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Formulation and Evaluation of Film Coated Conventional Tablet of Canagliflozin

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***Abstract*: The main aim of present work is to formulate safe, convenience dosage form. This study is conventional formulation of Drug as Antidiabetic agent drug strength 250 mg. Conventional dosage drug levels in short period of time. Is desirable for drugs having long biological half life, high bioavailability, and lower clearance and lower elimination half life but main criterion for dosage form is poor solubility and drug to treat disease. Canagliflozin belongs to a new class of anti-diabetic drugs that works by inhibiting the sodium-glucose transport protein (SGLT2). This transport protein is found in the kidney and is responsible for reabsorbing glucose that has been filtered. FDA approved on March 29, 2013.Canagliflozin (trade name Invokana or Sulisent) is a medication used for the treatment of type 2 diabetes. It is of the gliflozin class or subtype 2 sodium-glucose transport (SGLT-2) inhibitors class. In-vitro release profile studies of conventional Tablets were carried out using USP type II dissolution apparatus. Tablet was kept in a flask having paddle and paddle were rotated at 50 rpm. Medium used for release rate study was 900 ml SLS. During the course of study whole assembly was maintained at 37˚C ± 0.5ºC and 5 ml sample was withdrawn at time interval 5, 10, 15, 20, 25and 30 min. For FDA approval and bioequivalent product, it is important to compare the dissolution profile of product with the dissolution profile of reference-listed drug. test product with reference product. The present work concluded that all grades of MCC can be used for the formulation of Conventional tablets of Canagliflozin. However, finding showed that as the quantity of high molecular weight MCC increases, release of active drug decreases. Thus, requirement of the release retarding agents e.g. MCC can be selected in different combination or alone in different ratios for the desired product depending on the release profile of developing product by comparing with innovator product. Canagliflozin is effective in improving the glycemic control in type 2 DM.**

***Keywords*: Canagliflozin, Conventional, Film Coating, Dissolution, Diabetes Mellitus**

1. Introduction

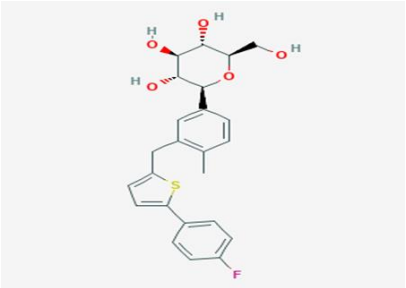
Drugs are rarely administered as pure chemical substances alone. they are almost always given as formulated preparations or medicines. These can vary from relatively simple solutions to complex drug delivery systems through the use of appropriate additives or excipients in the formulations. The excipients provide varied and specialized pharmaceutical functions. It is the formulation additives that, among other things, solubilize, suspend, thicken, preserve, emulsify, modify dissolution, improve the compressibility and flavor drug substances to form various preparations or dosage forms. [2]

Design of the appropriate dosage form or delivery system depends on the,

- Physicochemical properties of the drug, such as solubility, oil-to-waterpartition coefficient (Ko/w), pKa value, and molecular weight.
- Dose of the drug.
- Route of administration.
- Type of drug delivery systems desired.
- Pathologic condition to be treated.
- Desired therapeutic effect.
- Drug release from the delivery system.
- Bioavailability of the drug at the absorption site.
- Pharmacokinetics and Pharmacodynamics.

The oral route is the most common way of administering drugs, and among the oral dosage forms tablets are of most common type. Tablets represent unit dosage forms in which one usual dose of the drug has been accurately placed. Tablets are defined as 'solid preparations each containing a single dose of one or more active ingredients and obtained by compressing uniform volumes of particles'. Tablets may be swallowed whole or being chewed. Some are dissolved or dispersed in water before administration. Some are intended to put in oral cavity, where the active ingredient is liberated at a predetermined rate. Implants may also be presented in form of tablet. Tablet may vary in shape and differ greatly in size and weight depending on the amount of medicinal substance and the intended mode of administration.

2. Drug Profile



Synonyms: Invokana Anhydrous Canagliflozin
Molecular Formula: $C_{24}H_{25}FO_5S$
Molecular Weight: 444.517 g/mol
Chemical name: Canagliflozin anhydrous; Canagliflozin hemihydrates

Canagliflozin belongs to a new class of anti-diabetic drugs that works by inhibiting the sodium-glucose transport protein (SGLT2). This transport protein is found in the kidney and is responsible for reabsorbing glucose that has been filtered. FDA approved on March 29, 2013.Canagliflozin (trade name Invokana or Sulisent) is a medication used for the treatment of type 2 diabetes. It is of the gliflozin class or subtype 2 sodium-glucose transport (SGLT-2) inhibitors class. This mechanism is associated with a low risk of hypoglycaemia (too low blood glucose) compared to sulfonylureaderivatives and insulin. Canagliflozin is an inhibitor of subtype 2 sodium-glucose transport proteins (SGLT2), which is responsible for at least 90% of renal glucose reabsorption (SGLT1 being responsible for the remaining 10%). Blocking this transporter causes up to 119 grams of blood glucose per day to be eliminated through the urine Solubility: It is soluble in methanol and practically insoluble in ethanol and water.

- *Plasma half life:*11.8 (10–13) hours. The apparent terminal half-life (t1/2) was 10.6 hours and 13.1 hours for the 100 mg and 300 mg doses, respectively.
- *Bioavailability:* 65%
- *Dose:* 100 mg and 300 mg doses
- *Mechanism of Action:* Canagliflozin is an inhibitor of subtype 2 sodium-glucose transport proteins (SGLT2), which is responsible for at least 90% of renal glucose reabsorption (SGLT1being responsible for the remaining 10%). Blocking this transporter causes up to 119 grams of blood glucose per day to be eliminated through the urine,[6]corresponding to 476 kilocalories. Additional water is eliminated by osmotic diuresis, resulting in a lowering of blood pressure.This mechanism is associated with a low risk of hypoglycaemia (too low blood glucose) compared to other types of anti-diabetic drugs such as sulfonylureaderivatives and insulin.Sodium-glucose co-transporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Canagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RTG), and thereby increases urinary glucose excretion.

3. Material

- *Materials:* List of Drugs and Excipients used for the study.

Table 1
List of Drugs and Excipients

Sr. No.	Name of ingredients	Name of supplier
1	Canagliflozin	ZYDUS CADILA Telangana.
2	MCC	Cipla Ltd, Mumbai
3	Crosscarmellose sodium	Cipla Ltd, Mumbai
4	PVK-30	Cipla Ltd, Mumbai
5	IPA	Cipla Ltd, Mumbai
6	Magnesium stearate	Cipla Ltd, Mumbai
7	Talc	Cipla Ltd, Mumbai
8	Aerosil	Cipla Ltd, Mumbai

Table 2
List of Chemicals

Sr. no	Name of Chemicals	Grade	Name of supplier
1	Methanol	Laboratory Grade	Rankem Ltd., New Delhi
2	SLS	Analytical grade	Rankem Ltd., New Delhi
3	Potassium dihydrogen phosphate	Analytical grade	Rankem Ltd., New Delhi

Table 3
List of Equipments

Sr. No.	Equipment's Name	Name of manufacturer and model no.
1	Digital analytical Balance	Wensar high precision weighing balance
2	Dissolution apparatus	Electro lab TDT-08L
3	Texture analyzer	Brookfield, DV-E Viscometer
4	Ultraviolet Spectrophotometer	UV/Vis-Spectrophotometer, Shimadzu1800
5	Infra-Red Spectrophotometer	FT-IR, Infinity, Shimadzu
6	Differential-scanning calorimeter	Mettler Toledo
7	Digital pH meter	Q 610, Equip-tronics, India
8	Environmental stability chamber	DTC-968, Classic Scientific Mumbai.

A. Preformulation study

Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product. Followings are the test performed for the preformulation study.

1. Solubility of drug
2. Bulk density
3. Tapped density
4. Carr's index & Hausner's ratio
5. Flow property (Angle of repose)

- *Solubility study of canagliflozin in different solvents:-* Drug solubility was determined by canagliflozin preparing saturated drug solutions in methanol and buffer medium, maintained at 37 ± 0.5°C in a water bath and continually shaken using Mechanical stirrer up to 12 hrs. Withdrawn samples were filtered through a whatmann filter paper, and assayed using UV spectrophotometer (1800, SHIMADZU,) at 207 nm.
- *Determination bulk density:* Bulk density is defined as a mass of a powder divided by the bulk volume. A blend sample (30 gm) was introduced in 100 ml graduated cylinder. The volume of the material was noted on graduated cylinder. The bulk density was calculated in gm/cm^3 by the formula given below;
  Bulk density (ρ_0) = M/Vo
  Where, M = Mass of the powder V_o = Volume of the powder
- *Determination Tapped density:* The blend sample under test was screened through sieve no. 18 and the weight of sample equivalent to 20 gm was filled in 100 ml graduated cylinder. The tapping of the cylinder was carried out for 500 times using Bulk Density Apparatus and the tapped volume V_f was noted.

The tapped density was calculated in gm/cm3 by the formula;
Tapped density (ρ_t) = M/V_f
Where, M = Weight of sample powder taken V_f = Tapped volume.

Carr's Compressibility index & Hausner's Ratio: The compressibility index and Hausner ratio are measures of the propensity of powder to be compressed.

Table 4
Scale of Flowability

Compressibility index (%)	Flow character	Hausner ratio
≤ 10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

Carr's compressibility index and Hausner's ratio can be calculated as follows:
Carr's index = Tapped density - Bulk density / Tapped density X 100
Hausner's ratio = Tapped density / Bulk density.

B. Determination of flow property

The frictional force in the powder can be measured by the angle of repose. The angle of repose of final blend was determined using reposograph.

Angle of repose can be calculated by using following formula

$$\text{Tan } \theta = h/r$$

C. Formulation of Tablet by wet granulation Method

Procedure:

- Step 1: Weigh Canagliflozin, croscarmellose sodium and some quantity of mcc were sifted through sieve 60#, dry mixed in for 3 minutes.
- Step 2: Binder solution was prepared by dissolving PVK-30 in IPA q.s and chopper run to give good binding to granules.
- Step 3: Wet mass was passed from sieve 8 #.
- Step 4: Granules were dried in hot air oven at 55˚C for one hour. Dry granules were passed from sieve 22 #.
- Step 5: All lubricants were passed from sieve 60 #. magnesium stearate was added and Talc and Aerosil for 2 min as lubrication.
- Step 6: The blend was ready for compression.
- Step 7: Compression was done by 16 Station D-tooling machine using 18×7.8 mm oval with "139" debossed on one side and plain on other side punch set.

D. Tablet coating

For coating the tablets, non-aqueous film coating formulation using a widely used polymer PVA was used. These ready mix-coating agents used A weight gain of approximately 3.00% w/w was achieved and was found to adequately cover the tablet core. The selected batches from wet granulation were coated using ready mix. Titanium dioxide, PEG, talc, IPA, methylene chloride.

Coating solution formula:

Table 5
Formula for coating solution

Sr. No.	Ingredients	Qty/tablet (mg)	Function
1	HPMC	4.00	Coating material
2	Tio2	4.00	colorant
3	PEG	2.00	plasticizer
4	IPA	40.00	Solvent
5	Methylene chloride	74.00	Solvent

Procedure for preparation of coating suspension

- Weigh required quantity of PVA film coating system
- Weigh necessary quantity of IPA into the mixing.
- Steadily add PVA to the IPA, Tio2, PEG, Talc Increase the stirrer speed in order to maintain.
- After the complete addition reduce the mixer speed to nearly eliminate and mix for 45 min.

Coating:

Tablet from selected batches were taken for coating by using Ganson tablet coater, the following parameter were set during coating.

Table 6
Tablet coating parameter

Inlet (^{0}C)	Exhaust (^{0}C)	Atomization pressure (psig)	Pan speed (rpm)	Spray speed (rpm)
60	42	1.8	8-9	2-3

E. In-vitro release study

In-vitro release profile studies of conventional Tablets were carried out using USP type II dissolution apparatus. Tablet was kept in a flask having paddle and paddle were rotated at 50 rpm.

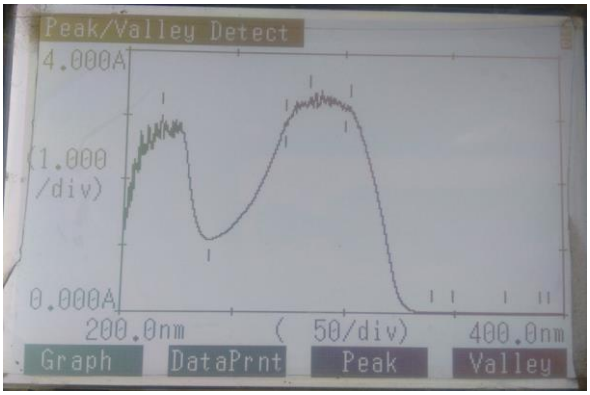
Medium used for release rate study was 900 ml SLS. During the course of study whole assembly was maintained at 37˚C ± 0.5ºC and 5 ml sample was withdrawn at time interval 5, 10, 15, 20, 25 and 30 min. For FDA approval and bioequivalent product, it is important to compare the dissolution profile of product with the dissolution profile of reference-listed drug. test product with reference product.

4. Results and discussion

A. *Preformulation Study*

Determination of λ max of Canagliflozin

The λ max of Canagliflozin was measured; and found to be in the range λ max 290.



B. *Identification of drug*

Identification test of drug was carried out by melting point, Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC).

C. *Melting point*

Melting point of Canagliflozin was measured; and found to be in the range of 900C. It was confirmed with the reported melting point of canagliflozin i.e. 90-950C

D. *Standard calibration curve in methanol*

Graph of absorbance Vs concentration was plotted and found to be linear over the range of 2 to 34 µg/ml indicating it is compliance with Beer's and Lambert's law. Results are shown in Table.

Table 7
Calibration curve of methanol

Concentration (µg/ml)	Absorbance
2	0.102
6	0.199
10	0.298
14	0.389
18	0.498
22	0.627
26	0.715
30	0.832
34	0.974

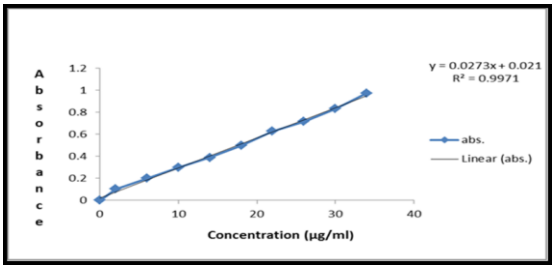


Fig. 3. Standard calibration curve of canagliflozin in methanol

E. *Differential Calorimeter Scanning*

The DSC thermo gram was used to assess the thermal behavior of the drug. DSC analysis showed a sharp endothermic peak at 90^0C which is indicated the melting point of Canagliflozin. The melting point range of API is 90-95^0C as per Indian pharmacopoeia. So, it was found to be near of official standard. Preliminary investigation of drug was carried out with different parameters, after determination the sharp melting point peak was obtained at 90ºC and solubility test of the API showed that the drug was freely soluble in methanol Analysis of λ_{max} of Canagliflozin with solvent methanol which showing peak wavelength on 290 nm. Identification of Lisinopril by DSC showed that the API was totally embedded within polymer matrix which also increases stability of drug within strip.

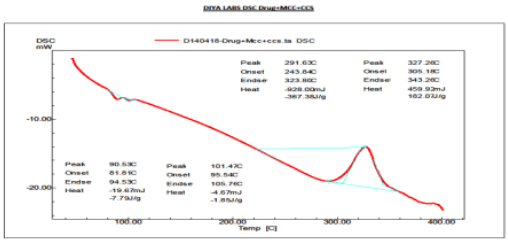


Fig. 4. DSC thermo gram of Canagliflozin

Fig. 4. DSC thermo gram of physical mixture of drug and MCC and CCS

1) *Solubility*

Solubility of the drugs is determined in different solvent which is given below

Table 8
Details of solubility of Canagliflozin

Solvent	Solubility
Methanol	Freely soluble
Water	Practically insoluble

Table 9
Observation of density and flow parameter

Density (g/cm^3)	Flow properties
Bulk	0.227
Tapped	0.349
Carr's index	37.286 %
Hausner Ratio	1.529

2) Density and flow properties

The above observation indicates that the canagliflozin have very poor flow property and very poor compressibility. the bulk density and tapped density of Canagliflozin is 0.227 gm/ml and 0.349 g/ml respectively indicates that canagliflozin is fluppy material and very poor flow.

3) Selection of excipients

The excipients used in the final formula are within the limit of inactive ingredient guide available by FDA.

Table 10
List of Excipients in the Final Formulation

Excipients	Function
MCC	Tablet diluents
Croscarmellose sodium	Disintegrant
PVK-30	Binder
Aerosil	Glidant
IPA	Aq. Vehicle
Magnesium stearate	Tablet lubricant
Talc	Glidant

Formulation trials:

Evaluation of pre-compression parameters of blend prepared by wet granulation method

Table 11
Pre-compression parameters of granules of batch B 01 – B 09

Batch no.	% LOD	Angle of repose	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index(%)	Hausner Ratio
B 01	-	30.12	0.53	0.67	13.25	1.14
B 02	-	31.11	0.55	0.69	13.58	1.16
B 03	1.42	31.24	0.52	0.65	14.91	1.15
B 04	1.01	29.19	0.49	0.54	13.30	1.13
B 05	1.32	30.18	0.54	0.59	14.14	1.11
B 06	1.25	29.24	0.44	0.52	14.49	1.12
B 07	1.16	28.11	0.48	0.60	13.63	1.20
B 08	1.21	29.40	0.46	0.54	14.35	1.17
B 09	1.01	28.43	0.43	0.55	13.22	1.11

In the above Table characteristics of the granules from batch no B 01- B 09 are given. From the values of angle of repose, Hausner ratio & Carr's Compressibility Index we can conclude that granules of the above batches have good flow property.

Evaluation of Post-compression parameters of tablets formulated by wet granulation method

Appearance

Circular shape white colored film coated tablets side plain. Average Weight, Thickness, Hardness, Friability, DT.

I n the B 01 to B 09 trials avg. wt. of tablet was 250 mg, Thickness was found to be 4.65. Hardness was found to have 4.8 N, Friability was found to be 0.08% and 190-205 sec.

In-vitro Dissolution profile:

Dissolution Summary:

Medium : SLS

Apparatus: Paddle

RPM : 50

Volume : 900 ml

Table 12
Post-compression parameters of tablets formulated by wet granulation method

Trials	Avg. Tab Wt. (mg)	Thickness (mm)	Hardness (N)	Friability (%)	Disintegration Time (sec.)
B 01	250.00	4.6	4.8	0.08	200+_2
B 02	250.00	4.6	4.7	0.09	205±2
B 03	250.00	4.6	4.2	0.05	205±2
B 04	250.00	4.7	5.2	0.07	205±2
B 05	250.00	4.6	5.1	0.08	197±3
B 06	250.00	4.6	5	0.06	195±3
B 07	250.00	4.6	5	0.06	192±2
B 08	250.00	4.6	5.1	0.06	191±2
B 09	250.00	5.65 - 5.70	180-190	0.37	190±2

Table 13
Dissolution profiles of Canagliflozin for trials (B 02- B 04) and marketed (Canagliflozin)

Time in min.	% drug released				
	Marketed	B 01	B 02	B 03	B 04
0	0	0	0	0	0
5	65.63	24.23	25.56	30.48	36.87
10	79.45	42.26	45.32	47.75	49.07
15	87.17	48.69	51.43	52.19	54.08
20	94.27	54.59	56.97	59.64	69.78
25	99.19	60.45	61.21	65.08	76.63

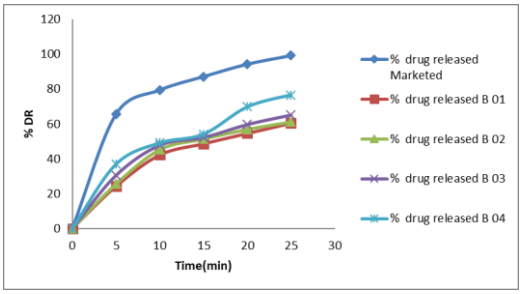


Fig. 5. Cumulative percent Canagliflozin release of trials B 02- B 04 conventional tablet

Table 14
Dissolution profiles of Canagliflozin for trials B 05- B 09

Time in min.	% drug released				
	B 05	B 06	B 07	B 08	B 09
0	0	0	0	0	0
5	37.15	49.43	52.26	58.45	63.34
10	49.32	62.32	63.60	71.33	78.22
15	55.30	74.73	75.21	79.44	85.34
20	71.22	88.32	91.11	90.34	92.12
25	77.27	89.22	92.31	95.27	98.63

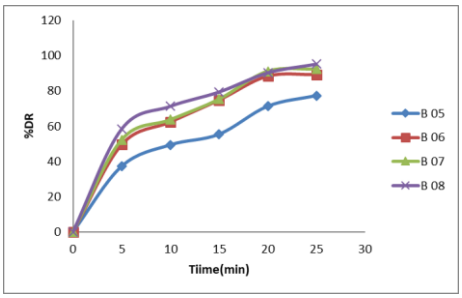


Fig. 6. Cumulative percent Canagliflozin release of trials B 05- B 08 conventional tablet

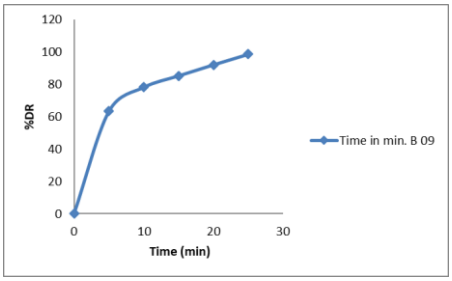


Fig. 7. Cumulative percent Canagliflozin release of trials B 09 conventional tablet

Table 15
Dissolution profiles of Canagliflozin for optimize batch B09

Time in min.	% drug released
	B 09
0	0
5	63.34
10	78.22
15	85.34
20	92.12
25	98.63

5. Conclusion

The present work concluded that all grades of MCC can be used for the formulation of Conventional tablets of Canagliflozin. However, finding showed that as the quantity of high molecular weight MCC increases, release of active drug decreases. Thus, requirement of the release retarding agents e.g. MCC can be selected in different combination or alone in different ratios for the desired product depending on the release profile of developing product by comparing with innovator product. Canagliflozin is effective in improving the glycemic control in type 2 DM. It was successfully developed for the treatment of diabetes mellitus which reduces the frequency of administration, improves the patient compliance and cost effectiveness. Hence to reduce the frequency of administration and to improve the patient compliance.

Coating Systems and pharmaceutical coating films are extensively used by pharmaceutical companies for coating solid oral dosage forms to protect against deterioration by environmental factors like sunlight, temperature variations, moisture, environmental gases etc. To mask taste, odour and to increase shelf-life.

Similarly, it was also concluded that Cross Carmelose sodium can act as a super disintegrator in order to the criteria of immediate release of drug to provide the instant drug at site of absorption. The work concluded with the designing of tablet of Canagliflozin instantly due to the effect of Cross Carmelose sodium and innovator product due to effect of high viscosity grade MCC. Based on the Results and discussion, we can conclude that Conventional tablets of Canagliflozin were prepared successfully by Wet Granulation Method using the combination of different concentration of polymers like MCC, CCS, PVP K-30 and other excipients. It was successfully formulated and evaluated.

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