Advances in Bioresearch
Adv. Biores., Vol 14 (1) January 2023: 52-60

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.14.1.5260

Advances in Bioresearch

REVIEW ARTICLE

Quantitative Determination of Novel SGLT2 Inhibitors Used in Treatment of Diabetes

Deepanti Gajjar*1, Dimalkumar A. Shah2

1. Research Scholar, Gujarat Technological University, Ahmedabad and Assistant Professor, Department of Quality Assurance, Parul Institute of Pharmacy & Research, Parul University, Vadodadra, Gujarat, India
2. Indukaka Ipcowala College of Pharmacy, (A Constituent College of CVM University), New Vallabh Vidyanagar, Anand, Gujarat, India

Email Id: gajjardeep@gmail.com

ABSTRACT

Analytical method development and validation are critical components of drug discovery because they are a continuous and interdependent task associated with pharmaceutical development and manufacturing. Method development is the process of demonstrating that an analytical method is suitable for measuring the concentration of an API in a specific compounded dosage form, allowing for the use of simplified procedures to verify that an analysis procedure accurately and consistently delivers a reliable measurement of an active ingredient in a compounded preparation. Effective method development and validation can result in significant increases in precision and a decrease in bias errors. Additionally, it can assist in avoiding costly and time-consuming exercises. Remogliflozin Etabonate, Dapagliflozin, Empagliflozin, and Canagliflozin are a new class of drugs for the treatment of type 2 diabetes mellitus. They have a novel mechanism of action and were recently approved by the US Food and Drug Administration for use in type 2 diabetes mellitus, either alone or in combination with other oral hypoglycemic agents and insulin. The purpose of this review is to discuss the quantitative determination of novel SGLT2 inhibitors using various analytical methods developed for novel drugs in bulk and pharmaceutical preparations alone or in combination with other hypoglycemic agents.

Key Words: *Remogliflozin Etabonate, Dapagliflozin, HPLC, HPTLC, LC-MS/MS.*

Received 14.09.2022 Revised 30.10.2021 Accepted 21.12.2022

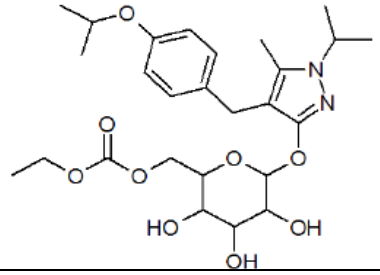
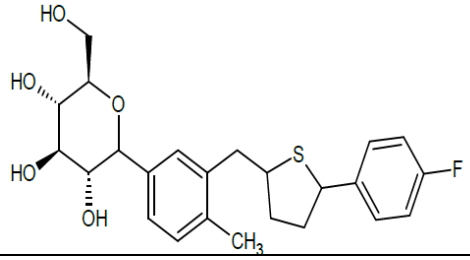
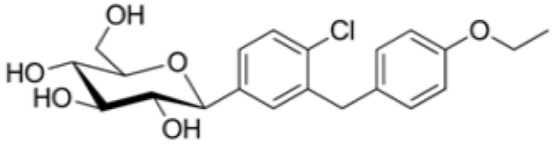
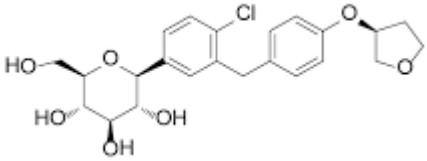
How to cite this article:
Deepanti G, Dimalkumar A. S. Quantitative Determination of Novel SGLT2 Inhibitors Used in Treatment of Diabetes. Adv. Biores. Vol 14 [1] January 2023. 52-60

INTRODUCTION

Type 2 diabetes mellitus is a cardio-renal-metabolic disorder which is commonly associated with a range of comorbid conditions including heart failure (HF), atherosclerotic cardiovascular disease (ASCVD), and chronic kidney disease (CKD). Because treating multiple comorbidities in patients with T2DM may result in polypharmacy and, as a result, an increased risk of adverse events, clinicians are interested in three medications that treat various illnesses. One such medication class is sodium-glucose co-transporter-2 (SGLT2) inhibitors.

The first four SGLT 2 inhibitors are dapagliflozin, canagliflozin, ertugliflozin and empagliflozin. Canagliflozin is the first of the four SGLT 2 inhibitors to receive FDA approval in the United States for use in individuals with T2DM in combination with diet and exercise to help control blood glucose levels. By blocking the SGLT-2-mediated uptake of glucose from proximal renal tubules, these medications were originally designed to improve renal glucose handling and manage hyperglycemia. [1]

Table 1: Structure of Drugs

Drug	Structure
Remogliflozin	
Canagliflozin	
Dapagliflozin	
Empagliflozin	

MECHANISM OF ACTION

SGLT2 inhibitors help to reduce hyperglycemia by blocking SGLT2, a high-capacity, low-affinity transporter found in the early portion of the proximal renal tubule. In normal conditions, SGLT2 is responsible for reabsorption of 90% of the glucose filtered at the glomerulus. SGLT1, which is found in the distal section of the proximal convoluted tubule, transports the remainder back into the systemic circulation. Because SGLT1, a low-capacity, high-affinity transporter, cannot reabsorb all of the filtered glucose, SGLT2 blockage results in glycosuria and a drop in blood glucose levels. SGLT2 inhibitors, on the other hand, only reduce renal glucose absorptive capacity by up to 50% due to physiological changes that occur in response to their administration. [1]

Analytical methods for determination of Remogliflozin:

Dimal et al. developed and validated an RPLC method for estimating RemogliflozinEtabonate in API and tablet formulation. A reverse phase C18 column served as the stationary phase. The mobile phase was a 70:30 v/v mixture of methanol and water. With a wavelength of 229 nm, the flow rate was 1 mL/min. According to the ICH guidelines, the method was validated for linearity, accuracy, precision, and robustness. With a correlation value (r2) of 0.997, the technique was linear in the concentration range of 1 – 25 g/mL. The deteriorated product's peak was distinguished from the pure drug's peak by a significant difference in retention time value. The drug was also discovered to be extremely susceptible to acid and base hydrolysis. [2]

Vidhi *et al*. carried out another study in which she developed and validated a precise, simple, and sensitive Spectrophotometry method for estimating RemogliflozinEtabonate in API and tablet dosage forms. In the 2-10 g/ml range, the substance has a maximum absorbance of 229 nm and follows Beer's law. The correlation coefficient was calculated as 0.9990. For interday and intraday precision, standard deviations for three concentrations and three replicates range from 0.050 percent to 0.254 percent and 0.058 percent to 0.258 percent, respectively. The recovery percentage was found to be between 98.94 and 99.86 percent. The LOD and LOQ were 0.037g/ml and 0.113g/ml, respectively. [3]

Itigimatha *et al.* developed and validated a straightforward, novel, and selective RP-HPLC and UV spectroscopy method for determining RemogliflozinEtabonate in bulk and dosage forms. The stationary phase was a C18 Kromasil column, and the mobile phase was a 50:45:05 ratio of 0.02 M ammonium acetate buffer, acetonitrile, and tetrahydrofuran (THF). The flow rate was 2.0 mL/min, and the wavelength was measured to be 228 nm. For UV spectroscopic analysis, remogliflozin was diluted with ethanol and showed maximum absorption at 228 nm. The RP-HPLC method had a linearity range of 10 g/mL to 50 g/mL, whereas the UV spectroscopic method had a linearity range of 100 to 250 g/mL. For both techniques, the regression coefficients (R2) were found to be greater than 0.999. [4]

Dimal et al. developed a high-performance thin-layer chromatographic (HPTLC) method for estimating RemogliflozinEtabonate in tablet formulation that indicates stability. The stationary phase consisted of silica gel 60 F254 precoated HPTLC plates; the mobile phase consisted of methanol, ethyl acetate, toluene, and NH3 (2:4:4:0.1, v/v/v); and densitometric estimation was performed in reflectance mode at 229 nm. The technique was found to be linear in the 500–8000 ng/band range. The Rf value of the drug was discovered to be 0.61. The drug was also subjected to forced degradation tests, which revealed that it was particularly susceptible to acid, base hydrolysis, and oxidative stress degradation. [5]

Tushar *et al.* developed and validated an RP-HPLC technique for the determination of RemogliflozinEtabonate in bulk and pharmaceutical dosage form. The samples were separated using Agilent technology HPLC. Column Agilent C18 (250mm x 4.6mm) In the Mobile Phase, methanol:0.1 percent orthophosphoric acid (80:20 percent v/v) was used. At a flow rate of 0.9ml/min, the analytes were detected at a maximum wavelength of 227 nm. Remogliflozinetabonate had a retention time of 4.881 minutes. The linearity range was determined to be (10–60g/ml), and the LOD and LOQ values were determined to be 0.2201 and 0.6669 g/ml, respectively. The accuracy's relative standard deviation was found to be less than 2%. The average recovery percentage ranged between 99.50 and 100.12 percent. Experiments on forced degradation were conducted using 0.01N NaOH, 1.0N HCl, and 3% H2O2. The greatest deprivation was observed at the fundamental condition, namely NaOH (5.06%), followed by HCl (4.71%), H_2O_2 (4.04%), and Thermal (5.45). [6]

Analytical Methods for determination of Dapagliflozin: [7-38]

Table 2: **Analytical Methods for determination of Dapagliflozin**

Sr. No.	Sample Matrix	Analytical method	Method description
1.	Bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 **Mobile phase:** Methanol:acetonitrile: orthophosphoric acid (75:20:5) **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 246nm
2.	Bulk & tablet dosage form	RP-HPLC	**Stationary phase:** BDS Coloumn **Mobile phase:** Orthophosphoricacid:acetonitrile (45:55) **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 254nm
3.	Bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 Coloumn **Mobile phase:** Acetonitrile:water acidified with 0.1% formic acid **(**42:58) **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 254nm
4.	Bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 Column **Mobile phase:** Acetonitrile:di-potassiumhydrogen phosphate at pH-6.5 maintained with ortho phosphoric acid **(**40:60) **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 222nm
5.	Bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 Column **Mobile phase:** Phosphate buffer: acetonitrile (60:40) **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 237nm
6.	Bulk & tablet dosage form	RP-HPLC	**Stationary phase:** BDS Column **Mobile phase:** 0.1% orthophosphoric acid buffer and acetonitrile 50:50 **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 245nm

7.	Bulk & tablet dosage form	RP-HPLC	**Statonary phase:** C-18 Column **Mobile phase:** Methanol: sodium 1-octanesulphonate (70:3) **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 203nm
8.	Bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 Column **Mobile phase:** Acetonitrile:di-potassium hydrogen phosphate at pH-6.5 maintained with OPA **(**40:60) **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 222nm
9.	Dapagliflozin & Metformin in bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 Column **Mobile phase:** 0.1% ortho phosphoric acid at pH 6.5 with triethylamine: acetonitrile (50:50) **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 240nm
10.	Dapagliflozin & Metformin in bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 Column **Mobile phase:** Phosphate buffer at pH 6.5:methanol:acetonitrile 50:30:20 **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 240nm
11.	Dapagliflozin& Metformin in bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 Column **Mobile phase:** Acetonitrile: water **(**75:25) **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 285nm
12.	Dapagliflozin& Metformin in bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 Column **Mobile phase:** 0.05M potassium dihydrogenortho phosphate buffer (pH-3.5, adjusted with 0.1% orthophosphoric acid): acetonitrile 50:50 **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 227nm
13.	Dapagliflozin & saxagliptin in bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 Column **Mobile phase:** Phosphate buffer at pH 4 and acetonitrile (50:50) **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 225nm
14.	Dapagliflozin&saxagliptin in bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 Column **Mobile phase:** Potassium dihydrogen phosphate buffer at pH 6 :acetonitrile (45:55) **Flow Rate:** 1.5 mL/min **Detection Wavelength:** 220nm
15.	Dapagliflozin&saxagliptin in bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 Column **Mobile phase:** 20 mM sodium dihydrogen phosphate (pH 5.5 ± 0.02 with orthophosphoric acid acetonitrile (53:47) **Flow Rate:** 1.2 mL/min **Detection Wavelength:** 230nm
16.	Dapagliflozin& glimepiride in bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 Column **Mobile phase:** Acetonitrile:10% orthophosphoric acid in water at pH 6 **(**70:30) **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 228nm
17.	Dapagliflozin in bulk & tablet dosage form	RP-HPLC	**Stationary phase:** BDS Column **Mobile phase:** Orthophosphoricacid:acetonitrile (60:40) **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 245nm
18.	Dapagliflozin in bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 Column **Mobile phase:** Acetonitrile: 0.1% triethylamine (pH-5) in the ratio of 50:50 **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 224nm

19.	Dapagliflozin in bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 Column **Mobile phase:** Phosphate buffer:methanol (35:65) **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 215nm
20.	Dapagliflozin in bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 Column **Mobile phase:** Potassium hydrogen orthophosphate (pH-4.2):methanol **(**65:35) **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 225nm
21.	Dapagliflozin, Canagliflozin, Empagliflozin& Metformin in combination	RP-HPLC	**Stationary phase:** C-18 Column **Mobile phase:** Acetonitrile: 0.05M di-potassium hydrogen phosphate at pH-4 **(**65:35) **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 212nm
22.	Dapagliflozin, & Metformin in bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 Column **Mobile phase:** Acetonitrile: 0.1M orthophosphoric acid (70:30) **Flow Rate:** 1.0 mL/min **Detection Wavelength:** 260nm
23.	Dapagliflozin, & Metformin in bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 Column **Mobile phase:** 0.1M dipotassium hydrogen phosphate:acetonitrile:methanol (60:30:10) **Flow Rate:** 1.2 mL/min **Detection Wavelength:** 285nm
24.	Dapagliflozin&Sexagliptin in bulk & tablet dosage form	UPLC	**Stationary phase:** C-18 Column **Mobile phase:** 0.1% orthophosphoric acid (40) :acetonitrile (60) **Flow Rate:** 0.3 mL/min **Detection Wavelength:** 254nm
25.	Dapagliflozin in bulk & tablet dosage form	RP-HPLC	**Stationary phase:** C-18 Column **Mobile phase:** Methanol: water **(**80:20% v/v) **Flow Rate:** 0.8 mL/min **Detection Wavelength:** 225nm
26.	Dapagliflozin in tablet dosage form	UV	**UV-Spectrophotometer :** Jasco V-630 and Shimadzu-1700 double beam **Solvent:** Methanol **Detection Wavelength:** 224nm
27.	Dapagliflozin in Bulk & Pharmaceutical Dosage form	UV	**UV-Spectrophotometer :** UV-1700 Pharmaspec, Schimadzu **Solvent:** 1:1 solution of Ethanol: Phosphate Buffer Solution (pH 7.2) **Detection Wavelength:** 233.65nm
28.	Dapalgliflozin Blood Plasma	UV	**UV-Spectrophotometer :** Shimadzu1800UV**-**visible spectrophotometer, **Solvent:** Blood sample **Detection Wavelength:** 224nm
29.	Dapagliflozin in bulk and tablet dosage form	HPTLC	**Stationary phase:** Merck TLC plates Silica gel 60F (10 x10 cm) **Mobile phase**:Chloroform: Methanol in the ratio of 9:1v/v **Detection Wavelength:** 223nm

Analytical Methods for determination of Canagliflozin:

M. Suma et al. developed and validated a simple and sensitive reverse phase high performance liquid chromatography method for the estimation of canagliflozin in tablet dosage form. Chromatographic conditions included an ODS column (4.6 x 150mm, particle size 5), water and acetonitrile (55:45v/v) as mobile phases, and a flow rate of 1.0 ml/min. After that, the eluent was detected at 214 nm. The study was conducted in accordance with ICH guidelines and the method is suitable for routine quality control of canagliflozin in laboratories and industries due to its speed, accuracy, precision, and sensitivity. [39]

Suneetha A et al. developed and validated a method for estimating canagliflozin's specificity, selectivity, linearity, accuracy, precision, and robustness in bulk and tablet dosage forms according to ICH guidelines.

The separation was accomplished using a Hypersil BDS column as the stationary phase, 0.1 percent orthophosphoric buffer and acetonitrile (53:47) as the mobile phase, and water and aetonitrile (50:50) as the diluent in isocratic mode. A flow rate of 1.1ml/min was optimised to detect the 240 nm wavelength. The assay method was found to be linear between 75 and 450 g/ml, with a correlation coefficient (r2) of 0.9999. The percentage recovery of the active ingredient in tablet dosage form was 99.83-100.27 percent. [40].

Ishpreet *et al*. developed and validated a UV spectrometric method for determining the stability of canagliflozin in bulk and pharmaceutical dosage form in accordance with ICH guidelines. Canagliflozin was analysed in degradation products and its linearity, precision, repeatability, limit of detection (LOD), limit of quantification (LOQ), accuracy, robustness, and ruggedness were all validated. The study lasted two hours and used methanol and distilled water as solvents. The drug exhibited a maximum absorbance at 290nm, which was consistent with Beer's law at concentrations of 5-10 mcg/mL.Canagliflozin tablets (INVOKANA®) were found to be more than 99 percent pure and to degrade in acid, alkaline, hydrogen peroxide, and photolytic conditions, but remained thermally stable. The amount of drug degraded was determined by measuring the absorbance at 290 nm. [41]

S. D'souza *et al*. developed and validated an easy, accurate, precise, and time-efficient RP-HPLC method for simultaneous estimation of metformin hydrochloride and canagliflozin. Chromatography was performed using a Grace Smart RP-18 column (250 4.6mm, 5) at a temperature of 30°C. As mobile phase, a mixture of acetonitrile (ACN) and ammonium acetate buffer in the ratio 45:55v/v at pH 4.5 was used at a flow rate of 1ml/min. It was detected at 252 nm using a photo diode array detector. The developed method was found to be linear, with correlation coefficients of 0.9993 and 0.9992 for metformin hydrochloride and canagliflozin, respectively, over the concentration range of 1-80g/ml. Stability studies were conducted on the drugs by subjecting them to acidic, basic, oxidative, thermal, and photolytic stress conditions and separating the drug peak from the degraded product peak. [42]

Marella V *et al.* developed a novel validated RP-HPLC method for the estimation of canagliflozin in bulk and pharmaceutical dosage forms that is simple, specific, and accurate. The separation was accomplished using intersil ODS-3 (250X4.6mm, 5) as the stationary phase and 0.02 percent formic acid: acetonitrile (40:60) as the mobile phase at a flow rate of 1.2 ml/min, with the eluents detected at 230 nm. The linearity was determined to be between 10 and 50g/ml, the coefficient of regression was (R2=0.999), and the assay percentage was determined to be 98.2 percent. [43]

Mohammad Tarikul Islam Bossunia et al. developed and validated a Quality-By-Design Approach for Stability Indicating RP-HPLC Method for Canagliflozin API Estimation. The stationary phase was Kromasil C18, 250 mm x 4.6 mm, 5; the mobile phase was Acetonitrile: 0.1 percent solution of Phosphoric acid (50:50); and the eluent was detected at 290 nm. [44]

Gaware D et al. developed a novel RP-HPLC method for determining the stability of Metformin and Canagliflozin in bulk and pharmaceutical dosage form. The stationary phase was a Kromosil C18 250 column, and the mobile phase was a 65:35 percent v/v mixture of phosphate buffer and acetonitrile maintained at a flow rate of 1.0ml/min. The method was linear in the concentration ranges of 50-300g/ml for Metformin and 5-30g/ml for Canagliflozin, respectively. The LOD and LOQ were determined to be 0.30g/ml and 0.91g/ml for Metformin, and 0.361g/ml and 1.094g/ml for Canagliflozin, respectively, indicating the method's sensitivity. [45]

Uttam et al. described a novel approach for developing and validating a rapid isocratic RP-HPLC method for concurrent estimation of Metformin and Canagliflozin in bulk and pharmaceutical dosage forms using forced degradation studies. The separation was carried out using a Kromasil C18 column (250mm4.6mm, 5mm particle size) as stationary phase and a mobile phase of 0.01M Ammonium acetate (pH 3.5 adjusted with orthophosphoric acid) and Acetonitrile (65:35, v/v). The flow rate was 1ml/min, and detection occurred at a wavelength of 254nm. Correlation coefficients (r2=0.999) were obtained between 50 and 300 g/ml for Metformin Hydrochloride and 530 g/ml for Canagliflozin. Parameters for validation were evaluated in accordance with the (ICH) Q2 R1 guidelines. Forced degradation experiments were conducted using HCl, NaOH, H2O2, thermal, UV, and water. Metformin Hydrochloride and Canagliflozin were both highly susceptible to oxidative degradation. [46]

Zaghary et al. developed a novel HPLC-UV method (method A) for the simultaneous determination of metformin (MET) and canagliflozin (CANA) in their tablet combination and compared it to another novel UPLC-UV method (method B). In terms of accuracy and precision, method A achieved 99.810.73 and 99.370.54 for CANA and MET, respectively, while method B achieved 99.471.03 and 99.730.89 for CANA and MET, respectively. Precision was determined to be less than 2% for three concentrations analysed three times. Although both methods are convenient for quality laboratories, the UPLC method had the advantage of shorter run times and increased sensitivity. [47]

CONCLUSION

The determination of RemogliflozinEtabonate, Dapagliflozin, and Canagliflozin has been reported using a number of different methods. On this page, you will find references to some articles that discuss the determination of RemogliflozinEtabonate, Dapagliflozin, and Canagliflozin in pharmaceutical dosage forms, either alone or in combination with metformin. According to a review of the literature, a variety of UV-VIS Spectroscopic, bioanalytical, RP-HPLC, and HPTLC methods have been developed and reported. The published methods have been validated for a variety of parameters in accordance with ICH guidelines.

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