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RESEARCH ARTICLE ON FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF CANAGLIFLOZIN BY DIRECT COMPRESSION METHOD

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ABSTRACT
Recent developments in fast dissolving/disintegrating tablets have brought convenience in dosing to elderly and children who have trouble in swallowing tablets. the present investigation was undertaken with a view to develop a fast disintegrating tablet of Canagliflozin which offers a new range of product having desired characteristics and intended benefits. The drug is poorly water soluble therefore to enhance the solubility and release of drug, solid dispersion of drug with mannitol was prepared by melt solvent method and melting method. In addition, the physical mixture was prepared for comparison. Different superdisintegrants such as croscarmellose sodium, sodium starch glycolate, crospovidone were used. Directly compressible mannitol was used as a carrier and to enhance the mouth feel and taste. The tablets were prepared by direct compression technique on rotary tablet machine. The tablets were evaluated for hardness, friability, weight variation, wetting time, dispersion time and uniformity of content and in vitro dissolution test. All the tablets had hardness 3-4.5 kg/cm^2 and friability of all formulations was less than 1%, weight variation and drug content were within official limit. Amongst all formulations, formulation F4 prepared with drug: mannitol (1:4) ratio by melting method and croscarmellose sodium as a superdisintegrants showed least disintegration time and faster dissolution.

KEYWORDS: Canagliflozin, superdisintegrants, solid dispersion, fast disintegrating tablets.

INTRODUCTION
The novel technology of fast-disintegrating dosage forms is known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets. However, the function and concept of all these dosage forms are similar. Oral route has been one of the most popular routes of drug delivery due to its ease and self administration, patient acceptance, least sterility constraints and flexible design of dosage forms drug that has a high aqueous solubility the dissolution rate is rapid the rate at which the drug crosses or permeates cell membrane is the slowest or rate limiting step.[2] A solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an fast-disintegrating dosage form.[13]

Canagliflozin (CGF) is an orally-active inhibitor of SGLT2. By inhibiting SGLT2, One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. The solubility of CGF in aqueous medium was very low i.e. 0.78 mg/ml in water. Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly, and is also seen in swallowing conventional tablets and capsules. An estimated 35% of the general population, and an additional 30–40% of elderly institutionalized patients and 18–22% of all persons in long-term care facilities, suffer from dysphagia. The most common complaint was tablet size, followed by surface, form and taste. The problem of swallowing tablets was more evident in geriatric and paediatric patients, as well as travelling patients who may not have ready access to water 14. The main possibilities for improving dissolution according to the analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid compound or by optimizing the wetting characteristics of the compound to decrease the boundary layer thickness, to ensure sink conditions for dissolution and to improve the apparent solubility of the drug under physiologically relevant conditions. Absolute bioavailability of the CGF was 99% and biological half-life is only 3.5 hours that results into poor bioavailability after oral administration. Conjugation of CGF with the different types of carriers to increases the solubility and dissolution rate of CGF. By increasing the solubility of CGF, its bioavailability is increased. From the above points, it is clear that, Canagliflozin is suitable drug to formulate into fast disintegrating tablet and may provide a better therapeutic profile than that of conventional dosage form. The main aim of present work is to formulate fast disintegrating

tablets by solid dispersion technique containing Canagliflozin, which give the application of solid dispersions results in increasing the solubility of many poorly soluble drugs is the objective of the present study, to investigate and to improve the solubility and consequently bioavailability of Canagliflozin by using Mannitol as carrier and different super disintegrants which gives more rapid onset of action compared to oral conventional dosage form and also to improve patient compliance Several methods are employed in the preparation of oral fast-disintegrating tablets, such as modified tableting systems, floss, or Shear form™ formation by application of centrifugal force and controlled temperature, and freeze drying. The inclusion of saccharides seems to be the basis for most of these technologies. The choice of material(s) depends on their rapid dissolution in water, sweet taste, low viscosity to provide 'smooth melt feeling', and compressibility. Even though the various formulations share some commonalties in terms of excipients selection, there is a distinct preparation method for each technology. The most common or conventional methods of oral disintegrating tablets involve:

1) Freeze drying
2) Tablet molding
3) Spray drying
4) Mass extrusion sublimation and
5) Direct compression As the Oral route of drug administration.

MATERIALS AND METHODS

The drug Canagliflozin was obtained by Spectrum Laboratories Pvt. Ltd, Microcrystalline cellulose, Cross carmellose sodium, Sodium starch glycolate and Cross povidone were donated as Gift Sample from KAPL, Bangalore. Mannitol was purchased from Qualigens Fine Chemicals., Mumbai. Magnesium stearate from Himedia Laboratories, Mumbai. Aerosil from S.D Fine Chemicals, Mumbai.

Preparation of fast disintegrating tablets

Direct compression method was established to manufacture fast disintegrating tablets of Canagliflozin. Prepared by using croscarmellose sodium, sodium starch glycolate, crospovidone. Mannitol physical mixtures and solid dispersions in different ratios by melt solvent and melting method. Accurately weighed quantities of drug and carrier were weighed taken in a glass mortar were mixed thoroughly. The resultant mixture was passed through sieve number #100 and was stored in desiccator for the complete removal of moisture and was tested for the content uniformity. Drug: polymer ratios of 1:1, 1:2, 1:3 and 1:4 were prepared.

Preformulation studies

a) Determination of melting point

Melting point of the drug was determined by taking small amount of Canagliflozin in a capillary tube closed at one end. The capillary tube was placed in an electrically operated melting point apparatus and the temperature at which the drug melts was recorded. This was performed thrice and average value was noted.

b) Drug–polymer compatibility studies

FT-IR spectroscopy was employed to ascertain the compatibility between Canagliflozin and the selected polymers. The pure drug and drug with excipient were scanned separately. Potassium bromide was mixed with drug and/or polymer in 9:1 ratio and the spectra were taken. FT-IR spectrum of Canagliflozin was compared with FT-IR spectra of Canagliflozin with polymers.

Micromeritic properties

a) bulk density : it is calculated by using the formula

Bulk density = W/V_o

b) tapped density

Tapped density = W/V_f

In which w = weight of the powder V_o= Initial volume of the powder. V_f = Final volume of the powder.

Carr's Compressibility Index

Compressibility Index is an important measure to calculate the flow ability of powders. It is represented as percentage.

Compressibility [%] = Tapped density – Bulk density / Tapped density x 100

Hausner's ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

Hausner's ratio = Tapped density / Bulk density

Angle of repose

The flow characteristics are measured by angle of repose. It is calculated by using formula: $\tan \theta = h / r$

In which $\theta = \tan^{-1} h/r$, h = height of pile, r = radius of the base of the pile, θ = angle of repose.

Post compression parameters

The prepared tablets were studied for weight variation, friability, hardness, disintigration test, Estimation of drug content, disintegration test, Uniformality of dispersion. the weight variation test test is performed to maintain the uniformity of weight of each tablet, which should be in the prescribed range. 20 tablets were selected randomly and individual weight as well as average weights was taken by using an electronic weighing balance.the strength of the tablet is expressed by measuring haedness and friability. The hardness of the tablet is tested by using Monsanto tester.

The friability of the tablets is tested by using Roche friabilator at 25 rpm, disintegration test is done by using disintegrator by placing the tablet in each glass tube.

Estimation of drug content

From each batch of prepared tablets, ten tablets were collected randomly and powdered. 50 mg of powder, which was equivalent to 10 mg of drug, was accurately

weighed and transferred to 100 ml volumetric flask. Then the volume was made up with, pH-6.8 phosphate buffer and shaken or 10 min to ensure complete solubility of the drug. Then the solution was filtered. Same concentration of standard solution was prepared by dissolving 10 mg of standard drug in pH-6.8 phosphate buffer. For both the sample and standard solutions absorbance was measured at 290 nm in UV-Visible spectrophotometer.

Uniformity of dispersion

Two tablets were kept in 100 ml of water and gentle stirred for 2 min. the dispersion was passed through #22 meshes. The tablets were considered to pass the test if no residue remained on the screen.

***In-vitro* dissolution**

The prepared tablets were subjected to *in vitro* dissolution. Dissolution test was carried out using USP23 paddle method. The stirring rate was 50 rpm, PH-6.8 phosphate buffer was used as dissolution medium and dissolution medium was maintained at 37±1^{o}C. Samples of 5 ml were withdrawn at regular intervals of time, filtered and replaced with 5 ml of fresh dissolution medium, dilutions were made wherever necessary and were analyzed for Canagliflozin at 290 nm by using UV-visible spectrophotometer.

Kinetics of drug release[67,68,69]

The mechanism of drug release from the Mannitol-Canagliflozin solid dispersions and tablets during the dissolution test in dissolution medium, (PH-6.8 phosphate buffer) was determined using zero order and first order.

Dissolution Efficiency[70]

DE is defined as the area under the dissolution curve up to a certain time 't' expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.

STABILITY STUDIES[71,72]

The objective of stability study is to identify and help avoid or control situations where the stability of the active ingredient may be compromised. For a drug substance to be developed into a tablet dosage form, this objective may be achieved by investigating the stability of the drug under the following three categories, (1) solid state stability of drug alone, (2) compatibility studies in presence of excipients, (3) solution phase stability.

RESULTS AND DISCUSSIONS

Direct compression method was established to manufacture fast disintegrating tablets of Canagliflozin. Canagliflozin (CGF) and Solid dispersions were prepared by taking different weight ratios of CGF: Mannitol [(1:1) (1:2) (1:3) (1:4)] by using physical mixture, melt solvent method and by melting method. The dispersions were subjected to *in-vitro* dissolution studies in dissolution medium (6.8 pH phosphate buffer) to select the optimized solid dispersion possessing enhanced *in vitro* dissolution. The melting point of CGF was found to 107^{0}C ± 2^{0}C. The maximum absorbance of Canagliflozin is found to be 290 nm. *In vitro* drug release study was carried out and based on the results F-4 was identified as the best formulation among all the other formulations .The interaction study in between the drug is evaluated by FTIR spectrometer. Differential thermal analysis of CGF: Mannitol (1:4) MM scanning range from 151.26^{O}C to 171.14^{O}C. shown in Fig. 21 Sharp endothermic peak of CGF at 153.13 ^{O}C and Mannitol at 166.76. Stability studies were performed as per ICH guidelines on F4, the CGF content varied slightly periodically. accelerated stability studies developed formulation was found to be stable for the tablets of the formulation F4. All the parameters tested, are within the acceptable limits and found to be suitable formulation the fast release of CGF**.** Dissolution of the Canagliflozin from solid dispersions followed first order dissolution rate.

Table 14: Dissolution data of Pure CGF and CGF: Mannitol (1:1).

TIME (min)	Cumulative % drug release (x ± S.D)*			
	PURE DRUG	P.M	M.S	M.M
0	0	0	0	0
5	12.11±0.35	22.12±0.97	24.78±0.16	27.11±1.32
10	16.80±1.03	25.26±0.86	30.40±0.88	37.17±1.02
15	22.61±0.95	27.18±0.52	38.90±0.78	44.86±0.65
30	31.86±0.24	33.60±0.97	40.66±0.55	47.13±0.95
45	35.94±0.66	37.82±0.64	44.40±0.22	54.43±0.12
60	43.11±0.57	52.10±1.40	58.10±1.12	69.26±0.98

***Mean± S.D, n=3, P.M= Pure Drug: Mannitol M.S= Melt Solvent, M.M =Melting Method**

In-vitro dissolution kinetic data for the melting method

Drug : Carrier	Ratio	Slope	R^2	K(min^{-1})
CGF : Mannitol	1:1	0.004	0.987	0.0093
	1:2	0.005	0.982	0.0125
	1:3	0.006	0.951	0.0128
	1:4	0.055	0.967	0.1233

Dissolution data of CGF and CGF: Mannitol (1:4) (MM) tablets

Time (min)	Cumulative % drug release (X± S.D)*					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	27.48±0.5	26.28±0.6	25.80±0.9	47.80±0.8	46.10±0.2	45.80±0.6
10	33.56±0.3	31.82±1.4	30.12±0.7	60.24±0.1	56.18±0.6	55.18±0.5
15	38.12±0.4	37.98±0.8	36.00±±1.8	70.18±0.9	68.10±0.2	62.20±0.2
30	45.45±0.7	50.24±1.2	48.24±1.1	93.92±0.5	90.28±0.4	88.88±0.9
45	52.85±0.2	53.84±0.7	50.26±0.9	99.22±0.8	98.18±0.9	97.18±0.2
60	68.12±0.7	63.10±0.5	62.18±0.8	---	---	---

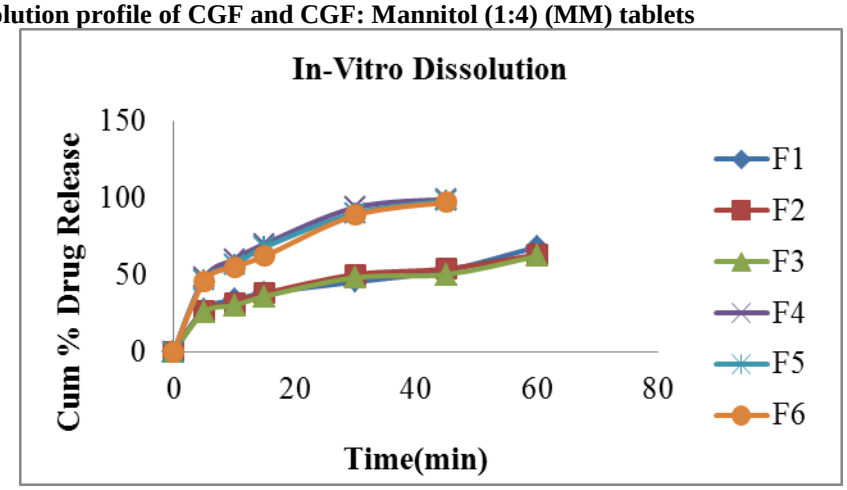
*** Mean ± S.D, n=3**

***In-vitro* release profile of F4 during Stability studies (40°C ± 2°C / 75% ± 5% RH)**

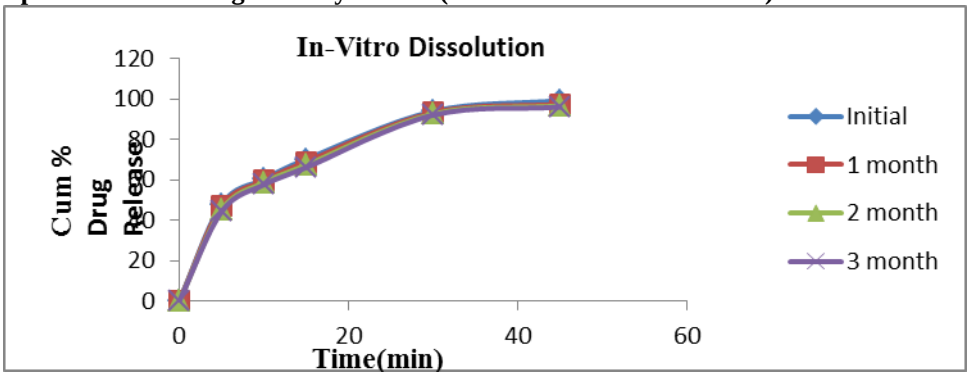
Time (min)	Cumulative % drug release (X± S.D)*			
	Initial	1month	2 month	3 month
0	0	0	0	0
5	47.80±0.8	46.85±0.6	45.12±0.7	44.23±0.6
10	60.24±0.1	59.45±0.2	58.65±0.4	57.56±0.5
15	70.18±0.9	68.91±0.1	67.31±0.4	66.19±0.1
30	93.92±0.5	93.24±0.9	92.61±0.5	92.01±0.9
45	99.22±0.8	97.41±0.9	96.56±0.1	96.01±0.5

***Mean ± S.D, n=3**

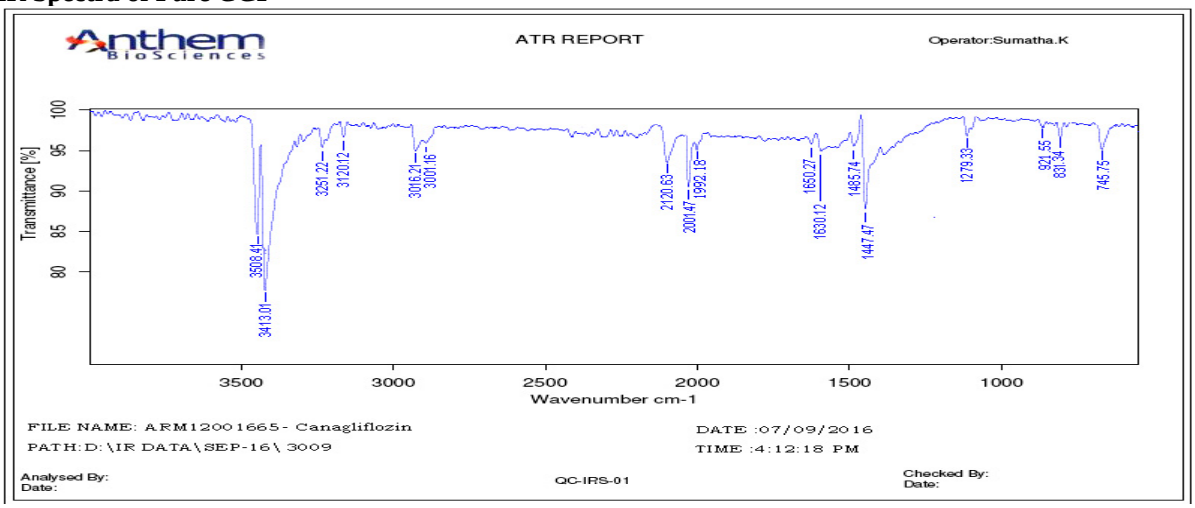
Comparative dissolution profile of CGF and CGF: Mannitol (1:4) (MM) tablets



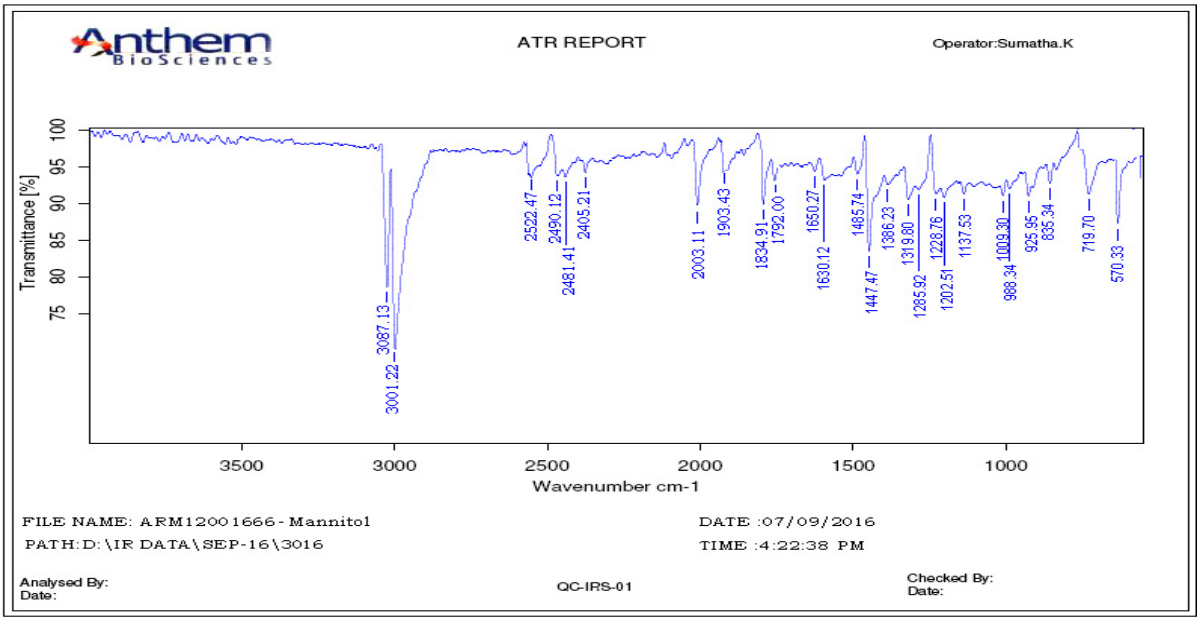
***In-vitro* release profile of F4 during Stability studies (40°C ± 2°C / 75% ± 5% RH)**



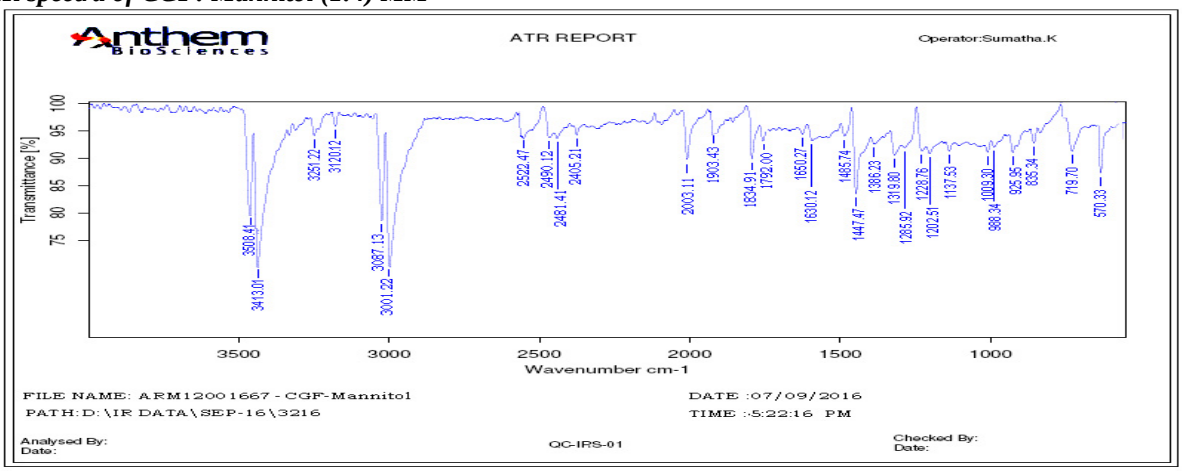
FT-IR Spectra of Pure CGF



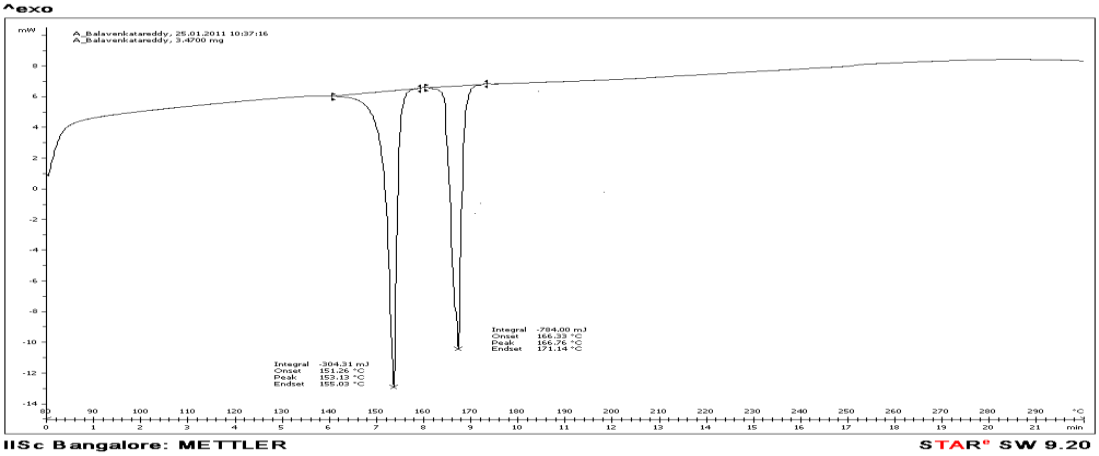
FT-IR spectra of Mannitol



FT-IR spectra of CGF: Mannitol (1:4) MM



DTA pattern of CGF:Mannitol(1:4) MM



CONCLUSION

Direct compression method was established to manufacture fast disintegrating tablets of Canagliflozin by using mannitol as a polymer. *In vitro* drug release study was carried out and based on the results; F-4 was identified as the best formulation among all the other formulations and *In vitro* release profiles was more than 93% within 30 minutes.

ACKNOWLEDGE

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