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A Review on: Validation of developed analytical methods for the determination of Metformin HCL, Vildagliptin, and Remogliflozin Etabonate in pharmaceutical dosage form.

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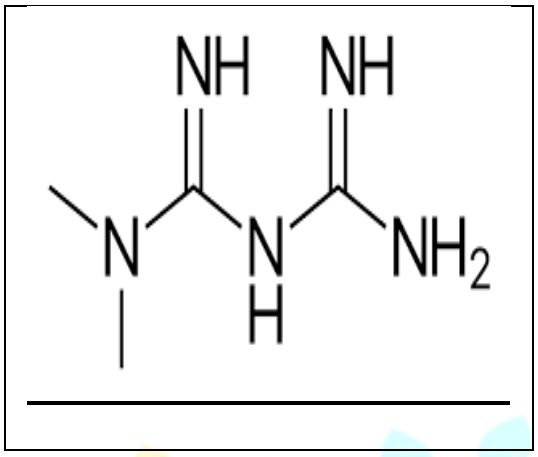
ABSTRACT:

Metformin HCL, Vildagliptin, and Remogliflozin Etabonate are comes under new class of sodium-Glucose Co-transporter 2 (SGLT-2) and dipeptidyl peptidase-4 (DPP-4) inhibitor respectively. The discovery, development and production of pharmaceuticals depend heavily on the development and validation of analytical methods. As more pharmaceuticals enter the market each year, it is imperative to create a new testing approach for these drugs. It is now important to validate the new analytical technique after development. The process of method development demonstrates that an analytical method is appropriate for application. Information on numerous phases and parameters, such as accuracy, precision, linearity, limit of detection, limit of quantification, specificity, range and robustness is provided through the validation of analytical methods. Validation should be carried out in accordance with regulatory standards, like the ICH standards. The development and validation of analytical methods are reviewed in this article. Dapagliflozin and Vildagliptin are alone estimated by RPHPLC, UV, RP-UPLC method.

Keywords: RP-HPLC, Metformin (MET), Vildagliptin (VDG) and Remogliflozin (RMG), Diabetes Mellitus.

INTRODUCTION:

Metformin hydrochloride



Molecular formula: C4H11N5

Molecular Weight: 129.16

Synonyms: Metfromin.

IUPAC Name: 3-(diaminomethylidiene)-1,1-dimethylguanidine;hydrochloride.

Solubility: Water,Methanol.

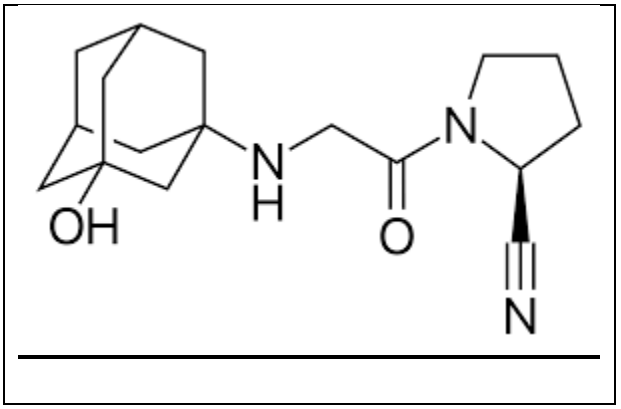
Category: Anti-diabetic agent.

Mechanism of action:

Metformin is an antihyperglycemic agent, which improves glucose tolerance inpatients with type 2 diabetes, lowering both basal and postprandial plasmaglucose. Its pharmacological mechanisms of action are different from other classesof oral antihyperglycemic agents. Metformin decreases hepatic glucose production,

decreases intestinal absorption of glucose, and improve insulin sensitivity byncreasing peripheral glucose uptake and utilization. Unlike sulfonylureas,metformin does not produce hypoglycemia in either patients with type 2 diabetes ornormal subjects and does not cause hyperinsulinemia. With metformin therapy,insulin secretion remains unchanged while fasting insulin levels and daylongplasma insulin response may actually decrease.

Vildagliptin



Molecular formula: C17H25N3O2

Molecular Weight: 303.399g/mol

IUPAC Name:(S)-1-[2-(3-Hydroxyadamantan-1-ylamino) acetyl]pyrrolidine-2-carbonitrile

Solubility: Water, Methanol.

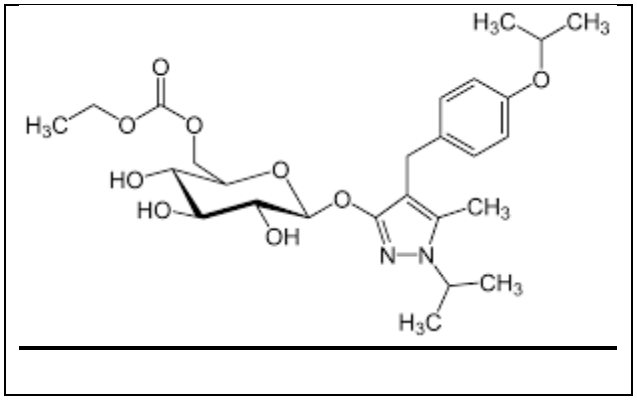
Category: Type-2 diabetes mellitus.

Mechanism of action:

Inhibition of dipeptidyl peptidase-4 (DPP-4) by vildagliptin preventsdegradation of glucagon-like peptide-1 (GLP-1) and reduces glycaemia inpatients with type 2 diabetes mellitus, with low risk for hypoglycaemia and noweight gain. Vildagliptin binds covalently to the catalytic site of DPP-4,eliciting prolonged enzyme inhibition. This raises intact GLP-1 levels, bothafter meal ingestion and in the fasting state. Vildagliptin has been shown tostimulate insulin secretion and inhibit glucagon secretion in a glucose-dependent manner. At hypoglycaemic levels, the counterregulatory glucagonresponse is enhanced relative to baseline by vildagliptin. Vildagliptin alsoinhibits hepatic glucose production, mainly through changes in islet hormone

secretion, and improves insulin sensitivity, as determined with a variety ofmethods. These effects underlie the improved glycaemia with low risk forhypoglycaemia. Vildagliptin also suppresses postprandial triglyceride (TG)-richlipoprotein levels after ingestion of a fat-rich meal and reduces fasting lipolysis,suggesting inhibition of fat absorption and reduced TG stores in non-fat tissues. The large body of knowledge on vildagliptin regarding enzyme binding, incretinand islet hormone secretion and glucose and lipid metabolism is summarized,with discussion of the integrated mechanisms and comparison with other DPP-4inhibitors and GLP-1 receptor activators, where appropriate..

Remogliflozin Etabonate



Molecular formula: C26H38N2O9 Molecular

Weight: 522.6

IUPAC Name: 5-Methyl-4-[4-(1-methylethoxy)benzyl]-1-(1-methylethyl)-1H-pyrazol-3-yl 6- O-(ethoxycarbonyl)-β-D-glucopyranosideSolubility: Methanol

Category: Oral hypoglycemic agent used to treat type-2 diabetes mellitus.Mechanism of action:

Remogliflozin etabonate is a pro-drug of remogliflozin. Remogliflozin inhibitsthe sodium- glucose transport proteins (SGLT), which are responsible forglucose reabsorption in the kidney. Blocking this transporter causes bloodglucose to be eliminated through the urine.[8] Remogliflozin is selective forSGLT2.

LITERATURE REVIEW OF REMOGLIFLOZIN ETABONATE:

REMOGLIFLOZIN ETABONATE is not official drug in any pharmacopoeia.

Table 1. Reported Methods for REMOGLIFLOZIN ETABONATE

<table>
<tr><th>Sr. No.</th><th>Title/Method</th><th>Description</th><th>Ref. No.</th></tr>
<tr><td>1.</td><td>A Validated Stability Indicating High Performance Thin Layer Chromatographic Method for Determination of Remogliflozin Etabonate in Tablet Dosage Form</td><td>Stationary Phase: Silica gel 60 F254 (100 mm ×100 mm, 250µm)
Mobile Phase: Toluene: Methanol (8.5:1.5% v/v)
Wavelength: 224nm
Rf value: 0.35±0.03
Linearity: 50-250 ng/band
Forced Degradation Study
<table>
<tr><th>Stress Condition</th><th>% Degradation</th></tr>
<tr><td>Acid Hydrolysis</td><td>18.39</td></tr>
<tr><td>Base Hydrolysis</td><td>18.40</td></tr>
<tr><td>Neutral Hydrolysis</td><td>13.60</td></tr>
<tr><td>Oxidative Hydrolysis</td><td>14.45</td></tr>
<tr><td>Thermal Hydrolysis</td><td>21.61</td></tr>
<tr><td>Photolytic</td><td>18.49</td></tr>
</table></td><td>11</td></tr>
</table>

		hydrolysis	
2.	Method Development and Validation of **UV Spectrophotometric** Estimation of **Remogliflozin Etabonate** in Bulk and Its Tablet Dosage Form	**Model**: Shimadzu 1800 **Solvent**: Methanol **Wavelength**: 229 nm **Linearity**: 2-10 µg/mL	12
3.	Development and Validation of Novel **RP-HPLC** Method for the Simultaneous Determination of **Remogliflozin** and **Vildagliptin** in Bulk and in Synthetic Mixture	**Stationary Phase**: Luna C18 (250mm ×4.6mm, 5µm) **Mobile Phase**: Acetate Buffer (pH 5.6): Methanol (30:70%v/v) **Wavelength**: 210 nm **Flow Rate**: 1.0 mL/min **Retention Time**: REM: 4.881 VDG: 6.334 **Linearity**: REM: 10-200µg/mL VDG: 10-200µg/mL	13
4.	Smart **UV Derivative Spectrophotometric** Methods for Simultaneous Determination of **Metformin** and **Remogliflozin** Development Validation and Application to The Formulation	**Model**: Shimadzu 1700 **Solvent**: Methanol, Water **Wavelength:** Third derivative Absorbance Method RGE:234.8nm MFH:240.1nm Zero cross point: RGE: 240.1nm MET: 234 nm Ratio Second derivative Method: Zero crossing point: RGE: 277.2nm MFH: 246.6nm Constant Centre Subtraction Method (Mixture of two analytes spectra into individual zero order	14

		spectra): **RGE: 226.2nm MFH: 232.9nm** **Linearity: RGE: 1-24µg/mL** **MFH: 2.5-30µg/mL**	

LITERATURE REVIEW OF VILDAGLIPTIN

VILDAGLIPTIN is not official drug in any pharmacopoeia

Table 2. Reported Methods for VILDAGLIPTIN

Sr. No.	Title/Method	Description	Ref. No.
1.	**RP-HPLC** Determination of **Vildagliptin** in Pure and In Tablet Formulation	**Stationary Phase**: Agilent C18, (150mm × 4.6mm ,5µm) **Mobile Phase**: Phosphate Buffer: Acetonitrile (85:15% v/v) **Wavelength**: 210nm **Flow Rate**: 1.0 mL/min **Retention Time**: 3.04 min **Linearity**: 10-150 mg/mL	15

2.	Second Order Derivative **UV Spectrophotometric** and **RP-HPLC** Method for The Analysis of **Vildagliptin** and Application for Study	**UV** **Model**: Shimadzu 1800 **Solvent**: Water **Wavelength**: Zero crossing point: 220 nm **Linearity**: 25-125µg/mL **RP-HPLC** **Stationary Phase**: C8 (150mm × 4.6mm, 5µm) **Mobile Phase**: Potassium Phosphate Buffer (pH 7): Acetonitrile (85:15 %v/v) **Wavelength**: 207nm	16

		Flow Rate: 1mL/ min **Linearity**: 10-90 µg/mL	
3.	Development and Validation of a **RP-HPLC** Method for the Assay of **Vildagliptin**	**Stationary Phase**: Symmetry C18 (4.6mm×150mm, 5µm) **Mobile Phase**: Buffer (pH 8.2): Acetonitrile: Methanol (450: 480:70%v/v) **Wavelength**: 254nm **Flow Rate**: 0.5mL/min **Retention Time**: 3.906 min **Linearity**: 50-90 µg/mL	17
4.	**RP-HPLC** Method Development and Validation of **Vildagliptin** in Bulk and Dosage Form	**Stationary Phase**: Phenomenex C18 (250mm×4.6mm,5µm) **Mobile Phase**: Methanol: Water (At pH 4.5 adjusted with OPA) (60: 40%v/v) **Wavelength**: 207nm **Flow Rate**: 0.8 mL/min **Retention Time**: 3.58 min **Linearity**: 10-60µg/mL	18
5.	Spectrophotometric Method for the Determination of **Vildagliptin** in Bulk and Pharmaceutical Dosage Forms	**Model**: Shimadzu 18001 **Solvent**: 0.5 m HCl **Wavelength**: 202.5nm **Linearity**: 10-40 µg/mL	19
6.	Method Development and Validation of **Vildagliptin** Using **UV Spectrophotometer**	**Model:** Shimadzu 1601 **Solvent**: Water **Wavelength**: 244 nm **Linearity**: 12.5-200 µg/mL	20

LITERATURE REVIEW OF METFORMIN HYDROCHLORIDE

Table 3. Official Method for Metformin Hydrochloride

Sr. No.	**Official In**	**Title/Method**	**Description**	**Ref. No.**
1.	**IP 2018**	Chromatographic Methods	**Stationary Phase**: A Stainless-Steel Column 30 cm × 4mm, Packed with Octadecylsilane bonded to porous silica (10 µm) **Mobile Phase**: A Solution Containing 0.087% w/v of Sodium Chloride, adjusted to pH 3.5 using 1% v/v solution of orthophosphoric acid **Flow Rate**: 1 mL/min **Wavelength**: 218nm **Injection Volume**: 20µl	21
2.	BP-2003	Liquid Chromatography	**Stationary Phase**: Irregular, Porous Silica gel to which Benzene sulphonic acid groups have been chemically bonded (0.25m, 4.7mm, 10µm) OR Regular, Porous Silica gel to which Benzene sulphonic acid groups have been chemically bonded (0.11m, 4.7mm, 5µm) **Mobile Phase**: 17g/l solution of ammonium dihydrogen phosphate R adjusted to pH 3.0 with phosphoric acid R. **Flow Rate**: 1mL/min **Wavelength:** 218nm **Injection Volume**: 20µl	22

Table 4. Reported Method for METFORMIN HYDROCHLORIDE

Sr. No.	Title/Method	Description	Ref. No.
1.	Development and Validation of **UV Spectrophotometric** Method for Estimation of **Metformin** in Bulk and Tablet Dosage Form	**Model**: Shimadzu 1800 **Solvent**: Sodium Hydroxide **Wavelength**: 233 nm **Linearity**: 1-25µg/mL	23
2.	**RP-HPLC** Method Development of **Metformin** in Pharmaceutical Dosage Form	**Stationary Phase**: Thermosil C18 **Mobile Phase**: Water: Acetonitrile (40: 60%v/v) **Wavelength**: 232nm **Flow Rate**: 1.0mL/min **Retention Time**: 3.25 min **Linearity**: 20-60µg/mL	24
3.	Development and Validation of a New Analytical **HPLC** Method for Simultaneous Determination of the Antidiabetic Drugs **Metformin** and **Gliclazide**	**Stationary Phase**: C18 (250mm×4.6mm ×5µm) **Mobile Phase**: Ammonium Formate Buffer (pH 3.5): Acetonitrile (45:55% v/v) **Wavelength**: Metformin: 234nm Gliclazide: 228nm **FlowRate**:1mL/min **Retention Time:** Metformin: 4.101min Gliclazide: 6.964min **Linearity**: Metformin: 2.5-150 µg/mL Gliclazide: 1.25-150 µg/mL	25

CONCLUSION

There have been several reported techniques for determining Metformin HCL, Vildagliptin, and Remogliflozin Etabonate .According to the article, RP-HPLC assay techniques were used to assess the amounts of Metformin HCL, Vildagliptin, and Remogliflozin Etabonate .In several publications, the pharmacological dosage forms of dapagliflozin, vildagliptin, metformin, saxagliptin, and remogliflozin are determined. Also reported are UV techniques. Additionally reported are studies on UPLC.

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