Review Article

Developed Analytical Methods and Validation for the Determination of Remogliflozin Etabonate, Vildagliptin and Metformin Hydrochloride in Pharmaceutical Dosage Forms – An Updated Review

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ABSTRACT

Vildagliptin, Remogliflozin Etabonate and Metformin Hydrochloride are used for treating type II diabetes, which belongs to the DPP-4, SGLT2 and Biguanide classes respectively. This review's primary objective is to provide an update on the techniques used to measure Vildagliptin, Remogliflozin Etabonate and Metformin Hydrochloride in pharmaceutical dosage forms and in bulk using chromatographic and spectrophotometric techniques. Vildagliptin, Metformin Hydrochloride and Remogliflozin Etabonate concentrations are estimated using the RP-HPLC, UV, RP-UPLC, GC, HPTLC, and LC-MS techniques. Analytical methodologies and method validation are already well-documented in the literature. The disclosed analytical techniques for establishing Remogliflozin Etabonate, Vildagliptin and Metformin Hydrochloride in their pharmaceutical preparations and biological matrices are described in the current review account. The present review provides a summary of the most popular approaches, including spectrometric and liquid chromatographic procedures. Spectrophotometric methods for Remogliflozin Etabonate, Vildagliptin and Metformin Hydrochloride alone and in combination include parameters like matrix, λ max, solvent, etc. HPLC methods in alone and in combination include parameters like retention time, flow rate, stationary phase, mobile phase composition detection wavelength, etc. HPTLC methods include parameters like stationary phase, mobile phase, Rf value etc. This literature research also provides detailed information on the separation conditions for Vildagliptin, Remogliflozin Etabonate and Metformin Hydrochloride alone and in combination with other drugs.

Keywords: Remogliflozin Etabonate, Vildagliptin, Metformin Hydrochloride, RP-HPLC, UV, GC/MS, HPTLC, UHPLC, LC-MS/MS.

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INTRODUCTION

Remogliflozin Etabonate class of $SGLT_2$ inhibitor is not available in any Pharmacopoeia, 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-2yloxyphenyl) methyl]pyrazol-3-yl]oxyoxan-2-yl]methyl carbonate, CAS no. 442201-24-3, molecular formula $C_{26}H_{38}N_2O_9$, molecular weight 522.6 g/mol, melting point 154-157°C, pKa value 1.33 and log P value 3.33.[1]

Vildagliptin is also not available in any Pharmacopoeia, chemically known as (2*S*)-1-[2-[(3-hydroxy-1-adamantyl) amino]acetyl]pyrrolidine-2-carbonitrile, CAS no. 274901-16-5, molecular formula $C_{17}H_{25}N_3O_2$, molecular weight 303.4 g/mol, melting point 149-152°C, pKa value 9.03 and log P value 1.12.[2]

Metformin Hydrochloride is belongs to biguanide class and available in IP/BP/EP/USP, is chemically known as 3-(diaminomethylidene)- 1,1-dimethylguanidine; hydrochloride, CAS no. 1115-70-4, molecular formula $C_4H_{12}ClN_5$, molecular weight 165.6 g/mol, melting point 222-226°C, pKa value 12.3 and log P value 1.8.[3]

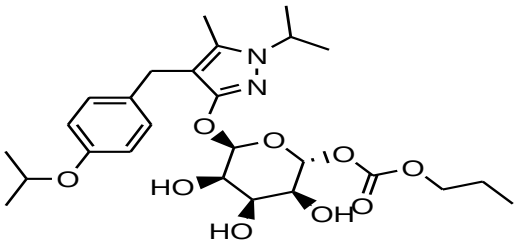

Figure 1: Chemical structure of Remogliflozin Etabonate

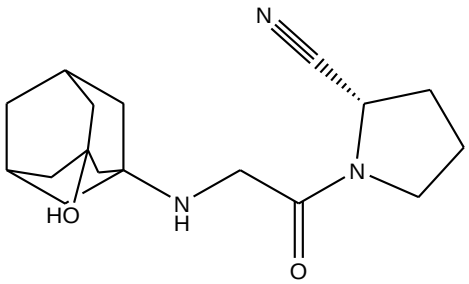

Figure 2: Chemical structure of Vildagliptin

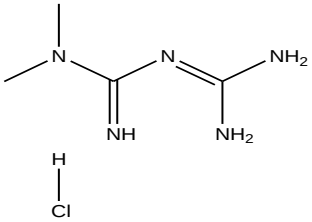

Figure 3: Chemical structure of Metformin Hydrochloride

LITERATURE REVIEW

Table 1: Reported analytical methods in combined dosage form

Sr.No	Drug	Method	Description	Detection wavelength	Ref no
1	Remogliflozin Etabonate, Vildagliptin and Metformin Hydrochloride	UV-VISIBLE spectroscopy	Solvent: Methanol Linearity: VLD: 1-5 µg/ml REM: 2-10 µg/ml MET: 10-50 µg/ml r^2: VLD: 0.9986 REM: 0.9973 MET: 0.9983 LOD: VLD: 0.0436 REM: 0.1015 MET: 0.0333 LOQ: VLD: 0.1322 REM: 0.3078 MET: 0.1009	VLD: 202 nm REM: 226-238 nm MET: 245 nm	4
2	Remogliflozin Etabonate, Vildagliptin and Metformin Hydrochloride	RP-HPLC	Mobile phase: Acetonitrile: Methanol:Water (60:10:30% v/v/v) (pH 4.5 adjusted with 1% OPA) Flow rate: 1.0 mL/min Retention time: VLD: 7.3 min REM: 4.4 min MET: 1.7 min	205 nm	

Remogliflozin Etabonate

Table 2: Analytical method development and validation for Remogliflozin Etabonate

Sr.No	Drug	Method	Description	Detection wavelength	Ref no
1	Remogliflozin Etabonate	UV spectroscopy	Solvent: Methanol Linearity: 2-10 µg/ml r^2: 0.999 LOD: 0.037 µg/ml LOQ: 0.113 µg/ml	229 nm	5
2	Remogliflozin Etabonate and Vildagliptin	Second derivative spectroscopy	Mobile phase: Ethanol Linearity: REM: 5-75 µg/ml VLD: 2-50 µg/ml r^2: REM: 0.9997 VLD: 0.9993 LOD: REM: 1.38 µg/ml VLD: 0.31 µg/ml LOQ: REM: 4.12 µg/ml VLD: 0.94 µg/ml	REM: 243 nm VLD: 221 nm	6
3	Remogliflozin Etabonate	RP-HPLC	Column: C18 (250 mm × 4.6 mm, 5 µm) Mobile phase: Methanol:Water (70:30% v/v) Flow rate: 1.0 ml/min Linearity: 1-25 µg/ml R^2: 0.997 LOD: 0.21 µg/ml LOQ: 0.66 µg/ml	229 nm	7
4	Remogliflozin Etabonate and Vildagliptin	RP-HPLC	Column: C18 (250 mm × 4.6 mm, 5 µm) Mobile phase: Water:Acetonitrile (60:40 % v/v) Flow rate: 1.0 ml/min Linearity: VLD: 5-40 µg/ml REM: 10-80 µg/ml	210 nm	8

			r^2: VLD: 0.9992 REM:0.9997 LOD: VLD: 0.029 µg/ml REM: 0.010 µg/ml LOQ: VLD: 0.088 µg/ml REM: 0.031 µg/ml		
5	Remogliflozin Etabonate And Metformin Hydrochloride	RP-HPLC	Column: C18 (250mm x 4.6mm, 5 µm) Mobile phase: Buffer (pH 4.0): methanol (60:40 % v/v) Flow rate: 1 ml/min Linearity: MET: 20-60 µg/ml REM: 5-15 µg/ml LOD: MET: 0.785 µg/ml REM: 0.764 µg/ml LOQ: MET: 2.380 µg/ml REM: 2.314 µg/ml	241 nm	9
6	Remogliflozin Etabonate and Metformin Hydrochloride	UHPLC/DAD	Column: C18 (5 µm, 4.6 mm x 150 mm) Mobile phase: Phosphate buffer (pH:4.5): Acetonitrile (60:40% v/v) LOQ: REM: 10 µg/ml MET: 50 µg/ml LOD: REM: 5 µg/ml MET: 10 µg/ml	230 nm	10

Vildagliptin

Table 3: Analytical method development and validation for Vildagliptin

Sr. No	Drug	Method	Description	Detection wavelength	Ref no
1	Vildagliptin	UV-VISIBLE spectrophotometric	Solvent: 0.1 N Hcl Linearity: 5–60 µg/ml r^2: 0.999 LOD: 0.951 µg/ml LOQ: 2.513 µg/ml	210 nm	11
2	Vildagliptin And Nateglinide	First Derivative Method	Solvent: Methanol Linearity: NGT: 9-45 µg/ml VLD: 5-25 µg/ml r^2: NGT: 0.9956 VLD: 0.9972 LOD: NGT: 2.105 µg/ml VLD: 1.986 µg/ml	NTG: 253 nm VLD: 270 nm	12
3	Vildagliptin	RP-HPLC	Column: C18 (150mm × 4.6mm, 5µm) Mobile phase: 1 ml of 25% Ammonium hydroxide:Methanol (60:40% v/v) (pH 9.5) Flow rate: 1.0 ml/min Linearity: 5-200 µg/ml r^2: 0.9997 LOD: 1.47 µg/ml LOQ: 4.90 µg/ml	210nm	13
4	Vildagliptin	RP-HPLC	Column: C18 (150mm × 4.6mm, 5µm) Mobile Phase: Acetonitrile: Triethylamine (pH 7.0) (15:85% v/v) Flow rate: 1.0 ml/min Linearity: 20–80 µg/ml r^2: 0.9999 LOD: 0.63 µg/ml LOQ: 2.82 µg/ml	207 nm	14

5	vildagliptin	RP-UHPLC	Column: C18 (150mm × 4.6mm, 5µm) Mobile Phase: Phosphate buffer (pH 6.8):Acetonitrile (67:33% v/v) Linearity: 10-50 µg/ml r^2: 0.9984 LOD: 0.01 µg/ml LOQ: 0.05 µg/ml	239 nm	15
6	vildagliptin	GC-MS	Column: (30 mm × 0.25 mm, 0.25 µm) Mobile phase: Methanol:Water (50:50% v/v) Linearity: 3.5–300 µg/mL r^2: 0.9968 LOD: 1.5 µg/ml LOQ: 3.5 µg/ml	-	16
7	Vildagliptin and Remogliflozin Etabonate	RP-UPLC	Column: C18 (2.1 × 50 mm, 1.7µm) Mobile phase: 0.1 M Acetate buffer(pH5.7): Methanol (25:75% v/v) Linearity: REM: 5-30 µg/ml VLD: 2.5-15 µg/ml r^2: REM: 0.9995 VLD: 0.9995 LOD: REM: 0.015 µg/ml VLD: 0.03 µg/ml LOQ: REM: 0.05 µg/ml VLD: 0.01 µg/ml	215 nm	17

Metformin Hydrochloride

Table 4: Analytical method development and validation for metformin Hydrochloride

Sr. No	Drug	Method	Description	Detection mode	Ref no
1	Metformin Hydrochloride	UV spectrophotometric	Solvent: Methanol Linearity: 8-13 µg/ml r^2: 0.9999 LOD: 1.0 µg/ml LOQ: 3.0 µg/ml	233 nm	18
2	Sitagliptin and Metformin Hydrochloride	UV-VISIBLE spectroscopy	Solvent: Distilled water Linearity: STG: 2-10 µg/ml MET: 20-60 µg/ml r^2: STG: 0.999 MET: 0.990 LOD: STG: 0.954 µg/ml MET: 1.2 µg/ml LOQ: STG: 2.89 µg/ml MET: 3.6 µg/ml	STG: 267 nm MET: 231 nm	19
3	Metformin Hydrochloride	HPLC	Column: C18 (250 mm x 4.6 mm, 5 µm) Mobile phase: 0.02 mM Acetate buffer (pH 3):Methanol (70:30% v/v) Linearity: 10-20 µg/ml r^2: 0.9999 LOD: 2.09 µg/ml LOQ: 3.46 µg/ml	235 nm	20
4	Saxagliptin Hydrochloride and Metformin Hydrochloride	HPLC	Column: C18 (4.6mm x 150 mm, 2.6 mm) Mobile phase: Acetonitrile: Phosphate buffer (pH 4.5) adjusted with orthophosphoric acid (13:87% v/v) Linearity: SAG: 5.58 µg/ml MET: 1000 µg/ml	220 nm	21

			r^2: SAG: 0.9998 MET: 0.9999 LOD: SAG: 0.478 µg/ml MET: 8.178 µg/ml LOQ: SAG: 1.447 µg/ml MET: 24.782 µg/ml		
5	Metformin Hydrochloride	GC-MS	Column: (30 mm x 0.25 mm x 0.25 µm) Solvent: Acetonitrile Linearity: 10-50 µg/ml r^2: 0.9972 LOD: 3.9 µg/ml LOQ: 12 µg/ml	-	22
6	Metformin Hydrochloride	HPTLC	Mobile phase: Ammonium sulfate (0.5%):2-Propanol:Methanol (8:1.6:1.6% v/v/v) R_f value: 0.50±0.03 Linearity: 200-1000 µg/ml r^2: 0.999 LOD: 95 µg/ml LOQ: 200 µg/ml	238 nm	23
7	Metformin Hydrochloride and Empagliflozin	RP-UPLC-DAD	Column: UPLC (100mm x 2.1 mm,1.8µm) Mobile phase: 0.1% Ortho Phosphoric acid buffer (pH 3.4) (with 0.1 N NaOH):Methanol (40:60% v/v) Flow rate: 0.25 ml/min Linearity: EMP: 15-75 µg/ml MET: 25-125 µg/ml r^2: EMP: 0.9995 MET: 0.999 LOD: EMP: 0.016 µg/ml MET: 0.072 µg/ml LOQ: EMP: 0.964 µg/ml MET: 0.330 µg/ml	254 nm	24
8	Metformin Hydrochloride, Glimepiride and Pioglitazone	LC-MS/MS	Column: C18 (33x 4.6 mm, 5µ) Mobile phase: Dichloromethane: Iso amyl alcohol (9:1% v/v) Flow rate: 1 ml/min Linearity: GLP: 2.5–500 µg/ml PGT: 2.5–1,000 µg/ml MET: 10–1,500 µg/ml r^2: 0.999	-	25

CONCLUSION

Various methods for the determination of Vildagliptin, Remogliflozin Etabonate and Metformin Hydrochloride have been reported individually or in combination with other drugs, and for this combination UV-VISIBLE spectrophotometric and RP-HPLC methods are reported. Some of the article's conclusions determine that RP-HPLC assay methods were used to estimate Remogliflozin Etabonate, Vildagliptin and Metformin Hydrochloride. Some articles provide the determination of Vildagliptin, Remogliflozin Etabonate and Metformin Hydrochloride in combination with Teneligliptin, Nateglinide, and Sitagliptin in pharmaceutical dosage forms. Research papers on UPLC, HPTLC, GC and LC-MS/MS are also reported. Novel RP-UPLC/DAD methods for Empagliflozin and Metformin Hydrochloride in bulk and tablet formulation are also reported.

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