



**A REVIEW ON ANALYTICAL METHODS FOR ESTIMATION OF REPAGLINIDE IN BULK AND IN PHARMACEUTICAL DOSAGE FORMS**

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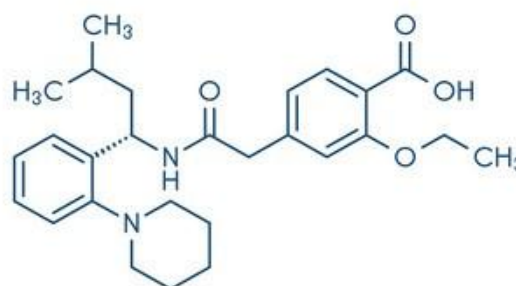
**ABSTRACT**

Repaglinide is the meglitinide class drug used in the management of type 2 diabetes mellitus also known as non-insulin dependent diabetes mellitus (NIDDM) to reduce blood glucose level. For determination of Repaglinide in bulk and in pharmaceutical dosage forms, several analytical methods like UV, HPLC and HPTLC techniques are found in literature. Methods using human and rat plasma, stability in different solvents are also available for repaglinide. For qualitative and quantitative estimation of not only Repaglinide but also for its related degradants in bulk formulations and biological fluids these analytical methods can be used. The present study depicts the review on analytical methods for the estimation of repaglinide and its combination with another antidiabetic drugs.

**KEYWORDS:** Antidiabetic, Repaglinide, RP-HPLC, HPTLC, UV-Spectroscopy.

**INTRODUCTION**

Type 2 diabetes is a long-term metabolic disorder where in the body becomes resistant to the effects of insulin, a hormone that regulates sugar absorption. Treatment of type-2 diabetes (noninsulin-dependent) is now possible with orally administered hypoglycemic agents that help to reduce blood sugar levels. Repaglinide is a carbomoxymethyl benzoic acid derivative, also known as 2-ethoxy-4-[2-[[[3-methyl-1-[2-(1-piperidiny)]phenyl]butyl]amino]-2-oxyethyl]. Repaglinide is a meglitinide antidiabetic drug used for the treatment of type-2 diabetes mellitus and it lowers blood glucose by stimulating the release of insulin from the pancreas. It achieves this by closing ATP-dependent potassium channels in the membrane of the  $\beta$ -cells.<sup>[1,2]</sup>



**Figure. 1: Repaglinide.**

**Table. Methods for determination of Repaglinide Single and combination with other drugs by UV Spectroscopy, HPLC and HPTLC.**

Sr. No.	Drugs	Method	Description	Ref. No.
1.	Repaglinide In bulk and formulation	UV-Visible Spectrophotometry	Detection wavelength - 485.2nm Solvent-Distilled Water Linearity- 15-50 $\mu$ g/ml Regression Coefficient-0.9995 %Recovery-99.42% LOD-2.17 $\mu$ g/ml LOQ-1.08 $\mu$ g/ml	[3]
2	Repaglinide In Bulk and Formulation	UV-Visible Spectrophotometry	ZERO ORDER DERIVATIVE Detection Wavelength – 293nm Solvent – Distilled Water Linearity – 10-80 $\mu$ g/ml Regression Coefficient-0.9995	[4]

			<p><b>%Recovery</b>-close to 100%  <b>LOD</b> – 0.00772 µg/ml  <b>LOQ</b> – 0.0316 µg/ml</p> <p><b>FIRST ORDER DERIVATIVE</b>  <b>Detection Wavelength</b> – 245nm  <b>Solvent</b> – Distilled Water  <b>Linearity</b> – 10-70 µg/ml  <b>Regression Coefficient</b>-0.9996  <b>%Recovery</b>-close to 100%  <b>LOD</b> – (-0.00846) µg/ml  <b>LOQ</b> –(-0.02618)µg/ml</p>	
3.	<b>Repaglinide In Bulk and Formulation</b>	<b>UV-Visible Spectrophotometry</b>	<p><b>Detection Wavelength</b> – 237nm  <b>Solvent</b> – Methanol  <b>Linearity</b> – 10-90 µg/ml  <b>Regression Coefficient</b>-0.999  <b>%Recovery</b>-99.62%  <b>%RSD</b> – 0.69353</p>	[5]
4.	<b>Repaglinide In Bulk and Formulation</b>	<b>UV-Visible Spectrophotometry</b>	<p><b>Detection Wavelength</b> – 237nm  <b>Solvent</b> – Methanol, Water  <b>Linearity</b> – 10-90 µg/ml  <b>Regression Coefficient</b>-0.999  <b>%Recovery</b>-99.2%  <b>LOD</b> -5.4603 µg/ml  <b>LOQ</b> – 16.5465 µg/ml</p>	[6]
5.	<b>Repaglinide In Bulk and Formulation</b>	<b>HPLC with UV</b>	<p><b>Detection Wavelength</b> – 235nm  <b>Column</b> : Shim- pack RP C<sub>18</sub>  <b>Mobile Phase</b>: MeoH: 0.1% triethylamine (50:50)(pH-7.0)  <b>Linearity</b> – 0.1-0.5 µg/ml  <b>Regression Coefficient</b> -0.9983  <b>%Recovery</b>-98.4%  <b>RetentionTime</b> - 3.4 min</p>	[7]
6.	<b>Repaglinide In Pharmaceutical Dosage Form</b>	<b>HPLC</b>	<p><b>Detection Wavelength</b> – 242nm  <b>Column</b> : C<sub>18</sub>  <b>Mobile Phase</b>: MeoH: Ammonium acetate buffer(80:20)(pH-4.0)  <b>Linearity</b> – 0.5-200µg/ml  <b>Regression Coefficient</b>-0.9998  <b>Flow Rate</b>: 1ml/min  <b>Injection Volume</b> - 20µL  <b>RetentionTime</b> - 6.2min  <b>Theoretical Plate</b> - 2747  <b>Tailing Factor</b> - 2.11  <b>Resolution</b> - 2.23  <b>LOD</b> - 5ng/ml  <b>LOQ</b> - 17ng/ml</p>	[8]
7.	<b>Repaglinide In Bulk and Formulation</b>	<b>UV-Visible Spectrophotometry+</b>	<p><b>METHOD : I</b>  <b>Detection Wavelength</b> – 438nm  <b>Solvent</b> – Phosphate Buffer (pH2.4)  <b>Linearity</b> – 5-25 µg/ml  <b>Regression Coefficient</b>-0.9969  <b>Precision</b> -1.183  <b>LOD</b>- 0.97 µg/ml  <b>LOQ</b>-3.27 µg/ml</p>	[9]

			<p><b>METHOD : II</b>  <b>Detection Wavelength</b> – 281.2nm  <b>Solvent</b> – Methanol  <b>Linearity</b> – 1-200µg/ml  <b>Regression Coefficient</b>-0.9995  <b>Precision</b> - 0.788  <b>LOD</b>- 0.26 µg/ml  <b>LOQ</b>-0.87 µg/ml</p> <p><b>METHOD : III</b>  <b>FIRST ORDER DERIVATIVE</b>  <b>Detection Wavelength</b> – 293nm  <b>Solvent</b> – Methanol  <b>Linearity</b> – 2-35µg/ml  <b>Regression Coefficient</b>-0.9996  <b>LOD</b>- 0.42 µg/ml  <b>LOQ</b> -1.39 µg/ml</p> <p><b>METHOD : IV</b>  <b>Detection Wavelength</b> -302nm  <b>Solvent</b> -0.1 N HCL  <b>Linearity</b> - 5-50µg/ml  <b>Regression Coefficient</b> - 0.9997  <b>LOD</b> - 1.16 µg/ml  <b>LOQ</b>- 3.86 µg/ml</p>	
8.	Repaglinide In Formulation	RP-HPLC	<p><b>Detection Wavelength</b> - 245nm  <b>Column</b> - C<sub>18</sub>  <b>Mobile Phase</b> -MeoH: Ammonium acetate  buffer(70:30)(pH-4.0)  <b>Linearity</b>-0.5-5µg/ml  <b>Regression Coefficient</b>-0.9991  <b>Flow Rate</b>-1ml/min  <b>Injection Volume</b>-20µL  <b>Retention Time</b> - 2.550min  <b>LOD</b>-0.275µg/ml  <b>LOQ</b>-0.833µg/ml</p>	[10]
9.	Repaglinide In Formulation	RP-HPLC	<p><b>Detection Wavelength</b> -230nm  <b>Column</b> - Varian C<sub>18</sub>  <b>Mobile Phase</b>- ACN : 10mM ammonium acetate  (70:30)(pH-3.0)  <b>Linearity</b> - 0.5-3µg/ml  <b>Regression Coefficient</b>-0.9993  <b>Flow Rate</b> - 1ml/min  <b>Injection Volume</b> - 20µL  <b>Retention Time</b> - 3.316min  <b>LOD</b>-0.056µg/ml  <b>LOQ</b>-0.0.172µg/ml</p>	[11]
10.	Repaglinide In Formulation	RP-HPLC	<p><b>Detection Wavelength</b> -230nm  <b>Column</b> - ACE C<sub>18</sub>  <b>Mobile Phase</b>-Potassium dihydrogen phosphate -MeoH  (80:20)  <b>Linearity</b> - 2.5-7.5µg/ml  <b>Regression Coefficient</b>-0.999  <b>Flow Rate</b>- 1ml/min  <b>Injection Volume</b>-20µL  <b>Retention Time</b> -3.016min  <b>LOD</b> - 2.5mg/ml  <b>LOQ</b> - 6.25mg/ml</p>	[12]

11.	Repaglinide In Formulation	RP-HPLC	<b>Detection Wavelength</b> -278nm <b>Column</b> - Luna C <sub>18</sub> <b>Mobile Phase</b> -ACN:Potassiumdihydrogen phosphate buffer pH(4.5) (60:40) <b>Linearity</b> -200-1000µg/ml <b>Regression Coefficient</b> -0.999 <b>Flow Rate</b> - 1ml/min <b>Injection Volume</b> - 20µL <b>%Recovery</b> - 100.15%	[13]
12.	Repaglinide In Plasma	RP-HPLC	<b>INDOMETHACIN Internal Standard</b> <b>Detection Wavelength</b> -242nm <b>Column</b> - Star C <sub>18</sub> <b>Mobile Phase</b> -ACN:AmmoniumFormate pH(2.7) (60:40) <b>Linearity</b> - 20-200µg/ml <b>Regression Coefficient</b> -0.9930 <b>Flow Rate</b> - 1ml/min <b>Injection Volume</b> - 20µL <b>Retention Time</b> - 6.2 min <b>LOD</b> - 10ng/ml <b>LOQ</b> - 20ng/ml <b>%Recovery</b> -109.09%	[14]
13.	Repaglinide In Plasma	HPLC	<b>Detection Wavelength</b> - 244nm <b>Column</b> -bondapack C <sub>18</sub> <b>Mobile Phase</b> -ACN: MeoH:Potassium dihydrogen Phosphate pH(2.5) (51:11:38) <b>Linearity</b> - 5-250µg/ml <b>Regression Coefficient</b> - 0.998 <b>Flow Rate</b> - 1.5ml/min <b>Injection Volume</b> - 20µL <b>Retention Time</b> - 4.5min <b>LOD</b> - 1ng/ml <b>LOQ</b> - 5ng/ml <b>%Recovery</b> - 98.3%	[15]
14.	Repaglinide In Formulation	UV-HPLC Comparison	<b>UV-METHOD</b> <b>Detection Wavelength</b> - 241nm <b>Solvent</b> - Methanol <b>Linearity</b> - 5-30µg/ml <b>Regression Coefficient</b> -0.9994 <b>%Recovery</b> -99.63% <b>LOD</b> - 1.15 µg/ml <b>LOQ</b> - 3.48 µg/ml	[16]
15.	Repaglinide In bulk and formulation	HPTLC	<b>Detection Wavelength</b> - 288nm <b>Mobile Phase</b> -Chloroform:MeoH:Ammonia (4.5:8:0.05) Camage TLC Scanner 3 <b>Linearity</b> - 5-30ng/spot <b>Regression Coefficient</b> - 0.998 <b>%Recovery</b> -97.99% <b>LOD</b> - 50ng/spot <b>LOQ</b> - 300ng/spot <b>Rf</b> - 0.55±0.03	[17]
16.	Repaglinide In bulk and formulation	HPTLC	<b>Detection Wavelength</b> - 254nm <b>Mobile Phase</b> -Chloroform:MeoH (9:1) Precoated Plate with silica gel 60 F 254 <b>Linearity</b> - 300-3000ng/spot <b>Regression Coefficient</b> -0.9991 <b>%Recovery</b> -97.99% <b>LOD</b> - 52.91ng/ml <b>LOQ</b> -176.39ng/ml	[18]

			<b>Rf</b> -0.41±0.018	
17.	Repaglinide In formulation	HPTLC Densitometry	<b>Mobile Phase</b> -MeoH : Ammonium sulphate (2.5:7.5) <b>Detection Wavelength</b> - MET:-243nm REP-236nm <b>R<sub>f</sub></b> - MET:0.34, REP-0.60 <b>Linearity</b> - MET-500-2500ng/band REP-100-500ng/band <b>Regression Coefficient</b> - MET- 0.999 REP-0.995 <b>Tailing Factor</b> - MET- 1.4 REP-1.31 <b>LOD</b> -MET-98ng/band REP:17ng/band <b>LOQ</b> -MET -296ng/band  REP -51mg/band <b>% Recovery</b> - MET-99.23% REP-98.35%	[19]
18.	Repaglinide & Metformin In Formulation	UV-Visible Spectrophotometry	<b>METHOD I</b> <b>Detection Wavelength</b> -MET-232nm REP-238nm <b>Solvent</b> –Phosphate Buffer (pH-6.8) <b>Linearity</b> - MET-10-60 µg/ml REP-1-6 µg/ml <b>Regression Coefficient</b> -MET-0.9997 REPA-0.9939  <b>LOD</b> - MET- 1.98 µg/ml REP-0.21 µg/ml <b>LOQ</b> -MET-6 µg/ml REP-0.64 µg/ml <hr/> <b>METHOD II</b> <b>Detection Wavelength</b> -MET-208nm REP-299nm <b>Solvent</b> - 0.1N HCL <b>Linearity</b> - MET-10-60 µg/ml REP-1-6 µg/ml <b>Regression Coefficient</b> -MET-0.9978 REPA-0.9887 <b>LOD</b> - MET- 1.30 µg/ml REP-0.19 µg/ml <b>LOQ</b> - MET-3.94 µg/ml REP-0.58 µg/ml	[20]
19.	Repaglinide In Formulation	HPLC	<b>Detection Wavelength</b> -288nm <b>Mobile Phase</b> - Phosphate buffer :ACN(45:55)(pH-6.0) <b>Flow Rate</b> - 1ml/min <b>Retention Time</b> –6.217 <b>Linearity</b> –10-60 µg/ml <b>LOD</b> -1 µg/ml <b>LOQ</b> -3 µg/ml <b>% Recovery</b> -97.9 – 100.1%	[21]
20.	Repaglinide & Metformin In Formulation	UV & HPLC	<b>Detection Wavelength</b> -240nm <b>Column</b> - C <sub>18</sub> <b>Mobile Phase</b> -MeoH : 0.2% heptane sulphonate sodium (70:30) <b>Linearity</b> - 1-10µg/ml(for both drug) <b>Regression Coefficient</b> - MET-0.997 REP-0.9982 <b>Flow Rate</b> - 1ml/min	[22]

			<b>Injection Volume</b> -20µL <b>Retention Time</b> - MET-3.42min REP-14.21min <b>Tailing Factor</b> - MET-1.091 REP-1.240 <b>Theoretical Plate</b> - MET-4761 REP- 6832 <b>Resolution</b> - 13.24 <b>LOD</b> - MET-0.28µg/ml REP-0.14ug/ml <b>LOQ</b> - MET-0.93µg/m REP-0.47ug/ml	
21.	<b>Repaglinide &amp; Metformin In Formulation</b>	<b>UV &amp; HPLC</b>	<b>UV-METHOD</b> <b>Detection Wavelength</b> - MET- 308nm REP-267nm <b>Solvent</b> - Methanol <b>Linearity</b> -5-50µg/ml(for both drugs) <b>Regression Coefficient</b> -MET-0.9999 REP-0.9950 <b>LOD</b> -MET-0.347 µg/ml REP-0.170 µg/ml <b>LOQ</b> - MET-1.156 µg/ml REP-0.568 µg/ml <b>HPLC- METHOD</b> <b>Detection Wavelength</b> - 255nm <b>Column</b> - C <sub>18</sub> <b>Mobile Phase</b> - ACN : O-Phosphoric acid pH(3) (40:60) <b>Linearity</b> - 5-50µg/ml(for both drugs) <b>Regression Coefficient</b> - MET-1.0000 REP-0.9999 <b>Flow Rate</b> -1ml/min <b>Injection Volume</b> -20µL <b>Retention Time</b> - MET-4.25min REP- 6.28min <b>LOD</b> - MET- 0.545µg/ml REP-0.601 µg/ml <b>LOQ</b> - MET-1.653 µg/ml REP : 1.821 µg/ml	[23]
22.	<b>Repaglinide &amp; Metformin In API &amp; Formulation</b>	<b>HPLC</b>	<b>Detection Wavelength</b> - 245nm <b>Column</b> - BDS Hypersil <b>Mobile Phase</b> -ACN : Buffer(58:42) <b>Linearity</b> -MET-25-150 µg/ml REP-0.1-0.6 µg/ml <b>Regression Coefficient</b> - MET-0.999 REP-0.999 <b>Flow Rate</b> - 1ml/min <b>Injection Volume</b> -20µL <b>Retention Time</b> - MET-2.050min REP- 5.337min <b>LOD</b> - MET- 3.732µg/ml REP-0.01291µg/ml <b>LOQ</b> - MET-11.64 µg/ml REP : 0.04030µg/ml <b>%Recovery</b> - MET-99.88% REP-99.89% <b>Theoretical Plate</b> - MET-616 REP-7196	[24]

23.	Repaglinide & Metformin In Formulation	HPLC	<b>Detection Wavelength</b> -242nm <b>Column</b> - Hypersil, C <sub>18</sub> <b>Mobile Phase</b> -MeoH: Buffer (40:60)(pH-6) <b>Linearity</b> -MET-100-1000µg REP-0.5-2 µg/ml <b>Regression Coefficient</b> - MET-0.999 REP-0.999 <b>Flow Rate</b> - 1ml/min <b>Injection Volume</b> -20µL <b>Retention Time</b> - MET-3.60min REP- 2.60min <b>LOQ</b> - MET-6.307µg/ml REP : 1.143µg/ml <b>%Recovery</b> -MET-100.28% REP-99.76%	[25]
24.	Repaglinide & Metformin In Formulation	HPLC	<b>Detection Wavelength</b> -223nm <b>Column</b> - C <sub>18</sub> <b>Mobile Phase</b> -ACN : Water (90:10) <b>Linearity</b> -MET-5-40 µg/ml REP-2-35µg/ml <b>Regression Coefficient</b> - MET-0.997 REP-0.995 <b>Flow Rate</b> -1ml/min <b>Injection Volume</b> -20µL <b>Retention Time</b> - MET-2.72min REP- 6.13min <b>LOD</b> - MET- 0.52µg/ml REP-0.10µg/ml <b>LOQ</b> - MET-1.59µg/ml REP : 0.31µg/ml <b>%Recovery</b> - MET-99.32% REP-99.32%	[26]
25.	Repaglinide & Metformin In Formulation	HPLC	<b>Detection Wavelength</b> -210nm <b>Column</b> - YMC Pack AM ODS <b>Mobile Phase</b> -MeoH : 10mM Potassium dihydrogen phosphate (pH) (70:30) <b>Linearity</b> -MET-5- 200µg/ml REP-1-200µg/ml <b>Flow Rate</b> - 1ml/min <b>Injection Volume</b> -20µL <b>Retention Time</b> - MET-2.6min REP- 11.3min <b>LOD</b> -MET- 0.3µg/ml REP-0.13µg/ml <b>Tailing Factor</b> -MET-1.39 REP-1.10 <b>Theoretical plate</b> -MET-5856 REP-8010 <b>Resolution</b> -2.72	[27]

### CONCLUSION

This review depicts the reported Spectroscopic and Chromatographic methods developed and validated for estimation of repaglinide. In the present study it was concluded that for repaglinide different Spectroscopic and Chromatographic methods are available for single and combination with other drugs. The mobile phase containing Phosphate buffer, Methanol and Acetonitrile were common for most of the chromatographic method to provide more resolution with flow rate in the range 1.0

– 1.5ml/min. For most of the Spectroscopic methods common solvent is Methanol. These all methods claimed to be simple, accurate, economic, precise and reproducible in nature. Most of these methods were using RP-HPLC and UV absorbance detection.

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