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Review Article

Review on Different Analytical Methods for The Estimation of Metformin Hydrochloride and Lisinopril

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ABSTRACT

The antihyperglycemic drug metformin hydrochloride is a biguanide. It works by lowering the liver's glucose synthesis and raising the insulin sensitivity of bodily tissues. Lisinopril is an antihypertensive drug that is used to treat excessive blood pressure, heart failure, and heart attacks. Metformin hydrochloride and lisinopril have been determined using a variety of analytical approaches. Chromatographic and UV spectrophotometric methods are examples of these methods. The uses of these approaches for the determination of metformin hydrochloride and lisinopril in pharmaceutical formulations are discussed in this review.


INTRODUCTION

The process of demonstrating that analytical processes are suitable for assessing pharmaceuticals, particularly the active pharmaceutical ingredient (API), is known as analytical method development and validation. Analytical processes are created to compare certain features of substances to predetermined acceptance criteria for those qualities. The process of method validation is performed to ensure that the analytical approach utilised for a specific test is appropriate for its intended usage. Method validation findings can be used to assess the quality, consistency, and reliability of analytical

results; it is an essential component of any effective analytical practise ^[1]. The goal of validation is to show that an analytical process is adequate for its intended purpose. Validation is proof that is documented and offers a high level of assurance for a given process. Variables such as elapsed assay times, different days, reagent lots, instruments, equipment, environmental conditions such as temperature, and so on can influence any developed method, so it is expected that after the method is developed and before it is communicated or transferred from one lab to another, it is properly validated and the results of validity tests are reported ^[2]. Spectroscopic

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methods such as visible spectrophotometry, ultraviolet spectrophotometry, infrared spectrophotometry, atomic absorption spectrophotometry, emission spectroscopy, flame photometry, fluorimetry, and others are used in the development of analytical method validation. Chromatographic methods such as HPLC, GC, and HPTLC are also used [3-5]. Ultraviolet-visible spectrophotometry is the study of absorption and reflectance spectroscopy in the ultraviolet and visible parts of the electromagnetic spectrum. This means it makes use of visible and neighbouring light. The visible spectrum ranges from 400 to 700 nm, while the UV ranges from 100 to 400 nm [6]. The measurement of the interaction of infrared radiation with materials by absorption, emission, or reflection is known as infrared spectroscopy (IR spectroscopy or vibrational spectroscopy). It is utilised to investigate and identify chemical compounds or functional groups that exist in solid, liquid, or gaseous forms. The most useful I.R. region lies between $4000 - 670\text{cm}^{-1}$ [7]. Atomic absorption spectroscopy (AAS) and atomic emission spectroscopy (AES) are Spectro analytical procedures that use the absorption of optical radiation (light) by free atoms in the gaseous state to determine chemical elements quantitatively. The absorption of light by free metallic ions is the basis for atomic absorption spectroscopy. Flame photometry or flame atomic emission spectrometry in which the species is examined in the form of atoms. An analytical method for detecting and measuring fluorescence in chemicals that involves activating the compounds with UV radiation, causing them to produce visible light is known as fluorimetry [8]. A technique in analytical chemistry called high-pressure liquid chromatography is used to separate, identify, and quantify each component in a mixture. Pumps are used to move a pressured liquid solvent containing the sample combination through a solid adsorbent material-filled column.

Each component in the sample interacts with the adsorbent material in a slightly different way, resulting in varying flow rates and separation of the components as they flow out of the column [9]. Gas chromatography (GC) is a type of analytical chemistry chromatography that is used to separate and analyse chemicals that may be vaporised without breakdown. GC is commonly used to determine the purity of a chemical or to separate the various components of a mixture [10]. HPTLC stands for high-performance thin-layer chromatography, which is a more advanced version of thin-layer chromatography (TLC). The basic process of thin-layer chromatography can be improved in a number of ways, including automating the various procedures, increasing the resolution achieved, and allowing more precise quantitative measurements [11].

The following are the most common types of analytical procedures that can be validated [12-13]:

- Identification tests;
- Quantitative tests for impurity content;
- Limit tests for impurity control;
- Quantitative testing of the active moiety in samples of drug substance or drug product, or other specified component(s) in the drug product.

Identification tests are used to guarantee that an analyte in a sample is what it claims to be. This is usually accomplished by comparing a sample property to that of a reference standard (e.g., spectrum, chromatographic behaviour, chemical reactivity, etc.). Impurity testing can be done in two ways: quantitatively or as a limit test for the impurity in a sample. Either test is designed to correctly reflect the sample's purity characteristics. A quantitative test requires different validation criteria than a limit test. Assay processes are used to determine the amount of analyte contained in a



sample. In the context of this publication, an assay is a quantitative measurement of the drug substance's principal component(s). Similar validation criteria apply when assaying for the active or other specified component in the drug product (s).

The following is a list of the various validation characteristics that are addressed in a validation exercise [14,15,16]:

1. Accuracy
2. Precision
3. Repeatability
4. Intermediate Precision
5. Specificity
6. Detection Limit
7. Quantitation Limit
8. Linearity
9. Range

Accuracy: The proximity of the test results obtained by the method to the true value can be characterised as the accuracy of an analytical method. It is a measure of the precision of the analytical method established, and it is commonly expressed as a percentage of analyte recovery by assaying a known amount of analyte. The method's accuracy can be determined by using it on samples or mixtures of excipients to which a known amount of analyte has been added both above and below the usual levels expected in the samples, and then calculating the percentage of analyte recovered by the assay based on the test findings. According to the ICH documents, accuracy should be evaluated using a minimum of nine determinations at three concentration levels, covering the defined range (i.e., three concentrations and three replicated of each concentration).

Precision: The degree of agreement among individual test results when the procedure is

applied repeatedly to several samplings of homogeneous samples is the precision of an analytical method. The standard deviation or relative standard deviation is commonly used to express this (coefficient of variation). Precision is a measurement of the analytical method's reproducibility or repeatability under typical working conditions.

Repeatability: The precision of a method when repeated by the same analyst under the same operational conditions such as the same reagents, equipment, settings, and laboratory over a short period of time is known as repeatability. According to the ICH standards, repeatability should be evaluated using a minimum of nine determinations that encompass the procedure's defined range (i.e., three concentrations and three replicates of each concentration or using a minimum of six determinations at 100 percent of the test concentration).

Intermediate Precision: Variations within laboratories are expressed by intermediate precision: various days, different analysts, different equipment, and so forth. Comparisons of data acquired by other analysts, using different equipment, or conducting the analysis at different periods might also yield useful information.

Specificity: The capacity to assess the analyte definitively in the presence of components that are expected to be present is known as specificity. Impurities, degradants, matrix, and other substances are examples of these.

Detection Limit: It is the lowest quantity of analyte that can be identified using a certain method under the relevant experimental conditions, but not necessarily determined quantitatively. The limit test simply confirms that the analyte concentration is above or below a predetermined threshold. At levels nearing the



LOD, the standard deviation (SD) of the response and the slope (S) of the calibration curve can be used to compute the LOD using the formula:

$$\text{LOD} = 3.3(\text{SD}/\text{S})$$

Quantitation Limit: Quantitative assays for low amounts of chemicals in sample matrices, such as contaminants in bulk medications and degradation products in finished pharmaceuticals, use the limit of quantitation as a parameter. When the requisite process is used, the limit of quantitation is the lowest concentration of analyte in a sample that can be determined with acceptable accuracy and precision. The calculation is based on the standard deviation (SD) of the response and the slope (S) of the calibration curve according to the formula

$$\text{LOQ} = 10(\text{SD}/\text{S})$$

Linearity: The capacity of an analytical process to produce test results that are directly proportional to the concentration (quantity) of analyte in the sample (within a specific range) is known as linearity. The concentration of the working sample and the samples evaluated for accuracy should be within the linear range.

Range: The range of an analytical technique is the range of concentrations (amounts) of analyte in the sample (including these concentrations) for which the analytical procedure has been proved to have an appropriate level of precision, accuracy, and linearity. Metformin hydrochloride and lisinopril can be measured using a variety of analytical methods. All of the analytical methods have been addressed in this article. As a result, the main purpose of this article is to hold a discussion on various existing analytical methods for quantification of metformin hydrochloride and lisinopril in bulk drugs or in combined dosage forms in pharmaceutical products, so that this article can provide researchers with a concise idea

of how to estimate these two drugs. All the methods have been validated as per ICH guidelines.

- Chemical structure of metformin hydrochloride (given in figure 1)
- Drug profile of metformin hydrochloride (shown in table 1) ^[17]
- Drug profile of lisinopril (shown in table 2) ^[18]
- Chemical structure of lisinopril (given in figure 2)

Patil et al., specified to develop and validate simple and precise stability indicating UV Spectrophotometric method for Metformin Hydrochloride in the bulk and tablet dosage form. The drug was separated from its degradation products using a UV Spectrophotometric technique that scanned between 200 and 400 nm and used distilled water. The highest absorbance was discovered to be at 232.2nm, and the linearity was found to be good over the range of 2-10g/ml, with a correlation coefficient of 0.998. The detection and quantification limits, respectively, were 0.5232µg/ml and 1.5856µg/ml. ^[19]. *Karim et al.*, discussed development and validation of UV spectroscopic method for the determination of metformin hydrochloride in tablet dosage form. Adequate drug solubility and maximum assay sensitivity was found in 0.01N sodium hydroxide at 233nm. Calibration graph constructed at 233nm was linear in concentration range of 1-25µg/ml with correlation coefficient of 0.9998. In terms of linearity (within 1-25 g/ml), accuracy (percent recovery), precision (inter-day and intraday), specificity, and robustness, the method was verified according to ICH recommendations. The LOD and LOQ were found to be 0.2226µg/ml and 0.6745µg/ml, respectively. ^[20]. *Patni et.al.*, evaluated Analytical Method Development and Validation for Estimation of Metformin in Bulk and Pharmaceutical Dosage Form by UV



Spectrometric Method. The spectrophotometric detection was carried out at a wavelength of 232 nm with a pH of 6.8 phosphate buffer as the solvent. Specificity, linearity, accuracy, precision, robustness, and ruggedness were all tested. With a correlation coefficient of 0.004, the detector response for the specified concentration range of 2 to 12 µg/ml showed linearity. According to the recovery study, the accuracy was found to be between 99.1 and 100.45% [21]. *Audumbar et al.*, studied development and validation of UV spectrophotometric estimation of lisinopril dihydrate in bulk and tablet dosage form using area under curve method. The standard and sample solutions were made with a solvent of double distilled water. The substance was measured quantitatively at wavelengths ranging from 202-216 nm. The linearity of lisinopril dihydrate was established over a concentration range of 10-30 µg/ml with a correlation coefficient of 0.9993. Percent relative standard deviation was found to be within acceptable bounds in accuracy studies. The average percentage recovery was 99.905% [22]. *Nikam et al.*, discussed Analytical Method Development and Validation of Metformin Hydrochloride by using RP-HPLC with ICH Guidelines. Metformin was separated on a C18 column [4.6x250mm, particle size 5µm] using a pH 3.0 phosphate buffer and Methanol at 238nm UV detection. Linearity, accuracy, precision, inter-day and intra-day fluctuation, and other statistical validation characteristics were examined. Metformin test studies were within 98% to 102%, demonstrating that the drug is effective. The proposed method can be used for Metformin quality control analysis [23]. *Basavaiah et al.*, specified RP-UPLC development and validation of metformin hydrochloride in pure drug and pharmaceutical formulations. Linearity, precision, accuracy, specificity, and selectivity were all tested. The calibration curve's linear regression analysis revealed an excellent linear correlation

over the concentration range of 0.1–300 µg/ml, with a regression coefficient of 0.9999. The limits of detection (LOQ) and (LOD) were 0.01 µg/ml and 0.002 µg/ml, respectively. Recovery trials using a typical addition approach were used to confirm the method's accuracy, with recoveries ranging from 100.7 to 101.4% [24]. *Sheetal Budhadev et al.*, discussed development and validation of simultaneous equation method for bilayer floating tablet of glipizide and lisinopril. Simultaneous Equation Approach was used to develop the method. Lisinopril was estimated at a wavelength of 204.5 nm, while Glipizide was estimated at a wavelength of 224.5 nm. In the range of 0.5-15 µg/ml, Glipizide and Lisinopril showed the similar linearity [25]. *Patel, et al.*, explained Simultaneous Estimation of Metformin and Repaglinide in Synthetic Mixture. For both metformin and repaglinide, linearity was observed in the concentration range of 4-24 µg/ml. The first technique uses simultaneous equations to determine the absorbances of both medicines at 240nm (λ max of metformin) and 291.5nm (λ max of repaglinide). The approach was tested for accuracy (99.24±0.99, 100.98±0.89) and precision (intra-day variations 0.58-1.21, 2.12-3.12 and inter-day variations 0.62-1.42, 2.20-3.08). The second approach is based on the Q-absorbance ratio; the absorbances of both medications were measured at 240nm (metformin's maximum absorbance) and at the isoabsorptive point (254.8nm). The q-absorption approach was tested for accuracy (98.57±1.05, 98.62±1.2402) and precision (intra-day variations 98.57±1.05, 98.62±1.2402 0.58-1.21, 1.01-3.53 and inter-day variations 0.62-1.42, 1.15-3.74) [26]. *Audumbar et al.*, discussed Simultaneous UV Spectrophotometric Methods for Estimation of Metformin HCl and Glimepiride in Bulk and Tablet Dosage Form. Method A is the Absorbance Maxima method, which is based on measuring absorption at maximum wavelengths of 236 nm



and 228 nm, respectively, for Metformin HCl and Glimepiride. Method B uses the area under the curve (AUC) method, which uses wavelengths of 217-247 nm for Metformin HCl and 213-239 nm for Glimepiride. In the concentration ranges of 5-25 μ g/ml for Metformin HCl and 5-25 μ g/ml for Glimepiride, detector response was linear. Recovery investigations determined that the techniques' accuracy was 100.23% for Metformin HCl and 99.67% for Glimepiride, respectively [27]. *Dadhania et al.*, reported Development and validation of spectrophotometric method for simultaneous estimation of gliclazide and metformin hydrochloride in bulk and tablet dosage form by simultaneous equation method. It uses two wavelengths of 227.0 nm and 237.5 nm to generate and solve a simultaneous equation. In the concentration ranges of 5-25 μ g/ml for Gliclazide and 2.5-12.5 μ g/ml for Metformin hydrochloride, this approach follows Beer's rule [28]. *J.V. Shah et al.*, specified Fast and sensitive LC-MS/MS method for the simultaneous determination of lisinopril and hydrochlorothiazide in human plasma. Solid phase extraction with 100 L of plasma using Waters Oasis HLB cartridges was followed by liquid chromatography on a Hypersil Gold C₁₈ (50 mm \times 3.0 mm, 5 μ m) column. Using acetonitrile-5.0mM ammonium formate, pH 4.5 (85:15, v/v) as the mobile phase, the analytes were eluted in 2.0 minutes. For both analytes, the technique demonstrated excellent linearity over the concentration range of 0.50–250.0 μ g/ml. The intra-batch and inter-batch precision (percent CV) were both 5.26%, with extraction recoveries ranging from 96.6 to 103.1% [29]. *I. Rubashvili et al.*, reported Simultaneous quantitative estimation of lisinopril and hydrochlorothiazide residues using HPLC for cleaning validation. The detection and quantitation limits for lisinopril were 0.039 μ g/ml and 0.155 μ g/ml, respectively, while for HCT were 0.012 μ g/ml and 0.025 μ g/ml [30]. *Sultana et. al.*, Development and validation of new

assay method for the simultaneous analysis of diltiazem, metformin, pioglitazone and risoglitazone by RP-HPLC and its applications in pharmaceuticals and human serum. All of the above medications were chromatographed in HPLC using the mobile phase acetonitrile-methanol-water (30:20:50, v/v, pH 2.59 \pm 0.02) at a flow rate of 1.0 ml/min at room temperature. The separation is performed on a Hiber 250-4.6 RP-18 column with a 230 nm UV-vis detector [31]. *Sultana et. al.*, explained An Ultra-Sensitive and Selective LC-UV Method for the Simultaneous Determination of Metformin, Pioglitazone, Glibenclamide and Glimepride in API, Pharmaceutical Formulations and Human Serum. For the drug and impurities, linear regression analysis demonstrated a high connection between peak reactions and concentrations (R² values of 0.9991–0.9999). The analytical parameters of linearity (r²>0.9996), LLODs (0.315, 2.3, 0.2, 0.1 ng ml⁻¹), LLOQs (0.95, 0.7, 0.59, 0.32 ng⁻¹), intra-day precision (0.001), and inter-day precision 0.9 reported as relative standard deviation were validated under FDA guidelines (R.S.D) [32]. *Elanfaly et.al.*, reported Simultaneous quantification of ramipril, glimepiride and metformin in human plasma by ultra-performance liquid chromatography – tandem mass spectrometry. The calibration curves for ramipril and glimepiride were linear (r² > 0.99) throughout a range of 0.1 to 1000 μ g/mL, and 250 to 2000 μ g/mL for metformin. The intra-day and inter-day precisions were both less than 14.32%, and the accuracy was all under \pm 15% [33]. *Kothapalli et. al.*, discussed Simultaneous spectrophotometric methods for estimation of metformin and fenofibrate in synthetic mixture. Metformin has an absorbance maximum of 237.5 nm and fenofibrate has an absorbance maximum of 287.5 nm, but the proposed procedures use a wavelength of 266.0 nm and methanol as the



solvent. In the concentration ranges of 5-30 μ g/ml for metformin and 0.8-4.8 μ g/ml for fenofibrate, linearity was seen. The first method relies on solving a simultaneous equation for both medications, whereas the second relies on multicomponent analysis. Both approaches' results have been statistically validated and determined to be acceptable. The recovery studies backed up the hypothesised method theory^[34].

CONCLUSION

Metformin hydrochloride and lisinopril can be measured using a variety of analytical methods. All of the analytical methods have been addressed in this article. As a result, the main purpose of this article is to hold a discussion on various existing analytical methods for quantification of metformin hydrochloride and lisinopril in bulk drugs or in combined dosage forms in pharmaceutical products, so that this article can provide researchers with a concise idea of how to estimate these two drugs. All the methods have been validated as per ICH guidelines.

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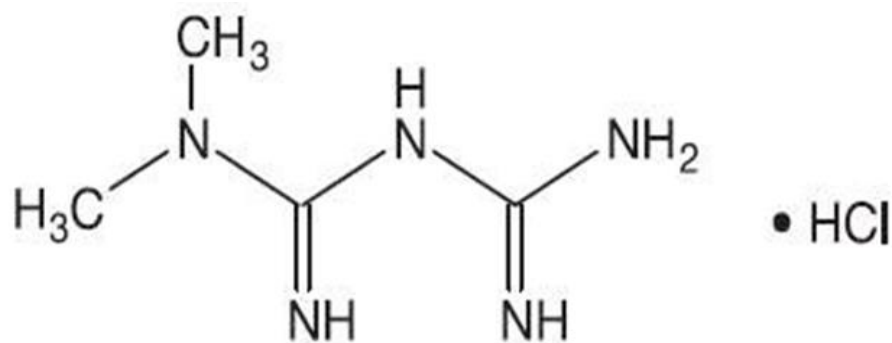


Figure 1: Chemical Structure of Metformin Hydrochloride

Table 1: Drug Profile of Metformin Hydrochloride

Drug name	Metformin Hydrochloride
IUPAC name (chemical name)	N, N- Dimethylbiguanide hydrochloride
Category	Biguanide antihyperglycemic agent
Molecular formula	C ₄ H ₁₂ ClN ₅

Molecular Weight	165.62g/mol
Appearance	White to off white crystalline powder
Solubility	Freely soluble in water and practically insoluble in acetone, ether, and chloroform.
Melting Point	221°C
pH	6.68 (1% solution)
pKa	12.4
Storage	Store at a room temperature in tightly closed container and away from sunlight.
Dose	500mg/1000mg

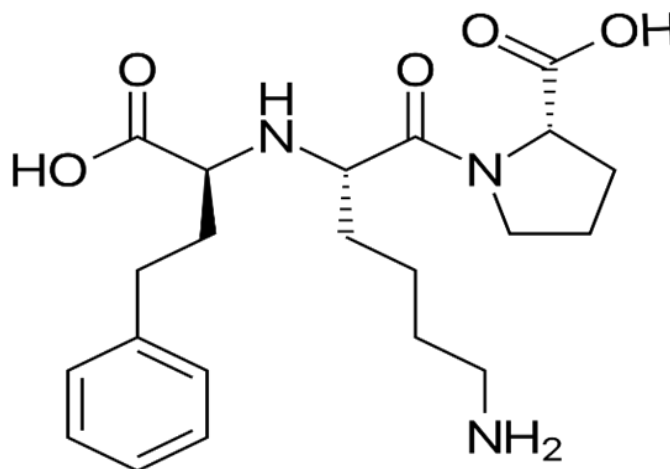


Figure 2: Chemical structure of lisinopril

Table 2: Drug Profile of Lisinopril

Drug Name	Lisinopril
IUPAC name (chemical name)	(S)-1-[N2-(1-carboxy-3-phenylpropyl)-L lysyl]-L-proline
Category	Angiotensin converting enzyme inhibitor (Antihypertensive).
Molecular Formula	C ₂₁ H ₃₁ N ₃ O ₅
Molecular Weight	405.5g/mol
Appearance	White to off-white crystalline, odorless powder
Solubility	Soluble in water and sparingly soluble in methanol and practically insoluble in ethanol.
Melting Point	148°C
pH	4.2
Storage	Store in cool, dry place, away from direct sunlight at 15-30°C
Dose	2.5mg, 5mg, 10mg, 20mg, 30mg, 40mg