Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com
ISSN: 2231-2781 (Print) | ISSN: 2249-3247 (Online)

Review Article

New Analytical Method Development and Validation of UV -visible Spectroscopy for the Estimation of Sulpiride: A Narrative Review

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Article History
Received : 10.01.2025
Revised : 12.02.2025
Accepted : 16.02.2025

DOI

10.5530/ajphs.2025.15.75

Keywords
Sulpiride
UV Spectroscopy
FTIR
ICH Guidelines

ABSTRACT

The aim is to develop novel analytical methods, and validation is a continuous and interdependent task associated with the research and development, quality control, and quality assurance departments. Analytical procedures play a crucial role in assessing and managing equivalence risk. It helps establish product-specific acceptance criteria and the stability of results. Validations determine that the analytical procedure is suitable for its intended purpose. The literature survey reveals that analytical methods are based on UV-Visible spectrophotometry for determining Sulpiride Bulk and in combination with different drugs, as well as the study of Chemical characteristics using FTIR Spectra. The parameters were validated according to ICH guidelines in terms of Accuracy, Precision, Robustness, Ruggedness, and other components of analytical validation. The developed methods are simple, sensitive, and reproducible, and can be used for the analysis of sulpiride in bulk and Tablet dosage forms. FTIR analysis reveals the presence of Various functional groups and the structure of sulpiride. Those Functional groups are essential for therapeutic and biomechanical applications as antipsychotic drugs.

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INTRODUCTION

Sulpiride belongs to the Benzamide class of Antipsychotic drugs and is primarily used in the treatment of schizophrenia and depression (Figure 1). It acts as a selective dopamine receptor antagonist, mainly affecting the limbic system while sparing the motor system, thus reducing the risk of extrapyramidal side effects. Sulpiride exhibits both antipsychotic and antidepressant properties, and it is used in the management of acute and chronic schizophrenia, vertigo, and certain cases of psychosomatic disorders. Its therapeutic effects are particularly useful in treating negative symptoms of schizophrenia and dysthymia. Moreover, sulpiride is often employed in low doses for the treatment of functional gastrointestinal disorders due to its Prokinetic properties. Its efficacy and tolerability make it a valuable choice in both psychiatric and gastroenterological settings.

Primarily acts as a selective dopamine D2 and D3 receptor antagonist, it exerts its therapeutic effects mainly by inhibiting dopaminergic neurotransmission in the central nervous system. Sulpiride shows both antipsychotic and antidepressant effects depending on the dosage: low doses preferentially block presynaptic D2 receptors, enhancing dopamine release, which helps in treating depression and negative symptoms of schizophrenia; whereas higher doses block postsynaptic D2 receptors, reducing dopaminergic activity, which is beneficial in treating psychosis and positive symptoms of schizophrenia. It has minimal affinity for serotonin, adrenergic, histaminergic, and cholinergic receptors, which results in a relatively favorable side effect profile compared to typical antipsychotics (Figure 2).

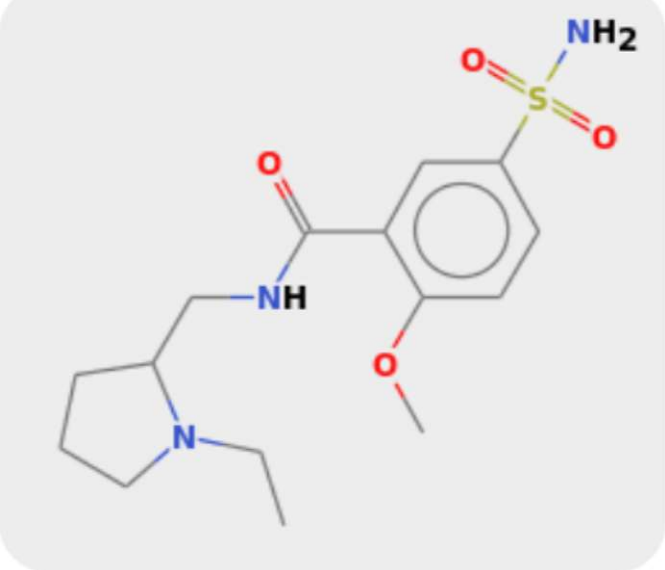

Figure 1: Structure of Sulpiride

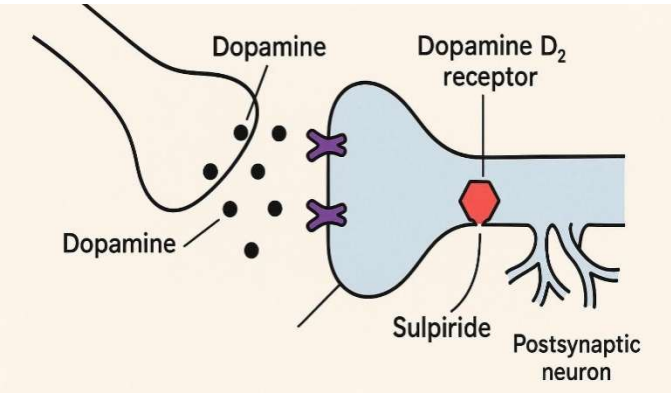

Figure 2: Mechanism of Action of Sulpiride.

REVIEW OF LITERATURE

The new spectrophotometric methods were based on the formation of Sulpiride yellow ion-pair complex with bromocresol green (BCG), Congo red (CR) or methyl orange (MO) in Britton-Robinson universal buffer of pH 3.0, 5.0, or 2.5, respectively [1]. The formed complexes with BCG, CR and MO were extracted with chloroform, and their absorbencies were measured at 420 nm, 515 nm, and 480 nm, respectively. Beer's law was obeyed over the concentration ranges of 2-14 µg/ mL, 2-16 µg/ mL, and 2-14 µg/ mL Sulpiride with BCG, CR and MO, respectively. The molar absorptivity (ε) of the formed colored complexes with BCG, CR and MO was 4.10×104, 2.10×104 and 3.50×104 L moL^{-1} cm^{-1} and the estimated limit of detection (LOD) of sulpiride was found to be 0.044, 0.095 and 0.064 µg/mL, respectively.

According to EI Wilily *et al.*, 1999, the first method depends on first-derivativeultraviolet spectrophotometry, with a zero-crossing measurement method. The first derivative amplitudes at 214.2 and 221.6 nm were selected for the assay of mebeverine hydrochloride (MB) and sulpiride (SU), respectively. Calibration graphs follow Beer's law in the range of 10-30 and 2-8 µg mL^{-}, and the linearity was satisfactory (r=0.9999), for MB and SU, respectively [2].

Hashim and colleagues developed a sensitive, robust, and simple method for the simultaneous analysis of levosulpiride and omeprazole in human plasma [3]. They also demonstrated the applicability of this method in determining pharmacokinetic drug-drug interactions. In the presented study, a reversed-phase HPLC-UV method was developed for the simultaneous determination of levosulpiride and omeprazole using pantoprazole as the internal standard. Experimental conditions were optimized and the developed method was validated as per standard guidelines (USP and ICH). Furthermore, the developed method was applied for the evaluation of the pharmacokinetics of drug-drug interaction between levosulpiride (50 mg) and omeprazole (40 mg) in healthy human volunteers. Sharpsil C8 column (4.6 × 250 mm, 5 µm), Ultisil C8 column (4.6 mm × 150 mm, 5 µm) and Agilent C18 column (4.6 × 250 mm, 5 µm) were evaluated as the stationary phase. The best resolution was achieved with an Agilent C18 (4.6 x 250 mm, 5 µm) column and was selected for further study. The mobile phase consisted of a

mixture of acetonitrile and phosphate buffer (pH 7.2) in 60:40 by volume, and was pumped at a flow rate of 1 mL/min. Detector wavelength was set at 280 nm.

A simple, sensitive, selective, and cost-effective spectrofluorimetric method has been established by Jasmin Shah *et al.*, 2013 for the quantification of Sulpiride after their complete alkaline hydrolysis [4]. The method is based on the condensation of the primary amino group of alkaline hydrolytic product ofsulpiride with acetyl acetone and formaldehyde in an acidic medium (0.25 M HCl) to form a fluorescent product. The reaction product formed shows maximum fluorescence intensity at 483 nm after excitation at 431 nm. The different reaction conditions influencing the condensation reaction were carefully optimized, and a linear range of 0.1-3.5 μg mL^{-1} with a good correlation coefficient between fluorescent intensity and concentration of sulpiride was found at optimum parameters. The LOD and LOQ were found to be 11 and 39 μg $mL^{-1,}$ respectively. The proposed method was successfully used for the quantification of sulpiride in bulk powder and commercial formulations. The effect of common pharmaceutical excipients and co-administered drugs was also studied and no interferences were observed. The validity of the method was tested by analyzing sulpiride in bulk powder and pharmaceutical formulations through recovery studies. Recoveries (%) were obtained from 98.62 to 100.24% for bulk powder, and 97.09 to 100.57% for commercial formulations.

In another study carried out by Walash*et al.*, 2012, a new simple, rapid and sensitive reversed-phase liquid chromatographic method was developed and validated for the simultaneous determination of Sulpiride (SUL) and mebeverine hydrochloride (MEB) in the presence of their impurities and degradation products [5]. The separation of these compounds was achieved within 6 min on a 250 mm, 4.6 mm i.e., 5 μm particle size Waters®-C18 column using an isocratic mobile phase containing a mixture of acetonitrile and 0.01 M dihydrogenphosphate buffer (45:55) at pH = 4.0. The analysis was performed at a flow rate of 1.0 mL/min with fluorescence detection at excitation 300 nm and emission at 365 nm. The concentration-response relationship was linear over a concentration range of 10-100 ng/mL for both MEB and SUL, with a limit of detection 0.73 ng/mL and 0.85 ng/mL for MEB and SUL, respectively.

The Levosulpiride in bulk and Pharmaceutical formulation was estimated by a validated UV-Visible spectrophotometer method. The λ_{max} obtained for Levosulpiride was 288.1 nm in 0.1 N HCl [6]. The drug shows linearity in a concentration range of 6- 36 μg/mL. The correlation coefficient for the standard graph was found to be 0.999. The assay percentage of the marketed formulation obtained using the proposed method was in good agreement with the label claim. The accuracy of the method was checked by a recovery experiment performed at three different levels (80%, 100%, and 120%), and the percentage recovery was in the range 98.00-102.00%. The % RSD found was low, which in turn is an indication of the accuracy and reproducibility of the method. A precision study of the method was carried out, examining intra-day, inter-day variations, and repeatability, which showed good agreement with % RSD. The proposed method was found to be rugged and robust. Hence, the above method can be applied for routine analysis of Levosulpiride in bulk and in pharmaceutical dosage form.

Validated sensitive and highly selective stability indicating methods are adopted by Naguib and Abdelkawy (2010)for simultaneous quantitative determination of sulpiride and mebeverine hydrochloride in the presence of their reported impurities and hydrolytic degrades, whether in pure forms or in pharmaceutical formulation [7]. The first method was High Performance Liquid Chromatography, where the mixture of sulpiride and mebeverine hydrochloride, together with the reported interferents plus metopimazine as internal standard, is separated on a reversed phase cyano column (5 μm ps, 250 mm × 4.6 id) using acetonitrile: water (70:30 v/v) adjusted to pH = 7 as a mobile phase. The drugs were detected at 221 nm over a concentration range of 5-40 μg mL^{-1} and 5-60 μg mL^{-1} with mean percentage recoveries of 99.75% (S.D. 0.910) and 99.99% (S.D. 0.450) for sulpiride and mebeverine hydrochloride, respectively.

Two simple, accurate, precise, economical procedures, entailing neither irksome sample treatment nor tedious extraction process, have been developed for the simultaneous estimation of Rabeprazole sodium and levosulpiride in combined tablet dosage form [8]. The first method was based on employing the simultaneous equation method for the analysis of both drugs. Rabeprazole sodium and

levosulpiride have shown absorbance maxima at 284 and 232 nm in methanol, respectively. The second method was based on the derivative spectrophotometric method, involving the determination of both drugs at their respective zero crossing points (ZCP).

Manjunath and colleagues developed four new, simple, precise, and economical spectrophotometric methods for the estimation of levosulpiride in bulk drug and pharmaceutical formulations [9]. Method A (1, 10-Phenanthroline) and method B (2, 2';-by pyridine) are based on oxidation followed by complex formation reaction. Method C (FC) and Method D ($KMnO_4$) are based on Oxidation/Reduction reactions. Levosulpiride was estimated at 506 nm, 531 nm, 726 nm and 609 nm for Methods A, B, C and D, respectively. Linearity ranges were found to be 50-250 µg/mL for Method A and B, and 10-50 µg/mL for Method C and D. The proposed methods were successfully applied for the determination of Levosulpiride in pharmaceutical formulations.

Simple, sensitive, and extraction-free spectrophotometric methods have been developed for the determination of three antipsychotic drugs, namely Aripiprazole (ARP), Clozapine (CLP), and Sulpiride (SUP), both in tablets and in biological fluids [10]. Methods: Two spectrophotometric methods are based on the formation of yellow colored ion-pair complexes between the studied drugs and two sulphonphthalein acid dyes, Bromophenol Blue (BPB) and Bromothymol Blue (BTB), with absorption maxima at 408 and 406 nm, respectively.

Parmar *et al.* (2012) used first-order derivative spectrophotometry to allow the simultaneous determination of levosulpiride and pantoprazole in fixed-dose combination products [11]. The wavelengths 252.5 nm and 291.0 nm of the first derivative spectrum were selected for the estimation of levosulpiride and pantoprazole, respectively, without mutual interference. The method was linear in the concentration range 25-125 µg/mL and 5-25 µg/mL for levosulpiride and pantoprazole, respectively. Validation studies confirmed the accuracy and precision of the proposed method. The result of the formulation analysis shows that the proposed method can be successfully used for the simultaneous estimation of both drugs in their combined capsule dosage form.

Kumar et al. (2017) developed a simple, accurate, precise, and economical spectrophotometric method for the estimation of levosulpiride in bulk form as well as in marketed formulations [12]. The estimation of Levosulpiride was done at 291.2 nm in a pH 6.8 phosphate buffer using a UV-Visible double beam spectrophotometer. In the developed method, linearity over the concentration range of 10-100 µg/mL of Levosulpiride was observed and was found in agreement with Beer's law. The linear regression was found to be 0.999. The results of the analysis have been validated statistically, and recovery studies confirmed the accuracy of the proposed method. The precision (intra-day and inter-day) of the method was found within limits (RSD<2%). The sensitivity of the method was assessed by determining the limit of detection and limit of quantification. The percentage of Levosulpiride in the marketed formulation (LEFIT-50) was observed to be 99.46%.

HariBhaskar *et al.* (2020) used a validated UV–Visible spectrophotometric technique to assess the levosulpiride concentration in both bulk drug and pharmaceutical formulations. In 0.1 N HCl, the maximum wavelength (λmax) for levosulpiride was measured at 288.1 nm [13] . The drug exhibited linearity over the concentration range of 6 to 36 µg/mL. The standard graph showed a correlation value of 0.999. The suggested procedure produced test percentages of commercial formulations that were consistent with the claims made on the label. A recovery experiment was conducted at three distinct levels (80%, 100%, and 120% recovery) to verify the method's accuracy. The percentage recovery ranged from 98.00% to 102.00%. The low % RSD confirmed the method's accuracy and repeatability. Experimentation with the method's repeatability, precision, and intra- and inter-day fluctuations showed that it agreed well with % RSD. The suggested approach was determined to be strong and resilient. Levosulpiride, both in bulk and medicinal dose form, may be routinely analysed using the approach above.

Mullapudi *et al.* (2013) [14] developed a simple, selective, rapid, precise, and economical reverse-phase high-performance liquid chromatographic method for the simultaneous estimation of levosulpiride and rabeprazole in pharmaceutical tablet dosage forms. The mobile phase consisted of 60:40% (v/v) of Methanol and

0.1% v/v orthophosphoric acid, operated in isocratic mode. The flow rate is 1.0 mL/min. Chromatographic separation of Levosulpiride and Rabeprazole was performed on AGILENT POLARIS C18 column (150 X 4.6 mm id, ODS 2, 5 μm). The wavelength of detection is 232 nm. The injection volume is 20 μL. The retention time of Levosulpiride and Rabeprazole are 2.1±0.10 min and 4.1±0.10 min, respectively. The run time of the analysis is 6 min. The developed method was validated for parameters such as accuracy, precision, linearity, limit of detection, limit of quantitation and solution stability. The influence of acid, alkaline, oxidative, and photolytic stress conditions on both drugs was studied. Results indicated complete degradation in alkaline medium for Levosulpiride and Rabeprazole. The proposed method has been successfully used for the estimation of tablet dosage forms.

Jain *et al.* (2012) [15] developed simple, accurate, reproducible, and economical methods that require no prior separation procedures for the simultaneous estimation of levosulpiride and esomeprazole in capsule dosage forms. The first method employs the formation and solving of simultaneous equations using 234 nm and 300 nm as analytical wavelengths for both drugs in methanol. The second method is based on Q value analysis, using the measurement of absorptivity at 241 nm (an isosbestic point) and 300 nm. Levosulpiride and esomeprazole, at their respective λmax of 234 nm and 300 nm and at the isosbestic point of 241 nm, show linearity over the concentration range of 1–20 μg/mL.

CONCLUSION

Literature surveys suggest that various UV and a few simultaneous methods have been developed and reported. Methods are developed based on their solubility and maximum absorbance at a specific wavelength within the ultraviolet region (200-400 nm). The published methods were validated for various parameters as per ICH guidelines. Statistical analysis proved that the published methods were reproducible and selective. Thus, it can be concluded that the reported and published methods can be successfully applied for the estimation of Sulpiride as API and pharmaceutical dosage form.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

FTIR: Fourier Transform Infrared spectroscopy; **μgm**: Micro gram; **HCl**: Hydrochloric Acid; **ICH**: International council of Harmonization.

SUMMARY

The overall Review of the literature survey reveals that the estimation of sulpiride using UV-VIS spectroscopy is a method development and Validation Approach as per the Quality Guidelines of the the International Council of Harmonization (ICH) and USFDA Guidelines. In this, we will obtain accurate, precise, and most Feasible Comprehensive information on Sulpiride Drug as API and Marketed dosage form. A novel developed method has the potential to yield the best Results and is less economical compared to other methods in terms of solvent usage and time.

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Cite this article : Nandankumar K, Kushala P, Harshitha A S, Shankar Prasad D B, Sanjay S. New Analytical Method Development and Validation of UV -visible Spectroscopy for the Estimation of Sulpiride: A Narrative Review. Asian J. Pharm. Health. Sci.. 2025;15(1):3041-3046. DOI: 10.5530/ajphs.2025.15.75