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Canagliflozin: A Literature Review On Analytical And Bioanalytical Method

Gowri Sankar Chintapalli[1], Kriti kumari[2], Hemant kumar Panday[2], Santanu Kumar Hotta[3], Snigdha Rani Behera[4*]

[1,] Assistant professor, ARKA JAIN University, Jamshedpur, Jharkhand.
[2,] Student, ARKA JAIN University, Jamshedpur, Jharkhand.
[3]Assistant professor, College of Pharmaceutical Sciences, Mohuda, Odisha
[4*] Associate Professor, School of Pharmacy, ARKA JAIN University, Jamshedpur, Jharkhand.

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ABSTRACT

Sodium-Glucose cotransporter-2 (SGLT2) inhibitors have emerged as a promising therapeutic option for the treatment of type-II diabetes, offering a new approach to managing the disease. Various analytical techniques have been employed to analyze Canagliflozin in biological samples. Spectroscopic methods, such as chromogenic and derivative techniques, have been utilized for qualitative and quantitative analysis of Canagliflozin. High-performance liquid chromatography (HPLC) and Ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) are among the most commonly used methods for the analysis of Canagliflozin in biological matrices. This review aims to provide a comprehensive overview of the analytical methods used for the analysis of Canagliflozin. It highlights the different spectroscopic and chromatographic techniques employed, as well as the sample processing options, chromatographic/detection settings, and validation parameters used in these methods. By compiling this information in a systematic manner, this review serves as a valuable resource for analysts looking to develop and validate analytical methods for Canagliflozin and similar drugs.

Keywords: Chromogenic, UPLC-MS/MS, HPLC, Canagliflozin

1. INTRODUCTION

As pharmaceuticals developing every day, revolutionary changes are found in human health. These pharmaceuticals can be created at regular intervals to generate drugs that are devoid of contaminants. Includes bulk drugs manufacture to final product packaging and storage (degradation). Impurities are most likely to arise during transportation and storage. Therefore, in these circumstances, contaminants must be observed and quantified. Identification and quantification rely heavily on analytical instruments and techniques. Intermediate pharmaceutical analysis is a significant technique for monitoring the therapeutic process since it involves several phases such as bulk drug testing, intermediate products, drug formulations, degradation products, drug chemical stability, and drug material harmful content. Polypharmacy is now nearly universal in the management of many diabetes patients. As a result, biological sample tests, as well as quality control testing of mixed formulations, have become crucial to boosting polypharmacy treatment. High blood sugar, or hyperglycemia, is a typical sign of diabetes mellitus (DM). [1]

Type 2 diabetes mellitus (T2DM) has resurfaced as a serious non communicable disease, affecting 366 million people worldwide. With 77 million people, India is considered the epicenter of diabetes, and it is expected to reach 134 million by 2045. Sodium-glucose transporters 2 (SGLT2) inhibitors are the most recent class of anti-diabetic medications

available on the market for the treatment of T2DM. They limit the re-absorption of glucose from the blood, which is filtered by the kidneys, hence allowing glucose excretion in urine. Canagliflozin (CGZ) is the first approved member of the SGLT2 inhibitor family by the US FDA in March 2013, applicable to patients with T2DM as an addition to exercise and diet to boost glycaemic management. [2] CGZ decreases the urinary glucose threshold by blocking SGLT2 inhibitors in the proximal renal tubules, hence increasing urine glucose excretion. Furthermore, coupled with type 2 diabetes, cardiopathy is regarded to be a frequently occurring aetiology that leads to morbidity and death in persons who have the disease condition. [3, 4] The treatment of cardiovascular diseases, including blood pressure, body weight, and urine function, was approved for CGZ in 2018. CGZ outperforms cardiovascular treatment and SGLT2 inhibitors when compared to other anti-diabetic drugs used to treat type 2 diabetes. Chemically, CGZ is (2S, 3R, 4R, 5S, 6R)-2-{3-[5-[4-Fluoro-phenyl)-thiophen-2-ylmethyl]-4-methyl-phenyl}-6-hydroxymethyl-tetrahydro-pyran-3, 4, 5-triol (Figure 1), with the molecular weight of 444.52 g·mol−1 and the chemical formula C24H25FO5S. CGZ is a drug that is insoluble in water but soluble in many organic solvents such as ethanol, methanol, tetrahydrofuran, acetone, DMSO, and dimethyl formamide. [5] The main issues facing people worldwide are the threat of sickness; the impoverished's access to healthcare, and the growing expense of pharmaceuticals. It is essential to reduce the costs of research and development, as well as the manufacturing process and quality control, in order to make affordable drugs available to people all over the world who are extremely poor and prone to large epidemics. Simple, fast (to reduce analytical downtime and thus revenue), and cost-effective analytical method development is an increasing concern in the pharmaceutical industry. Precise quality control techniques are needed for the evaluation of CGZ because of its importance to the general public. One of the key goals of analytical techniques is to ensure pharmaceutical product quality. As a result, there is a need for the collection of the reported analytical techniques of CGZ.

The primary goal of this article is to provide an overview of the various methods for estimating CGZ in biologic matrix, dosage form, and API independently as well as drug combinations.

In order to accurately determine the concentration of CGZ in pharmaceutical formulations, various analytical methods have been developed and validated. There are numerous techniques for analyzing the analytes (Figure 2) including UV Spectrophotometry, Ultra-performance liquid chromatography, and high-performance thin-layer chromatography, Gas Chromatography, Spectro-fluorimetry, and Mass Spectroscopy. [6] Figure 3 represents an overview of various analytical methods for the determination of CGZ from various databases like Science Direct, Springer, PubMed, Scopus, Taylor & Francis, and Web of Science for the estimation of CGZ. Figure 4 provides the graphical representation of the number of articles published for the quantification of CGZ from the Year 2014 to 2024.

2. SPECTROSCOPIC METHODS

2.1. UV-Visible spectroscopy

It is a conventional and extremely effective analytical technique. Identifying analytes present in the sample at micro or semi-micro amounts. It focuses on detecting the effects of electromagnetic radiation interact with absorbing substances, such as atoms, molecules, or ions in the UV and/or visible spectrums It is useful for analyzing various compounds, such as biomolecular. Compounds can be inorganic or organic. The findings of these analyses are employed. It is also utilized in clinical trials, manufacturing, and research. Useful for environmental samples. Therefore, it is essential to understand about the UV-VIS spectrum and its unique characteristics. [7]

2.2. HPLC

High-Performance Liquid Chromatography (HPLC) is a leading unique separation tool utilized in many aspects of drugs production and analysis. Because HPLC is very sensitive and specific, it yields precise results. However, HPLC is commonly employed largely for two reasons: firstly, qualitative analysis of unknown mixtures, and secondly, mixture separation for subsequent analysis.The separation mode depends totally on interacting relationship between the analytes, stationary Phase, mobile Phase. [8]

2.3. HPTLC

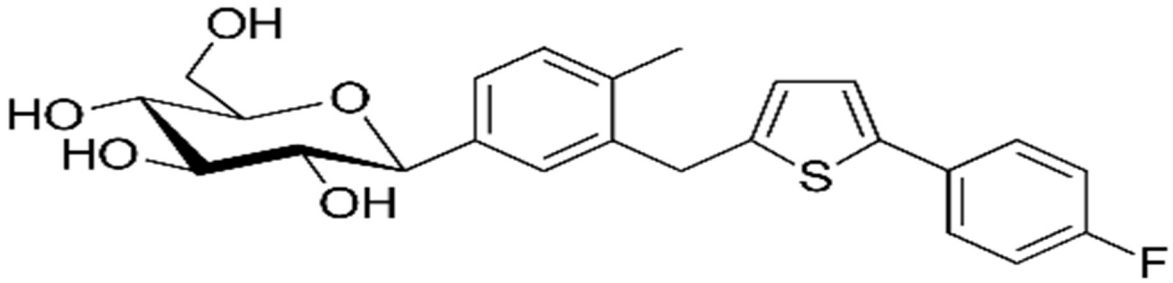
In the present period, high-performance thin-layer chromatography has evolved to provide superior separation. Greater functionality and detection limits than Gas Chromatography and HPLC. Because it is an easy adaptable analytical approach that can be utilized for both qualitative and Quantitative applications. Adsorption causes separation and partition, or each, depending on the type of adsorbents used. Plates and the development solvent system.[9]

2.4. LC/MS-MS

Liquid chromatography-mass spectrometry is the most powerful, sensitive, and selective analytical technology available. The hyphenated analytical technology known as LC-MS operates in tandem with two systems: mass spectrometry and liquid chromatography (LC)/(MS). [10] By moving through the column, the elements of HPLC (LC) separates mixtures, although it is unable to distinguish between Therefore, mass spectrometry aids in identifying the separated component unknown compounds and identify them, as well as provide helpful explanations for structures. Spectrum mixtures are quite complex due to spectra that overlap, by it; mass spectrometry isn't useful for recognizing mixes. Because of this, they are combined for greater precise outcome. Consequently, it is feasible to distinguish and ascertain simultaneous relative masses of molecules or atoms. [11]

Examples of SGLT2 inhibitors are Dapagliflozin, Canagliflozin, Empagliflozin, Ertugliflozin, Sotagliflozin, Tofogliflozin, Ipragliflozin, Luseogliflozin, Remogliflozin etabonate, Sergliflozin The details is in Tables 1. [12]

In order to assess Canagliflozin, this review paper focuses on a variety of analytical techniques, including electrochemical methods, RP-HPLC, HPTLC, UPLC-UV, LC-MS/MS, and UV/VIS Spectrophotometric methods. The information regarding the earlier research is covered in Tables 2, 3, 4, and 5.



(2S, 3R, 4R, 5S, 6R)-2-(3-(4-ethoxyphenyl)-4-ethoxyphenyl)-6-(hydroxymethyl) tetrahydro-2H-pyran-3, 4, 5-triol
Figure 1: Chemical structure and IUPAC name of Canagliflozin

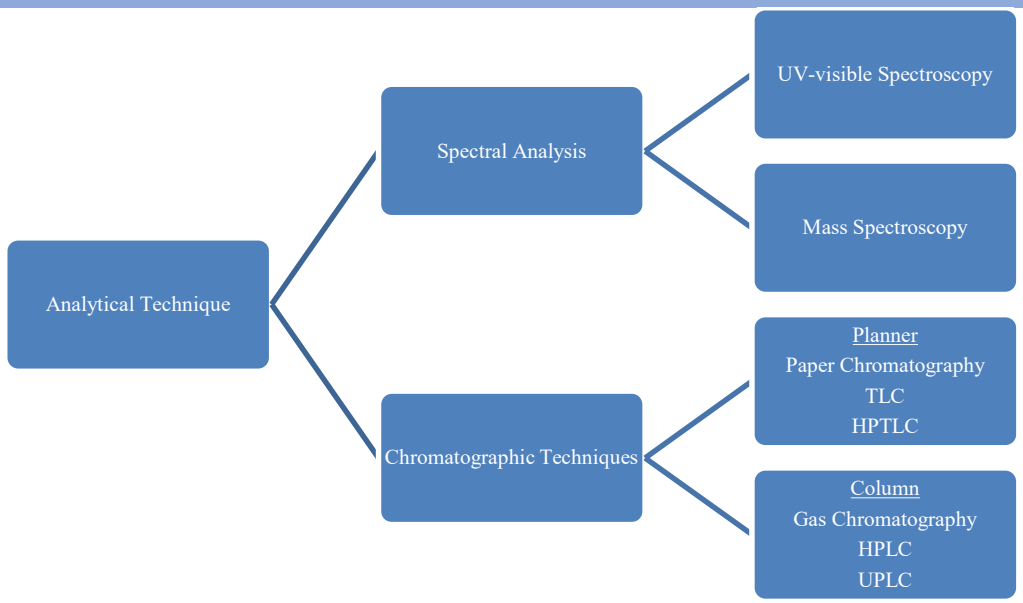


Fig. 2: Flowchart of analytical techniques

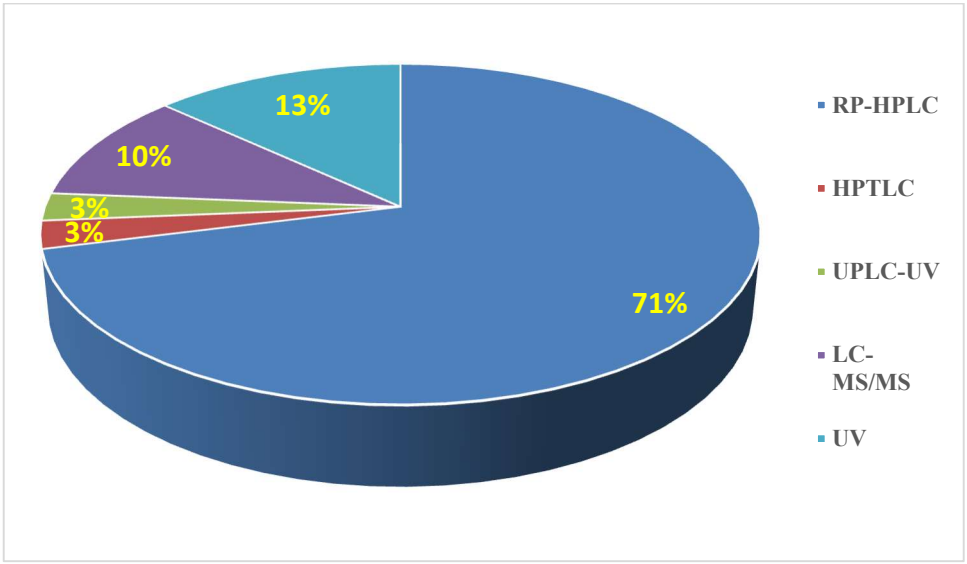


Figure 3: Analytical methods for the estimation of CGZ.

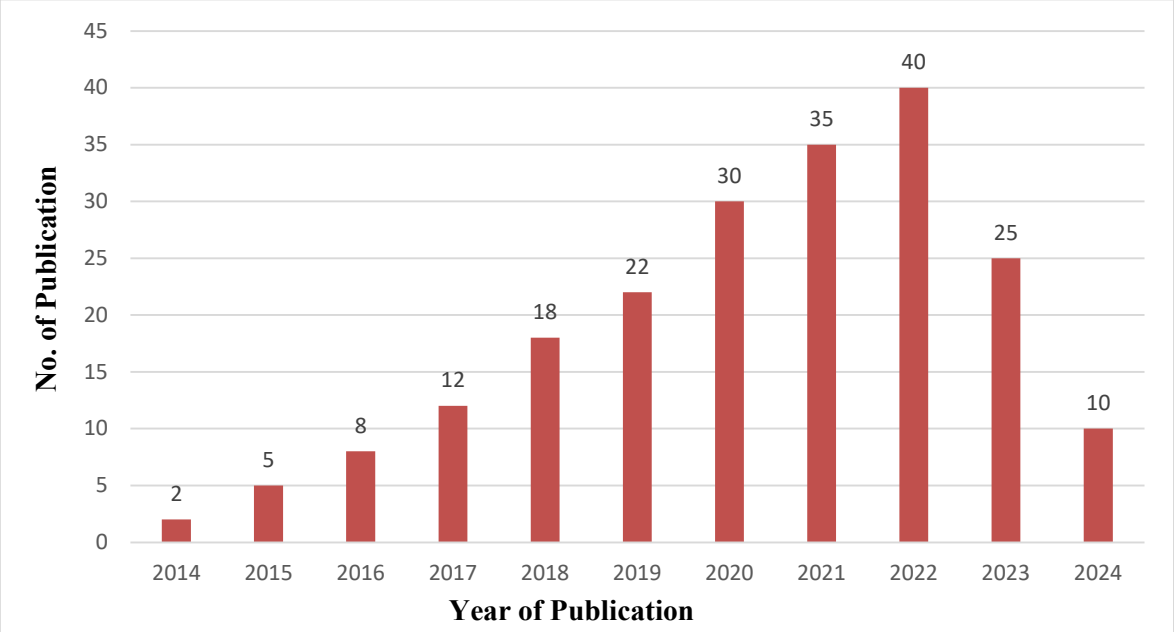
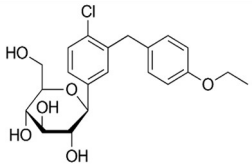
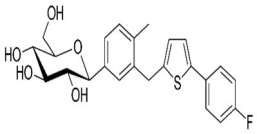
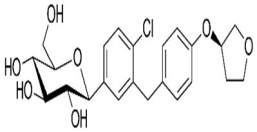


Figure 4: Number of analytical methods reported during 2014–2024. Database sources: ScienceDirect, Springer, PubMed, Scopus, Taylor & Francis, and Web of Science.

Table 1: Structure wise classification of Gliflozin derivatives

Drug	Structure	IUPAC Name	Molecular Weight	Solubility	Year (Country) Approved
Dapagliflozin		(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl) phenyl)-6-(methylthio) tetrahydro-2H-pyran-3,4,5-triol	408.73 g/mol	Water	2012 (EU), 2014 (USA), 2014 (Japan)
Canagliflozin		(2S,3R,4R,5S,6R)-2-(3-(4-ethoxyphenyl)-4-ethoxyphenyl)-6-(hydroxymethyl) tetrahydro-2H-pyran-3,4,5-triol	444.52 g/mol	Ethanol	2013 (USA), 2014 (EU), 2014 (Japan)
Empagliflozin		(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxyphenyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol	450.91 g/mol	Methanol	2014 (EU), 2014 (USA), 2015 (Japan)

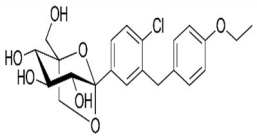
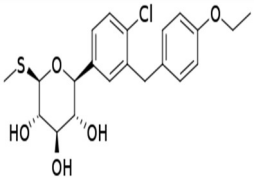
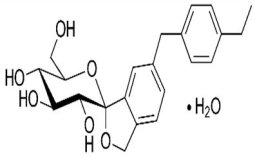
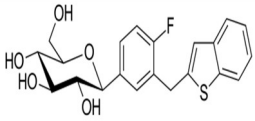
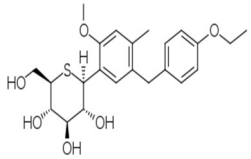
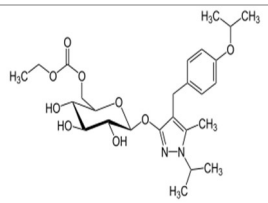
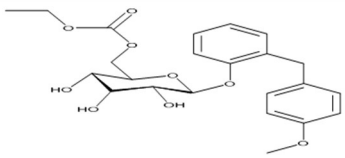
Ertugliflozin		(2S,3R,4R,5S,6R)-2-(3-(4-ethoxyphenyl)-4-ethoxyphenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol	436.89 g/mol	Acetonitrile	2017 (USA), 2017 (EU)
Sotagliflozin		(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol	424.94 g/mol	Water	2019 (USA)
Tofogliflozin		(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol	404.459 g/mol	Ethanol	2014 (Japan)
Ipragliflozin		(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol	404.45 g/mol	Methanol	2014 (Japan)
Luseoliflozin		(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol	434.55 g/mol	Acetonitrile	2014 (Japan)
Remogliflozin etabonate		(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol	462.55 g/mol	Water	2019 (India)
Sergliflozin etabonate		2-(4-methoxybenzyl)phenyl 6-O-(ethoxycarbonyl)-β-D-glucopyranoside	448.468 g/mol	Dimethyl sulfoxide (DMSO)	–

Table 2: Summary of methods related to RP-HPLC technique

Sl No.	Matrix	Method	Stationary Phase (column)	Mobile Phase (v/v)	pH	Wavelength (nm)	Flow rate (ml/min)	Reference
01	Canagliflozin	RP-HPLC	ODS (4.6×150mm, 5µ)	Water, Acetonitrile (55:45)	3.6	214	1.0	13

02	Canagliflozin	RP-HPLC	Hypersil BDS, C_{18}(100×4.6mm, 5µ)	0.1% Orthophosphoric Buffer and Acetonitrile (53:47)	-	240	1.1	14
03	Canagliflozin & Metformin	RP-HPLC	C_{18} Hypersil, (150*4.6mm ,3µ)	Phosphate buffer & Methanol (60:40)	3.6	357	1.0	15
04	Canagliflozin in Bulk	HPLC	Neosphere C_{18} (150*4.6 mm ,3.5 µm)	Water, Acetonitrile (50:50)	4.5	291	1.0	16
05	Bulk & Pharmaceutical Dosage form	RP-HPLC	C_{18} (250*4.6 mm, 5 µ)	Phosphate buffer & Acetonitrile (60:40)	5.0	290	1.0	17
06	Canagliflozin & Metformin	RP-HPLC	Agilent C_{18} (10*4.6 mm, 5 µm)	Methanol & Water (35:65)	3.0	245	0.7	18
07	Pharmaceutical Dosage form	RP-HPLC	C_{18}(250*4.6 mm, 5 µm)	Methanol & Water (80:20)	-	254	1.0	19
08	Canagliflozin & Metformin	RP-HPLC	Kromasil C_{18} (250×4.6mm,5µm)	Acetonitrile, Buffer & Methanol (52:38:10)	4.2	254	1.0	20
09	Canagliflozin	RP-HPLC	C_{18} (150×4.6mm,5µm)	Acetonitrile & Water (30:70)	-	264	1.0	21
10	Bulk & Pharmaceutical Dosage Form	RP-HPLC	Inertsil C_{18}(250×4.6mm, 5µ)	Acetonitrile, & Methanol (40:60)	-	254	1.2	22
11	Canagliflozin	RP-HPLC	C_{18}(250×4.6mm, 5µ)	Methanol & Water (90:10)	-	290	0.9	23
12	Canagliflozin	RP-HPLC	C_{18}(250×4.6mm, 5µm)	Methanol & Phosphate (65:45)	4	293	1.0	24
13	Canagliflozin & Metformin	RP-HPLC	WATER's (250×4.6mm,5µm)	0.1% OPA & Methanol (60:40)	-	273	0.5	25
14	Bulk & Pharmaceutical Dosage Form	RP-HPLC	ODS-3 (250×4.6mm,5µ)	0.02% Formic acid & Acetonitrile (40:60)	-	230	1.2	26

15	Bulk & Pharmaceutical Dosage Form	RP-HPLC	Agilent Eclipse plus C_8 (150×4.6mm,5µm)	Acetonitrile & Trifluoroacetic acid buffer (45:55)	-	290	1.0	27
16	Canagliflozin & Metformin	RP-HPLC	C_{18}(250×4.6mm, 5µm)	Acetonitrile & Posphate buffer(60:40)	5.0	290	1.0	28
17	Canagliflozin	RP-HPLC	C_{18}(250×4.6mm, 5µm)	Acetonitrile & Water (53:47)	-	214	1.0	29
18	Canagliflozin	RP-HPLC	C_{18}(250×4.6mm, 5µm Phenomenex)	0.1% Acetonitrile & Sodium acetate buffer (20:80)	4.6	291	1.0	30
19	Canagliflozin & Metformin	RP-HPLC	C_{18} Cosmosil (250×4.6mm,5µ)	Water & Methanol (50:50)	3.0	254	1.0	31
20	Canagliflozin	RP-HPLC	C_{18} (250×4.6mm, 5µ)	Methanol, Acetonitrile & 0.1% Ammonium acetate (40:40:20)	-	290	1.0	32
21	Biological sample	RP-HPLC	SPURSIL ODS C_{18} (150×4.6mm, 3µm)	Buffer & Acetonitrile (85:15)	-	254	1.0	33
22	Pharmaceutical dosage form	HPLC	C_{18} (100×4.6mm, 5µm)	Acetonitrile & Water (50:50)	2.5	269	1.0	34
23	Canagliflozin	RP-HPLC	INTERTSIL C_{18} (150×4.6mm,5µm)	Methanol, Acetonitrile & water (30:50:20)	-	250	-	35
24	Canagliflozin & Metformin	RP-HPLC	Intertsil ODS 3V C_{18}(150×4.6mm, 5µm)	Dipotassium phosphate+ Sodium phosphate, Acetonitrile & methanol(40:40:20)	5.0	251	1.0 ml/min	36
25	Canagliflozin	RP-HPLC	MICSIL 100 C_{18} (250*4.6mm, 5µm)	Acetonitrile & Water (70:30)	3.0	282	Ultra violet / 1.0 ml/min	37
26	Canagliflozin	RP-HPLC	C_{18}	Acetonitrile : & Phosphoric acid Buffer (50:50)	7.0	290	1.5 ml/min	38

27	Canagliflozin	HPLC	Supelcosil C_{18}(250 × 4.6 mm , 5µm)	0.2% v/v of trifluoroacetic acid in water and acetonitrile (80:20)	-	290	1.0 ml/min	39

Table 3: Summary of methods related to HPTLC method

Sl No.	Matrix	Method	Stationary Phase (column)	Mobile Phase (v/v)	Saturation time	Wavelength (nm)	Lamp	Reference
01	Canagliflozin	HP-TLC	Precoated Silica gel 60 F_{254} aluminium plate (20×10cm, 0.2mm thick)	Toluene, Ethyl acetate & Methanol (2:2:1)	30 mins	290	Deuterium	40

Table 4: Summary of methods related to UPLC-UV method

Sl. no	Matrix	Method	Stationary Phase (Column)	Mobile Phase (v/v)	pH	Wavelength	Detector / flow rate	Reference
01	Canagliflozin & Metformin (Combined)	UPLC-UV	Hypersil gold (50×2.1mm, 19µm)	Methanol & 0.03M Phosphate buffer (80:20)	3.5	240	0.4ml/min	41

Table 5: Summary of methods related to LC-MS/MS technique

Sl.no	Matrix	Method	Stationary Phase (Column)	Mobile Phase	pH	Temperature	flow rate	Reference
01	Human Plasma	LC-MS/MS	C_{18}	Methanol, Phosphate buffer (40:60)	2.5	25	1.0 ml/min	42
02	Canagliflozin	LC-MS/MS	C_{18} (250×4.6mm5µm)	Acetonitrile & Water (70:30)	3.0	25	1.0 ml/min	43
03	Healthy Rabbit	LC-MS/MS	Inertsil ODS C_{18} (50*4.6mm, 5µm)	0.01M Ammonium acetate &Methanol (30:70)	-	40	0.8 ml/min	44

04	Human Plasma	LC-MS/MS	Zorbax XDB Phenyl (75×4.6mm, 3.5mm)	Methanol & Acetate buffer (80:20)	-	-	1.0 ml/min	45

Table 6: Summery of Analysis of Canagliflozin by UV-Spectroscopy methods.

Sl.no	Matrix	Method	Description	Reference
01	Canagliflozin & Metformin	UV-Spectroscopy	Detection wavelength : Canagliflozin 319nm & metformin 240nm Linearity range: Canagliflozin 10-30µg/ml & metformin 4-12µg/ml Recovery range: close to 100% Co-relation coefficient: Canagliflozin 0.9995 & metformin 0.9997 LOD & LOQ value Canagliflozin 0.3325, 1.0076 & metformin 0.10431, 0.3161 RSD : <2%	46
02	Canagliflozin	UV-Spectroscopy	Detection wavelength : 224nm Linearity range: 10-60µg/ml Recovery range: 99.82 -100.09% Co-relation coefficient: 0.999 LOD 0.333µg/ml & LOQ 1.00µg/ml RSD : <2%	47
03	Canagliflozin & Metformin	UV-Spectroscopy	Detection wavelength : Canagliflozin 290nm & metformin 236nm Linearity range: Canagliflozin 2.5-15µg/ml & metformin 5-17.5µg/ml Recovery range: Canagliflozin 99.43% & metformin 98.82% Co-relation coefficient: 0.999 LOD & LOQ value Canagliflozin 0.43, 1.31 & metformin 0.49, 1.49 RSD : <2%	48
04	Canagliflozin	UV-Spectroscopy	Detection wavelength/ Linearity range: 5-40µg/ml Recovery range: 100.033% Co-relation coefficient: 0.9936 LOD 2.38µg/ml & LOQ 7.24µg/ml RSD : <2%	49
05	Canagliflozin & Metformin	UV-Spectroscopy	Detection wavelength : Canagliflozin 290nm & metformin 232nm	50

			Linearity range: Canagliflozin 8-12µg/ml & metformin 40-60µg/ml Recovery range: close to 100% Co-relation coefficient: Canagliflozin 0.9977 & metformin 0.9889 LOD & LOQ value : - RSD : <2%	

QUALITY BY DESIGN

Currently, the Quality by Design technique is widely used to enhance analytical methods. Quality by design (QBD), as discussed in ICH Q8, Q9, and Q2, is well established in the pharmaceutical manufacturing and development processes. It aids in the development of a robust method so that sources of variability can be effectively reduced. The success of transferring a method from the research level to the quality control department is higher. This approach allows for the development of new techniques by continuously improving throughout the lifecycle. [51].

CONCLUSION

In conclusion, the review of Spectrophotometric and Chromatographic methods for the estimation of Canagliflozin has shown that there are various reliable and accurate methods available for the analysis of this drug. A survey of current literature revealed that there are numerous spectroscopic and chromatographic approaches available for the investigation of CGZ. These methods have been developed for both single component formulations as well as combination formulations, with the most common combination being Canagliflozin with Metformin. The use of different mobile phases and solvents in these methods has been found to be effective in providing good resolution and retention times. it was observed that the mobile phase used in most of the studies consist of a combination of phosphate buffer, methanol, and acetonitrile. This combination of solvents was found to provide better resolution and separation of CGZ from other components in the sample. Additionally, a flow rate of 1.0 ml/min was commonly used to achieve optimal retention time in the chromatographic analysis.

On the other hand, for Spectroscopic methods, Methanol was found to be the common solvent used for the analysis of CGZ. Overall, the methods reviewed in this study have been shown to be uncomplicated, accurate, economic, precise, and reproducible in nature, making them suitable for routine analysis of CGZ in pharmaceutical formulations. The Spectrophotometric and Chromatographic methods reviewed in this study have proven to be effective in the estimation of CGZ. These methods offer a reliable and accurate means of determining the concentration of CGZ in pharmaceutical formulations, making them valuable tools for quality control and regulatory compliance in the pharmaceutical industry. By utilizing these methods, researchers and analysts can confidently determine the concentration of Canagliflozin in various samples, leading to a better understanding of its pharmacokinetics and pharmacodynamic. These methods offer a reliable and accurate means of analyzing this drug, allowing for better quality control and research in the field of diabetes management. Further research and validation of these methods may lead to even more advanced techniques for the analysis of Canagliflozin and other pharmaceutical compounds.

DATA AVAILABILITY

Not declared.

CONFLICT OF INTEREST

The authors affirm that they have no conflict of interest.

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