A review on analytical method development and validation of remogliflozin in bulk and combination dosage forms.

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***Abstract*— SGLT is newly developed class of antidiabetic medicine also called as gliflozins. Type II diabetes mellitus is treated with SGLT-2 class inhibitors, such as remogliflozin and ertugliflozin. This study focuses on the most recent chromatographic and spectrophotometric methods for determining remogliflozin in pharmaceutical dosage forms and in bulk. And RP-HPLC, UV, RP-UPLC, and LC-MS techniques are used to estimate Remogliflozin. Numerous articles that provide analytical techniques and method validation for the same have already been published. The current review summarizes the most widely used techniques, including liquid chromatographic and spectrometric methods. HPLC methods for Remogliflozin alone and in combination include parameters like matrix, stationary phase, mobile phase composition detection wavelength, etc., as well as spectrometric methods for Remogliflozin alone and in combination include parameters like λ max, solvent, matrix, etc.**

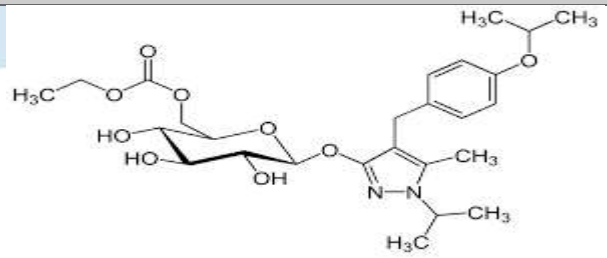
***Index Terms*— Remogliflozin etabonate (REM), Metformin (MET), Vildagliptin (VDG), RP-HPLC, UV, HPTLC, Diabetes Mellitus.**

I. INTRODUCTION

Remogliflozin belong to the gliflozin class. Type 2 diabetes mellitus is treated with remogliflozin and which block the sodium glucose transport protein (SGLT) is in charge of the kidney's reabsorption of glucose [1]. A fixed-dose of Remogliflozin has been approved by the Food and Drug Administration (FDA). Remogliflozin Etabonate (RGE) is a hypoglycemic medication taken orally [2]. A detailed analysis of the literature showed that there were few techniques for determining RMZ that had been created and verified by various analytical tools [3].

Several analytical techniques have been published for the quantitative analysis of Remogliflozin etabonate, according to a thorough literature review. There have been reports of using UV spectrophotometric techniques to determine the amount of Remogliflozin etabonate in bulk and tablet form, either alone or in combination with other medications. [4,5]. Methods for determining the amount of Remogliflozin etabonate in human plasma using liquid chromatography combined with mass spectrometry (LC-MS) are also documented [6,7]. Shah DA et al. reported one HPTLC method, (1) describing the stability indicating assessment of Remogliflozin etabonate after the medication was subjected to photolytic stress, oxidative stress, dry heat degradation, and acid and alkaline hydrolysis. Regretfully, this study did not report on the neutral hydrolytic degradation investigation, which is also required as advised by ICH. Additionally, the study found that Remogliflozin etabonate completely degraded when subjected to alkali hydrolysis, which is no longer advised. Because there is a dearth of literature, a new stability indicating densitometric approach for determining Remogliflozin etabonate needs to be developed. In order to address the limitations of the reported stability indicating method with a well-resolved peak from its degradation products and acceptable degradation, an effort was made in this study to develop and validate a more sensitive stability-indicating HPTLC method for the estimation of Remogliflozin etabonate in bulk and pharmaceutical formulation. To verify the stability in compliance with the International Conference on Harmonization Guidelines, the medication underwent neutral hydrolytic degradation as well as all other stress situations [8,9,10].

II. DRUG PROFILE

Particulars	Description
Drug name	Remogliflozin etabonate
Molecular structure	
Molecular formula	C26h38n2o9
Molecular weight	522.6 g/mol
IUPAC Name	5-methyl-4-[4-(1-methylethoxy) benzyl]-1-(1-methylethyl)-1h-pyrazol-3-yl 6- o (ethoxy carbonyl)-β-d-glucopyranoside
Solubility	Methanol
Category	Oral hypoglycemic agent used to treat type-2 diabetes mellitus.
Mechanism of Action	Remogliflozin etabonate is a pro-drug of remogliflozin. Remogliflozin inhibits the sodium- glucose transport proteins (SGLT), which are responsible for glucose reabsorption in the kidney. Blocking this transporter causes blood glucose to be eliminated through the urine.[8] Remogliflozin is selective forsglt2.

III. SPECTROPHOTOMETRIC METHODS

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

Sr. No.	Drug	Sample	Method	Description	Detection Mode	Ref no
1.	Remogliflozin	Bulk substances and tablet dosage form	Simple UV spectrophotometric method	**Mobile phase**: Methanol **Linearity:**2-10µg/ml with **r2**=0.999 **LOD**: 0.037 µg/ml **LOQ**: 0.113 µg/ml	UV 229 nm.	[1,13]

Table 2: Analytical method development and validation of Spectrophotometric Methods for Remogliflozin etabonate in combination.

Sr. No.	Drug	Sample	Method	Description	Detection Mode	Ref no
1.	Metformin and Remogliflozin	Tablet dosage form	form Third order derivative UV spectroscopy	**Mobile phase**: Ethanol and water (50:50) **Linearity:** 2.5 to 30 µg/ml MET and 1 to 24µg/ml REM with **r2**=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	[1,14]

IV. HPLC METHODS

Table 3. Analytical method development and validation of HPLC method for Remogliflozin etabonate in alone

Sr. No.	Drug	Sample	Method	Description	Detection Mode	Ref no
1.	Remogliflozin	Bulk substance	RP-HPLC	**Mobile phase** :0.02M ammonium acetate buffer (pH:4) acetonitrile and tetrahydrofuran in the ratio 50:45:05, respectively (v/v) **Colum:** C18, 5 µm, 4.6 mm x 250 mm kromasil column The flow: 2.0 mL min-1 **Linearity:** 10 µg mL-1 to 50 µg mL **LOD and LOQ** for RMZ: 1.0 µg/ml-1	228 nm	[3]
2.	Remogliflozin	Bulk and Dosage Form	RP-HPLC	**Mobile Phase:** 0.1% Triethylamine buffer pH 7.9 and methanol in the ratio of 70:30 (v/v%) **Column:** XBridge™ C18 column 5µ (250 mm x 4.6 mm) **Linearity**:05µg/ml to 30µg/ml **r2**: of 0.9999. **LOD** a: 0.42 µg/ml **LOQ**:1.41 µg/ml.	227 nm	[15]
3.	Remogliflozin	Remogliflozin etabonate in Human Plasma	RP-HPLC	**Mobile Phase:** methanol-0.1 % acetic acid (80:20 v/v) **Column** THERMO C_{18} (250×4.6 mm, 5 µm) **Linearity**:5-13 ug/ml **r2**: 0.9992 **LOD**:0.13 ug/ml **LOQ**:0.42 ug/ml **%RSD**: 2%	224 nm	[16]

Table 4. Analytical method development and validation of HPLC method for Remogliflozin etabonate in combination.

Sr. No.	Drug	Sample	Method	Description	Detection Mode	Ref no
1.	Remogliflozin etabonate and metformin HCL	Remogliflozin etabonate and metformin HCL Combination Dosage form	RP- HPLC	**Mobile Phase:** 45:55% v/v ratio of 0.02 M phosphate buffer and acetonitrile **Column:** Phenomenex C18 (250 mm × 4.6 mm, 5 µ) **Linearity:** Remogliflozin Etabonate:10-50 µg/mL Metformin Hcl: 50-150 µg/mL **LOD**:0.11 µg/mL **LOQ**: 0.35 µg/mL	PDA at 245nm	[17]
2.	Remogliflozin etabonate, metformin and vildagliptin	Remogliflozin etabonate, metformin and vildagliptin in Bulk Drug and Combination Tablet dosage Form	RP- HPLC	**Mobile Phase:** 20 M ammonium acetate: acetonitrile (75:25, v/v) **Column**: Acclaimed Mix Mode HILIC-1 column (150 mm × 4.6 mm, 5µm) **r2** = close to one (1 to 0.999)	ultraviolet detector was operated at 230 and 254 nm.	[18]

				Retention time for RGE:3.81+0.5min, VGN:4.86+0.5min, MET: 5.81+0.5min		
3	Remogliflozin Etabonate, Vildagliptin and Metformin	Remogliflozin Etabonate, Vildagliptin and Metformin in Tablet Dosage Form	RP-HPLC	**Mobile Phase**: Buffer: Methanol (85:15) **Column**: Hypersil BDS, C18 column, (250mm × 4.6mm, Particle size 5µm) **Linearity:** **Metformin:**2575µg/ml. R^2 = 0.9991 **Remogliflozin** etabonate:25-75µg/ml. R^2 = 0.999. **Vildagliptin** 25-75µg/ml. R^2 = 0.999.	233 nm	[19]
4.	Vildagliptin, and Remogliflozin Etabonate	Vildagliptin, and Remogliflozin Etabonate in synthetic Mixture	RP-HPLC	**Stationary Phase**: Luna C18 (250mm ×4.6mm, 5µm) **Mobile Phase:** Acetate Buffer (pH 5.6): Methanol (30:70%v/v) **Retention Time**: REM: 4.881 VDG: 6.334 **Linearity:** REM:10-200µg/mL VDG: 10-200µg/mL	210 nm	[20,21]
5.	Remogliflozin and Metformin	Synthetic mixture and tablet dosage form	RP-HPLC	**Mobile phase:** Buffer (pH 4.0): methanol (60:40) **Column:** Cosmosil C18 (250mm x 4.6mm, 5µm) **Linearity**: 5-15 µg/ml REM and 20-60 µg/ml MET **r2**=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	241nm	[1, 22]
6	Metformin And Remogliflozin	Bulk And Tablet Dosage Form	RP-HPLC	**Mobile phase:** 20mM Potassium phosphate buffer with hexane sulfonic acid pH 3.5±0.05: Acetonitrile with gradient elution) **Column:** Inertsil ODS 3V, 100x4.6mm, 5 µm column **Linearity:**12 5-375 µg/ml REM and 25-75 µg/ml MET with r2=0.999 MET and r2=0.9989 REM	230 nm	[1,23]

V. HPTLC METHOD

Table 5. Analytical method development and validation of HPTLC method for Remogliflozin etabonate in alone

Sr. No.	Drug	Sample	Method	Description	Detection Mode	Ref no.
1	Remogliflozin Etabonate	Remogliflozin Etabonate in tablet dosage form	HPTLC	**Mobile Phase:** Toluene: Methanol (8.5:1.5% v/v) **Stationary Phase:** Silica gel 60 F254 (100 mm ×100 mm, 250µm**)** **Rf value:** 0.35±0.03 **Linearity:** 50-250 ng/band	224nm	[21,24]

VI. CONCLUSION

Nemerous techniques for identifying Remogliflozin and other combination medications have been documented according to one article, rphplc testing techniques were employed to evaluate remogliflozin. There are additional reports of UV techniques. Additionally reported are research papers on LC-MS, UPLC, and LC-MS, RP-UHPLC/DAD techniques are described that use Metformin and remogliflozin in both bulk and dosage form. Remogliflozin Etabonate could be determined using the suggested RP-HPLC method efficiently. Every parameter used to analyze Remogliflozin Etabonate complied with the ICH standards for Method Validation. The routine measurement of Remogliflozin Etabonate in pharmaceutical formulations and bulk drugs may benefit from the use of these developed technologies.

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