

## A REVIEW OF ANALYTICAL METHODS FOR DETERMINATION OF TYPE- II ANTIDIABETIC DRUGS IN PHARMACEUTICALS AND BIOLOGICAL MATRICES

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Received: 19 October 2020, Revised and Accepted: 23 November 2020

### ABSTRACT

Its a meglitinide analog is an oral symptom designed to common hour aldohexose excursions. Through not an antidiabetic, it acts in AN analogous manner by binding to antidiabetic receptor likewise on alternative one distinct receptor-» closure of adenosine triphosphate dependent K<sup>+</sup> channel-» of depolarization-» internal secretion unharnesses. Repaglinide induces fast onset short-lasting internal secretion discharged. It is administered antero every main meal to stabilize postprandial hyperglycemia; the dose ought to be emitted if a food material is incomprehensible. Because of less permanent action, it perhaps had a lower risk of the seriousness of hypoglycemia. Repaglinide is indicated solely in type-II DM as another to sulfonylureas, or to supplement metformin/long internal secretion. It ought to be avoided in disease. This review delivers a detail description totally different of various analytical ways were printed for the estimation of repaglinide and its combination medicine in prescription drugs and biological matrices. This assessment encompasses different analytical ways such as chemical analysis ways, aggressive liquid activity (HPLC), superior thin-layer activity (HPTLC), liquid chromatography-mass spectroscopic analysis (LC-MS), and ultra-performance liquid activity (UPLC), GC-MS, [LC-ESI-MS-MS], capillary activity (CE), titrimetric and chemical science technique, and designation study for the estimation of repaglinide and together with a mixture.

**Keywords:** Biological matrices, Chromatography, Repaglinide, Analytical methods, Type-II diabetic drugs, ICH guidelines.

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### INTRODUCTION

Repaglinide is a new carboxymethyl benzoic acid derivative, also known as 2-ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl) phenyl] butyl] amino]-2-oxoethyl] (Fig. 1). It is a novel prandial glucose regulator for the treatment of type-II diabetes mellitus [1]. It reduces fasting glucose concentrations in patients with type-II diabetes mellitus. It helps to control the blood sugar levels by pancreas increases insulin levels. Repaglinide is an oral anti hyperglycemia agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It belongs to the meglitinide is an anti-Diabetic type-II class drug with of short-acting insulin secretagogues, which act by binding to the  $\beta$  cells of the pancreas, and it stimulates and releases the insulin secretion levels [2]. Repaglinide incites an insulin response to early meals reducing the postprandial blood glucose levels. May be 1 month of a course is needed for a decrease in fasting blood glucose levels is seen. Meglitinides may have a common effect on slight growth in weight. The total average weight gain caused by meglitinides appears to be lower than that is caused by sulfonylureas. Due to their own mechanism of action, meglitinides it may because hypoglycemia [3]. The risk is thought to be lower than that of sulfonyl urea's since their action is presence on glucose-dependent. In addition to reducing postprandial and fasting blood sugar, meglitinides are shown to decrease glycosylated hemoglobin (HbA1c) levels, which are reflective of the last 8–10 weeks of glucose control. Repaglinide is thoroughly metabolized in the liver and excreted in bile salts. Approximately 90% of a single orally administered dose is eliminated in the face and 8% in urine. The chemical formula of  $C_{27}H_{36}N_2O_4$  and it is soluble in methanol and methylene chloride. But practically insoluble in water-solubility of approximately 20  $\mu\text{g/ml}$  [4]. This review explores the reported analytical method, so far in the literature for the estimations of repaglinide in bulk drug, pharmaceutical formulation, and biological matrix. Various analytical methods such as spectrometric, high-pressure liquid chromatography (HPLC), high-performance thin-layer chromatography (HPTLC), liquid chromatography-mass spectrometry

(LC-MS), and ultra-performance liquid chromatography (UPLC), capillary electrophoresis (CE), GC-MS, LC-ESI/MS, and diagnosis study has been used for analysis of Repaglinide [5].

### SAMPLE PREPARATION

#### Solubility

According, to the Bio-pharmaceutical organization, the Repaglinide falls in BCS Class-II, which means high solubility and high permeability [6]. The pH scale of a saturated water resolution of repaglinide is bigger than seven the  $P^{ka}$  is 4.1–5.7 and partition coefficient is 3.8. The solubility of the drug was tested in solvents ordinarily used for analytical methodology [7].

#### Sample preparation strategies

About 90% of the whole analysis of your time relies on sample resolution preparation during a most of the strategies. The standard of sample resolution preparation may be a key issue for the success of study. In most of the chemical analysis methodology is employed to distil water, and in generally fuel is employed an agent sample. The sample resolution preparation methodology for the summary extraction of repaglinide from biological matrices (plasma, serum and urine) embody super molecule precipitation with acetonitrile (ACN) and fuel, solid section extraction (SPE) mistreatment methanol-phosphate buffer (PB), and methanol-water [8].

### ANALYTICAL METHODS

#### Spectrometry

In literature regarding some ways area unit mentioned, for the determination of repaglinide victimization chemical analysis, of that ten ways area unit for the estimation of repaglinide alone, whereas different the opposite is for quantifying the repaglinide together with other medicine substance. The epitome of reported chemical analysis ways indicating the fundamental the fundamental ( $\lambda_{max}$ ) solvent and limit of detection (LOD) is shown in Table 1.

## HPLC

### Biological samples

Method development and valid of liquid natural process technique for concurrent estimation of repaglinide, metformin, pioglitazone, sitagliptin, glibenclamide, and gliclazide - Applications for Counterfeit Drug Analysis, the actual RP-HPLC technique was developed, and wide used oral antidiabetic area unit antidiabetic drug coordination compound (MTF), with few ordinarily prescribed by oral anti-diabetics, namely, and repaglinide (RPG), gliclazide (GLZ), pioglitazone coordination compound (PGZ), sitagliptin phosphate (SIT), and glibenclamide (GLB). The activity technique is separation carryout using gradient elution mode, and this method was valid in keeping with ICH Guidelines [19].

Separation and quantification of eight kind-II antidiabetic medicine on a high- performance liquid chromatography: Its applications to human plasma assay. Technique development and an analytical supported isocratic RP-HPLC action technique were developed and valid for the quantification and separation of eight kind-II antidiabetic drugs: Repaglinide, Nate glinide, rosiglitazone, pioglitazone, glipizide, gliclazide, glibenclamide, and glimepiride for his or her applications are utilized in human plasma assay technique. Antidiabetic is utilized as IS. The analysis was performed on onyx C18 column (100×4.6 mm. 5 μm) employing a mixture of components [20].

### Pharmaceutical samples

Analytical methods for the determination of repaglinide in bulk drugs and pharmaceutical dosage forms using RP-HPLC are shown in Table 2.

## STABILITY INDICATING METHOD

In the literature few stability indicating methods are reported. Table 3 shows the summary of the methods.

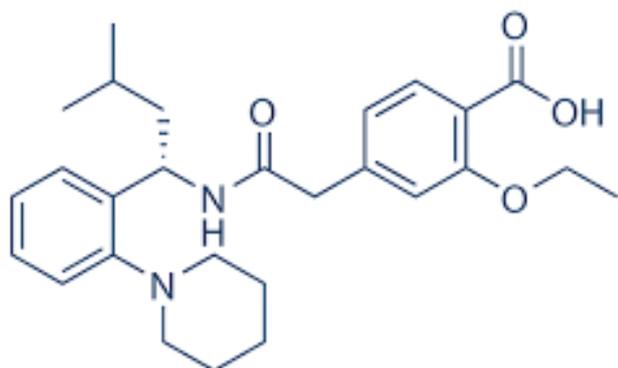


Fig. 1: Chemical structure of repaglinide

## LC-MS

Validation of high-performance liquid chromatography-tandem mass spectrographic analysis (LC-MS /MS) technique was developed for the determination of repaglinide in human plasma. The analytical internal standard of, diazepam, is measure extracted from the plasma (25 m/L) by liquid-liquid extraction with diethyl ether–dichloromethane (60:40, v/v). And separation on an XDB-C18 column, detection was administered into API 4000 mass spectroscopy with an ESI interface operative in numerous reactions watching mode [38].

Method for determination of LC-MS of anti-diabetic drug repaglinide in human plasma, the strategy was valid and developed over a linear range, and also the dried residue was reconstituted with 500 μL of mobile part, and it absolutely was a cinematographic separation was achieved on a C18 analytical column, the strategy of the mode using MRM transitions m/Z 453.3>162.2 and m/Z 389.0>201.1 for the drug, and IS, severally. This technique was with success applicable for additional authentic human plasma samples from bio-equivalence studies [39].

Determination of liquid chromatography-tandem spectroscopic analysis of repaglinide and antidiabetic in human plasma and its application to pharmaceutical bioequivalence study, and therefore the technique was valid and developed for the simultaneous estimation of repaglinide and antidiabetic in human plasma employing a D6- antidiabetic and D5-Repaglinide an internal standard. When protein precipitation using acetonitrile because the precipitation solvent, each analytes and ISS were separated on a Venusil ASB C18 [150 mm× 4.6 mm, 5 μm] through gradient elution using acetonitrile – 10 mmol L-1 ammonium ion acetate because the mobile phase. The strategy is linear complete the 0.2–60.0ng/ml concentration range of repaglinide and over the 4–1000 ng/ml range of antidiabetic. A cinematographic complete run time of 7.5 min was achieved. The valid technique was fully applied to clinical information [40].

A bio-analytical methodology using 96-blade in thin-film microextraction (TFME) and LC-MS/MS methodology for estimation of Repaglinide (RPG) and a couple of its main metabolites' strategies were valid and developed for used of an *in vitro* metabolism study. The target analyses are extracted from the human microsomal medium by a 96-blade-TFME system using the low-price image "SPME multi-sampler" using C18 coating. Methodology development and validation showed by recoveries of around 90% for each analyzer's and also the methodology was applied to an *in vitro* metabolism study of Repaglinide using human liver microsomes and established to be required for these functions [41].

Degradation product is below the high temperature/humidity, UV/ Visible lightweight, in varied pH and oxidization are varied conditions

Table 1: Summary of a spectrometric method for the analysis of repaglinide either alone or in combination with other drugs such as gliclazide (GLZ) and metformin (MET)

Compounds	Methods	Solvent/procedure	LOD (μg/ml)	λ <sub>max</sub> (nm)	Ref.
REPA, MET HCL	Second order method derivative	Methanol: heptane sulfonates sodium [70:30 v/v]	1.01, 0.32–0.39	234, 252	[9]
REPA	Zero order derivative method-A, first order derivative method-B [absorbance maxima]	Methanol and water	0.00772, -0.00864	245	[10]
REPA	Spectrophotometric method	methanol	1.15	241	[11]
REPA	Shim-pack method	methanol	0.5–0.1	235	[12]
MET, REPA	First-order derivative method [absorbance], second order derivative [Q- absorbance ratio]	alcohol	0.378, 0.686	240, 292	[13]
REPA	Multiple – wavelength method	Methanol, acidic, basic, buffers solvent	0.97, 0.26, 0.42, 1.16.	438, 281, 293, 302.	[14]
MET, REPA	UV Spectroscopic method	Methanol-water	0.3–0.13	210	[15]
REPA	Assay of UV spectrophotometric method	methanol	0.278	237	[16]
REPA	Spectrofluorimetric method	methanol	0.9986	379, 282	[17]
Empagliflozin, MET	Spectrofluorimetric method	methanol	0.20, 0.19	225, 237	[18]
REPA, MET HCL	Second order derivative	methanol	1.01, 0.32, 0.39	234, 252	[9]

**Table 2: Report of RP-HPLC method for determination of repaglinide either single or in a combination with other drugs in pharmaceutical dosage forms**

Study aim	Column	Mobile phase	Detection	$\lambda_{\max}$ (nm)	Flow rate ml/min	LOD $\mu\text{g/ml}$	Ref.
Chromatographic separation of REPA PK study	StarC18, analytical column [4.5 mm×150 mm, 5 $\mu\text{m}$ ]	ACN:ammonium formate, [60:40, v/v]	UV	244	1	10	[21]
An optimization of MET separation condition of REPA	BDS, Hypersil C18 [150 mm×4.6 mm, 5 $\mu\text{m}$ ]	ACN: phosphate buffer [60:40 v/v] with 1% triethylamine.	UV	254	0.8	135.6-18.15	[22]
REPA In bulk drug dosage form	C18 [100×4.6mm×5 $\mu\text{m}$ ], ODS Kromasil	Methanol:phosphate buffer [60:40v/v]	UV	242	1	0.5	[23]
Simultaneous estimation with MET	HypersilC18 [250×4.6mm, 5 $\mu\text{m}$ ]	Methanol:buffer [40:60v/v]	UV	242	1.0	0.5–2.0	[24]
Simultaneous REPA with MET HCl	C18	Methanol-0.2%: heptane sulfonates sodium [70:30v/v]	UV	234, 252	0.68–0.89, and 1.18–1.70	0.14–0.28	[9]
Determinations of REPA in the tablet dosage form	Agilent TC-C18 and C21 [250×4.6 mm, 5 $\mu\text{m}$ ]	Methanol:water [80:20v/v]	UV	241	1.0	0.73	[11]
Determination of REPA	RP-C18	Methanol:triethylamine with orthophosphoric acid [50:50v/v]	UV	235	1	0.5-0.1	[12]
Simultaneous with MET, REPA	YMC PACK AM ODS [250 mm×4.6 mm, 5 $\mu\text{m}$ ]	Methanol: potassium dihydrogen buffer [70:30v/v]	PDA	210	1	0.3, 0.13	[15]
Simultaneous with six antidiabetic drugs	Altima C18 [150×4.6 mm×5 $\mu\text{m}$ ]	Methanol: Phosphate buffer [70:30%v/v]	UV	230	1.0	-	[25]
Assay method (PK, PD), studies	$\mu$ -bond Apack C18 column	ACN:methanol:potassium dihydrogen phosphate [51:11:38v/v]	UV	245	1.5	1	[26]
Simultaneous with MET & REPA	Hypersil ODS C18 [250 mm×4.6 mm, 5 $\mu\text{m}$ ]	ACN:ammonium acetate buffer [0.05M] [60:40%v/v]	PDA	271	3.13, 10.01	0.5-3.0	[27]
Estimation of REPA drugs	Analytical C18 [250mm×4.6mm, 5 $\mu\text{m}$ ]	ACN:trifluoro acetic acid in a water [55:45%v/v]	UV	285	1	1.73	[28]
<i>In vitro</i> permeation analysis studies of REPA	RP C18 [250 mm×4.6 mm, 5 $\mu\text{m}$ ]	ACN:ammonium acetate [70:30%v/v]	UV	240	1	0.1–1.2	[17]

**Table 3: The summary of stability indicating HPLC methods for determination of repaglinide either alone or in combination with other drugs**

Study aim	Stress condition	Detection	Types of study	Ref.
REPA simultaneous with MET HCL in bulk drugs	Acid, alkali, oxidation, dry heat degradation	UV-230	Separation in presence of [dry heat] degradation product	[29]
REPA estimation with MET HCL in tablet dosage form	Acid, alkali, oxidation.	UV-232	Separation in presence of degradation product	[30]
MET simultaneous with REPA	Thermal, photolytic, hydrolytic, and oxidative.	UV-PDA-210	Separation of MET and REPA force degradation product.	[31]
REPA in bulk drug dosage	Acidic, alkaline, hydrolytic, and photolytic oxidation.	UV-237	Assay method of degradation absorbance	[16]
REPA in tablets	Oxidation	UV-243	Degradation pathway	[32]
REPA in pharmaceutical dosage	Stable to neutral and photolytic	UV-278	Separation in presence of REPA in force degradation	[33]
Determination of REPA	Acids, alkali, hydrolysis, oxidation	UV-240	Separation in presence of REPA in degradation product	[34]
REPA in bulk and dosage forms	Hydrolysis, oxidation, photolysis, and thermal	UV-216, 243	Separation in presence of REPA in degradation product	[35]
REPA in bulk drugs	Photolytic degradation	UV-237	Separation in presence of REPA degradation product	[36]
Determination of REPA, PGL, and RGL.	Acids, alkaline, oxidative	UV-225, 220, 240	Separation in presence of degradations and their preparation with good extraction recoveries	[37]

of repaglinide and metformin. And second, a primary valid technique was LC-UV is examined, whether or not it is valid and determined those drugs within the presence of their own pharmaceutical degradation product and whether or not it's similar for estimating the degradation kinetic process [42].

#### HPTLC

Assay of antidiabetic medication in bulk and optimized methodology of nanoemulsion by stability-indicating valid methodology of high-performance thin-layer chromatography techniques, a simple selective,

accurate, precise, and stability-indicating methodology of HPTLC, is analyzed by a repaglinide and each as pharmaceutical bulk product and in nanoemulsion pharmaceutical formulation methodology was valid. The technique was used in TLC metallic element pre-coated plates with colloid powder [G-60] F-254, as a stationary phase. The sample solvent system consists of chloroform/methanol/ammonia/glacial ethanoic acid (7.5:1.5:0.9:0.1, v/v). Furthermore, the degraded product is nicely separated from the pure drug. Densitometric analysis of repaglinide ultraviolet illumination absorbance mode at 240 nm was distributed, the regression knowledge for the activity plots are going to be excellently showed [43].

An isocratic technique is precise, and rapid, selective, and economically, and reverse-phase HPTLC technique was established for the simultaneous estimation of product of metformin hydrochloride and repaglinide. HPTLC technique was developed and valid by employing a pre-coated silica gel G-60 F254 plates as stationary phase, using a methanol: ammonia sulfate (0.25%) (pH-5.7) (2.5:7.5, v/v) as mobile phase. The SP plates were scanned at roughly 243–236 nm for HP-LC and HP-TLC both are respectively [44].

The determination of HPTLC technique was developed by a quantitative estimation of repaglinide during a single pharmaceutical formulation (2 mg). The action technique of repaglinide on silica Gel-60 powder F-254 TLC plate is SP and employing a chloroform:methanol:ammonia (4.5:0.8:0.05 v/v) as a mobile phase. Repaglinide showed a Rf worth  $0.55 \pm 0.03$  and scanned UV at 288 nm using Camag TLC Scanner three. The method development was to be success, used for determining the assay of repaglinide tablet formulations [45].

Repaglinide is a widely used meglitinide class drug to treat diabetes mellitus. The degradation product as per ICH guidelines (hydrolysis, photolysis, dry heat, and oxidation) and a sensitive optimized assayed, stability-indicating method as developed for repaglinide in bulk and pharmaceutical dosage forms. The peak purity and quality of the drug were observed. Using HPTLC method, aluminum plates precoated with Silica Gel 60 F254 is a stationary phase and mobile phase solution used to consisted of methanol:toluene (2:8) and quantitation was done at the wavelength found to be at 242 nm. The method was developed to be simple, specific, precise, and stability-indicating study [46].

High-performance thin-layer chromatography method has been A simple, accurate, precise, and rapid development and validated for the estimation of repaglinide in tablet dosage forms. The method development in TLC aluminum plates precoated with silica gel-G60-F 254 as a stationary phase. The mobile phase is used as a mixture of chloroform:methanol (9:1) v/v. The detection of the spot was carried out UV at 254 nm. The analytical calibration curves were found to be linear between 300 and 3000 ng mL<sup>-1</sup> Rf value is  $0.41 \pm 0.018$  with a regression coefficient of 0.9991. The proposed methods can be successfully used to determine the drug content of marketed pharmaceutical product formulation. The determined by recovery studies was founds to be 97.98–98.89%. The proposed method was validated according to various ICH guidelines [47].

#### UPLC

Method development and validation of simple stability indicating by UPLC method for the determination of repaglinide in pharmaceutical dosages, A simple, precise, and accurate stability-indicating isocratic reverse-phase ultra-performance liquid chromatography method are determined. The method was developed using Water Equity BEH C18 (100 Å 2.1) mm, 1.7 µm column with a mobile phase consisting of a mixture of potassium dihydrogen phosphate buffer of pH 3.2 and acetonitrile (40:60 v/v). The total run time for the assay was only 4 min. The elution compound was detected at 245 nm with a UV detector. The standardization curve of mean peak area versus concentration showed an excellent [48].

The detailed electrochemical method was study and novel voltmeter, and LC methods are presented for the determination of repaglinide

(RPG) in pharmaceuticals. The HP-LC and UPLC methods are developed using core-shell columns with mobile phase solution consisting of 50:50; ACN:water 0.05 % TFA; at PH: 3.0 (v/v) with UV detection at 215 nm. Finally, the proposed development method was successfully applied for the determination of repaglinide in pharmaceutical dosage forms [49].

A Novel method for liquid chromatography method was developed for the simultaneous determination of the widely used oral antidiabetic, metformin hydrochloride with anti-diabetics comprising the meglitinides class in bulk, laboratory-prepared mixtures, and pharmaceutical products. It was applied in the presence of metformin-reported by impurity (1-cyanoguanidine). Chromatography separation was achieved with isocratic elution mode using a mobile phase solution of acetonitrile: 0.01 M sodium dihydrogen phosphate (pH: 2.8) (67:33; v/v) flowing through a LiChrospher NH2 (amino) Agilent column (250 × 4.6 mm–5 µm) at a rate of 0.8 mL/min at ambient temperature in a run time of 4 min. The detections of UV were carried out at 220 nm. As per ICH guidelines, the present method was found to be rapid and simple, selective, economic, and needs for quality assessments of pharmaceutical products [50].

#### GC-MS

The short-acting insulin secretagogue commonly used as repaglinide for the treatment of type two diabetes. In this paper, metabolomics is the first research of dynamic urine metabolic profiling, and biomarkers of type-II antidiabetic mice treated with repaglinide based on GC-MS. Twenty diabetic KK-Ay mice are orderly assigned to four groups and fed with repaglinide for 6, 9, 12, and 14 weeks, respectively. Five C57BL/6 J mice are used as a good healthy control group and feed with water as a contrast. The PCA scores plot are identified 41 metabolites techniques, the results are demonstrated that repaglinide not only regulates the carbohydrates, and polyalcohol but also the organic acid in the organism. This work has illustrated the potential of metabolic to disease diagnosis, pharmacology, and pharma codynamics research studies [51].

#### CAPILLARY ELECTROPHORESIS

An applicability method was studied by 2,6-didi-o-methyl b-cyclodextrin (DM-b-CD) as the Chiral selector in capillary electrophoresis for fast and efficient chiral separation of repaglinide enantiomers. The method was systematically studied of the parameters affecting separation was performed with detection of UV at 243 nm. The proposed new method was very speed and systematically, determined by efficient of separating enantiomers, and its applicable for the analyzing repaglinide enantiomers in pharmaceutical quality control of pharmaceutical productions [52].

The method of separation of repaglinide, brompheniramine maleate, dioxo promethazine hydrochloride, liarozole, carvedilol, homatropine hydrobromide, homatropine methyl bromide, venlafaxine, sibutramine hydrochloride, zopiclone, chlorphenamine maleate, and promethazine hydrochloride, was investigated the influence of types of ionic liquids concentration of BGE PH, long-chain length of ionic liquid cations on the resolution are explained and finally, the proposed methods were applied for the chiral impurity determination of Eszopiclone in the pure product of pharmaceutical tablets [53].

The separation of CE method in the non-aqueous medium was developed and validated for the determination of repaglinide in pharmaceutical formulation. The capillary electrophoresis was performed using a 75 m × 90 cm fused silica capillary (76 cm effective length) and the detection of UV at 240 nm. 0.01 mol/l solution of ammonium acetate in the mixture solution of methanol-acetonitrile (3:7, v/v), 30 kV voltage, 30°C temperature and hydrodynamic injection (10 m bar, six s) was chosen as CE parameters studies. The solutions were prepared in methanol. The capillary electrophoresis method is demonstrated [54].

A method of capillary electrophoresis system for enantiomeric impurity test of repaglinide, un-coated fused silica capillary (50 m×50 cm, with an effective length of (41 cm) was used. The running buffer solution was composed of 30 mmol/L sodium dihydrogen phosphate and 5 mg/ml carboxymethyl-cyclodextrin (PH 3.5), and it can be used for determination of enantiomeric impurities in type-II antidiabetic [repaglinide] tablets [55].

#### TITRIMETRIC AND ELECTRICAL METHODS

An isocratic method was normal phase chiral HPLC method that was developed and validated for the enantiomeric separation of repaglinide, (S)- (+)-2-ethoxy-4-N [1-(2-piperidinophenyl)-3-methyl-1-butyl] Amino carbonyl methyl] benzoic acid, an antidiabetic in the bulk drug substance. The solution is played an important role, in enhancing chromatography efficiency and resolution between the enantiomers. The method was developed extensively validated and proved to be robust. The developed method was found to be enantiomer selectivity, accurate, precise, and suitable for the quantitative determination of (R)-enantiomer in the bulk drug pharmaceutical substance [56].

A simple and rapid, method for a sensitive HPLC method for employing dual-channel colorimetric detection for the determination of repaglinide in human plasma is presented. The method was assayed by involving the extraction of repaglinide by ethyl acetate and its isocratic reversed-phase liquid chromatography with dual-channel colorimetric detection. The mobile phase solution composition was 50 mm disodium hydrogen phosphate/acetonitrile (60:40, v/v), PH of the mobile phase 7.5 set up with phosphoric acid. A total analysis, the first cell working potential was found to be +380 mV, second was to be +750 mV (vs. Pd/H 2). It was confirmed that the method is suitable for pharmacokinetic studies or therapeutic study monitoring [57].

Stability-indicating studies of drugs are recognized as an essential part of the drug development method process. This rational study is used to, to understand the intrinsic stability indicating of the drugs and for the development of selective stability-indicating assay method was according to the ICH guidelines. As the stability stress studies of repaglinide have not been reported in the survey of literature review, the forced degradation product of repaglinide is generally carried out as per ICH guidelines, results in the formation of six pharmaceutical degradation products which have been characterized using LC-MS/MS in single and or combination with accurate mass measurements [58].

A method highly, sensitive and selective 3D excitation-emission of an accurate fluorescence technique was proposed to rapidly quantify the combined antidiabetics drug of repaglinide and irbesartan, and its application to PK study in rat and human plasmas with the Aid of second-order calibration curve method depending on alternating trilinear decomposition (ATLD) method. The enhanced excitation-emission of matrix fluorescence light of repaglinide and irbesartan can be accurately solved and can simultaneously attain the optimal concentration level in the presence of a potentially strong intrinsic fluorescence from complexes biological matrices, such as human plasma and Rat, using the ATLD method was used, the results can be shown in a developed method and to maintain a second-order advantage in simultaneous determinations of the weak fluorescent analyses of interest in various biological plasma matrices study [59].

The antidiabetes mellitus and osteoarthritis both are highly exceptional diseases, combinations of anti-diabetic agents like repaglinide, and nonsteroidal anti-inflammatory drugs, like celecoxib which is commonly used in the treatment of clinical practice. In this study, a simple and sensitive bioanalytical HPLC method combined with a fluorescence detector (HPLC-FL) was developed and completely validated for the simultaneous quantification of repaglinide and celecoxib. A simple proteins precipitation procedure and reversed

C18 column with an isocratic mobile phase solution (a mixture of ACN and PH 6.0 phosphate buffer).and stability-indicating for this method was determined and validated as per the current FDA guidelines. The bioanalytical method was applied to the study of pharmacokinetic interactions between repaglinide and Celecoxib *in vivo* study. Furthermore, an *in vitro* metabolism and protein binding study using human [plasma/urine]materials highlighted the possibility of metabolism-based interactions between Celecoxib and repaglinide in a study of clinical settings [60].

A rapid method of stability-indicating thin-layer chromatography method was developed by a quantitative analytical determination of repaglinide in pharmaceutical tablets dosages. Moreover, the method was performed on RP-8 TLC plates with acetonitrile-PH 6.0 phosphate buffer solution, 60 + 40% (v/v), as a mobile phase. The analytical method presented was found to be simple, reliable, accurate, and convenient for routine pharmaceutical analytical acceptance criteria established for TLC methods analytical performance fulfilled in the official literature [61].

For the point-of-care testing of the illegal fortification of repaglinide (Rep) in natural dietary supplements, a competitive chemiluminescent immunoassay (CLIA) was established, using horseradish peroxidase (HRP)-luminol-H<sub>2</sub>O<sub>2</sub> system for signal amplification. Polyclonal antibodies for repaglinide were produced various immunizations technique. The method provided a result consistent with those from HPLC, and the proposed method could be used for rapid screening of repaglinide in natural dietary supplements and detecting repaglinide in serum after administration [62].

A method for the separation of six selected anti-hyper glycemc (antidiabetic) drugs (Repaglinide, tolbutamide, gliclazide, glimepiride, glibenclamide, and glipizide) was developed with the use of micellar electrokinetic chromatography. Any Two non-ionic polys (ethylene glycol) are based on surfactants Triton X-114 (reduced) and Genapol X-080 was studies are neutral pseudo stationary phases. Pseudo stationary phase is obtaining by negative charges of separated anti-diabetic drugs and non-ionic surfactants were employed for selectivity was altered [63].

Electrochemical method of Repaglinide is described at a mercury electrode has been investigated using DC, DPP, and CV of Repaglinide Is exhibit. And well-defined as irreversible oxidation peaks over by the DPP was used to determine Repaglinide in pure form. The proposed method was exactly applied to the analysis of repaglinide in pure and pharmaceutical dosage forms with an average recovery of 98.8–103.2%. The results obtained agree good with the contents stated on the labels [64].

The sum of unknown impurities profiles of Repaglinide bulk drug product are detected by a simple isocratic method is reversed-phase high-performance liquid chromatography method. The impurities are isolated from the natural crude drug of repaglinide using an RP-HPLC method. Based on the spectroscopic data of IR, NMR, and MS the structures of these impurities I, II, and IV and bi-product (III) were characterized as 4-carboxymethyl-2-ethoxy-benzoic acid (I), 4-cyclohexyl amino carbamoyl methyl-2-ethoxy-benzoic acid (II), 1-cyclohexyl-3-[3-methyl-1-(2-piperidine-1-yl-phenyl)-butyl]-urea (IV), and 1,3-dicyclohexyl urea (III), respectively [65].

#### DIAGNOSIS

Diagnosis of antidiabetes can be by determining the method of blood glucose level. In fasting conditions, the blood glucose level could be >6.7 mmol/L or random glucose levels will be more than 10 mmol/considered as diabetes. If there occur any doubts in the diagnosis, glucose tolerance test must be conducted to measure the glucose level in blood. Before the test, the patient needs to be on fast at least 10–12 h. During the test, the patient is advised to take 75 mg glucose orally the test will be repeated after 2 h. Thus, from the results

observed can be determined by the glucose tolerance of the patient. In this diagnosis and therapy process, glucose levels can be determined using various pharmaceutical analytical methods.

#### UV SPECTROSCOPY

A blood glucose level can be determined by blood with a comparison of the UV spectrum of normal serum and antidiabetic blood serum. The antidiabetes mellitus leads to be changed in the condition of metabolism of fats acids, carbohydrates, lipids, and proteins. Moreover, the blood sample solution is usually collected from normal peoples and diabetic people the serum is separated by centrifugation of the blood samples solutions. The separated serum will further be diluted with de-ionized water and absorbance of the spectrum will be analyses [66].

#### LC-MS AND GC-MS

An analysis method of a 20 mL of the antecubital venous blood sample was collected and processed at 80°C for 6 h to take a serum sample can stand overnight at 4°C to achieve metabolic profiling. These samples are diluted to get 30 g/ml. The samples were mixed with internal standard and centrifuged for 10 min. The supernatant is used to metabolite profiling using GC-MS or LC-MS method. In the presence of amino acids such as a tryptophan leucine, isoleucine, and valine, free fatty acids such as a palmitic acid and stearic acid and glycerophosphatidylinositol confirms the occurrence of the diabetic patient condition [67].

Recent times HbA1c, the glycated hemoglobin was considered, as an important marker for the diagnosis of antidiabetes. Usually, HbA1c analytical methods are generally used, but based on differences in charge or structure. The different analytical techniques are included ion-exchange chromatography, CE, affinity chromatography, ELISA, and immune assay. Other analytical techniques methods are included in immune turbidimetry and ion-exchange HPLC. Among these methods, HbA1c measured by an HPLC is significantly greater than compared to other immune turbidimetry methods [68].

The assay method of a urine sample, fatty acid profiles were established and based on the ultra-performance liquid chromatography quadrupole time of flight mass spectrometer, in this way, 19 fatty acids are added, and two pairs of hard-resolved isomers are easily separated, applied in metabolomics research of diabetes mellitus. 13 min, Q-TOF mass spectrometer reduced the matrix interference of urine samples by the high resolution of exact molecular weights. 93 cases of urine samples are analyzed. This work is complementary to the clinical diagnosis of diabetes mellitus patients; additionally, non-invasive testing of urine samples made it more convenient for examination while decreasing the patient's pain and improving their patient living conditions [69].

#### CONCLUSION

This review geared toward specializing in numerous analytical strategies according for the assay of repaglinide. A broad vary of techniques is out there for the estimation of repaglinide and [type-II antidiabetics drugs] in biological samples, and pharmaceutical indefinite quantity type. The analysis of revealed information unconcealed that chemical analysis strategies are the straightforward and economical strategies for estimation of repaglinide in pharmaceutical formulation. For analysis of repaglinide, and type-II antidiabetic medicine, HPLC-UV provides correct results and low price compared to advance detection techniques. HPLC with personal organizer detection was extensively used for the event of stability-indicating assay strategies for separation and quantification of repaglinide within the presence of degradation product. This survey conjointly highlights the combined techniques that incorporate the economical separation of metabolites of repaglinide victimization HPLC with sensitive MS detection has become an imperative tool for quantification of repaglinide in biological fluids and pharmacokinetic studies. In comparison with activity strategies and its application of

capillary dielectrolysis and diagnosing being thought-about as an alternate technique for separation of repaglinide. This review includes the entire detail of analytical strategies obtainable on repaglinide which can be substantiative for any analysis on the drug.

#### AUTHORS' CONTRIBUTIONS

All authors have donated equally to prepare this review paper. The final editing of the manuscript was carried out by Badikela Ramakrishna. The final version of the paper was approved by all main authors.

#### CONFLICTS OF INTEREST

All the authors declared that they have no conflicts of interest.

#### AUTHORS' FUNDING

Nil/Self.

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