

## **A Concise Review Based on Analytical Method Development and Validation of Glimepiride in Bulk and Marketed Dosage Form**

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### **ABSTRACT**

*Glimepiride is a long acting Sulfonylurea imitative has its place to third generation sulfonylurea. It finds its application in the management of non-insulin contingent Type 2 diabetes mellitus and it is having a medium to long acting antidiabetic activity. For the persistence of clinical and pharmaceutical analysis, fruitful analytical procedures are obligatory to study quality control, pharmacodynamics and pharmacokinetic properties and stability studies as well. There are plenty of articles which have already been published describing analytical methods and method validation for the same. In present review account, the disclosed analytical methods are outlined for the establishment of Glimepiride in its pharmaceutical preparations and biological matrices. Most frequently used techniques such as spectrometric and liquid chromatographic methods are summarized in present review. Spectrometric methods for Glimepiride alone and in combination include parameters like  $\lambda$  max, solvent, matrix etc. and HPLC methods for Glimepiride alone and in combination including parameters like matrix, stationary phase, mobile phase composition detection wavelength etc. HPTLC methods including parameters like stationary phase, mobile phase combination, RF etc..*

**Keywords:** Glimepiride, UV Spectrophotometric, HPLC, HPTLC, LC-MS/MS

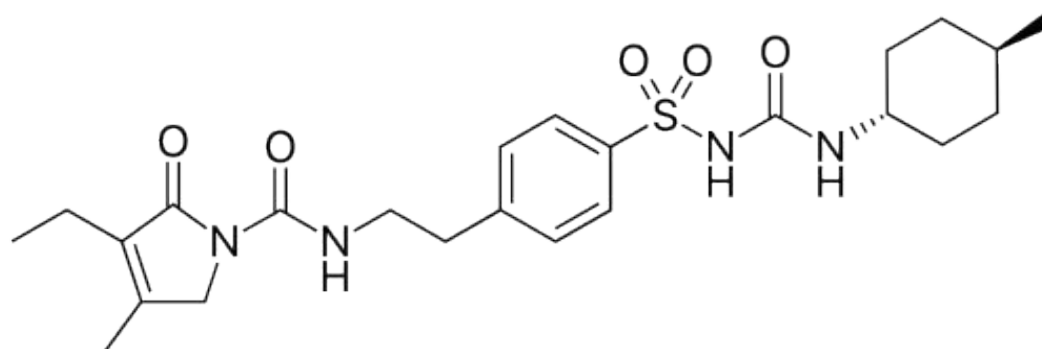
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### **ABBREVIATIONS**

MET: Metformin; PIO: Pioglitazone; DAPA: Dapagliflozin; ROSI: Rosiglitazone; VOG: Voglibose; RAM: Ramipril; ATR: Atorvastatin; GLIC: Gliclazide; FLU: Fluoxetine;  $\lambda$  max: Wavelength Maxima; LIN: Linearity; FR: Flow Rate; RT: Retention Time; RF: Retention Factor; UV-VIS: UV/Visible Spectrophotometry; HPLC: High Performance Liquid Chromatography; RP-HPLC: Reverse Phase Liquid Chromatography; HPTLC: High Performance Thin Layer Chromatography; LC-MS/MS: Liquid Chromatography Mass Spectrometry/Mass Spectrometry; UPLC-MS/MS: Ultra Pressure Liquid Chromatography-Mass Spectrometry-Mass Spectrometry; ODS: Octadecyl Silane; KH<sub>2</sub>PO<sub>4</sub>: Potassium Dihydrogen Phosphate; OPA: Orthophosphoric Acid; IUPAC: International Union of Pure and Applied Chemistry; ATP: Adenosine Triphosphate; Ca<sup>2+</sup>: Calcium<sup>2+</sup>; IP: Indian Pharmacopoeia; Cm; Centimetre; mm: Millimetre; nm: Nanometre;  $\mu$ L: Micro Litter;  $\mu$ g: Microgram; REF: Reference; DMF: Dimethylformamide; NaOH: Sodium Hydroxide; KOH: Potassium Hydroxide; ACN: Acetonitrile; MeOH: Methanol; EtOH: Ethanol; GAA: Glacial Acetic Acid; LOD: Limit of Detection; LOQ: Limit of Quantification.

### **INTRODUCTION**

The IUPAC name for Glimepiride is given as 3-Ethyl-4-methyl-N-[2-(4-{{(trans-4-methylcyclohexyl) carbamoyl} sulfamoyl} phenyl) ethyl]-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide (**Figure 1**). It is a solid having melting point of 207°C; it is insoluble in water [1]. It is very similar to Glipizide with the exclusion of their heterocyclic rings as an alternative of pyrazine ring originate in Glipizide, Glimepiride holds a pyrrolidine system. It is metabolized principally through oxidation of the alkyl side chain of the pyrrolidine, with a petty metabolic route involving acetylation of the amine [2]. It exerts its action by dropping blood glucose level by interfering with ATP sensitive k<sup>+</sup> channels on



**Figure 1:** Chemical structure of glimepiride.

pancreatic beta cells [3] (**Figure 2**).

#### MODE OF ACTION

The mechanism of action of Glimepiride in depressing blood glucose seems to be reliant on triggering the release of insulin from functioning pancreatic beta cells, and accumulating sensitivity of bordering tissues to insulin. Glimepiride likely impasses to ATP-sensitive potassium channel receptors on the pancreatic cell surface, dropping potassium conductance and triggering depolarization of the membrane. Membrane depolarization motivates calcium ion influx over voltage-sensitive calcium channels. This proliferates in intracellular calcium ion concentration convinces the secretion of insulin [3].

#### METABOLISM OF GLIMEPIRIDE

Glimepiride is completely metabolised by oxidation of the pendant methyl substitution on the cyclohexane ring to a Hydroxymethyl metabolite (3a) and a carboxylic acid (2b). The Hydroxymethyl metabolite consumes almost one third of the hypoglycaemic activity of the parent in an animal model, whereas the order was not active [4]. Glimepiride is pumped out of the body with a half-life of about 9 hours, and metabolites, but no parent drug found in both urine (60%) and feces (40%), with (3b) the prime species in urine and (3a) in feces [5]. The schematic pathway for metabolism of Glimepiride is shown in **Figure 3**.

#### ANALYTICAL ACCOUNTS ON GLIMEPIRIDE

The widespread literature survey exposed numerous analytical techniques viz. UV/Visible- Spectrophotometry, HPLC, HPTLC and UPLC-MS-MS (**Figure 4**) for the fortitude of GLIM in bulk and pharmaceutical formulations. The reported methods describe the estimation of GLIM in various dosage forms as single constituent and in combination with Metformin Hydrochloride, Pioglitazone, Dapagliflozin, Rosiglitazone Maleate, Voglibose, Ramipril Atorvastatin Gliclazide. **Figure 4** spectacles different analytical methods implemented for estimation of GLIM.

#### PHARMACOPOEIAL STATUS

IP portrayed HPLC assay method consuming a stainless steel 25 cm x 4.0 mm, packed with endcapped octadecylsilane bonded to porous silica (4  $\mu$ m), as a static phase and mobile phase comprised of a fusion of 50% volumes of a solution prepared by dissolving 0.5 g of sodium dihydrogen orthophosphate in 500 mL of water, adjusted to pH 2.5 with Orthophosphoric acid and 50% volumes of acetonitrile, keeping the flow rate of 1 mL/min. Column effluent was scrutinized at 228 nm, and injection volume set at 20  $\mu$ l [5].

#### SPECTROPHOTOMETRIC METHODS

Till the date lots of spectrophotometric methods have been accounted for the determination of Glimepiride alone and in combination. This review compiles six papers describing spectrophotometric methods for estimation of Glimepiride alone and eight papers for the same in combination [6-11]. **Table 1** consists of spectrophotometric method for Glimepiride alone and **Table 2** consist of spectrophotometric methods for Glimepiride in combination [12-19].

Sakala et al., conveyed a modest spectrophotometric scheme for determination of Glimepiride in tablet dosage form consuming chloroform as a solvent. The reported method involves the calculation of absorbance at 249 nm [1].

Abdul et al., settled a spectrophotometric scheme for analysis of Glimepiride in pure and its marketed preparation

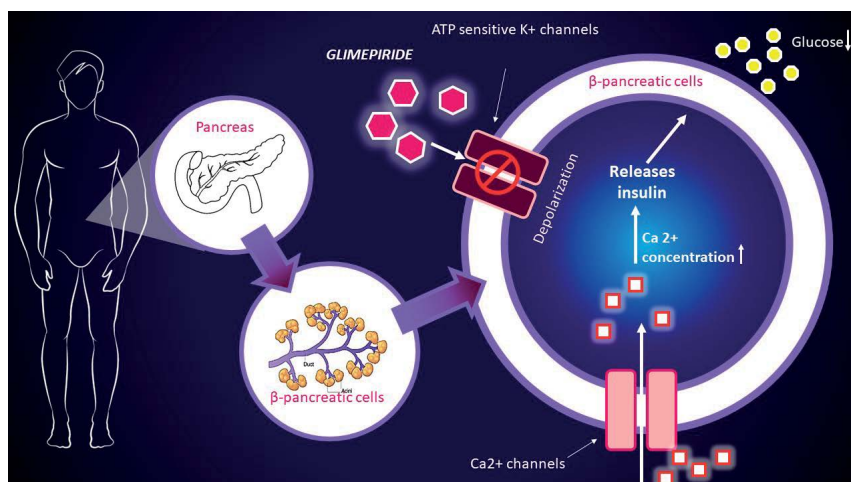


Figure 2: Mechanism of action of Glimepiride.

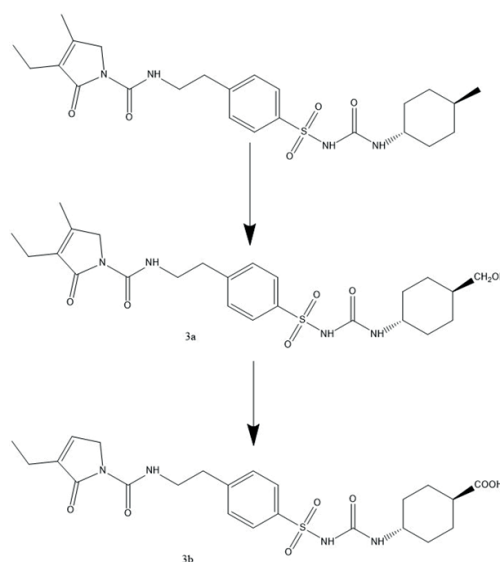


Figure 3: Metabolism of GLIM.

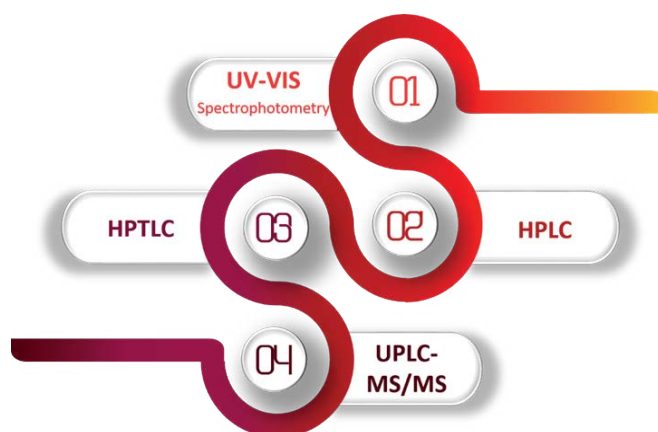


Figure 4: Analytical accounts on glimepiride.

Sl. No.	Compounds	Matrix	Method	Detection ( $\lambda_{max}$ ) nm	Solvent
1	GLIM	Bulk drug and tablet [6]	Simple UV spectrophotometric method	249 nm	Chloroform
2	GLIM	Bulk drug and combined tablet [7]	Spectrophotometric method through ion-pair complex formation using bromocresol green	416 nm	Na <sub>2</sub> CO <sub>3</sub> , chloroform
3	GLIM	Bulk drug and tablet [8]	UV-vis. Spectroscopy	231 nm	NaOH
4	GLIM	Bulk drug and tablet [9]	Simple UV spectrophotometric method	226 nm	Methanol
5	GLIM	Bulk drug and tablet [10]	Second order derivative UV spectrophotometry	268.2 and 271.8 nm	Dimethylformamide (DMF)
6	GLIM	Bulk drug and tablet [11]	UV spectrophotometric & HPLC	230 nm (0 <sup>o</sup> order)	NaOH

**Table 1:** Spectrophotometric methods for analysis of glimepiride.

Sl. No.	Drug	Matrix	Method	Detection	Solvent
1	Metformin hydrochloride and Glimepiride	Bulk drug and tablet [12]	UV-Visible spectrophotometry	233.2 (MET) 228.0 (GLI)	0.05 M KOH & water
2	Pioglitazone and Glimepiride	Tablet [13]	Simultaneous estimation method (multiwavelength spectroscopy)	280.0(PIO) 238.0 nm (GLI)	0.1 N NaOH
3	Metformin HCl and Glimepiride	Bulk and Tablet Dosage Form [14]	Simultaneous estimation method and AUC	236 (MET) 228 (GLI)	Methanol
4	Dapagliflozin Propanediol And Glimepiride	Synthetic mixture [15]	Derivative spectroscopy and RP-HPLC	224 (DAPA) 228(GLI)	Methanol
5	Pioglitazone (PIO) and Glimepiride (GLIM)	Bulk and Tablet Dosage Form [16]	Simultaneous estimation method	216 (PIO) 225 (GLIM)	0.1N NaOH
6	Metformin Hydrochloride, Glimepiride and Pioglitazone	Bulk and Tablet Dosage Form [17]	First Generation Chemometric Methods	200-400	Methanol
7	Rosiglitazone maleate and glimepiride	Tablet Dosage Form [18]	Simultaneous Estimation Method	244 (GLI) 257.2 (ROSI)	0.1N NaOH
8	glimepiride and metformin	Tablet Dosage Form [19]	Simultaneous Estimation Method and Derivative Spectroscopy	222 (GLI) 228 (MET)	0.1M NaOH

**Table 2:** Spectrophotometric methods for analysis of glimepiride in combination.

through formation of composite with Bromocresol green. The method encompasses the development of yellow ion-pair complex among Bromocresol green reagent and Glimepiride. The modeled complexes were scrutinized at a wavelength of 416 nm against the blank prepared in identical fashion. It is stated that aliquots in the series of 0.981-

9.812  $\mu\text{g/ml}$  conform Beers law. (LOD) and (LOQ) are mentioned as 0.088 and 0.29  $\mu\text{g/ml}$ , accordingly [7].

Dyade et al., outlined a spectrophotometric scheme for simultaneous estimation of Glimepiride and metformin hydrochloride consuming mutual tablet formulation via water and 0.5 M KOH as a solvent system. Separation was carried out by extraction of tablet triturate with chloroform and the rest of the residue with 0.5 M KOH. Analysis was performed at a wavelength of 233.2 nm for metformin and 228.0 nm for Glimepiride. It is prostrated that Glimepiride conforms Beers law in the concentration arrays from 5 to 30 mcg/ml [12]. Apart from Pharmacopoeial methods many HPLC methods have been reported the determination for GLIM alone and in combination. In current review, a sum of total six papers for estimation of GLIM alone are presented, while total sum of 11 papers are presented for estimation of GLIM in combination are presented [20-25]. The summary of the reported HPLC methods particularizing the mobile phase used for determination, sample matrix,  $\square$  max and linearity for GLIM alone is shown in **Table 3** while the summary of the reported HPLC methods for GLIM in combination is shown in **Table 4** [26-35].

Sl. No.	Drug	Matrix	Method	Stationary phase	Mobile phase	Detection (nm)	FR	RT
1	GLIM	Tablet [20]	RP-HPLC	Hypersil C18 column (250 m $\times$ 4.6 mm, 5 $\mu\text{m}$ )	ACN: potassium dihydrogen phosphate (0.02 M) buffer (60:40 v/v)	232	1.0	5.420
2	GLIM	Rat serum [21]	RP-HPLC	LiChrosphere 100 RP 18 e (125 $\times$ 4.0 mm i.d., 5 $\mu\text{m}$ )	MeOH: Pot. dihydrogen orthophosphate (10 mM) buffer (80:20 v/v)	230	1.0	5.5
3	GLIM	Bulk drug and tablet [22]	Normal phase Chiral HPLC	Chiralpak IC (250 $\times$ 4.6) mm, 5 $\mu\text{m}$	n-Hexane: EtOH (25:75v/v)	228	0.6	
4	GLIM	Tablet [23]	Hydrophilic interaction liquid chromatography (HILIC).	Waters Spherisorb S5NH2 column (250 $\times$ 4.6 mm, 5 $\mu\text{m}$ ; Waters, Milford, MA)	ACN and Aq. Acetate buffer (5.0 mM) (60:40)	228	1.0	4.6
5	GLIM	Human serum [24]	HPLC	Agilent LiChrospher 100, C <sub>18</sub> column, 5 $\mu\text{m}$ , 250 $\times$ 4 mm I.D., with a 2 mm precolumn filter	ACN: water (containing GAA (0.1 mM, pH=2.5–2.7) 50:50 v/v	228	0.7	
6	Glimepiride	Bulk drug and tablet [25]	RP-HPLC	Octadecyl silane (ODS) column (250 $\times$ 4.6 mm) 5 $\mu\text{m}$	acetonitrile: 0.2 M phosphate buffer (pH=7.4) 40:60 v/v	228	1.0	3.529

**Table 3:** HPLC methods for analysis of glimepiride (GLIM).

### HPLC

Vaishali prostrated an RP-HPLC method for the assessment of Glimepiride (GLM) from bulk drug and Pharmaceutical formulation. Author spent a Hypersil C18 column (250 mm $\times$ 4.6 mm, 5  $\mu\text{m}$ ) by isocratic elution. Mobile phase system is a blend of ACN: Buffer (60:40 v/v), with an aid of buffer comprises of 0.02 M Potassium Dihydrogen Phosphate buffer (KH<sub>2</sub>PO<sub>4</sub>) with a pH of 4.5 adjusted by OPA, keeping a constant flow rate of mobile phase as 1.0 mL/min and detection is archived by means of a UV detector at 232 nm wavelength. Drug GLIM was found to have retention time of 5.420 min. A linear calibration curve was obtained in the concentration series of 50  $\mu\text{g/mL}$  to 150  $\mu\text{g/mL}$  [20].

Sl. No.	Drug	Matrix	Method	Stationary phase	Mobile phase	Detection (nm)	F.R.	R.T.
1	MET+ VOG+ GLIM	Bulk and Combined Tablet Dosage Form [26]	Gradient RP-HPLC	Inertsil ODS 3V (150×4.6 mm, i.d., 5 µm) column	ACN: water 0.02 M phosphate buffer (50:50)	230	1.0	(MET) 2.426 (VOG) 8.198 (Gli) 11.693
2	GLIM+PIO+MET	Bulk and Combined Tablet Dosage Form [27]	RP-HPLC	Inertsil ODS-3 V (250 mm×4.6 mm, 5 µm) Column	buffer, acetonitrile, tetrahydrofuran (40:50:10).	228	1.7	5.043 (GLI) 3.977 (PIO) 1.342 (MET)
3	GLIM+ PIO.HCL+ MET.HCL	Combined Tablet Dosage Form [28]	RP-HPLC	(XBridge C <sub>18</sub> , 250×4.6 mm; 5 µm	Methanol: Phosphate Buffer: (60:40)	257	1.0	4.750 (MET), 7.083 (PIO) 11.367 (GLIM)
4	PIO+ GLIM	Tablet Dosage Form [29]	RP-HPLC	Phenomenex Luna C <sub>18</sub> column (4.6×150 mm)	Acetonitrile: KH <sub>2</sub> PO <sub>4</sub> buffer (60:40%v/v) (Ph6)	230	1.5	4.4 (PIO) 2.7(GLIM)
5	MET. HCL+ RAM+ GLIM	Bulk and Combined Tablet Dosage Form [27]	RP-HPLC	Hypersil BDS C <sub>18</sub> , 250×4.6 mm, 5 µm	Methanol:0.02M KH <sub>2</sub> PO <sub>4</sub> buffer in the ratio of 850:150 v/v ,	210	0.8	3.920 (MET) 4.433 (RAM) 4.837 (GLIM)
6	MET+ PIO+ GLIM	Tablet Dosage Form [30]	HPLC & UV Derivative Spectrophotometric Methods	Phenomenex RP- C <sub>18</sub> (150×4.6 mm, 5 µm)	ACN and phosphate buffer (pH 3) (65: 35)	245	0.5	2.75 (MFN) 4.35 (PLZ) 8.75 (GLIM)
7	MET. HCl+ RAM+ GLIM	Bulk and Combined Tablet Dosage Form [31]	RP-HPLC	Inertsil ODS C <sub>18</sub> , 150×4.6 mm, L1 packing,	Methanol and pH 3.0 KH <sub>2</sub> PO <sub>4</sub> Buffer(50:50) v/v	228	1.0	4.9929 (MET) 2.602 (RAM) 3.789 (GLIM)
8	GLIM+ ATR	Human Serum [32]	HPLC	Inertsil C <sub>18</sub> (25 cm, 4.6mm i.d., 5 µm) at 30°C	ACN: water (containing 1%triethylamine) 55:45 v/v	230	1.0	9.80 (GLIM) 6.92 (ATN)
9	ROSI. Maleate + GLIM	Combined Tablet Dosage Form [33]	HPLC	Hi Q Sil C <sub>18</sub> HS (250 mm×4.6 mm, 5.0 µm)	Methanol:20 mM ammonium dihydrogen phosphate [78:22 (v/v); pH 3.85]	240	1.0	3.32 (ROSI) 8.42 (GLIM)
10	PIO+ GLIM	Bulk and Combined Tablet Dosage Form [34]	RP-HPLC	Inertsil ODS (250×4.6 mm, 5µm)	Acetonitrile and Ammonium acetate (pH 4.5; 20 mM) 60:40 (v/v).	230	1.0	7.0 ± 0.1 (PIO) 10.2 ± 0.1 (GLIM)

11	ROSI+ GLIM	Human plasma [35]	RP-HPLC	150×4.6 mm i.d., 5 µm particle size Symmetry C <sub>18</sub> column	ACN :0.02 M phosphate buffer (pH 5)  (60: 40, V/V)	235	1.0	ROS (3.7), GLIM ( 4.66)
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**Table 4:** HPLC methods for analysis of Glimepiride in combination.

Sl. No.	Drugs	Matrix	Method	Stationary phase	Mobile phase	Detection (nm)	R <sub>F</sub>
1	GLIM +MET. HCL	Bulk drug [36]	Stability Indicating HPTLC	Silica gel 60F <sub>254</sub> HPLC Plates	0.5% Amm. Sulphate: MeOH (7.5:2.5 v/v)	228	0.739 (GLIM)
2	PIO+ GLIM	Tablet [37]	HPTLC	Silica gel 60F <sub>254</sub> HPLC Plates (16x10cm)	Toluene, Ethyl Acetate, MeOH And GAA (70:15:10:5 v/v/v/v).	235	0.42 (PIO) 0.279 (GLIM)
3	ROSI+ GLIM	Fixed Tablet Dosage Form [38]	(HPTLC) densitometry	Silica gel 60F <sub>254</sub> HPLC Plates	MeOH: Toluene: Ethyl Acetate (1:8:1, v/v/v).	228	0.39 ± 0.03 (ROSI) 0.20 ± 0.04 (GLIM)
4	PIO+MET+ GLIM	Tablet [39]	HPTLC	Silica gel 60F <sub>254</sub> HPLC Plates	ACN, MeOH, Propyl alcohol, And Amm. Acetate (7:2:1:1 v/v)	240	0.83 (PIO), 0.21 (MET), 0.89 (GLIM)
5	ATR+ GLIM +MET	Combined Dosage Form [40]	HPTLC	Silica gel 60F <sub>254</sub> HPLC Plates	Water, MeOH, Amm. Sulphate (3.5:3.5:12.6, v/v/v)	245	0.50 ± 0.01 (ATR), 0.65 ± 0.01 (GLIM), 0.33 ± 0.01 (MET)
6	MET.HCL+ ATR+ GLIM	Bulk Drug and Formulation [41]	HPTLC	Silica gel 60F <sub>254</sub> HPLC Plates	Water, MeOH: Amm. Sulphate (1: 1: 4 v/v/v).	237	0.37 ± 0.02 (MET) 0.59 ± 0.02 (ATV), 0.75 ± 0.02 (GLIM)
7	MET+GLIC+ GLIM	Tablet [42]	HPTLC	Silica gel 60F <sub>254</sub> HPLC Plates (10×10 cm).	Amm. Sulphate (0.25%): MeOH: Ethyl Acetate (10.0:2.5:2.5 v/v/v)	285	0.69 (MET) 0.39 (GLIM)

**Table 5:** HPTLC methods for analysis of Glimepiride in combination.

Neelima et al., settled a RP-HPLC scheme for the concurrent estimation of Metformin (MET), Voglibose (VOG) and Glimepiride (GLIM) in loose and in their collective tablet formulation, consuming an inertsil ODS 3V (150×4.6 mm, i.e. 5 µm) column as a static phase and 0.02 M Phosphate buffer balanced to pH 2.5 with an aid of dilute

Sl. No.	Drug	Matrix	Stationary phase	Mobile phase	Method	Detection /Detector	Discussion	FR/RT
01	GLIM+ ATR	Human plasma [43]	ACE5C18 (50×4.6 mm, ACE, Scotland) column	0.1% formic acid: acetonitrile (30:70, v/v)	LC-MS/MS	MDS Sciex (Foster City, CA, USA) API-4000 mass spectrometer	Linearity: 0.2-30 ng/mL (ATR) 1-250 ng/mL (GLIM)	FR:0.5 ml/min RT: 1.91 (ATR) 1.89 (GLIM)
02	MET+ GLIM+ PIO	Human plasma [44]	UPLCTM BEH C18 (100.0×2.1 mm, 1.7 μm) column	ACN-2mM ammonium acetate (50:50, v/v)	UPLC/Q-TOF-MS	Tuneable MS detector.	Linearity: 1-1000 ng/mL	FR:0.20 mL/min RT: 0.50 (MET) 1.40 (GLIM) 1.22 (PIO)
03	GLIM+ FLU	Human plasma [45]	Acquity UPLC BEH C18 column	ACN-1% formic acid in water	UPLC-MS/MS	QTrap 5500 mass spectrometer	Linearity: 2.5-300 ng/mL (GLIM) 0.1–20 ng/mL (FLU)	FR:0.40 mL/min 1.46 (GLIM) 1.27 (FLU)

Orthophosphoric acid (solvent A) and ACN (solvent B) as a mobile phase at a flow rate of 1 mL/min. keeping wavelength of PDA detector at 230 nm. The drugs MET, VOG and GLIM shown RT at a time interval of 2.423, 8.191, and 11.708 min. correspondingly [26].

### CONCLUSION

The present review illustrates various analytical approaches exercised for the appraisal of GLIM. Numerous investigation has been performed including HPLC, HPTLC (**Table 5**), UV/Vis-Spectroscopy, LC-MS/MS, UPLC-MS/MS etc. for estimation of GLIM in loose and in its collective pharmaceutical preparations and in plasma [36-42]. Liquid chromatography with UV detection has been found to be most deliberate for assessment of GLIM in bulk as well as pharmaceutical dosage forms, while hyphenated UPLS-MS/MS, LS-MS/MS methods are conveyed for determination of GLIM and its metabolite in plasma and other biological fluids (**Table 6**) [43-45]. Further, methods were reported for its pharmacokinetic as well as bioequivalence studies. Few chromatography methodologies like HPTLC and Stability-indicating HPLC and HPTLC are also reported in literature.

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