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Analytical Profile of Trelagliptin: A Review

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ABSTRACT

Trelagliptin succinate is the most potent inhibitor of dipeptidyl peptidase-4 (DPP-4) to prevent the inactivation of incretin hormone and increase glucagon-like peptide (GLP-1) to treat type 2 diabetes. The chase to improve the quality of life has stimulated desirable changes in research to design and develop a new drug and enhance its safety and effectiveness. Thus, there is a gradual rise in demand to develop susceptible and specific analytical techniques for newly developed drugs. To test purity, identity and quantity of Trelagliptin in dosage forms and biological samples always needs different analytical methods such as spectroscopic, chromatographic, electro analytical methods and microbiological assays. This review depicts several published analytical methods along with instrumental conditions for the detection and quantification of Trelagliptin during the last 8 years. From literature reviews, HPLC with UV detection is majorly used for the quantification of Trelagliptin in pharmaceutical formulations and LC-MS for biological samples. Moreover, his review also discusses the Trelagliptin chemical structure, mechanism of action, and pharmacodynamics/pharmacokinetics properties. The present review can be effectively explored to conduct future analytical investigations for the estimation of Trelagliptin.

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INTRODUCTION:

Trelagliptin succinate (TLN, Figure 1) is the most potent inhibitor of dipeptidyl peptidase-4 (DPP-4) to prevent the inactivation of incretin hormone (release of insulin) and increasing glucagon-like peptide (GLP-1) to treat type 2 diabetes. In addition to its insulin secretagogue effect, it also improves insulin resistance. It had been approved for use in Japan in March 2015 by Takeda Pharmaceutical Company as Zafatek® tablets. As a once-weekly drug, it enhances the patient's adherence to the treatment regimen instead of the other previously approved gliptins. TLN showed a high safety profile with patients suffering from end-stage renal disease or even with renal impairment. Moreover, TLN was repositioned as a potential therapeutic agent for metabolic syndrome with polypharmacologic effects that will lower the treatment cost as one drug with multifaceted therapy. Also, the repositioning of TLN and its sister gliptins for neurodegenerative diseases is suggested based on improving insulin resistance in the brain. TLN is a well-tolerated drug with less dosing frequency and less serious adverse events. TLN clinical trials have confirmed that it can effectively control the plasma concentration of glucose and HbA1c in type 2 diabetic patients [1-2]. Chemically TLN is a 2-[[6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxopyrimidin-1-yl] methyl]-4-fluorobenzonitrile; butane dioic acid with molecular formula and its molecular weight is $C_{22}H_{26}FN_5O_6$ and 475.5 g/mol [3]. TLN is soluble in Dimethyl sulfoxide (DMSO), Dimethyl formamide (DMF) and Phosphate-buffered Saline (PBS) at pH 7.2 [4-5]. It should be stored at -20^{o} C. Trelagliptin showed the favorable PK-PD profiles in dogs and monkeys with half-life 4.8 h and 6.2 h, respectively. It inhibited more than 80% of plasma DPP-IV activity after 24 h at a single oral dose of 7.0 mg/kg [6].

The main aim of the study is to provide comprehensive information on TLN-like profile, available marketed formulations (Table1), Mechanism of action (Figure 2), and pharmacological and analytical methods reported (Table 2 and Table 3) reported so far. And it may helpful for potential future research to be carried out on the TLN.

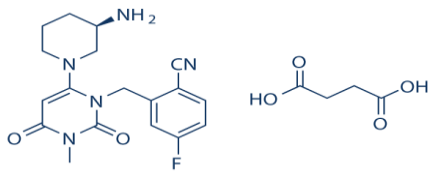

Figure 1: Chemical structure of Trelagliptin succinate

Mechanism of action: Trelagliptin succinate inhibits dipeptidyl peptidase- 4 to prevent the inactivation of incretin hormone (release of insulin) and increases the concentration of GLP-1(glucagon-like peptide) [6].

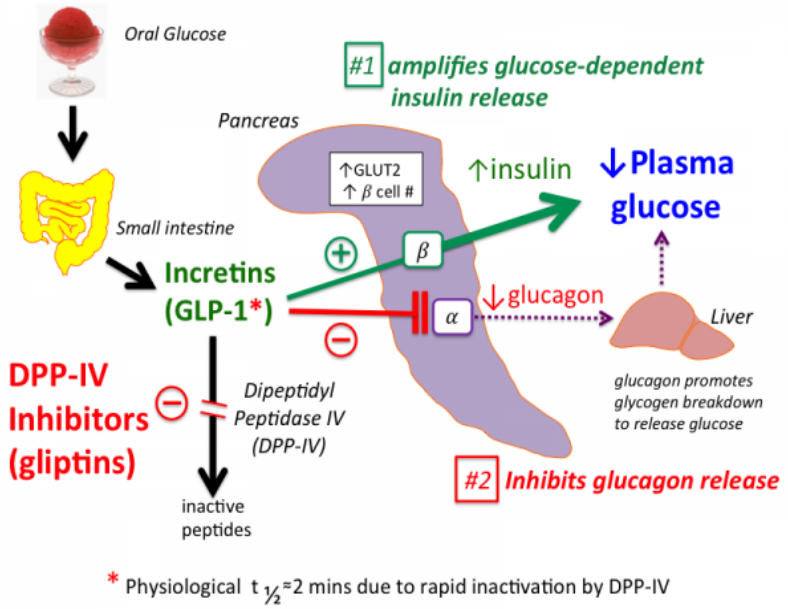

Figure 2: Mechanism of action of Trelagliptin succinate

Table 1: Available marketed formulation

S.No.	Trade name	Formulation	Dosage and Strength	Manufacturer
1	Zafatek	Tablets	50 mg,100 mg	Takeda Pharmaceutical Company, Japan
2	Wedic	Tablets	100 mg	Beacon Pharmaceuticals Ltd. Bangladesh
3	Triliptin	Tablets	100 mg	Drug International Ltd. Bangladesh

Table 2: LC-MS/MS Methods for Trelagliptin succinate

S.No.	Method	Stationary phase (Column)	Mobile phase	Flow rate (mL/min)	Detection wavelength (nm)	Linearity (µg/mL)	Ref.No.
1	RP-HPLC	Cosmosil (250mm × 4.6mm; 5µm)	Buffer and acetonitrile (20:80 v/v)	1.0	225	0.25-1.32	7
2	RP-HPLC	Waters X select CSH™ C_{18} (250 mm × 4.6 mm, 5.0 µm)	0.05% Trifluoroacetic acid in water as well as ACN containing 0.05% Trifluroacetic acid	1.0	224 275	-	8
3	RP - HPLC	Chiral Pak AD-3 (250×4.6 mm, 3 µm)	Hexane, ethanol and diethyl amine (70:30:0.1 v/v)	1.0	275	0.1220-2.2485	9
4	RP-HPLC	Chiral Pak AD (250 × 4.6 mm;5 µm)	n-hexane and 2-propanol (90:10 v/v)	1.0	260	0.005–2	10
5	UPLC-MS/MS	Agilent SB- C18 (1.8 µm) 50×2.1 mm	Acetonitrile - formic acid 0.1% (80:20, v/v)	0.3	274	50–800 ng/mL	11
6	UPLC-UV	Hypersil Gold C18(1.9 µm) 50 mm×3 mm	Acetonitrile – potassium dihydrogen phosphate buffer 0.05M (50:50 v/v)	0.5	274	2.5–80	
7	HPLC-UV	BDS Hypersil C18(3 µm) 100 mm ×3 mm	Acetonitrile – potassium dihydrogen phosphate buffer 0.05M (50:50, v/v)	0.5	274	5–100	
8	UHPLC-UV	Symmetry C18 (2.2 µm) 100 mm ×2.1 mm column	Acetonitrile – potassium dihydrogen phosphate buffer 0.05M (50:50, v/v)	0.5	274	5–100	
9	UV	-	Methanol	-	274	5–50	
10	UV	UV spectrophotometer (S/N C367961148, Japan, JASCO)	Methanol		274	5-50	12

S.No.	Method; Internal Standard	LC Instrument	Chromatographic conditions	MS-Conditions	Ref.No.
11	LC-MS/MS Alogliptin	Waters® UPLC-TQ, and Mass Lynx software	**Column:** Phenomenex C18 (150 × 2.1 mm; 1.6 µm) **Mobile phase:** Acetonitrile: 0.1% formic acid (90:10 v/v) **Flow rate:** 0.3 mL/min **Linearity:** ng/mL	**Cone voltage:** 25V and 30 V for TLN and IS (Alogliptin), **Collision energy:** 60 eV and 55 eV for TLN and IS (Alogliptin), respectively. **MRM:** m/z 358.2 to 133.9 for TLN and m/z 340.2 to 116.0 for IS **Ionization:** ESI positive mode	13
12	LC-MS/MS (R)-Rabeprazole	The LC–MS/MS system consists of Agilent 1100 liquid chromatography (Agilent Technologies, Palo Alto, CA, USA) and an API 3000 triple quadrupole mass spectrometer (AB Sciex, Toronto, Canada) equipped with an electrospray ionization (ESI) interface by positive ion mode	**Column:** A Chiral cel OX-3R (150 × 0.46 mm, 3 µm) **Mobile phase:** 10 mmol/L ammonium bicarbonate (mobile phase A) and acetonitrile (mobile phase B) **Flow rate:** 0.6 mL/min **Linearity:** 5- 2000 ng/mL	**Declustering potential:** 41 V **Entrance potential:** 10 V **Collision energy:** 20 V and **Collision exit potential:** 21 V **IS** were 37, 10, 20 and 12 V. **Collision gas: high, curtain gas** 20 psi, **Ion source gas 1:** 55 psi, **Ion source gas 2:** 40 psi, **Ion spray voltage:** 5000 V **and source temperature:** 500◦C **MRM transitions:** m/z 358.1→341.2 TRG and 359.9→150.1 IS. Chromatographic data acquisition and processing were performed by Analyst version 1.5.2 from AB Sciex.	14
13	UHPLC–MS/MS Carbamazepine	Agilent 1290 system (Agilent Technologies, USA) which was equipped with a HiP sampler	RRHD Eclipse Plus C18 (2.1 × 50 mm, 1.8 µ) Column Temp. 30 °C **Mobile Phase**: Acetonitrile and formic Acid (0.1% v/v) **Injection volume:** 2 µL. **Total run time:** 3.9 min, **Stop Time:** 2.4 min and **Post time:** 1.5 min **Flow rate:** 0.4 mL/min **Linearity:** 5- 4000 ng/mL	**The capillary Voltage:** 4.0 kV in positive mode **The nebulizer was** set to 45 psi. **The gas temperature:** 350 °C, while its flow was 10 L/min. Data were obtained by Mass Hunter workstation 6 software and Qualitative Analysis software (version	15

				B.07.00) **MRM transitions:** *m/z* 358.2→133.9 for trelagliptin, *m/z* 237.1→194.0 for IS. It was performed in positive-ion Electrospray.	

Conclusion:

The present review provides a summary of various analytical methods reported for the determination of TLN in bulk, pharmaceutical formulations and also in various biological matrices like blood plasma and urine. The reported analytical methods consisting of Spectroscopy chromatography, and hyphenated techniques, were employed for the determination of TLN.The reported data for analysis of TLN revealed that HPLC with UV detection is the most frequent technique employed for the determination of TLN in pharmaceutical dosage forms. For analysis of TLN in biological matrices like blood plasma, urine LC-MS with MS detection is appropriate since this strategy gives precise outcomes and minimal effort. Furthermore, employing MS techniques in LC offered unique selectivity and sensitivity as well as a choice of method for analysis of TLN and its metabolites in biological samples. This review will be useful in the further development of the analytical methods for TLN estimation and also gives a glimpse of the drug profile.

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Conflicts of interest:

All the authors declare that they do not have any conflicts of interest.

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