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The Methods of Analysis for Determination of Metformin and Glimepiride in Different Matrices

Lobna M. Abdel-Aziz[1], Ahmed S. Abdelkhalek[1], Alyaa Antar[1], Emad H. Abdelraziq[1], Emad A. Farghaly[1], Emad M. Elsayed[1], Emad Y. Metwally[1], Ammar T. Khalifa[1], Ammar Y. Khalil[1], Mahmoud M. Sebaiy[1,*]

[1]Medicinal Chemistry Department, Faculty of Pharmacy, Zagazig University, Sharkia, 44519, Egypt

[*]Correspondence should be addressed to Mahmoud M. Sebaiy, mmsebaiy@zu.edu.eg, sebaiym@gmail.com

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Abstract

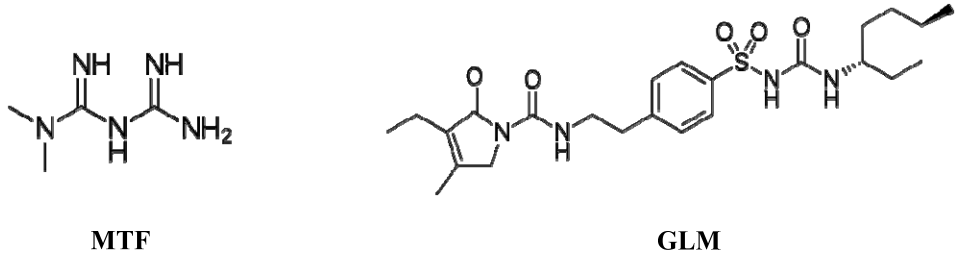
In this literature review, we will introduce pharmacology in addition to most of the up-to-date reported methods that have been developed for determination of important oral hypoglycemic drugs which are metformin and glimepiride in their pure forms, combined forms with other drugs, combined forms with degradation products, and in biological samples.

Keywords: Literature review, Metformin, Glimepiride; Degradation products, Biological samples

Introduction

Diabetes mellitus is characterized by abnormally high levels of sugar (glucose) in the blood, When the amount of glucose in the blood increases, e.g., after a meal, it triggers the release of the hormone insulin from the pancreas. Insulin stimulates muscle and fat cells to remove glucose from the blood and stimulates the liver to metabolize glucose, causing the blood sugar level to decrease to normal level. In people with diabetes, blood sugar levels remain high. This may be because insulin is not being produced at all, or is not made at sufficient levels, or is not as effective as it should be. The most common forms of diabetes are type-1 diabetes (5%), which is an autoimmune disorder, and type 2 diabetes (95%), which is associated with obesity. Gestational diabetes is a form of diabetes that occurs in pregnancy, and other forms of diabetes are very rare and are caused by a single gene mutation [1].

Metformin (MTF, as seen in **Figure 1**), sold under the brand name Glucophage, among others, is the first-line medication for the treatment of type 2 diabetes. MTF is an antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. MTF decreases hepatic glucose



MTF GLM

Figure 1. Chemical structures of Metformin (MTF) and Glimepiride (GLM).

production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. MTF does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia. With MTF therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may decrease [2-4].

Glimepiride (GLM, as depicted in **Figure 1**) is indicated for the management of type 2 diabetes in adults as an adjunct to diet and exercise to improve glycemic control as monotherapy. It may also be indicated for use in combination with metformin or insulin to lower blood glucose in patients with type 2 diabetes whose high blood sugar levels cannot be controlled by diet and exercise in conjunction with an oral hypoglycemic (a drug used to lower blood sugar levels) agent alone [5].

Its mechanism of action is based on ATP-sensitive potassium channels on pancreatic beta cells that are gated by intracellular ATP and ADP. The hetero-octomeric complex of the channel is composed of four pore-forming Kir6.2 subunits and 4 regulatory sulfonylurea receptor (SUR) subunits. Alternative splicing allows the formation of channels composed of varying subunit isoforms expressed at different concentrations in different tissues [7]. In pancreatic beta cells, ATP-sensitive K channels play a role as essential metabolic sensors and regulators that couple membrane excitability with glucose-stimulated insulin secretion (GSIS). When there is a decrease in the ATP:ADP ratio, the channels are activated and open, leading to K+ efflux from the cell, membrane hyperpolarization, and suppression of insulin secretion. In contrast, increased uptake of glucose into the cell leads to elevated intracellular ATP:ADP ratio, leading to the closure of channels and membrane depolarization. Depolarization leads to activation and opening of the voltage-dependent Ca^{2+} channels and consequently an influx of calcium ions into the cell. Elevated intracellular calcium levels cause the contraction of the filaments of actomyosin responsible for the exocytosis of insulin granules stored in vesicles [3]. GLM blocks the ATP-sensitive potassium channel by binding non-specifically to the B sites of both sulfonylurea receptor-1 (SUR1) and sulfonylurea receptor-2A (SUR2A) subunits as well as the A site of SUR1 subunit of the channel to promote insulin secretion from the beta cell [6].

Review of Analytical Methods

Various techniques were used for the analysis of MTF and GLM in its pure forms, in pharmaceutical formulations and in biological fluids. The available reported methods in the literature can be summarized as follows:

Spectroscopic Methods

Spectrophotometric methods						
Drugs	**Matrix**	**Method or reagent**	**λ_{max} (nm)**	**Linearity range**	**LOD**	**Ref.**
MTF	Tablets	Ninhydrin in alkaline medium	570	8-18 µg/mL	----------	[7]
MTF, Anagliptin	Tablets	Q – Absorption ratio method	233 & 238	5–30 µg/mL.0	0.167 & 0.320 µg/mL	[8]
MTF	Tablets	Charge-transfer complex with iodine	295	2-12 µg/mL	----------	[9]
MTF	Tablets and industrial waste water	Oxidation using sodium hypochlorite in alkaline medium	385	0.5-4 µg/mL	0.083 µg/mL	[10]
MTF	Tablets	Cu^{2+} in basic medium	540	0.5-2 mg/mL	----------	[11]
GLM	Tablets	UV spectrophotometry.	249	5-30 µg/mL	0.4 µg/mL	[12]
GLM	Tablets	Derivative UV spectrophotometry	279.0, 257.5 & 256.3	2-40 mg/L	1.311 mg/L	[13]
GLM	Tablets	Derivative UV spectrophotometry	263.3–268.2	1- 500 µg/mL	0.4 µg/mL	[14]
GLM	Tablets	2,3,5-Triphenyl-2H-tetrazolium chloride in basic media	413.5	40–160 µg/mL	----------	[15]
GLM	Tablets	1-Charge-transfer complex using TCNQ 2-Ion-pair complex using bromo thymol blue	. 843	10–80 µg/mL 20–120 µg/mL	2.6 µg/mL 2.8 µg/mL	[16]
GLM	Tablets	Ion-pair complex formation using bromocresol green	416	0.981-9.812 µg/mL	0.088 µg/mL	[17]
GLM	Tablets	UV spectrophotometry	231	0.5-22 µg/mL	0.35 µg/mL	[18]

Spectrofluorometric methods							
Drug	**Matrix**	**Fluorogenic method**	**λ_{max}**	**λ_{em}**	**Linearity range**	**LOD**	**Ref.**
MTF	Tablets	Chrysenequinone in alkaline medium	450	520	20-200 µg/mL	----------	[11]
MTF, Glibenclamide	Tablets	9,10-phenanthraquinone in alkaline media	240	416	0.04-1.2 µg/mL	0.01 µg/mL	[19]

Chromatographic methods

HPLC-UV methods							
Drugs	**Matrix**	**Column**	**Mobile phase**	**UV-Detector (nm)**	**Linearity range**	**LOD**	**Ref.**
MTF	Tablets & formulated microspheres	phenomenex C_{18} ODS (5 µ, 250 × 4.60 mm)	Acetonitrile:phosphate buffer (65:35) pH adjusted to 5.75 with o-phosphoric acid	233	0-25 µg/mL	--------	[20]
MTF	Human plasma	RP C_{18} (250 × 4.6 mm, 5 µm)	34% acetonitrile & 66% aqueous phase, containing 10 mM KH_2PO_4 and 10 mM SLS.	233	0.125-2.5 µg/mL	62 ng/mL	[21]
MTF, nateglinide	Tablets	Inertsil C_{18}-ODS 3V (250 × 4.6 mm, 5 µm)	Phosphate buffer (pH4.0): Acetonitrile: methanol (30:60:10)	221	60-140 µg/mL	2.18 µg/mL	[22]
MTF, Gliclazide & GLM	Tablets	Thermo Scientific® BDS Hypersil C_8 (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)	235	5-100 µg/mL	0.05 (MET), 0.11 µg/mL (GLM)	[23]
MTF, ertugliflozin	Tablets	Kromasil C_{18} (150 mm × 4.6 mm, 5 µm)	0.1% ortho-phosphoric acid buffer (pH 2.7):acetonitrile (65:35% v/v)	224	62.5-375 µg/mL	0.87 µg/mL	[24]
MTF, Repaglinide	Tablets	XBridge C_{18} column (4.6 x 150 mm, 3.5 µm)	Potassium dihyrogen ortho phosphate (2.2 pH): Acetonitrile (35:65%v/v)	240	5-50 µg/mL	0.018 µg/mL	[25]
MTF, pioglitazone & GLM	Tablets	Inertsil-ODS-3 C_{18} (250 × 4.60 mm, 5 µm)	Methanol–phosphate buffer (pH 4.3) in the ratio of 75:25 v/v	258	10-5000 (MET), 1-10 µg/mL (GLM)	--------	[26]
MTF, atorvastatin & GLM	Tablets	Grace Smart Altima C_8 (250 × 4.6 mm, 5 µm)	Acetonitrile : phosphate buffer (60 : 40 (v/v), pH 3.0)	235	20- 200 µg/mL	--------	[27]
MTF, Sitagliptin	Tablets	Li-chrosphere-100 C_{18} ODS (250 × 4.6 mm, 5 µm)	Methanol: potassium di-hydrogen phosphate buffer at a ratio of 70:30 v/v	266	20-100 µg/mL	0.14 µg/mL	[28]
MTF	Tablets	RP C_{18} (250 mm x 4.6 mm, 5.0 µm)	34% acetonitrile and 66% 10 mM KH_2PO_4 and 10 mM sodium lauryl sulfate (pH 5.2)	233	2.5-20 µg/mL	0.1 µg/mL	[29]

MTF, gliclazide	Tablets	Alltima CN (250 mm × 4.6 mm x5µm)	20 mM ammonium formate buffer (pH 3.5) and acetonitrile (45:55, v/v)	227	2.5-150 µg/mL	0.8 µg/mL	[30]
GLM	Self-nanoemulsifying powder (SNEP) formulation	octadesyl silane (ODS) (250 x 4.6 mm, 5µm)	Acetonitrile: 0.2 M phosphate buffer (pH= 7.4) 40:60 v/v	228	0.2-2 µg/mL	0.38 µg/mL	[31]
GLM	Rat serum samples	LiChrosphere 100 RP 18 e (125 × 4.0 mm, 5 µm)	MeOH: 10mM Phosphate buffer (80:20 v/v) adjusted to pH 3.0 with orthophosphoric acid	230	0.5-500 µg/mL	0.15 µg/mL	[32]
GLM	Tablets	Hypersil C_{18} (15 cm x 3.9 mm)	Acetonitrile 0.05 M monobasic potassium phosphate (pH 6.0) 40:60 v/v	210	10–40 µg/mL	0.8 µg/mL	[33]
GLM	Tablets	Lichrosorb RP-18 (125 x 4 mm, 5µm)	Acetonitrile-water-glacial acetic acid (550:450:0.6 v/v)	230	15-120 µg/mL	4 ng	[34]
GLM	Tablets	spherisorb S_5NH_2 (250 mm x 4.6 mm, 5 µm)	40% acetonitrile and 60% aqueous acetate buffer (5.0 mM at pH 6.3)	228	50.0 µg/L - 6.0 mg/L	15.0 µg/L	[35]
MTF, pioglitazone & GLM	Tablets	Phenomenex-ODS-3 C_{18} (250 × 4.60 mm, 5 µm)	MeOH:acetonitrile:15 mM KHPO4 (pH 4), 40:35:25	240	0.2-50 (MET), 0.2-30 µg/mL (GLM)	0.04 (MTF), 0.08 µg/mL (GLM)	[36]
MTF, pioglitazone & GLM	Human plasma	MAGELLEN 5U C_{18} (5 µm, 150 mm × 4.60 mm)	MeOH-0.025 M KH2PO4 adjusted to PH 3.20 using O-phosphoric acid (85:15, v/v)	235	2.50-100 µg/mL	0.05 (MET), 0.10 µg/mL (GLM)	[37]

HPLC-MS methods							
Drugs	**Matrix**	**Column**	**Mobile phase**	**UV-Detector (nm)**	**Linearity range**	**LOD**	**Ref.**
MTF	Tablets & formulated microspheres	phenomenex C_{18} ODS (5 µ, 250 × 4.60 mm)	Acetonitrile:phosphate buffer (65:35) pH adjusted to 5.75 with o-phosphoric acid	233	0-25 µg/mL	--------	[20]
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MTF, Gliclazide & GLM	Tablets	Thermo Scientific® BDS Hypersil C_8 (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)	235	5-100 µg/mL	0.05 (MET), 0.11 µg/mL (GLM)	[23]
MTF, ertugliflozin	Tablets	Kromasil C_{18} (150 mm × 4.6 mm, 5 µm)	0.1% ortho-phosphoric acid buffer (pH 2.7):acetonitrile (65:35% v/v)	224	62.5-375 µg/mL	0.87 µg/mL	[24]
MTF, Repaglinide	Tablets	XBridge C_{18} column (4.6 x 150 mm, 3.5 µm)	Potassium dihyrogen ortho phosphate (2.2 pH): Acetonitrile (35:65%v/v)	240	5-50 µg/mL	0.018 µg/mL	[25]

MTF, pioglitazone & GLM	Tablets	Inertsil-ODS-3 C_{18} (250 × 4.60 mm, 5 µm)	Methanol–phosphate buffer (pH 4.3) in the ratio of 75:25 v/v	258	10-5000 (MET), 1-10 µg/mL (GLM)	--------	[26]
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MTF	Tablets	RP C_{18} (250 mm x 4.6 mm, 5.0 µm)	34% acetonitrile and 66% 10 mM KH_2PO_4 and 10 mM sodium lauryl sulfate (pH 5.2)	233	2.5-20 µg/mL	0.1 µg/mL	[29]
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GLM	Self-nanoemulsifying powder (SNEP) formulation	octadesyl silane (ODS) (250 x 4.6 mm, 5*µ*m)	Acetonitrile: 0.2 M phosphate buffer (pH= 7.4) 40:60 v/v	228	0.2-2 µg/mL	0.38 µg/mL	[31]
GLM	Rat serum samples	LiChrosphere 100 RP 18 e (125 × 4.0 mm, 5 µm)	MeOH: 10mM Phosphate buffer (80:20 v/v) adjusted to pH 3.0 with orthophosphoric acid	230	0.5-500 µg/mL	0.15 µg/mL	[32]
GLM	Tablets	Hypersil C_{18} (15 cm x 3.9 mm)	Acetonitrile 0.05 M monobasic potassium phosphate (pH 6.0) 40:60 v/v	210	10–40 µg/mL	0.8 µg/mL	[33]
GLM	Tablets	Lichrosorb RP-18 (125 x 4 mm, 5 µm)	Acetonitrile-water-glacial acetic acid (550:450:0.6 v/v)	230	15-120 µg/mL	4 ng	[34]
GLM	Tablets	spherisorb S_5NH_2 (250 mm x 4.6 mm, 5 µm)	40% acetonitrile and 60% aqueous acetate buffer (5.0 mM at pH 6.3)	228	50.0 µg/L - 6.0 mg/L	15.0 µg/L	[35]
MTF, pioglitazone & GLM	Tablets	Phenomenex-ODS-3 C_{18} (250 × 4.60 mm, 5 µm)	MeOH:acetonitrile:15 mM KHPO4 (pH 4), 40:35:25	240	0.2-50 (MET), 0.2-30 µg/mL (GLM)	0.04 (MTF), 0.08 µg/mL (GLM)	[36]
MTF, pioglitazone & GLM	Human plasma	MAGELLEN 5U C_{18} (5 µm, 150 mm × 4.60 mm)	MeOH-0.025 M KH2PO4 adjusted to PH 3.20 using O-phosphoric acid (85:15, v/v)	235	2.50-100 µg/mL	0.05 (MET), 0.10 µg/mL (GLM)	[37]

HPTLC methods

Drug	Matrix	Stationary phase	Mobile phase	Detector	Linearity range	LOD	Ref.
GLM, Empagliflozin & Linagliptin	Tablets	Aluminum plates precoated with silica gel 60 F254	Toluene: methanol: ethyl acetate (4: 3: 2 v/v/v)	Reflectance/ fluorescence mode at λ_{max} 228 nm and λ_{em} 320 nm	2.61–60 ng/band	1.84 ng/band	[48]
MTF, Atorvastatin & GLM	Tablets	Silica gel 60 F254	Water: methanol: ammonium sulphate (1: 1: 4 v/v/v)	Densitometric detection at 237 nm	200-700 (MET), 600-2100 ng/spot (GLM)	100 (MET), 500 ng/spot (GLM)	[49]

MTF, GLM	Tablets	TLC aluminium plates precoated with silica gel 60 F254	0.5% Ammonium Sulfate: Methanol (7.5:2.5 v/v)	Densitometric detection at 228 nm	200-700 (MET), 600-2100 ng/ band (GLM)	0.32 (MET), 0.05 ng/ band (GLM)	[50]
MTF, Nateglinide	Tablets	TLC aluminium plates precoated with silica gel 60 F254	Chloroform:ethyl acetate:acetic acid (4:6:0.1 v/v/v)	Reflectance/ absorbance mode at 216 nm	500–3000 ng/ band	0.022 ng/ band	[51]
GLM, Rosiglitazone	Tablets	Silica gel 60 F254	Methanol: toluene: ethyl acetate (1:8:1, v/v/v)	Densitometric detection at 228 nm	100 - 1500 ng/spot	30 ng/spot	[52]

Electrochemical methods

Drug	Matrix	Electrode	Linearity range	LOD	Ref.
MTF	Tablets	Glassy carbon	1.0 nmol L^{-1} - 1.0 µmol L^{-1}	0.3 nmol $L^{-1.}$	[53]
MTF	Tablets	Carbon paste	0.1 - 80 µM	0.014 µM	[54]
MTF	Tablets	Glassy carbon	10 - 70 µM	0.7 µM	[55]
MTF	Tablets	Glassy carbon	0.5 - 25 µM	0.12 µM	[56]
MTF	sol–gel matrix	Citrate-capped gold nanoparticle	0.02 - 80 ng mL^{-1}	0.005 ng mL^{-1}	[57]
MTF	Tablets	Carbon paste	0.1–65 µM	30 nM	[58]
MTF	Tablets	Pencil graphite	0.1–1000 µM	6.8 nM	[59]
MTF	Urine	Mercury drop	5×10^{-8} - 4×10^{-6} mol l^{-1}	1.8×10^{-8} mol l^{-1}	[60]
MTF	Tablets & human serum	Carbon paste	10.4-1125.0 µM	3.4 µM	[61]
MTF	Tablets & urine	Carbon paste	50 nM - 60 µM	9 nM	[62]
MTF	Tablets	CB[6]-modified gold electrode	10 pmol/L - 20 nmol/L	1.35 pmol/L	[63]
MTF	Biological samples	Copper hydroxide - carbon ionic liquid electrode	1 µM–4 mM	0.5 µM	[64]
GLM	Tablets	Glassy carbon Carbon paste	1.0×10^{-5} - 3.2×10^{-5} mol l^{-1} 2.0×10^{-6} - 1.5×10^{-5} mol l^{-1}	2.0×10^{-6} mol l^{-1} 7.5×10^{-7} mol l^{-1}	[65]
GLM, Valsartan	--------	Hanging mercury drop electrode (HMDE)	$0.25x10^{-7}$ - $3.25x10^{-7}$ M	$3.48x10^{-8}$ M	[66]

By the end of this literature review, we would like to emphasize that we continue in our current project to provide an updated review on diseases and drugs chemistry that help the humanity all over the world [67-102].

Conclusion

In this literature review, we shed the light on pharmacology of metformin and glimepiride in addition to most of up-to-date reported methods related to their determination in their pure forms, combined forms with other drugs, combined forms with degradation products, and in biological samples.

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