IJBPAS, October, 2024, 13(10): 5066-5076

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

OVERVIEW OF ANALYTICAL TECHNIQUES ON TENELIGLIPTIN HYDROBROMIDE HYDRATE, PIOGLITAZONE HYDROCHLORIDE, METFORMIN HYDROCHLORIDE AND THEIR COMBINATIONS

PATEL PH* AND SHARMA P

Department of Quality Assurance, Faculty of Pharmacy, Parul Institute of Pharmacy & Research, Parul University, Post Limda, Vadodara, 391760, Gujarat, India

***Corresponding Author: Ms. Pinkal H. Patel: E Mail: pinkal.patel@paruluniversity.ac.in**

Received 24th Sept. 2023; Revised 25th Oct. 2023; Accepted 8th Jan. 2024; Available online 1st Oct. 2024

https://doi.org/10.31032/IJBPAS/2024/13.10.8397

ABSTRACT

This study's objective is to offer an in-depth overview of the various analytical procedures used to determine Teneligliptin Hydrobromide Hydrate, Metformin Hydrochloride, Pioglitazone Hydrochloride, and their combinations in marketed formulations. This study contains UV, RP-HPLC, TLC, and other procedures that have been reported to date. Teneligliptin Hydrobromide Hydrate is approved as monotherapy or with other oral hypoglycaemic medicines (e.g., metformin, pioglitazone, sulfonylureas, glinides, and glucosidase inhibitors). Pioglitazone Hydrochloride is a thiazolidinedione that improves the body's sensitivity to insulin. Metformin Hydrochloride is a biguanide that reduces sugar production and absorption in your body while improving the usage of current insulin. They work in tandem to improve blood sugar control. This review summarizes the studies done on the medications indicated above, either alone or in combination with or without the presence of contaminants.

Keywords: Anti- diabetic, Teneligliptin Hydrobromide Hydrate, Metformin Hydrochloride, HPLC, UV

INTRODUCTION:

Several new oral medicines for type 2 diabetes control have been licensed in recent years, to maximize oral pharmacological therapy for diabetes. In addition to the older treatments Since a long time ago, Teneligliptin Hydrobromide has been

recommended as an oral diabetic medication. It is one of the ingredients in the prescription for the treatment of type 2 diabetes mellitus. It works by stopping the liver's synthesis of glucose **[1]**.

Metformin increases hepatic and peripheral tissue insulin sensitivity without causing severe lactic acidosis, whereas Teneligliptin has been shown to improve insulin action on body peripheral tissues and hence modify abnormal glucose and fat metabolism associate with resistance of insulin **[2]**.

Pioglitazone Hydrochloride is generally well tolerated; the most common emerging side effects are weight gain and oedema. In clinical studies, pioglitazone, either alone or in combination, improve the glycaemic control and serum lipid profiles **[3]**.

Teneligliptin Hydrobromide Hydrate

Physical and Chemical Properties

Teneligliptin Hydrobromide Hydrate is a crystalline powder that is white to off-white in colour. Its name is [(2S,4S)]. -4-[4-(5-methyl-2-phenylpyrazol-3-yl) piperazin-1-yl] pyrrolidin-2-yl] pyrrolidin-2-yl –[1,3-thiazolidin-3-yl] methanone; Penta Hydrobromide. Teneligliptin Hydrobromide Hydrate has the chemical formula $C_{22}H_{30}N_6OS.\ 2.5HBr \bullet H_2O$ and the molecular mass of 426.6 g/mol. It dissolves readily in ethanol and dimethyl formamide **[4]**.

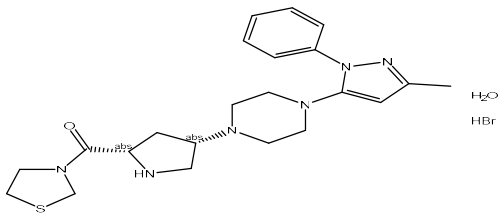

Fig1: Structure of Teneligliptin Hydrobromide Hydrate

The alimentary canal produces glucagon-like peptide-1 (GLP-1) in response to food, which activates pancreatic insulin production and contributes in the regulation of blood sugar levels after meals by controlling glucagon output. Teneligliptin Hydrobromide Hydrate reduces DPP4 activity, which limits GLP-1 breakdown. The kidney excretes 34% of the medicine unchanged, whereas the liver excretes 65.6% **[5]**.

Metformin Hydrochloride

Physical and Chemical Properties

Metformin Hydrochloride is a white, hygroscopic, bitter-tasting powder. Metformin hydrochloride's IUPAC name is 1-carbamimidamid -N,N-dimethyl methanimidamide hydrochloride. Metformin Hydrochloride has the chemical formula $C_4H_{12}ClN_5$ and the molecular mass of 165.625 g/mol. Metformin HCl dissolves rapidly in solvents such as ethanol, DMSO [Dimethyl sulfoxide] DMF[Dimethyl formamide], and distilled water [2gm/20ml] **[6]**.

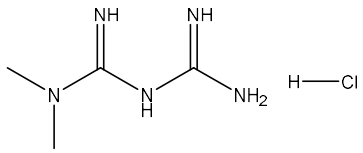

Fig2 : Structure of Metformin Hydrochloride

Mode of Action

Metformin Hydrochloride operates on the liver directly or indirectly to reduce glucose synthesis, and on the stomach to promote glucose utilisation, raise GLP-1, and modify the bacterial ecosystem. Metformin inhibits the mitochondrial respiratory chain in the liver, activating AMPK, increasing insulin sensitivity (via lipid metabolism impacts), and decreasing cAMP, hence decreasing the synthesis of gluconeogenic enzymes **[7]**.

Pioglitazone Hydrochloride

Physical and Chemical Properties

The powder form of pioglitazone hydrochloride is white to off-white in colour. Its IUPAC name is 5-[4-{2-(5-ethylpyridin-2-yl) ethoxy] phenyl} methyl]. -1,3-thiazolidine-2,4-dione. Pioglitazone has the molecular mass of 392.2 g/mol and the chemical formula $C_{19}H_{20}N_2O_3S$ • HCl. It dissolves somewhat in dimethyl formamide and ethanol and is just marginally soluble in acetone and acetonitrile. It is insoluble in water or ether **[8]**.

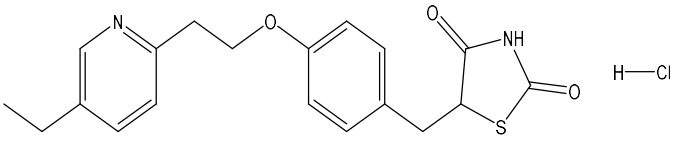

Fig3: Structure of Pioglitazone Hydrochloride

Mode of Action

Through PPAR gamma 1 and PPAR alpha, pioglitazone hydrochloride improves blood sugar management by enhancing insulin sensitivity. As a result of these interactions, increased levels of various glucose transporters, decreased levels of unbound fatty acids, improved insulin signalling, decreased levels of endotoxin-induced factor in serum and adipose tissue remodelling. Together, they can improve glucose uptake and utilization in the peritoneal tissues while reducing gluconeogenesis in the liver, hence reducing insulin resistance **[9]**.

Analytical methods for Metformin Hydrochloride, Teneligliptin Hydrobromide Hydrate, Pioglitazone Hydrochloride and their combinations.

Table 1

Sr. No	Drug	Method	Analytical Conditions	Ref. No
1	Teneligliptin Hydrobromide and Metformin Hydrochloride	RP HPLC	Stationary phase: C_{18} [250mm x 4.6mm, 5µm] Mobile Phase: Buffer: Acetonitrile [85:15% v/v] and Methanol: Acetonitrile [50:50 % v/v] Flow Rate: 0.8 ml/min Detection Wavelength: 249nm Regression Coefficient: 0.9979	10
2	Teneligliptin Hydrobromide Hydrate	Rp-HPLC / UPLC Tandem mass spectroscopy	Stationary phase: C_{18} [250mm x 4.6mm, 5µm] Mobile phase: Acetonitrile: Phosphate buffer [40:60 v/v] Flow rate: 1.0 ml/min Wavelength: 246nm Linearity: 100–500µg/ml Retention time: 2.966 Regression Coefficient: 0.999	11
3	Teneligliptin Hydrobromide Hydrate	HPTLC	Stationary phase: Aluminium plates pre-coated with Silica Gel 60 F_{254} Mobile Phase: Water: Butanol: Glacial acetic acid [2:6:2 v/v/v] Retention Factor: 0.33 ± 0.0. Densitometric scanning: 245nm % Recovery: 98.34 %.	12
4	Teneligliptin Hydrobromide Hydrate	RP-HPLC	Stationary phase: C_{18} [250mm x 4.6mm, 5µm] Mobile phase: Methanol: Water [90:10] Detection wavelength: 248nm Flow rate: 0.8 ml/mins Retention time: 6.36 mins	13
5	Teneligliptin and Metformin Hydrochloride	RP HPLC	Stationary phase: C_{18} [250mm x 4.6mm. 5µm] Mobile phase: Buffer: Acetonitrile: methanol [65:25:10] Detection wavelength: 210nm Retention time: Metformin: 2.701 mins Teneligliptin: 2.842 mins	14
6	Metformin Hydrochloride and Teneligliptin Hydrobromide Hydrate	RP-HPLC	Stationary phase: Hypersil BDS C_{18},[250mm x 4.6mm, 5µm] Mobile phase A: Triethylamine and Octane sulfonic acid pH- 3.0 Mobile phase B: Acetonitrile Flow Rate: 1.0ml/min Detection wavelength: 210nm	15
7	Metformin Hydrochloride and Teneligliptin Hydrobromide Hydrate	RP HPLC	Stationary phase: Hyper BDS C_{18} column, [250mm x 4.6mm, 5µm] Mobile phase: Water: Acetonitrile [90:10v/v] Detection wavelength: 247.5nm Flow rate: 1.0 ml/min Retention time: Teneligliptin: 3.010 mins Metformin: 5.393 mins Regression Coefficient: Teneligliptin: 0.998 Metformin: 0.999	16
8	Metformin Hydrochloride and Teneligliptin Hydrobromide Hydrate	UV- visible	Solvent: Methanol Detection wavelength: Teneligliptin: 238nm and 230nm Metformin: 238nm and 249nm % Recovery: Teneligliptin: 98.54 % Metformin: 101.55 % Regression Coefficient: Teneligliptin: 0.9929 Metformin: 0.9998	17
9	Pioglitazone Hydrochloride	HPTLC	Stationary phase: Silica Gel 60 F_{254} Aluminium Plate Mobile Phase: Methanol: Toluene: Ammonia [3:7:0.1 v/v/v]	18

			Retention factor: 0.50±0.03 **Linearity: 200- 1200 ng/spot** **Precision;** **Intra-day: 0.6 to 3.4%** **Inter-day: 0.8 to 3.8%** **Accuracy: 98.7 to 102.5%** **LOD: 5 ng/spot** **LOQ: 20 ng/spot**	
10	**Metformin Hydrochloride**	**RP HPLC**	**Stationary phase: C_{18} Column** **Mobile phase: Water: Methanol [70:30 v/v]** **Flow rate: 0.5 ml/min** **Wavelength: 233nm** **Retention time: 4.4 mins** **Injection Volume: 20 µl**	**19**
11	**Metformin Hydrochloride and Pioglitazone Hydrochloride**	**RP HPLC**	**Stationary phase: C_{18} [25cm x 4.6mm,5µm]** **Mobile phase; Phosphate buffer: Acetonitrile 50:50 v/v pH- 5.0** **Flow rate: 1.0 ml/min** **Wavelength: 258 nm** **Retention time:** **Metformin: 4.75 mins** **Pioglitazone: 6.44 mins** **Injection Volume: 50 µl** **Linearity range:** **Metformin: 20.0-80.0 µg/mL** **Pioglitazone: 0.5-3.5 µg/mL**	**20**
12	**Metformin Hydrochloride, Pioglitazone Hydrochloride and Glimepiride**	**RP HPLC**	**Stationary phase: C_{18} Column [250mm x 4.6mm, 5µm]** **Mobile phase: Methanol: Phosphate buffer [75:25 v/v] pH- 4.3** **Flow rate: 1.0 ml/min** **Retention time:** **Glimepiride:10.17 mins** **Metformin: 2.66 mins** **Pioglitazone: 7.12 mins**	**21**
13	**Metformin Hydrochloride, Pioglitazone Hydrochloride and Glibenclamide**	**RP HPLC**	**Stationary phase; C_{18} [250mm x 4.6mm, 5µm]** **Mobile phase: Acetonitrile-Potassium dihydrogen phosphate buffer [55:45 v/v]** **Flow rate: 1.5 ml/min** **Retention time:** **Metformin:1.362 mins** **Pioglitazone: 3.418 mins** **Glibenclamide:7.395 mins**	**22**
14	**Pioglitazone Hydrochloride and Glimepiride**	**RP HPLC**	**Stationary phase: ODS Inertsil [250mm x 4.6mm, 5 µm]** **Mobile phase: Ammonium acetate: Acetonitrile [40:60 v/v] pH- 4.5** **Flow rate: 1.0 ml/min** **Wavelength: 230nm** **Retention time:** **Pioglitazone-7.0 mins** **Glimepiride-10.21 mins**	**23**
15	**Pioglitazone Hydrochloride**	**RP HPLC**	**Stationary Phase: C_{18} column [250 x4.6mm]** **Mobile phase: Buffer: Acetonitrile [55:45v/v]** **Flow rate: 1.0 ml/min** **Wavelength: 254nm** **Retention time; 9.767** **Correlation coefficient: 0.999** **% Recovery range: 100.09-103.11%**	**24**
16	**Pioglitazone Hydrochloride**	**UV- visible**	**Solvent: Phosphate Buffer** **Concentration range: 10-50 mcg/ml** **Wavelength: 238nm** **Correlation coefficient: 0.999** **% Recovery: 98.01 %**	**25**
17	**Metformin Hydrochloride, Repaglinide, Glibenclamide and**	**HPTLC**	**Stationary phase: Silica Gel G_{60} F_{254}** **Mobile phase: Ethyl acetate- Toluene in Methanol [3.5: 3.5: 3.0 v/v/v]** **Wavelength range :200-400nm**	**26**

	Pioglitazone Hydrochloride		**Scanner: TLC scanner IV Retention factor; Metformin: 0.13 Repaglinide: 0.37 Glibenclamide: 0.70 Pioglitazone: 0.82**	
18	**Metformin Hydrochloride, Pioglitazone Hydrochloride and Glibenclamide**	**UV- visible**	**Solvent: Methanol UV range: 200-400nm Correlation coefficient: Metformin: 0.9987 Pioglitazone: 0.9997 Glibenclamide: 0.9992 Standard Deviation: Metformin: 0.044 Pioglitazone: 0.32 Glibenclamide: 0.96**	**27**
19	**Pioglitazone Hydrochloride**	**RP-HPLC**	**Stationary phase: C_{18} [25 cm x 4.6mm, 5µm] Mobile phase: 0.01M Potassium dihydrogen phosphate pH- 3.5, Buffer: Methanol [55:45 v/v] Flow rate: 1.5 ml/min Retention time: 6.15 mins Correlation coefficient: 0.9998 Wavelength: 241nm % Recovery range: 100.45-100.53%**	**28**
20	**Pioglitazone Hydrochloride and Metformin Hydrochloride**	**UV- visible**	**Solvent: 0.1M NaOH Blank Sol: 0.1M HCl Wavelength: Pioglitazone: 228.1nm Metformin: 228.2nm % Recovery: Metformin: 99.8 % Pioglitazone: 98.0%**	**29**
21	**Teneligliptin**	**UV- visible**	**Solvent: Distilled water Maxima: 244nm Wavelength range: 238.6-247.8nm Correlation coefficient: 0.999 % Recovery: 100.17-100.74%**	**30**
22	**Gemigliptin and Teneligliptin**	**LC- Tandem Mass Spectrometry**	**Stationary phase: C_{18} [100mm x 2.1mm, 2.7µm] Mobile phase: Acetonitrile in gradient elution: Formic acid in water [0.1% v/v] Internal STD: Pioglitazone Mass Transitions: Pioglitazone: 357.1 [m/z] Gemigliptin: 490.1 [m/z] Teneligliptin: 427.2 [m/z] % Recovery: Gemigliptin: 98.8± 0.76 % Teneligliptin: 98.6±0.98 %**	**31**
23	**Metformin Hydrochloride and Pioglitazone Hydrochloride**	**HPTLC**	**Stationary phase: Silica Gel plate 60 F_{254} Mobile phase: Butanol: 1,4- dioxane: Glacial Acetic acid [5:3:2 v/v/v] Wavelength: 226nm Retention factor: Metformin: 0.17 Pioglitazone: 0.72 Linearity: Metformin: 2000-18000 ng/band Pioglitazone: 60-540 ng/band**	**32**
24	**Metformin Hydrochloride and Pioglitazone Hydrochloride**	**UV- visible**	**Solvent: 0.1N sodium hydroxide Wavelength: 233 and 265.5nm Linearity range (µg/ml): Metformin: 2-20 µg/ml Pioglitazone: 5-25 µg/ml LOD: Metformin: 0.067 Pioglitazone: 0.0077**	**33**

<table>
<tr><td></td><td></td><td></td><td>LOQ:
Metformin: 0.2055
Pioglitazone: 0.0235</td><td></td></tr>
<tr><td>25</td><td>Metformin Hydrochloride Teneligliptin and Hydrobromide Hydrate</td><td>UV- visible</td><td>Solvent: Methanol
Wavelength: 237 and 246nm
Linearity range (µg/ml): 1-20 µg/ml for both drugs
LOD (µg/ml):<table><tr><th>WL</th><th>TEN</th><th>MET</th></tr><tr><td>237 nm</td><td>0.16</td><td>0.05</td></tr><tr><td>246 nm</td><td>0.29</td><td>0.18</td></tr></table>LOQ (µg/ml):<table><tr><th>WL</th><th>TEN</th><th>MET</th></tr><tr><td>237 nm</td><td>0.49</td><td>0.15</td></tr><tr><td>246 nm</td><td>0.89</td><td>0.55</td></tr></table></td><td>34</td></tr>
<tr><td>26</td><td>Remogliflozin Etabonate and Teneligliptin Hydrobromide Hydrate</td><td>RP HPLC</td><td>Stationary phase: C₁₈ [250mm x 4.6mm, 5µm]
Mobile phase: Methanol: Phosphate buffer [7.0: 30]
Flow rate: 1.0ml/min
Retention time:
Remogliflozin: 16.1 mins
Teneligliptin: 3.4 mins
Correlation coefficient:
Remogliflozin: 0.9998
Teneligliptin: 0.9984</td><td>35</td></tr>
<tr><td>27</td><td>Teneligliptin Hydrobromide Hydrate</td><td>RP HPLC</td><td>Stationary phase: C₁₈ Column [250mm x 4.6mm, 5µm]
Mobile phase: Methanol: Phosphate buffer [25:75] pH 5.5
Flow rate: 1.2 ml/min
Wavelength: 270 nm
Retention time: 2.5194 min
Correlation coefficient: 0.9972</td><td>36</td></tr>
</table>

CONCLUSION

According to the review, no analytical approach on the combination of Teneligliptin hydrobromide Hydrate, Metformin Hydrochloride, and Pioglitazone Hydrochloride has been documented. Teneligliptin Hydrobromide Hydrate quantification methods in this case comprised UV, HPLC, Stability Indicating HPLC, HPTLC, and UPLC. With the exception of UPLC, the same has been reported for Pioglitazone hydrochloride and Metformin Hydrochloride, either alone or in combination with other medications.

The details in this review are beneficial for upcoming investigations for academics or in quality design studies.

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