PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

Review Article

A Review on Analytical Methods for Determination of Levosulpiride in Pharmaceutical Dosage Forms and Biological Sample

Monika A. Rana*, Hasumati A. Raj
Department of Quality Assurance
Shree Dhanvantary College of Pharmacy,
Kim, Gujarat, India
*monika92rana@gmail.com

ABSTRACT

Levosulpiride is an atypical antipsychotic agent. Levosulpiride is the levo enantiomer of sulpiride. It is a substitute benzamide which is meant to be used for several indications: depression, psychosis, somatoform disorders, emesis and dyspepsia. It blocks the presynaptic dopaminergic D2 receptor. Chemically it is N-[[(2S)-1-Ethylpyrrolidin-2-yl] methyl]-2-methoxy-5 sulfamoylbenzamide. several method such as HPLC in human plasma, area under curve, stability by RP-HPLC is done. The parent drug is given in a dose of 400-1800 mg orally. According to literature survey study of impurity profiling of LIVOSULPIRIDE in presence of intermediate has not been reported.

Keywords: Levosulpiride, Analytical method

INTRODUCTION [1-2]

Levosulpiride is the levo enantiomer of sulpiride. Sulpiride contain NLT 98.5% and NMT the equivalent of 101.0 % of (RS)-5-sulphamoly-N-[(1-ethylpyrrolidine-2-yl)methyl]-2-methoxybenzamide. Levosulpiride is N-[[(2S)-1-Ethylpyrrolidin-2-yl] methyl]-2-methoxy-5 sulfamoylbenzamide. It is antipsychotic agent. It is almost white, crystalline power. The plasma t1/2 of the drug is about 6-8 hours. The drug is chiefly excreted through the renal route. Its chemical structure is as follows:

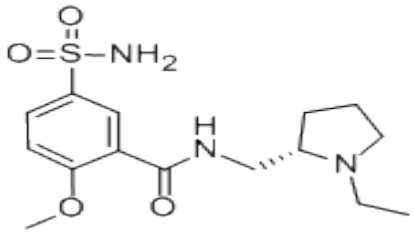

Figure No:1 Levosulpiride

TABLE NO:1Reported Analytical Methods for LEVOSULPIRIDE in Pharmaceutical Dosage form and Active Pharmaceutical Ingredient.

Drug /Drug combination	Matrix	Method	Description	Ref. No
Levosulpiride	Pharma	UV	Levosulpiride was estimated at 291 nm in 0.1N	[3]

How to cite this article: MA Rana, R Hasumati; A Review on Analytical Methods for Determination of Levosulpiride in Pharmaceutical Dosage Forms and Biological Sample; PharmaTutor; 2014; 2(11); 66-74

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

	ceutical dosage form	spectrophotometry, Derivative spectroscopy	NaOH (Method A), 288.7 nm in Methanol (Method B) and first order derivative spectrum in Methanol at 282.4 nm with n=1 (Method C). Linearity range was found to be 25-125 µg/ml in all the three methods. The apparent molar absorptivity was found to be 2.14 X 103 lmol-1cm-1 (Method A), 2.39 X 103 lmol-1cm-1 (Method B) and 2.07 X 103 lmol-1cm-1 (MethodC).	
Levosulpiride	Tablet	Area under curve, difference spectroscopy	AUC in which area under curve was integrated in the wavelength range of 284–294 nm using methanol as solvent. Difference Spectroscopic method, the proposed method is based on the principle that Levosulpiride can exhibit two different chemical form in basic and acidic medium that differ in the absorption spectra in basic acidic medium. The difference spectrum of Levosulpiride in 0.01N NaOH was recorded by taking Levosulpiride in 0.01N HCL solution as blank. The difference spectrum showed that the maxima at 227nm and minima at 246nm. Linearity for the detector response was observed in the concentration range of 5-25 µg/ml for both the methods. The linear regression for Method A and B were found to be 0.999 and 0.999respectively.	[4]
Levosulpiride	Tablet	HPLC	Peak area ratio of the analyte to internal standard was used for the quantification of serum samples. The study was conducted using an open, randomized crossover design to determine relative bioavailability of levosulpiride tablets (test and reference preparations) in twelve healthy male volunteers following single oral administration. The pharmacokinetic parameters like area under the plasma-concentration-time curve from zero to the last measurable levosulpiride sample time and to infinity (AUC0-t and AUC0-∞), maximum concentration (Cmax), time to maximum concentration (Tmax), and elimination rate constant (Ke) and elimination half-life (T1/2) were determined by non compartmental method. The bioequivalence between the two formulations was assessed by calculating individual peak plasma concentration (Cmax) and area under the curve (AUC0-t) ratio (Test/Reference). The assay showed excellent relationships between peak height ratios and plasma concentrations ($r^2 \geq 0.9925$). The	[5]

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

			geometric mean of Levosulpiride 100 mg tablet (test/ reference) individual percentage ratio was 100% for AUC0-t and 99% for Cmax. The 90% confidence intervals were 99.2-100.1% and 98.4-99.9%, respectively. The relative bioavailability between test and reference was 99.54%. Since the 90% CI for both AUC0-α, and Cmax lies within the 80-125% proposed by the FDA, it was concluded that both preparations of levosulpiride 100 mg tablets were bioequivalent in terms of both the rate and extent of absorption.	
Levosulpiride HCL	Tablet	Stability Indicating RP-HPLC	A sunfire C-18, 4.5mm column with mobile phase containing methanol-water (10:90, v/v) was used. The flow rate was 1.0 mL min^{-1} and effluents were monitored at 232 nm. The retention time of Levosulpiride was 5.5 min. Levosulpiride stock solutions were subjected to acid and alkali hydrolysis, chemical oxidation, wet hydrolysis, dry heat degradation and sun light degradation. The degraded product peaks were well resolved from the pure drug peak with significant difference in their retention time values. Stressed samples were assayed using developed LC method.	[6]
Levosulpiride	Tablet	Stability Indicating HPTLC	In this method mobile phase consisting of ethyl acetate:methanol:toluene: triethylamine (4.5:3.5:2: 0.2v/v/v/v) and detection was carried out at 238 nm. Linearity was observed over the concentration range 100 500 ng/spot. Levosulpiride was subjected to stress conditions including acidic, alkaline, oxidation and photolytic degradation. Levosulpirideis more sensitive towards alkaline degradation. The content of levosulpiride in marketed formulation was found to be 99.13 %±0.38 of labeled amount.	[7]

TABLE NO:2 Reported Analytical Methods for LEVOSULPIRIDE AND IT COMBINATION in Pharmaceutical Dosage form and Active Pharmaceutical Ingredient.

Drug /drug combination	Matrix	Method	Description	Ref. No
Levosulpiride and pantoprazole	Pharmaceutical dosage form	UV for simultaneous estimation	In this study a first-derivative spectroscopic method was used for simultaneous determination of pantoprazole and levosulpiride using the zero-crossing technique. The measurements were carried out at wavelengths of 269 and 249 nm for	[8]

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

			Pantoprazole and Levosulpiride respectively. The method was found to be linear (r2>0.9929) in the range of 10-50 µg/ml for Pantoprazole at 269 nm. The linear correlation was obtained (r2>0.9948) in the range of 10-50 µg/ml for Levosulpiride at 249 nm. The limit of determination was 0.69 and 0.58 µg/ml for pantoprazole and levosulpiride respectively. The limit of quantification was 2.06 and 1.69 µg/ml.	
Levosulpiride and pantoprazole sodium	Capsule	Simultaneous Equation Spectrophotometric Method	Simultaneous equation was developed at 290 and 232 nm. The method was found to be linear in the range of 4–12 µg/mL for pantoprazole sodium and 8–20 µg/mL for levosulpiride while accuracy of the method was confirmed by recovery studies of capsule dosage form and was found to be 100.23–100.99% and 100.51–100.94% for pantoprazole sodium and levosulpiride, respectively, in their capsule dosage form.	[9]
Levosulpiride and pantoprazole sodium	Capsule	Simultaneous estimation	Simultaneous estimation and Q-absorbance Ratio method by using 287 nm and 231 nm as absorbance maxima (λ max) for Pantoprazole sodium and Levosulpiride respectively and 248 nm (isoabsorptive point).A methanol was used as Solvent. Linearity was observed in the concentration range of 5-30 µg/mL for pantoprazole sodium and 5-30 µg/mL for Levosulpiride.	[10]
Levosulpiride and rabeprazole sodium	Tablet	Simultaneous equation method, Derivative spectrophotometry	The first method was based on employing simultaneous equation method for 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 derivative spectrophotometric method involving the determination of both the drugs at their respective zero crossing point (ZCP). The first order derivative spectrum was obtained in methanol and the determinations were made at 231.2 nm (ZCP of levosulpiride) for rabeprazole sodium and 246.2 nm (ZCP of rabeprazole sodium) for levosulpiride. The linearity was obeyed in the concentration range of 1-20 µg/ml for both drugs. The medium of dissolution was used 900 ml of phosphate buffer pH 7.4 using a USP type 2 apparatus at a stirring rate of 100 rpm. The drug release was evaluated by developed spectroscopic	[11]

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

			methods.	
Levosulpiride and Rabeprazole sodium	Tablet	Simultaneous estimation by UV	The method is based on the measurement of absorbance of Rabeprazole sodium and Levosulpirideat 260 nm which is the Isobestic point and 284 nm the λmax of Rabeprazole Sodium. The method obeyed Beer's law in the concentration range of 3-18 µg /ml forRabeprazole sodium and15-90 µg /ml for Levosulpiride.	[12]
Levosulpiride and Esomeprazole	Capsule	Simultaneous estimation	Estimation was carried out by multicomponentmode of analysis at selected wavelength of 277 nm and 283 nm for Levosulpiride and Esomeprazolerespectively in methanol. The method was found to be linear in the range of 1-40 µg/ml for Levosulpiride and 1-30µg/ml for Esomeprazole while accuracy of the method was confirmed by recovery studies of solid dosages forms andwas found to be for batch-A 98.33% and 98.44% for Batch-B 99.24% and 98.77% for Levosulpiride andEsomeprazole respectively. Initially lab samples were utilized to validate developed method according to ICHguidelines followed by determination of % concentration of Levosulpiride and Esomeprazole in marketedformulation that was found to be for Batch-A 98.07 ±0.51 and 96.81± 0.51 for Batch-B 98.23 ±0.65 and 97.98± 0.65respectively. The values of precision and robustness lie within acceptable limit.	[13]
Levosulpiride and pantoprazole sodium		HPLC	In this Hyperchrom ODS-BP C18250 x 4.6 mm i.d., (5 mm) was used as Stationary Phase. Acetonitrile: 0.05 M Potassium Dihydrogen Ortho Phosphate (50:50v/v) (pH 3.0 adjusted by O-phosphoric acid) as mobile phase. LEVO and PANTO showed Rt value 3.344 + 0.005 and 4.753 + 0.006 and scanned at 288 nm. The method was validated in terms of linearity 38 – 114 µg/ml for LEVO and 20 – 60 µg/ml for LEVO .The limit of detection for LEVO and PANTO were found to be 1.0178 µg/ml and 0.5481 µg/ml, respectively and limit of quantification for LEVO and PANTO were found to be 3.0818 µg/ml and 1.660 µg/ml, respectively. The mean recovery was 98.32– 101.00% and 98.50– 101.85 % for LEVO and PANTO respectively.	[14]

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

Levosulpiride and Rabeprazole	Combined dosage form	Simultaneous estimations by HPLC	The linearity range for LS and RS was found to be 30-150 µg/ml and 8-40 µg/ml, respectively. The recovery studies were performed at three different levels and the average results were found to be in the range of 99.14-100.64 % for LS and 99.47-100.46% for RS.	[15]
Levosulpiride and Esomeprazole	Capsule	RP-HPLC	Chromatographic separations was achieved on a C-18 (5µm, 250x4.6 mm) HPLC column within a runtime of 10 min. Isocratic mobile phase contain methanol: buffer (pH 3) (65:35% v/v) and flow rate was maintained at 1.0 mL/min. Elute was monitored at 260 nm. Levosulpiride was eluted at 2.7 min and Esomeprazole at 5.7 min. Linearity was studied in the concentration range of 5 to 30 µg mL-1 and 10 to 60 µg/ mL for esomeprazole and levosulpiride respectively, with a correlation coefficient of 0.9995 and 0.9993 respectively.	[16]
Levosulpiride and Rabeprazole	Tablet	Simultaneous estimation by RP-HPLC	The detection was carried out at 216 nm for both drug. The retention time for LEVO and RAB were found to be 4.918 min and 5.873 min, respectively. Linearity was observed in the concentration range from 50% to 150% of nominal concentration of RAB and LEVO correlation coefficient was 0.999 for both drugs. The limit of detection and quantification of LEVO were 0.021 mg/ml and 0.0731 mg/ml respectively while for RAB it was 0.06 % mg/ml and 20% mg/ml respectively. The % recovery was found to be within the limits of the acceptance criteria with average recovery of 101.3% for LEVO and 99.3% for RAB. The % RSD below 2.0 shows the high precision of proposed method.	[17]
Levosulpiride and Rabeprazole sodium	Tablet	STABILITY INDICATING RP-HPLC	The quantification of the drug was carried out using Hypersil BDS C18 250mm × 4.6mm × 5/m or its equivalent in isocratic mode, with mobile phase compressing of Buffer: Acetonitrile (72:28) the flow rate was 1.5ml/min and the detection was carried at 282nm. The retention time for Levosulpiride and Rabeprazole sodium was found to be 2.23and 7.27min respectively. The percent assay was found to be 99.7%.	[18]

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

Levosulpiride and Esomeprazole	Capsule	HPTLC	Separation of Levosulpiride and Esomeprazole was achieved on precoated aluminum plates with silica gel 60 F254. Solvent system used for separation was ethyl acetate: methanol: ammonia (9: 1: 0.5, v/v/v). Detection wavelength selected for the scanning in reflectance absorbance mode was 216 nm. The retardation factor (Rf) for LSP and ESP were found to be 0.30 ± 0.02 and 0.64 ± 0.02, respectively. The method was validated as per the ICH Q2 (R1) guidelines.	[19]
Levosulpiride and Rabeprazole sodium	Tablet	UV and RP-HPLC	Simultaneous equation method at 232 nm for Levosulpiride and 284 nm for Rabeprazole Sodium. 1st order derivative method utilize absorbance measurement at 247 nm for Levosulpiride and 291.60 nm for Rabeprazole Sodium. In RP-HPLC method for simultaneous estimation of Levosulpiride and Rabeprazole Sodium separation was achieved on a Phenomenexluna ODS C18 (250mm X 4.6 mm i.d., 5 µm particle size) with an mobile phase acetonitrile: phosphate buffer pH 5 (adjusted with Sodium hydroxide) in the ratio of 55:45 v/v. The mobile phase at a flow rate of 1.0 ml/min, Injection volume 20µl and detection wavelength was kept at 288 nm. The retention time Levosulpiride and Rabeprazole Sodium was 2.31±0.1min and 3.85 ±0.1min, respectively. The linearity lies between 5-30 µg/ml for Levosulpiride and 2-12 µg/ml for Rabeprazole Sodium.	[20]
Levosulpiride and rabeprazole	Capsule	UPLC	A desirability function applied to the optimized conditions predicted the peak resolution between 2.2 and 2.7 for the Rabeprazole & Rabeprazole Sulfone impurity. The chromatographic method employed an Acquity UPLC, BEH C18 column (100 x 2.1 mm i.d., 1.7 µm particle size) with the mobile phase consisting of a phosphate buffer, pH 6.5, and acetonitrile in a gradient program. The flow rate and injection volumes were 0.45 mL/min & 5 µl, respectively, and detection was done at 254 nm.	[21]

CONCLUSION

According to the literature review I concluded that for Levosulpiride and its combination with other drug spectroscopy and chromatography method available. This all methods found to be simple, accurate, economic and reproducible in nature.

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

↓ REFERENCES

1. Sparsh Gupta, G. R. G., Sumita Halder, Krishna Kishore Sharma. "Levosulpiride : A Review." Drug Review Vol, October 2007. 10 (No.2): 14-146.
2. British Pharmacopoeia The Department of Health, London:The stationary Office,1252-1253, (1998)
3. Shobha Manjunath, V. C., S.Sandeep. "Spectrophotometric Estimation Of Levosulpiride In Bulk Drug And Formulations." International Journal of Pharmacy and Pharmaceutical Sciences 2011, Vol 3(Issue 2): 135-137.
4. Dhwani D. Brahmbhatt*, M. B. P., Jignesh C. Patel. "Development and validation for Estimation of Levosulpiride by Area Under Curve and Difference Spectrophotometric Method." International Journal of ChemTech Research. July-Sept 2012, Vol.4(No.3): pp 945-950.
5. Bijay Kumar Sahoo*, A. D., Jayanti Mukherjee, Soumendra Darbar and Tapan Kumar Pal. "Determination of Levosulpiride in Human Plasma Using HPLC Method and its Application to Bioequivalence Study." Research Article. 2012, Volume 1(Issue 11): Page 2 of 5.
6. Chhalotiya, U. K.. "Development of Stability Indicating RP-HPLC Method for Determination of Levosulpiride Hydrochloride In Bulk And Pharmaceutical Dosage Form." International Journal of Advances in Pharmaceutical Analysis. 2012, Vol 2(No 2).
7. Parmar Gunjansinha*, N. K., Shah Shailesha, Chauhan Renua & Shah Dinesha. "Development and Validation of Stability Indicating HPTLC Method for the Estimation of Levosulpiride in Tablet Dosage Form." Analytical Chemistry. 2013, Volume 3(Issue 5-6).
8. Sahdev Chosla*1, V. B., Hiren Kadikar1. "Development and Validation of UV Spectrophotometric Method for Simultaneous Estimation of Pantoprazole and Levosulpiride in Pharmaceutical Dosage form." American Journal Of Pharmatech Research. Sun, 6 Jul 2014
9. Dimal A. Shah, A. P., Sunil L. Baldania, Usmangani K. Chhalotiya, and Kashyap K. Bhatt. "Simultaneous Estimation of Pantoprazole Sodium and Levosulpiride in Capsule Dosage Form by Simultaneous Equation Spectrophotometric Method." International Scholarly Research. 2013, 4.
10. Tulsi J. Chaudhary*1, S. B.. "Development and Validation of Analytical Methods for Simultaneous Estimation of Pantoprazole Sodium and Levosulpiride in Bulk and their combined dosage form." American Journal Of Pharmatech Research. Tue, 8 Jul 2014.
11. Poornima R. Shetty, D. D. P.. "Applications of simultaneous equation method and derivative method for the determination of rabeprazole sodium and levosulpiride in pharmaceutical dosage form and dissolution samples." Journal of the Association of Arab Universities for Basic and Applied Sciences. April 2014, Volume 15: Pages 53–60.
12. Yoganand B. Deulgaonkar*, J. A. P., Moreshwar P. Mahajan and Sanjay D. Sawant. "UV spectrophotometric method for simultaneous estimation of rabeprazole sodium and levosulpiride in bulk and tablet dosage form." Scholars Research. 2013, 5(3): 163-168.
13. Yogesh P. Agrawal1, S. P. G., Ajay Verma2, Mona Y. Agrawal3 and Arun K. Gupta4. "Simultaneous estimation of esomeprazole and levosulpiride in solid dosage form." Pelagia Research Library. 2012, 3(3): 337-342.
14. Silkan Patel, K. P., Nikhil Parmar, Jagdish Kakadiya, Nehal Shah. "Development and Validation Of High Performance Liquid Chromatographic method for Levosulpiride and Pantoprazole sodium in Combined Dosage Form." Inventi Journals. 2013
15. S KPatel, P. P. D., M A Raval*. "Development And Validation of HighPerformance Liquid Chromatography Method For Simultaneous Estimation of Levosulpiride and Rabeprazole sodium In Combined Pharmaceutical Formulation." Inventi Journals. 2012.
16. Rakeshr. Jain, P. P., Sanjayb. Bari "Simultaneous Estimation Of Esomeprazole and Levosulpiride in

ISSN: 2347-7881

Bulk and in Capsule Formulation by RP-HPLC."
17. A. Sirisha*, A. R. K.. "Method Development and Validation of Simultaneous Estimation of Levosulpiride and Rabeprazole in bulk and pharmaceutical dosage form by RP-HPLC." International Research Journal of Pharmaceutical and Applied Sciences. 2012, 2((4):): 49-55.
18. B.Jagadeesh*2, N. A. A.. "Development And Validation Of Stability Indicating RP-HPLC Method For Simultaneous Estimation Of Levosulpiride and Rabeprazole Sodium." International Journal of Pharma and Bio Sciences. 2012 Oct, 3(4): 718 – 726.
19. Pravin D. Pawar, S. Y. G., Sachin E. Potawale, Kakasaheb R. Mahadik. "Validated Normal Phase HPTLC Method For Simultaneous Quantification Of Levosulpiride And Esomeprazole In Capsule Dosage Form." International Journal of Pharmacy and Pharmaceutical Sciences. 2014, Vol 6(Issue 2): 347-350.
20. Thakkar*, D. G. "Development and Validation of UV Spectroscopic and RP-HPLC method for Simultaneous Estimation of Levosulpiride and Rabeprazole Sodium in bulk and tablet dosage form." Journall Of Pharmaceutical science and bioscientific research. (May June 2013)Volume 3(Issue 3): 108-114.
21. Veera Raghava Raju thummala * 1, R. K. S., Satya Sankarsana Jagan Mohan Tharlapu 1, Mrutyunjaya Rao Ivaturi 2, Someswara Rao Nittala 2. "Development and Validation of a UPLC Method by the QbD-Approach for the Estimation of Rabeprazole and Levosulpiride from Capsules." Research article. 2014, 82: 307–326.