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ANALYTICAL AND BIOANALYTICAL METHODS FOR ESTIMATION OF ERTUGLIFLOZIN ALONE AND IN COMBINATION: A COMPREHENSIVE REVIEW

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ABSTRACT

Sodium-Glucose cotransporter-2 (SGLT2) inhibitors are an emerging therapeutic prospective for treating type-II diabetes and have revolutionized the concept of diabetes management. This review work compiles information from previously published techniques for analyzing Ertugliflozin either alone or infusing with other drugs. Several spectroscopic methods such as chromogenic technique and derivative technique have been used. This review has emphasized the different methods of HPLC and UPLC-MS/MS that have been used to analyze Ertugliflozin in several biological matrices. Relevant useful information on sample processing options, chromatographic/detection settings, and validation parameters of the selected Ertugliflozin procedures has been methodically gathered here in a simple manner. This brief review work would certainly lead an analyst to choose the appropriate method(s) for fresh analytical method development and validation of Ertugliflozin and similar drugs.

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

INTRODUCTION

As pharmaceuticals developing every day, revolutionary changes are found in human health. These pharmaceuticals can show the best activity if these are free from impurities. There have been several chemical and instrumental methods

developed at periodic intervals to produce drugs free from impurities. Starting from manufacturing of bulk drug to packaging of finished product and further up to storage (degradation). Transportation and storage are the two stages where impurities may occur frequently. Therefore in these conditions impurities must be identified and quantitated. Analytical instrumentation and techniques play an important part in identification and quantification **[1, 4]**. Intermediate pharmaceutical analysis is an important tool for therapeutic process monitoring as it includes different stages such as bulk drug testing, intermediate products, drug formulations, degradation products, drug chemical stability, and drug material toxic content. Currently, poly-pharmacy is almost inevitable in the treatment for many diabetic patients. Hence, the assays of biological samples, as well as quality control testing of combined formulations, are also essential for the improvement of poly-pharmacy therapy. High blood sugar, or hyperglycemia, is a common symptom of diabetes mellitus (DM) **[5, 8]**. The clinical investigation of diabetes relies on one of the four criteria of Plasma Glucose level (PG): (i) elevated fasting plasma glucose (FPG) (> 126 mg / dL), (ii) 2 hr PG during a 75 g oral glucose tolerance test (OGTT) (> 200 mg) / dL), (iii) random PG (> 200 mg / dL) with classic signs and symptoms of hyperglycemia and (iv) haemoglobin A1C level > 6.5% **[09, 11]**. Drugs that are used to treat diabetes include biguanides, sulfonylureas, meglitinide and thiazolidinedione (TZD), as well as inhibitors of DPP-4, sodium glucose cotransporter 2 (SGLT2), and -glucosidases (-glucosidase inhibitor). The FDA has approved sodium-glucose cotransporter-2 inhibitors as an antihyperglycemic drug category (SGLT2). High affinity but low-capacity glucose transporters are sodium-glucose cotransporter-1 (SGLT1) proteins. They are located in the small intestine as well as in the proximal tubule of the kidneys **[12, 14]**. SGLT1 inhibition has been linked to gastrointestinal problems, including severe diarrhoea **[15]**. SGLT1 proteins in the proximal convoluted tubule of the kidney are responsible for less than 10% of filtered glucose reabsorption **[16-19]**. The function of SGLT1 proteins in the intestine is still understudied but can play a considerable role as shown by evidence from studies on dual inhibitors. Sodium-glucose cotransporter-2 (SGLT2) proteins are exhibited in the proximal convoluted tubule of the kidneys. These cotransporters are an optimal target for the treatment of diabetes because they are accountable for approximately 90 percent re-absorption of filtered glucose **[20, 23]**. The standard renal glucose re-absorption threshold correlates to a serum glucose concentration of 180

mg/dL. For the patients suffering from type2 diabetes, the threshold may be raised and hence the expression of SGLT2 may be up-regulated, triggering a maladaptive reaction that worsens hyperglycemia **[24]**. Selective inhibition of the SGLT2 transporter minimizes this threshold to a level of 40 to 120 mg/dL **[25]**. Comparatively, the people with this rare "nondisease," familial renal glucosuria (FRG), do not have functional SGLT2 proteins. Individuals with FRG seldom have hypotension or hypoglycemia **[26, 27]** recommending the efficacy of both short and long-term usage of SGLT2 inhibitors. Examples of SGLT2 inhibitors are Ipragliflozin, Luseogliflozin, Canagliflozin, Tofogliflozin, Dapagliflozin, Ertugliflozin, Remogliflozin etabonate, Sotagliflozin, Empagliflozin, Sergliflozin **[28]**.

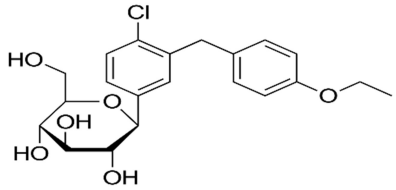
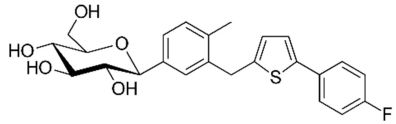
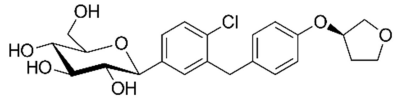
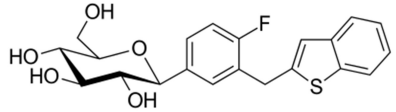
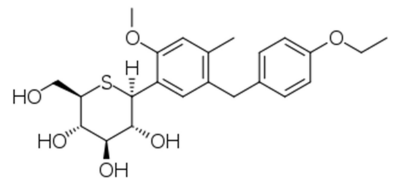
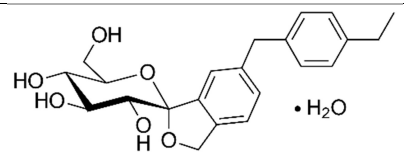
Ertugliflozin

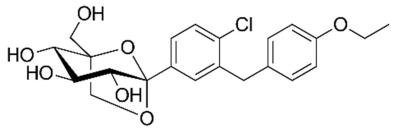
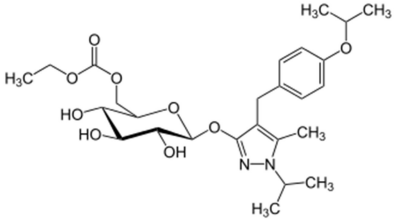
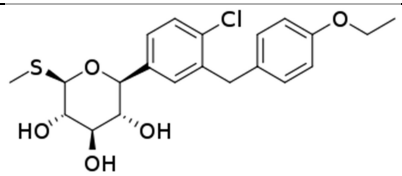
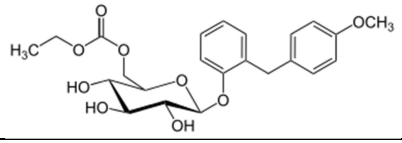
From all these gliflozin derivatives in this present journal about Ertugliflozin is discussed briefly. Ertugliflozin (EZG) chemically, (1S,2S,3S,4R,5S)-5-[4-Chloro-3-(4-ethoxybenzyl)- phenyl]-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol **(Figure 1)** is an oral hypoglycaemic drug belongs to Sodium-Glucose cotransporter-2 (SGLT2) inhibitors **[29]**.

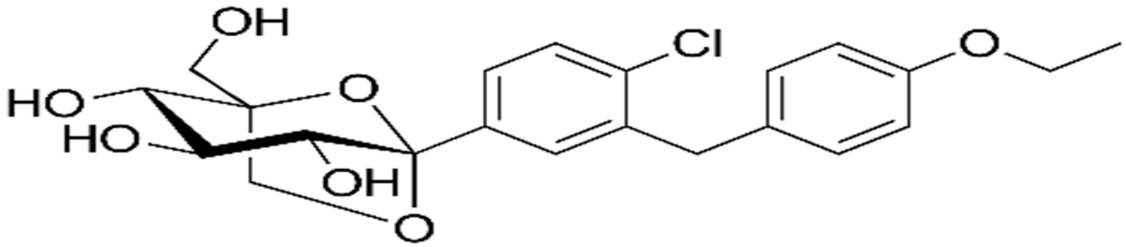
SGLT-2 inhibitors represent a new therapeutic approach for the management of type-2 diabetes. Ertugliflozin is found to be accountable for approximately 90% of glomerulus glucose re-absorption. Compounds that inhibit the sodium-glucose transporter2 can reduce blood sugar by inhibiting the glucose reabsorption in the kidneys and are therapeutically used for type 2 diabetes mellitus. Ertugliflozin was approved by the relevant approving bodies of the U.S and Europe.

The chemical structure and IUPAC name of Ertugliflozin has been approved by the United States Food and Drug Administration (USFDA) **[30]**. In March 2018 it has been approved In Europe, its bioavailability 70-90%, metabolism via hepatic, biological half-life 11-17hr, and It were eliminated 50% in Urine and 41% in feces. For the determination of pharmacokinetic parameters of Ertugliflozin in plasma, urine of humans, several analytical methods based on UV, RP-HPLC, and LC-MS/MS were reported. This review paper emphasizes different analytical techniques such as electrochemical methods, UV/VIS-Spectrophotometric methods, UPLC/MS-MS, and Gas Chromatography for the evaluation of Ertugliflozin. The details about the previous studies are discussed in **Tables 2, 3, 4, and 5, 6**.

Table 1: Structure wise classification of Gliflozin derivatives

Drug	Structure	IUPAC Name	Molecular Weight	Solubility
Dapagliflozin		**(2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl) phenyl]-6-(hydroxymethyl) tetrahydro-2H-pyran-3,4,5-triol**	**408.88 g·mol−1**	**Soluble in ethanol, DMSO, and dimethylformamide**
Canagliflozin		**(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**	**444.52 g·mol−1**	**Soluble in ethanol, DMSO, and dimethyl formamide**
Empagliflozin		**(2S,3R,4R,5S,6R)-2-[4-Chloro-3-[[4-[(3S)-oxolan-3-yl]oxyphenyl]methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol**	**450.91 g·mol−1**	**Very slightly soluble in water, acetonitrile and ethanol, sparingly soluble in methanol, and insoluble in toluene**
Ipragliflozin		**(1S)-1,5-Anhydro-1-[3-(1-benzothiophene-2-ylmethyl)-4-fluorophenyl]-D-glucitol**	**404.45 g·mol−1**	**Soluble in ethanol, DMSO, and dimethylformamide**
Luseogliflozin		**(2S,3R,4R,5S,6R)-2-[5-[(4-ethoxyphenyl)methyl]-2-methoxy-4-methylphenyl]-6-(hydroxymethyl)thiane-3,4,5-triol**	**434.55 g·mol−1**	**Soluble in water**
Tofogliflozin		**(1S,3'R,4'S,5'S,6'R)-6-(4-Ethylbenzyl)-6'-(hydroxymethyl)-3',4',5',6'-tetrahydro-3H-spiro[2-benzofuran-1,2'-pyran]-3',4',5'-triol hydrate (1:1)**	**404.459 g·mol −1**	**Soluble in ethanol, DMSO, and dimethyl formamide**

Ertugliflozin		**(1S,2S,3S,4R,5S)-5-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol**	**436.89 g·mol−1**	**Soluble in ethanol, DMSO, and dimethyl formamide**
Remogliflozin etabonate		**5-Methyl-4-[4-(1-methylethoxy)benzyl]-1-(1-methyl ethyl)-1H-pyrazole-3-yl 6-O-(ethoxycarbonyl)-β-D-glucopyranoside**	**522.595 g·mol−1**	**Soluble in ethanol, DMSO, and dimethylformamide**
Sotagliflozin		**(2S,3R,4R,5S,6R)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6-methylsulfanyloxane-3,4,5-triol**	**424.94 g·mol−1**	**Soluble in ethanol, DMSO, and dimethylformamide**
Sergliflozin		**2-(4-methoxybenzyl)phenyl 6-O-(ethoxycarbonyl)-β-D-glucopyranoside**	**448.468 g·mol−1**	**Sparingly soluble in organic solvents, sparingly soluble in organic solvents**



(1S, 2S, 3S, 4R, 5S)-5-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-1-(hydroxymethyl)-6,8 dioxabicyclo[3.2.1]octane-2,3,4-triol

Figure 1: Chemical structure and IUPAC name of Ertugliflozin

Table 2: Summary of methods related to HPLC technique

S. No.	Stationary Phase (Column)	Mobile Phase(With ratio)	pH	Wavelength	Flow rate	Reference
ERTUGLIFLOZIN with SITAGLIPTIN						
1	C18(150mm x 4.6, 5µm)	A mixture of Potassium dihydrogen Ortho Phosphate: Acetonitrile (70:30 v/v)	03	240 nm	1.0 ml/min.	31
2	C18(150mm x 4.6, 5µm)	mixture of 0.5 mM potassium dihydrogen ortho phosphate buffer: Methanol (55:45,v/v)	5.3	215 nm	1.0 ml/min.	32
3	C18(150mm x 4.6, 5µm)	Mixture of OPA (Ortho Phosphoric acid) : Acetonitrile (60:40, v/v)	=	250 nm	1.0 ml/min.	33
4	C18(150mm x 4.6, 5µm)	A mixture of dipotassium hydrogen phosphate: methanol (65:35, v/v)	3.5	225 nm	1.0 ml/min.	34
5	C18(150mm x 4.6, 5µm)	Mixture of TFA: Methanol: Acetonitrile (30: 60: 10, v/v)	-	250 nm	1.0 ml/min.	35
ERTUGLIFLOZIN with METFORMIN						
6	C18(150mm x 4.6, 5µm)	A mixture of Potassium dihydrogen Ortho Phosphate : Acetonitrile (70:30,v/v)	-	240 nm	1.0 ml/min.	36
7	C18(100mm × 2.1 mm, 1.7µ)	Mixture of OPA Phosphate : Acetonitrile (50:50,v/v)	-	240 nm	0.3 ml/min	37
8	C18(150mm x 4.6, 5µm)	A mixture of buffer: acetonitrile (55:45 v/v)	-	224 nm	1.0 ml/min	38
9	C18(150mm x 4.6, 5µm)	Mixture of ortho-phosphoric acid :acetonitrile (65:35 v/v)	2.7	224 nm	1.0 ml/min	39
10	C18(150mm x 4.6, 5µm)	Mixture of 0.1 M sodium dihydrogen phosphate:methanol (50:50 v/v)	4.0	238nm	1.0 ml/min	40
11	C18(150mm x 4.6, 5µm)	A mixture of potassium dihydrogen: methanol (65:35 v/v)	4.0	220nm	1.0 ml/min	41
12	C18(150mm x 4.6, 5µm)	A mixture of Potassium dihydrogen Ortho Phosphate: Acetonitrile (70:30v/v)	=	240nm	1.0 ml/min	42
13	C18(150mm x 4.6, 5µm)	A mixture of 0.01 N KH2 PO4: acetonitrile (60:40 V/V)	5.4	224 nm	1.0 ml/min	43
14	C18(150mm x 4.6, 5µm)	A mixture of acetonitrile:	5.4	215 nm	1.0 ml/min	44

		phosphate buffer(50:50 V/V)				
15	C18(150mm x 4.6, 5µm)	Mixture of 0.1 M sodium dihydrogen phosphate:methanol (50:50 v/v)	4.0	238nm	1.0 ml/min	45
16	C18(150mm x 4.6, 5µm)	Mixture of 0.1% OPA: acetonitrile (60:40 v/v)	-	220nm	1.0 ml/min	46
17	C18(150mm x 4.6, 5µm)	Mixture of potassium orthophosphate hydrogen: methanol (55:45 v/v)	5.3	215nm	1.0 ml/min	47

Table 3: Summary of methods related to HPLC technique with plasma

S. No.	Stationary Phase (Column)	Mobile Phase(With ratio)	pH	Wavelength	Flow rate	Reference
01	C18(150mm x 4.6, 5µm)	Mixture of potassium phosphate: Acetonitrile (65:35, v/v)	6.0	277nm	1.0 ml/min	48

Table 4: Summary of methods related to UPLC-MS-MS technique with plasma

S. No.	Stationary Phase (Column)	Mobile Phase(With ratio)	Detector	Interface	Reference
1	C18 (2.1 mm x 50 mm, 1.7 µm)	A mixture of Acetonitrile: water:0.1% formic acid	XEVO TQ-S triple quadrupole mass spectrometer	Electrospray Ionization	49

Table 5: Summary of methods related to GAS CHROMATOGRAPHY technique

S. No.	Stationary Phase (Column)	Mobile Phase(With ratio)	Temp	Flow rate	Reference
01	25 m CP-ChirasilL-Val column with 0.25 mm internal diameter and 0.12 µm	Helium	250 °C	1.5 mL/min	50

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

S. No.	Drug	Method	Description	Reference
1	Estimation of Ertugliflozin and Sitagliptin	UV-VIS spectroscopic Method by Using Simultaneous Equation Method	Detection wavelength:221nm for Ertugliflozin and 210nm for Sitagliptin Linearity range: 4.2- 6.3µg/m for Ertugliflozin & 7.0-42µg/ml for Sitagliptin Co-relation Co-efficient: 0.999 for Ertugliflozin and Sitagliptin. Recovery range: 100.34-99.95% % RSD: ≤ 2%	51
2	Estimation of Ertugliflozin in its Active Pharmaceutical Ingredient form and Tablet dosage form	Spectroscopic method	Detection wavelength: Linearity range: 10-70µg/m Co-relation Co-efficient: > 0.999 Recovery range: 100.34-99.95% % RSD: ≤ 2%	52

Quality by Design

Currently, the Quality by Design technique is widely used to improve the analytical method. Quality by design (QBD) which is discussed in ICH Q8, Q9 and Q2 is well established for the manufacture and development of pharmaceuticals **[53]**.

Benefits of Quality by Design Method

It helps in the establishment of a robust method so that sources of variability can be minimized effectively. Method Transfer success is greater when a method is transferred from the research level to the quality control department. This technique gives a space for the invention of new techniques by continuous improvement throughout the lifecycle **[54]**.

CONCLUSION

This review illustrates the Spectrophotometric and Chromatographic methods; developed and validated for the estimation of Ertugliflozin. Based on this review it was summarized that for Ertugliflozin different Spectroscopic & Chromatographic methods are available for the single component as well as for combination and also it was found that the mobile phase comprises phosphate buffer, methanol and acetonitrile were common for most of the chromatographic method to provide more resolution. It was observed that the most common combination of Ertugliflozin was with Sitagliptin (ex. STEGLUJAN). For the chromatographic method, the flow rate is observed only 1.0 ml/min to get a good retention time. For most of the Spectroscopic methods, the common solvent is Methanol. Hence all these methods are found to be uncomplicated, accurate, economic, precise, and reproducible in nature. But from this review, it was clear that available methods can be enhanced by using the Design of Expert (DOE) technique, which will give a more accurate and precise result.

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DATA AVAILABILITY

Not declared.

CONFLICT OF INTEREST

The authors affirm that they have no conflict of interest.

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