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Exploring Methods for the Detection and Analysis of Antidiabetic Drugs in Pharmaceutical Formulations

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ABSTRACT
Analytical methods are employed for determining the chemical or physical properties of an analyte, chemical substance, chemical element, or mixture. Various analytical techniques are employed in the pharmaceutical industry to estimate the qualitative and quantitative concentration of drugs in biological fluids, including human plasma, serum, urine, as well as in their formulations, including tablets, capsules, and bulk drugs. (1) The objective of this analysis is to present an overview of the current analytical methods for the analysis of Peroxisome proliferator activated (PPAR) agonist as well as Dipeptidyl peptidase-4 (DPP4) inhibitor. The review is based on the estimation of Sitagliptin, Saxagliptin, Alogliptin, Gemifibrozil, Troglitazone, Pioglitazone, Linagliptin, and Rosiglitazone in active pharmaceutical ingredients, biological fluids, as well as various formulations, as reported in a variety of research articles. The analytical techniques that are employed to estimate these drugs include RP-HPLC, HPTLC, UPLC-MS/MS, LC-MS/MS, MALDI-TOF mass spectrometry, Raman spectroscopy, Liquid chromatography, Tandem mass spectrometry, TLC-densitometry with fluorescent detector, and LC-ESI-MS-MS (2). In this paper, UV Spectroscopy, HPLC, and HPTLC methods were studied. By referring to tabulated extensive conditions, the review assists in the appropriate selection of analytical technique, mobile phase, column, and detector based on the available analytical instruments and chemicals. Hypoglycemia, weight loss, and type 2 diabetes are all treated with DPP4 inhibitors. PPAR agonists are also employed in the treatment of type 2 diabetes, with the primary objective of reducing triglycerides as well as blood sugar levels in metabolic syndrome. (3)

Keywords: *Analytical techniques, Biological fluids, DPP4 inhibitor, PPAR agonist, Diabetes.*

1. INTRODUCTION

Diabetes mellitus is a prevalent chronic metabolic disorder defined by abnormal blood glucose levels, either due to insulin resistance or insufficient insulin secretion. As the global incidence of diabetes continues to rise, the demand for effective antidiabetic drugs has increased, alongside the need for reliable analytical methods to monitor their efficacy, safety, and quality. Antidiabetic drugs, including oral hypoglycemics such as sulfonylureas, biguanides, thiazolidinediones, and DPP-4 inhibitors, as well as injectable medications like insulin and GLP-1 receptor agonists, are commonly prescribed to manage blood glucose levels in diabetic patients (4). To ensure their therapeutic success, rigorous analysis is essential not only for quality control during drug manufacturing but also for pharmacokinetic studies, therapeutic drug monitoring, and pharmacovigilance. Analytical techniques play a crucial role in the pharmaceutical industry and clinical settings, as they provide valuable data for the quantification, identification, and purity assessment of these drugs. In the past few decades, significant advancements in analytical techniques have been made, leading to more precise, accurate, and efficient methods for antidiabetic drug analysis (5). These methods range from traditional approaches such as chromatography and spectroscopy to modern innovations like biosensors and HPLC. This analysis aims to provide an overview of the various analytical methods used for the analysis of antidiabetic drugs, highlighting their advantages, limitations, and application areas. By examining key methodologies such as HPLC, UV spectrophotometry, and HPTLC, this paper seeks to emphasize the importance of robust analytical methods in ensuring the safety, efficacy, and quality of antidiabetic therapies. Furthermore, the article discusses the evolving landscape of analytical research, addressing emerging trends such as microfluidics, nanotechnology, and point-of-care diagnostic tools that promise to revolutionize the way antidiabetic drugs are analyzed and monitored in clinical practice (6).

2. ANALYTICAL METHODS

A) High-Performance Liquid Chromatography (HPLC):

Because of high specificity, sensitivity as well as versatility, HPLC remains the gold standard for quantifying antidiabetic drugs. Reverse-phase HPLC with UV or fluorescence detection is often used for biguanides, sulfonylureas, and thiazolidinedione.

1. Instrumentation and Modes:

HPLC analysis typically involves a detector, pump, column, injector as well as data processing system. For antidiabetic drugs, the most commonly employed modes are:

- **Reverse-Phase HPLC (RP-HPLC):** Dominantly used due to its efficiency in separating compounds based on hydrophobic interactions.
- **Ion-Exchange HPLC:** Suitable for polar drugs like metformin.
- **Chiral HPLC:** Used to analyze enantiomeric purity, especially in drugs like pioglitazone.

2. Mobile Phase Selection:

Choosing of the mobile phase is critical for achieving optimal resolution. Combinations of water(H_2O), methanol(CH_3OH), and acetonitrile(C_2H_3N), often buffered with agents like phosphate(PO_4^{3-}) or acetate($C_2H_3O^{2-}$), are commonly used. Gradient elution is frequently employed for complex mixtures.

3. Columns and Detectors:

- **Columns:** C18 columns are the most commonly used due to their stability and broad applicability.
- **Detectors:** UV-Visible detectors are typical, although fluorescence and mass spectrometric detectors are gaining popularity for their sensitivity and specificity.

HPLC Applications for Specific Drug Classes:

Biguanides (e.g., Metformin):

- **Sample Preparation:** Protein precipitation/solid-phase extraction (SPE) is frequently employed for biological matrices.
- **Method Parameters:** Analysis is typically performed using RP-HPLC with a UV detector at wavelengths around 230 nm.
- **Challenges:** High polarity requires careful mobile phase optimization.

Sulfonylureas (e.g., Glimepiride, Glibenclamide):

- **Mobile Phase:** Acetonitrile-water mixtures buffered at acidic pH.
- **Key Insights:** Stability studies often utilize HPLC to detect degradation products.

DPP-4 Inhibitors (e.g., Sitagliptin):

- **Advanced Techniques:** Coupling with LC-MS/MS enhances sensitivity for pharmacokinetic studies.
- **Mobile Phase:** Acidified acetonitrile and water mixtures.

SGLT2 Inhibitors (e.g., Empagliflozin, Dapagliflozin) :

- **Focus:** HPLC methods are used for both assay and impurity profiling.
- **Detector Options:** Fluorescence detection provides enhanced sensitivity for these compounds.

Insulin and Insulin Analogs:

- **Techniques:** Size-exclusion HPLC and reversed-phase methods are frequently used.
- **Challenges:** Stability and aggregation studies require specific column chemistries.

Advantages of HPLC in Antidiabetic Drug Analysis:

1. **Versatility:** Suitable for a broad range of drugs and matrices.
2. **Sensitivity:** Allows for detection at low concentration levels.
3. **Specificity:** Enables separation of closely related compounds, including enantiomers and metabolites (7-10).

B) UV-Visible Spectroscopy:

In the literature, spectrometry is mentioned in conjunction with chemical analysis for the analysis of repaglinide. Ten of these techniques are used in calculating repaglinide alone, while the other technique is employed to quantify repaglinide in conjunction with other medications. The most comprehensive report of chemical analysis methods that indicate the fundamental solvent (λmax) and limit of detection (LOD). This method is widely used due to its simplicity, cost-effectiveness, and rapidity. It is particularly useful for drugs like metformin and sulfonylureas, which exhibit characteristic absorption maxima in the UV-visible range. However, its lack of specificity often necessitates complementary techniques.

1. Principle of UV Spectroscopy in Antidiabetic Drug Analysis:

UV spectroscopy measures the absorption of UV light by a drug molecule at specific wavelengths, which corresponds to the electronic transitions in its structure. Most antidiabetic drugs exhibit characteristic absorption maxima (λmax) in the UV range, making them suitable for this technique.

2. Advantages of UV Spectroscopy:

- **Cost-Effective and Accessible:** Minimal instrumentation and reagents are required compared to other sophisticated methods like HPLC or LC-MS.
- **Rapid Analysis:** Suitable for routine quality control and high-throughput screening.
- **Non-Destructive:** Leaves the sample intact for further analysis.

3. Applications

- **Quantification in Pharmaceuticals:** UV spectroscopy is widely used to assay the active pharmaceutical ingredient (API) content in tablets, capsules, and other formulations.
    - Example: Metformin hydrochloride exhibits λmax around 233 nm, allowing its rapid quantification.
- **Drug Stability Studies:** Stability of antidiabetic drugs under various conditions (e.g., pH, temperature, and UV exposure) can be assessed by monitoring changes in absorption spectra.
- **Dissolution Testing:** Determination of drug release profiles during dissolution studies is a routine application.

4. Common Techniques:

- **Derivative Spectroscopy:** Enhances sensitivity and specificity by minimizing baseline noise and overlapping peaks.
- **Simultaneous Estimation:** Used in multi-drug formulations. For instance, glimepiride and metformin can be simultaneously estimated using multi-wavelength methods.
- **Validation of Methods:** Analytical methods have been evaluated by ICH guidelines, which assess parameters such as precision, accuracy, linearity, as well as detection limits (11-12).

C) Ultra-Performance Liquid Chromatography (UPLC):

UPLC is an advanced form of HPLC, employing smaller particle sizes (less than 2 µm) for the stationary phase. This allows for higher efficiency, shorter run times, and better resolution compared to traditional HPLC. The method is particularly suitable for complex matrices and low-concentration analytes, making it ideal for the analysis of antidiabetic drugs.

Applications in Antidiabetic Drug Analysis:

UPLC has been extensively employed to analyze a variety of antidiabetic drug classes, such as:

1. **Biguanides (e.g., Metformin):** UPLC methods offer excellent sensitivity and specificity for metformin, with minimal sample preparation. Studies report rapid retention times and the ability to separate impurities effectively.
2. **Sulfonylureas (e.g., Glibenclamide):** UPLC enables precise quantification of sulfonylureas in combination with other antidiabetic agents in fixed-dose formulations.
3. **Thiazolidinediones (e.g., Pioglitazone):** UPLC has proven efficient in separating pioglitazone and its metabolites in plasma, aiding pharmacokinetic studies.
4. **DPP-4 Inhibitors (e.g., Sitagliptin):** The high resolution of UPLC is ideal for separating sitagliptin from its degradation products, ensuring accurate stability assessments.
5. **SGLT2 Inhibitors (e.g., Empagliflozin):** UPLC has been employed for quantifying SGLT2 inhibitors in combination therapies, providing rapid and reproducible results.

Advantages of UPLC in Antidiabetic Drug Analysis:

- **Enhanced Resolution:** Smaller particle sizes allow better separation of closely related compounds.
- **Speed:** UPLC reduces analysis time significantly compared to HPLC, enabling high-throughput workflows.
- **Sensitivity:** It offers lower limits of quantification (LOQ) and detection (LOD), critical for trace-level analysis.
- **Robustness:** UPLC is highly reproducible, ensuring consistent results across runs.
- **Green Chemistry:** Reduced solvent consumption aligns with eco-friendly practices (13).

D)LC-MS/MS:

The integration of tandem mass spectrometry (MS) and liquid chromatography (LC) has revolutionized drug analysis, enabling highly sensitive and specific quantification in complex biological matrices. It is commonly used for pharmacokinetic and bioequivalence studies. LC-MS/MS integrates LC for separation and MS for detection, offering high precision and accuracy. Its advantages include:

- High sensitivity, suitable for trace-level quantification.
- Capability for multiplexing, allowing simultaneous analysis of multiple drugs.
- Robust performance in handling complex biological samples like plasma, serum, or urine.

Applications in antidiabetic drug analysis include quantifying metformin, glimepiride, sitagliptin, and newer agents like SGLT2 inhibitors (e.g., empagliflozin, dapagliflozin).

2. Sample Preparation Techniques:

Efficient sample preparation is critical to minimize matrix effects and improve analyte recovery. Common techniques include:

- **Protein Precipitation (PPT):** Simple and cost-effective for removing proteins.
- **Liquid-Liquid Extraction (LLE):** Provides cleaner extracts, enhancing sensitivity.
- **Solid-Phase Extraction (SPE):** Offers high purification but is time-intensive.

3. Chromatographic Methods:

The choice of chromatographic conditions influences the resolution and analysis time.

- **Columns:** C18 and phenyl-hexyl columns are commonly used due to their versatility in separating polar and non-polar compounds.
- **Mobile Phases:** Mixtures of water with modifiers including formic acid, ammonium acetate($C_2H_7NO_2$), and organic solvents (e.g., acetonitrile, methanol) are optimized for improved peak shapes and ionization efficiency.
- **Gradient Elution:** Often employed to handle complex mixtures and achieve better resolution.

4. Mass Spectrometric Detection:

- **Ionization Techniques:** Electrospray ionization (ESI) is the most widely used method due to its effectiveness for polar antidiabetic drugs.
- **Multiple Reaction Monitoring (MRM):** The preferred mode in LC-MS/MS for its specificity and sensitivity.
- **Matrix Effects:** Addressed through the use of isotopically labeled internal standards to correct for variability.

5. Recent Advances:

- **Microfluidic LC-MS/MS:** Enhances sensitivity and reduces sample consumption.
- **High-Resolution Mass Spectrometry (HRMS):** Provides structural insights into drug metabolites and impurities.
- **Green Analytical Chemistry Approaches:** Focus on eco-friendly methods with reduced solvent use.

6. Applications in Pharmacokinetics and Clinical Studies:

LC-MS/MS has been pivotal in studies assessing the absorption, distribution, metabolism, and excretion (ADME) profiles of antidiabetic drugs. These methods support the development of bioequivalent formulations and assess drug-drug interactions in poly pharmacy (14).

Table 1: Quantitative Applications by HPLC/UPLC Method:

Drug	Method	Specification	Mobile phase	retention times	Reference
Glimepiride	HPLC	LiChrosorb C18column (125 x 4 mm, particle size 5µm)	C_2H_3N: H_2O: glacial acetic acid in ratio (550:450:0.6).	7 minutes.	15
Rosiglitazone and Glimepiride	"HPLC	150mm×4.6mm i.d., 5µm particle size Symmetry® C18 column.	TheC_2H_3N: (60) and buffer of 0.02M PO_4^{3-} (40) (at pH=5, V/V) mixture, at a flow rate of 1mL/min is pumped	GLM (tR = 4.66min. nicardipine (tR,6.37min).	16
Metformin and Glipizide, Gliclazide, Glibenclamide	HPLC	C18 Supelco analytical column(250 mm×4.6 mm, 5; Sigma, Poole, England). The guard column was a Supelco Discovery (20 mm×4 mm,5;	Sodium dodecyl sulfate (37.5%) and potassium dihydrogenphosphate (62.5%) in C_2H_3N: (2 mM) (from 0.02 M)	For M was 4.7 min, P12.5min, Gm 8.4 min, and Gb 6.2"min.	17
Rosiglitazone Maleate	"HPLC	(250×4.6- mm, 5µm) column. The flow rate was adjusted to 1mL/min.	A mixture(v/v) of 50:50 of C_2H_3N: and buffer.	30mins	18
Metformin Hydrochloride and 1-cyanoguanidine	HPLC	Nova-Pak silica (4µg), (150 mm length, 3.9 mm inner diameter)	1.0 mL min^{-1}flow rate: injection, Ammonium dihydrogen phosphate buffer and CH_3OH(21:79, v/v) as mobile phase.	0.36 for 1-Cyanoguanidine 1.00 for Metformin Hydrochloride	19
Rosiglitazone maleate and Metformin Hydrochloride	HPLC	(4.6mm i.d. $ 250mm, 5lm particle; Phenomenex, TX, USA), with a guard column (4mm $3mm i.d.; Phenomenex)	30:70, v/v, Acetonitrile-o-nitric acid (pH=3) at 1.0mlmin^{-1} flow rate.	-	20
Glipizide	HPLC	C18 column (250,4.5mm id)	A and B consist of CH_3OH(60+40, v/v) and (20+80, v/v), respectively, with a 0.5mL/min of flow rate.	Below 4 % and calculated amount is above 1.65% of" drug.	21
Rosiglitazone and Glimepiride	"HPLC	150mm×4.6 mm i.d.,5µm particle size Symmetry® C18 column.	A 60:40 (V/V) mixture of C_2H_3N: and 0.02 M PO_4^{3-} buffer of pH 5 was pumped at a flow rate of 1 mL/min.	GLM (tR=4.66 min.),ROS(tR=3. 7 min),	22

Glibenclamide	RP-HPLC	Gemini C18 reversed phase column (Phenomenex, Torrance, USA)150×4.6mm i.d., 5µmdimensions	At 1 ml min^{-1} flow rate was set and the mixture was composed of C_2H_3N: CH_3OH, 0.05% triethylamine (pH-3.5, adjusted with orthophosphoric acid).	"5.5 and 5.5 min for GBM for 100 and 120%	23
Sitagliptin Phosphate Monohydrate and Metformin Hydrochloride	UPLC	BEH C8100 x2.1mm,1.7µm, column	In a gradient program", C_2H_3N: is employed as an organic solvent. 0.2mLmin^{-1} was the flow rate.	Around 2.2min	24
Tolbutamide	RP-HPLC	C18 column (250mm×4.6 mm×5µ particle size)	CH_3OH: 0.1% Mobile phase: Orthophosphoric acid: C_2H_3N (10:30:60)	4.60" min	25
Metformin , Glimepiride ,Pioglitazone	"RP-HPLC	C18 column (100×4.6mm×5 µ)	At a flow rate of 1.0 ml/min, CH3OH, and PO_4^{3-} buffer (p11 adjusted with ortho phosphoric acid) were combined in a 75:25v/vratio.	Metformin, Pioglitazone, and Glimepiride were found to be 2.717, 5.801, and 9.968.	26
Metformin Hydrochloride and Glyburide	HPLC	C8 column (250×4.6mm i.d.,5µm particle size)	A 0.1M$C_2H_7NO_2$(pH 5.0) and CH_3OH(23:77, v/v) mixture was administered at a flow rate of 0.7mLmin^{-1}.	About 4.2, 6.8 and 10.6 min for MET, GLY, and BCM"	27
Metformin and Glibenclamide	RP-HPLC	C18 Column (150mmx4.6mm,5µm)	C_2H_3N:CH_3OHmixture: H_2Oin a 30:60:10 (v/v) ratio, with a flow rate of 1.0ml/min	Metformin and Glibenclamide had retention times of 3.17 and 8.10 minutes, respectively.	28
Pioglitazone	HPLC	Zorbax Bonus RP18 column (150mm× 4.6mm, 3.5µm).	$C_2H_7NO_2$(pH 4.0) at a concentration of 0.005M.	7.2 min.	29
Metformin and Sitagliptin	"LC-MS-MS	Column with a particle size of 5mm, Biobasic SCX 50 4.6mm	$C_2H_7NO_2$(pH 4.5+0.2): C_2H_3N: (50:50, v/v): 20mM used at a flow rate of 1.0mL/min	Metformin D6 was 2.38min. sitagliptin and Sitagliptin D4 were1.37.	30
Sitagliptin	HPLC	C18 ODS Hypersil column with a 150×4.6 mm id and a 5µm particle size.	At a flow rate of 1.0mL/min, C_2H_3N: and 0.01N" potassium dihydrogen phosphate are utilized in a 70:30 atio.	5.6min.	31
Sitagliptin	HPLC	C18column (36mm in length,4.6mm in internal	The flow rate was set at 1 mL/min, and the pH of the $CH_3OH$and 2M$C_2H_7NO_2$buffer was	0.509min	32

		diameter, and 4µm particle size)	adjusted to 4.5 using acetic acid.		
Dapagliflozin and Saxagliptin	RP-HPLC	C8 column (50×4.6mm, 5µ)	Potassium dihydrogen Phosphate: C_2H_3N in a ratio of 55:45 at a flow rate of 1 ml/min.	Dapagliflozin: 0.5 Saxagliptin: 0.5	33
Semaglutide	RP-UPLC	C18 (50mm x 1.6mm) 1.8mcolumn	50:50 v/v, 0.01N potassium dihydrogen phosphate (3.2 pH): C_2H_3N.0.4ml/min was the flow rate that was maintained.	1.026min	34
Vildagliptin and Metformin Hcl	RP-HPLC	"Xterra C18 column (250 mmL×4.6mm I.D×5µ)	The mobile phase consisting of C_2H_3N, phosphate buffer (pH 6.0), and H_2O(65: 20: 15v/v/v) was used at a flow rate of 1.0ml/min.	Vildagliptin : 2.28min Metformin : 4.27min	35
Metformin	RP-HPLC	C18 column [4.6x250mm,5µm particle size]	The mobile phase was composed of PO_4^{3-} buffer with a pH of 3.0 and CH_3OH, with varying ratios and flow rates. Ultimately, a flow rate of 1 mL/min was established for the 30:70 v/v PO_4^{3-} buffer with a pH of 3.0and CH_3OH.	4.2min	36
Pioglitazone Hydrochloride	RP-HPLC	Phenomenex Luna C18 column (250x4.6mm, 5µm)	A 75:25 mixture of $CH_3OH$and $H_2O$with a flow rate of 1 ml/min.	3.28mins.	37
Sitagliptin	RP-HPLC	C18, 5µm, 15cmx 4.6mm i.d. column	(0.05 mM) C_2H_3N (30:70) (pH-2.8) PO_4^{3-} buffer at a flow rate of 1.0 ml/min.	3.687min"	38
Metformin Hydrochloride	"RP-HPLC	C18,25cmx4.6 mmx5µm column	pH was adjusted to 5.75 with 85 v/v by adding 65% C_2H_3N and 35% PO_4^{3-} buffer. Orthophosphoric acid was employed at a flow rate of 1.0 ml/min.	4.2 min	39
Metformin and Sitagliptin	HPLC	C18column.	The concentration of C_2H_3N and acetate buffer (pH=5) was 35:45 v/v, with a flow rate of 1 ml/min.	Metformin:1.893 min and Sitagliptin:4.851 min"	40
Detemir	"HPLC	C4 column (5µm,250× 4.6mm),	50mM PO_4^{3-} buffer pH 2.7, C_2H_3N, sodium sulfate(0.02 g ml^{-1}), and triethylamine (62:37:1)	7 and 6 min	41

			were administered isocratically at a flow rate of 1.5 ml min^{-1}.		
Glimepiride	RP-HPLC	C18 column 150×4.6mm, with 5µm	Dissolving 0.5gram of monobasic sodium phosphate in 500 mL of distilled H_2O, the pH of the solution was adjusted to 2.1 to 2.7 with 10% phosphoric acid, and added 500 mL of C_2H_3N. At a flow rate of 1mL/min.	9.30 minutes"	42
Pioglitazone	HPLC–MS/MS	C18 column (2.6µm particle size, 50×2.1mm	A solution of formic acid 0.1% in H_2O and a solution of formic acid 0.1% in C_2H_3N (B) was the following (t(min), %B): (0, 10), (4, 74), (4.5, 90), (6, 90), (6.1, 10), (10, 10)	3 min	43
Ertugliflozin	RP-HPLC	C18 Hypersil ODS Column (250mmx4.mm ,5µm)	Acetate buffer and C_2H_3N 60:40 (v/v).	2.30±0.04min	44
Glibenclamide, "Liraglutide, Nateglinide, Sitagliptin, Tolbutamide	Uplc and Hplc	C18,300 Å, 1.7µm,2.1×150 mmColumn	0.3% formic acid in $H_2O$and C_2H_3N: CH_3OH(50:50) at a flow rate of 0.3mL/min.	4.77min	45
Empagliflozin and Linagliptin	HPLC	C18(100 X 2.1mm id) column	CH_3OH and H_2Oin the ratio of 60:40 eluted at a flow rate of 0.5ml/min.	1.320and 2.343mins"	46
Imeglimin "Hydrochloride	RP-UHPLC	(150x4.6 mm,3micron) column	At a flow rate of 1ml/min, the mixture of $H_2O$and C_2H_3N is maintained at a ratio of (15:85% v/v).	3.831min	47
Metformin and Linagliptin	RP-HPLC	Thermo, C18, 250cmx4.6mm, 5µm	Isocratic mode employed at a flow rate of 1.0 mL/min, with a ratio of KH2PO4 to $CH_3OH$of 65:35.	Metformin:3.132 min and Linagliptin 3.728 min".	48
pyrazosulfuron ethyl and pretilachlor	RP-HPLC	Agilent Eclipse XDB C-18 column (150 x 4.6mm; 3.5µm),	0.1 % (ortho phosphoric acid) with H_2O: C_2H_3N(30:70) at a column rate of flow 1.2mL per minute	4.58 minute, correspondingly with runtime of 7 min.	49
Empagliflozin and Linagliptin	RP-HPLC	Agilent C18 column (50µm, 4.6×250mm)	$CH_3OH$and 0.1% ortho phosphoric acid in H_2O(45:55, pH 2.5) at a 0.7mL/min flow rate	Empagliflozin :4.186 min and Linagliptin :6.532min	50
Glipizide	RP-HPLC	Hypersil ODS 18 column.	10 mM PO_4^{3-} buffer (pH, 3.5) and CH_3OH(25:75,	7.32 and 9.02min	51

			v/v) with a flow rate of 1mL/min.		
Imeglimin HCL	RP-HPLC	A Credchrom C18 column (250mmx4.6mm x5µm)	PO_4^{3-} Buffer and C_2H_3N(80:20, v/v).	2.5 minutes	52
Sitagliptin	HPLC	C18 BDS (150x4.5mm x5µ)	potassium dihydrogen phosphate (3.2 pH): C_2H_3Nin the ratio of 60:40 % v/v at a flow rate of 1mL/min.	2.70 mins	53
Saxagliptin	HPLC	Column: Kromasil C18 column (150 mm × 4.6 mm i.d., 5 µm)	PO_4^{3-} buffer (pH 4.5) : CH_3OH(65:35) Flow rate : 1.0 ml/min	1.0 mins	54
Repaglinide	HPLC, LC-MS	C18 column (100×4.6mm5µm), -C18 column,	C_2H_3N– 10 mmol L^{-1} ammonium ion acetate.	"7.5 min	55
Pioglitazone HCl and Glimepiride	RP-HPLC	C-18 bonded silica column (250 x4.6mm,5um, Phenomenex Inc.)	Potassium dihydrogen phosphate buffer (KH2PO4) at pH 3.4 and C2H3N in the ratio of 40:60 (v/v). The flow rate was at 0.8 min/min.	Pioglitazone : 4.5 ± 0.1 min and Glimepiride :10.0 ± 0.1 min"	56
Metformin Hydrochloride and Rosiglitazone	"RP-HPLC	C18 bonded silica column (ODS) (250 x4.6mm,5µ)	sodium dihydrogen phosphate (NaH2PO4) buffer (pH 3.5) and C_2H_3N(60:40, v/v) at a flow rate of 0.7 ml/min.	Metformin Hydrochloride : 3.35 min and Rosiglitazone: 11.95 min	57
Canagliflozin Hemihydrate	HPLC	C18 (100mmx4.6mm5µm) column	C_2H_3N: H_2Oph 2.5 adjusted with orthophosphoric acid, 50: 50 v/v, at a flow rate of 1.0mL/min.	2mins	58
Metformin, Voglibose, Glimepiride	RP-HPLC	Inertsil ODS 3V(150×4.mm, i.e. 5µm) column.	0.02 m PO_4^{3-} buffer was adjusted to pH 2.5 using dilute orthophosphoric acid (solvent A) and C_2H_3N(solvent B) and was delivered at a flow rate of 1 ml/min under gradient programming for 18 minutes.	Metformin : 2.423, Voglibose: 8.191, and Glimepiride :11.708"	59
Rosiglitazone	HPLC	"ODS column with porus silica 5µm	Dihydrogen phosphate orthophosphate buffer pH adjusts to 3.0 with dilute phosphoric acid, $C_2H_3N$and CH_3OH having a flow rate of 1.0ml/min.	5.75 min	60
Glitazones,	HPLC	C18	0.7 ml/min flow rate; 7, 9,	7, 9.8, and 21 mins	61

Gliptins, Gliflozins and Glinides	and LC-MS	(150x4.6mm, 5µm);	8, and 21 minutes; glacial acetic acid C_2H_3N-$C_2H_7NO_2$(1:25:25).		
pioglitazone	RP-HPLC	ODS C18 (150mm×4.6mm, 5µm) column	$C_2H_7NO_2$buffer with $C_2H_3N$and Glacial acetic acid in the ratio 50:50:1 (v/v) with flow rate of 0.7ml/min.	10.789 mins"	62
Metformin	RP-HPLC	Shimadzu shim-pack GIST C18 column with specification (5µm×4.6×250 mm).	70% buffer and 30% C_2H_3N. The buffer used for analysis is Tetra-Butyl Ammonium Hydroxide (0.002%), and the flow rate was maintained at 0.5ml/min.	3.5 min	63
Glibenclamide, Gliclazide, Glipizide, Pioglitazone, Repaglinide and Rosiglitazone	HPLC	ODS 3V column (4.6×250 mm,5µm)	0.01 m formic acid (pH 3.0), C_2H_3N, Milli Q $H_2O$and CH_3OH.	RGL: 11.4, PGL: 13.3, GLZ 14.8, GLC: 17.6, GLB: 20.78, IS: 22.1, RGL: 25.4 mins.	64
Metformin Phenformin), ('Pioglitazone, Rosiglitazone, Ciglitazone, Troglitazone), (Acarbose), (Vildagliptin, Sitagliptin, Alogliptin, Teneligliptin, Saxagliptin')	HPLC	Thermo C18 column (250 x4.6x5µparticle size), Grace vyadyec genesis CN (150×4.6mm, 4µm) column , C18column (300mm × 3.9mm,5µm, particle size)	Phase of mobility: CH_3OH-0.2% Heptane Sulphonate Sodium (70:30 V/V) and C_2H_3N: PO_4^{3-} buffer PO_4^{3-} buffer (Ph4.0), 70:30%v/v, pH-5.5: C_2H_3N: CH_3OH(30:60:10), C_2H_3N, and 0.01M di-potassium hydrogen PO_4^{3-} buffer in a 75:25 ratio, and pH 7.0 is adjusted with orthophosphoric acid. Flow rate: 1.0 ml/min	Repaglinide : 14.21min, Nateglinide : 4.47min , Metformin : 2.25min , Phenformin : 11.06min, Pioglitazone : 8.08min , Rosiglitazone : 6.5min , Troglitazone : 14.21min	65
Metformin	"RP-HPLC	C18 analytical reverse-phase column.	CH_3OH-H_2O(30:70 v/v), pumped at a flow rate of 0.5ml/min.	4.4min	66
Metformin and Dapagliflozin	HPTLC, RP-HPLC	5 micro-column isocratic flow (4.6 x 150mm, 5m). C18 column,	C_2H_3N(70:30, v/v) and orthophosphoric acid buffer were added to the mobile phase as the flow rate rose (0.1M). C_2H_3N: Triethylamine (pH-5.0) in the ratio of 50:50 v/v, flow rate of 1 mL/min.	Metformin: 2.097 minutes and Dapagliflozin: 3.691 minutes. 5.163 minutes"	67
Glimepiride	RP-HPLC	5-µm particle octadecyl silane (ODS) column (250 ×4.6mm)	C_2H_3N: 0.2 M PO_4^{3-} buffer (pH = 7.4) 40:60 v/v at a flow rate of 1 mL/min.	1.0min	68
Pioglitazone	"RP-HPLC	C18 column (300mm ×	C_2H_3N: PO_4^{3-} buffer, (50:50 v/v) as mobile	8.08mins	69

		3.9mm, 5µm, particle size)	phase at a flow rate of 1.00ml/min		
phenacetin, coumarin, tolbutamide, chlorzoxazone, testosterone	LC	C18 analytical column	$C_2H_3N$and 0.02% aqueous phosphoric acid.	3.791, 5.348, 6.244, 8.272, 9.094, Mins	70
Pioglitazone and Glimepiride	RP-HPLC	C18 (2) column of dimensions 250×4.6 mm, 5µ was used.	$CH_3OH$and H_2O	Glimepiride :4.34 min and Pioglitazone :5.19"	71
Metformin HCL and Sitagliptin	"RP-HPLC	Phenomenex Gemini C18 (250 × 4.6mm) 5µ column	Solvent a - Buffer Solvent b- $C_2H_3N$with Solvent Ratio: 55:45% V/V of A: B	Metformin HCL: 0.7 and Sitagliptin: 2.4min.	72
Glimepiride, Pioglitazone, and Metformin	RP-HPLC	Inertsil ODS-3V (250mm × 4.6mm, 5μm) column	C_2H_3N, tetrahydrofuran, and buffer at pH 5; the flow rate of 1.7mL/min.	Glimepiride: 5 minutes, Pioglitazone: 3.9 minutes and Metformin: 1.3minutes	73
pioglitazone and Teneligliptin	RP-HPLC	C18(4.8 x150mm,5µm)	The ratio of $CH_3OH$to 0.01N K2HPo4 was 55:45, with a flow rate of 0.9ml/min.	pioglitazone :2.320 min and Teneligliptin :3.256min"	74
Sitagliptin phosphate	"RP-HPLC	Zorbax Eclipse XDB C18 (150×4.6mm,5 µ)	0.01M KH2PO4: CH_3OHin a 50:50 % v/v ratio, with a pH of 2.5 that has been adjusted with 0.2% orthophosphoric acid. With a flow rate of 0.7ml/min.	1.43mins	75
Sitagliptin phosphate	RP-HPLC	Thermo scientific C18 column, (250x4.6 particle size of 5µ)	CH_3OHat a flow rate of 1 ml/min.	1.91min.	76
Sitagliptin	HPTLC	TLC aluminum plates precoated with silica gel 60F254	Ethyl acetate: CH_3OH: formic acid (8.5:1:0.5v/v/v)	0.50±0.04".	77

Table 2: Quantitative Applications by UV Spectrophotometric Method:

Drug	Method	Specifications	λmax	Reference
Saxagliptin hydrochloride and metformin hydrochloride	Uv	"The percentage recovery of Saxagliptin (API) was 100.10%, while Metformin (API) was 99.98%. In the concentration range of 50-90 µg/ml for Saxagliptin and 2-10 µg/ml for Metformin, Beer's laws" were adhered to.	Saxagliptin: 274nm and Metformin: 231nm.	78
Vildagliptin	Uv	The accuracy was found between 98–101%. Precision for intraday and interday was found to be 1.263 and 1.162 respectively	"210nm	79
Metformin Hydrochloride and 1-Cyanoguanidine	Uv	Linearity within the metformin hydrochloride concentration range of 0.01-0.03 mg mL^{-1}. The accuracy of the method is 100.4%. The percentage of duplicates is 0.30%.	232nm	80
Glibenclamide	Uv	Accuracy of developed 95-105%. The precision percent relative standard deviation (%RSD) was determined to" be<3%.	229.5nm	81
Saxagliptin hydrochloride and Metformin hydrochloride	Uv	The recovery percentages of Saxagliptin and Metformin were 100.1 and 99.98, respectively. Beer's laws were observed in the concentration range of 50-90 µg/ml for Saxagliptin and 2-10 µg/ml for Metformin.	Saxagliptin and Metformin were found to be 274 nm and 231nm.	82
Sitagliptine phosphate monohydrate	Derivative Spectroscopy	the precision of intra-day and inter-day is in the limit of ≤ 2%.	213nm	83
Sitagliptin	Uv	Linearity is range 10-60 µg/ml with a correlation coefficient value 0.998. The accuracy is 80%, 100%, and 120 %. The % recovery was found to be in the range 98.54%–99.98%	267nm	84
Dapagliflozin and Metformin Hydrochloride	"Uv	The standard deviation (S.D.), relative standard deviation (%R.S.D.), and standard error (S.E.) calculated are low, indicating a high degree of precision of the method. The %R.S.D. is less than 2% as required by USP and ICH guidelines.	225nm and 237nm	85
Saxagliptin hydrochloride and Metformin Hydrochloride	Uv	The percentage recovery of Saxagliptin (API) was 100.10%, while Metformin (API) was 99.98%. In the concentration range of 50-90 µg/ml for Saxagliptin and 2-10 µg/ml for Metformin, Beer's laws were adhered to.	Saxagliptin: 274nm and Metformin: 231nm.	86
Pioglitazone	Uv	The linearity range for pioglitazone hydrochloride was in the range of 10-	268nm"	87

Hydrochloride		50µg/ml with a correlation coefficient of 0.999. The precision was found to be less than 2.		
Semaglutide	Uv	The concentration range of 1-15µg/ml. The accuracy was found to be 99.8%-102% for method A and 98%-100.8% for method B.	293nm	88
Evogliptin Tartarate	Uv	The Calibration curves of Evogliptin tartrate show linearity over the concentration range from 10-100 µg/mL with a correlation coefficient (R2=0.992). The percent relative standard deviation<2.0%. Recovery (98.86-99.51) with a low percent relative error proved the accuracy of method.	267nm	89
Metformin and Remogliflozin	Uv	The range of 2.5-30µg/ml and 1 to 24 µg/ml for MET and REM correspondingly by all three methods. The mean% recovery was found to be in the range of 99.08% to 100.15% for MET and 98.73% to 100.27% for REM.	226.2nm	90
chlorpropamide	Uv	In Accuracy, the % RSD value was determined and found to be 2. In Precision the % RSD was found to be<2, LOD and LOQ has been determined to be 2.99g and 8.89g	580nm	91
Imeglimin Hydrochloride	Uv	Linearity in the range 1 to 16 µg/ml, Range is Lowest concentration to highest concentration is 1 µg/ml to 16 µg/ml, Ruggedness (Intermediate Precision) on different days (inter-day & intra-day) by different analysts (analyst 1 & analyst 2).	240nm	92
Glimepiride	“Uv	Linearity 5%, Accuracy 98.0 up to 102.0%, Precision<2%, Robustness 0.0009, LOD and LOQ values are respectively1.311and 4.371mgL^{-1}.	300nm.	93
Metformin	Uv	The intra-day and inter-day precision for MET were 1.312 and 0.093. The LOD is the lowest concentration of the analyte in ratio (1:3) is precision and accuracy with signal to noise ratio (1:10). The LOD of MET was 1.0 µg/mL & LOQ of MET was 3.0 µg/mL.	233nm	94
Canagliflozin	Uv	The LOD and LOQ were determined to be 0.084 mcg/ml and 0.255mcg/ml, respectively, within the concentration range of 5-10mcgmL^{-1}, as per Beer's law. A recovery of Canagliflozin in tablet formulation was observed within the 80.00-120.00% range.	290nm”	95

3. CONCLUSION

The evaluation of analytical methods for antidiabetic drugs reveals significant advancements and challenges in their development and application. A variety of techniques, including chromatographic, spectroscopic, electrochemical, and bioanalytical methods, have been employed to ensure the accurate quantification, quality control, and pharmacokinetic profiling of these drugs. HPLC, often coupled with Mass Spectrometry (MS), remains a gold standard due to its sensitivity, precision, and versatility. Emerging methods such as green analytical techniques and sensor-based approaches are gaining attention for their environmental friendliness and real-time monitoring capabilities. However, challenges such as complex sample matrices, the need for cost-effective methods, and ensuring compliance with regulatory requirements persist.

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