REVIEW ON ANALYTICAL METHODS FOR QUANTITATIVE ESTIMATION OF REMOGLIFLOZIN ETABONATE AND METFORMIN HYDROCHLORIDE IN PHARMACEUTICAL DOSAGE FORM

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ABSTRACT
Remogliflozin etabonate chemical name is Ethyl [(2R, 3S, 4S, 5R, 6S)-3,4,5 trihydroxy-6-[[ 5 methyl-1-(propan-2-yl) -4-[[4-(propan-2-yloxy) phenyl] methyl]-1H-pyrazol-3-yl] oxy] oxan-2-yl ] methyl carbonate. Metformin hydrochloride chemical name is 3-(diaminomethylidene)-1,1- dimethyl guanidine; hydrochloride. This both drugs used as anti-hyperglycemic agent. Remogliflozin etabonate is Inhibitor of Sodium-Glucose Co-transporter-2 that is responsible for glucose reabsorption in the kidney, blocking this transporter causes blood glucose to be eliminated from the urine; it is a selective SGLT-2. Metformin hydrochloride is decreasing in blood glucose by decreasing hepatic glucose production, decreasing in intestinal absorption of glucose and by improving insulin sensitivity by increasing the peripheral glucose uptake neutralization. All of this are mediated by ability of metformin to activate AMPk- activated protein kinase. So, both this combination is used as anti-hyperglycemic agent. A comprehensive literature review is prepared for Remogliflozin etabonate and metformin hydrochloride.

KEYWORDS:- Remogliflozin etabonate, Metformin hydrochloride, Anti-hyperglycemic agent, Analytical methods.

INTRODUCTION
Remogliflozin etabonate is chemically known as Ethyl [(2R, 3S, 4S, 5R, 6S)-3, 4,5...
trihydroxy-6-{[5 methyl-1-(propan-2-yl) -4-{[4-(propan-2-yl)oxy) phenyl] methyl-1H-pyrazol-3-yl] oxy] oxan-2-yl] methyl carbonate. Inhibitor of Sodium-Glucose Co-transporter-2 that is responsible for glucose reabsorption in the kidney, blocking this transporter causes blood glucose to be eliminated from the urine, it is a selective SGLT-2. It is used for type-2 diabetes. Also use in case of non-alcoholic hepatitis. Metformin hydrochloride chemically known as 3-(diaminomethylidene)-1, 1- dimethyl guanidine; hydrochloride. Decreasing in blood glucose by decreasing hepatic glucose production, decreasing in intestinal absorption of glucose and by improving insulin sensitivity by increasing the peripheral glucose uptake neutralization. All of this are mediated by ability of metformin to activate AMPk- activated protein kinase.

**Physical properties and chemical properties**[3-7]

Remogliflozin etabonate is White powder its IUPAC name is Ethyl [(2R, 3S, 4S, 5R, 6S)-3,4,5 trihydroxy-6-{[5 methyl -1-(propan-2-yl) -4-{[4-(propan-2-yl)oxy) phenyl] methyl]-1H-pyrazol-3-yl] oxy] oxan-2-yl] methyl carbonate, its molecular formula is C_{26}H_{38}N_{2}O_{9}, its category is Anti-hyperglycemic agents. Molecular weight is 522.6 g/mol. It is soluble in methanol, ethanol and slightly soluble in water.

Metformin Hydrochloride is White or almost White crystalline powder its IUPAC name is 3-(diaminomethylidene)-1,1- dimethyl guanidine; hydrochloride, its molecular formula is C_{4}H_{12}ClN_{5}, its category is Anti-hyperglycemic agent. Molecular weight 165.6 g/mol. It is soluble in Methanol, water.

![Remogliflozin etabonate](image1)

*Fig. 1: Remogliflozin etabonate.*

![Metformin hydrochloride](image2)

*Fig. 2: Metformin hydrochloride.*
Marketed formulation of remogliflozin etabonate and metformin hydrochloride

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Brand name</th>
<th>Company name</th>
<th>Formulation</th>
<th>Dose</th>
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<tr>
<td>1</td>
<td>ZUCATOR 500</td>
<td>Glenmark Pharmaceuticals Ltd, Himachal Pradesh</td>
<td>Tablet</td>
<td>100/500</td>
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<tr>
<td>2</td>
<td>REMO M 500</td>
<td>Glenmark pharmaceuticals Ltd., Solan</td>
<td>Tablet</td>
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<tr>
<td>3</td>
<td>SGLTR-M</td>
<td>Mankind pharma Ltd, New Delhi</td>
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</table>

Analytical method development\(^{[1,2]}\)

Analytical chemistry may be explained as the science and art of governing the composition of material in terms of elements or compounds contained in it. Analytical chemistry is separated into two branches namely quantitative and qualitative. Qualitative analysis provides guidance about the identity of atomic or molecular species or functional groups in sample whereas quantitative analysis gives numerical direction as to the respective amount of one or more of these components. The instrumental methods are simple, precise and reproducible as compared to classical methods. Therefore, analytical methods developed using sophisticated instruments such as spectrophotometer, HPLC, GC and HPTLC have wide applications in satisfying the quality and quantity of raw materials and finished products.

Need for drug analysis:

- An actual analytical procedure for drug may not be obtainable in the literature due to patent regulations.
- Analytical methods are not accessible for the drug in the form of a formulation due to the interference originated by the formulation excipients.
- Analytical techniques for drug in combination may not be obtainable with other drugs.
- Present analytical method involves expensive reagents and solvents may involve unmanageable extraction and separation procedure

Different methods, which are used, for the analysis of multi component are as follows:

1) Simultaneous Equation Method
2) Derivative spectrophotometric method
3) Absorbance ratio method (Q – absorbance method)
4) Area under curve method
5) Dual wavelength method
6) Difference spectrophotometry

Analytical methods are the methods utilized for the determination of the concentration of a
chemical compound or chemical constituent. There is a vast variety of techniques used for analysis, from simple weighing (gravimetric analysis) to titrations (titrimetric analysis) to very advanced techniques using highly specialized instrumentation (spectrometry and chromatography).

Types of Analytical methods the pharmaceutical analysis can be conducted with various methods, which are classified accordingly as mentioned below:

1. Qualitative analysis: the qualitative analysis finds the nature of the substance, and if it is a mixture, the nature of the components present.
2. Quantitative analysis: the Quantitative analysis determines the elemental composition of constituent and the quantitative allocation of each component.

**Further, they are classified as**

a. Instrumental methods
b. Non-instrumental method
   - Analytical techniques for the quantitation of the drug in the biological fluids may not be accessible.
   - Analytical techniques for the drugs in the combination with other drugs are not convenient. It may also require unhandy extraction and separation process and these may not be reliable.
   - The existing analytical process may require costly reagents and solvents.
   - Analytical techniques that are mainly used for drug analysis are biological and microbiological methods, radioactive methods, physical methods and miscellaneous techniques like conventional Titrimetric, gravimetric and Polarimetric methods.
➢ Literature review

Remogliflozin etabonate

It is not official in any pharmacopoeia

➢ Reported method of remogliflozin etabonate

<table>
<thead>
<tr>
<th>Sr. no.</th>
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<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Stability indicating liquid chromatographic method for the estimation of Remogliflozin Etabonate</td>
<td><strong>Model:</strong> Agilent HPLC system  <strong>Stationary phase:</strong> Shimadzu C18 column  <strong>Mobile phase:</strong> Methanol : Water (70:30 %v/v)  <strong>Wavelength:</strong> 229 nm  <strong>Flow rate:</strong> 1 mL/min  <strong>Linearity:</strong> 1-25 µg/mL  <strong>Retention Time:</strong> 10.4 min</td>
<td>[8]</td>
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% Degradation:

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<tr>
<td>Base</td>
<td>30 min</td>
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<td></td>
<td>15 min</td>
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<td></td>
<td>5 min</td>
<td>25.64</td>
<td>6.62</td>
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<tr>
<td>Acid</td>
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<td>-</td>
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<td>30 min</td>
<td>42.45</td>
<td>6.24</td>
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<td>Oxidative</td>
<td>2 hr</td>
<td>89.76</td>
<td>6.34</td>
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<tr>
<td>Dry heat</td>
<td>2 hr</td>
<td>94.31</td>
<td>8.46</td>
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<tr>
<td>Photolytic</td>
<td>24 hr</td>
<td>98.08</td>
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➢ Official method of metformin hydrochloride

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<th>Methods</th>
<th>Description</th>
<th>Ref no.</th>
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<tr>
<td>1</td>
<td>IP 2018</td>
<td>Liquid chromatography</td>
<td><strong>Stationary Phase:</strong> a stainless steel (30 cm x 4mm, 10µm)  <strong>Mobile phase:</strong> 0.087 % w/v Sodium pentane sulphonate and 0.12% w/v of sodium chloride pH 3.5 using OPA  <strong>Flow rate:</strong> 1 mL/min.  <strong>Wavelength:</strong> 218 nm  <strong>Injection volume:</strong> 20µl</td>
<td>[9]</td>
</tr>
<tr>
<td>2</td>
<td>BP 2010</td>
<td>HPLC</td>
<td><strong>Stationary Phase:</strong> a stainless steel (250mm x 4mm, 10µm)  <strong>Mobile phase:</strong> Ammonium Dihydrogen Phosphate pH 3.0 with Phosphoric Acid.  <strong>Flow rate:</strong> 1mL/min.  <strong>Wavelength:</strong> 218 nm  <strong>Injection volume:</strong> 20µL</td>
<td>[10]</td>
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- **Reported method for metformin hydrochloride:-**

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<tr>
<th>Sr. no.</th>
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<th>Description</th>
<th>Ref no.</th>
</tr>
</thead>
</table>
| 1       | Development and Validation of UV-Spectrophotometric Method for Estimation of Metformin in Bulk and Tablet Dosage Form | Model: Shimadzu UV-1800 UV/VIS spectrophotometer  
Solvent: distilled water  
Wavelength: 234 nm  
Linearity: 10-50 µg/mL | [11] |
| 2       | Development and validation of UV-Visible spectroscopy method for simultaneous estimation of Saxagliptin Hydrochloride and Metformin Hydrochloride in tablet dosage form | Model: Shimadzu UV-630 UV/VIS spectrophotometer  
Solvent: Distilled water  
Method: Simultaneous equation method  
Wavelength: MET: 231nm  
SAXA: 274 nm  
Linearity: MET: 2-10 µg/mL  
SAXA: 50-90 µg/mL | [12] |
| 3       | Simultaneous Equation Method Development and Validation for the Simultaneous Estimation of Teneligliptin hydrobromide hydrate and Metformin hydrochloride in Tablet Dosage Form | Model:- Shimadzu UV-VIS 1800 spectrophotometer  
Solvent: Distilled water  
Wavelength:  
For Simultaneous equation method  
MET:233 nm  
TEN: 243nm  
For absorbance ratio method  
Iso-absorptive point: 249.20 nm  
λmax of teneligliptin: 233 nm  
Linearity: MET: 6-16 µg/mL  
TEN: 6-16 µg/mL | [13] |
| 4       | Analytical Method Development and Validation of Metformin Hydrochloride and Benfotiamine in Bulk and Marketed Formulations | Model: Shimadzu UV/VIS 1800 spectrophotometer  
Solvent: Distilled water  
Wavelength:  
For Simultaneous equations Method:  
MET: 230 nm  
BEN:246 nm  
For Q – Absorbance Ratio Method:  
Iso-absorptive point: 239 nm  
λmax of Benfotiamine: 246 nm  
Linearity: MET: 2-16 µg/mL  
BEN: 2-18 µg/mL | [14] |
| 5       | Analytical method development and validation for simultaneous estimation of Teneligliptin hydrobromide hydrate and Metformin | Model: Shimadzu UV-VIS 1800 spectrophotometer  
Solvent: Methanol  
Wavelength:  
Simultaneous equation method  
MET: 246nm  
TEN: 237nm | [15] |
| 6 | Development and Validation of UV Spectrophotometric Method for Simultaneous Estimation of Metformin and Glipizide in Tablet Dosage Form | Model: Shimadzu UV-1800 UV/VIS spectrophotometer  
Solvent: Distilled water  
Method: Simultaneous equation method  
Wavelength:  
MET: 272 nm  
GPZ: 232 nm  
Linearity:  
MET: 5-25 μg/mL  
GPZ: 20-50 μg/mL | [16] |
|---|---|---|---|
| 7 | Spectrophotometric determination and Validation of Metformin hydrochloride and Glimepiride in bulk and tablet dosage form | Model: Shimadzu UV-1800 UV/VIS spectrophotometer  
Solvent: Methanol  
Method: Simultaneous equation method  
Wavelength:  
MET: 236 nm  
GLP: 228 nm  
Linearity:  
MET: 5-25 μg/mL  
GLP: 5-25 μg/mL | [17] |
| 8 | Simultaneous UV Spectrophotometric Methods for estimation of Metformin HCL and Glimepiride in bulk and tablet dosage form | Model: Shimadzu UV-1800 UV/VIS spectrophotometer  
Solvent: Methanol  
Wavelength:  
For Simultaneous equation method  
MET: 236 nm  
GLP: 228 nm  
For area under curve Method:  
MET: 117-147 nm  
GLP: 213-239 nm  
Linearity:  
MET: 5-25 μg/mL  
GLP: 5-25 μg/mL | [18] |
| 9 | Development and validation of UV spectrophotometric method for simultaneous estimation of metformin hydrochloride and Alogliptin benzoate in bulk drugs and combined | Model: Shimadzu UV-1800 UV/VIS spectrophotometer  
Solvent: Methanol  
Wavelength:  
For simultaneous equation method  
MET: 232 nm  
ALG: 277 nm  
For Absorbance ratio Method: | [19] |
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<tr>
<th>Case Study</th>
<th>Description</th>
<th>Model</th>
<th>Method</th>
<th>Solvent</th>
<th>Wavelength</th>
<th>Linearity</th>
<th>Retention time</th>
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<td>10</td>
<td>Simultaneous estimation of Sitagliptin and Metformin hydrochloride in bulk and dosage form by UV spectrophotometry</td>
<td>Shimadzu UV-1800 UV/VIS spectrophotometer</td>
<td>First order derivative spectroscopic method</td>
<td>0.1N NaOH</td>
<td>MET: 216 nm (Zero crossing point)</td>
<td>MET: 2-20 µg/mL</td>
<td>4.2 min</td>
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<tr>
<td>11</td>
<td>Analytical Method Development and Validation of Metformin Hydrochloride by using RP-HPLC with ICH Guidelines</td>
<td>HPLC-3000 system</td>
<td></td>
<td>50:50 %v/v</td>
<td>238 nm</td>
<td>10-20 µg/mL</td>
<td>11.12 min</td>
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<td>12</td>
<td>Development and Validation of A Reverse Phase HPLC Method for the Determination of Metformin HCl in Pharmaceutical Dosage Forms</td>
<td>HPLC system with Waters 2690</td>
<td></td>
<td></td>
<td>218 nm</td>
<td>20-60 µg/mL</td>
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<td>13</td>
<td>Development And Validation Of RP- HPLC Method For The Determination Of Metformin In Human Plasma</td>
<td>HPLC system Waters 2695</td>
<td></td>
<td></td>
<td>240 nm</td>
<td>0.05 - 5 µg/ml</td>
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<td>14</td>
<td>RP- HPLC Method Development and Validation for Simultaneous Estimation</td>
<td>Shimadzu HPLC system</td>
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<td>15</td>
<td>Method Development and Validation for Simultaneous estimation of Metformin HCL and Sitagliptin by RP-HPLC in Tablet Dosage Form</td>
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<tr>
<td>Method</td>
<td>Model: Shimadzu HPLC system Software (Prominence SPINCHROM) Stationary phase: Zodiac C18 (250mm x 4.6 mm, 5μm) Flow rate: 1 mL/min Mobile phase: phosphate buffer (pH 5.8 adjusted by NaOH): acetonitrile (55:45 %v/v) Wavelength: 244 nm Linearity: MET: 75-175 μg/mL SITA: 7.5-17.5 μg/mL Retention time: MET: 2.1 min SITA: 4.9 min</td>
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<tr>
<th>16</th>
<th>Analytical Method Development and Validation of Canagliflozin and Metformin HCl by Using RP - HPLC</th>
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<tr>
<td>Method</td>
<td>Model: HPLC system Waters 2695 Stationary phase: Column C18 (250mm x 4.6mm, 5μm) Mobile phase: 0.1% OPA: Methanol (60:40 %v/v) Flow rate: 0.5 mL/min Wavelength: 273 nm Linearity: MET: 50-300 μg/mL CANA: 5-30 μg/mL Retention time: MET: 2.693 min CANA: 4.227 min</td>
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<table>
<thead>
<tr>
<th>17</th>
<th>A new validated RP-HPLC method for the determination of Metformin HCl and Empagliflozin in its bulk and pharmaceutical dosage forms</th>
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<tbody>
<tr>
<td>Method</td>
<td>Model: RP-HPLC system Waters 2695 Stationary phase: Column C18, (150mm x 4.0mm, 5μm) Mobile phase: Methanol: phosphate buffer (pH 3 adjusted by OPA) (70:30 %v/v) Flow rate: 1mL/min Wavelength: 240 nm Linearity: MET: 50 - 250 μg/mL EMPA: 5-25 μg/mL Retention time: MET: 2.403 min EMPA: 3.907 min</td>
</tr>
</tbody>
</table>
| 18 | Simultaneous Estimation Validation and Force Degradation Study of Metformin Hydrochloride and Empagliflozin by RP-HPLC Method | Model: HPLC system Waters 2695  
Stationary phase: Column C18 (250mm x 4.6mm, 5μm)  
Mobile phase: Methanol: Potassium Dihydrogen phosphate buffer (pH:3 adjusted by OPA) (60:30 %v/v)  
Flow rate: 1.0 mL/min  
Wavelength: 227 nm  
Linearity:  
MET: 40-200 μg/mL  
EMPA: 1-5 μg/mL  
Retention time:  
MET: 5.2 min  
EMPA: 6.5 min | [26] |
| 19 | Development and Validation of Analytical Method for Simultaneous Estimation of Metformin Hydrochloride and Teneligliptin Hydrobromide Hydrate in Pharmaceutical Dosage Form | Model: Shimadzu HPLC system  
Stationary Phase: Column C18 (250 mm x 4.6 mm, 5μm)  
Mobile Phase: Water (pH 4.0 adjust with 1% Orthophosphoric acid) : Methanol (60:40, %v/v)  
Flow Rate: 1.0 mL/min  
Wavelength: 236 nm  
Linearity:  
MET: 25-75 µg/mL  
TEN: 1-3 µg/mL  
Retention Time:  
MET: 3.317 min  
TEN: 4.783 min | [27] |
| 20 | Development and validation of RP- HPLC method for simultaneous estimation of Metformin hydrochloride and Glipizide in bulk and pharmaceutical dosage form | Stationary phase: Column C18 (250 mm x 4.6 mm, 5μm)  
Mobile phase: Methanol: Water (60:40, %v/v) (pH:3 adjusted by OPA)  
Flow rate: 0.8 mL/min  
Wavelength: 226 nm  
Linearity:  
MET:100-500 µg/mL  
GPZ: 1–5 μg/mL  
Retention time:  
MET: 4.15 min  
GLP: 5.587 min | [28] |
| 21 | Development of Reverse Phase HPLC Method and Validation for the Estimation of Metformin Hydrochloride and Glipizide in Combined Dosage Form | Stationary phase: A Symmetry C18 (4.6 mm x 150 mm, 5μm)  
Mobile phase: methanol: phosphate buffer (pH 4.5 adjusted by OPA) (65:35 %v/v)  
Flow rate: 0.8 mL  
Wavelength: 225 nm  
Retention time:  
MET: 2.572 min  
GLP: 3.833 min | [29] |
<table>
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<tr>
<th>Page</th>
<th>Method/Model Description</th>
<th>Model/Stationary Phase/Mobile Phase/Flow Rate/Wavelength/Linearity/Retention Time</th>
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<tr>
<td>22</td>
<td>Method development and validation of simultaneous estimation of Alogliptin and Metformin Hydrochloride by RP-HPLC</td>
<td>Model: HPLC-Shimadzu LC- 2010 binary system&lt;br&gt;Stationary phase: Agilent C18 (250mm x 4.6mm, 5µm)&lt;br&gt;Mobile phase: Phosphate buffer (pH 3.0 adjusted by 0.1% OPA): methanol (20:80 %v/v)&lt;br&gt;Flow rate: 0.7 mL/min&lt;br&gt;Wavelength: 242 nm&lt;br&gt;Linearity: 10-30 µg/mL for both&lt;br&gt;Retention time: MET: 1.727 min&lt;br&gt;ALG: 2.90 min</td>
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<tr>
<td>23</td>
<td>Development And Validation Of Stability Indicating RP-HPLC Method For The Simultaneous Estimation Of Metformin Hydrochloride And Empagliflozin In Bulk And In A Synthetic Mixture</td>
<td>Model: HPLC system Waters 2965&lt;br&gt;Stationary phase: Kromosil (250 x 4.6 mm, 5µm)&lt;br&gt;Mobile phase: 0.1% Orthophosphoric acid Buffer : Acetonitrile (45:55 %v/v)&lt;br&gt;Flow rate: 0.8 mL/min&lt;br&gt;Wavelength: 233 nm&lt;br&gt;Linearity: MET: 125-750 µg/mL&lt;br&gt;EMPA: 3.125-18.75 µg/mL&lt;br&gt;Retention Time: MET: 2.270 min&lt;br&gt;EMPA: 3.413 min</td>
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<td>24</td>
<td>RP- HPLC method for Simultaneous Estimation of Pioglitazone Hydrochloride Metformin Hydrochloride and Glibenclamide in Multicomponent Tablet Dosage Form</td>
<td>Model: Agilent HPLC system&lt;br&gt;Stationary Phase: Agilent (250 mm×4.6 mm, 5µm)&lt;br&gt;Mobile phase: acetonitrile: methanol: water (70:10:20 %v/v/v)&lt;br&gt;Flow rate: 1.0 mL/min&lt;br&gt;Wavelength: 227 nm&lt;br&gt;Linearity:&lt;br&gt;PIO: 5-30 µg/mL&lt;br&gt;MET: 50-300 µg/mL&lt;br&gt;GLB: 2-10 µg/mL&lt;br&gt;Retention Time:&lt;br&gt;PIO: 6.82 min&lt;br&gt;MET: 2.42 min&lt;br&gt;GLB: 9.40 min</td>
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<td>25</td>
<td>Rapid RP-HPLC Method for Simultaneous Estimation of Metformin, Pioglitazone, and Glimepiride in Human Plasma</td>
<td>Model: Agilent HPLC system&lt;br&gt;Stationary phase: Magellen C18 (150 mm x 4.60 mm, 5 µm)&lt;br&gt;Mobile phase: potassium dihydrogen phosphate (pH 3.2 adjusted by using OPA) : methanol (85:15 %v/v)&lt;br&gt;Flow Rate: 1 mL/min&lt;br&gt;Wavelength: 235 nm&lt;br&gt;Linearity:&lt;br&gt;MET: 2.50–100 µg/mL&lt;br&gt;PIO: 2.50–100 µg/mL</td>
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<tr>
<td>Page</td>
<td>Description</td>
<td>Methodology</td>
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</table>
| 26   | Simultaneous estimation of Metformin, Pioglitazone and Glimepiride in bulk samples and in tablet dosage forms by using RP-HPLC in an Isocratic mode | **Model:** Shimadzu HPLC system  
**Stationary phase:** Xterra column C18 (460mm x 150 mm, 5 μm)  
**Mobile phase:** phosphate buffer (pH 3.0 adjusted by using OPA) : methanol (25:75 %v/v)  
**Flow rate:** 1.0 mL  
**Wavelength:** 254 nm  
**Linearity:** PIO: 2.4-3.6 μg/mL  
GLP: 0.16-0.24 μg/mL  
MET: 80-120 μg/mL  
**Retention Time:** PIO: 3.238 min  
GLP: 4.042 min  
MET: 1.997 min |
| 26   | Analytical method development & validation of Metformin, Pioglitazone & Glimepiride by RP-HPLC in tablet dosage forms | **Model:** Shimadzu HPLC system  
**Stationary phase:** Thermo column C18, (250mm x 4.6mm, 5μm)  
**Mobile phase:** phosphate buffer (pH 3.0 adjusted by using OPA) : methanol (60:40 %v/v)  
**Flow rate:** 1.0 mL /min  
**Wavelength:** 273nm  
**Linearity:**  
PIO: 5-200 μg/mL  
GLP: 5-200 μg/mL  
MET: 5-200 μg/mL  
**Retention Time:**  
PIO: 6.4 min  
GLP: 9.7 min  
MET: 4.7 min |
| 27   | Novel RP-HPLC method development and validation for simultaneous estimation of Metformin, Voglibose and Pioglitazone in bulk and triple fixed drug combinations pharmaceutical dosage form | **Model:** Younglin (SK) gradient System with UV 730 D detector  
**Stationary phase:** Cosmosil column C18 (250 x 4.6 mm, 5μm)  
**Mobile phase:** 0.1% v/v Acetonitrile: Triethylamine (30:70, %v/v)  
**Wavelength:** 232nm  
**Flow rate:** 0.8 mL /min  
**Linearity:** MET: 200-600 μg/mL  
VOG: 30-90 μg/mL  
PIO: 0.08-0.24 μg/mL |
| 28   | Simultaneous HPTLC analysis of Gliclazide and Metformin hydrochloride in bulk | **Stationary phase:** Silica gel 60 F254  
**Mobile phase:** Toluene: acetonitrile: ethanol: Ammonium sulphate (0.25%) (4 : 4 : 3, %v/v/v/v) |
<table>
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<tr>
<th>Page</th>
<th>Method Description</th>
<th>Stationary Phase</th>
<th>Mobile Phase</th>
<th>Wavelength</th>
<th>Linearity</th>
<th>Rf value</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>A Rapid Validated Unidimensional Double Development 21c5 For Simultaneous Estimation Of Metformin Hydrochloride, Gliclazide And Pioglitazone Hydrochloride</td>
<td>Silica gel 60F&lt;sub&gt;254&lt;/sub&gt;</td>
<td>Ammonium Sulphate: Methanol: Acetonitrile: Water (4:3:2:1 %v/v/v/v)</td>
<td>237 nm</td>
<td>MET: 3000-8000 ng/spot</td>
<td>MET: 0.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GLZ: 360-960 ng/spot</td>
<td>GLZ: 0.69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PIO: 90-240 ng/spot</td>
<td>PIO: 0.48</td>
</tr>
<tr>
<td>30</td>
<td>Validated HPTLC Method For Simultaneous Determination Of Metformin Hydrochloride And Glibenclamide In Combined Dosage Form</td>
<td>Silica gel 60 F&lt;sub&gt;254&lt;/sub&gt;</td>
<td>Methanol: Water: 0.4 % sodium sulphate in water (7: 5:11 %v/v/v/v)</td>
<td>232 nm</td>
<td>MET: 250-1750 ng/spot</td>
<td>MET: 0.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GLB: 250 - 1750 ng /spot</td>
<td>GLB: 0.80</td>
</tr>
<tr>
<td>31</td>
<td>Development and validation of HPTLC method for simultaneous estimation of Metformin Hydrochloride and Alogliptin Benzoate in bulk drugs and combined dosage forms</td>
<td>Silica gel 60 F&lt;sub&gt;254&lt;/sub&gt;</td>
<td>Acetonitrile: 1% ammonium acetate in methanol (4.5:5.5 %v/v)</td>
<td>253 nm</td>
<td>MET: 100-2500 ng/spot For both drugs</td>
<td>MET: 0.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GLB: 100-2500 ng/spot</td>
<td>ALG : 0.35</td>
</tr>
<tr>
<td>32</td>
<td>HPTLC method for simultaneous estimation of Metformin HCl and Sitagliptin in pharmaceutical dosage form</td>
<td>Silica gel 60 F&lt;sub&gt;254&lt;/sub&gt;</td>
<td>Ammonium sulphate(0.5%): 2-Propanol :Methanol (8:1.6 %v/v)</td>
<td>254 nm</td>
<td>MET: 7-15 ng/spot</td>
<td>MET: 0.63</td>
</tr>
</tbody>
</table>
33 Development and Validation of HPTLC Method for Simultaneous Estimation of Anti-Diabetic Drugs from Their Combined Dosage Form Metformin hydrochloride, Pioglitazone hydrochloride, Glibenclamide

Stationary phase: Silica gel 60 F$_{254}$
Mobile Phase: Methanol: aqueous ammonium sulfate (8:2, %v/v)
Wavelength: 208 nm
Linearity: LINA and SAXA: 0.05–0.5 µg/band
MET: 5–40 µg/band
VID: 0.2–2 ng/band
Rf value: MET: 0.22
LINA: 0.44
SAXA: 0.51
VID: 0.46

34 Validated HPTLC Method for Simultaneous Estimation of Sitagliptin and Metformin Hydrochloride in Bulk Drug and Formulation

Stationary phase: Silica gel 60 F$_{254}$
Mobile Phase: Methanol: glacial acetic acid: ammonia (9.4:0.4:0.2%v/v/v)
Wavelength: 214 nm
Linearity:
MET: 1000–11000 ng /band
STG: 100–1100 ng band
Rf value:
MET: 0.28
STG: 0.61

Reported method of remogliflozin Etabonate and Metformin hydrochloride

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Methods</th>
<th>Description</th>
<th>Ref no.</th>
</tr>
</thead>
</table>
| 1       | Development and Validation of Green UV Derivative Spectrophotometric Methods for Simultaneous Determination Metformin and Remogliflozin from Formulation: Evaluation of Greenness | Model: Shimadzu UV Spectrophotometer (UV-1700) Solvent: Water
Model:- First Derivative Spectroscopic Method (FDS)
Wavelength:-
REMO:- 233nm
MET:- 252nm
Linearity:-
REMO:- 1 to 20 µg/mL
MET:- 2.5 to 35 µg/mL
Model:- Ratio Absorbance Method (RAD)
Wavelength:-
REMO:- 277.8nm
MET:- 248.6nm
Linearity:-
REMO:- 1 to 20 µg mL−1
MET:-2.5 to 35 µg mL−1
Model:-Ratio Derivative Method (RFD)
Wavelength:-
REMO:-288.4nm
MET:-251.7nm
Linearity:-
REMO:- 1 to 20 µg mL−1
MET:- 2.5 to 35 µg mL−1 | [44] |
<table>
<thead>
<tr>
<th>Model</th>
<th>Shimadzu UV–VIS-1700 spectrophotometer, HPLC system</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Stationary phase:</em></td>
<td>Column C18 (50 mm x 4.6 mm, 5 μm)</td>
</tr>
<tr>
<td><em>Mobile phase:</em></td>
<td>acetonitrile : mixture of sodium dodecyl sulfate and potassium dihydrogen phosphate (pH 3.5) (42:58% v/v)</td>
</tr>
<tr>
<td><em>Flow rate:</em></td>
<td>2 mL/min</td>
</tr>
<tr>
<td><em>Retention time:</em></td>
<td>MET: 0.66 min, REMO: 1.31 min</td>
</tr>
<tr>
<td><em>Wavelength:</em></td>
<td>HPLC method: MET: 230 nm, REG: 230 nm</td>
</tr>
<tr>
<td></td>
<td>UV method: MET: 235 nm, REG: 243 nm</td>
</tr>
<tr>
<td><em>Linearity:</em></td>
<td>MET: 5-200 μg/ml, REG: 2-150 μg/mL</td>
</tr>
<tr>
<td></td>
<td>UV method: MET: 2-30 μg/mL, REG: 1-24 μg/mL</td>
</tr>
</tbody>
</table>

**Model:** UPLC-PDA

**Stationary phase:** Spherisorb C18, (4.6 mm x 150 mm, 5 μm)

**Mobile phase:** phosphate buffer (pH: 4.5): acetonitrile (60:40% v/v)

**Flow rate:** 1.0 mL/min

**Retention time:** REMO: 3.017 min, MET: 5.011 min

**Wavelength:** 245 nm

**Linearity:** MET: 10-100 ng/mL, REMO: 50-500 ng/mL

**CONCLUSION**

This review study compiles the information for the development of analytical methods for simultaneous estimation of the Remogliflozin etabonate and Metformin hydrochloride that will be helpful for further research work on this combination. The present survey reveals that literature survey provides information on the analytical methods like UV, HPLC, HPLC stability, HPTLC has been reported on for Remogliflozin etabonate and metformin hydrochloride and along with other drugs. The analysis on this combination reveals that UV methods, one HPLC and One UPLC method has been reported.

**REFERENCE**
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   https://go.drugbank.com/drugs/DB12935
   https://go.drugbank.com/salts/DBSALT000114
15. Sen A, Hinsu D. Analytical method development and validation for simultaneous


