ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF REMOGLIFLOZIN ETABONATE: REVIEW

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ABSTRACT

Analytical method development and validation are the continuous and inter-dependent task associated with the research & development, quality control and quality assurance departments. Analytical procedures play a critical role in equivalence and risk assessment, management. It helps in establishment of product-specific acceptance criteria and stability of results. Validations determine that the analytical procedure is suitable for its intended purpose. Literature survey reveals that the analytical methods based on UV spectrometry, RP-HPLC and HPTLC for the determination of Remogliflozin etabonate personally and in combination with different drugs. The parameters were validated according to ICH guideline in terms of accuracy, precision, robustness, and other components of analytical validation. The developed methods are simple, sensitive and reproducible and can be used for the analysis of Remogliflozin etabonate in bulk and Tablet dosage form.

KEYWORDS: Remogliflozin Etabonate, UV, HPLC, Validation, ICH Guidelines.

INTRODUCTION

Remogliflozin etabonate is an orally available prodrug of Remogliflozin, a benzyl pyrazole glucoside-based inhibitor of renal sodium-glucose co-transporter subtype 2 (SGLT2) with antihyperglycemic activity. Upon administration and absorption, the inactive prodrug is converted to its active form Remogliflozin and acts selectively on the sodium-glucose co-transporter subtype 2 (SGLT2).[1-2]

STRUCTURE
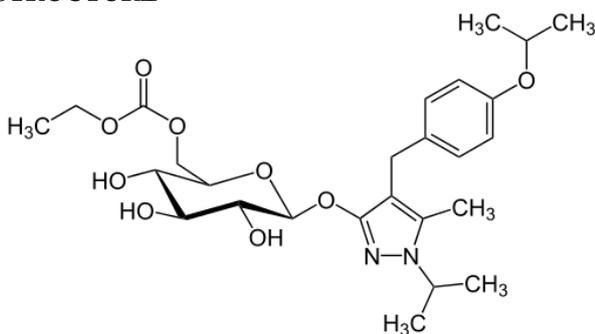
Remogliflozin etabonate is chemically known as 5-Methyl-4-[4-(1-methylethoxy) benzyl]-1-(1-methylethyl)-1H-pyrazol- 3-yl 6-O- (ethoxy carbonyl)-β-D-glucopyranoside, with a molecular formula of $C_{26}H_{38}N_2O_9$ and a molecular weight of 522.595 g.mol⁻¹. Remogliflozin etabonate is a White Solid powder and it is soluble in organic solvents such as Dimethyl sulfoxide and Ethanol, insoluble in water. And consisting a dose range of 100mg.[3]

REVIEW OF LITERATURE

1. **Paresh Patel[4]** *et al.,* have developed, A simple, precise and sensitive UV spectrophotometric method has been developed for the estimation of Remogliflozin etabonate in bulk and pharmaceutical dosage Form. Remogliflozin etabonate shows Maximum Absorbance at 229nm. Beer's law was obeyed in range of 2-10μg/ml. The correlation coefficient was found to be 0.9990. The result of interday and intraday precision shows standard deviation ranging from 0.050% - 0.254% and 0.058% - 0.258% for three concentration and three replicates. The Percentage recovery was found to be in the range of 98.94% - 99.86%. The LOD and LOQ were found to be 0.037μg/ml and 0.113μg/ml respectively. The purposed method was novel and successfully applied for the determination of Remogliflozin Etabonate in Tablet Dosage Form. The method was successfully validated according to ICH guidelines

2. **Husnain Fathima[5]** *et al.,* have developed new, A simple, sensitive, accurate, rapid and economical Spectrophotometric method was developed for estimation and validation of Remogliflozin Etabonate in pure drug and tablet dosage form. The absorbance was measured at 239.8nm using

Ethanol as solvent system. It obeyed Beer's law at the concentration range of 2-14µg/ml with coefficient of correlation (r2) of 0.997. Limit of detection (LOD) was found to be 1.220µg/ml and Limit of quantitation (LOQ) was found to be 5.220µg/ml. The proposed analytical method was validated according to ICH guidelines, yielded good results concerning range, linearity, precision, accuracy, robustness and ruggedness.

3. **Attimarad[6],** *et al*. have developed, the result of pharmaceutical industry research for the new class and the new combination of drugs for the treatments of diabetes is the newly approved combination of metformin (MET) and remogliflozin (REM). For the quality control of this formulation, three smart, reproducible and non-sophisticated spectroscopic techniques were developed by modification of UV spectra. The first two methods were based on the measurements of the peak height of the third derivative and second derivative ratio spectra of MET and REM and the third method was the constant centre spectrum subtraction method. The proposed methods exhibited Beer's law in the range of 2.5 to 30 µg/ml and 1 to 24 µg/ml for MET and REM correspondingly by all three methods. The mean percentage recovery was found to be in the range of 99.08% to 100.15% for MET and 98.73% to 100.27% for REM. The suggested techniques are simple, accurate and reproducible, hence could be used for regular quality control of formulation consisting of MET and REM.

4. **Itigimatha[7]** *et al*., have developed, Simple, novel and selective reverse phase-high performance liquid chromatography (RP-HPLC) and ultraviolet (UV) spectroscopic methods have been developed and optimized for the determination of remogliflozin etabonate (RMZ) in bulk and dosage forms. In the HPLC method, the principal peak and internal standard peak were eluted separately at different retention times (RT) with the chromatographic conditions such as, mobile phase consisting of 0.02 M ammonium acetate buffer (pH was adjusted to 4.0 by 1.0 M ortho phosphoric acid), acetonitrile and tetrahydrofuran in the ratio 50:45:05, respectively (v/v) and the stationary phase used was C18, 5 µm, 4.6 mm x 250 mm kromasil column. The flow rate was 2.0 ml/min, sample injection volume was 10 µL, and the wavelength of detection was fixed at 228 nm. In case UV spectroscopic method, the RMZ was diluted with pure ethanol. The RMZ showed a maximum absorbance at 228 nm. Hence throughout analysis 228 nm was used for the determination of RMZ.The RT of RMZ and internal standard, atorvastatin (ATST) were 6.2 min and 7.0 min, respectively. The resolution between the peaks was found to be more than 2.0. The total run time was fixed at 10 min. The linearity range for RP-HPLC method was found to be 10 µg/ml to 50 µg/ml, at a

fixed concentration of ATST. The linearity range for the UV spectroscopic method was found to be in the range of 100 to 250 µg/ml. Regression coefficients (R2) were found above 0.999 for both of the techniques. The limit of detection and quantification for RMZ were found to be 1.0 µg/ml and 3.5 µg/ml respectively, in RP-HPLC method and 10.0 µg/ml and 40 µg/ml, respectively, in UV spectroscopic method. The developed methods were found to be simple, accurate, reproducible, and precise. The RMZ can be analysed in dual techniques, *i.e.*, chromatographic and UV spectroscopic methods for its routine analysis.

5. **Dr. R. Srinivasan[8]** *et al.,* SGLT is the newly developed class of antidiabetic medicine also called as gliflozins. Remogliflozin and Ertugliflozin 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 Ertugliflozin in bulk and in pharmaceutical dosage forms using chromatographic and spectrophotometric methods. Remogliflozin and Ertugliflozin is estimated by RP-HPLC, UV, RP-UPLC, LC-MS methods. In present review account, the disclosed analytical methods are outlined for the establishment of Remogliflozin and Ertugliflozin 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 Remogliflozin and Ertugliflozin alone and in combination include parameters like λ max, solvent, matrix etc. and HPLC methods for Remogliflozin and Ertugliflozin 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.

6. **Trivedi[9]** *et al.,* have developed A simple, rapid, economical, precise and accurate Stability indicating RP- HPLC method for simultaneous estimation of Remogliflozin Etabonate and Metformin HCl in their Synthetic Mixture and tablet dosage form has been developed. A reverse phase high performance liquid chromatographic method was developed for the simultaneous estimation of remogliflozin etabonate and metformin HCl in their Synthetic Mixture has been developed. The separation was achieved by Cosmosil C18 (250mm x 4.6mm, 5µm) column and Buffer (pH 4.0): methanol (60:40) as mobile phase, at a flow rate of 1 ml/min. Detection was carried out at 241 nm. Retention time of remogliflozin etabonate and Metformin HCl were found to be 5.493 min and 3.183 min respectively. The method has been validated for linearity, accuracy and precision. Linearity observed for remogliflozin etabonate 5-15 µg/ml and for

Metformin Hcl 20-60 μg/ml. Developed method was found to be accurate, precise and rapid for simultaneous estimation of remogliflozin etabonate and Metformin Hcl in their Synthetic Mixture. The proposed method was successfully applied for the simultaneous estimation of both the drugs in commercial synthetic mixture.

7. **Mahesh Attimarad[10]** *et al.,* have developed a new formulation containing metformin HCl (MFH) and remogliflozin etabonate (RGE) has been approved for the management of diabetes mellitus. However, only one analytical method has been reported for the simultaneous determination of both the analytes. Therefore, the current study was designed to develop simple UV derivative spectroscopic and rapid RP-HPLC methods for simultaneous determination of MFH and RGE. The chromatographic separation of MFH and RGE was performed using a monolithic C18 column with an optimized chromatographic condition carried out by full factorial Box–Behnken design model. The spectroscopic technique was based on the determination of peak amplitude of second-order derivative UV spectra at zero crossings. Further, UV spectroscopic and HPLC procedures showed good linearity in the range of 1–24 μg/mL and 2–150 μg/mL for RGE and 2–30 μg/mL and 5–200 μg/mL for MFH, respectively. The average percent assay was found to be 99.51% and 99.80% for MFH and 99.60% and 100.07% for RGE by spectroscopic and HPLC methods, respectively. The proposed methods were simple, accurate, precise, and rapid. Therefore, they can be used for regular quality control of MFH and RGE formulations and dissolution studies as well.

8. **Attimarad[11]** *et al.,* For the treatment of diabetes mellitus type 2, a new formulation containing vildagliptin and remogliflozin was developed. A simple and rapid RP-HPLC method employing linagliptin as an internal standard was developed for quality control of this medicine. Formulation analytes, including IS, were separated on a ZorbaxC18 column with isocratic elution of acetonitrile and phosphate buffer (pH 5) 55:45 v/v at a flow rate of 1.2 mL/min. The experiment was carried out at room temperature and monitored at a wavelength of 210 nm. The optimized HPLC approach revealed a satisfactory linearity in the concentration ranges of 10-60 μg/mL and 10-100 μg/mL for VIL and REM respectively, with good regression coefficient (R2≥0.998). The average accuracy for VL and REM was 99.57 percent and 100.59 percent, respectively, with allow percentage relative error. The method's precision was proven by the low percentage relative standard deviation. As a result, it might be utilized in any analytical laboratory for quality control of this formulation.

9. **Patel Richiben Vinod Bhai[12]** *et al.,* have developed a simple, precise, accurate and cost-effective RP-HPLC method for estimation of Remogliflozin etabonate and Vildagliptin from pharmaceutical dosage form. The chromatographic method was carried out using Agilent C18 (150mm*4.6mm) 5μm using mobile phase Methanol: Buffer pH3.5: Ceric ammonium nitrate (55:35:10 %v/v)). The flow rate was set 1.0ml/min with 20μL injection volume. Total run time 10min. Detection was carried out at wavelength of 254nm. The detector response was linear in the range of 150-450μg/ml for Remogliflozin etabonate and 75-225μg/ml for Vildagliptin. The % recoveries for Remogliflozin etabonate and Vildagliptin obtained in the accuracy study were 99.07-100.38% and 99.69-100.70% respectively. The LOD for Remogliflozin etabonate and Vildagliptin were found to be 0.0053μg/ml and 0.0038μg/ml respectively. LOQ for Remogliflozin etabonate and Vildagliptin were found to be 0.016μg/ml and 0.0011μg/ml respectively. Remogliflozin etabonate and Vildagliptin were also subjected to various stress condition like acid and alkali hydrolysis, oxidation, photolysis, and thermal degradation. The developed method is successfully applied for estimation of Remogliflozin etabonate and Vildagliptin from pharmaceutical dosage form.

10. **Mankar and Younas[13]** *et al.,* The recent analysis is required to do novel and simple, sensitive, efficient, precise, instant and reproducible RP-HPLC method for estimation of antidiabetic drug in the unit dosage form. Validation of this method is also planned to make it suitable for the actual use.

11. **V. A. Patel[14]** *et al.,* have developed for the treatment of diabetes mellitus, a new formulation containing remogliflozin etabonate (REMO) and metformin HCl (MET) has recently been approved. This study is aimed to develop simple and quick RP-UHPLC methods for measuring REMO and MET simultaneously. REMO and MET chromatographic separation were carried out on a Zorbax Eclipse Plus C18 (150×4.6 mm, 5 μm) column with acetonitrile: phosphate buffer (pH: 3) (60:40 %, v/v) mobile phase, 10 μl sample volume and 1.0 ml/min flow rate at 230 nm in a diode array detector. REMO had a99.51 % average percent assay, while MET had a 99.60 % average percent assay. The methods projected were simple, precise, accurate, and fast. They can also be used to verify the consistency of REMO and MET formulations regularly.

12. **Ahire and Balap[15]** *et al.,* Remogliflozin Etabonate (RE) is the latest addition to the sodium-glucose transport proteins 2 inhibitor class of drugs recently approved in India to manage type 2 Diabetes Mellitus. The present work describes the development and validation of an HPTLC method for RE. The chromatography was performed on pre-coated silica gel 60 F 254 plates using methanol:

toluene: ethyl acetate (1:4:5) v/v/v as mobile phase. A thin layer chromatographic (TLC) scanner set at 228 nm was used to directly evaluate the chromatograms in reflectance/absorbance mode. The drug was satisfactorily resolved with Rf 0.45. The method was validated according to the International Council on Harmonization (ICH) guidelines. The calibration plot was linear between 50–300 ng/b and respectively. In stability testing, RE was found to be susceptible to alkaline degradation. Because the method could effectively separate the drugs from their degradation products, it may be used as a stability-indicating method.

13. **Shah[16]** *et al.,* A sensitive, precise, and stability-indicating high-performance thin-layer chromatographic (HPTLC)method has been developed for the analysis of Remogliflozin etabonate in tablet formulation. HPTLC plates precoated with silica gel 60 F254 were used as the stationary phase; methanol: ethyl acetate: toluene: NH_3(2:4:4:0.1,v/v) was used as mobile phase, and densitometry was used for the quantitative estimation of the drug. The proposed method was validated with respect to linearity, accuracy, precision, and robustness and applied for the estimation of drug in tablet dosage form. Results: The Rf value of Remogliflozin etabonate was observed to be 0.61. The densitometric estimation was performed in reflectance mode at 229 nm. The method was found to be linear in the range of 500–8000 ng/band for Remogliflozin etabonate. The possible degradation pathway was estimated by performing forced degradation studies. The degradant peaks were well resolved from the drug peak with acceptable resolution in their Rf value. An accurate and precise high-performance thin-layer chromatographic method has been developed for the quantification of Remogliflozin etabonate in tablets. Forced degradation studies were performed, and drug was found to be highly susceptible to acid, base hydrolysis, and oxidative stress degradation and gets converted into active drug Remogliflozin. Both Remogliflozin etabonate and Remogliflozin bands were well resolved. The method was applied for the analysis of drug in tablet formulation, and it can be used for routine quality control analysis, as well as for the analysis of stability samples.

14. **Dhara[17]** *et al.*, A simple, sensitive, precise, accurate and specific Chromatography RP-HPLC method has been developed and validated for estimation of Remogliflozin Etabonate and Vildagliptin in Pharmaceutical dosage form. RP-HPLC method was carried out by Isocratic mode technique on a Reversed-Phase Cosmosil C18 (250 mm × 4.6 mm, 5 µm i.d) column. Detection wavelength was at 210 nm and mobile phase Acetonitrile: Water (60:40 % v/v). The flow rate was used 1.0 ml/min. The average retention times

for Remogliflozin Etabonate and Vildagliptin were 3.29 min and 5.64 min, respectively. The calibration curves were linear (r2 > 0.999) over the concentration rage 10-80 µg/ml for Remogliflozin Etabonate and 5-40 µg/ml for Vildagliptin. The r2 values was found to be 0.9997 and 0.9992 for Remogliflozin Etabonate and Vildagliptin, respectively. LOD was found to be 0.010 µg/ml and 0.029 µg/ml for Remogliflozin Etabonate and Vildagliptin, respectively and LOQ was found to be 0.031 µg/ml and 0.088 µg/ml respectively. Suitability of method for quantitative determination of compounds was confirmed by validation in accordance with the requirements of ICH guidelines.

15. **VD Suryavanshi[18]** *et al.,* A simple, rapid, economical, precise and accurate RP-HPLC method for simultaneous estimation of Remogliflozin Etabonate and Metformin HCl in their tablet dosage form has been developed. The separation was achieved by C18 (4.6 mm X 10 cm) column containing packing L1 and HPLC Grade water: methanol (60:40) as mobile phase, at a flow rate of 0.7 ml/min. Detection was carried out at 230 nm. Retention time of Remogliflozin etabonate and Metformin HCl were found to be 4.351 min and 3.294 min respectively. The method has been validated as per ICH guidelines for linearity, accuracy, repeatability, precision, and robustness. Linearity observed for Remogliflozin etabonate 20-100 µg/ml and for Metformin HCl100-500 µg/ml with correlation coefficient greater than 0.999. Developed method was found to be accurate, precise and rapid for simultaneous estimation of Remogliflozin etabonate and Metformin HCl in their Synthetic Mixture.

16. **S. V. Badke[19]** *et al.,* Within the scope of this investigation, an HPTLC technique for measuring the concentrations of Remogliflozin etabonate (REMO) and Vildagliptin (VIL) in a commercial product named REMO-V, which contains 100 mg of REMO and 50 mg of Vildagliptin (VIL), was developed. It was necessary to evaluate the new approach for linearity, precision, specificity, and robustness in order to ensure that it operated properly. The chromatograms were created using a mobile phase containing Chloroform as follows: The concentrations of toluene, methanol, and n-butanol (4.5:4:1:0.5, v/v) were measured on a pre-coated TLC aluminium pre-coated plate (60F 254), and the absorbance at 233 nm was used to determine the amount of each component present. It was necessary to conduct forced degradation testing on bulk medicinal material in order to demonstrate the new method's capacity to demonstrate how stable and specific it is. The Rf values for Remogliflozin etabonate (0.63), Vildagliptin (0.75), and Remogliflozin etabonate (0.63), respectively, were 0.63 and 0.75. On the REMO side, the linearity of

the technique was found to be between 20 and 60 g/band; on the VIL side, it was found to be between 10 and 30 g/band. Having R2 values of 0.9939 for both REMO and VIL, it is clear that there is significant linearity in the way they interact with one another. These are the lower limits of detection and quantification for REMO, which were 0.09 for VIL and 0.38 for REMO, respectively, when compared to the upper limits of detection and quantification for VIL. The lower detection and quantification limits for VIL are also the same as for other pathogens. RSD was less than 2 percent in this study. Thus, the approach was shown to be accurate and exact for both interday and intraday accuracy, indicating that it is reliable. The amount of REMO or VIL that might be recovered is as follows: 98.7 percent to 101.27 percent, and 97.37 percent to 100.83 percent were the results. It was discovered that the method for determining Remogliflozin and Vildagliptin was easy, accurate, and stable in both its pure form and its tablet dose form and that it could be used to both (REMO-V, Glenmark, Ltd).

17. **Padmanabh B. Deshpande**[20] *et al.,* The present work describes development and validation of a new simple, accurate and precise stability-indicating high performance thin layer chromatographic (HPTLC) method for determination of Remogliflozin etabonate as bulk drug and in tablet dosage form. As stability testing is major step in the development of new drug as well as formulation, stress degradation studies were carried out according to ICH guidelines. Remogliflozin etabonate was found susceptible to all the analysed stress conditions. HPTLC plates precoated with silica gel 60 F254 were used as the stationary phase and chromatographic separation was achieved by using Toluene: Methanol (8.5:1.5,v/v) as mobile phase. Densitometric detection was carried out at 224 nm. The retention factor was found to be 0.35 ± 0.03. The developed method was validated with respect to linearity, accuracy, precision, limit of detection, limit of quantitation and robustness as per ICH guidelines. The developed method was found to be linear in the concentration range of 50-250 ng band-1. The LOD and LOQ for Remogliflozin etabonate was found to be 13.04 ng band-1and 35.04 ng band-1, respectively. The developed method has been effectively applied for the drug estimation in tablet dosage form.

CONCLUSION
Literature survey suggested that various UV[4-8], HPLC[9-15], HPTLC[16-20] and few simultaneous methods were developed and reported. The published methods were validated for various parameters as per ICH guidelines. Statistical analysis proved that the published methods were reproducible and selective. Thus, it can be concluded that the reported and published methods can be successfully applied for the estimation of the Remogliflozin etabonate in pure and pharmaceutical dosage form.

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