Review Article

Validation of Developed Analytical Methods for the Determination of Remoglifozin and Ertuglifozin in Pharmaceutical Dosage Forms - An Updated Review

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ABSTRACT

SGLT is the newly developed class of antidiabetic medicine also called as gliflozins. Remoglifozin and Ertuflifozin are the SGLT-2 class inhibitors for the treatment of type II diabetes mellitus. The aim of this review is to focus on update of determination of Remogliflozin and Ertuglifozin in bulk and in pharmaceutical dosage forms using chromatographic and spectrophotometric methods. Remogliflozin and Ertuglifozin is estimated by RP-HPLC, UV, RP-UPLC, LC-MS methods. There are plenty of articles which have already been published describing analytical methods and method validation for the same. In present review account, the disclosed analytical methods are outlined for the establishment of Remoglifozin and Ertuflifozin in its pharmaceutical preparations and biological matrices. Most frequently used techniques such as spectrometric and liquid chromatographic methods are summarized in present review. Spectrometric methods for Remoglifozin and Ertuflifozin alone and in combination include parameters like λ max, solvent, matrix etc. and HPLC methods for Remoglifozin and Ertuflifozin alone and in combination including parameters like matrix, stationary phase, mobile phase composition detection wavelength etc. HPTLC methods including parameters like stationary phase, mobile phase combination, RF etc. This review also provides detailed information on separation conditions for Remogliflozin and Ertuglifozin alone, in the presence combination with other drugs and in presence of its degradation products.

Keywords: Remoglifozin, Ertuglifozin, RP-HPLC, UV, RP-UPLC, LC-MS/MS.

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INTRODUCTION

Remoglifozin and ertuglifozin is a drug of class gliflozin class. Remoglifozin and ertuglifozin is the treatment of type 2 diabetes mellitus, and inhibit sodium glucose transport protein (SGLT) which are responsible for glucose reabsorption in the kidney.[1] Remoglifozin is chemically known as ethyl [(2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-trihydroxy-6-[5-methyl-1-propan-2-yl-4-[(4-propan-2-yloxyphenyl)methyl]pyrazol-3-yl]oxyoxan-2-yl]methyl carbonate, molecular formula $C_{26}H_{38}N_2O_9$ with molecular weight 522.595 g/mol.

Ertuglifozin is chemically known as (1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-1-(hydroxymethyl)-6,8 ioxabicyclo[3.2.1]octane-2,3,4-triol;(2*S*)-5-oxopyrrolidine-2-carboxylic acid, molecular formula $C_{27}H_{32}ClNO_{10}$ with molecular weight 566.0 g/mol.[2]

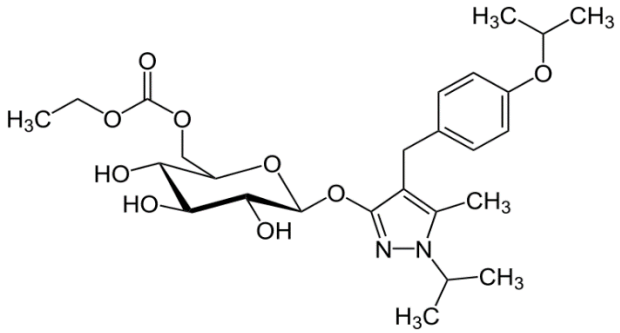

Figure 1: Structure of Remoglifozin

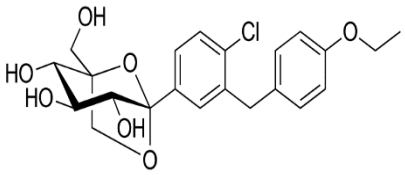

Figure 2: Structure of Ertuglifozin

Mode of Action

Glifozin is a selective Sodium glucose co transporters or sodium-glucose linked transporter (SGLTs) are newly available drug which are used in treatment of early and late type 2 diabetes. It blocks the glucose reabsorption in kidney and increase urinary glucose excretion. Glucose excreted and plasma levels drop down lead to development of all glycemic parameters. This mechanism of action is depended on blood glucose level as well as

different actions of thiazolidinediones (mediated through GLUTs), is independent of the actions of insulin. Therefore, there is minimum potential for hypoglycemia, not risk of overstimulation or tiredness of beta cells. Because their mode of action relies upon normal renal glomerular-tubular function, SGLT-2 efficacy is reduced in persons with renal impairment.[3]

Spectrophotometric Methods

Table 1: Analytical method development and validation of Spectrophotometric method for Remoglifozin etabonate in alone

Sr. No	Drug	Sample	Method	Description	Detection mode	Ref no
1.	Remoglifozin	Bulk substance and tablet dosage form	Simple UV spectrophotometric method	Mobile phase: Methanol Linearity: 2-10 µg/ml with r2=0.999 LOD: 0.037 µg/ml LOQ: 0.113 µg/ml	UV 229 nm	4

Table 2: Analytical method development and validation of Spectrophotometric method for Remoglifozin etabonate in combination

Sr. No	Drug	Sample	Method	Description	Detection mode	Ref no
1.	Metformin and Remoglifozin	Tablet dosage form	Third order derivative UV spectroscopy	Mobile phase: Ethanol and water (50:50) Linearity: 2.5 to 30 µg/ml MET and 1 to 24 µg/ml REM with r^2=0.9985 MET and 0.993 REM LOD: 0.76 µg/ml MET and 0.31 µg/m REM LOQ: 2.18 µg/ml MET and 0.94 µg/ml REM	240.1 nm MET and 234.8 nm REM	5

HPLC Methods

Table 3: Analytical method development and validation of HPLC method for Remoglifozin etabonate in alone

Sr. No	Drug	Sample	Method	Description	Detection mode	Ref no
1.	Remoglifozin	Bulk substance and tablet dosage form	RP-HPLC	Column: Reverse phase C18 column Mobile phase: methanol:water (70:30%, v/v) Flow rate: 1.0 ml/min linearity: 1-25 µg/ml with r2=0.997	229 nm	6
2.	Remoglifozin	Bulk substance and tablet dosage form	RP-HPLC	Column: Primacel C18 (150 × 4.6mm, 5µm) Mobile phase: Acetonitrile: Water (70:30, v/v) Flow rate: 1.0 ml/min Linearity: 25-150 µg/ml with r^2=0.999 LOD: 0.12 µg/ml LOQ: 0.35 µg/ml	280 nm	7

Table 4: Analytical method development and validation of HPLC method for Remoglifozin etabonate in combination

Sr. No	Drug	Sample	Method	Description	Detection mode	Ref no
1.	Remoglifozin and Metformin	Synthetic mixture and tablet dosage form	RP-HPLC	Column: Cosmosil C18 (250mm x 4.6mm, 5µm) Mobile phase: Buffer (pH 4.0): methanol (60:40) Linearity: 5-15 µg/ml REM and 20-60 µg/ml MET with r^2=0.999 LOD: 0.764 µg/ml REM and 0.785 µg/ml MET LOQ: 2.314 µg/ml REM and 2.380 µg/ml MET	241 nm	8
2.	Metformin and Remoglifozin	Bulk and tablet dosage form	RP-HPLC	Column: Inertsil ODS 3V, 100x4.6mm, 5 µm column Mobile phase: 20mM Potassium phosphate buffer with hexane sulfonic acid pH 3.5±0.05: Acetonitrile with gradient elution) Linearity:12 5-375 µg/ml REM and 25-75 µg/ml MET with r^2=0.999 Met and r2=0.9989 REM	230 nm	9

HPTLC Method

Table 5: Analytical method development and validation of HPTLC method for Remoglifozin etabonate in alone

Sr. No	Drug	Sample	Method	Description	Detection mode	RF	Ref no
1.	Remoglifozin	Tablet dosage form	Stability Indicating HPTLC	HPTLC Plates: Silica gel 60 F254 Mobile phase: methanol: ethyl acetate: toluene: NH3 (2:4:4:0.1, v/v/v)	229 nm	0.61	10

UHPLC Method

Table 6: Analytical method development and validation of UHPLC/DAD method for Remoglifozin etabonate in combination

Sr. No	Drug	Sample	Method	Description	Detection mode	Ref no
1.	Remoglifozin and Metformin	Bulk substance and tablet dosage form	RP-UHPLC/DAD	Column: Zorbax Eclipse Plus C18 (150×4.6 mm, 5 µm) Mobile phase: acetonitrile: phosphate buffer (pH: 3) (60:40 %, v/v) Flow rate: 1.0ml/min Linearity: 20-100 µg/ml REM and MET with r^2=0.996 REM and r2=0.993 MET LOD: 1.47 µg/ml REM and 4.92 MET LOQ: 1.93 µg/ml REM and 6.44 MET	PDA 230 nm	11

Ertuglifozin

HPLC Method

Table 7: Analytical method development and validation of HPLC method for Ertuglifozin in combination

Sr. No	Drug	Sample	Method	Description	Detection mode	Ref no
1.	Ertuglifozin and Metformin	Bulk substance and tablet dosage form	HPLC method	Column: inertsil C18 (250 × 4.6 mm) Mobile phase: buffer (potassium dihydrogen pH 4.0) and methanol (65:35 v/v) Flow rate: 1.0 ml/min Linearity: 1.5-4.5 µg/ml ERT and 100-300 µg/ml MET with r2=0.999 LOD: 1.04 µg/ml ERT and 9.61 µg/ml MET LOQ: 0.0007 µg/ml ERT and 0.006 µg/ml MET	220 nm	12
2.	Ertuglifozin and Metformin	Bulk substance and tablet dosage form	HPLC method	Column: Kromasil C18 Mobile phase: 0.1 M sodium dihydrogen phosphate methanol (50:50, by volume, pH 4.0) Flow rate: 1.0 ml/min Linearity: 250-750 µg/ml MET and 3.75-11.25 µg/ml ERT with r2=0.999 LOD: 0.563 µg/ml MET and 0.038 µg/ml ERT LOQ: 1.878 µg/ml MET and 0.127 µg/ml ERT	PDA 238 nm	13
3.	Ertuglifozin and Sitagliptin	Tablet dosage form	Simultaneous equation method	Mobile phase: SGT and ETR respectively in Mixture of 0.1% OPA buffer and acetonitrile. Linearity: 7.0-42 µg/ml SGT and 4.2-6.3 µg/ml ETR	210 and 221 nm	14
4.	Ertuglifozin and Sitagliptin	Bulk and tablet dosage form	RP-HPLC Method	Column: Cosmicsil C8 column (250 mm × 4.6 mm I.D., 5 µm Mobile phase: 0.1 Molar dipotassium hydrogen phosphate and methanol (65:35, v/v). Flow rate: 1.0 ml/min Linearity: 7.5 -22.50 µg/ml ERT and 50-150 µg/ml SIT with r2=0.999 LOD: 0.087 µg/ml SIT and 0.071 µg/ml ERT LOQ: 0.291 µg/ml SIT and 0.237 µg/ml ERT	225 nm	15

5.	Ertuglifozin and Metformin	Tablet dosage form	HPLC Method	Column: Phenomenex C18 column (150 mm × 4.6 mm, 5 µm) Mobile phase: acetonitrile and 0.1% OPA buffer, with a proportion of 40: 60% v/v Flow rate: 1.0 ml/min Linearity: 25-150 µg/ml MET and 0.375-2.25 µg/ml ERT with r2=0.997 LOD: 0.10 µg/ml MET and 0.2 µg/ml ERT LOQ: 0.03 µg/ml MET and 0.09 µg/ml ERT	220 nm	16
6.	Ertuglifozin pidolate and Metformin	Bulk and tablet dosage form	RP-HPLC Method	Column: C18 column (150mm× 4.6 mm, 5 µm Mobile phase: 0.1% ortho-phosphoric acid buffer (pH 2.7):acetonitrile (65:35% v/v Flow rate: 1.0 ml/min Linearity: 0.9375–5.625 µg/ml for ERT pidolate and 62.5–375 µg/ml for MET r2=0.999 LOD: 0.025 µg/ml ERT pidolate and 0.87 µg/ml MET LOQ: 0.076 µg/ml ERT pidolate and 2.63 µg/ml MET	224 nm	17
7.	Metformin and Ertuglifozin	Tablet dosage form	RP-HPLC	Column: Denali C18 (150 x 4.6 mm, 5 µm) Mobile phase: 0.01 N KH2PO4: acetonitrile (60:40 V/V), pH adjusted 5.4 with 0.01% ortho phosphoric acid Flow rate: 1.0 ml/min Linearity: 62.5–375 µg/ml for MET and 0.9375–5.6250 µg/ml for ERT r2=0.999	224 nm	18
8.	Sitagliptin and Ertuglifozin	Bulk and tablet dosage form	RP-HPLC	Column: ODS (4.6×150mm, 5µ) column in isocratic mode Mobile phase: 0.1% TFA: Methanol: Acetonitrile (30: 60: 10) Flow rate: 1.0 ml/min Linearity: SIT 40-200µg/ml and ERT 6-30µg/ml r2=0.999 LOD: 2.1 µg/ml ERT and 6.9 µg/ml SIT LOQ: 3.0 µg/ml ERT and 10.89 µg/ml SIT	250 nm	19
9.	Ertuglifozin and Sitagliptin	Bulk and tablet dosage form	RP-HPLC	Column: C18 column capacitate (250X4.6 mm, 5 µm particle size) Mobile phase: 0.5 mM potassium dihydrogen ortho phosphate buffer: Methanol in the ratio of 55:45 v/v, pH 5.3 was adjusted with HCl Flow rate: 1.0 ml/min Linearity: 37.5-112.5 and 250-750 µg/mL for Ertugliflozin and Sitagliptin r2=0.999 LOD: 0.1 µg/ml ERT and 0.3 µg/ml SIT LOQ: 0.4 µg/ml ERT and 1 µg/ml SIT		20

LC-MS Method

Table 8: Analytical method development and validation of LC-MS method for Ertuglifozin in combination

Sr. No	Drug	Sample	Method	Description	Detection mode	Ref no
1.	Sitagliptin and Ertuglifozin	Tablet dosage form	Rat plasma by LC-MS Method	Column: Xetrra C18 (150mm x 4.6mm, 2µm) Mobile phase: acetonitrile and OPA buffer (50:50v/v) at a flow rate of 1ml/min in isocratic mode Linearity range: 5.00- 75.00pg/mL for SIT and 0.75- 11.35pg/mL ERT Matrix effect: (%CV) was 0.02% and 0.12% for sitagliptin at HQC and LQC and 0.08% and 0.33% for ertugliflozin at HQC and LQC	Sitagliptin and Ertuglifozin	21

UPLC Method

Table 9: Analytical method development and validation of UPLC method for Ertuglifozin in combination

Sr. No	Drug	Sample	Method	Description	Detection mode	Ref no
1.	Ertuglifozin and Metformin	Bulk substance and tablet dosage form	UPLC method	Column: UPLC HIBRA C18 (100mm × 2.1mm, 1.8µ) Mobile phase: Buffer (0.01N sodium hydrogen phosphate) pH adjusted to 4.0 with dil. orthophosphoric acid: Acetonitrile in the ratio of 60:40%v/v on isocratic mode Flow rate: 0.3 ml/min Linerity: 3.75µg/mL to 22.5µg/mL for ERT and 25µg/mL to 150µg/mL for SIT r2=0.999 LOD: 0.09 µg/ml ERT and 0.28 µg/ml SIT LOQ: 0.32 µg/ml ERT and 0.95 µg/ml SIT	220 nm	22
2.	Ertuglifozin and Metformin	Bulk substance and tablet dosage form	UPLC method	Column: HSS C18 (100 × 2.1 mm, 1.7µ) Mobile phase: 50% OPA (0.1%): 50% Acetonitrile Flow rate: 0.3 ml/min Linerity: 1.875 µg/mL to 11.25 µg/mL for ERT and 125µg/mL to 750µg/mL for MET r2=0.999 LOD: 0.02 µg/ml ERT and 1.04 µg/ml MET LOQ: 0.18 µg/ml ERT and 3.16 µg/ml MET	240 nm	23

CONCLUSION

Various methods for determination of Remoflifozin and Ertugliflozin have been reported. Some article determines RP-HPLC assay methods were used to estimate Remogliflozin and Ertuglifozin. Some articles provide determination of Remogliflozin and Ertuglifozin alone or in combination with Metformin, Sitagliptin in pharmaceutical dosage forms. UV methods are also reported. Research papers on UPLC, LC-MS, and LC-MS/MS are also reported. Novel RP-UHPLC/DAD methods are also reported in which Remogliflozin and Metformin in bulk and formulation.

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