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A Review on Method Development and Validation of RP-HPLC Method for Simultaneous Estimation of Teneligliptin, Metformin Hydrochloride and Pioglitazone Hydrochloride in Pharmaceutical Dosage Form

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Keywords: Teneligliptin, Pioglitazone hydrochloride and Metformin hydrochloride RP-HPLC, Mobile Phase, Column, Wavelength, Flow rate.

ABSTRACT

Diabetes Mellitus is a Chronic Progressive disease. It is characterized by Hyperglycaemia. This review article is intended to highlight the analytical method of Teneligliptin, Pioglitazone hydrochloride and Metformin Hydrochloride in individual as well as combined pharmaceutical Tablet dose forms. Teneligliptin, Pioglitazone Hydrochloride and Metformin Hydrochloride play important role in Diabetes Mellitus disease. As for the treatment of Diabetes Mellitus type 2 in combination form Teneligliptin, Pioglitazone Hydrochloride and Metformin Hydrochloride is used. The aim of this review is to focus on update of determination of Teneligliptin, Pioglitazone hydrochloride and Metformin hydrochloride in bulk and in pharmaceutical preparation used in RP-HPLC, UV- Spectroscopic method. This review provides detail information on separation for Teneligliptin, Pioglitazone hydrochloride and Metformin hydrochloride in single and in combination form.

INTRODUCTION TO ANALYTICAL METHOD

Many analytical methods are employed for estimation these days. Numerous analytical methods are employed in the analysis, including as aqueous and non-aqueous titrations, HPLC, and potentiometers. Both aqueous and non-aqueous titrations are employed in the field of analysis. But these days, HPLC is crucial for quantitative determination in the analysis industry. The separation technique known as high pressure liquid chromatography, or HPLC, uses a liquid mobile phase and a solid stationary phase.[1] A process of mass transfer called chromatography involves adsorption. The column's active element is the adsorbent, which is a granular substance made of solid particles (silica, polymers). Adsorption, in which the substances move or separate in accordance with their respective affinities, provides the basis for separation in both the normal phase mode and the reverse phase mode. In the field of pharmaceutical analysis nowadays, HPLC is essential for separating different chemicals from mixtures of substances.[2]

INTRODUCTION TO DRUG PROFILE

Teneligliptin [3]

Teneligliptin is an oral DPP-4 inhibitor that reduces blood sugar levels. It was granted a license by the Japanese government in September 2012 to treat type 2 diabetes. Teneligliptin is part of a class of diabetes medications known as "Gliptins," or Dipeptidyl Peptidase-4 Inhibitors. Because of its unique J-shaped or anchor-locked domain structure, it significantly inhibits the DPP 4 enzyme. Glycaemic variables are successfully and safely controlled with Teneligliptin; patients with renal impairment do not need to modify their dose.

Dipeptidyl Peptidase-4 is a member of the related protein family called prolyl oligopeptides (DPP-4). DPP-4 is an integral membrane protein distributed across a variety of tissues, including the pancreas, intestinal and renal brush border membranes, vascular endothelium, and glandular epithelial cells. Another term for it is the T-cell differentiation antigen (there).

DPP-4 cleavage is the initial and principal pathway for GLP-1 metabolism, which is necessary for it to work. If not, when the DPP-4 pathway was disrupted, alternative clearance mechanisms would take over and stop the intact peptide's levels from increasing. lowering plasma DPP-4 activity to totally stop intravenous GLP-1 injection oxidation Furthermore, the correlation between this and a high insulin response implied that DPP-4mediated degradation

was a major factor in lowering GLP-1's insulinotropic action. One potential treatment for type 2 diabetes is to inhibit the catalytic activity of DPP-4.

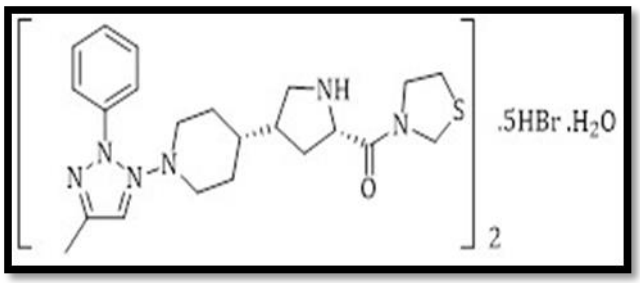

Figure 1 Chemical Structure of Teneligliptin

Mode of Action of Teneligliptin[4]**:** The body's glucose level rises with food consumption. The small intestine responds by secreting more incretins, which are vital for maintaining blood glucose homeostasis but are rapidly destroyed by an enzyme (DPPP-4).

Teneligliptin suppresses the insulin-lowering hormone glucagon and boosts the pancreas' manufacture of the hormone insulin, which further lowers blood sugar levels. It also slows down the incretins' rapid breakdown by suppressing the activity of DPP-4 enzymes.

Metformin Hydrochloride [5]

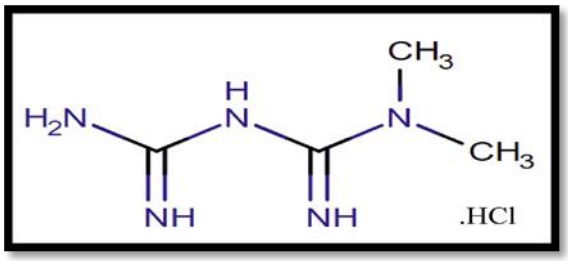

Figure 2 Chemical Structure of Metformin Hydrochloride

A medication from the biguanide class increases the synthesis of adenosine 5′-triphosphate (ATP) while inhibiting the mitochondria's ability to produce reactive oxygen species. The liver kinase B1–5′ AMP-activated protein kinase (LKB1–AMPK) signaling pathway is activated in response to elevated ATP levels. The route is essential for maintaining cellular energy homeostasis. When the pathway is activated in energy-stressed situations, energy-consuming processes including protein and fatty acid synthesis are downregulated to raise ATP levels**.**

Mode of Action of Metformin Hydrochloride:

Apart from managing energy metabolism within cells, the LKB1-AMPK pathway has evolved to perform increasingly specialized functions in overseeing energy metabolism throughout the entire body. Activation of the LKB1-AMPK pathway in the unique circumstances of hepatocytes inhibits gluconeogenesis, the process by which hepatocytes export energy to the body in the form of glucose. The central nervous system is linked to the system's regulation of appetite. As a result, blood glucose levels are suppressed, which significantly lowers insulin levels. At this time, biguanides are thought to be beneficial in treating type II diabetes in part because they suppress hepatic gluconeogenesis through the activation of LKB1-AMPK and/or other pathways.

Pioglitazone Hydrochloride [6]

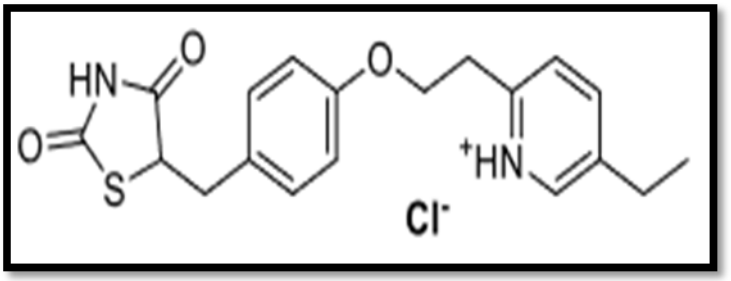

Figure 3 Chemical Structure of Pioglitazone Hydrochloride

After being granted a patent in 1985, pioglitazone was utilized for the first time in medicine in 1999. It is sold as a generic medication. It was the 168th most popular medicine in the US in 2020 with over 3 million prescriptions written for it. It belongs to the group of drugs called "Thiazolidinediones or Glitazones" that treat diabetes. Encoded by the PPARG gene in humans, Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ or PPARG) is a type II nuclear receptor that functions as a transcription factor. It is also referred to as the Glitazone reversal insulin resistance receptor. To encourage adipogenesis and fatty acid absorption, they firmly attach to the peroxisome proliferator activated receptor gamma on adipocytes (in peripheral but not visceral fat). The medications increase the sensitivity of their patients to insulin by lowering the levels of circulating fatty acids and the availability of lipid in the liver and muscle. Thiazolidinediones influence adipocyte hormone levels favourably, especially adiponectin. Their impact on blood lipid levels is not constant, and they increase total body fat.

Mode of Action of Pioglitazone Hydrochloride [7]:

A treatment with thiazolidinediones achieves maximum effect on blood glucose levels after just one to two months. It enhances muscle absorption of glucose while decreasing muscular glucose outflow from the liver. It increases the efficiency of endogenous insulin while reducing the quantity of exogenous insulin needed to maintain a specific blood glucose level by roughly 30%. Reduces in free fatty acid and insulin in circulation are typically linked to lower blood glucose levels.

Summary Of Analytical Methods

Reported analytical methods for Teneligliptin

Sr. No.	Drug	Method	Brief Description
1.	Teneligliptin [8]	**UV**	**Solvent:** Distilled Water **Wavelength:** 244 nm **Linearity range:** 5-70 µg/ml
2.	Teneligliptin [9]	**RP-HPLC**	**Column:** Grace Smart C_{18} column (250 x 4.6mm, 5µm) **Mobile phase:** 0.05M KH_2PO_4 pH 4.0: Acetonitrile (80:20 % v/v) **Detected Wavelength:** 242 nm **Flow rate:** 1 ml/min **Retention time**: 7.443 min **Linearity range**: 500-3000 µg/ml
3.	Teneligliptin [10]	**HPLC**	**Column:** Protecol C_{18} ENDURO (250×4.6mm ,5µm) **Mobile phase:** Methanol: Buffer pH 3.5(72:28% v/v) **Detected Wavelength:** 243.5 nm **Flow rate:** 1 ml/min **Retention time**:5.8 min **Linearity range**:10-90 µg/ml
4.	Teneligliptin [11]	**Stability studies by RP-HPLC**	**Column:** Kromasil C_{18} (250×4.6mm, 5µm) **Mobile phase:** pH 6.0 phosphate buffer: Acetonitrile (60:40 %v/v) **Detected Wavelength:** 246 nm **Flow rate:** 1.0 ml/min **Retention time:** 25 min **Linearity range:**100 -500 µg/ml
5.	Teneligliptin [12]	**Stability indicating RP-UPLC**	**Column:** C_8phenomenex (250 ×4.6 mm ,5 µm) **Mobile phase:** Formic acid: Methanol: Acetic acid

			(25:75:0.1, v/v/v) **Detected Wavelength:** 245 nm **Flow rate:** 0.4 mL/min **Retention time**: 4.982±0.02 min **Linearity range**: 1–100 µg/ml
6.	Teneligliptin and Pioglitazone[13]	**RP-HPLC**	**Column:** Peerless C_{18} (250 × 4.6 mm, 5 µm) **Mobile Phase:** Methanol: Phosphate Buffer: Acetonitrile (pH 3.3 with OPA) (50:25:25%v/v) **Detected Wavelength:** 225 nm **Flow Rate:** 1 ml/min **Retention time**: Teneligliptin: 2.58 min Pioglitazone: 6.13 min **Linearity range:** Teneligliptin:1-5 µg/ml Pioglitazone:1.5-7.5µg/ml
7.	Teneligliptin and Metformin Hydrochloride[14]	**RP-HPLC**	**Column:** Thermo C18, (250 × 4.6mm, 5µm) **Mobile Phase:** 0.1M KH_2PO_4 buffer: Methanol (60:40%v/v) **DetectedWavelength:**280nm **Flow rate:** 1.0ml/min **Retention time:** Teneligliptin**:** 4.421 min Metformin**:** 3.421 min **Linearity range:** Teneligliptin**:** 50- 150µg/ml Metformin**:** 50- 150µg/ml
8.	Teneligliptin and Metformin[15]	**Stability indicating RP-HPLC**	**Column:** Kromasil C18 (250×4.6 mm, 5 µm) **Mobile phase:** 0.1% orthophosphoric acid buffer: Acetonitrile: Methanol (65:25:10, v/v/v) **Detected Wavelength:**254 nm **Flow rate :**1.0 ml/min **Retention time:** Teneligliptin: 2.842 min Metformin :2.017 min **Linearity range:** Teneligliptin :5-30 µg/ml Metformin :125-750 µg/ml

Summary of Analytical methods for Metformin Hydrochloride

Official compendial Method for Metformin Hydrochloride

Sr. No.	Official in	Brief Description
1.	IP 2018[16]	**LIQUID CHROMATOGRAPHY** **Column**: Stainless steel column (30 cm x 4 mm, 10µm) **Mobile phase:** Solution containing 0.087% w/v of Sodium Pentane sulphonate and 0.12% w/v of Sodium chloride (adjusted to pH 3.5 using 1% v/v Orthophosphoric acid. **Flow rate:** 1 ml/min **Detection Wavelength:** 218 nm **Injection volume:** 20 µL
2.	BP 2020[17]	**LIQUID CHROMATOGRAPHY** **Column:** (0.25 m x 4.6 mm, 10 µm) **Mobile phase:** 17 g/L solution of Ammonium Dihydrogen phosphate (adjusted to pH 3.0) with Phosphoric acid. **Flow rate:** 1.0 mL/min **Detection Wavelength:** 218nm **Injection volume:** 20 µL
3.	USP 2019[18]	**LIQUID CHROMATOGRAPHY** **Column:** (4.6 mm x 25 cm) **Mobile phase:** Solution in water, containing 17g of monobasic Ammonium phosphate adjusted with Phosphoric acid to a pH f 3.0. **Flow rate:** 1.0-1.7 mL/min **Detection Wavelength:** 218 nm **Injection volume:** 20 µL

Reported Analytical Methods for Metformin Hydrochloride

Sr. No.	Drug	Method	Brief Description
1.	Metformin Hydrochloride[19]	**UV**	**Solvent**: Methanol **Wavelength:** 233 nm **Linearity range:** 1-25 µg/ml **r^2:** 0.999 **LOD**: 1.0 µg/ml **LOQ**: 3.0 µg/ml
2.	Metformin Hydrochloride[20]	**HPLC**	**Column**: C_{18} (250 x 4.6 mm, 5 µm) **Wavelength:** 235 nm **Mobile phase**:0.02 M Acetate buffer (pH

			3): Methanol (70:30 v/v) **Flow rate:** 1.0 ml/min **Linearity**: 10-2000 µg/ml **r^2**: 0.9999 **LOD**: 25.09 µg/ml **LOQ**: 29.46 µg/ml
3.	Metformin Hydrochloride [21]	**RP-HPLC**	**Column**: C_{18} (250 mm x 4.6 mm) **Wavelength:** 232 nm **Mobile phase**: 10m.mol 1-Octane Sulfonic acid: Acetonitrile (80:20 v/v) **Flow rate:** 1.0 ml/min **Linearity**: 1-250 µg/ml **r^2**: 0.9995
4.	Metformin and Teneligliptin [22]	**RP-HPLC**	**Column:** C_8 Phenomenex (250 × 4.6 mm, 5 µm) **Mobile Phase:** Methanol: formic acid: acetic acid (75:25:0.1, v/v/v) **DetectedWavelength**:210nm **Flow rate:** 0.5 mL/min **Retention time:** Teneligliptin**:** 6.234±0.03min Metformin**:** 4.024±0.02min **Linearity range:** Teneligliptin**:** 50- 150µg/ml Metformin**:** 50- 150µg/ml
5.	Metformin and Teneligliptin [23]	**Stability indicating RP-HPLC**	**Column**: Discovery (250 X 4.6 mm: 5 µm) **Mobile phase** :0.1% orthophosphoric acid buffer: acetonitrile (65:35, v/v) **Detected Wavelength**:260nm **Flow rate**: 1 ml/min **Retention time:** Metformin:2.517min Teneligliptin:3.687min **Linearity range:** Metformin:125-750 µg/ml Teneligliptin:5-30 µg/ml
6.	Metformin Hydrochloride, Alogliptin Benzoate, and Repaglinide [24]	**RP-HPLC**	**Column**: C_{18} (250 mm, 4.6 mm, 5 µm) **Mobile phase**: Acetonitrile: Phosphate buffer (pH 2.5) with o-phosphoric acid): 0.3% Sodium heptane sulfonate in water (60:20:20, *v/v/v*) **Retention time:** ALO: 4.19 min REP: 8.73 min MET: 1.92 min **Flow rate**: 1.0 ml/min **Linearity**: ALO: 1.7–42.5 µg/ml REP: 0.1–40 µg/ml

			MET: 2.5–62.5 µg/ml **r^2**: ALO: 0.9995 REP: 0.9999 MET: 1 **LOD**: ALO:0.383 µg/ml REP: 0.027 µg/ml MET:0.391 µg/ml **LOQ**: ALO:1.161 µg/ml REP: 0.081 µg/ml MET:1.185 µg/ml

Summary of Analytical Methods for Pioglitazone Hydrochloride

Official compendial methods for Pioglitazone Hydrochloride

Sr. No.	Official in	Method	Description
1.	IP 2010 [25]	**Liquid Chromatography**	**Column:** ODS C18(250 × 4.6mm, 5.0 µm) **Mobile Phase:** KH_2PO_4 buffer: Acetonitrile (50:50%v/v) **Flow rate:**1.0 ml/min **Wavelength:**225 nm
2.	BP 2020 [26]	**Liquid Chromatography**	**Column:** ODS C18(150 × 4.6mm, 5.0 µm) **Mobile Phase:** Glacial acetic acid: Acetonitrile: Ammonium Acetate (1:25:25 v/v/v) **Flow rate:**0.7 ml/min **Wavelength:**269 nm

Reported Analytical methods for Pioglitazone hydrochloride

Sr. No.	Drug	Method	Brief Description
1.	Pioglitazone Hydrochloride [27]	**UV**	**Solvent**: Methanol **Wavelength**:268nm **Linearity range**:10-50µg/ml
2.	Pioglitazone Hydrochloride [28]	**UV**	**Solvent**: Methanol **Wavelength**:270 nm **Linearity range**:10-50µg/ml

3.	Pioglitazone Hydrochloride [29]	**RP-HPLC**	**Column:** C_{18} column (250 X 4.6 mm, 5µm) **Mobile phase:** Methanol: pH4.6 buffer adjusted with 0.1 % v/v glacial acetic acid (80:20 %v/v) **Detected Wavelength:** 273 nm **Flow rate:** 1.5 ml/min **Retention time:** 3.4 min **Linearity range**: 5-30 µg/ml
4.	Pioglitazone [30]	**RP-HPLC**	**Column:**C_{18} column (300× 3.9 mm, 5 µm) **Mobile phase:** Acetonitrile: phosphate buffer, (50:50%v/v) **Detected Wavelength:** 267 nm **Flow rate:** 1.00 ml/min **Retention time:**8.08 min **Linearity range**:10-30µg/ml
5.	Pioglitazone Hydrochloride [31]	**RP-HPLC**	**Column:** Hypersil BDS, (250 x 4.6mm, 5 µm) **Mobile phase:** 0.01M KH_2PO_4: acetonitrile, (40:60 %v/v) **Detected Wavelength:**225 nm **Flow rate:** 1.0 ml/min **Retention time:**4.726 min **Linearity range**:80- 320 µg/ml
6.	Metformin Hydrochloride and Pioglitazone [32]	**UV**	**Solvent:** Methanol **Wavelength:** Metformin Hydrochloride:231 nm Pioglitazone: 269 nm **Linearity range**: Metformin Hydrochloride: 5-30 µg/ ml Pioglitazone: 2-12 µg/ ml
7.	Metformin Hydrochloride and Pioglitazone [33]	**UV**	**Solvent:** Methanol **Wavelength:** Metformin Hydrochloride:237.4 nm Pioglitazone:225.4 nm **Linearity range**: Metformin Hydrochloride :5-40µg/ ml Pioglitazone:5-40µg/ ml
8.	Dapagliflozin and Pioglitazone Hydrochloride [34]	**RP-HPLC**	**Column:** Kromstar Vertex C_{18} column (250 ×4.6 mm, 5µm) **Mobile phase:** Acetonitrile: KH_2PO_4 Buffer (pH 4) adjusted with OPA (25:75%v/v) **Detected Wavelength:**228nm **Flow rate:** 1 ml/min **Retention time:** Dapagliflozin: 3 min Pioglitazone: 6.5 min **Linearity range**: Dapagliflozin: 2-10 µg/ml Pioglitazone: 3–15 µg/ml

9.	Pioglitazone and Rosiglitazone [35]	**RP-HPLC**	**Column:** Inertial ODS (150x4.6mm, 3.5 µm) **Mobile phase:** buffer containing 0.1% formic acid: Acetonitrile (30:70% v/v) **Detected Wavelength:**261nm **Flow rate:**1 ml/min **Retention time:** Rosiglitazone:5.118 min Pioglitazone:2.770 min **Linearity range**: Rosiglitazone:1-15 µg/ml Pioglitazone:3-45 µg/ml
10.	Alogliptin and Pioglitazone [36]	**RP-HPLC**	**Column:** Develosil ODS C_{18} column (4.6mm×250mm, 5µm) **Mobile phase:** Acetonitrile: Methanol: 1% Orthophosphoric acid (50:30:20% v/v) **Detected Wavelength:** 242 nm **Flow rate:** 1.0 ml/ min **Retention time:** Alogliptin**:** 2.24 min Pioglitazone**:** 5.44 min **Linearity range:** Alogliptin**:** 30-70 µg/ml Pioglitazone**:** 60-140µg/ml
11.	Metformin and Pioglitazone [37]	**RP-HPLC**	**Column:** A Gemini C18 column (150x4.6mm, 5µm) **Mobile phase:** Acetonitrile: Ammonium Acetate buffer (pH-3) (42: 58% v/v) **Detected Wavelength:**255 nm
12.	Pioglitazone and Glimepiride [38]	**RP-HPLC**	**Column** Bridge C_{18}, (250 X 4.6 mm,5µm) **Mobile phase:**KH_2PO_4Buffer: Acetonitrile (60:40%v/v) **Detected Wavelength:**257nm **Flow rate:**1.0 ml/min **Retention time:** Glimepiride: 2.66min Pioglitazone: 4.49min **Linearity range**: Glimepiride: 32-50µg/ ml Pioglitazone: 240-350µg/ ml
13.	Alogliptin and Pioglitazone [39]	**Stability indicating RP-UPLC**	**Column:** BEH C_{18}(2.1× 50 mm,1.7 µm) **Mobile phase:** Phosphate buffer (pH 3): Methanol (45:55 % v/v) **Detected Wavelength:** 280nm **Flow rate:** 0.3 ml/min **Retention time:** Alogliptin: 0.4 min Pioglitazone: 0.529 min **Linearity range**: Alogliptin: 6.25–37.5µg/ ml Pioglitazone: 15–90µg/ ml
14.	Glimepiride and Pioglitazone [40]	**RP-HPLC**	**Column:** Luna C_{18} (150mm x 4.6mm; 5-µm) **Mobile phase:** Phosphate Buffer pH 3.0: Acetonitrile (45:55% v/v)

			Detected Wavelength:228nm **Flow rate:** 1.0 ml/ min **Retention time:** Glimepiride: 6.9min Pioglitazone: 2.36min **Linearity range**: Glimepiride: 4-12µg/ ml Pioglitazone: 30-90µg/ ml

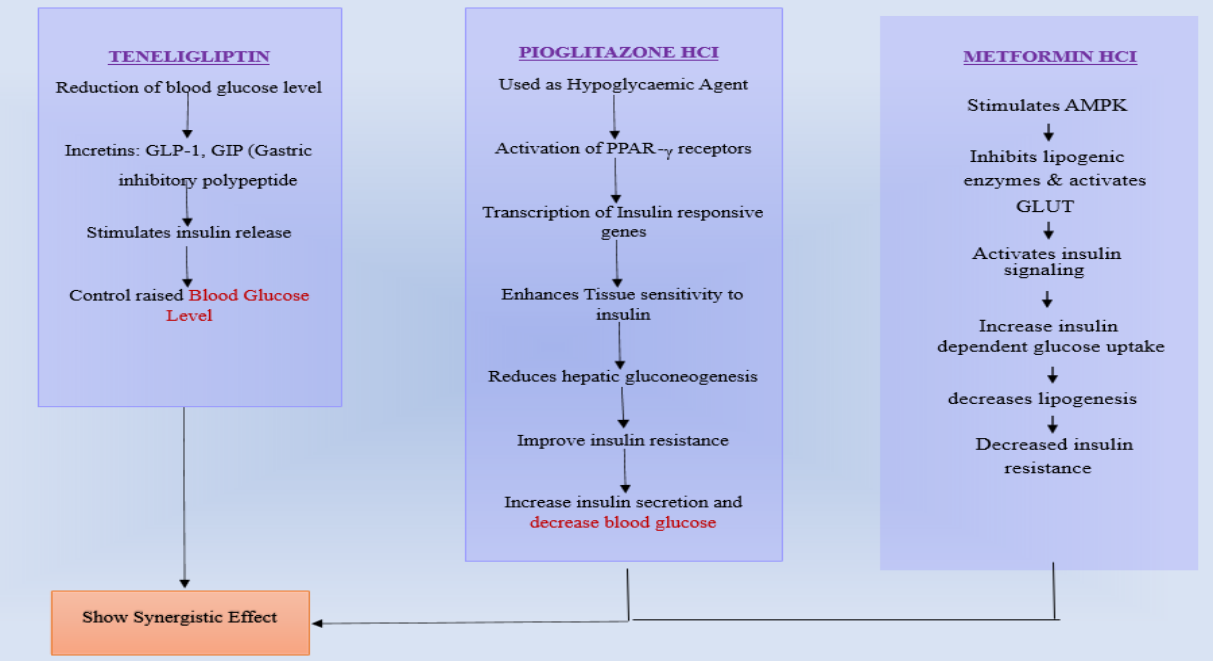

Fig 4. Combine effect of Teneligliptin, Metformin Hydrochloride and Pioglitazone Hydrochloride

CONCLUSION

A better approach for treating Type 2 Diabetes Mellitus may involve combining the drugs Teneligliptin Hydrobromide Hydrate, Metformin Hydrochloride and Pioglitazone Hydrochloride. The combination of these three drugs performs well together and have no negative drug interactions and have synergistic effect. Teneligliptin increases the release of insulin from the pancreas and decreases the hormone (glucagon) that raises blood sugar levels. This reduces the fasting and post meal sugar levels. Metformin decreases the amount of glucose absorbed from your food and the amount of glucose made by the liver. It also increases the body's response to insulin, a natural substance that controls the amount of glucose in the blood. Pioglitazone primarily acts on muscle, fat, and liver cells to enhance their response to insulin, making it easier for these cells to take up glucose from the bloodstream. It also reduces the production of glucose by the liver, which is a common

problem in people with type 2 diabetes. According to literature survey method validation available only for two combinations e.g. metformin hydrochloride with pioglitazone and teneligliptin with the other two but, there is no such, method available for RP- HPLC method for simultaneous estimation method for these three drugs in combination. Therefore, it is worthwhile to develop and validate an RP-HPLC method for the simultaneous estimation of Teneligliptin, Metformin Hydrochloride and Pioglitazone Hydrochloride.

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