



A Critical Review of UV Spectrophotometry and HPLC Methods for the Quantitative Determination of Metformin Hydrochloride and Glimepiride

Ramakrishnan.M¹, Manoj V², Gokulamanikandan M³, Saravanan. V.S⁴, Prabhu.S^{*5}

^{1,2,3,4,*5}Department of Pharmaceutical Analysis, The Erode College of Pharmacy, Veppampalayam, Erode, Tamilnadu, India.

*Corresponding Author.

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Abstract: Metformin hydrochloride and glimepiride are frequently used in combination for the treatment of type 2 diabetes mellitus and are marketed as fixed dose combination formulations with drastically varying medication concentrations and physicochemical properties. These discrepancies cause difficulties in the development of appropriate analytical processes for the individual and simultaneous determination. The present study deals with the reported analytical methods for metformin hydrochloride and glimepiride in bulk medicines and pharmaceutical dosage forms with special emphasis on UV spectrophotometry and high performance liquid chromatography (HPLC). The UV methods evaluated were direct spectrophotometry, simultaneous equation methods, derivative spectrophotometry, absorbance ratio methods and chemometric approaches. The HPLC methods specifically reversed phase HPLC are discussed in terms of chromatographic separation detection validation performance and application stability indicating analysis. The methods have been compared on the basis of selectivity, sensitivity, linearity, accuracy, precision, robustness, analytical range and practical application. UV spectrophotometric methods are simple, rapid and generally inexpensive to use. HPLC offers improved separation and selectivity for complex mixtures, impurity testing and degradation investigations. The evaluation additionally underlines the demand of superior simultaneous procedures with greener analytical circumstances, systematic method optimization, chemometric strategies and strong stability indicating approaches. Generally, comparative assessment is useful for selection of adequate analytical methods and definition of the perspectives of further development of effective and reliable procedures for quality control of metformin hydrochloride and glimepiride.

Keywords: Metformin hydrochloride, Glimepiride, UV Spectrophotometry, RP-HPLC, Simultaneous determination, Chemometrics, Stability indicating methodologies, Analytical validation.

1. Introduction

Diabetes mellitus is a chronic metabolic disease and an important global health burden. It affects the way the body regulates and utilizes glucose and may arise from abnormalities in insulin production, insulin action, or both. Type 2 diabetes mellitus (T2D) is the commonest subtype of diabetes and involves a progressive insulin resistance with inadequate insulin secretion. The disease has long term complications such as cardiovascular disease, cognitive impairment, kidney failure and reduction in life expectancy. Therefore, effective pharmacotherapy is important to maintain glycemic control and reduce the risk of complications. As T2D involves multiple physiological abnormalities including elevated hepatic glucose production and

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reduced glucose utilization, combination therapy may be needed to achieve adequate glycemic control. Metformin hydrochloride (MET), 1,1-dimethylbiguanide hydrochloride, is a widely prescribed first line treatment for T2D, and is a member of the biguanide drug class. It reduces hepatic glucose production and increases insulin sensitivity to stimulate glucose uptake and utilization. Metformin does not directly stimulate insulin secretion and therefore is associated with a relatively low risk of hypoglycemia when used as monotherapy. Metformin hydrochloride is a white, crystalline, hygroscopic powder, which dissolves readily in water [1,2]. Glimepiride (GLM) is a third generation sulfonylurea drug used to lower blood glucose levels by stimulating insulin secretion. In comparison to metformin, glimepiride is dosed at a much lower dose and has limited aqueous solubility. These differences in dose, polarity, and solubility are important considerations in the development of analytical methods for their individual and simultaneous estimation [10-12].

2. Survey of Analytical Techniques

2.1 UV Spectrophotometric Analysis

UV spectrophotometric analysis is based on the Beer-Lambert law, according to which absorbance is related to the concentration of the absorbing substance and the optical path length. Quantitative analysis is commonly performed in the ultraviolet region, approximately 200–400 nm. The wavelength at which maximum absorbance occurs has been termed λ_{max} . The λ_{max} values of metformin hydrochloride are generally reported around 232–234 nm, although the wavelength used depends on the solvent and the analytical conditions used [1,2,6]. Zero-order UV spectrophotometry is simple when a single analyte can be measured without significant interference. However, in multicomponent formulations such as combinations of metformin hydrochloride and glimepiride, overlapping spectra may prevent direct measurement. Therefore, simultaneous-equation methods, derivative spectrophotometry, ratio methods and chemometric approaches have been investigated to improve the selectivity without the need for physical separation [33-35].

2.2 Vierordt's Simultaneous-Equation Method

Vierordt's method, also known as the method of simultaneous equations, involves determining the concentrations of two components by measuring their absorbances at two selected wavelengths and using the respective absorptivity coefficients. The method can be applied when the individual spectra and absorptivities of the components are sufficiently different at the selected wavelengths.

2.3 Derivative Spectrophotometry and Absorbance-Ratio Methods

Derivative spectrophotometry uses the first or higher derivatives of the normal absorption spectrum to improve spectral resolution and reduce the influence of baseline effects. The absorbance-ratio or Q-analysis approach uses an isoabsorptive point together with a selected λ_{max} to determine the components of a mixture. These approaches can be useful when the spectra of the components overlap substantially [11,26,35].

2.4 Reversed-Phase HPLC

Reversed-phase high-performance liquid chromatography (RP-HPLC) is a selective separation technique in which analytes are distributed differently between a nonpolar stationary phase and a relatively polar mobile phase. A C18 column is commonly used as the stationary phase, while mobile phases may contain methanol or acetonitrile together with an aqueous buffer. Because analytes have different affinities for the stationary and mobile phases, they elute at different rates. The time required for an analyte to elute from the column is termed its retention time (R_t). In RP-HPLC, the highly polar metformin generally exhibits weaker retention than the more hydrophobic glimepiride, making method development particularly important for simultaneous analysis [13,14,21]. HPLC is widely used in pharmaceutical analysis because of its specificity, accuracy, precision, and sensitivity. An important advantage is its ability to separate active pharmaceutical ingredients from excipients and degradation products, making it particularly valuable for stability-indicating analysis [24,29,31,32].

3. UV Techniques for the Estimation of Metformin Hydrochloride and Glimepiride

3.1 UV Methods for Metformin Hydrochloride

Metformin hydrochloride is highly polar and readily soluble in water. Its UV absorption characteristics have been used for direct spectrophotometric estimation in bulk drug and pharmaceutical dosage forms. Distilled water and methanol have been used as solvents in reported procedures [1,2,6,15]. Reported maximum absorption wavelengths for metformin hydrochloride in aqueous media are generally in the range of 232–234 nm. Examples include methods using water at 234 nm and 233 nm. Metformin has also been measured at approximately 233 nm in methanolic media, depending on the analytical conditions [1,2,6,15]. Besides direct zero-order measurement, colorimetric procedures have been described. In one approach, the primary amino groups of metformin react with ninhydrin under alkaline conditions to produce a violet-colored complex with maximum absorbance around 570 nm. This approach provides an alternative when a conventional UV method is not sufficiently sensitive or when simple colorimetric instrumentation is preferred [1,2,6,15].

Reported linear ranges vary according to the method and solvent and include approximately 10–50 mg/mL in distilled water, 8–13 $\mu\text{g/mL}$ in methanol, 1–16 $\mu\text{g/mL}$ in distilled water, and 8–18 $\mu\text{g/mL}$ for the ninhydrin-based color complex [1,2,6,15]. Validation studies generally reported recoveries of approximately 99–101% and precision values below 2% RSD. Reported LOD and LOQ values varied considerably with the analytical procedure, including approximately 1.0 and 3.0 $\mu\text{g/mL}$ in one procedure and 22.34 and 67.69 ng/mL, respectively, in a more sensitive method [1,2,6,15]. Forced-degradation

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observations reported for UV-based procedures indicated that metformin was comparatively stable under thermal and photolytic stress but showed greater degradation under acidic and alkaline conditions in the reported studies [1,2,6,15].

3.2 UV Methods for Glimepiride

Glimepiride is a third-generation sulfonylurea with limited aqueous solubility and a lower therapeutic dose than metformin. Therefore, UV methods for glimepiride often use organic solvents, derivative techniques or color-forming reactions to improve sensitivity and selectivity [10-12].

Direct UV measurement of glimepiride has been reported at approximately 249 nm in chloroform. Derivative spectrophotometry has also been applied to reduce interference from tablet excipients. A second-derivative procedure has been reported for glimepiride in sodium hydroxide, with analytical wavelengths selected according to the formulation and derivative response [10,11].

Ion-pair spectrophotometric procedures have also been described. Glimepiride has been reacted with acidic dyes such as cresol red and bromophenol blue to produce colored ion-pair complexes, measured at approximately 450 nm and 578 nm, respectively [10-12]. Reported linear ranges include approximately 5–30 µg/mL for chloroform-based direct measurement, 2–40 µg/mL for a second-derivative method in sodium hydroxide, 10–60 µg/mL for the cresol-red ion-pair method, and 2–20 µg/mL for the bromophenol-blue method [10-12]. Validation studies generally reported recoveries within approximately 98–102% and precision values below 2% RSD. Reported LOD values included approximately 0.4 µg/mL for direct UV measurement, 0.1179 µg/mL for the cresol-red ion-pair method, and 0.6173 µg/mL for the bromophenol-blue procedure [10-12].

3.3 UV Combination Methods for Metformin Hydrochloride and Glimepiride

The simultaneous UV determination of metformin hydrochloride and glimepiride is challenging because their spectra may overlap and their label claims can differ substantially, commonly from 500 mg of metformin to 2 mg of glimepiride. Several mathematical and multivariate approaches have therefore been explored [33-35].

Simultaneous-equation procedures have been reported using different solvents and wavelength combinations. Examples include measurements around 226 nm for glimepiride and 233 nm for metformin in phosphate buffer, measurements at 233 nm and 228.4 nm in acetonitrile, and measurements at 232 nm and 272 nm in aqueous media. The wavelengths are selected from the absorption characteristics of the individual drugs to establish equations using their absorptivity values [33,35].

Dual-wavelength, ratio and absorbance-ratio approaches have also been explored for multicomponent antidiabetic formulations. Chemometric techniques such as principal component regression (PCR), partial least-squares regression (PLSR), classical least squares (CLS) and inverse least squares (ILS) utilize information from the entire UV spectrum, instead of individual wavelengths. These methods are capable of resolving overlapping spectral responses and have been applied to combinations of metformin, glimepiride and other antidiabetic drugs [4,20,34]. The reported concentration ranges for combination procedures are around 5–10 µg/mL metformin and 3–18 µg/mL glimepiride in acetonitrile, 5–25 µg/mL metformin and 20–50 µg/mL glimepiride in aqueous media and around 2–10 µg/mL for chemometric analysis in methanol [33-35].

4. HPLC Methods for Metformin Hydrochloride and Glimepiride

4.1 HPLC Analysis of Metformin Hydrochloride

Metformin hydrochloride is low molecular weight and highly polar, which could lead to poor retention on conventional reversed-phase stationary phases. Accordingly, C18 columns are commonly used with modified mobile phases, while hydrophilic interaction liquid chromatography (HILIC) provides an alternative approach for improved retention of polar analytes [13,14,17,21].

Reported RP-HPLC methods have used 250 × 4.6 mm or 150 × 4.6 mm columns with 5-µm particles. Examples include a C18 µ-Bondapak column using methanol–water (30:70, v/v) and methods using phosphate buffer with an ion-pairing reagent such as octane-1-sulfonic acid. Another method used acetonitrile with an aqueous phase containing potassium dihydrogen phosphate and sodium lauryl sulfate. HILIC has also been applied using a 150 × 4.6 mm column with sodium acetate buffer and acetonitrile [13,14,17,21].

Reported flow rates for these methods are generally between 0.5 and 1.3 mL/min, while UV detection is generally around 233–236 nm. Linearity ranges reported are approximately 2.5–20 µg/mL, 0.039–1.25 µg/mL and 0.312–5 µg/mL, depending on the method. Validation studies generally reported intra-day and inter-day precision below 2% RSD and recoveries of approximately 98–102%. Robustness assessments showed that selected methods remained suitable following small changes in flow rate, mobile-phase composition, and buffer pH [13,14,17,21].

4.2 HPLC Procedures for Glimepiride

The relatively low dose and low water solubility of glimepiride can impact the development of the HPLC technique for glimepiride. RP-HPLC analysis usually employs greater concentrations of organic solvents to provide an adequate elution and detection of glimepiride [23,25].

One described RP-HPLC procedure was carried out using a C18 column (150 × 4.6 mm, 5 µm). The mobile phase consisted of acetonitrile and monobasic sodium phosphate buffer (50:50 v/v). Glimepiride was detected at 228 nm and the retention time was found to be around 9.3 min at the flow rate of 1.0 mL/min [25].

The HILIC method is another method for the analysis of glimepiride other than RP-HPLC. One was an amino stationary phase with a mobile phase of acetonitrile and aqueous acetate buffer. The retention time was reported to be ~4.13 min [23].

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Stability indicating RP-HPLC methods are helpful in studying glimepiride particularly in assessing the degradation of the drug under various stress conditions. These approaches can be useful to assess stability of glimepiride in pharmaceutical preparations.

Reported forced-degradation studies indicated greater stability under photolytic and thermal conditions and more pronounced degradation under acidic and oxidative conditions [23,25].

Published HPLC methods demonstrated linearity over a range appropriate to the intended application, with reported recoveries around 99.3–103%. Reported sensitivity included an LOD of approximately 0.354 µg/mL, while repeatability and intermediate precision were generally associated with low RSD values, often below 1% for peak area and retention time [23,25].

4.3 Combination HPLC Methods for Glimepiride and Metformin Hydrochloride

The substantial difference in the label claims of metformin hydrochloride and glimepiride and their different physicochemical properties makes simultaneous determination by RP-HPLC analytically challenging. Nevertheless, several methods have achieved satisfactory separation in a single chromatographic run [29,31,32].

Common simultaneous methods use C18 analytical columns, frequently 250 × 4.6 mm with 5-µm particles. Reported mobile phases include combinations of methanol, acetonitrile, and phosphate buffer, while ion-pairing reagents such as hexane-1-sulfonic acid have been used to improve metformin retention. Other reported media include potassium dihydrogen phosphate buffer in acetonitrile. These approaches balance the retention requirements of highly polar metformin and more hydrophobic glimepiride [29,31,32].

In these methods, metformin generally elutes before glimepiride, with reported retention times of approximately 2.4–3.5 min for metformin and 4.2–5.9 min for glimepiride. Detection has commonly been performed in the 229–242 nm region, with approximately 230 nm selected in some procedures [29,31,32].

Validation of simultaneous methods generally demonstrated mean recoveries of approximately 98–102% and intra-day and inter-day precision below 2% RSD. Reported linearity ranges were selected according to the dose ratio, including examples such as 5–30 µg/mL for metformin and 1–10 µg/mL for glimepiride [29,31,32].

4.4 Impurity Profiling and Stability-Indicating RP-HPLC

Stability-indicating RP-HPLC methods are particularly important for separating metformin hydrochloride and glimepiride from degradation products generated during acid or base hydrolysis, oxidation, and photolysis. Reported studies indicate that metformin and glimepiride show different degradation behavior under stress conditions. Gradient methods have also been developed to monitor selected related substances, including glimepiride sulfonamide, glimepiride urethane, and metformin-related compound A, thereby supporting broader pharmaceutical quality-control assessment [24,29,31,32].

5. Considerations for Analytical Method Validation

Analytical method validation establishes whether a procedure is suitable for its intended purpose. Methods reported for metformin hydrochloride and glimepiride have generally been evaluated using parameters described in applicable ICH analytical-validation guidance [1,13,29].

5.1 Linearity and Range

Linearity describes the ability of an analytical procedure to obtain results that are proportional to analyte concentration over a defined range. It is usually determined by calibration curve and regression analysis. The correlation values for HPLC and UV techniques are often more than 0.999, which indicates the strong linear relationship for the ranges examined [1, 13, 29]. The analytical range is the interval in which the required accuracy and precision are proven.

5.2 Accuracy

Accuracy is the proximity of a measurement to the genuine value of the quantity being measured. Often, recovery experiments are conducted by spiking the formulation matrix or placebo with known quantities of pure medication. Reported mean recoveries for metformin and glimepiride in the examined procedures are generally in the range of ~98–102% [1, 13, 29].

5.3 Precision

Precision is the degree of agreement between repeated measurements. Repeatability is the precision over a short period of time under the same operating conditions. Intermediate precision is the precision between laboratories (on different days, with different analyzers, etc.). The results are typically reported as a percent relative standard deviation (%RSD). The precision of the analyzed UV and HPLC procedures is normally < 2% RSD [1, 13, 29].

5.4 Limit of Detection and Limit of Quantification

Limit of Detection (LOD): The lowest amount of analyte in a sample that can be detected but not quantified under the stated parameters of the test. LOQ (limit of quantification) is the lowest concentration of analyte in a sample that can be determined with acceptable precision and accuracy. These parameters may be estimated using signal-to-noise approaches or from the standard deviation of the response and the slope of the calibration curve. HPLC procedures generally provide lower LOD and LOQ values than simple UV methods because of the greater separation and detection capability [1,13,29].

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5.5 Robustness

Robustness describes the ability of an analytical procedure to remain unaffected by small, deliberate variations in method parameters. Typical variations evaluated in the reviewed procedures include detection wavelength, mobile-phase composition, flow rate, and buffer pH. A method is considered robust when such changes do not cause a significant effect on analytical performance or system-suitability parameters [1,13,29].

5.6 Specificity

Specificity is the ability of an analytical procedure to measure the analyte response in the presence of potentially interfering substances such as excipients, impurities, and degradation products. This parameter is particularly important for simultaneous analysis and stability-indicating methods. HPLC generally provides stronger specificity than direct UV spectrophotometry because the analytes are physically separated before detection [1,13,29].

5.7 Summary of Typical Validation Characteristics

Validation parameter	Typical value/criterion reported in the reviewed methods
Linearity	r^2 commonly >0.999
Accuracy	Recovery generally 98–102%
Precision	%RSD generally <2%
Robustness	No significant effect from small deliberate changes
Specificity	Adequate discrimination from excipients and/or degradation products
LOD/LOQ	Method-dependent; generally lower for HPLC than direct UV

6. UV Spectrophotometry vs HPLC Comparison

Both UV spectrophotometry and HPLC provide accurate and precise quantitative results if correctly developed and validated. The choice of method depends on the required selectivity, sensitivity, complexity of the sample, infrastructure, time of analysis, and cost.

Parameter	UV spectrophotometry	RP-HPLC
Selectivity	Moderate; spectral overlap may limit selectivity in combinations	High because analytes are physically separated
Sensitivity	Generally suitable for routine assay; method-dependent	High and suitable for lower-level measurements and impurities
Cost	Relatively low equipment and operating cost	Higher equipment, column, and solvent requirements
Analysis time	Rapid measurement	Typically several minutes per chromatographic run
Method complexity	Generally simple; derivative/chemometric methods require additional processing	Requires chromatographic method development and system suitability
Routine tablet assay	Highly suitable for simple formulations	Highly suitable, particularly for complex formulations
Stability studies	Limited when degradation products overlap spectrally	Highly suitable for stability-indicating separation

7. Application of UV Spectrophotometry in Routine Quality Control

UV spectroscopy is a simple, rapid, and economical approach for the analysis of single-drug preparations and uncomplicated tablet formulations. For example, metformin tablets containing a comparatively high dose can often be analyzed using a simple aqueous or methanolic UV procedure without the need for chromatographic separation [1,2,6].

UV spectrophotometry is also useful in dissolution testing, where rapid measurement of drug concentration is required at multiple sampling points. Derivative spectroscopy and chemometric techniques such as PLSR and PCR have expanded the application of UV methods to multicomponent formulations by allowing overlapping spectral responses to be mathematically resolved [33-35].

8. Application of HPLC in Pharmaceutical Analysis

RP-HPLC is particularly useful when high specificity is required. This is relevant to fixed-dose combinations containing

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substantially different quantities of metformin hydrochloride and glimepiride, such as formulations containing 500 mg metformin and 2 mg glimepiride. Chromatographic separation can reduce the possibility of interference from the high-dose component and allows more reliable measurement of the lower-dose component [29,31,32]. A major advantage of HPLC is its suitability for stability-indicating analysis. HPLC can separate the active pharmaceutical ingredient from major degradation products formed under stress conditions such as acid/base hydrolysis and oxidation. This capability is important for impurity profiling and for evaluating the chemical stability of pharmaceutical products [24,29,31,32].

9. Facilities and Regulatory Considerations

Selection of method depends on the laboratory infrastructure, analytical workload and regulatory constraints. Simple UV techniques are useful for routine high volume testing where the formulation is simple and spectral interference is negligible. Chromatographic methods are more appropriate when it is necessary to separate the degradation products, contaminants or other active compounds [13,29]. HPLC has significantly expanded the use of organic solvents and the associated environmental issues. These reasons have also aroused interest in greener analytical procedures with reduced solvent usage and more efficient chromatographic techniques. Hence, UV- spectrophotometry is still effective for quick routine analysis whereas, HPLC is more useful in complicated formulations, stability studies and assessment of contaminants [19].

10. Future Perspectives

It is expected that the principles of green analytical chemistry will increasingly impact the future development of analytical techniques for glimepiride and metformin hydrochloride. Many common organic solvents are quite damaging to the environment. The common organic solvents can be replaced by other less hazardous alternatives such as safer solvents, acidified aqueous systems etc. which can help reduce the environmental impact. Such reduction can be achieved by the use of safer solvents, acidified aqueous systems and other less hazardous alternatives. Safer solvents, acidified aqueous systems and other less hazardous alternatives can reduce the environmental impact of common organic solvents. Greenness-estimation methods such as AGREE [19] assess the environmental performance of analytical processes. Quality-by-Design (QbD) concepts and systematic optimization may also be part of analytical method development. with the analytical method development. These approaches may be useful to identify important technique parameters and to increase the efficiency and robustness. High sensitivity in complex matrix such as plasma has made high performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS) and its related techniques increasingly important in clinical and bioanalytical applications. These methods are applicable in pharmacokinetic and bioequivalency studies requiring quantitation of low concentrations of glimepiride or metformin. These methods allow the determination of low concentration of glimepiride or metformin. These approaches can be useful for pharmacokinetic and bioequivalence studies that need to measure glimepiride or metformin at low levels. by these means. UV spectroscopy is becoming more useful for multicomponent analysis without prior physical separation by chemometric techniques such as PLSR and PCR [34].

11. Conclusion

UV spectrophotometry and HPLC are complementary analytical approaches for the quantitative estimation of metformin hydrochloride and glimepiride. UV methods offer simplicity, rapidity, and low operating cost and are therefore appropriate for routine analysis of bulk materials and relatively uncomplicated pharmaceutical dosage forms. Derivative, simultaneous-equation, ratio, and chemometric approaches can extend the applicability of UV spectroscopy to multicomponent preparations. RP-HPLC provides greater selectivity, sensitivity, and specificity because the analytes are separated chromatographically before detection. This advantage is especially important for fixed-dose combinations of metformin hydrochloride and glimepiride, where the label claims differ substantially, and for stability-indicating and impurity-profiling studies. Overall, UV methods are valuable for rapid routine quality control, whereas HPLC remains particularly important when complex separation and regulatory-quality stability assessment are required

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