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An Overview on Analytical Estimation of Linagliptin

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ABSTRACT

Linagliptin (LINA) is having competitive, reversible DPP-4 inhibitory action used in treatment of diabetes mellitus. The plethora subscribed in this work is directed towards the collection of various important methods used for the estimation of Linagliptin, from its bulk and formulations. As the newer guidelines from ICH had been directed towards the qualitative estimation of drugs from its bulk and formulations are made significant as it directly related towards the effectiveness of the drugs.

Key-words: Linagliptin, analytical, method, estimation, bulk, formulation.

I. INTRODUCTION

Diabetes mellitus (DM) belongs to a category of metabolic disorder, characterized by chronichyperglycaemia occurring due to deficiency in insulin secretion or action or both. People withtype 2 DM are susceptible to various short term as well as long term complications includingpremature deaths and coma [1]. The combination of linagliptin and empagliflozin is on themarket as tablets formulation for oral use for the management of type 2diabetes andcardiovascular risk. Empagliflozin (EMPA) is used as a sodium glucose cotransporter-2(SGLT-2) inhibitor to improve glycemic control in adult patients with type 2 diabetes. SGLT-2 co-transporters reabsorb glucose from the glomerular filtrate in kidney and the glucureticaction resulting from inhibition of SGLT-2 which reduces renal absorption and lowers downthe renal threshold for glucose, therefore increases glucose excretion which reduceshyperglycaemia and also helps in blood pressure reduction [2, 3]. Chemically EMPA is 1-chloro-4-(glucopyranos-1-yl)-2-(4-(tetrahydrofuran-3-yloxy)benzyl)benzene and havingempirical formula is C23H27ClO7 with molecular weight 450.91 g/mole (Fig. 1). Linagliptin(LINA) is having competitive, reversible DPP-4 inhibitory action which is responsible forAnalytical method development and validation are the continuous and inter-dependent task associated with the research and development, quality control and quality assurance departments. Analytical procedures play a critical role in equivalence and risk assessment, management. It helps in establishment of product-specific acceptance criteria and stability of results. Validation should demonstrate that the analytical procedure is suitable for its intented purpose. An effective analytical method development and its validation can provide significant improvements in precision and a reduction in bias errors. Linagliptin, sold under the brand name Trajenta among others, is a medication used to treat diabetes mellitus type 2. It is generally less preferred than metformin and sulfonylureas as an initial treatment. It is used together with exercise and diet. It is not recommended in type 1 diabetes. It is taken by mouth.[4]

Linagliptin was approved for medical use in the United States in 2011.In 2018, it was the 177th most commonly prescribed medication in the United States, with more than 3 million prescriptions. As of August 2021, linagliptin is available as a generic medicine in the US.

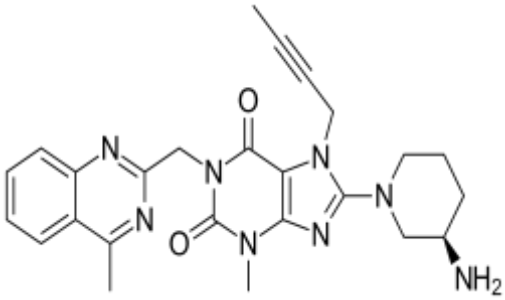

Fig. no. 01: Structure of Linagliptin

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II. ANALYTICAL METHODS USED FOR THE ESTIMATION OF LINAGLIPTIN

[1]. S Shirisha et al in the year 2014 had been reported witha simple, accurate, precise HPLC method for the estimation of Metformin and Linagliptin. The chromatographic separation was achieved on a Hypersil BDSC18column (4.6x250 mm, 5µmparticlesize).Different mobile phase systems in different proportions were tried. For HPLC method a mobile phase consisting of KH2Po4 and acetonitrile (40:60) produced symmetric peak shape with good resolution for both the drugs. Next, the drugs were chromatographed under different flow rates from which a flow rate of 1.0 ml/min was selected. The retention times of Metformin and Linagliptin were found to be 2.464 min and 4.011 min, respectively. The proposed method was found to have excellent linearity in the concentration range of 100-600 and 0.5-3 µg/ml with correlation coefficient r2=0.999 and 0.999 for Metformin and Linagliptin respectively. The method was validated for linearity, precision, LOD, LOQ and robustness. The proposed method optimized and validated as per ICH guidelines [5]

[2]. Md Zubair et al in the year 2014 had been reported withquantitative determination of Linagliptin. Chromatography was carried out by gradient technique on a reversed phase C18 (4.6 x 100 mm, 5 mm, Make: Phenomenon (50:50 v/v) used as mobile phase and the pH was adjusted to 3 by using with O 0.8 ml/min. The chromatogram was recorded at isosbestic point of 238nm. The different analytical performance parameters such as linearity, precision, accuracy, ruggedness, and robustness, limit of detection (LOD) and limit of quantification (LOQ) were determined. The linearity of the calibration curve of the analyte in the desired concentration range is good (r>0.9). The recovery of method is highly sensitive, precise and accurate and it can be successfully applied for the reliable quantification of API content in the commercial formulations of Linagliptin [6]

[3]. Udai Bhan Singh Rathore et al in the year 2020 had been reported withan innovative, rapid, precise, selective and sensitive reverse phase high-performance liquid chromatography method for the quantitative determination of Empagliflozin (EMPA) and Linagliptin (LINA) in bulk and pharmaceutical dosage form as per International Conference on Harmonization (ICH) guidelines. In the present work, good chromatographic separation was achieved by isocratic method using a Thermo C18 column (250 mm ×4.6, 5µm) and a mobile phase consisting of acetonitrile: methanol in the ratio 50:50% v/v, at a flow rate of 1 ml/min. The effluents obtained were monitored at 280nm with the UV-visible detector.[7]

[4]. Joy Chandra Rajbangshi et al in the year 2018 had been reported with Liquid chromatography was performed on HPLC system and 20µl of samples were injected into a C18 column (150 x 4.6 mm i.d., 5µm particle size) and the eluents were monitored through a PDA detector at 239 nm. An isocratic method with a flow rate of 1 ml/min was used to elute the compounds with a mobile phase comprised of 70:30 v/v mixture of phosphate buffer (pH 6.8±0.2) and acetonitrile. The retention time of the compound was found to be 2.8 minutes.[8]

[5]. Lakshman Raju Badugu et al in the year 2012 had been reported with Linagliptin frequently associated in pharmaceutical a formulation that reduces blood sugar levels in patients with type 2 diabetes. Their quantification presents several problems. A HPLC method for the determination of these compounds in pharmaceutical formulations, including the separation of impurities and excipients has been developed and validated. The method was simple, selective, linear, precise and accurate. Isocratic elution at a flow rate of 1ml min-1 was employed on a symmetry C18 column at ambient temperature. The mobile phase consisted of Methanol: Water 83:17(v/v) and pH of the mobile phase was adjusted to 4.1 with 0.1% Orthophosphoric Acid.[9]

[6]. Hoda Mahgoub et al in the year 2016 had been reported with a sensitive and reproducible HPLC method for the determination of linagliptin (LNG) in rat plasma was developed and validated using pindolol (PIN) as the internal standard. Both LNG and PIN were separated on a Zorbax Eclipse XDB C18 column kept at ambient temperature using as mobile phase a

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combination of 75% methanol: 25% formic acid 0.1% pH 4.1 at a flow rate of 1.0 mL min−1. UV detection was performed at 254 nm.[10]

[7]. P. Madhusudhan et al in the year 2015 had been reported witha novel, simple rapid reverse phase high performance chromatography (RPHPLC) method has been developed and validated for the determination of Linagliptin and Empagliflozine in tablet dosage form. Isocratic chromatography has been developed on a ODS column (250 x 4.6mm, 5µ) with a mobile phase consists of buffer and Acetonitrile (45:50) with the flow rate of 1ml/min with PDA detector at 245 nm. The total run time was 7 minutes. The retention time for Lingaliptin and Empagliflozine were found to be 2.2 and 3.6 min respectively. Chromatography parameters were validated as per ICH guidelines and can be applied for routine quantitative analysis of drugs in combined tablet dosage form.[11]

[8]. M.Archana et al in the year 2013 had been reported withA novel isocratic reverse phase liquid chromatography method for determination of Linagliptin was developed and validated after optimization of various chromatographic conditions. A Khromosil C18, 5µm column having 150×4.6 mm i.d., with mobile phase containing 0.02 M potassium dihydrogen phosphate : acetonitrile (70:30, v/v, pH 5.0 adjusted with 1% OPA solution) was used. The flow rate was 1.2 mL min-1and effluents were monitored at 226 nm. The retention time of Linagliptin was 4.2min. The linearity for Linagliptin was in the range of 0-75µg mL-1 with coefficient of correlation 0.999. The proposed method was validated with respect to linearity, accuracy, precision and robustness [12]

[9]. Kavitha. K. Y. et al in the year 2013 had been reported with A simple, RP-HPLC method was established for determining linagliptin and metformin in pharmaceutical formulations. Linagliptin , metformin and their degradation products were separated using C8 column with Acetonitrile: Water: Methanol (25:50:25 (v/v/v) to pH 4.1 with 0.1% orthophosphoric acid as the mobile phase. Detection was performed at 243 nm using a diode array detector [13]

[10]. Prathyusha Vemula et al in the year 2015 had been reported with To enhance patient compliance toward treatment in diseases like diabetes, usually a combination of drugs is prescribed. Therefore, an anti‐diabetic fixed‐dose combination of 2.5 mg of linagliptin 500 mg of metformin was taken for simultaneous estimation of both the drugs by reverse phase‐high performance liquid chromatography (RP‐HPLC) method. The present study aimed to develop a simple and sensitive RP‐HPLC method for the simultaneous determination of linagliptin and metformin in pharmaceutical dosage forms [14]

[11]. R. Maruthi et al in the year 2018 had been reported with A simple, RP-UFLC method was established for determining Linagliptin in Active Pharmaceutical Ingredients. Linagliptin is a DPP-4 inhibitor developed by BoehringerIngelheim (German Pharmaceutical Company) for treatment of type II diabetes. Linagliptin was approved by the US FDA on 2 May 2011 for treatment of type II diabetes. Linagliptin and their degradation products were separated using C18 column with Acetonitrile: Methanol (50:50 (v/v) as the mobile phase [15]

[12]. P. B. N. Prasad et al in the year 2016 had been reported with the method was developed on a LiChrosphere 100 RP 18e (125× 4.0 mm, 5 µm) column with the mobile phase composed of 70:30 (v/v) mixture of methanol and 0.05 M potassium dihydrogen orthophosphate (pH 4.6 adjusted with o-phosphoric acid). Absorption of the elution was measured at 267 nm. The developed method was subjected to validation according to ICH guidelines [16]

III. CONCLUSION

The analytical chemist mainly directs his research towards the development and validation of analytical methods for the estimation of Drugs from its bulk and formulations. In the view of this fact here a details about the various methods used for the estimation of Linagliptinform bulk and formulations had been studied expensively for its application in further research.

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