

AN OVERVIEW OF ANALYTICAL METHODS FOR DETERMINING METFORMIN HYDROCHLORIDE AND PIOGLITAZONE HYDROCHLORIDE IN BULK AND PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

Diabetes mellitus is one of the world's major disease and is the third leading cause of death in the United States after heart disease and cancer. In the India, about 2-6% population suffer from diabetes or related complications. Anti-diabetic drugs treat diabetes mellitus by lowering glucose level in the blood. Mostly anti-diabetic drugs are administered orally except the insulin, exenatide and pramlintide. There are different types of anti-diabetic drugs, and there selection depends on the nature of diabetes, age and situation of the person and many other factors. Treatments include the agents which include the agents which increase the amount of insulin secreted by the pancreas, or increases the sensitivity of target organs to insulin, and agents which

decrease the rate at which glucose is absorbed from the gastrointestinal tract. People are mainly focused on insulin, insulin analogues, oral hypoglycemic agents and various other complementary and alternate medicines to control the blood glucose levels in diabetes. The present review summarizes in brief about the drugs used for treatment of diabetes mellitus.

WORDS TO REMEMBER: Diabetes Mellitus, Glucose, Anti-diabetic Drugs, PPAR, Insulin.

INTRODUCTION

The word diabetes Mellitus means excessive excretion of sweet urine'. Diabetes mellitus is a group of metabolic Diseases characterized by hyperglycemia resulting from defects in insulin secretion, action or both. Chronic hyperglycemia of diabetes is associated with long term damage, dysfunction, and failure of various organs specially the eyes, kidneys, nerves, heart and blood vessels. Insulin is either not secreted in sufficient amount or does not effectively stimulate its target cells, hyperglycemia occurs. In hyperglycemia blood glucose level becomes so high that glucose “spills over” in urine. However, cells starve since glucose stimulated entry into the cells is impaired. Apparent symptoms of hyperglycemia are excessive thirst and frequent urination. Chronic hyperglycemia causes damage to the eyes, kidneys, nerves, heart and blood vessels.

Causes of diabetes mellitus

Main causes of diabetes mellitus are

- Genetic defects of beta cell functions
- Genetic defects in insulin action.
- Diseases of the exocrine pancreas.

Endocrinopathies, i.e., changes in hormonal secretion and, Drugs or chemical induced

Types of diabetes mellitus

- Insulin dependent or juvenile-onset diabetes mellitus
- Non insulin dependent or maturity-onset diabetes

Type 1 diabetes mellitus

Insulin dependent Diabetes mellitus (IDDM) i.e patients require periodic doses of insulin it can occur at any age, commonly occurs in children, Characterized by the marked inability of the pancreas to secrete insulin because of autoimmune destruction of the beta cells. Kidney malfunctioning, nerve impairment, cardiovascular disease and retinal degeneration occur.

Type 2 diabetes mellitus

Type 2 diabetes is non-insulin dependent diabetes mellitus (NIDDM). It accounts for about 90% of diagnosed cases of diabetes and affects 18% of the population over 65 years of age. Insulin receptors on insulin responsive cells do not respond normally to insulin and are therefore called as “insulin resistant”, thereby increasing blood glucose level.

Anti-diabetic drugs

1. Metformin hydrochloride

Metformin Hydrochloride is in a class of drugs called biguanides. Chemically it is 1,1-Dimethyl biguanides hydrochloride. It is used to treat Type 2 diabetes. It helps to control amount of glucose in the blood. It decreases the amount of glucose you absorb from your food and the amount of glucose made by liver. Metformin also increases body response to insulin, a natural substance that controls the amount of glucose in the blood. The empirical formula of Metformin Hydrochloride is $C_4H_{12}N_5$ and its molecular weight is 165.62g/mol.

Structure of metformin hydrochloride

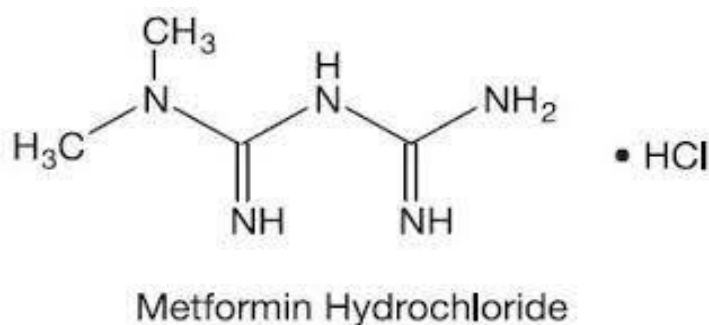


Figure 1: Metformin hydrochloride.

2. Pioglitazone hydrochloride

Pioglitazone Hydrochloride is the hydrochloride salt of an orally -active thiazolidinedione with antidiabetic properties and potential antineoplastic activity. Pioglitazone Hydrochloride chemically it is 5-(4-(2-(5-ethylpyridin-2-ylethoxy)benzyl))thiazolidine2,4dione hydrochloride. Pioglitazone activates peroxisome proliferator-activated receptor gamma (PPAR-gamma), a ligand -activated transcription factor, thereby including cell differentiation and inhibiting cell growth and angiogenesis. This agent also modulate the transcription of insulin -responsive genes, inhibits macrophage and monocyte activation, stimulates adipocyte differentiation. It is used to treat Type 2 diabetes. The empirical formula of Pioglitazone hydrochloride is $C_{19}H_{20}N_2O_3S$ and its molecular weight is 356.4gm/mol.

Structure of pioglitazone hydrochloride

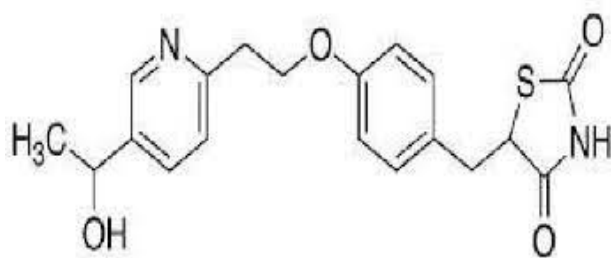


Figure 2: Pioglitazone hydrochloride.

The following factors are taken into account when categorizing reported methods:

1. UV-Spectroscopy, chromatography and other procedures for determining Metformin Hydrochloride alone and in combination with other medications.
2. UV-Spectroscopy, chromatography and other procedure for determining Pioglitazone Hydrochloride alone and with other medications.
3. UV-Spectroscopy, chromatography, and other techniques for determining Metformin Hydrochloride coupled with Pioglitazone Hydrochloride.

Sr. no.	Drugs	Method	Description	Re.no.
1	Metformin hydrochloride In bulk and tablet dosage form	U.V-Visible spectrophotometry	Detection Wavelength -234nm Solvent-Methanol Linearity Range-10-50µg/ml Regression Coefficient-0.9998 % Recoveries-99-100% RSD-0.5390 %RSD-53.90	[5]
2	Pioglitazone hydrochloride In Pharmaceutical dosage form	U.V-Visible Spectrophotometry	Detection Wavelength-224nm Solvent-Ethanol Linearity Range-5-25µg/ml Regression Coefficient-0.999 % Recoverie-100% RSD-0.1468	[6]
3	Metformin hydrochloride and Pioglitazone hydrochloride In tablet dosage form	U.V-Visible Spectrophotometry	Detection Wave length - MH-237nm PH-225nm Solvent-Methanol Linearity Range(µg/ml) HH-2-10(µg/ml) PH-2-20(µg/ml) Regression Coefficient- MH-0.993 PH-0.994 % Recoveries- MH-99.8% PH-100.4%	[7]

			LOD($\mu\text{g/ml}$)- MH-40.41 PH-40.80 LOQ($\mu\text{g/ml}$)- MH-122.45 PH-123.65	
4	Pioglitazone Hydrochloride In tablet dosage form	HPLC	Detection Wavelength-225nm Column-Nova-pakC18 Column Mobile Phase-Ammonium Formate Buffer:Acetonitrile(75:25v/v) Regression Coefficient-0.999 Flow Rate-1.0/ml Injection Volume-20l/ml Retention time-3min Detector-U.Vdetector %Recoverie-101% LOD-0.2 $\mu\text{g/ml}$ LOQ-0.5 $\mu\text{g/ml}$	[8]
5	Metformin Hydrochloride and Pioglitazone Hydrochloride In pharmaceutical dosage form	HPLC	Detection Wavelength- MH-235nm PH-266nm Column-ODS/Cyano;ACE Mixed column (1004.6mm;5m) Mobile Phase-Acetonitrile: Phosphate buffer(50:50v/v)(pH-5) Linearity Range-025- 20($\mu\text{g/ml}$) Regression Coefficient-0.9995 Flow Rate-1.2ml/min Injection Volume-20l/ml MH-5l/ml PH-20l/ml Retention Time- MH-1.07min PH-1.85min Detector-UV detector %Recoveries- MH-100.13% PH-100.22% LOD($\mu\text{g/ml}$)- MH-3.3 PH-0.33 LOQ($\mu\text{g/ml}$)- MH-10 PH-10	[9]
6	Pioglitazone Hydrochloride	RP-UPLC	Detection Wavelength-220nm	[10]

	In dosage form		<p>Column-UPLC-BEHC-18 (1002.1mm) Mobile Phase-Acetonitrile and Buffer(v/v)(pH-3.2) Linearity Range($\mu\text{g/ml}$)-0.05-300 Regression Coefficient-0.9999 Flow Rate-0.20min/ml Injection Volume-2l Retention Time-2.1min Detector-U.V detector % Recoverie-94.4-101.4% LOD($\mu\text{g/ml}$)-0.05 LOQ($\mu\text{g/ml}$)-0.01</p>	
7	Metformin hydrochloride In tablet dosage form	RP-HPLC	<p>Detection Wavelength-233nm Column-ODS C18Bondapak column(0.425cm)0.5m Mobile Phase-Water:Methanol (70:30v/v) Linearity Range-0.312-5$\mu\text{g/ml}$ Regression Coefficient-0.999 Flow Rate-0.5ml/ml Injection Volume-20 Retention Time-4.4min Detector-U.V detector % Recoveries-101% LOD-0.1$\mu\text{g/ml}$ LOQ-0.3$\mu\text{g/ml}$</p>	[11]
8	Pioglitazone hydrochloride In tablet dosage form	RP-HPLC	<p>Detection Wavelength-266nm Column-Hypersil C8(mm) Mobile Phase-Acetonitrile: Water(60:40v/v)(pH-6) Regression Coefficient-0.9996 Flow Rate-1ml/min Injection Volume-20l/ml Retention Time-6.40min Detector- U.V detector % Recovere-99.9% LOD($\mu\text{g/ml}$)- 0.0319 LOQ($\mu\text{g/ml}$)-0.968</p>	[12]
9	Metformin Hydrochloride and Pioglitazone Hydrochloride In tablet dosage form	RP-HPLC	<p>Detection Wavelength-230nm Column-C18 Reverse Phase Column (150mm 4.6mm,5m) Mobile phase-Methanol ;Ortho-phosphoric acid(45:55) Regression Coefficient-0.9996 Flow Rate-1min/ml Injection Volume-20l Retention Time- MH-1.63min</p>	[13]

			PH-3.8min Detector-U.V detector % Recoveries- MH-101% PH-120% LOD($\mu\text{g/ml}$) MH-0.00554 PH-0.01678 LOQ($\mu\text{g/ml}$)- MH-0.01648 PH-0.02281	
10	Metformin Hydrochloride and Pioglitazone Hydrochloride In bulk and tablet dosage form	RP-HPLC	Detection Wavelength-242nm Column-ODS HG-5RP C18 Column (150 4.6mm,i.d 5mm) Mobile Phase- Acetonitrile:Potassium dihydrogen phosphate buffer(pH-3)(80:20v/v) Linearity Range- MH-0-750 $\mu\text{g/ml}$ PH-0-25 $\mu\text{g/ml}$ Regression Coefficient-0.999 Flow Rate-1ml/min Injection Volume-20l/ml Retention Time- MH-1.97min PH-5.43min Detector-U.V Detector % Recoveries- MH-101% PH-102% LOD($\mu\text{g/ml}$)- MH-0.1 PH-0.03 LOQ($\mu\text{g/ml}$)- MH-0.3 PH-0.09	[14]
11	Metformin Hydrochloride and Pioglitazone Hydrochloride In combined dosage form	RP-HPLC	Detection Wavelength-230nm Column-Luna C18 (5mm, 25cm4.6) Mobile Phase-Acetonitrile: Water: Acetic Acid (60:40:0.3) (pH-5.5) Linearity Range- MH-0.5-4.0 $\mu\text{g/ml}$ PH-0.0015-0.120g/ml Regression Coefficient- MH-0.9992,PH-0.9975 Flow Rate-1ml/min Injection Volume-20l	[15]

			Retention Time- MH-2.1min PH-5.35min % Recovery- MH-99.95% PH-99.85% Detector-U.V detector LOD- MH-0.001(µg/ml) PH-0.007(µg/ml) LOQ- MH-0.002(µg/ml) PH-0.002(µg/ml)	
12	Metformin Hydrochloride and Pioglitazone Hydrochloride In bulk and formulation dosage form	RP-HPLC	Detection Wavelength-228nm Column-Hypersil BDS C18 (250mm4.6mm,0.5m) Mobile Phase- Acetonitrile:0.01m Sodium dihydrogen phosphate(60:40) Linearity Range- MH-20-120(µg/ml) PH-0.6-3.6(µg/ml) Regression Coefficient-0.999 Flow Rate-1min/ml Injection Volume-20l Retention Time- MH-2.280min PH-3.850min Detector-U.V Detector % Recoveries- MH-101% PH-100% LOD(µg/ml)- MH-2.38 PH-0.09 LOQ(µg/ml)- MH-7.282 PH-0.28	[16]
13	Metformin Hydrochloride and Pioglitazone Hydrochloride In pharmaceutical dosage form	RP-HPLC	Detection Wavelength-255nm Column-C18 Column(150mm4.6mm,5) Mobile Phase-Acetonitrile : Ammonium Acetate Buffer(pH-3)(42:58) Linearity Range- MH-0.5-50(g/ml) PH-0.3-30(g/ml) Regression Coefficient-0.999 Flow Rate-0.3ml/min Injection Volume-20l	[17]

			Retention Time- MH-5.16min PH-8.1min Detector-U.V detector %Recovery- MH-98.23% PH-100.11% LOD($\mu\text{g/ml}$)- MH-0.003 PH-0.0061 LOQ($\mu\text{g/ml}$)- MH-0.01 PH-0.02	
14	Metformin Hydrochloride and Pioglitazone Hydrochloride In dosage form	RP-HPLC	Detection Wavelength-228nm Column-C- 18 Column Mobile Phase- Phosphate Buffer: Acetonitrile (pH-3.4)(35:65v/v) Linearity Range($\mu\text{g/ml}$)- MH-50-100 PH-20-180 Regression Coefficient-0.999 Flow Rate-1ml/min Injection Volume-20l Retention time- MH-5min PH-6min Detector-U.V detector %Recoveries- MH-100.5% PH-98.3% LOD($\mu\text{g/ml}$)- MH-1.52 PH-20.2 LOQ($\mu\text{g/ml}$)- MH-12.4 PH-13.5	[18]
15	Metformin Hydrochlorid and Pioglitazone Hydrochloride In tablet dosage form	RP-HPLC	Detection Wavelength-228nm Column-Hypersil BDS C18 (2504.6mm5) Mobile Phase-Acetonitrile: 0.01M Sodium Dihydrogen Phosphate (60:40%) Linearity Range($\mu\text{g/ml}$)- MH-20-120 PH-0.6-3.6 Regression Coefficient- Flow Rate-1ml/min Injection Volume-20l Retention Time-	[19]

			MH-2.280min PH-3.960min Detector-U.V Detector % Recovery- MH-99.57 PH-100.93 LOD($\mu\text{g/ml}$)- MH-2.38 PH-0.09 LOQ($\mu\text{g/ml}$)- MH-7.282 PH-0.28	
16	Metformin Hydrochloride, Pioglitazone Hydrochloride and glimepiride In tablet dosage form	RP-HPLC	Detection Wavelength-258nm Column-Inertsil –ODS-3 C18 column (2504.60mm,5) Mobile Phase- Methanol:Phosphate Buffer(pH-4.3)(75:25v/v) Linearity Range- MH-10-5000 $\mu\text{g/ml}$ PH-10-150 $\mu\text{g/ml}$ Glim-1-10 $\mu\text{g/ml}$ Regression Coefficient-(all 3) close to 1 Flow Rate-1min/ml Injection Volume-20l/ml Retention Time- MH-2.66+0.5min PH-7.12+0.5min Glim-10.17+0.5min Detector-U.V detector % Recoveries- MH-101% PH-101% Glim-100%	[20]
17	Metformin Hydrochloride, Voglibose, and Pioglitazone Hydrochloride In pharmaceutical dosage form	RP-HPLC	Detection Wavelength-232nm Column- Cosmosil C18(2504.6mm,5m) Mobile Phase -0.1% v/v Acetonitrile:Triethylamine(30: 70% v/v)(pH-2.5) Linearity Range($\mu\text{g/ml}$)- MH-200-600 Vog-30-90 PH-0.08-0.24 Regression Coefficient-0.9996 Flow Rate-0.8ml/min Injection Volume-20 $\mu\text{g/ml}$ Retention Time- MH-2.6min	[21]

			Vog-7.12min PH-10.12min Detector-U.V.detector % Recoveries- MH-100% Vog-99.9% PH-101% LOD($\mu\text{g/ml}$)- MH-5.43 Vog-0.93 PH-0.0032 LOQ($\mu\text{g/ml}$)- MH-16.52 Vog-2.83 PH-0.0097	
18	Metformin Hydrochloride ,Rosiglitazone and Sitagliptin	RP-HPLC	Detection Wavelength-210nm Column-ACE (3150mm4.6,3.5m column) Mobile Phase-10mM Sodium hexane sulphonate monohydrate and 10mM Potassium dihydrogen phosphate buffer with Acetonitrile and methanol Linearity Range-12-100 $\mu\text{g/ml}$ Regression Coefficient-0.9993 Flow Rate-1.5ml/min Injection Volume-20l/ml Retention Time- MH-1.445min Rosi-7.270min Sita-8.154min Detector-U.V detector % Recoveries- MH-100% Rosi-101% Sita-100% RSD(%)- MH-0.91 Rosi-0.72 Sita-1.121	[22]
19	Metformin Hydrochloride, Nateglinide, Pioglitazone Hydrochloride In dosage form	HPLC	Detection Wavelength-227nm Column-C18 Column (25cm44.6mmi.d5m) Mobile Phase- 20mM Methanol: Potassium dihydrogen phosphate buffer(85:15v/v) Linearity Range($\mu\text{g/ml}$)- MH-50-250	[23]

			<p>Nate-3.0-15.0 PH-2-10 Regression Coefficient-0.999 Flow Rate-1.2ml/min Injection Volume-20l Retention Time- MH-2.15min Nate-3.787min PH-4.47min Detector-U.V detector % Recovery- MH-100.03 Nate-99.84 PH-99.40 LOD($\mu\text{g/ml}$)- MH-0.03 Nate-0.22 PH-0.008 LOQ($\mu\text{g/ml}$)- MH-0.09 Nate-0.067 PH-0.02</p>	
20	<p>Pioglitazone Hydrochloride, Metformin Hydrochloride and Glibenclamide In Multicomponent dosage form</p>	RP-HPLC	<p>Detection Wavelength-227nm Column-Agilent-TC C18Column (250mm4.6mmi.d.5m) Mobile Phase- Acetonitrile: Methanol: Water (70:10:20v/v) Linearity Range($\mu\text{g/ml}$)- PH-5-30 MH-50-300 Glib-2-10 Regression Coefficient-0.9996 Flow Rate-1min/ml Injection Volume-20l Retention Time- PH-6.82min HH-2.42min Glib-9.40min Detector-U.V detector % Recoveries- MH-99.76% PH-100.12% Glib-98.88% LOD($\mu\text{g/ml}$)- PH-0.09 MH-0.46 Glib-0.32 LOQ($\mu\text{g/ml}$)-</p>	[24]

			PH-0.16 MH-1.2 Glib-0.91	
21	Metformin Hydrochloride and Pioglitazone Hydrochloride In bulk dosage form	RP-TLC	Plate-Pre-Coated Silica-gel Aluminum plate (2010cm60F254) Mobile Phase- Toulene:Methanol:Acetic Acid (5:5:0.5) Detection Wavelength- MH-255nm PH-268nm Linearity Range($\mu\text{g/ml}$)- MH-3-12 PH-3-20 Regression Coefficient- MH-0.9999 PH-0.9999 Rf Value- MH-0.8 PH-0.2 %Recoveries- MH-99.9 PH-100.0	[25]
22	Pioglitazone Hydrochloride and Metformin Hydrochloride	RP-TLC	Plate-Pre-Coated Silica –gel Aluminum Plate (2010cm101060F254 Mobile Phase-Butanol: 1,4dioxane:Glacial Acetic acid (5:3:2v/v/v) Detection Wavelength-226nm Linearity Range($\mu\text{g/ml}$)- MH-2000-18000 PH-60-540 Regression Coefficient-0.999 Rf Value- MH-0.17-0.02 PH-0.72-0.01 %Recoveries- MH-98.62 PH-100.62 LOD($\mu\text{g/ml}$)- MH-5.65 PH-17.64 LOQ($\mu\text{g/ml}$)- MH-0.259 PH-0.786	[26]
23	Metformin Hydrochloride and Pioglitazone Hydrochloride	HP-TLC	Plate-Aluminum Sheets of Silica Gel 60F254 Mobile phase-	[27]

	In Tablet Formulation		Butanol:1,4dioxane :Glacial Acetic Acid (5:3:2v/v/v) Detection Wavelength-226nm Linearity Range($\mu\text{g/ml}$)- MH-2000-20000 PH-60-600 Regression Coefficient- MH-0.9999 PH-0.9999 Rf value- MH-0.36 PH-0.73 % Recoveries- MH-99.6 PH-99.7 LOD($\mu\text{g/ml}$)- MH-629.8 PH-1908.76 LOQ($\mu\text{g/ml}$)- MH-8.51 PH-25.77	
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CONCLUSION

The study summarizes the reported spectroscopic method for estimating Metformin Hydrochloride and Pioglitazone Hydrochloride in bulk and pharmaceutical dosage forms that have been developed and validated. In this investigation, it was discovered that multiple spectroscopic and chromatographic approaches are available for Metformin Hydrochloride and Pioglitazone Hydrochloride both alone and in combination with other medicines. These approaches are said to be simple, accurate, cost-effective, precise, and repeatable. RP-HPLC and UV absorbance detection were used in the majority of these procedures.

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