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A COMPREHENSIVE STUDY OF ANALYTICAL METHODS FOR RECENTLY APPROVED FDC DRUGS: TENELIGLIPTIN AND PIOGLITAZONE

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ABSTRACT

Fixed dose combination (FDC) has two or more active components in a single dosage form. There are several advantages that support FDCs. These include minimizing the risk of undesirable drug effects improving therapeutic effectiveness, offering pharmacokinetic benefits, reducing the dose of specific medications, and slows down resistance to drugs. Teneligliptin (20 mg) and Pioglitazone (15 mg) are recommended to improve glycaemic control in adult patients with insulin resistance. Individual quantitation of Teneligliptin (TNG) and Pioglitazone (PIO) is done using analytical methods. This review will emphasize on recent advances in analytical methodologies for assessing TNG and PIO because no method for this combination has been reported. However, UV, stability indicating RP-HPLC and HPTLC methods have been reported for Teneligliptin and Pioglitazone individual and along with other drugs.

Keywords: FDCs, Analytical techniques, RP-HPLC, HPTLC, Stability indicating methods

INTRODUCTION

Type 2 diabetes, sometimes referred as non-insulin-dependent diabetes. Teneligliptin and pioglitazone are the recommended second-line treatments for type 2 diabetes. Teneligliptin (2S,4S)-4- [4-] (3-methyl-1-phenyl-1H- pyrazol-5-yl) piperazin-1-yl] pyrrolidin-2-yl} (1,3-thiazolidin-3-yl) (1,3-thiazolidin-3-yl) Methanogen hemi Penta

has a distinctive, peptidomimetic structure with five successive rings. The crucial interaction between the pyrazole's phenyl ring and the S2 extended subsite of DPP-4, which boosts the drug's potency and selectivity, which is seen in an X-ray co-crystal structure of teneligliptin with DPP-4 **[1, 2, 3]**.

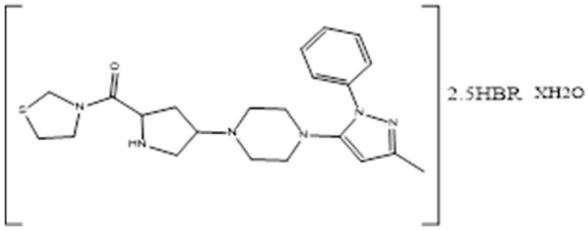

Figure 1: Chemical structure of Teneligliptin

Teneligliptin reduces glucagon release by raising incretin levels (GLP-1 and GIP), which also boosts insulin secretion, slows down stomach emptying, and lowers blood glucose levels **[4, 5, 6]**.

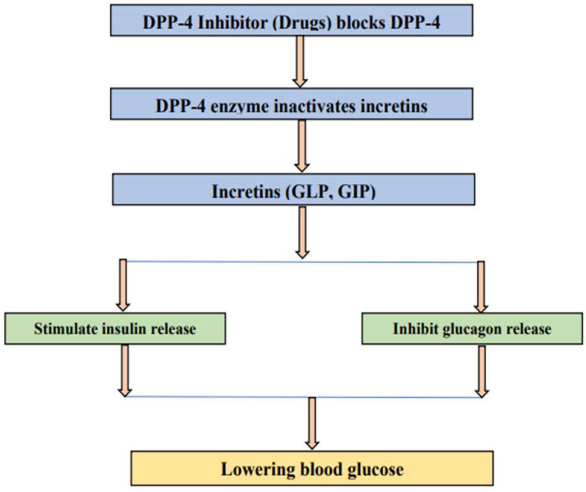

Figure 2: Mechanism of action of Teneligliptin

Pioglitazone known by its chemical name (RS)-5-(4-[2-(5-ethylpyridin-2-yl) ethoxy] benzyl) thiazolidine-2,4-dione), is a member of the thalidonedione class of oral hypoglycaemic medications.

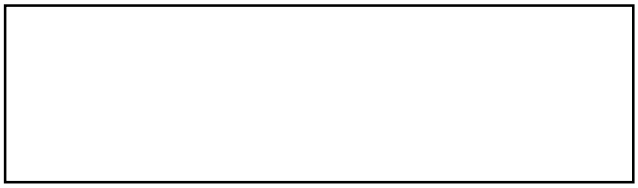

Figure 3: Chemical structure of Pioglitazone

Thiazolidinediones are high-affinity ligands for PPARγ, a member of the nuclear receptor superfamily of ligand activated nuclear receptors. When a ligand activates PPARγ, it forms a heterodimer with another nuclear receptor which is retinoid-X receptor **[7, 8]**. In order to control the transcriptional activity of the target genes involved in glucose and lipid metabolism, this heterodimer first binds to particular DNA sequences and regulates transcriptional activities. **[9, 10]**. Different PPARγ agonists, such as, rosiglitazone, pioglitazone and troglitazone, have different effects on the regulation of more than 100 PPAR γ -responsive agents. This may be because different ligands have different coactivator protein interactions and different receptor conformations. The activation of PPAR γ by Pioglitazone leads to increased peripheral, hepatic and adipocyte insulin sensitivity and its active metabolites, the hydroxy derivatives MII and MIV, and the keto derivative MIII, improve disordered glucose homeostasis by reducing insulin resistance **[11]**.

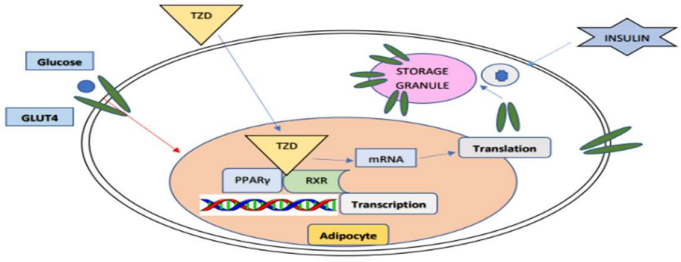

Figure 4: Mechanism of action Pioglitazone

Analytical methods:

The discovery, development and production of pharmaceutical products all depend on the development and validation of analytical methods. Method development is the process of demonstrating that an analytical method is suitable for determining the API concentration in a certain dosage form. Every year, more drugs are introduced onto the market. It is essential to develop novel analytical methods for such pharmaceuticals because these drugs may be either new moiety or structural modification of an existing one, making it possible that the analytical processes for the new drugs may not be included in pharmacopoeias. Official test procedures are used by quality control laboratories to guarantee the authenticity, purity, and potency of drug substances. The analyte is analysed using High Performance Thin Layer Chromatography, UV Spectrophotometric, Ultra Performance Liquid Chromatography, Stability Indicating High Performance Liquid

Chromatography, spectrofluorimetric LC-MS/MS, and other methods. There hasn't been a method published for the combination of teneligliptin and pioglitazone yet, according review of the literature. However, procedures for Teneligliptin and Pioglitazone alone and in combination with other medications have been discovered using UV, HPLC, Stability indicating RPHPLC, and HPTLC are listed below **[12, 13, 14]**.

Table 1: Reported UV methods for assessing of Teneligliptin and Pioglitazone:

Sr. No	Drugs	Model	Solvent	Method	Wavelength (nm)		Linearity ($\mu g.ml^{-1}$)	Ref.
1.	TNG	Shimadzu 1800 UV VIS	Distilled Water	Zero order	244 nm		5-70 (µg/ml)	[15]
				First order	266.4 nm			
				AUC	238.6-247.2 nm			
2.	TNG	Shimadzu 2450 UV VIS	Methanol: water (50:50)	245 nm			10-35 (µg/ml)	[16]
3.	TNG	Sytronic 2201 UV VIS	Dimethyl sulphoxide (DMSO)	267.2 nm			20-100 (µg/ml)	[17]
4.	TNG and MET	UV VIS Cary 600 Agilent technology	Distilled Water	Simultaneous	TNG	245nm	MET - 2-12 (µg/ml) TNG - 5-55 (µg/ml)	[18]
					MET	230 nm		
				Q-Absorbance	TNG	240 nm		
					MET	230 nm		
5.	TNG and ROSU	Shimadzu 1800 UV VIS	Methanol	First order	TNG	230.03nm	1-42 (µg/ml)	[19]
					ROSU	222.66nm		
7.	TNG and PIO	Shimadzu 1800 UV VIS	Methanol	TNG:246 nm PIO: 269 nm			TNG-2-10 (µg/ml) PIO -3-15(µg/ml)	[20]
8.	PIO	Shimadzu 1700 UV VIS	Methanol	PIO - 238nm			10-50 (µg/ml)	[21]
9.	PIO	Shimadzu 1800 UV VIS	Methanol	PIO - 234 nm			0.2-1.2 (µg/ml)	[22]
10.	PIO and GLMP	Shimadzu 1700 UV VIS	Methanol	PIO-279 nm GlMP-238 nm			PIO-1-12 (µg/ml) GLMP-2-30 (µg/ml)	[23]
11.	PIO and MET	UV spectroscopy	Methanol	Simultaneous	PIO	225.4 nm	5-40 (µg/ml)	[24]
					MET	237.4 nm		
				Dual Wavelength	PIO	232.8-272.8 nm		
					MET	264.8-272.8 nm		

Table 2: Reported HPLC methods for assessing of Teneligliptin and Pioglitazone:

Sr. No	Drug	Stationary phase	Mobile phase	Flow rate (ml/min)	Wavelength (nm)	Linearity ($\mu g.ml^{-1}$)	Retention time (min)	Ref.
1	TEN	Cosmosil C18 (250mm×4.6ID×5µm)	70:30(Methanol: Phosphate buffer pH-3) v/v	0.8 (ml/min)	246 nm	10-50 ((µg/ml)	4.2 min	[25]
2	TEN and RMG	Zorabx C_{18}	(3,4,5 % of Acetonitrile (50%,55% and 60%)	(1,1.2,1.4) (ml/min)	210 nm	TEN-2-60 (µg/ml) RMG-5-100 (µg/ml)	TEN-1.65 min RMG-2.48 min	[26]

3	TEN and MET	Cosmosil C_{18}(250mm × 4.6mm × 5µm)	Methanol: Water (50:50 v/v) pH-3.5	0.7 (ml/min)	TEN-246 nm MET-232 nm	TEN-2-10 (µg/ml) MET-50-250 (µg/ml)	TEN-6.27 min MET-2.38 min	[27]
4	TEN and ROSU	Hyperchrom ODS BP column (250 × 4.6mm × 5µm)	Phosphate buffer (pH 3.5): Methanol (70:30) v/v	1 (ml/min)	240 nm	10-30 (µg/ml)	TEN-4.31 min ROSU-5.93 min	[28]
5	PIO	Phenomenex Luna C_{18} (250mm×4.6mm×5µm)	Methanol: Water (75:25) v/v	1 (ml/min)	268 nm	10-18 (µg/ml)	3.28 min	[29]
6	PIO and ALO	BEH C_{18} (2.1×50mm×1.7µ)	Phosphate buffer pH-3: Methanol (45:55) v/v	0.3 (ml/min)	280 nm	PIO -15-90 (µg/ml) ALO -6.25-37.5 (µg/ml)	PIO-0.529 min ALO -0.4 min	[30]
7	PIO and STG	Phenomenex C_{18} column (150mm×4.6mm×5µm)	Acetonitrile: Methanol: Water (30:30:40) v/v/v	1 (ml/min)	270 nm	PIO - 3-15 (µg/ml) STG -10-50 (µg/ml)	PIO-2.8 min STG-5.6 min	[31]

Table 3: Reported HPTLC methods for assessing of Teneligliptin and Pioglitazone

Sr. No	Drug	Stationary Phase	Mobile Phase	Wavelength	Linearity	R_f Value	Ref.
1.	TNG	Silica gel $60F_{254}$	Butanol: Water: Glacial Acetic Acid (6:2:2%v/v/v)	254 nm	250-1250 ng/band	0.65	[32]
2.	TNG and MET	Silica gel $60F_{254}$	Methanol: Ammonium Sulphate: Triethylamine (9:2.7:0.5%v/v/v)	237 nm	TNG -4-28 ng/band MET -100-700 ng/band	TNG -0.63 MET -0.19	[33]
3.	PIO and TEL	Silica gel $60F_{254}$	Toluene: Ethyl Acetate: Methanol (7:2:1 v/v/v)	269 nm	PIO - 30-150 ng/spot TEL – 40-200 ng/spot	PIO - 0.56 TEL – 0.32	[34]
4.	PIO and MET	Silica gel aluminium plates (20×10 cm; F_{254})	Toluene: Methanol: Acetic Acid (5:5:0.5) v/v/v	240 nm	MET-3-12 µg/band PIO-3-20 µg/band	MET-0.2 PIO-0.8	[35]
5.	PIO, MET and GLI	Al^{+3} 60 F_{254}	Butanol:1,4-dioxane: Glacial Acetic Acid (5:3:2 v/v/v) + 2 drop of formic acid	226 nm	PIO -60-540 ng/band MET-2000-18000 ng/band GLI-10-100 ng/band	PIO -0.72 MET -0.15 GLI -0.85	[36]

CONCLUSION

The analysis of the reported data indicates that no method for the fixed dose combination of TNG and PIO was reported. Multiple analytical methods such as HPTLC, and Stability indicating RP-HPLC, UV and HPLC Methods have been noted for TNG and PIO individually and in combination with other medications, based on an analysis of the literature. therefore, a

need for researchers to create new analytical techniques for combining TNG and PIO. This review provided a summary of the most recent, cutting-edge analytical methods for identifying TNG and PIO. which is essential for further research on this combination. Understanding the essential solvents and the tools accessible in the analytical laboratory will also benefit from the review. The techniques are also beneficial for manufacturing API in-process evaluation.

ABBREVIATION	
Drug Name	**Abbreviation**
Teneligliptin	**TNG**
Metformin	**MET**
Rosuvastatin	**ROSU**
Pioglitazone	**PIO**
Glimipiride	**GLMP**
Remogliflozin	**RMG**
Alogliptin	**ALO**
Sitagliptin	**STG**
Telmisartan	**TEL**
Glibenclamide	**GLI**

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