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# ANALYTICAL AND BIO-ANALYTICAL METHODS OF ERTUGLIFLOZIN-AN OVERVIEW

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## ABSTRACT

Ertugliflozin is a class of sodium glucose co-transporter type 2 (SGLT2) inhibitor. It acts by increasing the glucose excretion by reducing the glucose reabsorption in the proximal tubules. It is available as single drug and in combination with metformin hydrochloride or sitagliptin. Analytical and bio-analytical methods available for the estimation of ertugliflozin alone and in combination with metformin or sitagliptin are included in this review.

**KEYWORDS:** Ertugliflozin, SGLT2 inhibitor, Analytical and bio-analytical methods.

## INTRODUCTION

Ertugliflozin L-pyroglutamic acid (Fig.1) is a sodium glucose co-transporter type 2 (SGLT2) inhibitor, acts by increasing the glucose excretion by reducing the glucose reabsorption in the proximal tubules.

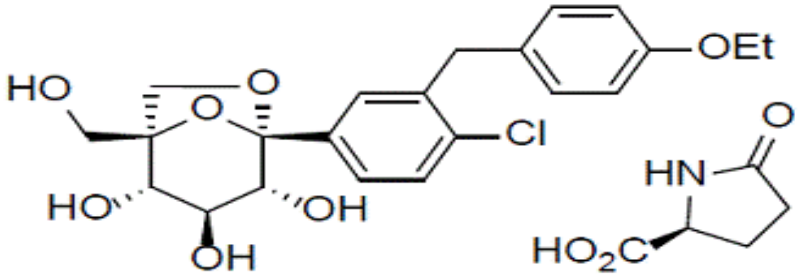


**Fig. 1: Structure of ertugliflozin L-pyroglutamic acid.**

Chemically ertugliflozin L-pyroglutamic acid is (1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo$^{[3.2.1]}$octane-2,3,4-triol, compound with (2*S*)-5-oxopyrrolidine-2-carboxylic acid. Molecular weight is 566.00. It is white to off-

white powder, very slightly soluble in water. It is soluble in ethanol and acetone and slightly soluble in ethyl acetate and acetonitrile. In the market it is available as single drug and in combination with metformin hydrochloride or sitagliptin. Literature survey revealed that few analytical and bioanalytical methods are available for the estimation of ertugliflozin alone and in combination with metformin or sitagliptin.

## METHODS

Miao *et al* studied about pharmacokinetics, metabolism and excretion of ertugliflozin in healthy male human subjects. Ertugliflozin and its metabolites were identified and quantified by using HPLC and LC-MS/MS technique. HPLC was performed by using mobile phase comprised of 5 mM ammonium formate pH 3.0 and acetonitrile in a gradient mode. The major biotransformation pathway was found to be glucuronidation, ertugliflozin-4- *β-O*-glucuronide and ertugliflozin-3- *β-O*-glucuronide are the main metabolites. Oxidation by cytochrome P450 is the minor metabolic fate yielded monohydroxylated metabolites and des-ethyl ertugliflozin.[1]

Nizami *et al* developed a HPLC method for simultaneous estimation of ertugliflozin and metformin in tablet dosage form. Mobile phase consists of a potassium dihydrogen orthophosphate, acetonitrile in the ratio of 70:30. Separation was performed on a C18 column and detection wavelength was 240 nm.[2]

China babu *et al* developed stress indicating RP-HPLC method for simultaneous estimation of ertugliflozin and sitagliptin . Separation was carried out on a Waters C18 Column, mobile phase comprised of 0.5 mM a potassium dihydrogen orthophosphate buffer pH 5.3 and methanol in the ratio of 55:45. Ertugliflozin is eluted at 2.39 min and sitagliptin is eluted at 4.60 min.[3] They also developed stress indicating RP-HPLC method for simultaneous estimation of ertugliflozin and metformin in bulk and tablet dosage forms. Separation was carried out on a Waters C18 column with mobile phase consisted of 0.75 mM sodium dihydrogen orthophosphate buffer pH 8.5 and acetonitrile in the ratio of 60:40. Flow rate was 1.5 ml/min and detection was carried out at 263 nm.[4]

D-G Han *et al* developed HPLC method with fluorescent detection for the estimation of ertugliflozin in rat plasma. Separation was carried out on a C18 column with mobile phase consisting of acetonitrile and 10 mm potassium phosphate buffer (pH 6.0). Excitation and emission wavelength for the fluorescent detector was 277 and 320 nm. The developed

method was also used to assess the pharmacokinetic interaction potential of ertugliflozin with mefenamic acid and ketoconazole.[5]

X. Qiu *et al* developed UPLC-MS/MS method for the determination of ertugliflozin and sitagliptin in rat plasma. Separation was performed on C18 column at 45 $^{0}$C. Mobile phase used is acetonitrile and 0.1% formic acid in gradient mode with a flow rate of 0.4 ml/min. The developed method was successfully applied to pharmacokinetic study of ertugliflozin and sitagliptin in rats.[6]

Venkateswara rao *et al* developed RP-HPLC method for simultaneous estimation of metformin and ertugliflozin in pharmaceutical formulations. Separation was performed on C8 column with mobile phase composition of 0.01% potassium dihydrogen phosphate and acetonitrile in the ratio of 55:45 at a flow rate of 1ml/min., detection was carried out at 224 nm. The drug was stable in acidic, basic, peroxide, photolytic and thermal stress conditions.[7] Jagadeesh, K. and A. N. developed HPLC method for simultaneous estimation of metformin and ertugliflozin using 0.1 M sodium dihydrogen phosphate buffer of pH 4.0 and methanol in the ratio of 50:50 as mobile phase and detection was performed at 238 nm.[8]

Amtul Hadi Hadiya and Mohammad Yunoos developed HPLC method for the simultaneous estimation of sitagliptin and ertugliflozin in pure drug and pharmaceutical dosage forms. Separation was performed on a C18 column using mobile phase acetonitrile and phosphate buffer of pH 5.4 in 50:50 ratio at a flow rate of 1 ml/min. Retention time of sitagliptin was found to be 2.156 min and for ertugliflozin 3.067 min.[9]

V.K. Dawra *et al* studied effect of rifampin on the pharmacokinetics of ertugliflozin. Rifampin decreased 39% of total exposure of ertugliflozin. Pharmacokinetic assessment was performed on HPLC-MS/MS. HPLC analysis was performed on C18 column with gradient mobile phase contained 0.1% formic acid, 2 mm ammonium acetate in water, and 0.1% formic acid in acetonitrile.[10]

## CONCLUSIONS

HPLC and LC-MS/MS have been used for the estimation of ertugliflozin in the pharmaceutical formulations and biological fluids. HPLC with UV detection is used in most of the methods. In one method HPLC with fluorescent detection is used for the estimation of

ertugliflozin in rat plasma. Pharmacokinetic assessment was also performed by HPLC and LC-MS/MS.

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