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A Review Article on HPLC Method Development and Validation for the Estimation of Metformin and Linagliptin Tablets

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ABSTRACT

Clinical studies have confirmed that the various analytical techniques are used to develop a rapid and accurate analytical procedure for Metformin and Linagliptin. These techniques are most commonly used in the pharmaceutical industry that produces a significant amount of organic toxic waste at various phases of the manufacturing process. Therefore, it is essential that the Green analytical chemistry (GAC) principles should be applied to pharmaceutical analysis. This analysis confirm's that the procedure is environmentally benign in terms of green solvent use, chemical composition, energy use, and waste generation. In this article, an overview of green strategies that can be easily applied in developing eco-friendly analytical methods for the estimation of Metformin and Linagliptin in formulations by using green solvents like Ethanol is given.

Keywords: Linagliptin, Metformin, RP -HPLC, Simultaneous analysis, Tablets.

INTRODUCTION:

Compound 1: Metformin is a oral tablet available as generic drugs and brand names are Glucophage, fortamet and glumetza. Metformin decreaseshepatic glucose production, decreases intestinal aborrption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

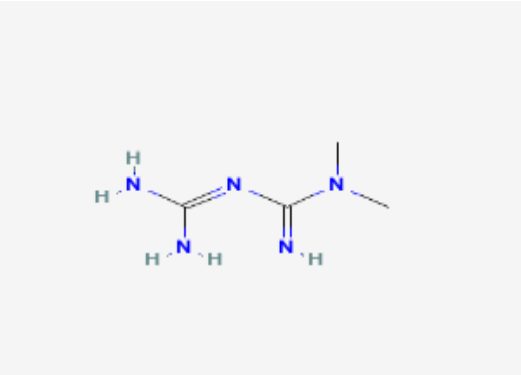

FIGURE 1:STRUCTURE OF METFORMIN

Figure-1: Structure of Metformin:

Chemical name : N, N-Dimethylimidodicarbonimidic diamide.

Chemical Formula : C4H12N5

Molecular weight: 129.16 g/mol

Category : Anti-hyperglycemic agent.

Mechanism of action:

Metformin's mechanisms of action are unique from other classes of oral antihyperglycemicdrugs. Metformin decreases blood glucose levels by decreasing hepatic glucose production (also called gluconeogenesis), decreasing the intestinal absorption of glucose, and increasing insulin sensitivity by increasing peripheral glucose uptake and utilization. It is well established that metformin inhibits mitochondrial complex I activity, and it has since been generally postulated that its potent antidiabetic effects occur through this mechanism.The above processes lead to a decrease in blood glucose, managing type II diabetes and exerting positive effects on glycemic control.

Compound 2: Brand name of drug is tradjenta and generic name is linagliptin. It is a DPP-4 inhibitor developed by Boehringer Ingelheim for the treatment of type II diabetes. Two pharmacological characteristics that sets linagliptin apart from other DPP-4 inhibitors is that it has a non-linear pharmacokinetic profile and is not primarily eliminated by the renal system.

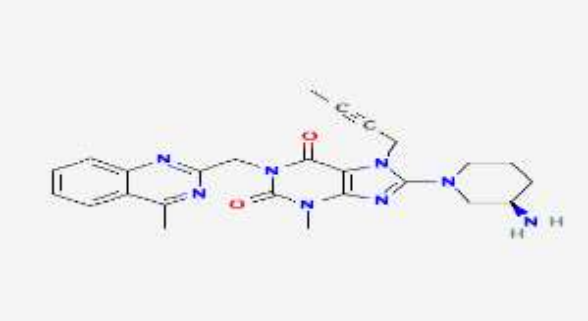

Figure 2: STRUCTURE OF LINAGLIPTIN

Linagliptin:

Chemical name: 8-[(3R)-3-aminopiperidin-1-y]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-dione.

Chemical Formula : C25H28N8O2.

Molecular weight: 472.5 g/mol.

Category: Anti-hyperglycemic agent.

Mechanism of Action

Linagliptin is a competitive, reversible DPP-4 inhibitor. Inhibition of this enzyme slows the breakdown of GLP-1 and glucose-dependant insulinotropic polypeptide (GIP). GLP-1 and GIP stimulate the release of insulin from beta cells in the pancreas while inhibiting release of glucagon from pancreatic beta cells5. These effects together reduce the breakdown of glycogen in the liver and increase insulin release in response to glucose.

Table 1: HPLC methods reported in the literature for the determination of Metformin and Linagliptin.

Author Name/ Journal Name	**Title of the Journal**	**Chromatographic Conditions**	**Results**	**References**
Tarekegn tadesse unade, krishnamanjari pawa**[2023}**	New validated stability indicating rp-hplc method for the simultaneous determination of metformin hydrochloride, linagliptin and empagliflozin in bulk and pharmaceutical dosage form.	Columns:Agilent Eclipse XDB-C18 (250 mm x 4.6 mm, 5 µm) Flow rate:1ml/min. Mobile Phase: 0.1 % TEA adjusted to pH 3 withorthophosphoric acid and acetonitrile in a ratio of 40: 60 (v/v) Wavelength: 240 nm	**Retention time**:2.660 min, 3.586 min. **LOD**:4.00 µg/ml, 0.02 µg/ml	**1**

Nagunath Sirigiri,Siva Subramanian ,Naveen Kumar Reddy{2017}	Stability Indicating Method Development and Validation for Simultaneous Estimatiof Linagliptin and Metformin HCl in Tablets by HPLC.	**Column**:Waters Spherisorb SCX 10 µm, 250 × 4.6 mm.**Mobile Phase**:buffer, acetonitrile and methanol in the ration 60:20:20	**Flow rate:**1.0 ml/min.**Wavelength**:272nm.	**4**
Rutvik H Pandya*, Rajeshwari Rathod and Dilip G. Maheswar**{2018}**	Bio analytical method development and validation forsimultaneous determination of linagliptin and metformin drugs in human plasma by rp-hplc method.	Columns:Grace vyadyec genesis CN (150 × 4.6 mm, 4 µm) . Flowrate:1ml/min. Mobile pase:f acetonitrile and 0.01M di-potassium hydrogen phosphate buffer in ratio of (75:25). Wavelength: 237 nm.	The precision and accuracy for MET at LLOQ level were found to be 4.81 %CV. LNG and METrespectively were within 97-103% and 99-104%	**2**
Prathyusha Vemula, Dilip Dodda, Umamahesh Balekari, Shyam Panga, and Ciddi Veeresham **{2015}**	Simultaneous determination of linagliptin and metformin by reverse phase-high performance liquid chromatography method: An application in quantitative analysis of pharmaceutical dosage forms.	**Column:** LiChrosphere 100 RP 18e (125 mm × 4.0 mm i.d, 5 µm) column. **Mobile phase**:70:30 (v/v) mixture of methanol and 0.05 M potassium dihydrogen orthophosphate. **Flow rate**:0.6ml/min. **Wavelength**:267nm.	**Retention time**:4.6 and 6.3min	**6**
Chandrabatla Varaprasad, Md. Asif and K.Ramakrishna **{2015}**	RP-HPLC method for simultaneous estimation of metformin and linnagliptin in tablet dosage form	**Column**:Waters Xbridge C18, 4.6*150mm. **Mobile Phase:** Acetonitrile: 0.02 M phosphate buffer (pH5.0): 35:65 v/v **Flow rate:** 1.0ml/min. **Wavelength**: 225 nm.	**Linearity:**250-2500µ g/mL[Met] and 1.25-12.5µ g/mL[Lin] **Acurracy**:its is equal to 50%,100%,150%. **Repeatabilty**:RSD<2. **LOD:**2.66µg/mLmet] and 8.05µg/mL[lin] **LOQ:** 0.05µg/ml[met] and 0.16µg/ml[lin]	**3**

S Shirisha*, M Akiful Haque, D Sireesha, Vasudha Bakshi, S Harshini **{2014}**	Development and Validation of RP HPLC Method forSimultaneous Estimation of Metformin and Linagliptin In Combined Pharmaceutical	**Column:**Hypersil-BDS C18 coloumn. **Mobile Phase:** KH2Po4 ,Acetonitrile at the ratio(40:60). **Flowrate:**1.0ml/min. **Wavelength:** 250nm.	**Linearity**:100-600[met] and 0.5-3[lin]. **LOD**:0.29[met] and 0.06[lin]. **LOQ;**0.88[met] and 0.08[lin]. **%RSD:**0.72[met] and 0.66[lin]	

CONCLUSION

According to the review's findings, there are numerous HPLC methods available for studying antihyperglycemic drugs such as metformin and linagliption. It was discovered that the majority of the chromatographic methods included a mobile phase consisting of acetonitrile, methanol, water, and ammonium acetate to improve resolution. For the chromatographic approach, the flow rate and an appropriate retention period are recorded. Consequently, it has been determined that every procedure is simple, accurate, repeatable, economical, and exact. HPLC was the method most often employed because it provided the best possible sensitivity, reproducibility, dependability, and analysis time.

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