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Sensitive Analytical Liquid Chromatography-Tandem Mass Spectroscopy Method for the Estimation of Dexlansoprazole in Pharmaceutical Formulations

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ABSTRACT

A sensitive LC-MS/MS method has been developed and validated for the quantitative determination of Dexlansoprazole from the commercially available formulations. Omeprazole was used as the internal standard. Isocratic separation was achieved using Zorbax SB C_{18} column (4.6 × 100 mm, 3 μm) as a stationary phase and the mobile phase consists of (0.5 mM) Ammonium Acetate adjusted to pH 3.5: acetonitrile (30:70 V/V) with a flow of 0.5 mL/min. Detection was carried out by triple quadrupole mass spectrometry with electrospray ionization in positive mode with proton adducts at m/z 370.05 to 251.95 and 346.00 to 198.05 to monitor Dexlansoprazole and Omeprazole. The linearity of the method was found over a concentration range of 0.5-3000 ng/mL with a regression analysis of 0.9994. The percentage recovery of the present method was found to be 94.33 to 99.97%. The LC-MS/MS method was validated as per ICH guidelines. The developed method can be successfully applied for the estimation of Dexlansoprazole in the commercial formulation and in bulk drug.

INTRODUCTION

Dexlansoprazole 2-(R)-(+)-2-([3-methyl-4-(2,2,2 trifluoroethoxy)pyridine-2-yl]methylsulfinyl)-1H-benzo[dimidazole)} is a proton pump inhibitor (Figure 1). It is an enantiomer of lansoprazole (Nagaya, 1990; Metz, 2009). Dexlansoprazole is commercially available as delayed-release capsules (30 and 60 mg) (Dexilant, 2017; Dexlanzoprazole, 2017). Dexlansoprazole is used in the healing of erosive esophagitis, in maintaining of healed erosive esophagitis and non-erosive gastroesophageal reflux disease (Barbara and Radwan, 2015; Aslam et al., 2009) (GERD) associated with heartburn.

The literature survey revealed a stability method and an analytical method for Dexlansoprazole (DLP) was estimated by HPLC (Hotha et al., 2012; Sriharshaet al., 2015; Yanamadala et al., 2013) and to best of our knowledge, liquid chromatography-tandem mass spectroscopy has been previously reported in human plasma.

The aim of the current study was to develop a highly sensitive method for the estimation of Dexlansoprazole bulk and formulations and validate as per ICH guidelines (ICH, 1996).

MATERIALS AND METHODS

Materials

Working standard of Dexlansoprazole was provided as a gift sample from Indian Pharmacopoeia Commission, New Delhi, India and internal standard Omeprazole was purchased from Drugs testing laboratory, JSS College of Pharmacy, Ooty, India. Acetonitrile of LC-MS/MS grade by Sigma Aldrich, Ammonium Acetate by Rankem Fine Chemical Limited and Water of LC-MS/MS grade from Milli-Q RO system (Millipore, Bedford, USA) were used.

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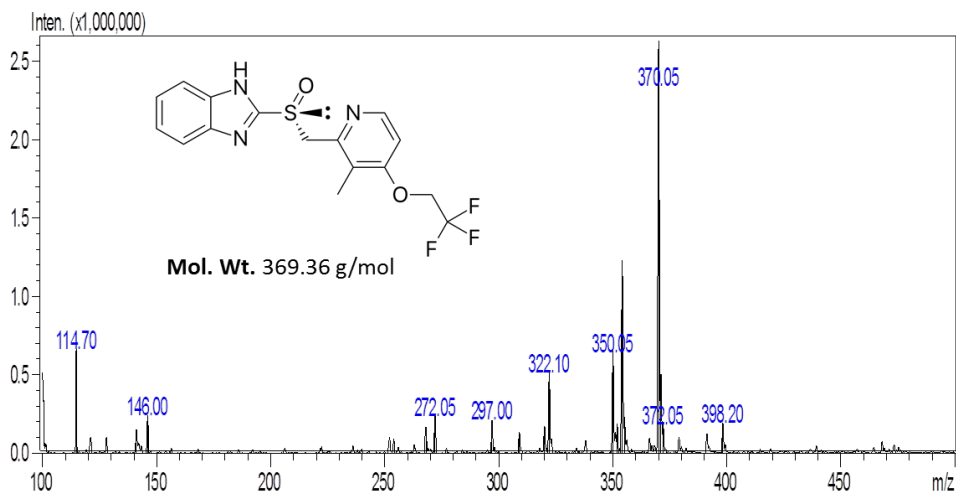*E-mail: snmeyyanathan @ jssuni.edu.in*

Fig. 1: Mass scan spectra of dexlansoprazole in positive mode.

Equipment and chromatographic conditions

LC system coupled with tandem quadrupole mass spectrometry (Shimadzu 8030, Tokyo Japan) equipped with electrospray ionization (ESI) interface, LC-20AD pump, SPD-M20 PDA detector, CTO-20AC column oven, CBM-20 alite controller and SIL-20AC autosampler was used. The data were recorded using Lab solution data station software. Isocratic separation was achieved using Zorbax SB C_{18} column (4.6 × 50 mm, 3 µm) as a stationary phase and the mobile phase consists of (0.5 mM) Ammonium acetate (pH 3.5): acetonitrile (30:70 V/V) with a flow of 0.5-mL/min and injection volume of 10 µl was employed.

Selection of a mass range

A 1000 ng/mL of Dexlansoprazole and Omeprazole was infused into the mass spectrometer directly and the conditions for the operation were optimized. Obtained transitions were 255→237.1 and 195→138.1 m/z was used to monitor Dexlansoprazole and Omeprazole (IS) (Figure 2b).

Sample preparation

Preparation of working standard solution

Dexlansoprazole was dissolving in 10 mL of acetonitrile to produce a concentration of 1 mg/mL. The stock solution was refrigerated at 2-8°C and stored. Further, the working solutions were obtained by diluting the stock solution with diluent acetonitrile.

Preparation of working omeprazole solution (IS)

Omeprazole solution was dissolving in 10 mL of acetonitrile to produce a stock solution of 1 mg/mL. The stock solution was refrigerated at 2-8°C and stored. Further, working solutions were obtained by diluting the stock solution with diluent acetonitrile.

Preparation of sample solution

Dexlansoprazole equivalent to 0.10 g was taken in a volumetric flask and dissolved in methanol and marked up with

acetonitrile to get 10 µg/mL. Further dilution of the above solution with the diluent acetonitrile to produce the concentration of 15, 750, 2500 ng/mL (LQC, MQC, and HQC).

Method validation

Validation of the method for specificity, linearity, accuracy, precision, range, quantitation limit, and detection limit, robustness, and system suitability as per the ICH guidelines (ICH, 1996).

Specificity

The analyte response measurement in the presence of other drugs, excipients, and their potential impurities can be termed as specificity.

Linearity

The average of six determinations at ten concentration levels covering the range of 0.5-3000 ng/mL for DLP, the evaluation of linearity was performed. Calculation of the coefficient correlation, slope and intercept values was done by using calibration curve for linearity evaluation.

Accuracy

The accuracy of the method was determined by recovery studies according to ICH guidelines. The pre-analyzed samples were spiked with standard drug DLP.

Precision

Evaluation of precision was carried out by inter-day and intra-day precision. Study samples consisted of three concentration levels (six replicates) of low (LQC), medium (MQC) and high (HQC) quality controls, i.e. 15, 750, 2500 ng/mL, respectively. The report used for precision was from the regressed concentration of the percent relative standard deviation (%RSD).

Limit of detection (LOD) and limit of quantification (LOQ)

Determination of LOD and LOQ was by the signal-to-noise ratio. LOD ratio was 3:1 whereas LOQ, the drug could be quantified with minimum peak area in the ratio of 10:1.
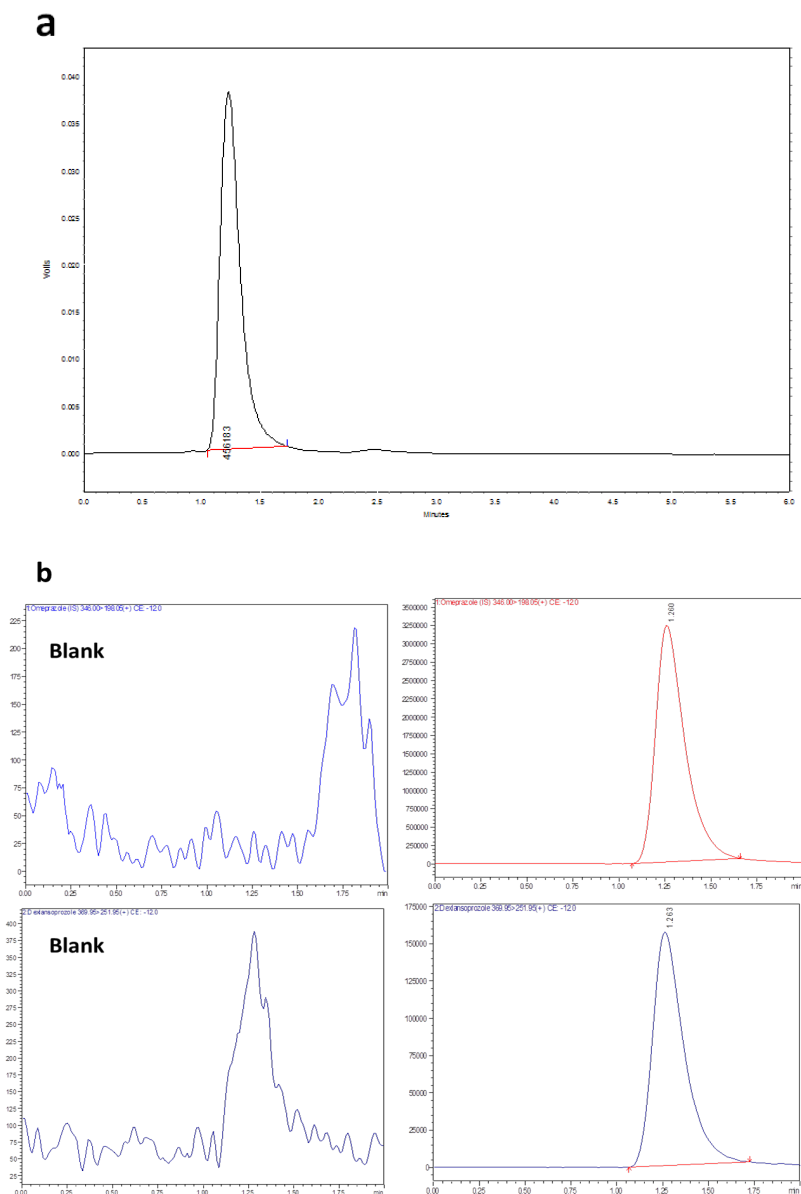
Fig. 2: (a) Typical HPLC chromatogram of dexlansoprazole in the formulation and (b) Typical LC-MS/MS chromatogram of dexlansoprazole in the formulation.

Robustness

The alteration in the condition of the experiment like operators, the source of reagents, similar type column and optimized conditions like pH, mobile phase ratio, and flow rate were studied for the robustness of the method.

System suitability

For method development, the test for system suitability is an integral part. Three replicates injections of the sample solution were evaluated for retention time (RT), a number of theoretical plates (N) and Tailing factor (T).

RESULTS AND DISCUSSION

Specificity

To determine that the excipients used are not interfering with the main compound peak, test for specificity needs to be done. No peaks were eluted along with the retention time of DLP (Figure 2a). Hence, the developed method results showed that it was selective for determination of DLP in the formulation.

Calibration curve

The evaluation of the method to be linear was by six determinations at ten concentration levels with a range of 0.5-3000 ng/mL for DLP and the standard deviation (SD) were found to be within the limits. A calibration curve was found to be linear with a mean regression of equation ($Y = 15.944x + 538.34$, $r^2 = 0.99942$, S.D. = 0.68) respectively, where the analyte peak area ratio to the IS (Omeprazole) is the Y and the analyte concentration in ng/mL is the X (Figure 3).
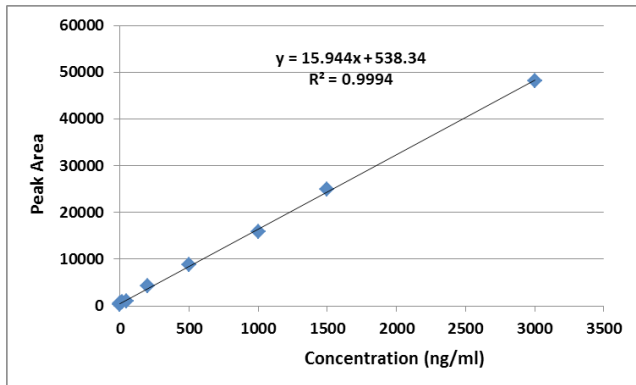
Fig. 3: Calibration curve of Dexlansoprazole at ten concentration levels (0.5-3000 ng/mL).

Accuracy

The accuracy of the method was carried out for three quality control (LQC, MQC, and HQC) samples by standard addition method, and the accuracy was found to be 96.00 to 99.83%. Application of the developed method for the estimation of a commercial formulation of DLP (Table 1).

Table 1: Accuracy and precision studies for the determination of Dexlansoprazole.

QC samples	Mean Conc. found (ng/mL) ± SD	Intraday		Inter-day	
		Accuracy (% N)	Precision (% CV)	Accuracy (%N)	Precision (% CV)
15	12.83 ± 0.12	96.00	2.83	84.0	2.23
750	720.7 ± 0.08	97.81	2.78	96.36	2.92
2500	2498 ± 0.02	99.83	0.96	98.14	2.03

Table 2: Recovery studies for formulation.

Formulation	Label claim	Amount taken for Assay (ng/mL)	Amount found ± SD (n = 6)	% Recovery
T₁	30 mg	15	14.55 ± 0.01	97.00
		750	749.9 ± 0.03	99.80
		2500	2499.5 ± 0.03	99.90
T₂	60 mg	15	14.15 ± 0.01	94.33
		750	748.45 ± 0.05	99.79
		2500	2499.3 ± 0.15	99.97

Precision

The precision of the method was determined by the intra-day and inter-day precision studies at three different concentrations and they were found to be within the limits (Table 1).

Limit of detection and limit of quantification

The lowest limit detected for the method for DLP was at 0.3 ng/mL based on the signal-to-noise ratio 3:1. Due to the increase in the sensitivity of the method, quantification was done at 0.5 ng/mL for Dexlansoprazole.

Robustness

The robustness of the method was determined by alteration of the chromatographic conditions and the results obtained were found to be within the limits proving that the developed method was found to be robust.

CONCLUSION

A novel simple, precise, accurate and a validated, liquid chromatography-tandem mass spectroscopy method has been developed and validated. The developed method can be successfully applied for the estimation of DLP in the commercial formulation and in bulk drug.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

ACKNOWLEDGMENT

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