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# ANALYSIS OF CANAGLIFLOZIN, REVIEW

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## ABSTRACT

Canagliflozin, being a Sodium Glucose co-Transporter type 2 (SGLT2) Inhibitor, as a new class for treatment of Type 2 diabetes mellitus, offer a novel mechanism of action, which has been recently approved by USFDA for use in type 2 diabetes mellitus, either alone or in combination with other oral hypoglycaemic agents and insulin. The aim of this review firstly to focus on a comprehensive update of chromatography determination of Canagliflozin in bulk and in pharmaceutical preparations, In which has been described using TLC, HPLC/MS, RP-HPLC and UV methods. Secondly to localize the chromatographic conditions for separation and quantification. This review provides detailed information on separation conditions for Canagliflozin alone, with Metformin and in the presence of its degradation products.

**KEYWORDS**: Canagliflozin, Chromatography, HPLC, HPTLC, UV.

## INTRODUCTION

Canagliflozin is available commercially as INVOKANA and chemically known as (2S,3R,4R,5S,6R)-2-{3- [5-(4-fluoro-phenyl)-thiophen-2-ylmethyl]-4-methyl-phenyl} -6-hydroxymethyltetrahydro-pyran-3,4,5-triol Figure (1), the empirical formula is $C_{24}H_{25}FO_5S$ with a molecular weight of 444.52 g/mol. It is white to off white solid with a melting point of 95-105°C. It is soluble in many organic solvents (methanol, Dimethyl sulfoxide) and insoluble in aqueous media.[1]

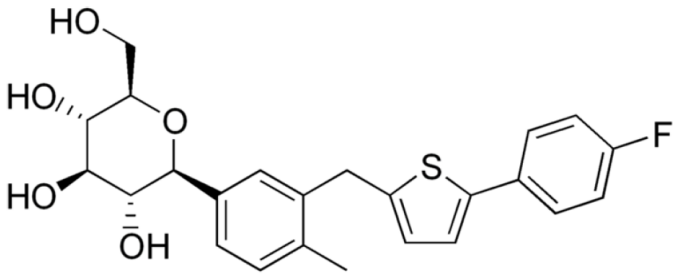


**Figure (1)**

**Mechanism of action**

Canagliflozin acts by inhibiting the SGLT2 which accounts for more than 90% of renal glucose reabsorption.[2]

Hence the efficacy of this drug also is dependent upon the amount of glucose which is filtered through the glomeruli and enters the tubular lumen and therefore shows maximal effect in patients with uncontrolled T2DM.[3]

Apart from bringing down the blood glucose levels, it has many other beneficial actions like reduction of the glycosylated hemoglobin levels due to the better control of blood glucose levels. It additionally improved the sensitivity of liver to insulin by reducing the blood glucose levels thereby reducing the glucose production from liver. This reduces the general gluco-toxic state of the body in patients with T2DM and helps in bringing down the serum insulin levels. Since the calories are lost from the body in the form of glucose in urine of the patients taking this drug, it causes a negative energy balance and loss of weight, which is again beneficial in patients of T2DM. This drug also helps in reduction of blood pressure owing to the mild weight loss and diuretic action caused by it. It has a positive effect on blood lipids as well due to mild weight loss caused by it.[4,5,6]

**Pharmacokinetics**

It is given orally and reaches the peak concentration in plasma in about 1-2 hours. The steady state of plasma concentration is achieved in around 4-5 days. Oral bioavailability of Canagliflozin is approximately 65%. It has a high plasma protein binding (99%) and it binds mainly to albumin.[7]

Food does not interfere with its absorption. It has a half-life of 11 hours with a 100 mg dose and of 13 hrs with a dose of 300 mg and is mainly metabolized via glucuronidation.[8,9]

A small part (~7%) of absorbed drug also undergoes oxidation through CYP3A4 enzyme.

Hence drugs which induce this enzyme e.g. rifampicin, phenytoin, ritonavir etc. will decrease the plasma level of Canagliflozin. Therefore, its dose has to be increased to 300 mg/day when used in combination with these drugs. It increases the plasma concentration of digoxin, so the drug levels need to be monitored to avoid the development of digoxin toxicity. Renal function needs to be assessed whenever this drug has to be started and is contraindicated when the glomerular filtration rate is less than 45 ml/min/1.73m$^2$.[7]

In a study done to assess the pharmacokinetics and pharmacodynamics of Canagliflozin, it was established that the profile of the drug is meant for once daily regimen.[10]

**Indications**

Canagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[11]

**Dosage and Administration**

The recommended starting dose of Canagliflozin is 100 mg once daily, taken before the first meal of the day. In patients tolerating Canagliflozin 100 mg once daily who have an eGFR of 60 mL/min/1.73 m$^2$ or greater and require additional glycemic control, the dose can be increased to 300 mg once daily.[11]

**HPLC METHODS FOR DETERMINATION OF CANAGLIFLOZIN**

*Suneetha et al.* has developed and validated a simple, specific, precise and accurate RP-HPLC method for estimation of Canagliflozin in raw material and pharmaceutical dosage form. Chromatographic conditions consisted of a column ( Hypersil BDS, C18 100 x 4.6 mm, 5µ) and a mobile phase composed of (0.1% ortho phosphoric buffer: acetonitrile (53:47), water and acetonitrile (50:50) as diluent in isocratic mode. The flow rate was 1.1ml/min and the detection wavelength was at 240 nm. The retention time (Rt) was around 3.3±0.2 min. The method was validated as per ICH guidelines. The assay method was linear within the range of 75-450 µg/ml with a Correlation coefficient ($R^2$) 0.9999. The percentage recovery of active pharmaceutical ingredient from tablet dosage form ranged 99.83-100.27%. The LOD and LOQ were 0.23µg/ml and 0.7µg/ml, respectively. Stress conditions of degradation in acidic, alkaline, peroxide, thermal and UV radiation were studied and found that Canagliflozin is sensitive to alkali degradation.[12]

Another study by *Maddu et al.* described a simple and sensitive RP-HPLC method for the determination of Canagliflozin in pharmaceutical dosage form. The chromatographic separation was achieved using ODS column (4.6 x150mm, 5µ particle size). Water and acetonitrile (55:45v/v) as a mobile phase, the flow rate was 1.0 ml/min. The eluent was monitored using PDA detection at 214 nm. Canagliflozin was resolved at 2.8 minutes. Validation parameters were studied as per ICH guidelines. The author concluded that his method can be employed for routine QC of Canagliflozin tablets in pharmaceutical industry.[13]

*Kaur et al.* developed and validated a simple and stability indicating HPLC method for determination of Canagliflozin in bulk and pharmaceutical dosage forms as per ICH Q2 R1 Guidelines. Chromatographic separation was achieved using C18 Column (250×4.6 mm, 5 µm particle size) with a mobile phase composed of Acetonitrile: orthophosphoric acid 55:45 v/v. the flow rate was 1 ml/min and the injected volume was 20 µL. The proposed method was validated with different parameters such as Linearity, Precision Accuracy, Robustness, Ruggedness, Limit of Detection (LOD) and Limit of Quantification (LOQ). The separation was achieved at a temperature of 30°C and the detection was observed by PDA detector at 290 nm. A linear range of 1-6 µg/ ml with a correlation coefficient of 0.998 unfolds good linear relationship between area and concentration in calibration curve. The retention time obtained was at 6.29 min. The LOD and LOQ were found to be 0.41 µg/ml and 1.24 µg/ml respectively. A recovery of Canagliflozin in tablet formulation was observed in the range of 99.6-99.8%. Percentage assay of Canagliflozin tablets (INVOKANA®) was 99.92%. The stability of the method was demonstrated by forced degradation studies of drug in which it was degraded under conditions of hydrolysis (acidic and alkaline), oxidation, photolytic and thermal stress as per ICH guideline Q1A (R2). Conclusion: The proposed method is definite, meticulous and reproducible and can be used for routine analysis of Canagliozin in bulk and pharmaceutical dosage form.[14]

*Sonia et al.* focused in their study on developing and validating an HPLC method to simultaneously estimation of Metformin hydrochloride and Canagliflozin in bulk using GraceSmart RP-18 column (250× 4.6mm, 5µ)at 30°C. Combination of acetonitrile(ACN) and ammonium acetate Buffer in the ratio of 45:55v/v with pH 4.5 was used as mobile phase with 1ml/min flow rate. It was detected by photo diode array detector at 252 nm. The retention Time observed for metformin hydrochloride and canagliflozin were found to be 4.00 and 5.76

min respectively. The method was developed and found to be linear with correlation coefficients r2 of 0.9993 and 0.9992 for metformin hydrochloride and canagliflozin respectively within a concentration range of 1- 80µg/ml. Stability studies were performed by exposing the drugs to acidic, basic, oxidative, thermal and photolytic stress conditions with Samples with drawn at different time intervals. Analysis of the samples were done by the developed method. The method to estimate metformin hydrochloride and canagliflozin in bulk drug is easy, accurate, precise and less time consuming.[23]

**UV/VIS METHODS FOR DETERMINATION OF CANAGLIFLOZIN**

Few researchs for Determination of Canagliflozin using UV/VIS spectroscopy were reported. *Ishpreet et al.* has developed and validated a simple, sensitive, precise, rapid and cost effective method for determination of Canagliflozin in bulk and pharmaceutical formulations as per ICH Guidelines. A simple double beam UV Spectrophotometric method has been developed and validated with different parameters such as Linearity, Precision, Repeatability, Limit of Detection (LOD), Limit of Quantification (LOQ), Accuracy, Robustness and Ruggedness. Canagliflozin in methanol shows maximum absorbance at 290 nm. Beer's law was obeyed in the concentration range of 5-10 mcg $mL^{-1}$, The LOD and LOQ were found to be 0.084 mcg/ml and 0.255 mcg/ml respectively. A recovery of Canagliflozin in tablet formulation was observed in the range of 80.00-120.00%. Percentage assay of Canagliflozin tablets (INVOKANA®) was found to be more than 99%.[15]

Another study depending on UV spectroscopy has been developed for the estimation of Canagliflozin in tablet formulation. Canagliflozin was estimated by using the mode at 290 nm in their solution in methanol. The Beer's law obeyed the concentration range of 5-25µg/ml for Canagliflozin. Mean recovery of 100.47% for Canagliflozin signifies the accuracy of the method. This method can be used for the routine UV estimation of canagliflozin in industries and other analytical laboratories.[22]

**HPTLC METHODS FOR DETERMINATION OF CANAGLIFLOZIN**

One study for determination of Canagliflozine has been reported by *Ishpreet et al.* who developed and validated a simple, authentic and stability indicating high performance thin-layer chromatographic method for determination of Canagliflozin in bulk and pharmaceutical formulations as per ICHQ2 R1 Guidelines. HPTLC aluminium plates Precoated with Silica Gel $60F_{254}$ using Toluene: Ethyl acetate: Methanol (2:2:1, v/v/v) as mobile phase were used for the chromatographic separation and it was validated with different parameters. Also,

Forced degradation study was carried out in different media. The densitometric analysis of the spots was performed at 290 nm. The Linearity was achieved over the range of 10-500ng/spot with a good correlation coefficient of 0.9988. The LOD and LOQ were found to be 0.39 and 1.19 respectively. A recovery of Canagliflozin in tablet formulation was observed in the range of 99.04-99.82%. Percentage assay of Canagliflozin tablets (INVOKANA®) was found to be 99.8%. Forced degradation studies of canagliflozin showed the degradation in acidic, alkaline, photolytic and oxidation but were most stable in thermal degradation.[16]

**DETERMINATION OF CANAGLIFLOZIN AND METFORMIN COMBINATION IN DOSAGE FORMS**

*Deepak et al.* has developed a new stability indicating RP-HPLC method for estimation Metformin and Canagliflozin in bulk and pharmaceutical dosage form. To choose the mobile phase various combinations of organic solvents were used on Kromosil $C_{18}$ 250 column, Then the mobile phase containing a mixture of phosphate buffer and acetonitrile in the ratio of 65:35% v/v was selected at a flow rate of 1.0ml/min and a peak with a good shape and resolution was found resulting in short retention time. The retention time of metformin and canagliflozin were 2.413 and 3.548 min respectively, quantitative linearity was obeyed in the concentration range of 50-300µg/ml and 5-30 µg/ml of Metformin and Canagliflozin respectively. LOD and LOQ were found to be 0.30µg/ml and 0.91µg/ml (Metformin), 0.361µg/ml and 1.094µg/ml (Canagliflozin) respectively, which indicated the sensitivity of the method. The high percentage recovery indicated that the proposed method was accurate, no interfering peaks in the chromatogram which indicate that the excipients used in tablet formulation didn't interfere with the estimation of the drug by the proposed method.[17]

*Uttam et al.* reported a novel approach to develop and validate a rapid isocratic RP-HPLC method for simultaneous estimation of Metformin and Canagliflozin in bulk and pharmaceutical dosage form with forced degradation studies. The separation was performed by Kromasil C18 column (250mm×4.6 mm, 5mm particle size), Waters Alliance e2695 HPLC system with 2998 PDA detector and mobile phase consisted of a mixture of 0.01M Ammonium acetate (pH adjusted to 3.5 with orthophosphoric acid) and Acetonitrile (65:35, v/v). The flow rate was 1ml/min and the detection achieved at 254nm. The retention time of Metformin Hydrochloride and Canagliflozin was 2.440min and 3.713min respectively. Linearity was established in the range of 50-300µg/ml for Metformin Hydrochloride and 5-30µg/ml for Canagliflozin with correlation coefficients (r2=0.999). The percentage recoveries

were between (99.45%-100.65%) and (99.95%-100.74%) for Metformin Hydrochloride and Canagliflozin respectively. Validation parameters were evaluated according to the (ICH) Q2 R1 guidelines. The forced degradation studies were performed by using HCl, NaOH, $H_2O_2$, thermal, UV radiation and water. Metformin Hydrochloride and Canagliflozin were sensitive towards oxidative degradation condition. The developed method was successfully applied for the quantification and hyphenated instrumental analysis.[18]

Another study by *Nareddy et al.* who has developed a new HPLC method for simultaneous estimation of Metformin and Canagliflozin in pharmaceutical dosage forms. Chromatography was carried out on an ODS 250mm x 4.6 mm, 5µ particle size with an isocratic mobile phase composed of Buffer, Acetonitrile and methanol at a flow rate of 1mL/min. The column temperature was maintained at 30°C and the detection was carried out using a PDA detector at 212 nm. Validation parameters such as system suitability, linearity, precision, accuracy, specificity, limit of detection (LOD), limit of quantification (LOQ), Stability of sample and standard stock solutions and robustness were studied as reported in the International Conference on Harmonization guidelines. The retention times for Metformin and Canagliflozin were 2.783 min and 3.781 min respectively. The percentage recoveries of Metformin and Canagliflozin were 100.1% and 100.2% respectively. The relative standard deviation for assay of tablets found to be less than 2%. The method is fast, accurate, precise and sensitive hence it can be employed for routine quality control of tablets containing both drugs in quality control laboratories and pharmaceutical industries.[19]

**DETERMINATION OF CANAGLIFLOZIN IN HUMAN/RAT PLASMA**

The first reported study for determination of Canagliflozin in human plasma depended on a simple and sensitive HPLC assay with a florescence detector, the method was developed for accurate quantification of canagliflozin in human plasma using telmisartan as the internal standard (IS). Plasma samples were extracted by a liquid–liquid extraction method using diethyl ether as an extracting solvent. Chromatographic separation of canagliflozin and IS was performed on a Nucleodur Isis C18 column with an isocratic mobile phase of 20 mM potassium dihydrogen orthophosphate : acetonitrile (45: 55, v/v) at a flow rate of 1 mL $min^{-1}$. Canagliflozin and IS were eluted at 2.8 and 5.8 min, respectively and detected at 280 and 325 nm for excitation and emission, respectively. The plasma calibration curve displayed excellent linearity over the concentration range of 16.13–6000 ng mL−1. The assay was fully

validated in terms of selectivity & specificity, linearity of the calibration curve, accuracy & precision, recovery and stability under various storage conditions.[20]

Another simple, specific, sensitive, precise, selective and accurate RP-HPLC method has been developed for the determination of Canagliflozin in human plasma as per US-FDA guidelines. Plasma samples were extracted by protein precipitation method using methanol as extracting solvent. The chromatographic separation was performed with WATERS EA874 (250 ×4.6 mm, 5 µm) column and mobile phase composed of 36.46 mM Acetate buffer: acetonitrile: methanol (30:50:20, v/v), pH 4.5 adjusted with acetic acid at a flow rate of 1.0 ml/min. Canagliflozin was detected at 290 nm with retention time of 5.1 min. Linearity was found to be 0.9929 over the range of 33.33 – 233.33 ng/ml and percentage recoveries were found to be 94.68 - 103.76%. The validation was successfully performed by means of accuracy and precision, selectivity and specificity, linearity, recovery and stability under various conditions. This developed method can be successfully employed for the determination of Canagliflozin in human plasma.[21]

A sensitive UHPLC-MS/MS assay for rapid determination of canagliflozin in rat plasma was developed and validated by *Muzzafar et al*. Chromatographic separation of Canagliflozin and Zafirlukast (IS) was carried out on Acquity BEH C18 column (100×2.1mm, i.d. 1.7µm) using acetonitrile-water (80:20, v/v) as mobile phase at a flow rate of 0.3mLmin(-1). Canagliflozin and IS were extracted from plasma by protein precipitation method using acetonitrile. The mass spectrometric detection was performed using electrospray ionization source in negative mode to avoid canagliflozin adduct ions formation. Multiple reaction monitoring were used for quantitation of precursor to product ion at m/z 443.16 >364.96 for canagliflozin and m/z 574.11>462.07 for IS, respectively. The assay was fully validated in terms of selectivity, linearity, accuracy, precision, recovery, matrix effects and stability. The validated method was successfully applied to the characterization of oral pharmacokinetic profiles of canagliflozin in rats. The mean maximum plasma concentration of canagliflozin of 1616.79ngmL(-1) was achieved in 1.5h after oral administration of 20mgkg(-1) in rats.[24]

Another validated liquid chromatography-tandem mass spectrometry (LC- MS/MS) method for the quantitative analysis of canagliflozin in a lower volume of rat plasma (0.1 mL) was established and applied to a pharmacokinetic study in rats. Following liquid-liquid extraction by tert-butyl methyl ether, chromatographic separation of canagliflozin was performed on a Quicksorb ODS (2.1 mm i.d. × 150 mm, 5 µm size) using acetonitrile-0.1% formic acid

(90:10, v/v) as the mobile phase at a flow rate of 0.2 mL/min. The detection was carried out using an API 3200 triple-quadrupole mass spectrometer operating in the positive electrospray ionization mode. Selected ion monitoring transitions of m/z = 462.0 [M + NH4 ](+) → 191.0 for Canagliflozin and m/z = 451.2 [M + H](+) → 71.0 for Empagliflozin (internal standard) were obtained. The validation of the method was investigated and it was found to be of sufficient specificity, accuracy and precision. Canagliflozin in rat plasma was stable under the analytical conditions used. This validated method was successfully applied to assess the pharmacokinetics of canagliflozin in rats using 0.1 mL rat plasma.[25]

## CONCLUSION

Many methods for determination of Canagliflozin have been reported. Some HPLC assay methods were used to monitor canagliflozin. Methods for the analysis of active and inactive metabolites of canagliflozin in plasma have also been reported. Some articles related to the determination of canagliflozin alone or in combination with metformin in pharmaceutical dosage forms have been mentioned.

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