https://doi.org/10.48047/AFJBS.6.12.2024.4439-4447

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Comprehensive Review on Analytical Methods of Canagliflozin

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Article History
Volume 6, Issue 12, 2024
Received: 15 June 2024
Accepted: 05 July 2024
doi:
10.48047/AFJBS.6.12.2024.4439-4447

Abstract
Canagliflozin, an inhibitor of the Sodium glucose transport protein (SGLT2), represents a pivotal advancement in the management of type 2 diabetes mellitus. SGLT2 inhibitors is successfully reduced the risk of heart failures in patient with type 2 diabetes Mellitus. This comprehensive review aims to provide a detailed examination of the analytical methods employed for the quantitative and qualitative analysis of Canagliflozin such as chromatography, spectrophotometry, and hyphenated techniques, such as Liquid chromatography with tandem mass spectrometry (LC-MS/MS) and Ultra performance liquid chromatography with tandem mass spectrometer (UPLC-MS)as well as emerging methods like capillary electrophoresis (CE) and electrochemical methods for the analysis of Canagliflozin. By consolidating and evaluating the current state-of-the-art analytical methodologies for Canagliflozin, this review seeks to provide valuable insights for researchers, analysts, and practitioners involved in drug development, regulatory compliance, and clinical investigations. Ultimately, a comprehensive understanding of these analytical methods is essential for ensuring the efficacy, safety, and quality of Canagliflozin-based therapies. It was concluded that many methods for determination of Canagliflozin have been reported. Methods for the analysis of active and inactive metabolites of Canagliflozin also been reported. Some articles related to the determination of Canagliflozin alone or in combination with metformin in pharmaceutical dosage forms have been mentioned.

Keywords: *Canagliflozin, Pharmacological data, Chromatographic Methods, Spectrophotometric Methods.*

Introduction:

Canagliflozin is a medication used primarily in the management of type 2 diabetes mellitus. It belongs to a class of drugs known as Sodium glucose transport protein (SGLT2) inhibitors. These medications work by inhibiting the SGLT2 protein in the kidneys, which is responsible for reabsorbing glucose back into the bloodstream from the urine. By inhibiting this protein, Canagliflozin helps to increase the excretion of glucose in the urine, thereby lowering blood sugar levels in people with diabetes.[2]It belongs to a new class of anti-diabetic drugs that

works by inhibiting the sodium-glucose transport protein (SGLT2). Canagliflozin is chemically known as (1S)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl] methyl]-4-methylphenyl]-D-glucitol hemihydrate and its molecular formula is $C_{24}H_{25}FO_5S \cdot 1/2\ H_2O$ and molecular weight is 453.53. 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 from pH 1.1 to 12.9.[1]

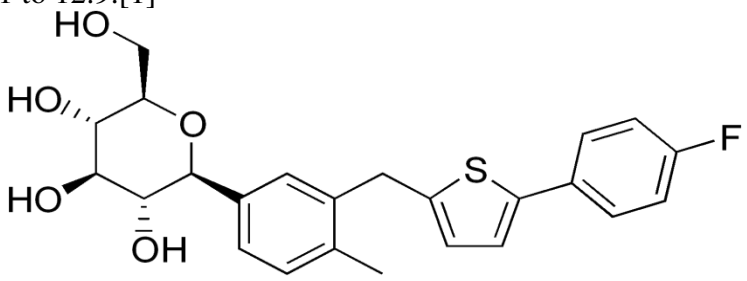

Figure 1: Structure of Canagliflozin hemihydrate

It was developed by Mitsubishi Tanabe Pharma and is marketed under license by Janssen, a division of Johnson & Johnson. Canagliflozin was approved by the FDA on 29 March 2013and became the first SGLT2 inhibitor in the United States,in the European Union in November 2013,in Australia in September 2013 and the Canadian market in 2014.[20] Canagliflozin, sold under the brand name "Invokana" among others, is a medication used to treat type 2 diabetes. Canagliflozin was approved for medical use in Australia in September 2013. It was approved for medical use in the European Union in November 2013. It is used together with exercise and diet. It is not recommended in type 1 diabetes. It is taken by mouth.SGLT2 inhibitors are drugs designed to lower blood sugar in adults with type 2 diabetes by helping remove excess sugar from the body through the urine. SGLT2 inhibitors are used along with diet and exercise either alone or in combination with other specific agents that control blood sugar. Three SGLT2 inhibitors are currently available in: Invokana (Canagliflozin), Forxiga (Dapagliflozin) and Jardiance (Empagliflozin).[20]

It is available in various dosage strengths (such as 100 mg and 300 mg tablets) and can be prescribed alone or in combination with other antidiabetic medications.

Clinical Pharmacology

Mechanism of Action: 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 (RT), and thereby increases urinary glucose excretion (UGE). Canagliflozin increases the delivery of sodium to the distal tubule by blocking SGLT2- dependent glucose and sodium reabsorption. This is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure. [17]

Pharmacokinetics:

Canagliflozin is rapidly absorbed after oral administration, with peak plasma concentrations reached within 1 to 2 hours. It is extensively distributed throughout the body, primarily binding to plasma proteins (about 99%). Canagliflozin is metabolized in the liver primarily via the UGT1A9 enzyme and to a lesser extent by UGT2B4. The metabolites are mainly excreted in the urine (about 30% as unchanged drug) and feces. The elimination half-life is approximately 10.6 hours, allowing for once-daily dosing in most patients.

Recommended Dosage of Canagliflozin once-daily 100 mg or 300 mg for 14 days taken before the first meal of the day. [17]

Determination of Canagliflozin by Chromatographic Methods:

HPLC Methods

HPLC is the most versatile and conventional separation technique in modern pharmaceutical and biomedical analysis due to highly efficient separation and enhanced detection sensitivity. Most of the drugs are analyzed by HPLC method due to its accuracy, ease of automation, reproducibility.

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 parameters 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 detection wavelength was at 240 nm and the retention time (Rt) was around 3.3±0.2 min. The flow rate was 1.1ml/min. The LOD and LOQ were 0.23µg/ml and 0.7µg/ml, respectively. The method was validated as per ICH guidelines [3].

Maddu et al. described a simple and sensitive RP-HPLC method for the determination of Canagliflozin in oral 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. The retention time (Rt) was around 2.8 min. [4]

Kaur et al. developed and validated a simple and cost effective method for stability indicating HPLC method for determination of Canagliflozin in drug substance and drug product 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 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.

Stress conditions of degradation in acidic, alkaline, peroxide, thermal and UV radiation were studied and found that Canagliflozin is sensitive to alkali degradation.[5]

HPTLC Methods

HPTLC is a powerful and novel technique for qualitative and quantitative analysis. It contains chromatographic layers with the highest separation efficiency, the possibility to use multiple detection methods on the same sample and plate. Accurate quantitative measurements and high resolution makes HPTLC to meet all quality requirements for analytical labs.

Another Chromatographic method (HPTLC) for estimation of Canagliflozin has been reported by *Ishpreet et al.* who developed a simple, traditional authentic high performance thin layer chromatographic method for determination of Canagliflozin in pharmaceutical formulations. HPTLC aluminium plates Precoated with Silica Gel 60F254 using Toluene: Ethyl acetate: Methanol (2:2:1, v/v/v) as mobile phase were used for the chromatographic separation. 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 study was carried out in different media. Forced degradation studies of canagliflozin showed the degradation in acidic, alkaline, photolytic and oxidation but were most stable in thermal degradation. [7]

UPLC technique:

UPLC is a novel separation technique which reduces the cost and increases the reproducibility and efficiency of analysis required for developing and validating the method.

Wafaa et al. developed and validated an UPLC method for the determination of Metformin and Canagliflozin in tablets using Hypersil Gold (50 mm × 3 mm, 1.9 µm) as the stationary phase (Column) and methanol:0.03 M phosphate buffer (80:20) considered as the mobile phase at 0.4 mL/min flow rate. The Rt of Canagliflozin and Metformin was 1.0 and 0.5 min using a detection wavelength of 240 nm. Accuracy of Canagliflozin and Metformin was 99.47% ± 1.03% and 99.73% ± 0.89% with a linearity of 0.1–50 and 0.25–100 µg/mL−1 for Canagliflozin and Metformin, respectively [8].

Determination of Canagliflozin and other combination of drug substance in Dosage Forms

Sonia et al. is developing HPLC method to simultaneously estimation of Metformin hydrochloride and Canagliflozin in oral dosage form using GraceSmart RP-18 column (250× 4.6mm, 5µ) at 30°C. Combination of acetonitrile and ammonium acetate Buffer in the ratio of 45:55v/v with pH 4.5 was used as mobile phase and flow rate was 1ml/min. At 252nm wavelength detected by photo diode array detector. The retention time was observed for metformin hydrochloride 4.00 minutes and Canagliflozin 5.76 minutes. 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. This less time consuming and easy method to estimate metformin hydrochloride and Canagliflozin in bulk drug is accurate and precise.[9]

Deepak et al. was developed a new RP-HPLC method for estimation Metformin and Canagliflozin in pharmaceutical dosage form. Kromosil C18 250 column was used and mixture of phosphate buffer and acetonitrile in the ratio of 65:35% v/v was selected combinations of organic solvents as a mobile phase. The flow rate was 1.0 ml/min. The retention time of metformin and Canagliflozin were 2.413 and 3.548 min 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 of recovery indicated that the method was more accurate, precise and validated with all validation parameter as per ICH guidelines. In addition there is no interfering peak in chromatogram of Metformin and Canagliflozin which is also indicating method accuracy and efficacy. [10]

Nareddy et al. was developed a new HPLC method for estimation of Metformin and Canagliflozin combination oral dosage forms. Column was ODS 250mm x 4.6 mm, 5µ particle size usedand Column temperature was maintained at 30°C. The isocratic mobile phase composed of Buffer, Acetonitrile and methanol at a flow rate of 1mL/min. The detected by using a PDA detector at 212 nm wavelength. 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. All Validation parameters was validated such as system suitability, linearity, precision, accuracy, specificity, limit of detection (LOD), limit of quantification (LOQ), The method is fast, accurate, easy and sensitive hence it can be used for routine quality control of tablets containing both drugs combination in pharmaceutical industries. [11]

Spectrophotometric Method:

UV-Vis spectroscopy methods are employed in pharmaceutical product estimation for their simplicity, accuracy, speed, and cost-effectiveness. Over a 40 years period, it has become the most important analytical instrument where expensive instruments like HPLC, Gas chromatography, Liquid chromatography with tandem mass spectrometry (LC-MS/MS) are not available.

Singh et al. developed a UV spectroscopic method using methanol as a diluent and measured the absorbance at 280 nm with a linearity of 5–50 µg·mL−1. [12]
Chinta et al. reported a UV spectroscopic method using phosphate buffer as diluent at an absorbance wavelength of 289 nm and attained 99% purity with a linearity of 1–6 µg·mL−1. [13]
Vichare et al. have reported two simultaneous methods, one based on absorbance correction UV spectroscopy (absorbance measurement at wavelengths 233 nm (λmax of metformin)) and 291 nm (λmax of Canagliflozin) and another based on first order derivative spectroscopy overlain spectra wavelengths 243 nm (zero absorbance of Canagliflozin) and 318 nm (zero absorbance of metformin) with a linearity of 0.75–4.5 µg·mL−1 for Canagliflozin and 2.5–15 µg·mL−1 for metformin, respectively. The percentage drug contents were found to be 98.48% ± 0.83% and 100.76% ± 1.29% for method A and 97.94 ± 0.96 and 97.22 ± 1.15 for Canagliflozin and metformin, respectively. [14]
Ishpreet et al. has developed and validated a simple, sensitive and cost effective method for determination of Canagliflozin in drug formulations. A simple double beam UV Spectrophotometric method has been developed. Canagliflozin in methanol shows maximum absorbance at 290 nm and 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%. This method was validated with different parameters such as Linearity, Precision, Repeatability, Limit of Detection (LOD), Limit of Quantification (LOQ), Accuracy, Robustness and Ruggedness. Percentage assay of Canagliflozin tablets (INVOKANA®) was found to be more than 99%. 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 as cost effective and business case variability. [6]
Shilpi *et al.* was developedSimple and sensitive spectroscopic methods in UV region and visible region were developed for the estimation of Canagliflozin in its pharmaceutical dosage forms. The development and validation of these methods as a stability indicating assay based on the forced degradation studies. Method A was based on Canagliflozin showing its absorption maxima at 290 nm in ethanol. The method B was based on Canagliflozin showing its absorption maxima at 280 nm in methanol. The method C was colorimetric. It involved the reaction of Canagliflozin with ceric ammonium sulphate in presence of H_2SO_4 and crystal violet that produced a blue colour, showed absorption maxima at 578 nm. These methods obey Beer-Lambert law at concentration ranges of 5-25 µg/mL, 8-12 µg/mL and 5-25 µg/mL respectively. The percent recoveries were found out to be 98–102%. The results obtained with the proposed methods were in good agreement with the labeled amount when tablet dosage forms were analyzed. [15]

Spectrofluorimetry method:

Spectrofluorimetry is a very sensitive analytical method for the determination of fluorescent compounds at nanogram or lower level.
Nirav et al. was developed a specific, accurate and robust spectrofluorometric method using methanol as the solvent, which emission λmax at 293 nm and emission λmax at 349 nm. The method was linear over the range of 100–500 ng·mL−1 with a percentage recovery of 99.42–99.81%. The LOD and LOQ for the developed method were found to be 13.58 and 41.15 ng·mL−1 , respectively. The method was novel, sensitive it can be applied for the routine analysis by spectrofluorimetry. [16]

Determination of Canagliflozin in Human/Rat Plasma

The first reported study for determination of Canagliflozin in human plasma by HPLC with a florescence detector and detected at 280 and 325 nm for excitation and emission respectively, 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 parameter consist of a Nucleodur Isis C18 column was used with an isocratic mobile phase of 20 mM potassium dihydrogen orthophosphate: acetonitrile (45: 55, v/v) at a 1 mL/min flow rate. Canagliflozin and IS were eluted at 2.8 and 5.8 min, respectively. The plasma calibration curve displayed excellent linearity over the concentration range of 16.13–6000 ng mL−1. This method is validated of all parameter as per ICH guideline such as selectivity & specificity, linearity of the calibration curve, accuracy & precision, recovery and stability under various storage conditions. The method is accurate, precise and sensitive. [17]

Figure 1 HPLC Method for Determination of Canagliflozin in Human Plasma

Parameter	Details
Detector Type	Fluorescence Detector
Excitation Wavelength (nm)	280
Emission Wavelength (nm)	325
Internal Standard	Telmisartan
Extraction Method	Liquid-liquid extraction
Extracting Solvent	Diethyl ether
Column Type	Nucleodur Isis C18
Mobile Phase	20 mM potassium dihydrogen orthophosphate: acetonitrile (45:55, v/v)
Flow Rate (mL/min)	1
Retention Time (Canagliflozin) (min)	2.8
Retention Time (IS) (min)	5.8
Calibration Range (ng/mL)	16.13–6000
Linearity	Excellent linearity
Validation Guidelines	ICH
Validation Parameters	Selectivity & Specificity, Linearity, Accuracy & Precision, Recovery, Stability

Another simple and accurate RP-HPLC method was 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 column WATERS EA874 (250 ×4.6 mm, 5 µm) 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 290 nm detection wavelength with a flow rate of 1.0 ml/min. The retention time of 5.1 min. Linearity was found to be 0.9929 and percentage recoveries were found to be 94.68 - 103.76%. The complete validation parameters were successfully performed such as 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 in future prospective. [18]

Bioanalytical techniques (UHPLC-MS/MS and LC- MS/MS):

Bioanalytical techniques are used for the quantitative determination of drugs and their metabolites in biological fluids, which plays a major role in the interpretation of bioequivalence, pharmacokinetic, and toxicokinetic studies. Hence, the development of

selective, sensitive, and reliable bioanalytical methods for the quantitative evaluation of drugs and their metabolites in biological matrices is important. An analytical method for the quantification of Canagliflozin in human plasma has been developed, validated, and enforced for the analysis of samples.

Muzzafar et al. A sensitive UHPLC-MS/MS assay for rapid determination of canagliflozin in rat plasma was developed and validated. Chromatographic separation of Canagliflozin and Zafirlukast (IS) was carried out. Acquity BEH C18 column (100×2.1mm, i.d. 1.7µm) was used with acetonitrile-water (80:20, v/v) as mobile phase at a flow rate of 0.3mLmin(-1). The mass spectrometric detection was performed using electrospray ionization source in negative mode to avoid canagliflozin adduct ions formation. Canagliflozin and IS were extracted from plasma by protein precipitation method using acetonitrile. 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 1616.79 ngmL(-1) was achieved in 1.5h after oral administration of 20mgkg(-1) in rats. [17]

Another sensitive method was developed and validated as 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. Liquid-liquid extraction by tert-butyl methyl ether and Quicksorb ODS (2.1 mm i.d. × 150 mm, 5 µm size) column was used for chromatographic separation of canagliflozin 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 method was found to be validated as per ICH guideline parameters. This validated method can be successfully applied to assess the pharmacokinetics of canagliflozin in rats using 0.1 mL rat plasma.

Multiple spectroscopic methods:

Elnadi et al. reported three novel, simple and accurate methods for the determination of canagliflozin using FTIR, spectrofluorimetry, a stability-indicating UV-Vis spectroscopic method for the simultaneous estimation of canagliflozin and Metformin.

Method A is a green FTIR method using KBr disc for canagliflozin determination measuring alkyl halide C–F peak area centered on 1,230 cm−1.

Method B is a spectrofluorimetry method using $\Delta\lambda$ = 50 nm synchronous mode at a peak maximum of 291.8 nm for canagliflozin determination using methanol as diluent.

Method C is a stability-indicating MCRS method measuring the peak amplitude of canagliflozin and Metformin at 306.2 and 246.6 nm, respectively, in their mixture with complete canagliflozin oxidation degradation. All the three spectroscopic methods can be used efficiently for routine analysis in QC laboratories. [19]

Discussion:

Talk: Since 2013, canagliflozin has made a significant global impact and is regarded as the major member of the gliflozins family. In order to provide a precise and trustworthy method for estimating canagliflozin individually and combining dose forms created by UV/Vis spectrophotometric method, some researchers used methanol as the diluent. Using methanol as the diluent, one of the researchers talks about two analytical techniques for the simultaneous estimate of metformin and canagliflozin. When used for routine pharmaceutical analysis, both methods demonstrate improved accuracy and repeatability. The HPLC-based bioanalytical approach is more affordable than the more complex LC-MS/MS methods. But in

contrast to HPLC methods, LC-MS/MS techniques are more selective and sensitive. According to ICH criteria, all reviewed procedures underwent validation.

Conclusion:

Talk: Since 2013, canagliflozin has made a significant global impact and is regarded as the major member of the gliflozins family. In order to provide a precise and trustworthy method for estimating canagliflozin individually and combining dose forms created by UV/Vis spectrophotometric method, some researchers used methanol as the diluent. Using methanol as the diluent, one of the researchers talks about two analytical techniques for the simultaneous estimate of metformin and canagliflozin. When used for routine pharmaceutical analysis, both methods demonstrate improved accuracy and repeatability. The HPLC-based bioanalytical approach is more affordable than the more complex LC-MS/MS methods. But in contrast to HPLC methods, LC-MS/MS techniques are more selective and sensitive. According to ICH criteria, all reviewed procedures underwent validation.

Acknowledgements:

The authors are privileged to thank the Management and Principal (Dr. Ashish Jain) of Shri D. D. Vispute College of Pharmacy & Research Center, Panvel and My husband Mr. Mayur Khinvasara for helping and motivate us to carry out this work.

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