Review Article

Advanced Analytical and Bioanalytical Estimation of Ertugliflozin – An Overview

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ABSTRACT

Ertugliflozin is a drug for the treatment of type 2 diabetes. It is used as a monotherapy and as a fixed dose combination with either sitagliptin or with metformin. Ertugliflozin is a sodium/glucose cotransporter 2 (SGLT2) inhibitor and is in the class of drugs known as gliflozins. The review describes different procedures for the analysis of Ertugliflozin as a single drug or in combinations available in the currently available literature in analytical and bioanalytical techniques. The analytical methods described here are explained in two parts Spectroscopy and Chromatography. Advance analytical techniques like 3D fluorescence Spectroscopy, HPLC, HILIC and UPLC MS/MS were used to estimate Ertugliflozin in pure, dosage forms and in rat plasma. This paper certainly helpful for the researchers engaged in method development and validation of Ertugliflozin.

Keywords: Ertugliflozin, UPLC MS/MS, HILIC, SGLT2 inhibitors, Analytical and bioanalytical techniques.

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INTRODUCTION

Ertugliflozin is a drug used for the treatment for the type 2 diabetes. It is a sodium glucose co-transporter (SGLT2) inhibitor. SGLT2 inhibitors decrease renal glucose reabsorption and increase urinary glucose excretion, reducing fasting and postprandial blood glucose levels.

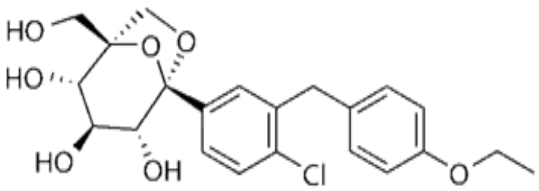

Figure 1: Showing structure of Ertugliflozin

IUPAC Name of ertugliflozin is (1S,2S,3S,4R,5S)-5-[4-chloro-3-[(4-ethoxyphenyl) methyl] phenyl]-1-(hydroxymethyl)-6,8-dioxabicyclo [3.2.1] octane-2,3,4-triol

Molecular formula: $C_{22}H_{25}ClO_7$

Molecular weight:436.9 Daltons.[1]

It is white in colour and powder in form soluble in ethanol and acetone, slightly soluble in ethyl acetate and acetonitrile and sparingly soluble in water. It is commercially available in single drug form and also combination with the Sitagliptin and metformin Hydrochloride. Collection of articles indicates the few bioanalytical, analytical method development and validation and stability indicating studies are available with the drug (ertugliflozin) and also with the combination of Sitagliptin and metformin. [2]

Ertugliflozin (trade name Steglatro) is a drug for the treatment of type 2 diabetes. In the United States, it was approved by the Food and Drug Administration for use as a monotherapy and as a fixed dose combination with either sitagliptin or with metformin. In Europe, it was approved in March 2018 for use as a monotherapy or combination therapy. Ertugliflozin is a sodium/glucose cotransporter 2 (SGLT2) inhibitor and is in the class of drugs known as gliflozins. A combination with metformin is marketed as Segluromet and a combination with sitagliptin is marketed as Steglujan.

MATERIALS AND METHODS

Author searched various online libraries available online related to determination of Hydroxychloroquine. The databases searched are, pubmed, wiley, science direct, taylor and francis, nature, BMJ and google scholar. The keywords used for search are 'determination of Ertugliflozin', 'estimation of Ertugliflozin', and 'Analytical and bioanalytical estimation of Ertugliflozin'.

Analytical methods

China babu, *et al.,* developed a stress indicating RP-HPLC method and validated for the simultaneous estimation of Ertugliflozin and Sitagliptin in Bulk and its formulation. The experiment was done in the Waters HPLC and separation took place in the c18 column capacitate (250X4.6 mm, 5 µm particle size) (Waters), mobile phase was composed of 0.5mM of potassium dihydrogen orthophosphate (buffer) Ph 5.3 and methanol (55:45) v/v peak elution of ertugliflozin at 2.3 min and Sitagliptin at 4.6 min they used the PDA (photo diode array detector) at 215 nm run time was 6 min. LOD & LOQ values was found to be 0.3µg/ml& 0.1µg/ml for Ertugliflozin and Sitagliptin respectively.

They also develop a stress indicating studies in RP HPLC method mobile phase as 0.75mM di hydrogen orthophosphate buffer at pH 8.5 and acetonitrile in the ratio of 60:40 v/v PDA detector was used and the detection was carried out at 263nm with flow rate of 1.5ml/min. The validation parameters include system suitability, specificity, precision, linearity, accuracy, LOD& LOQ and robustness. The linearity of ertugliflozin and Sitagliptin was found to be 0.9998&0.9996 respectively. The theoretical plates of ertugliflozin and Sitagliptin was found to be 3985& 6425. The accuracy mean %recovery of Ertugliflozin &Sitagliptin was found to be 99.90 & 100.91. The robustness of the method was performed by change of flow rate, temperature and mobile phase composition.[3]

Nizami *et al.,* developed an analytical method and validated for simultaneous estimation of Ertugliflozin and Metformin in tablet dosage form by RP-HPLC method. The experiment was done on Waters HPLC and separation took place in the c18 column (150 mm x 4.6 mmd, 5µm) (Waters), mobile phase was composed of Potassium dihydrogen Ortho Phosphate: Acetonitrile (70:30v/v) and the flow rate of 1ml/min. PDA detector was used and the detection took place at 240nm. Retention time for ertugliflozin was at 3.2 min and for Metformin was at 2.1 min. In this method they validated parameters like linearity, accuracy, precision, selectivity, LOD&LOQ etc. Theoretical plates for Ertugliflozin & metformin is 4435& 4430[4]. The validation parameters according to ICH includes linearity over a range of1.5-4.5µg/mL and 100-300µg/ml for ertugliflozin and metformin respectively. The percentage recovery obtained was found to be in the range of 99.889% - 99.631% for metformin and 100.181% - 100.814% for Ertugliflozin. LOD & LOQ values were found to be 0.43µg/ml & 1.30µg/ml for Ertugliflozin and Metformin. [4]

Harshalatha P, *et al.,* developed a novel RP-HPLC method for simultaneous determination of Ertugliflozin and Sitagliptin in bulk and tablet dosage forms the experiment was done in the Waters HPLC separation take place in c18(250 mm X 4.6 mm; 5µm) column by using the mobile phase composition of 0.2%orthophosphoricacid and acetonitrile (60:40) v/v. Flow rate was fixed at 1 mL/min and the detection takes place with the photo diode array detector at 250nm runtime is 6min the peak elution of Ertugliflozin and Sitagliptin is 2.3 and 3.9 min. The validation parameters according to ICH includes selectivity, linearity, limit of detection, limit of quantification, robustness, precision, sensitivity & accuracy. Theoretical Plate for Ertugliflozin& Sitagliptin is 8496& 6482[5]. Linearity of ertugliflozin and Sitagliptin was obtained at a concentration of 32.50 – 97.50 µg/ml and 216.50 – 649.50 µg/ml respectively. Recovery study was carried out by analysing the samples at three different concentrations at 50, 100 and 150%. Robustness was assessed by changing in temp of column, flow rate, pH of mobile phase. [5]

Amtul Hadi Hadiya and Mohammad Yunoos developed a new validated stability indicating RP-HPLC method for the simultaneous estimation of Sitagliptin and ertugliflozin in bulk and tablet dosage forms. Chromatographic separation was carried out on Agilent ODS C18 (4.6 x 150 mm, 5µ particle size) column using a mobile phase composed of acetonitrile: phosphate buffer (adjusted to pH 5.4 with 0.1 % ortho phosphoric acid) in the ratio of 50:50 % v/v at a flow rate of 1.0 ml/min. The analyte was monitored using UV detector wave length at 215nm and the runtime is 10 min peak elution of ertugliflozin and Sitagliptin at 2.4 and 4.5 min respectively. The theoretical plates of Ertugliflozin was found to be 3493 sitagliptin was found to be 4706.The method was validated according to ICH guidelines. Linearity range for Sitagliptin was 25-125 µg/ml and for Ertugliflozin was 3.75- 22.5µg/ml. Using standard addition method at three different concentrations 50%, 100% and 150 % the % recovery of accuracy was demonstrated. Robustness was estimated at deliberate changes in flow rate, mobile organic phase, temperature. Stress studies were performed. [6]

P.V. Rao*et al.,* developed a new stability indicating RP-HPLC method for simultaneous estimation of ertugliflozin and Sitagliptin in bulk and pharmaceutical dosage forms. The experiment was carried out in HPLC (Waters) and separation took place in the Agilent column (150×4.6, 5µm) dimensions. The mobile phase consists of buffer (Potassium di hydrogen Ortho Phosphate): Acetonitrile (70:30 V/V). The flow rate was maintained at 1.0 ml/min. Retention time was 3.2min (Ertugliflozin), 2.106min (Sitagliptin) Photo Diode Array detector effluent monitored at 240 nm. Acetonitrile and Water taken in the ratio of 50:50 used as a diluent. The method was validated according to ICH guidelines, linearity of Ertugliflozin and Sitagliptin was found in the range of 3.75-22.5µg/ml and 25-0.150µg/ml respectively. The mean recovery of Ertugliflozin and Sitagliptin were calculated and accepted with 100±2%. Robustness includes the changes inflow rate, column temperature, mobile phase composition (Acetonitrile proportion). Degradation studies were conducted.[7]

Venkateswara Rao *et al.,* developed and validated a new stability indicating reverse phase HPLC method for simultaneously determination of metformin hydro chloride and ertugliflozin bulk and pharmaceutical dosage form. The experiment was done in Waters HPLC and

separation take place in column BDSc8 (150mm×4.6mm×5mm) and mobile phase was composed of buffer: acetonitrile (55:45v/v). The flow rate was maintained at 10ml/min and detection was carried out by using photo diode array (PDA). Retention time for metformin was 2.33 ml/min and for Ertugliflozin was 3.136 ml/min. the validation parameters for this experiment was system suitability, linearity, precision, accuracy, robustness, LOD and LOD. The linearity values for metformin and Ertugliflozin was 125-170mg/ml and 1.875-11.25mg/ml. LOD and LOD was 1.70mg/ml- 5.16mg/ml for metformin and Ertugliflozin was 0.07mg/ml-0.21 mg/ml. Accuracy value for metformin was 99.13%-101.63% and Ertugliflozin was 99.05%- 101.10%. Robustness was estimated by changing oven temperature(±5^{0}c) mobile phase composition and flow rate was (±0.1 ml/min).[8]

Xiangjun Qiu *et al.,* developed a UPLC MS/MS method for the quantification of ertugliflozin and Sitagliptin in rat plasma. The experiment was done in the UPLC MS/MS and separation takes place in the BEH c18 column (2.1mm×50mm×1.7mm), mobile phase was composed of acetonitrile and water with o.1% formic acid by gradient elution. Ertugliflozin was detected by m/z 437.2- 329.0 transition for quantification and the m/z 437.2- 207.5 transition for qualification, and Sitagliptin was monitored by m/z 408.2-235.0 transition for quantification and m/z 408.2-174.0 transition for qualification by multiple reaction monitoring (MRM) in positive electrospray ionization. The concentration of ertugliflozin was ranged from 1 to 1000mg/ml and Sitagliptin was ranged from 2 to 2500mg/ml the method exhibits good linearity. For both drugs intraday and inter day precision values was 1.6 - 10.9% and 0.8-13.3%.and accuracy values from 15.7-14.6%. The run time set as 3min and flow rate was 0.4 ml/min. Quantification was achieved by multiple reaction monitoring (MRM) mode with transitions of m/z 437.2→329.0 and m/z 437.2→207.5 for ertugliflozin, m/z 408.2→235.0 and m/z 408.2→174.0 for sitagliptin and m/z 285.0→154.0 for IS, respectively. Data acquisition and control of instrument were done by Masslynx 4.1 software.[9]

Yali Liang *et al.,* studied effect of food on the pharmacokinetics of Ertugliflozin and its fixed dosage combinations (Ertugliflozin /Sitagliptin and Ertugliflozin/ metformin) was done in the Waters atlantis HILIC and separation take place in the column (3mmx2.1×50mm)mobile phase was composed of acetonitrile: water (80:20 v/v) containing 10 ml ammonium acetate (pH4.7) and detection was performed by sciex API4000 in the positive ion mode and MRM values for Sitagliptin was m/z 408-235 and metformin for 130-71 and plasma concentrations was determined based on the pharmacokinetics parameters like AUC, C_{max}, T_{max}. The T_{max} value for metformin was 2.3hours(fasted) 4.0hours(fed) and Sitagliptin was 3.0hours(fasted), 1.8 hours(fed). AUC was within the bioequivalence range 80%- 125% for Ertugliflozin and C_{max} value for metformin decreased to 29% in fed state and Sitagliptin was 90%. [10]

M.Anjali, *et al.,* developed and validated an UV method on Ertugliflozin and Sitagliptin by Using Simultaneous Equation Method. The experiment was done in the UV spectrophotometer (PG instruments) This Method solving of simultaneous equations based on the measurement of absorbance at two wavelengths, 210 nm and 221nm. Mixture of HPLC grade water and Acetonitrile taken in the ratio 1:1 v/v used as diluent and sonicated for 15min Working solutions of both drugs were scanned in the UV range 200–400 nm. The overlay spectra of both drugs were recorded. The wavelengths 210 nm (of STG) and 221 nm (of ETR) were selected for analysis of both drugs using simultaneous equation method (210 nm for Sitagliptin and 221 nm for Ertugliflozin). The method was validated according to ICH guidelines. Specificity, precision and ruggedness was estimated and% RSD was found to be less than 2%. Robustness of the method was evaluated by changing the wavelength by±2 nm. % RSD obtained was less than 2%. [11]

Wenjing wang *et al.*, study on the interaction of ertugliflozin in human serum albumin invitro by multiple spectroscopic methods and molecular docking and molecular dynamics simulation. The experiment was performed using multiple spectroscopic methods, they are as follows:

a. **Fluorescence spectroscopy:** Excitation wavelength 280nm and emission spectra was measured at 290-500nm at the temperatures of 298,304 and 310 k. HSA solution diluted to 2µm and ertugliflozin final concentrations from 0 to 140µm.

b. **Fluorescence lifetime:** Excited wavelength 280nm emission wavelength 337nm. HSA concentration was 2µm and ertugliflozin was 80 and 140µm.

c. **3D fluorescence spectroscopy:** Excitation and emission wavelength of HSA was found to be 280, 335 nm and 225,334nm for peak 1 and peak 2 respectively. Excitation and emission wavelength of Ertugliflozin-HSA (30:1) was found to be 280,329nm and 225,322nm for peak 1 and peak 2 respectively. [12]

Laxmi, *et al.,* developed a RP-HPLC method for simultaneous estimation of Ertugliflozin and Sitagliptin in bulk and tablet dosage forms. The experiment was done in the waters HPLC and separation takes place in the C18 column(250mm × 4.6mm I.D., 5µm), mobile phase used for separation is 0.1M dipotassium hydrogen phosphate and methanol (65:35)v/v. Peak elution of ertugliflozin was at 3.02 min and run time is 7min and detected by PDA detector at 225nm wavelength, flow rate is 1 ml/min and pH is adjusted to 3.5.The method was validated according to ICH guidelines. The relationship was found to be linear in the range 50–150µg/ml for Sitagliptin and 7.5-22.50µg/ml for ertugliflozin. The robustness of method was tested by assessing the effect of minor changes in the Flow rate of mobile phase (± 0.1 ml/min) pH, detection λ, mobile phase ratio, Column temperature (± 2°C). The LOD & LOQ was found to be 0.071 and 0.237 µg/ml. [13]

D.G. Han, *et al.,* developed a HPLC method combined with fluorescence detection for determination of ertugliflozin in rat plasma. They described a novel bioanalytical method using high-performance liquid chromatography (HPLC) coupled with fluorescence detection. separation was performed on a Kinetex C18 column (250 × 4.6 mm, 5µm, 100 Å; Phenomenex, Torrance, CA, USA) protected by a C18 guard column with an isocratic mobile phase comprising acetonitrile and 10 mM potassium phosphate buffer (pH 6.0). The flow rate of 1 mL/min. Injection volume was 20µL and total run time was 20min. The peak was detected by a fluorescence detector at an optimized excitation & emission wavelength pair of 277&320nm respectively. The method was validated according to ICH guidelines. Calibration curves (n = 5) were constructed by plotting the peak area ratios of ERTU to IS (y-axis) versus the concentration ratios of ERTU (4–2000ng/mL) to IS (1000 ng/mL) in plasma (x-axis) using linear regression analysis. [14]

A Lakshmana Rao& U Krishnaveni, developed a stability indicating RP-HPLC method for simultaneous estimation of metformin and ertugliflozin. The analysis of drugs was carried out on Waters HPLC 2695Isocratic separation was achieved on Denali C18 (150 x 4.6mm, 5µm) column with mobile phase comprising of 0.01 N KH_2 PO_4: acetonitrile (60:40 V/V), pH adjusted to 5.4 with 0.01% ortho phosphoric acid. The flow rate was maintained at 1 mL/min and analytes were detected with UV detector at 224 nm and run time kept was 6 min. peak elution of Ertugliflozin and metformin is 3.20 min and 2.35min respectively. The sample injector volume was 20µL with analysis being carried out at ambient temperature. The method was validated according to ICH guidelines. Theoretical plates for metformin and ertugliflozin were 5675& 7593. Linearity concentrations of Metformin was 62.5-375µg/mL and Ertugliflozin was 0.9375-5.625µg/mL. The mean percentage recovery at each level was not less than 98% and not more than 102%. Robustness was evaluated by changing in flow rate, mobile phase composition and temperature. [15]

Syed Wajahat Shafaat, *et al.,* developed the analytical method development and validation for simultaneous estimation of ertugliflozin and metformin HCl in bulk and pharmaceutical dosage form by HPLC experiment done in HPLC in gradient type &the column is C18 (250 × 4.6 mm) mobile phase was composition of Potassium dihydrogen phosphate buffer and methanol (65:35) v/v and the flow rate was maintained at 1.0 mL/min. Detection took place in UV detector at the wave length of 220 nm and the run time is 6min.Peak elution of Ertugliflozin and metformin HCl is at 3.2 min and 2.1 min.[16]

The following table gives details about discussed Chromatographic methods:

Authors	Method	Column	Mobile phase	Flow Rate (ml/min)	Detection wavelength	Rt (min)	LOD (µg/ ml)	LOQ (µg/ml)	Ref
China babu, *et al.,*	RP-HPLC	C18 capacitate	0.5mM potassium dihydrogen phosphate (buffer of pH 5.3): methanol (55:45) v/v	1	PDA with 215 nm	2.3	0.3	0.1l	3
Nizami, *et al.,*	RP-HPLC	C18	Potassium dihydrogen ortho phosphate: Acetonitrile (70:30) v/v	1	PDA with 240 nm	3.2	0.43	1.30	4
Harshalatha P, *et al.,*	RP-HPLC	C18	0.2% ortho phosphoric acid: Acetonitrile (60:40) v/v	1	UV with 250 nm	2.3	0.0068	0.029	5
Amtul Hadi Hadiya and Yunoos	RP-HPLC	ODS C8	Acetonitrile: phosphate buffer (pH 5.4 with 0.1 % ortho phosphoric acid) (50:50) v/v	1	UV with 215 nm	2.4	0.08	0.244	6
P. V. Rao *et al.,*	RP-HPLC	Agilent column	Potassium dihydrogen ortho phosphate (buffer): Acetonitrile (70:30) v/v	1	PDA with 240 nm	3.2	0.43	1.31	7
Venkateswara Rao *et al.,*	RP-HPLC	BDS C8	Potassium dihydrogen ortho phosphate (buffer): acetonitrile (55:45) v/v	1	PDA with 224 nm	3.13	0.07	0.21	8
Xiangjun Qiu*et al.,*	UHPLC-MS/MS	BEH C18	Gradient elution Acetonitrile (A) and water with 0.1 % formic acid (B)	0.4	MS with triple quadrupole and m/z of 437.2 >329.0 432.7>20	1.44	__	1ng/ml	9

Laxmi, *et al.*,	RP-HPLC	C18	0.1M dipotassium hydrogen phosphate: methanol (65:35) v/v	1	PDA with 225 nm	3.028	0.071	0.237	13
D.G. Han, *et al.*,	RP-HPLC	C18	Acetonitrile and 10mM potassium phosphate buffer (pH 6) (65:35) v/v	1	Fluorescence with excitation wavelength - 277nm Emission wavelength - 320nm	11.1	__	4ng/ml	14
A Lakshmana Rao & U Krishnaveni	RP-HPLC	Denali C18	0.01N KH_2PO_4: acetonitrile (60:40) v/v pH adjusted to 5.4	1	UV with 224nm	3.2	0.72	0.04	15
Syed Wajahat Shafaat, *et al.*,	HPLC	Inertsil C18	Buffer: methanol (65:35) v/v pH:4.0	1	220nm	7.35	9.61	0.006	16

NOTE: -Rt-Retention time, **LOD**-Limit of detection, **LOQ**-Limit of quantification, **Ref**-Reference, **min**-minute.

Tabulation Showing Spectrophotometric data of Ertugliflozin

Parameters	Sitagliptin	Ertugliflozin	LIMIT
Linearity Range (µg/ml)	7-42 µg/ml	1.05-6.30 µg/ml	R<1
Solvent			
LOD	0.07	0.0105	NMT 3
LOQ	0.21	0.0315	NMT 10
Wavelength (λ_{max})	210nm	221nm	---
Reference	11		

CONCLUSION

Most of the methods discussed used HPLC with UV detection for estimation of Ertugliflozin. HPLC and LC MS/MS were used for the estimation of drug in biological fluids. One method discussed about interaction of ertugliflozin in human serum albumin invitro by multiple spectroscopic methods like Fluorescence spectroscopy, Fluorescence life time and 3D fluorescence spectroscopy. Pharmacokinetic study of Ertugliflozin and its fixed dosage combinations by using HPLC and LC MS/MS was discussed. Different spectrophotometry and chromatographic methods were presented here in a systematic way and easy understandable language.

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