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Review Article

Literature Review on Instrumental Analysis of Metformin Hydrochloride, Glibenclamide, Glimepiride and Pioglitazone Hydrochloride in Different Matrices

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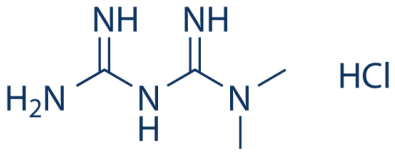
ABSTRACT

In this literature review, we will introduce mode of action and most of up-to-date reported methods that have been developed for determination of certain oral hypoglycemic drugs, such as metformin hydrochloride, glibenclamide, glimepiride and pioglitazone hydrochloride in their pure form, combined form with other drugs, combined form with degradation products, and in biological samples. Most of the reported methods include spectrophotometric and chromatographic methods in addition to some electrochemistry methods.

INTRODUCTION

The term Diabetes Mellitus (DM) describes a metabolic disorder of multiple etiologies. DM is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long–term damage, dysfunction and failure of various organs [1]. The WHO Expert Committee proposed two major classes of diabetes mellitus and named them Insulin-dependent diabetes mellitus (IDDM) or Type 1, and non-insulin-dependent diabetes mellitus (NIDDM) or Type 2. The terms Type 1and Type 2 were omitted, but the classes IDDM and NIDDM were retained, and a class of Malnutrition–related Diabetes Mellitus (MRDM) was introduced, other classes of diabetes were introduced later, such as Impaired Glucose Tolerance (IGT) and Gestational Diabetes Mellitus (GDM) [2]. Anti-diabetic drugs are used to lower the concentration of glucose in the blood of people with diabetes mellitus to keep the blood glucose level at or close to the normal range [3]. As such, in this review article, four antidiabetic drugs have been studied in respect of physical, chemical characters, mode of action and most reported analytical methods that have been developed for determination of these drugs in different matrices.

Metformin Hydrochloride (MET)



- **Chemical name:** 1,1-Dimethylbiguanide hydrochloride
- **Molecular formula:** $C_4H_{11}N_5$, HCl.
- **Molecular weight:** 165.6 gm. /mol.
- **Physical properties:** White or almost white crystals. It is freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride [4].
- **Melting point:** (222-226) °C [5].
- **Pharmacological action:** MET is a Biguanide anti-diabetics, the major action of MET lays in increasing glucose transport across the cell membrane in skeletal muscle. There is also some evidence *in vitro* that it can inhibit the formation of advanced glycosylation end-products [4].
- **Methods of determination:** Literature review revealed several methods reported for the analysis of MET:

Official method: MET is an official drug in BP 2013; the method depends on potentiometric titration against 0.1 N Perchloric acid using anhydrous formic acid and acetonitrile as solvent [4].

Spectroscopic methods: Literature describes different spectroscopic methods for determination of MET, such as charge transfer at 295 nm [6] and Direct Spectrophotometric determination of MET in Pure Form and in drug formulations at 234 nm [7]. Derivative spectrophotometry, ratio derivative, isosbestic and chemometric-assisted spectrophotometric methods were used for the determination of MET at 247 nm [8]. A spectrofluorimetric method has been reported for determination of MET depending on the reaction of MET with chrysenequinone in alkaline medium to give a Schiff's base, which upon hydrolysis gives the free base. The latter in the presence of 1-naphthol gives a fluorescent product with excitation and emission maxima at 450 and 520 nm, respectively [9]. A complex formation with cupper was measured spectrophotometrically at maximum wavelength 540nm [9] and at 400 nm after oxidation with hydrogen peroxide [10].

Chromatographic methods: Several chromatographic methods were described for the determination of the proposed drug either in pure or in combination with other drugs summarized in (Table 1).

Table 1: Chromatographic methods for the determination of MET in pure form or in combination with other drugs.

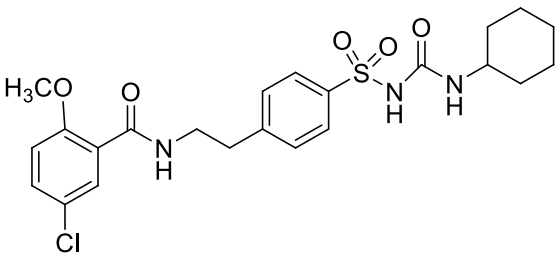
Drugs	Method	Column	Mobile phase	Detector	λ	Ref.
MET and Gliclazide and Glimepiride	HPLC	Thermo Scientific® BDS Hypersil C_8 column (5µm, 2.50 x 4.60 mm)	MeOH : 0.025M KH_2PO_4 adjusted to pH 3.20 using ortho - phosphoric acid (70 : 30, v/v)	UV	235 nm	[11]
MET and Teneligliptin	RP-HPLC	Octa-decyl C_{18} column (5 µm, 25 cm × 4.6 mm, i.d)	Methanol: water in the ratio of 70:30 and pH 3 adjusted with OPA	UV	235 nm	[12]
MET and Gliclazide	HPLC	Zorbax Eclipse XDB-C_{18} 150x4.6 mm i.d. (5µm)	acetonitrile: methanol (1:1v/v) and sodium dodecylsulphate 5mM, pH=3.5 with H_3PO_4 85%	UV	236 nm	[13]
MET and Buformin	*HPLC*	Inertsil ODS-3 column (C_{18} column; 250 mm4.6 mm i.d., 5 µm)	20 mm phosphate buffer (pH 6.3) and acetonitrile (95:5, v/v)	UV	233 nm	[14]
MET	*HPLC*	150mm×4.6mm	Mixture of phosphate	UV	236 nm	[15]

		i.d., 4µmMetaSil-Phenyl column (MetaChem®)	buffer 0.02M(pH 7.0) and acetonitrile (50:50, v/v)			
Vildagliptin, Pioglitazone Hydrochloride and MET	*RP-LC*	Symmetry® Waters C_{18} column (150 mm × 4.6 mm, 5 µm)	Potassium dihydrogen phosphate buffer pH (4.6) - acetonitrile - methanol (30:50:20, v/v/v) Potassium dihydrogen phosphate buffer pH (4.6) - acetonitrile (60:40, v/v)	UV	220 nm	[16]
MET and Rosiglitazone	*HPLC-MS*	Phenomenex Luna 5u CN 100A (150 mm × 2.0 mm i.d.)	methanol:30 mm amm onium acetate pH 5.0 (80:20, v/v)	Mass spectroscopy	The ion transitions monitored were *m/z*13 0.27 → 71.1 1 for MET	[17]
MET and glyburide	*HPLC-MS*	Hypersil, hypurity C_{18} (50mm×4.6mm i.d., 5_m)	Mixing 700 ml of acetonitrile with 300 ml of 5mM ammonium acetate pH 3.0 adjusted with glacial acetic acid.	Mass spectroscopy	Ion transitions for MET (130.1→60. 1)	[18]
MET and Fenofibrate	*HPLC*	Inertsil octadecylsilane C_{18} (250 mm x 4.6 mm i.d., 5 µm particle size)	acetonitrile - water (adjusted to pH 3 using orthophosphoric acid) in proportion of 70:30 v/v	UV	250 nm	[19
METand Pioglitazone Hydrochloride	**RP-HPLC**	Luna C_{18} (5mm, 25cm×4.6 mm i.d.) Phenomenex	acetonitrile:water:acetic acid (60:40:0.3) and the pH was adjusted to 5.5 by adding Triethylamine	UV	230 nm	[20]
MET and Pioglitazone	*RP-HPLC*	A Gemini C_{18} column (150x4.6mm, 5µ)	Mixture of Acetonitrile and Ammonium Acetate buffer (pH-3) in the ratio of 42: 58	UV	255nm	[21]
MET	*UPLC-MS*	An Acquity UPLC HSS column (50 mm 3 2.1 mm, 1.8 mm (Waters Corp, Milford, MA,)	Consisted of 2 solvent compositions: solvent A: 10 mm ammonium format and 1% acetonitrile in water (pH = 3, adjusted with formic acid) and solvent B: 0.2% formic acid in acetonitrile	Mass spectroscopy	Multiple reaction monitoring of the transitions of m/z 130.25!71.3 5 for MET	[22]
MET, Cyanoguanidine and Melamine	HILIC	A 5 µm, 250 × 4.6 mm Atlantis HILIC–Si column (Waters, Ireland; Part No. 18600203)	A mixture of acetonitrile and buffer (25 mm NaH_2PO_4, pH adjusted to 3.0 with OPA), in the ratio of 84:16, *v/v*	UV	218 nm	[23]
MET	*HILIC*	GL Sciences Inertsil HILIC	Water/acetonitrile (30:70, v/v) and 0.1% formic acid.	**Tandem mass spectrometry**	Monitoring in positive ion electrosp	[24]

					ray mode with transitions of *m/z* 130–71 and *m/z* 136–77	
METand other Biguanides	*LC-MS*	Sequant ZIC HILIC (5 µm, 200 Å, 2.1 mm i.d. ×150 mm) column	Consisted of water, Methanol and acetonitrile, respectively, which were both acidified with 0.1% formic acid.	Mass spectrometry	positive ion mode with a probe voltage of 4000 V and an extractor potential of3 V.	[25]
MET and Glyburide	*HPTLC*	Thin layer chromatography plate (silica gel 60 F_{254})	Water/methanol/ammonium sulfate (2/1/0.5 w/v)	densitometry	237 nm	[26]
MET with GliclazideandGlimepiride	*HPTLC*	Silica gel precoated aluminum plate 60 F_{254}, (20 cm_10 cm with 250 mm thickness	Ammonium sulfate (0.25%): Methanol:ethyl acetate in the ratio of 10.0:2.5:2.5 (v/v/v),	UV	238nm	[27]
Pioglitazone, MET, and Glimepiride	*HPTLC*	Silica gel 60 F_{254} HPTLC plates	acetonitrile, Methanol, propyl alcohol, and ammonium acetate solutions in the proportion of 7:2:1:1 (v/v)	densitometry	240 nm	[28]
MET, Gliclazide and Glimepiride	*RP-HPLC*	Thermo Scientific® BDS Hypersil C_8 column (5µm, 2.50 x 4.60 mm)	MeOH : 0.025M KH_2PO_4 adjusted to pH 3.20 using ortho - phosphoric acid (70 : 30, v/v)	UV	235 nm	[29]

Miscellaneous methods: Many voltametric methods have been reported for determination of MET [30-32], flow injection analysis [33], potentiometric methods [34] and also capillary electrophoresis methods [35-38].

Glibenclamide (GLB)



- **Chemical name:** 5-chloro-N-(4-(N-(cyclohexyl carbamoyl) sulfamoyl)phenethyl)-2-methoxybenzamide.
- **Molecular formula:** $C_{23}H_{28}ClN_3O_5S$.
- **Molecular weight:** 494 gm. /mol.
- **Physical properties:** White or almost white, crystalline powder, practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in alcohol and methanol [4].
- **Melting point:** (169 – 174) °C [39].
- **Pharmacological action:** GLB is a potent and long acting second generation oral sulfonylurea anti-diabetic agent, it is widely used to lower blood glucose levels in patients with type II NIDDM and gestational diabetes mellitus. GLB acts mainly by stimulating the release of endogenous insulin from beta cells of the pancreas. It is rapidly and completely absorbed from the gastrointestinal tract. 100% of the oral

- dose is bio-available for the reason that there is no significant first pass metabolism. GLB plasma concentration time curves exhibit biphasic elimination with a terminal elimination rate of 1.4–5 h [40-42].
- **Methods of determination:** Literature review revealed several methods reported for the analysis of GLB:

Official method: GLB is an official drug in BP 2013; the method depends on direct titration against 0.1 N sodium hydroxide using phenolphthalein as indicator [43].

Spectroscopic methods: Literature describes different spectroscopic methods for determination of GLB, it was determined using chloroform as solvent at the same wavelength of 242 nm [44]. A method for determination of GLB in bulk and in pharmaceutical formulations was introduced, the method is based on extraction of the drug into chloroform as ion-pair with sulphonphthalein dyes as Bromocresol Purple (BCP) and Bromothymol Blue (BTB). The absorbance of the yellow products formed was measured at 418 nm for GLB-BCP and 424 nm for GLB-BTB [45]. GLB was also determined in bulk and pharmaceutical formulation using the extract of Beta vulgaris roots; due to the presence of betanin group of compounds, which have polyphenolic nature similar to synthetic dyes like methyl orange and bromocresol green which are commonly used as coloring agent to form a color complex with amide group. The absorbance of the colored complex was measured at 533 nm against reagent blank [46]. Another spectrophotometric method for simultaneous estimation of GLB in presence of MET in combined dosage form was developed. The method employed simultaneous equation method for analysis using methanol as a solvent. The two wavelengths 229.5 nm and 237 nm were selected for estimation of GLB and MET, respectively [47]. Also, GLB was determined in tablet dosage form ,the method is based on measurement of absorption at maximum wavelength of 242 nm [48].

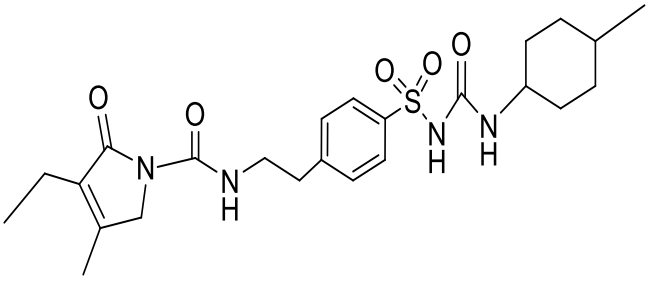
Chromatographic methods: Several chromatographic methods were described for the determination of the proposed drug either in pure or in combination with other drugs summarized in Table 2.

Table 2: Chromatographic methods for the determination of GLB in pure form or in combination with other drugs.

Drugs	Method	Column	Mobile phase	Detector	λ	Ref.
GLB	RP-HPLC	Symmetry C_{18} (250x4.6mm, 5µm)	0.1% Orthophosphoric acid: acetonitrile: methanol 20:50:30 (v/v)	UV	210 nm	[49]
GLB	RP-HPLC	C_{18} analytical column	acetonitrile and 25 mm phosphate buffer pH 3.5 at 3:2 ratios	UV	253 nm	[50]
GLB	HPLC	Hypersil C_8 analytical column (3 _m particle size 100×30.2 mm)	acetonitrile/water/acetic acid (500:500:0.3, by volume),	UV	325 nm	[51]
GLB	HPLC	Agilent Hypersil ODS (25cm x 4.6mm, i.d. 5µ)	acetonitrile: mono basic sodium phosphate Buffer (50:50) and the pH of buffer was adjusted to 2.5 using 2M Orthophosphoric acid	UV	228 nm	[52]
Rosuvastatin and GLB	RP-HPLC	C_{18} (ZORBAX Eclipse Plus 4.6 mm×150 mm, 5µm)	Methanol: acetonitrile: 0.02 M phosphate buffer pH 3.5 (60:20:20 v/v/v)	UV	237 nm	[53]
Amlodipine and GLB		RP C_{18} (125 mm × 4 mm, i.d., 5 µm) and guard column RP C_{18} (4 mm × 4 mm, i.d., 5 µm)	acetonitrile: phosphate buffer pH 3.0 (20:80)	Fluorescence	235 nm for λ excitation and 354 nm for λ emission for GLB	[54]
GLB and MET	HPTLC	Stationary phase of aluminum plate coated with the silica Gel 60 F_{254}	Methanol: Water: 0.4 % sodium sulphate (7:5:11)	UV	190 nm to 400 nm	[55]
GLB	HPTLC	Silica Gel 60 F_{254} TLC plate	Toluene: ethyl acetate: methanol in the ratio of 8.0: 0.5: 1 (v/v/v)	UV	229 nm	[56]

Miscellaneous methods: Literature review showed radio-immunological method for determination of GLB and its metabolites in serum [57] and a radioimmunoassay method for determination of GLB was also reported [58].

Glimepiride (GMP)



- **Chemical name:** 1-((p-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl] phenyl) sulfonyl)-3-(trans-4-methylcyclohexyl) urea.
- **Molecular formula:** $C_{24}H_{34}N_4O_5S$
- **Molecular weight:** 490.6gm. /mol.
- **Physical properties:** White to almost white powder. Practically insoluble in water; sparingly soluble in dichloromethane; soluble in dimethyl formamide; slightly soluble in methyl alcohol. It dissolves in dilute alkali hydroxides and in dilute acid [59].
- **Melting point:** (205 – 207) °C [60].
- **Pharmacological action:** GMP is a potent and long acting second generation oral sulfonylurea anti-diabetic agent [61], it is widely used to lower blood glucose levels in patients with type II NIDDM and gestational diabetes mellitus [62]. GLM acts mainly by stimulating the release of endogenous insulin from beta cells of pancreas [63]. It is rapidly and completely absorbed from the gastrointestinal tract [64].
- **Methods of determination:** Several methods have been reported for analysis of GMP in tablets and in biological fluids

Official methods: The Official method for GMP in USP36 is a chromatographic method using mobile phase of monobasic sodium phosphate 0.1% and acetonitrile (50:50), UV detector at 228 nm, column size (4mm x 25cm), flow rate about1 ml/min. And temperature not exceeding 12°C [65]. GMP is also reported in British Pharmacopeia 2013 [4].

Spectroscopic methods: The literature describes different spectroscopic methods for determination of GMP. It was estimated in tablet form at 249 nm using chloroform as solvent [66], using derivative UV spectrophotometric method [67]. A second-order derivative UV spectrophotometric method for quantification of GMP in dimethylformamide was performed in the wavelength range of 245–290 nm [68].

Three methods for simultaneous estimation of rosiglitazone maleate and GMP in combined tablet dosage form have been developed. The first method is based on formation and solving of simultaneous equation at 238 nm ,the second method makes use of two wavelength spectroscopy using 244.8 nm and 257.2 nm and the third method depends on first derivative using 252 as zero crossing point for estimation of GMP [69].

Another method was developed for estimation of rosiglitazone maleate and GMP in combined tablets. The method was based on application of Vierordt's method which involves the formation and solving of simultaneous equations at 247.0 and 228.0 nm, as absorbance maxima of rosiglitazone maleate and GMP, respectively [70].

Two UV methods were developed for the simultaneous estimation of MET and GMP in bulk and pharmaceutical dosage form. The first method is an absorbance maxima method, which is based on measurement of absorption at maximum wavelength of 236 nm and 228 nm for MET and GMP, respectively. The second method was based on area-under-curve measuring in the wavelength range of 217-247 nm for MET and 213-239 nm for GMP [71]. Four methods were developed for the simultaneous determination of Pioglitazone hydrochloride and GMP in their pharmaceutical formulations. The methods adopted were direct absorbance, first derivative (1D), second-derivative (2D) and first-derivative of ratio spectra [72]. A first derivative spectrophotometric method was performed using 0.1M sodium hydroxide and distilled water (50:50v/v) for determination of GMP in presence of Pioglitazone and MET [73].

Chromatographic methods: Several chromatographic methods were described for the determination of the proposed drug either in pure or in combination with other drugs summarized in Table3.

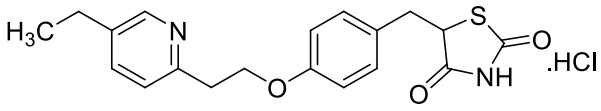
Miscellaneous methods: Liquid chromatography was employed for determination of GMP in human plasma by liquid chromatography–electrospray ionization tandem mass spectrometry; the compounds were separated on a pre-packed C_{18} column by using a mixture of acetonitrile, methanol and ammonium acetate buffer as mobile phase. A Finnegan LCQ^{DUO} ion trap mass spectrometer was connected to an Alliance Waters HPLC to develop and validate the method [83].

The simultaneous estimation of Atorvastatin and GMP in human plasma was performed by the using liquid chromatography tandem mass spectrometry (LC-MS/MS)method [84]. LC was used also for determination of GMP from its degradation products in tablet form. GMP was subjected to forced decomposition under the conditions of hydrolysis, oxidation, dry heat and photolysis. The reaction solutions were chromatographed on reversed phase C_8 (150 mm × 4.6 mm i.d., 5µm) analytical column [85].

Table 3: Chromatographic methods for the determination of GMP in pure form or in combination with other drugs.

Drugs	Method	Column	Mobile phase	Detector	λ	Ref.
MET and GMP	UPLC-MS	BEH C_{18} column (50 mm x 2.1 mm, 1.7 µm particle size)	0.05% (v/v) aqueous formic acid solution and acetonitrile using a gradient elution program, at a flow rate of 0.3 ml/min.	Mass spectrometry	The ESI+ optimal conditions were as follows: source (capillary 1.50 kV, sampling cone 40 V, source offset 80 V), temperatures (source 120 0C, desolvation 400 0C), gas flows (cone gas 30 L·h-1, desolvation gas 400 L·h-1).	[74]
GMP	**HPLC**	Waters Spherisorb S_5NH_2 hydrophilic column	40% acetonitrile and 60% aqueous acetate buffer (5.0 mM) at pH 6.3,	UV	**228 nm**	[75]
GMP and Rosiglitazone	RP-HPLC	150 mm × 4.6 mm i.d., 5 µm particle size Symmetry® C_{18} column,	Mixture of acetonitrile and 0.02 M phosphate buffer of pH 5 (60: 40, V/V)	UV	235 nm	[76]
GMP	HPLC	Lichrosorb® (RP-C_{18} column)	acetonitrile – water – glacial acetic acid (550:450:0.6 v/v)	UV	230 nm	[77]
MET, Pioglitazone, and GMP	RP-HPLC	Inertsil-ODS-3 C_{18} Column (250 × 4.60 mm, 5 µm)	Methanol–phosphate buffer pH 4.3 in the ratio of 75:25 v/v	UV	258 nm	[78]
MET, Pioglitazone, and GMP	RP-HPLC	ODS, 5 µm particle size, (250 × 4.6) mm	Sodium dihydrogen O-phosphate monohydrate pH- 5.0 and acetonitrile, Buffer: acetonitrile (55:45 % v/v)	PDA	230 nm	[79]
MET, Pioglitazone, and GMP	RP-HPLC	Phenomenex C_{18} column (250 x 4.6 mm i.d., 5 µm particle sizes).	Methanol and phosphate buffer (pH 3) (75:25 (v/v))	UV	230 nm	[80]
MET and GMP	HPTLC	TLC aluminum plates precoated with silica gel $60F_{254}$	0.5% Ammonium Sulfate: Methanol (7.5:2.5 v/v)	Densitometric analysis	228 nm	[81]
Atorvastatin, GMP and MET	HPTLC	TLC aluminum plates Precoated with silica gel $60F_{254}$	Water: methanol: ammonium sulphate (3.5: 3.5: 12.6, v/v/v)	Densitometric analysis	245 nm	[82]

Pioglitazone Hydrochloride (PGZ)



- **Chemicalname:** (±)-5-(p-[2-(5-Ethyl-2-pyridyl) ethoxy] benzyl)-2,4-thiazolidinedione hydrochloride.
- **Molecular formula:** $C_{19}H_{20}N2O_3S.HCl$
- **Molecular weight:** 392.9 gm/mol.
- **Physical properties:** White crystalline powder, odorless and slightly bitter. Freely soluble in Dimethylsulfoxide, soluble in methanol and Dimethylformamide, Sparingly soluble in glacial acetic, practically insoluble in water and insoluble in ether [4].
- **Melting point:** 188-192°C [86].
- **Pharmacological action:** PGZ is a thiazolidinedione oral antidiabetic similar to rosiglitazone. It is used in the management of type 2 NIDDM. It is given orally as monotherapy, particularly in patients who are overweight and for whom MET is contra-indicated or not tolerated.
- **Methods of determination:** Several methods have been reported for analysis of PGZ in tablets and in biological fluids.

Official methods: PGZ is an official drugin BP 2013;the method was established by LC using mobile phase of glacial acetic acid, acetonitrile R, 7.71 g/L solution of ammonium acetate R (1:25:25 V/V/V), Column (4.6 mm x 15 cm; 5µm), Flow rate: 0.7 ml/min, Detector UV at 269 nm [4].

Spectroscopic methods: Literature describes different spectroscopic methods for determination of PGZ, a method was reported for the simultaneously estimation of PGZ with MET by two techniques; derivative spectrophotometry and Q analysis. The absorption maxima at 231 nm and 269 nm were used for the estimation of MET and PGZ, respectively [87]. Two spectrophotometric methods were also developed; the first method based on application of Vierordt's method, which involves the formation and solving of simultaneous equations at 225 nm and 237 nm as absorbance maxima PGZ and MET, respectively. The second method based on the absorption correction method, which involves direct estimation of PGZ at 267 nm, as at this wavelength MET has zero absorbance and shows no interference [88]. PGZ was also determined in a multi-component tablet in presence of atorvastatin and MET by UV spectrophotometric technique at 210 nm for Atorvastatin maximum absorbance and for PGZ at 225 nm. The overlain spectra showed maximum absorbance at 242 nm [89]. PGZ was also determined with MET in tablet dosage form at maximum absorbance of PGZ was found to be 269.8 nm in methanol: water: hydrochloric acid (250:250:1) [90]. PGZ and MET were simultaneously estimated in a binary mixture without previous separation using simultaneous equation method depending on their absorptivity values of at selected wavelengths 233 nm and 265.5 nm respectively [91].

HPLC methods: Several chromatographic methods were described for the determination of the proposed drug either in pure or in combination with other drugs summarized in Table 4.

Miscellaneous methods: Other reported techniques were voltammetry [105], flow-injection chemiluminometric determination [106], polarography [107] and potentiometry [108] and capillary electrophoresis method [109] have been introduced.

CONCLUSION

This literature review represents an up-to-date survey about all reported methods that have been developed for determination of certain oral antidiabetic drugs, such as metformin hydrochloride, glibenclamide, glimepiride and pioglitazone hydrochloride in their pure form, combined form with other drugs, combined form with degradation products, and in biological samples, such as liquid chromatography, spectrophotometry, and electrochemistry.

Table 4: Chromatographic methods for the determination of PGZ in pure form or in combination with other drugs.

Drug	Method	Column	Mobile phase	Detector	λ	Ref.
PGZ, GLB, Gliclazide, Glipizide, Repaglinide and Rosiglitazone	HPLC	Inertsil ODS 3V column (4.6 × 250 mm, 5 µm)	0.01 m formic acid (pH 3.0), acetonitrile, Milli Q water and methanol.	UV	260 nm	[92]
PGZ and losartan potassium	HPLC	Phenomenex column (100×4.6mm, 5 µm particle size)	Aqueous phosphate buffer (0.05M, pH 3.5) and acetonitrile (70:30, % v/v)	PDA	225nm	[93]
PGZ	HPLC	Macherey-Nagel Column C_{18}, (dimensions: 5 µm; 250 × 4.6mm)	Acetonitrile, 0.1 M ammonium acetate and glacial acetic acid (25:25:1 v/v/v)	UV	269 nm	[94]
PGZ and GMP	HPLC	Cosmosil C_{18} column (150 mm · 4.6 mm, 5 µm particle)	45:35:20 (v/v) mixture of 0.01 m triammonium citrate (pH adjusted to 6.95 with orthophosphoric acid), acetonitrile, and methanol	UV	228 nm	[95]
PGZ	HPLC	Nova-Pak C_8 column	Mixture of acetonitrile–140mM K_2HPO_4 (40:60, v/v, pH = 4.45)	UV	269 nm	[96]
PGZ	HPLC	Chromolithfi Performance RP-C_{18} (1004.6mm)	acetonitrile: mixed phosphate buffer (pH 2.5; 10mM) (30:70, v/v)	UV	221 nm	[97]
PGZ	HPLC-MS	Luna C_{18} column (4.6mm×50 mm, 5 µm)	50% of 10mM Ammonium acetate in 10% acetonitrile/90% water(mobile phase B) and 50% of 10% water/90% acetonitrile (mobile phase C)	Mass spectrometry	The monitoringions were set from *m/z* 357 to 134	[98]
MET, GMP and PGZ	HPLC-MS	Peerless Basic C_{18} (33 9 4.6 mm, 5 l particle size)	A mixture of methanol: water (containing 0.5% formic acid) 8:2	Mass spectrometry	PIO at the m/z 357.00 precursor ion to the m/z 134.10 and m/z 446.10 precursor ion to the m/z 286.10 product ion for IS	[99]
PGZ	RP-HPLC	ODS C_{18}column (4 6 mm×250 mm,filler:Kromasil, size:5 µm)	Acetonitrile: water: acetic acid (45:55:0 3, to make up the pH 5 50±0 05 with ammonia)	UV	269 nm	[100]
Telmisartan and PGZ	RP-HPLC	Phenomenex C8 (250 × 4.6 mm, 5µ)	Acetonitrile and ammonium di- hydrogen phosphate (pH 4.5; 20mM) in proportion of 65:35 (v/v).	UV	210 nm	[101]
PGZ and GMP		Aluminum sheet of silica gel 60F254	Toluene: ethyl acetate: methanol (50: 45: 5 v/v/v)	UV	230 nm	[102]
PGZ		Silica Gel 60 F254 TLC plate	Toluene: methanol: ammonia (7: 3:0.1 v/v)	UV	268 nm	[103]
MET, PGZ, and GMP	RP-HPLC	MAGELLEN 5U C18 (5 µm, 150 mm × 4.60 mm)	MeOH–0.025 M KH2PO4 adjusted to pH 3.20 using ortho-phosphoric acid (85:15, v/v)	UV	235 nm	[104]

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