Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1107-1116 | ISSN:2251-6727

Review on Analytical Methodology for Estimation of Vildagliptin & Metformin in Drug Substance, Pharmaceutical Formulations & Biological Metrices

Aditi. V. Momale[1]*, Akshay. P. Patil [1], Nagaraju. C. Davala[1], Dr. Sarita. Pawar[2]

[1]Department of Quality Assurance Techniques, Sanjivani College of Pharmaceutical Education and Research, Kopargaon, Maharashtra, India-423601.

[2]Department of Pharmaceutical Chemistry, Sanjivani College of Pharmaceutical Education and Research, Kopargaon, Maharashtra, India-423601.

(Received: 04 February 2024 Revised: 11 March 2024 Accepted: 08 April 2024)

KEYWORDS

Diabetes Mellitus, Dipeptidyl peptidase 4 inhibitor, Vildagliptin, Metformin, Analytical Methodology

ABSTRACT:

Type 2 diabetes is a common disease that is becoming increasingly common and is a major public health concern worldwide. According to the Centers for Disease Control and Prevention, 29.1 million adults in the United States (9.3% of the population) were diagnosed with diabetes in 2012. Since the discovery of insulin, many antidiabetic drugs have been approved and discontinued. US Food and Drug Administration (FDA) for the treatment of diabetes. Vildagliptin and metformin are approved by the US Food and Drug Administration. Both oral hypoglycemic drugs are in the new class of dipeptidyl peptidase-4 (DPP-4) drugs. These analytical methods are based on four basic principles: electrochemistry, spectroscopy, chromatography and spot formation. Various analytical methods are used for the analysis of antidiabetic drugs, such as spectroscopy, LC-MS, HPLC, HPTLC, UPLC, capillary electrophoresis (CE), GC-MS, LC-ESI/MS for diagnostic studies. Metformin works primarily by reducing endogenous glucose production in the liver. Vildagliptin works mainly by inhibiting DPP-4, an enzyme involved in the breakdown of hormones GLP-1 (glucogen-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide). In this review, we determine the analytical legend, formulation and biological activity of the antidiabetic drugs metformin and vildagliptin.

1. Introduction

Diabetes mellitus (DM) is a complex chronic disease caused by hyperglycemia, impaired secretion, impaired function, or both. The chronic metabolic imbalance associated with this disease puts patients at risk of long-term macrovascular and microvascular complications, including frequent hospitalizations and cardiovascular disease, if not treated appropriately. [1]In the world. The International Diabetes Federation estimates that

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1107-1116 | ISSN:2251-6727

approximately 387 million people worldwide have diabetes. [2]According to the Centers for Disease Control and Prevention, 29.1 million adults in the United States, or 9.3% of the population, were diagnosed with diabetes in 2012. In that year, 1 million people had diabetes, and 15-30% of them developed full-blown diabetes. [3]Overall, 1.4 million new cases of cancer occur in the United States each year. If this trend continues, it is estimated that one-third of Americans will have diabetes by 2050. People with diabetes have health problems such as myocardial infarction, stroke, kidney failure, vision loss, and premature death. Diabetes and its complications are the seventh leading cause of death in the United States. The World Health Organization predicts that diabetes-related deaths will double by 2030 if no deliberate action is taken. [4]Every year, Americans die from this virus. The increasing trend in the incidence and prevalence of diabetes is alarming and places a significant burden on health care costs and existing health care systems. [5]Due to the complexity of T2DM, there is great interest in developing new drug therapies to control diabetes. The US Food and Drug Administration (FDA) has approved several drug therapies that address the various biological systems and mechanisms involved in the disease. [6]In this rapidly growing field of pharmacology, hundreds of compounds with antiglycemic properties have been discovered or synthesized. [7]In addition, there are many drugs targeting established pathways and novel mechanisms of action of antidiabetic agents in various stages of clinical development. Excellent reviews have been published that focus on specific aspects of diabetes drug discovery, such as FDA-approved hypoglycemic drugs, specialized delivery systems to improve drug efficacy, and specific targets sought in clinical development. However, the approval status of antidiabetic drugs fluctuates, with approvals and withdrawals.[8,9]

2. Objectives

1. Metformin:

Metformin is a biguanide and is the main oral drug for the management of T2 diabetes in all age groups. Metformin activates hepatic adenosine monophosphate-activated protein kinase, causing hepatic glucose uptake and inhibition of gluconeogenesis through complex effects on mitochondrial enzymes. [10]Metformin is well tolerated with mild side effects, low risk of hypoglycemia, and low potential for weight gain. Metformin has been shown to reduce the progression of T2DM by reducing hepatic glucose synthesis (gluconeogenesis) and increasing the sensitivity of peripheral tissues to insulin, reducing the risk of complications and reducing patient mortality. In addition, it improves insulin sensitivity by activating insulin receptor expression and increasing tyrosine kinase activity. Recent evidence also suggests that metformin lowers plasma lipid levels and prevents CVD via the peroxisome proliferator-activated receptor (PPAR)-α pathway.[1,10]

IUPAC name: 3-(diaminomethylidene)-1,1-dimethylguanidine

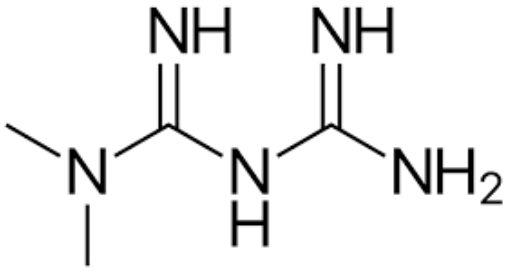

Figure 1: Chemical structure of Metformin ($C_4H_{11}N_5$)

2. Vildagliptin:

A drug Galvus (vildagliptin) was registered in Russia in 2008. This drug is effective as

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(3), 1107-1116 | ISSN:2251-6727

monotherapy along with blood sugar lowering agents and insulin. DPP-4 inhibitors are a new treatment for type 2 diabetes. Literature review showed that there is only one spectrophotometric method for measuring vildagliptin by the same author in this study. 3-Amino-1-adamantanol (AAD), reported in the synthesis of vildagliptin, is expected to be an impurity of vildagliptin. Since there is no published liquid chromatography method for vildagliptin, the aim of this study was to develop a reversed-phase liquid chromatography (RP-LC) method for the measurement of vildagliptin alone or in the presence of AAD.[12]

IUPAC name: S-1-[N-(3-hydroxy-1-adamantyl) glycyl] pyrrolidine-2-carbonitrile

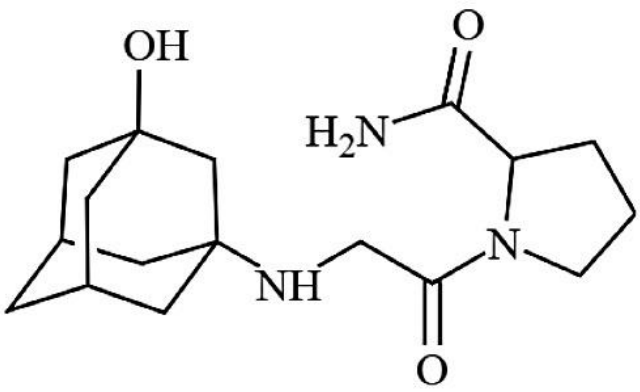

Figure 2: Chemical structure of Vildagliptin ($C_{17}H_{25}N_3O_2$)

3. Analytical Methods

Analytical methods are an interesting part of chemical analysis and can be defined as tools that interact with all branches of chemistry and disciplines of pure and applied sciences. Analytical tools play an important role in the development and evaluation of new products. These devices provide the detection limits needed to ensure the safety of food, medicine, water and air. This analytical method is based on four main principles: electrochemistry, spectroscopy, chromatography and linear methods. [13]spectroscopy, liquid chromatography-mass spectrometry (LC-MS), high performance liquid chromatography (HPLC), high performance thin layer chromatography (HPTLC), ultra-high performance liquid chromatography (UPLC) and capillary electrophoresis (CE), GC - MS, LC-ESI/MS and diagnostic tests are used to analyze antidiabetic drugs.[14]

1. Spectrophotometry:

Since the vildagliptin molecule does not have a conjugated double bond system, there is no absorption peak in the UV spectrum. This spectrum has a peak around 260 nm. However, the reported study suggests a valid spectrophotometric method for the detection of vildagliptin using a test solution concentration of 200 µg/mL, water as solvent, and an analytical wavelength of 266 nm. 11 This report shows the analytical wavelength of 244 nm. At a vildagliptin test solution concentration of 25 µg/mL, a wavelength of 202.5 nm in 0.5 M HCl is reported. 12 A spectrophotometric method for measuring vildagliptin with metformin hydrochloride using the first derivative spectrum is described. We also evaluate vildagliptin using second derivative spectrometry. [13,14,15]

A simple and sensitive spectrophotometric method for the estimation of metformin hydrochloride in bulk and tablet formulations has been developed and validated. The primary amino group of metformin hydrochloride reacts with ninhydrin in an alkaline environment to form a purple chromogen that is measured spectrophotometrically at 200-400 nm. [16]In the range of 18-8 µg/ml, beer from the laws of The recovery of the drug by the proposed method is 97-100%, which indicates that there is no interference from side substances in the tablets.[17]

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1107-1116 | ISSN:2251-6727

Table 1: Optical parameters of Vildgliptin and metformin

Sr. No.	Parameters	Vildagliptin	Metformin
1	Wavelength of maximum	244-266 nm	200-400 nm
2	Beer's law limit	30-70 µg/ml	8-18 µg/ml
3	Regression Equation	Y=0.011x – 0.029	Y=0.080x + 0.088
4	Slope	0.011	0.080
5	Corel. Coeff. (r^2)	0.990	0.990
6	Molar absorptivity (L mol^{-1} cm^{-1})	0.0462 X 10^{-4}	1.334 X X 10^{-4}
7	Sandell's Sensitivity	0.00358 X 10^{-4}	0.440 X 10^{-4}

2. High-performance liquid chromatography MS/MS (HPLC):

High-performance liquid chromatography (HPLC) is an ideal technique for routine analysis because its sensitivity, reproducibility, and ability to separate compounds from a variety of matrices result in high resolution and short analysis times. Despite these advantages, existing HPLC methods can only monitor vildagliptin and metformin.[18] In addition, the same dose may not contain compounds related to metformin as recommended by European and US pharmacopoeias.[19] Longer wavelengths (263 and 293 nm) have been used to improve selectivity in some HPLC methods, but are not used as chromophore molecules of vildagliptin and metformin, which causes a decrease in sensitivity. In other cases, the sensitivity is increased by using shorter wavelengths (210-220 nm), but the selectivity of the method is not sufficient. This validation is an important step to prove that the method is in accordance with the intended purpose.[20]

HPLC tandem mass spectrometry (MS/MS) has been shown to offer several advantages over other methods, including the ability to analyze drugs in complex matrices with high sensitivity and selectivity. HPLC-MS/MS is a promising method for simultaneous quantification of vildagliptin and metformin.[21.]

3. High-performance thin-layer chromatography (HPTLC):

A high-performance thin layer chromatography (HPTLC) method was developed for the simultaneous evaluation of major and commercial combination dosage forms of metformin hydrochloride (MET) and vildagliptin (VLD). The HPTLC method was developed using the Camag HPTLC system. A TLC plate coated with silica gel 60GF254 is used as the stationary phase. Mobile phase ammonium acetate (1% w/v) in methanol: toluene; This is (10:0.5). Spot detection is performed by densitometry at absorbance at 214 nm. Rf values of MET and VLD were found to be 0.44 and 0.55, respectively. The performance characteristics of the HPTLC method for the simultaneous estimation of MET and VLD and the commercially available combination doses were statistically validated according to the recommendations of the ICH guidelines for the validation of the analytical method. [22] The HPTLC method was linear between 1000 and 5000 ng/spot and 2000 and 500 ng/spot for MET and VLD, respectively. For HPTLC, the LOD values for MET and VLD were 17.22 ng/dot and 34.60 ng/dot, respectively, and the LOQ values for MET and VLD were 52.20 ng/dot and 104.85 ng/dot, respectively. The HPTLC method is simple, accurate, linear, accurate, precise and reliable, so this method can be used for the routine analysis required and simultaneous evaluation of formulations containing MET and VLD.[22,23]

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(3), 1107-1116 | ISSN:2251-6727

4. Ultra-performance liquid chromatography (UPLC):

Ultra-performance liquid chromatography (UPLC), a new category of separation technology, is the most promising development in high-speed chromatographic separation with high chromatographic resolution, speed, and analytical sensitivity. A new, sensitive and rapid screening method using ultra-performance liquid chromatography (UPLC) was developed and validated according to ICH guidelines for the simultaneous determination of two binary mixtures. Vildagliptin and Metformin Hydrochloride and Ciprofloxacin Hydrochloride and Dexamethasone Sodium Phosphate.[24,25].

5. Capillary electrophoresis (CE):

Capillary electrophoresis (CE) is now a safe and reliable method for drug analysis and is recommended by several pharmacopoeias, including the British Pharmacopoeia and the US Pharmacopoeia (USP 34 2011; BP 2012). Capillary zone electrophoresis (CZE) and micellar electro kinetic chromatography (MEKC) are two widely used techniques for the separation of pharmaceuticals (whether pharmaceutical formulations or body fluids) and anti-drugs. Various substances such as pollutants.[26,27]

CE is important for drug quality control in quantitative and qualitative analysis and is now as important as HPLC in drug analysis. Quantitative analysis is mainly determined by comparing the migration time and standard deviation of the target compound. Quantitative analysis of abnormal nature calculated according to the standard calibration curve. CE separation relies on the interaction of solutes in an electric field, and electrophoresis is performed in a narrow-angle capillary filled with background electrolyte (BGE).[28,29].

6. Gas-chromatography-mass spectrometry (GC-MS):

The new analytical technique of gas chromatography-mass spectrometry (GC-MS) is mainly used to analyze volatile drugs and waste solutions, some weak compounds and the absence of chromophores. GC-MS offers several advantages for the analysis of metformin and vildagliptin compared to HPLC, including higher throughput, sensitivity, specificity, shorter analysis time, and lower sample volume.[30,31]

7. Liquid Chromatography with tandem mass spectrometry (LC-MS-MS):

Liquid chromatography and tandem mass spectrometry (LC-MS-MS) is a powerful analytical technique that combines the separation power of liquid chromatography with the sensitive and selective mass spectrometry capabilities of a quadrupole mass spectrometer. The sample solution containing the desired analyte is transferred through the mobile phase to the stationary phase (LC column) under high pressure. The chemical interaction between the sample components, the stationary phase, and the mobile phase affects the different migration rates through the LC column and affects the separation. A variety of combinations of stationary and mobile phases allows the separation to be customized for many complex solutions. [33,34]

After washing through the LC column, the liquid is sent to the mass spectrometer. The mass spectrometer of the LC/MS/MS system contains an ionization source that atomizes, dissolves, and ionizes the LC column flow to produce charged particles.[34].

Pharmaceutical fixed-drug combinations of vildagliptin and metformin:

Fixed drug combinations containing metformin and other anti-diabetic drugs are available to speed up treatment without increasing the pill burden. FDC has been shown to reduce complications, improve adherence and glycemic control, and improve treatment satisfaction compared with patients receiving free drug combinations. [35,36]

Vildagliptin belongs to the group of DPP4 inhibitors (gliptins) and is usually recommended as

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(3), 1107-1116 | ISSN:2251-6727

a second or subsequent treatment with metformin. [37]Both drugs have complementary mechanisms of action. Metformin improves blood glucose control by decreasing hepatic glucose production, decreasing glucose uptake, and increasing insulin-mediated glucose uptake. Inhibition of DPP4 delays the inactivation of the incretin hormones that are dependent on glucose-glucose insulinotropic polypeptide (GIP) and GLP-1, thereby increasing their plasma levels and prolonging their action. It stimulates the release of insulin from the beta cells of the pancreas and inhibits the release of glucagon from the alpha cells of the pancreas. Ultimately, both effects lead to a decrease in fasting and postprandial hepatic glucose production, thereby reducing hyperglycemia. [38]The addition of vildagliptin to metformin improves glycemic control by regulating haemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) and Hbc1 levels. [39] Vildagliptin has low hypoglycemic and gastrointestinal effects, is independent of weight gain, and is cardiovascular safe. Therefore, depending on the patient's needs, metformin is recommended as an additional therapy. Treatment costs must also be considered, so generic products, which are often inexpensive, can be a low-cost treatment option.[40]

Metformin immediate-release –Vildagliptin FDC Therapy:

Vildagliptin is a DPP-4 enzyme inhibitor that inactivates incretin hormones such as GLP-1 and glucose-dependent insulinotropic polypeptide hormones and contributes significantly to maintaining glucose homeostasis. [41]A double-blind, randomized, multicentre, parallel-group study of HbA1C and fasting plasma. [42] Metformin Immediate-release (IR) -Vildagliptins provides superior efficacy by showing additional plasma glucose lowering effects in addition to beneficial effects on FDC beta cell function. [43]Until recently, metformin was administered as an IR formulation at doses of 500 mg, 850 mg, or 1000 mg three times a day. [44] Metformin IR therapy is associated with multiple doses (2-3 times a day) and few gastrointestinal side effects. This leads to patient non-compliance and high HbA1c levels, making it difficult for doctors to optimize the dose. Although FDC is associated with better glycemic control than metformin monotherapy, FDC IR-vildagliptin metformin shows common problems associated with metformin IR monotherapy.[45-47].

Role of Metformin sustained release therapy in improved treatment satisfaction:

Sustained-release (SR) metformin therapy has been introduced to overcome all of the above limitations associated with IR metformin therapy.[48]

Unlike metformin IR, which releases 90% of the drug in 30 minutes, metformin SR has a delay of 4-7 hours in plasma concentration, a longer gastric retention time, and is easier to clear from the upper digestive tract. Slowly absorbed. Therefore, once-daily dosing has been shown to improve gastrointestinal tolerance. [49]After 6 months of single treatment, metformin SR prevented gastrointestinal side effects in 77% of patients, and 83% of patients prescribed metformin SR at the end of treatment. [50]Biological activities of combination of Metformin and vildagliptin:

T2DM treatment aims to achieve optimal metabolic control and maximum safety. Metformin is recommended as first-line therapy and diet therapy. [51,52] If metabolic control is not achieved, adding another drug as combination therapy is recommended. and/or sulfonylureas.[53,54] Dipeptidyl peptidase-4 (DPP-4) inhibitors, such as Vildagliptin, have advantages over conventional secretagogues in that they significantly reduce hypoglycemia through the mechanism of glucose-dependent insulin secretion stimulation. [55]

Vildagliptin is an orally active, potent, and selective dipeptidyl peptidase-IV (DPP-4) inhibitor that causes type 2 diabetes mellitus (T2DM) primarily by improving pancreatic function (α and β). Improve blood sugar control. [56] Thus, vildagliptin increases insulin secretion and inhibits inappropriate glucagon secretion in patients with

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1107-1116 | ISSN:2251-6727

type 2 diabetes. It lowers HbA1c when used as a medicine. Metformin, which has a different mechanism of action that does not resolve cellular dysfunction, has been used for almost 50 years and is a universal first-line treatment in all indications.[57]

Conclusion:

Diabetes mellitus (DM) is a metabolic disease caused by decreased insulin activity and/or insulin secretion in the body. This rapidly growing field of pharmacology has generated hundreds of natural or synthetic compounds with antiglycemic properties in recent years, many of which are currently in clinical trials.

Recently, several combinations of the antidiabetic drugs metformin hydrochloride, vildagliptin, and saxagliptin have been approved for type II diabetes. For Metformin and Hydripidoc Wild Koch, various methods are used such as liquid chromatography, fluorescence, high performance liquid chromatography, high performance thin layer chromatography, spectrophotometry, gas chromatography, UV spectroscopy, mass spectrometry or tandem mass spectrometry. . Metformin works primarily by reducing endogenous glucose production in the liver. Vildagliptin works primarily by inhibiting DPP-4, an enzyme involved in breaking down the hormones GLP-1 (glucan-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide)

References:

1. Chaudhury A, Duvoor C, Reddy Dendi VS, *et al.* Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. Front Endocrinol (Lausanne). *2017;24;8:6*.
2. Mancia G. Preventing new-onset diabetes in thiazide-treated patients. Lancet Diabetes Endocrinol. *2016;4(2):90–2.*
3. Centers for Disease Control and Prevention. Diabetes Latest. 2014.
4. Sukhija R, Prayaga S, Marashdeh M, Bursac Z, Kakar P, Bansal D, et al. Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients. J Investig Med. 2009;57(3):495–9.
5. Standards of medical care in diabetes-2016: summary of revisions. Diabetes Care. 2016;39(Suppl 1):S4–5.
6. Gourgari E., Wilhelm E. E., Hassanzadeh H., Aroda V. R., Shoulson I. A Comprehensive Review of the FDA-Approved Labels of Diabetes Drugs: Indications, Safety, and Emerging Cardiovascular Safety Data. J. Diabetes Complications. 2017;31(12):1719–1727.
7. Artasensi A., Pedretti A., Vistoli G., Fumagalli L. Type 2 Diabetes Mellitus: A Review of Multi-Target
Drugs. Molecules. 2020;25(8):25-36.
8. Chikara G., Sharma P. K., Dwivedi P., Charan J., Ambwani S., Singh S. A Narrative Review of Potential Future Antidiabetic Drugs: Should We Expect More? Indian J. Clin. Biochem. 2018;33(2):121–131.
9. Dahlén AD, Dashi G, Maslov I, Attwood MM, Jonsson J, Trukhan V, Schiöth HB. Trends in Antidiabetic Drug Discovery: FDA Approved Drugs, New Drugs in Clinical Trials and Global Sales. Front Pharmacol. 2022;12:807548.
10. Viollet B, Guigas B, Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metfromin: an overview. Clin Sci (Lond). 2012;122(6):253–70.
11. Polyakova EB, Sabirzyanov DR, Prozorova NA, Foteeva AV. Physicochemical Properties and Methods of Analysis of Vildagliptin (Review). Pharm Chem J. 2022;56(1):110-117.
12. El-Bagary RI, Elkady EF, Ayoub BM. Liquid chromatographic methods for the determination of vildagliptin in the presence of its synthetic intermediate and the simultaneous determination of pioglitazone hydrochloride

and metformin hydrochloride. Int J Biomed Sci. 2011;7(3):201-8.
13. Varma DS, Dighe PR. Analytical Methods of Antidiabetic Drugs – Sitagliptin, Saxagliptin, Linagliptin, Alogliptin, Gemifibrozil, Troglitazone, Pioglitazone and Rosiglitazone: A Review. Res. Jr. Pharma. Disage form and Tec. 2022;14(4):324-330.
14. Ramaksrishna B, Mondal S. A review of analytical methods for determination of type II antidiabetic drugs in pharmaceutical and biological matrices. AJPCR. 2021;14(1):69-76.
15. Prasad PV et al. Analytical Method Development and Validation for the Estimation of Vildagliptin in Bulk and its Dosage Form Using UV Spectrophotometer. Indo American Journal of Pharmaceutical Research.2017:7(12):1069-1076.
16. Mubeen G, Noor K. Spectrophotometric method for analysis of metformin hydrochloride. Indian J Pharm Sci. 2009;71(1):100-2.
17. Vesterquist O, Nabbie F, Swanson BJ. Determination of metformin in plasma by HPLC after ultrafiltration. J Chromatogr, B Boimed. Sci Appl. 1998;176:299–304.
18. Latha KP, Ramachandran D. Method development and validation for the simultaneous estimation of vildagliptin and metformin in tablet dosage form by RP-HPLC. Int J Pharm Pharm Sci 2013;5(1):459-63.
19. Mohammad AM, Elkady EF, Fouad MA. Development and validation of a reversed-phase column liquid chromatographic method for simultaneous determination of two novel gliptins in their binary mixtures with Metformin. Eur J Chem 2012;3(2):152-5.
20. Varma D, Lakshmana RA, Dinda SC. Simultaneous determination of metformin and vildagliptin in solid dosage form by stability indicating RP-HPLC method. Int Res J Pharm 2013;4(1):122-8.
21. Uber CP, Pontes FL. et al. HPLC-MS/MS method for simultaneous quantification of vildagliptin, metformin, and metformin-related compounds in tablets. 2014;6(11):203-207.
22. Shirode, A. R., Maduskar, P. D., Deodhar, M. S. and Kadam, V. J. "RP-HPLC and HPTLC Methods for Simultaneous Estimation of Metformin Hydrochloride and Vildagliptin from Bulk and Marketed Formulation: Development and Validation", Journal of Pharmaceutical Research International, 2014;4(20):2370–2386.
23. Jayaprakash R, Natesan SK. Stability indicating RP-HPLC method development and validation for the simultaneous determination of vildagliptin and metformin in pharmaceutical dosage form. Int J Pharm Pharm Sci 2017;9:150-7.
24. Pharne AB, Santhakumari B et al. Bioanalytical method development and validation of Vildagliptin a novel dipeptidyl peptidase IV inhibitor by RP-HPLC method. International Journal of Pharmacy and Pharmaceutical Sciences 2012;4(3):119-123.
25. Fouad MM. RP-UPLC method development and validation for simultaneous estimation of vildagliptin with metformin hydrochloride and ciprofloxacin hydrochloride with dexamethasone sodium phosphate. Manal Fouad, World J Pharm Sci 2015;3(9):1755-1762.
26. Terabe S. Micellar electrokinetic chromatography for highperformance analytical separation. Chem Rec 2008;8: 291–301.
27. Petersen JR, Okorodudu AO, Mohammad A, Payne DA. Capillary electrophoresis and its application in the clinical laboratory. Clin Chim Acta 2003;330: 1–30.
28. Suntornsuk L. Recent advances of capillary electrophoresis in pharmaceutical analysis. Anal Bioanal Chem 2010;398: 29–52.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1107-1116 | ISSN:2251-6727

29. Altria KD, Elder D. Overview of the status and applications of capillary electrophoresis to the analysis of small molecules. J Chromatogr A 2004;1023: 1–14.
30. Ucakturk E. Development of Sensitive and Specific Analysis of Vildagliptin in Pharmaceutical Formulation by Gas Chromatography-Mass Spectrometry. J Anal Methods Chem. 2015;2015:707414.
31. Goedecke C, Fettig I, et al. A novel GC-MS method for the determination and quantification of metformin in surface water. Anal. Methods, 2017;9:1580-1584.
32. Pitt JJ. Principles and applications of liquid chromatography-mass spectrometry in clinical biochemistry. Clin Biochem Rev. 2009;30(1):19-34.
33. Hong Liu, Cheng Xu, Wei Wang, Yue Zhao, Development and Validation of an LC-ESI-MS/MS Method for Simultaneous Determination of Ligustroflavone and Rhoifolin in Rat Plasma and Its Application to a Pharmacokinetic Study, Journal of Chromatographic Science, 2017;55:267–274.
34. Han S, Iglay K, Davies MJ, Zhang Q, Radican L. Glycemic effectiveness and medication adherence with fixed-dose combination or coadministered dual therapy of antihyperglycemic regimens: a meta-analysis. Curr Med Res Opin. 2012;28(6):969–977.
35. Hutchins V, Zhang B, Fleurence RL, Fleurence RL, Krishnarajah G. A systematic review of adherence, treatment satisfaction and costs, in fixed-dose combination regimens in type 2 diabetes. Curr Med Res Opin. 2011;27(6):1157–1168.
36. Ahren B, Schweizer A, Dejager S, Villhauer EB, Dunning BE, Foley JE. Mechanism of action of the dipeptidyl peptidase-4 inhibitor vildagliptin in humans. Diabetes Obes Metab. 2011;13:775–783.
37. Bailey CJ, Campbell IW, Chan JCN, Davidson JA, Howlett HCS, Ritz P, editors. Metformin: the gold standard. A scientific handbook. Chichester: Wiley; 2007.
38. Campbell IW, Howlett HCS, Holman RR, Bailey CJ, editors. Metformin—60 years of clinical experience: addendum to the scientific handbook Chapter 5 Metformin and the heart. Weinheim: Wiley-VCH Verlag; 2017.
39. Schnaars Y, Gaikwad S, Gottwald-Hostalek U, Klingberg U, Vadla HKC, Prathap VR. Bioequivalence Studies of New Generic Formulations of Vildagliptin and Fixed-Drug Combination of Vildagliptin and Metformin Versus Respective Originator Products in Healthy Volunteers. Diabetes Ther. 2022;13(6):1215-1229.
40. Ahren B, Gomis R, Standl E, Mills D, Schweizer A. Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes. Diabetes Care. 2004;27:2874–2880.
41. Bosi E., Camisasca R.P., Collober C., Rochotte E., Garber A.J. Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. Diabetes Care. 2007;30:890–895.
42. Halimi S., Schweizer A., Minic B., Foley J., Dejager S. Combination treatment in the management of type 2 diabetes: Focus on vildagliptin and metformin as a single tablet. Vasc. Health Risk Manag. 2008;4:481–492.
43. Derosa G., D'Angelo A., Romano D., Maffioli P. Effects of metformin extended release compared to immediate release formula on glycemic control and glycemic variability in patients with type 2 diabetes. Drug Des. Dev. Ther. 2017;11:1481–1488.
44. Florez H., Luo J., Castillo-Florez S., Mitsi G., Hanna J., Tamariz L., Palacio A., Nagendran S., Hagan M. Impact of metformin-induced gastrointestinal symptoms on quality of life and adherence in patients with type 2 diabetes. Postgrad. Med. 2010;122:112–120.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1107-1116 | ISSN:2251-6727

45. Gohel N., Patel D.M., Patel K., Modi J. Formulation development and evaluation of modified release tablet using a fixed dose combination of antidiabetic agents. Int. J. Pharm. Sci. Rev. Res. 2017;42:139–145.
46. Bonnet F., Scheen A. Understanding and overcoming metformin gastrointestinal intolerance. Diabetes Obes. Metab. 2017;19:473–481.
47. McCreight L.J., Bailey C.J., Pearson E.R. Metformin and the gastrointestinal tract. Diabetologia. 2016;59:426–435.
48. Senjoti F.G., Mahmood S., Jaffri J.M., Mandal U.K. Design and in-vitro evaluation of sustained release floating tablets of metformin HCl based on effervescence and swelling. Iran J. Pharm. Res. 2016;15:53–70.
49. Kim C.H., Han K.A., Oh H.J., Tan K.E., Sothiratnam R., Tjokroprawiro A., Klein M. Safety, tolerability, and efficacy of metformin extended-release oral antidiabetic therapy in patients with type 2 diabetes: An observational trial in Asia. J. Diabetes. 2012;4:395–406.
50. Levy J., Cobas R.A., Gomes M.B. Assessment of efficacy and tolerability of once-daily extended release metformin in patients with type 2 diabetes mellitus. Diabetol. Metab. Syndr. 2010;2:16.
51. Menéndez Torre E, Lafita Tejedor J, Artola Menéndez S, et al. Recommendations for the pharmacological treatment of hyperglycemia in type 2 diabetes. Working Group for Consensus and Clinical Guidelines of the Spanish Diabetes Society. Rev Clin Esp. 2011;211:147–155.
52. Inzucchi SE, Bergenstal RM, Buse JB, et al.American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Diabetes Care. 2012;35:1364–1379.
53. Puigdevall Gallego V, Laudo Pardos C, del Río Mayor MJ, Velasco Martín A. New drugs for the treatment of type-2 diabetes. Rev Clin Esp. 2000;200:151–156.
54. The ADVANCE Collaborative Group Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560–2572.
55. Sicras-Mainar A, Navarro-Artieda R. Use of metformin and vildagliptin for treatment of type 2 diabetes in the elderly. Drug Des Devel Ther. 2014 Jun 18;8:811-8.
56. Virally M, Blickle JF, Girard J, et al. Type 2 diabetes mellitus: epidemiology, pathophysiology, unmet needs and therapeutical perspectives. Diabetes Metab. 2007;33:231–44.
57. Halimi S, Schweizer A, Minic B, Foley J, Dejager S. Combination treatment in the management of type 2 diabetes: focus on vildagliptin and metformin as a single tablet. Vasc Health Risk Manag. 2008;4(3):481-92.