. Basing on the results, F7 and F13 are found to be the best formulations. F7 had a drug release rate of 99.29% in 30 minutes while F13 had a release rate of 98.2% in 40 minutes, indicating the immediate release property of Self-Microemulsifying Drug Delivery Systems (SMEDDS). The particle sizes of the optimized formulations F7 and F13 were 348.4 and 384 nm, respectively, which is imperative of increased solubility and bioavailability.

1. Introduction:

The aim of an ideal drug delivery system is to achieve desired therapeutic effect with minimal to zero adverse events. In recent years, there have been significant advancements in drug delivery technologies that allow for more precise and controlled release rates [1]. However, due to physiological constraints within the gastrointestinal (GI) tract, it has been difficult for even advanced drug delivery techniques to create commercially viable oral dosage forms [2]. This has led researchers around the world looking into novel ways of creating effective oral dosage forms using cutting-edge technology solutions [3]. However, the simplest and most cost-effective method of noninvasive administration is through an oral route; that dominates much of today's global market when it comes to drug delivery systems as they are both economical and convenient compared with other methods such as intravenous or intramuscular injections which require medical supervision from trained personnel [4].

Therefore, this research paper aims at exploring Self-Micro emulsifying Drug Delivery Systems (SMEDDS) that aids in the drug delivery of poor water soluble drugs using canagliflozin as a model drug.

SMEDDS is a type of drug delivery system that uses lipids to solubilize hydrophobic drugs, allowing them to be administered orally in an efficient and cost effective manner [5]. Lipid-based formulations, such as SMEDDS, have been developed to increase the solubility of drugs that are not easily water soluble. These formulations provide benefits such as improved chemical and physical stability, the ability to fill into unit dosage forms, and improved patient compliance and tolerance. Literature review suggests that lipid-based drug delivery systems are a potential approach in improving solubility and bioavailability of drugs having poor water solubility and bioavailability like canagliflozin [6].

Canagliflozin is SGLT2 inhibitor used to treat type II diabetes mellitus. It is a BCS class IV drug which implies

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that it has poor water solubility as well as low permeability across the cell membrane [7]. Therefore, this research paper aims at improving the solubility of canagliflozin (thereby increasing its bioavailability) by formulating it into SMEDDS using oil as lipid carrier so that rate of release could be increased significantly while also making sure there are no adverse effects on patient's health after administration[8].

The main objective of the study is to create a large interfacial area by the small oil droplets scattered in the GI fluids due to fine o/w emulsion and thereby enhancing the solubility and bioavailability of canagliflozin via SMEDDS.

2. Materials:

The drug used in the study**,** canaglifozin is obtained as a gift sample from Aurobindo Pharma Limited, Hyderabad. This study used a variety of excipients in order to create an effective SMEDDS. These included lipids such as castor oil, Oleic acid, Ethyl oleate and Olive oil; surfactants like Tween 20 and Tween 80; co-surfactant propylene glycol (PG); solubilizers including ethanol, PEG 400 and Transcutol HP ; preservatives such as sodium benzoate , potassium sorbate etc. All the chemicals are of laboratory grade and procured from SD Fine chemicals Ltd, Chennai, Tamil Nadu.

3. Methodology:

3.1 Analytical method for estimation of canagliflozin: UV-Visible Spectroscopy (UV Equipment model) method was used for the estimation of canagliflozin in this study [9].

3.1.1 Stock solution: A stock solution containing 1000 µg/ml of canagliflozin was prepared by accurately weighing 10 mg of canagliflozin, dissolving it in 2 ml of methanol, and diluting it up to the mark using distilled water.

3.1.2 Working standard solution: To obtain 100 µg /ml of canagliflozin, 10 ml of canagliflozin standard stock solution was transferred into a 100 ml volumetric flask and diluted with 40 ml methanol and 60 ml distilled water.

3.1.3 Construction of standard calibration curve:

Aliquots ranging between 0.2-1 mL were withdrawn from this working standard solution followed by dilution upto 10mL using solvent like Methanol or Acetonitrile etc., thus obtaining calibration standards containing 2-10 µg/mL of canagliflozin respectively. These samples were analyzed at λ_{max} 293nm wavelength in UV-Visible spectrophotometer [9]. The equation from the straight line obtained from standard calibration curve allows us to calculate exact amount present within each sample accordingly.

3.2. Solubility studies: Solubility studies involve the use of various solvents to determine how much drug can be dissolved in a given solvent. This is done by measuring the amount of drug that dissolves over time and then calculating its concentration based on this data [10].

3.3 Construction of ternary phase diagram: Ternary phase diagrams are used to visualize different combinations of components (lipids, surfactants etc.) which form an optimal microemulsion system for improved bioavailability. The diagram helps identify regions where these systems exist as well as their stability at various temperatures and pH levels [11].

3.4 Optimization of the process variables: Optimization process parameters refer to adjusting certain variables such as temperature, pressure or stirring speed so that they reach optimum values for maximum efficiency during formulation development stage [12]. These adjustments help ensure better performance from SMEDDS formulations while also reducing cost associated with production significantly.

3.5 Preparation of SMEDDS containing canagliflozin:

The preparation of SMEDDS containing Canagliflozin involves a few steps as mentioned below:

- Initially, the calculated amounts (shown in Table 1) of lipids and surfactants are mixed together which is then homogenized using high shear mixing techniques for better dispersion.
- Secondly, solubilizers such as ethanol or PEG 400 along with co-surfactant propylene glycol (PG) are added into this mixture so that it can effectively dissolve drug molecules within its structure. This helps improve bioavailability significantly while also ensuring no adverse effects after administration [13].
- Lastly, preservatives like sodium benzoate & potassium sorbate may be included depending on requirements followed by addition of water until desired concentration level is achieved in order to form an oil-in-water microemulsion [14].

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Table 1: Composition of SMEDDS containing canagliflozin.

Formulation no.	Canagliflozin (% v/v)	Peceol (% v/v)	Tween 80 (% v/v)	Transcutol (% v/v)	Stirring time (min)	Water (ml)
F1	100 mg	36.8	31.5	31.5	15	4
F2	100 mg	34	33	33	30	5
F3	100 mg	36	32	32	15	4
F4	100 mg	40	30	32	15	4
F5	100 mg	20	40	40	45	6
F6	100 mg	10	70	20	30	5
F7	100 mg	45	31	24	30	3
F8	100 mg	40	44	16	30	2
F9	100 mg	36	55	9	30	2
F10	100 mg	69	23	8	15	1
F11	100 mg	57	23	20	15	2
F12	100 mg	53	23	24	15	2
F13	100 mg	26	64	10	45	3
F14	100 mg	17	73	9	30	3
F15	100 mg	8	83	9	45	3

3.6 Characterization of SMEDDS

Characterization and evaluation of SMEDDS is carried out by using following quality control tests

3.6.1 ***Physical appearance:*** Firstly, the physical appearance of the prepared formulations such as clarity, color & viscosity are observed in order to determine if they meet desired standards or not [15].

3.6.2 ***Particle size analysis:*** Particle size analysis is performed by using photon correlation spectroscopy (Instrument model) that helps measure average droplet diameter present within formulation. This information can then be used for further optimization purposes during development stage itself [16].

3.6.3 Zeta Potential*:* The determination of Zeta potential of particles in SMEDDS helps in determining the stability of the system. The use of phase analysis light scattering to measure Zeta potential involves the application of an electrical field to charged particles in the preparation. The oily phase in SMEDDS has a negative surface charge due to the presence of carboxylic groups of fatty acids. Incorporation of cationic lipids can result in positive Zeta potential values between 35 and 45 mV [17].

3.6.4 ***Drug content uniformity:*** The drug content uniformity tests help ensure that each unit dosage form contains same amount of active ingredient while also checking its stability over time by performing accelerated storage studies at various temperatures & humidity levels respectively [11].

3.6.5 ***Emulsification of prepared SMEDDS:*** To evaluate the emulsification abilities of prepared formulations, distilled water was added to a 250 ml glass beaker at room temperature, and the mixture was gently agitated. When an emulsion tends to form transparent or clear, that is good; conversely, when that formation is poor or milky, then it is thought to be a bad emulsion. For 24 hours, the solution was observed to detect for any drug precipitation [18].

3.6.6 ***Conductance:*** By measuring conductivity, the presence of oil in the water emulsion formulation was confirmed. A conductivity meter was used to test the electro conductance of the micro emulsion system. Each measurement was performed three times [19].

3.6.7 ***Percentage transmittance:*** A UV-visible spectrophotometer was used to measure the sample's percentage transmittance that helps in determining the translucency and thereby its proper formation [20].

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***3.6.8 In vitro* dissolution study:** Using the USP Dissolution Apparatus I, an *in vitro* dissolution rate investigation of all produced formulations containing 100 mg of canagliflozin was conducted. As a dissolving medium, 0.1N HCl was kept at 37°c and 50 rpm. To keep the sink condition, 5 ml aliquots of fresh buffer were replaced with the same quantity at predetermined intervals. Using a UV double beam spectrophotometer, the collected aliquots were examined for drug content at λmax of 293 nm. Measurements were performed in triplicate [3].

3.6.9 *Stability studies:* Testing for stability is done to show how a drug substance's or drug product's quality changes over time. The recommended storage conditions, re-test intervals, and shelf life are determined by a number of environmental elements, including temperature, humidity, and light. The performance of lipid-based formulations depends on their stability, which is negatively impacted by drug precipitation. Additionally, formulations with low stability cause phase separation, which affects the formulation's functionality and appearance [21].

In accordance with ICH recommendations, the canagliflozin loaded optimised SMEDDS (F7 and F13) formulations were tightly packed in glass vials and stored in accelerated storage conditions (45 °C/75% RH) over three months. Samples were removed and assessed at the end of each month.

4. Results:

4.1 Analytical method for estimation of canagliflozin:

A calibration curve is constructed using the concentrations and absorbances in water and 0.1N HCl. The straight-line equation of the calibration graph in water is y=0.054x + 0.003 with an r2 value of 0.999 indicating linearity of the data. On the other hand, the equation of calibration graph in 0.1N HCl is y = 0.073x + 0.141 with an r^2 value of 0.998. The calibration curve of canagliflozin was used in the further analysis of prepared formulations for carrying out solubility studies and drug content uniformity. The results are shown in Table 2 while the calibration curves are shown in Figure 1 and 2.

Table 2: Standard calibration graph of canagliflozin in water and 0.1N HCl

Concentration(µg/ml)	Absorbance measured at 293nm* in	
	Water	0.1 N HCl
2	0.106 ±0.004	0.281±0.01
4	0.244±0 .001	0.450±0.01
6	0.339±0.003	0.584±0.006
8	0.440±0.002	0.750±0.008
10	0.530±0.008	0.860±0.01

(Mean + SD, n = 3 observations)

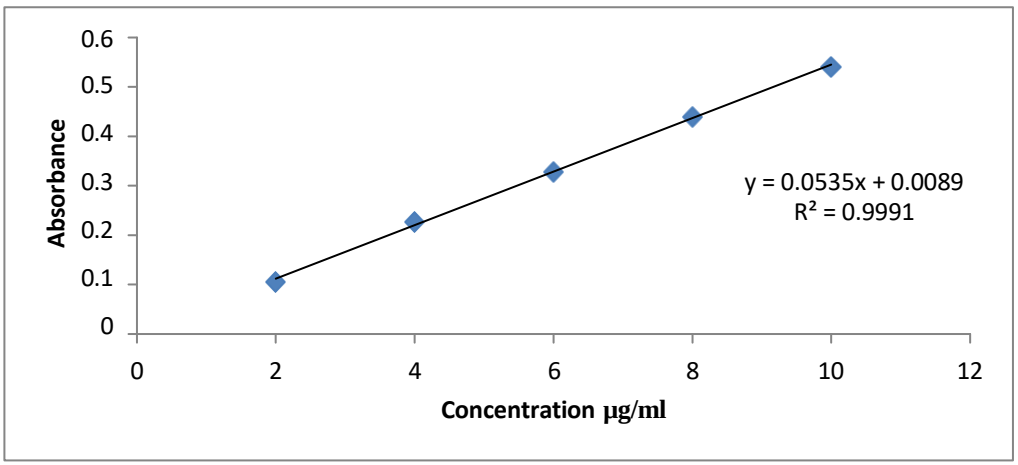

Figure 1: Standard graph of canagliflozin in water

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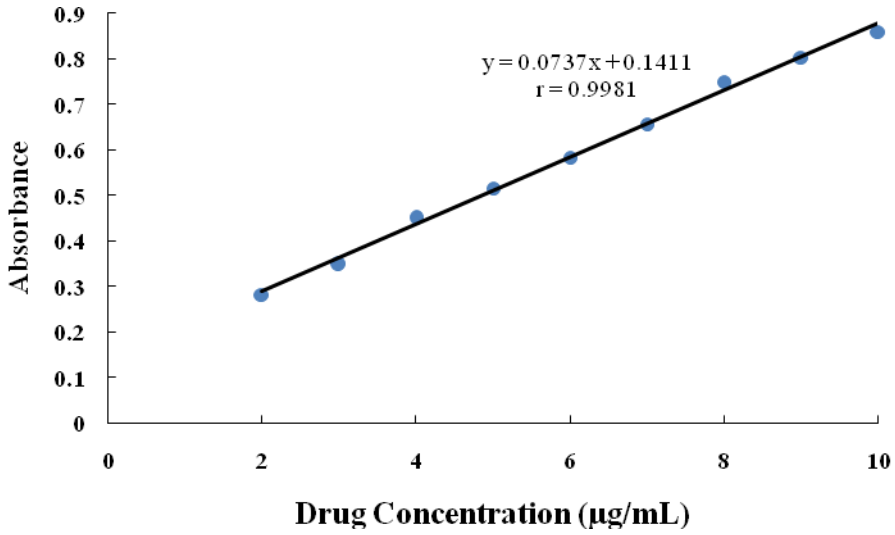

Figure 2: Standard graph of canagliflozin in 0.1 N HCl

4.2 Solubility Studies

The solubility of canagliflozin in various solvents is studied to select the aqueous and oily phase for the preparation of SMEDDS. Solubility of canagliflozin was observed to be highest in solvents methanol and 0.1 N HCl. With respect to lipids, drug solubility is more in transcutol, followed by peceol and Tween 80. Depending upon these solubility of canagliflozin the peceol is employed as oil phase, Tween 80 is used as the surfactant and Transcutol is employed as the co-surfactant in preparing the formulations. Tween 80 is selected as main surfactant owing to its ability to prepare stable microemulsions as reported in past literature. The results are shown in the table 3 and figures 3 and 4.

Table 3: Solubility of canagliflozin in various solvents and lipids

Solvent	Concentration (µg/ml)	Lipids	Concentration µg/ml
Methanol	44.6	Castor oil	35.4
DMSO	33.04	Oleic acid	31.0
Water	21.94	Ethyl oleate	36.9
0.1 N HCL	39.61	Olive oil	25.4
pH 3.5	31.36	Isopropyl myristate	46.5
pH 4.6	20.06	Tween 20	63.2
pH 6.0	17.56	Tween 80	137.9
pH 6.8	18.46	Transcutol	234.8
pH 7.0	28.86	PEG 400	76.64
pH 7.5	37.64	Peceol	156.9

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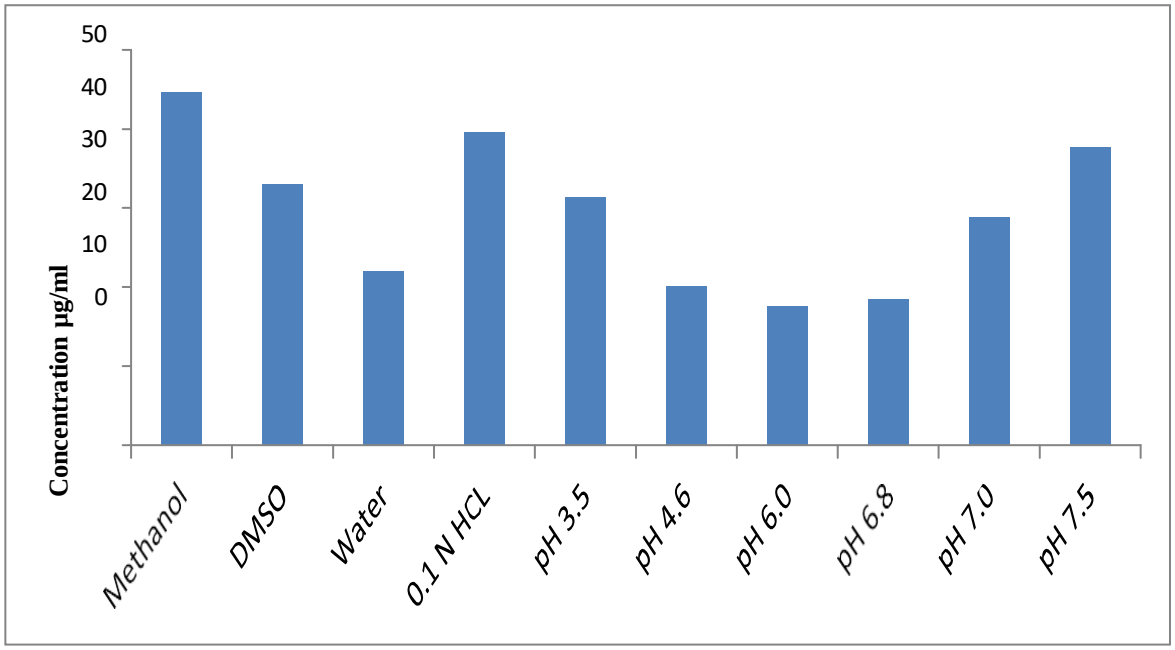

Figure 3: Solubility of canagliflozin in various solvents

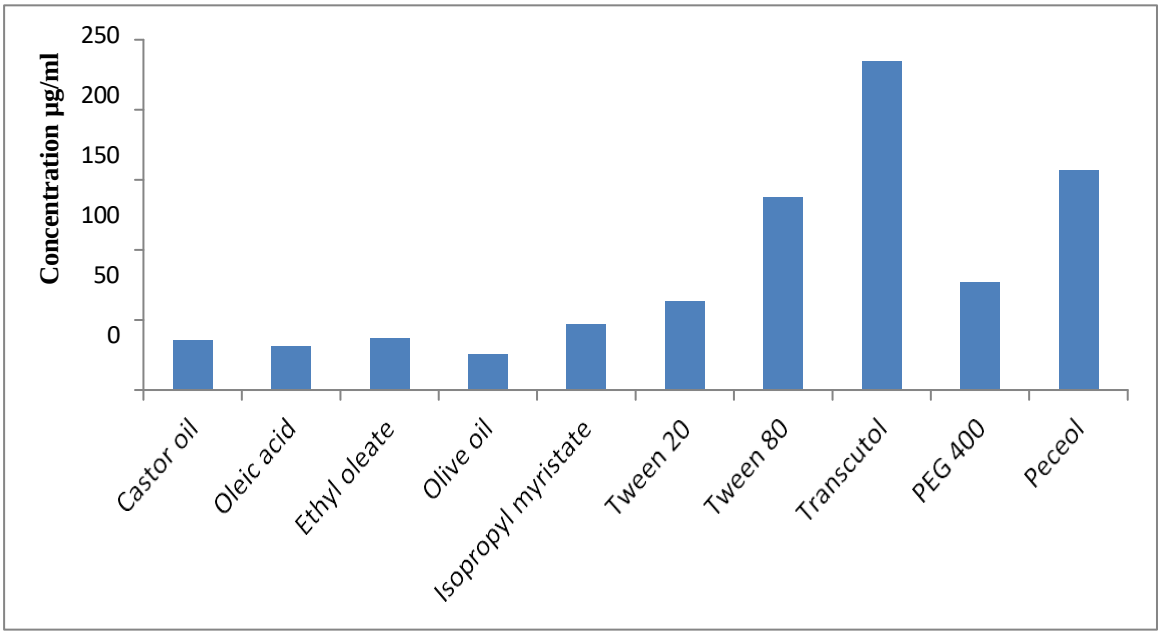

Figure 4: Solubility of canagliflozin in lipid excipients

4.3 Construction of Ternary Phase

Diagram

For each apex of the ternary graph, surfactant, co- surfactant and oil were taken, and ternary diagrams were built individually for each group to find SMEDDS areas. This would help in determining the proportions of surfactant, co-surfactant and oil. The results are shown in Figure 5.

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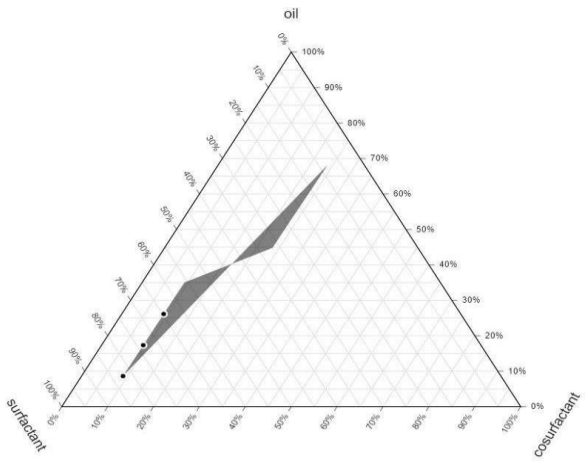

Figure 5: Ternary Phase diagram

4.4 Characterization and evaluation of SMEDDS

4.4.1 *Emulsification*

After emulsification, the formulations were visually examined after 24 hours to check for clarity, phase separation and drug precipitation. After 24 hours it was observed that formulations F7 and F13 were clear whereas the other formulations were found to be either cloudy or turbid or opaque which can be due to precipitation of the drug. The results are shown in Table 4.

4.4.2 *Conductance*

Conductivity of formulations F1-F15 was tested for the presence of oil in water emulsion. The conductance values are in the range of 39.8 µs/cm to 59.4 µs/cm. Formulation F13 followed by F7 have the highest conductance that could be attributed to their stable electrical double layer system. Higher conductance is an indication of better stability of the system. The conductivity of the microemulsion was used to react to the solubilized drug's impact on the microstructure of the microemulsion and also the structural transitions that occurred upon dilution with water.

Table 4: Results of the quality control parameters of formulations F1-F15

Formulation	Phase Separation	Clarity	Conductance (µs/cm)	Transmittance (%T)	Drug content (%)
F1	No	Cloudy	42.1	71	94.2 ± 0.01
F2	No	Turbid	44.7	53	97.0 ± 0.01
F3	No	Opaque	46.3	75	94.5 ± 0.06
F4	No	Opaque	45.9	41	96.1 ± 0.02
F5	No	Cloudy	42.3	62	95.7 ± 0.08
F6	No	Cloudy	41.7	56	91.88 ± 0.01
F7	No	Clear	58.0	95	99.5 ± 0.02
F8	No	Turbid	51.1	69	97.2 ± 0.001
F9	No	Opaque	39.8	86	96.3 ± 0.003
F10	No	Cloudy	47.2	49	98.6 ± 0.008

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JCHR (2023) 13(6), 3889-3902 | ISSN: 2251-6727

Table 4: Results of the quality control parameters of formulations F1-F15

Formulation	Phase Separation	Clarity	Conductance (µs/cm)	Transmittance (%T)	Drug content (%)
F11	No	Turbid	43.2	70	93.0 ± 0.001
F12	No	Cloudy	46.6	81	97.5 ± 0.005
F13	No	Clear	59.4	97	98.8 ± 0.01
F14	No	Opaque	44.3	52	92.1 ± 0.003
F15	No	Turbid	45.1	77	98.0± 0.009

4.4.3 *Percentage transmission*

Transmittance was determined for formulations F1-F15 to determine their transparency. Formulations were considered clear and transparent if their percentage transmittance value was close to 100%. In addition to indicating the formulation's clarity, it also suggests that the micro emulsion formulation's globules are probably in the nanometer range in size. F7 and F13 has more transmittance. The results are shown in table 4.

4.4.4 *Drug content*

The drug content of canagliflozin in SMEDDS formulation was analyzed using UV spectrophotometric method. The drug content of the prepared formulations is in the range of 91.88 to 99.5%. Drug content of canagliflozin was found to be highest in formulations F7 and F13. The results are shown in table 4.

4.4.5 *In vitro dissolution studies*

All formulations (F1 to F15) are subjected to *in vitro* dissolution experiments and the drug release is analyzed using UV spectrophotometer. Formulation F7 has shown fastest drug release i.e 99.29% drug release in 30 minutes followed by the formulation F13 which has shown a drug release of 98.2% in 40 minutes. The results are shown in table 5 and figures 6, 7, and 8. The order of drug release (from fastest to slowest) is as follows:
F7>F13>F14>F6>F10>F9>F12> F11> F15> F8> F1> F4>F2

Table 5: Results of *in vitro* drug release studies

Time min	% Cumulative drug release														
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
5	22.06	14.2	12.6	13.1	19.8	18.9	**49.39**	35.52	31.9	36.2	27.1	26.1	**69.3**	17.7	31
10	24.22	19.1	22.5	18.4	21.98	20.01	**57.7**	49.16	32.1	36.9	28.0	27.8	**80.1**	58.9	32.5
15	26.32	25.32	27.3	22.2	34.9	25.1	**67.07**	52.85	42.3	37.9	30.5	32.2	**86.1**	59.4	35.9
20	36.09	32.6	32.6	29.9	37.9	37.9	**84.93**	61.03	54.7	40.3	32.6	36.4	**90.4**	59.7	44.6
25	44.6	35.6	35	32.5	42.3	42.4	**93.44**	68.38	59.1	50.3	44.6	48.4	**92.5**	60.2	52.7
30	53.7	41.8	41.8	56.3	46.5	56.31	**99.29**	76.75	61.2	52.4	55.8	50.3	**93.5**	63.5	68.96
35	66.3	53.6	64.2	59.6	52.68	61.76	---	79.33	79.8	61.1	66.4	68.3	**93.9**	78.1	69.9
40	69.8	64.2	68.5	65.2	62	69.89	---	85.32	86.9	72.3	71.8	79.4	**98.2**	83.2	76.1
45	72.4	74	72.7	66.5	77.8	71.54	---	87.53	88.6	79.9	83.4	82.5	---	96.6	85.3
50	85.1	76.7	80.2	75.9	84.4	81.1	---	89.02	94.9	86.4	92.1	94.6	---	97.29	90.1
55	90.8	80.24	88.6	83.3	87.1	95.6	---	90.30	97.21	95.2	95.8	95.2	---	---	92.6
60	91.2	88.67	92.4	90.2	93.5	---	---	91.78	---	---	95.9	97.6	---	---	94.9

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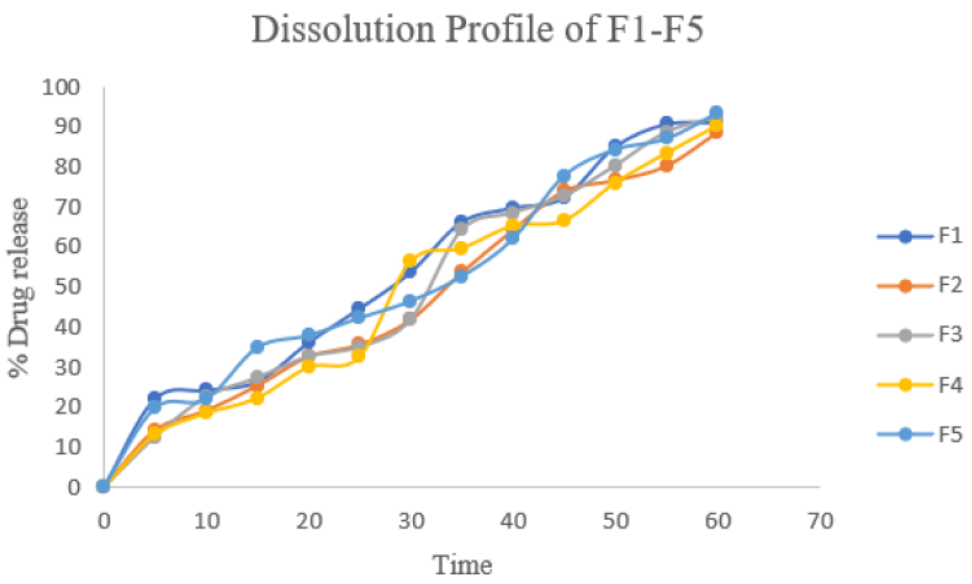

Figure 6: Dissolution profile of formulations F1-F5

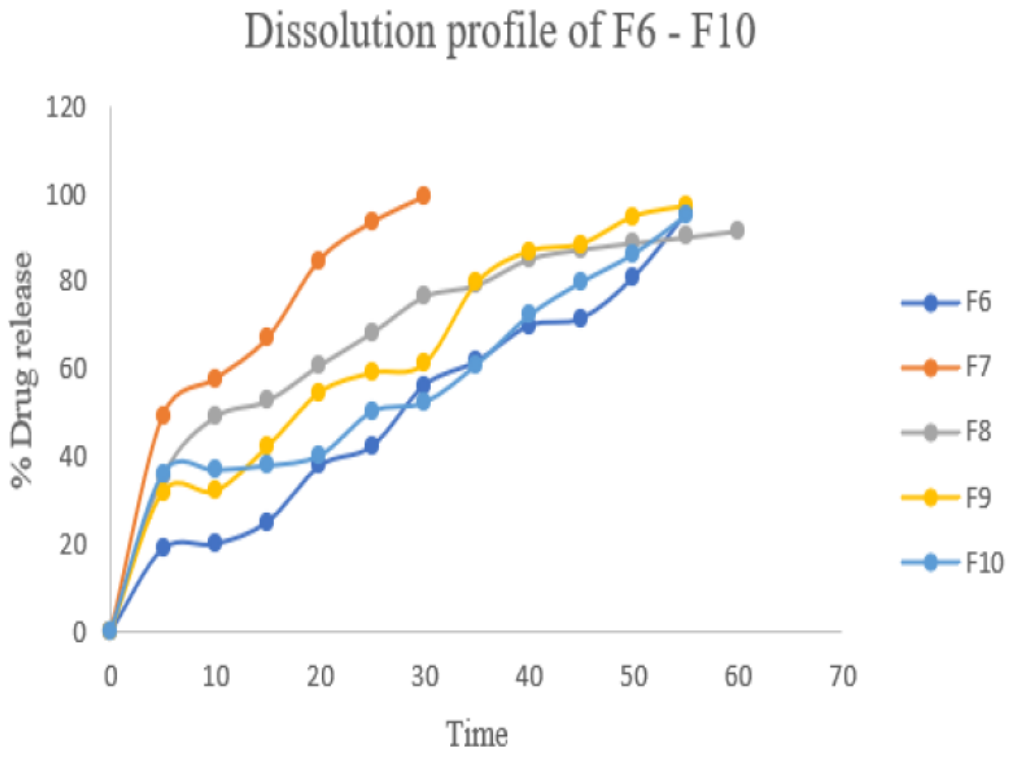

Figure 7: Dissolution profile of formulations F6-F10

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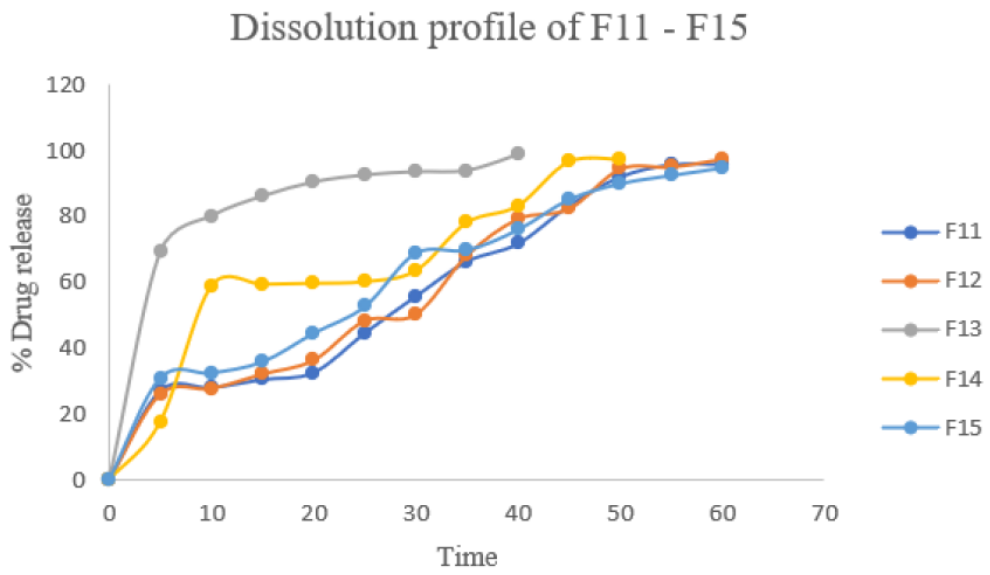

Figure 8: Dissolution profile of formulations F11-F15

4.4.6 ***Measurement of particle size:***

Based on the drug release, drug content, conductance, and transmittance reports formulations F7 and F13 are considered to be optimized. These optimized formulations are further evaluated for particle size, stability studies. Particle sizes of optimized formulations F7and F13 were found to be 348.2nm and 384nm which clearly falls under the hood of microemulsions. The results are shown in table 6 and figures 9, 10.

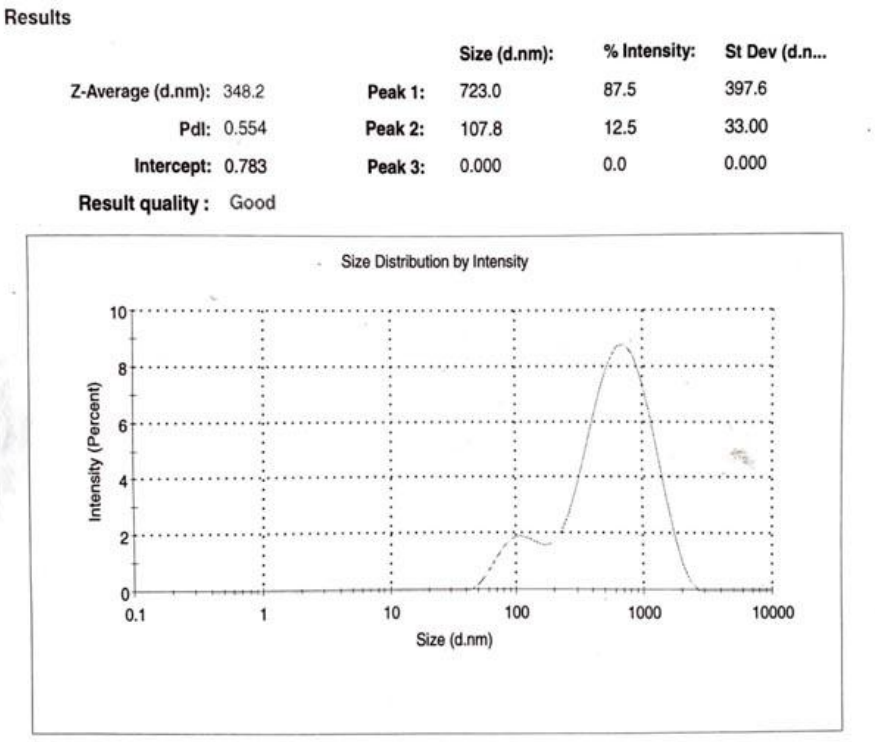

Figure 9: Particle size determination of formulation F7

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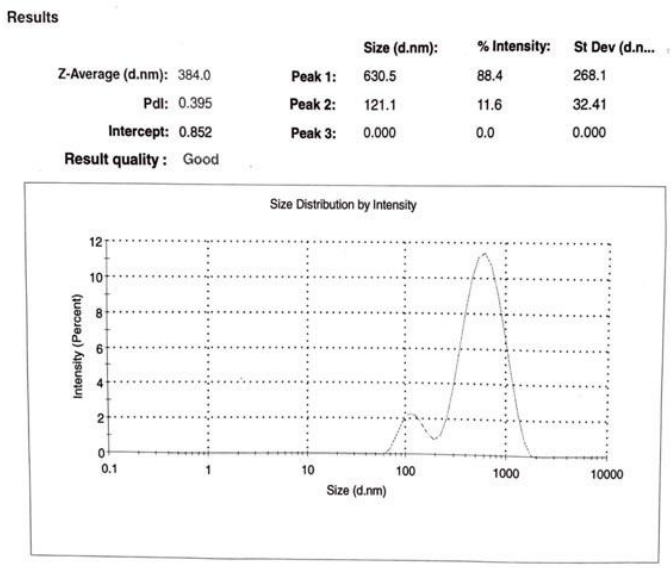

Figure 10: Particle size determination of formulation F13

Table 6: Particle size of canagliflozin loaded SMEDDS

S. No.	Formulation	Z – average (nm)
1	F7	348.2
2	F13	384.0

4.4.7 Stability studies:

Optimized formulations F7 and F13 were subjected to stability experiments. The drug content and drug release are within acceptable limits and the formulations have shown adequate ruggedness to withstand environmental stress as evident from the stability studies. The results are shown in table 7 and 8

Table 7: Stability studies for optimized formulation F7

F7				
Test	**Initial**	**1 month**	**2 months**	**3 months**
Drug content (%)	99.5	98.4	96.2	95.9
Drug release in 1 hour (%)	99.29	98.1	96.0	95.6

Table 8 stability studies of optimized formulation F13

F13				
Test	**Initial**	**1 month**	**2 months**	**3 months**
Drug content (%)	98.8	97.1	96.8	95.7
Drug release in 1 hour (%)	98.2	97.5	96.2	95.6

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JCHR (2023) 13(6), 3889-3902 | ISSN: 2251-6727

5. Discussion:

This study aimed to prepare a self-micro emulsifying drug delivery system (SMEDDS) for the antidiabetic drug canagliflozin, which has low water solubility and permeability. Canagliflozin is used to treat type II Diabetes mellitus and has a long half-life when taken orally. A lipid-based drug delivery system was chosen due to canagliflozin's lipophilic properties. The solubility of canagliflozin was tested in different solvents, and the best solvent was used to create a standard graph that followed Beer-Lambert's law. Oily carriers, surfactants, co-surfactants, and co-solvents are commonly used in drug formulations, with the oily carrier helping to dissolve the lipophilic drug and the surfactant aiding in dispersing the oil [22]. Solubility studies were conducted to choose suitable lipid excipients, and peceol, tween 80, and transcutol were selected as the oil, surfactant, and co-surfactant, respectively. Constructing a ternary phase diagram is important for lipid-based drug delivery systems as it helps predict the formation of a microemulsion region and determines oil, surfactant, and co-surfactant ratios. The diagram is plotted by taking oil, surfactant, and co-surfactant at each apex, and the microemulsion region is used to determine the quantities of each component needed in formulations. Based on the microemulsion region, 15 formulations (F1- F15) were developed with the same drug quantity, varying the time and amount of water added during vortexing. The formulations (F1-F15) were evaluated for phase separation and precipitation, emulsification capacity, and clarity of the emulsion using conductivity studies and percentage transmittance. Emulsification was evaluated for all formulations, with F7 and F13 being clear, while F1, F5, F6, F10, and F12 were cloudy, and F2, F8, F11, and F15 were turbid. Conductance values were determined for all formulations, and the values for F7 and F13 were higher than other formulations, indicating the presence of an o/w emulsion. The conductance values for F1-F15 ranged from 30-60 µs/cm. The percentage transmittance and clarity of formulations F1-F15 were determined, with all formulations showing a percentage transmittance of 40-100. F7 and F13 had the highest clarity, with a percentage transmittance of 95 and 97, respectively. Drug content was determined using UV-spectrophotometer, with all formulations possessing percentage drug content between 90-100%, within where F7 and F13 had the highest values of 99.5 and 98.8, respectively. *In vitro* dissolution experiments were conducted for all formulations, with F7 and F13 releasing drug within 30-40 minutes, indicating an increase in solubility and bioavailability. Based on the results obtained from emulsification, conductance, transmittance, drug content, and dissolution studies, F7 and F13 were chosen as the optimized formulations. These formulations were further evaluated for particle size and stability studies to determine efficacy. Stability studies were conducted on two optimized formulations F7 and F13 under adverse storage conditions, and *in vitro* dissolution data was analyzed to identify the drug's release mechanism from the

formulations. Formulation F7 was found to follow zero order release, and the particle size of both formulations was determined to be in the range of microemulsions with improved thermodynamic stability that self-emulsify in interaction with aqueous fluids based on globule size [23].

6. **Conclusion**:

In conclusion, this study successfully developed an optimized Self-Micro emulsifying Drug Delivery System (SMEDDS) formulation for the low-solubility drug canagliflozin. It is found that lipid-based drug delivery systems can effectively improve the solubility and bioavailability of weakly soluble drugs. The results showed that the particle size of SMEDDS formulations had a significant impact on the drug's absorption and bioavailability, with smaller particle sizes leading to better dissolution rates and oral bioavailability. Peceol and transcutol were effective lipid excipients for formulating SMEDDS for canagliflozin and the formulations F7, F13 are found to be optimized formulations with desirable characteristics. The future scope of this work includes further research on optimizing SMEDDS formulations, formulating drugs for gastric environment, and studying ex vivo and in vivo correlations. Overall, this study has important implications for developing effective drug delivery systems for low-solubility drugs.

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