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ANALYTICAL TECHNIQUES FOR THE ESTIMATION OF MELOXICAM IN BULK AND PHARMACEUTICAL DOSAGE FORMS: A REVIEW

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ABSTRACT

Meloxicam is 4-hydroxy-2-methyl-N-(5-methyl-1,3-thiazol-2-yl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide is an selective to cyclooxygenase-2 (Cox-2) inhibitor and used in analgesic, antipyretic activities belongs to (NSAIDS)and in rheumatoid arthritis. Literature survey reveals that meloxicam is estimated individually by uv spectrometry, RP-HPLC, LC/MS, LC/MS/MS and stability indicating HPLC and TLC.

Keywords: Meloxicam, RP-HPLC,LC/MS/MS.LC/MS.HPTLC,TLC.

INTRODUCTION

Meloxicam is 4-hydroxy-2-methyl-N-(5-methyl-1,3-thiazol-2-yl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide having molecular formula C14H13N3O4S2, molecular weight 351.4, melting point 254ºc (structure). It is practically insoluble in water, slightly soluble in acetone, soluble in dimethyl formamide, very slightly soluble in ethanol (96%), and methanol. Meloxicam is a non steroidal anti-inflammatory oxicam derivative, which selectively inhibits cyclooxygenase-2 (Cox-2) and has analgesic and antipyretic activities [1, 2]. The usual dosage of meloxicam is 7.5 mg once in a day, which may be doubled to 15 mg per day in acute painful conditions with severe pain like rheumatoid arthritis.Various analytical techniques viz, UV spectrophotometry, fluorimetry, capillary electrophoresis, pulse polarography ,electrochemical oxidation, electrochemical reduction and voltametry are reported for the analysis of MLX in pharmaceuticals. HPLC is the most commonly used method for analysis of MLX. An extensive literature survey reveals few HPLC methods for estimation of MLX in pharmaceutical dosage forms as well as biological fluids; however, not all of these are stability indicating and some of them make use of buffer in the mobile phase. Most of the reported methods either do not include stress degradation studies or are not completely validated, and they are cumbersome, time-consuming and expensive.

ANALYTICAL METHODOLIGIES

A simple, precise, accurate and economical RP-HPLC method has been developed and validated for the assay of Meloxicam tablets. The method was developed using pH 7.0 Phosphate buffer: Acetonitrile (40:60 v/v) in isocratic mode and Waters Xterra C 18 (150 X 4.6mm), 5µ column. Flow rate and detection wavelengths were fixed at 0.8 ml/min and 344 nm. Retention time for Meloxicam was found to be 2.448 minutes. Method was validated as per ICH guidelines to test its suitability for intended purpose. Linearity range for Meloxicam was set at 10-75 µg/ml with correlation coefficient 0.999. Accuracy values for method were found to be 99.53- 99.66%. Method found to be robust against changes in flow rate, organic composition, pH of mobile phase and detection wavelength. The proposed method is suitable for quality control analysis of Meloxicam tablets. Key words: Meloxicam, RP-HPLC, Method development and Validation [3].

A simple, accurate and sensitive UVSpectro

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photometric method was developed for the analysis of MEL in tablets. The analyses were performed in 100 mM borate buffer (pH 8.5). The measurement of UV absorbance was done at 363 nm. The developed method was validated respect to stability, linearity, precision, accuracy, selectivity / sensitivity, robustness and ruggedness and applied to the determination of MEL in six pharmaceutical preparations including two dosage forms. The obtained data from developed method was compared with the CE method in the literature. It was concluded that the developed method was suitable for the quality control of MEL in pharmaceuticals [4].

Developing and validating a simple, economic, sensitive and selective HPLC method with UV detection (362nm) for the quantitative determination of meloxicam (MLX) in bulk drug, pharmaceutical dosage form and human plasma. Reversed phase chromatographic analysis was performed on a C18 HI-Q-Sil column with acetonitrile: water: 1% aqueous (aq.) glacial acetic acid [56:34:10 % v/v/v] as the mobile phase system. Mobile flow rate was 1ml/min. Piroxicam was used as the internal standard (IS). The method was validated as per International Conference on Harmonization (ICH) guidelines. The developed method demonstrated good resolution between MLX and IS. It was selective to MLX and was able to resolve the drug peak from IS and formulation excipients. The retention time for MLX and IS were approximately 6.9 and 5.8 min, respectively. The polynomial regression for the calibration plots showed good linear relationship with coefficient of correlation, r = 0.9995 ± 0.0002; slope = 28729.04 ± 274.17 and intercept = 20725.38 ± 3191.08 (n=3) over the concentration range studied. The range of reliable quantification was set at 0.3-20 µg/ml, LOD and LOQ were found to be 0.39µg/ml and 1.19µg/ml respectively. Accuracy ranged from 99.96-103.75% and the % relative standard deviation (RSD) for both intra-day and inter-day precision was less than 2%. MLX showed minor degradation in acidic and basic conditions. There was no degradation of MLX in the presence of oxidative, neutral, photolytic, dry heat and wet heat stress conditions. In plasma studies, following a single-step liquid- liquid extraction (LLE) with methanol: 0.1N HCl (1:1), the analyte and IS were separated using the isocratic mobile phase system. The percent recovery of MLX was found to be 90.46 ± 0.53. A linear range of 0.3-5µg/ml was established (r2 =0.9982). LOD and LOQ were 0.28µg/ml and 0.85µg/ml, respectively. The mean accuracy was 86.86-109.66%. The HPLC method was validated with inter- and intra-day precision of 0.71-1.58% and 0.83-2.1% respectively. The proposed method was validated statistically by performing recovery studies by standard addition method, good recoveries from 96.57%-97.68% were found. The stability of MLX in plasma was confirmed by short term and long term stock stability, bench top stability and freeze thaw stability. The proposed methods are simple, economic, precise, reproducible and specific [5].

The present study was undertaken to develop a validated, rapid, simple and economic stability indicating reverse phase HPLC method for estimating meloxicam (MLX) in bulk and commercial preparations. Method: Reversed phase chromatographic analysis was performed on a C18 Hi Q Sil column with acetonitrile-water-glacial acetic acid [55:40:5 (% v/v)] at a flow rate of 1ml/min and detection wavelength of 355 nm. System suitability tests essential for the assurance of quality performance of the method were performed. The drug was subjected to stress degradation studies under acidic, basic and oxidative conditions. The method was validated for accuracy, precision, reproducibility, specificity, robustness, limit of detection (LOD) and limit of quantification (LOQ), as per International Conference on Harmonization (ICH) guidelines.

RESULTS

A single sharp peak was obtained for MLX at Rt of 6.8 ± 0.01min. The polynomial regression data for the calibration plots exhibited good linear relationship (r = 0.9995) over a concentration range of 4–20µg/ml and the linear regression equation was y = 57257.38x + 3443.07. Accuracy ranged from 99.27 to 100.78% and the % coefficient of variation (CV) for both intra-day and inter-day precision was less than 2%. MLX showed minor degradation peak in acidic conditions at Rt of 2.24min. The LOD and LOQ values were 360 ng/ml and 510 ng/ml, respectively.

DISCUSSION AND CONCLUSION

The proposed method gave good resolution of MLX and its degradants. System suitability tests and statistical analysis performed prove that the method is precise, accurate and reproducible, and hence can be employed for routine analysis of MLX in bulk and commercial formulations [6].

A rapid, precise, selective and sensitive, stability-indicating HPTLC method for quantitative estimation of Meloxicam (MLX) has been developed and validated. TLC aluminium plates (Merck) precoated with silica gel 60F254 was used as the stationary phase. The solvent system comprising of toluene: ethyl acetate: methanol: glacial acetic acid in the ratio of 4:4:1.6:0.4 (v/v/v/v) gave a dense compact spot with an Rf value of 0.61± 0.02, n=6. Densitometric analysis was carried out in reflectance-absorbance mode at 358 nm. The method was validated in compliance with ICH Harmonized Tripartite Guideline Q2 (R1) for linearity, limit of detection (LOD), limit of quantification (LOQ), precision, specificity, accuracy, repeatability and robustness. The drug response with respect to peak area was linear over the concentration range 200-700 ng/spot (n=6). The mean (±SD) values of the slope, intercept and correlation coefficient were 8.192 (±0.089), 1640.1 (±24.516) and 0.9965 (±0.00083),

Fig 1. Structure of Meloxicam

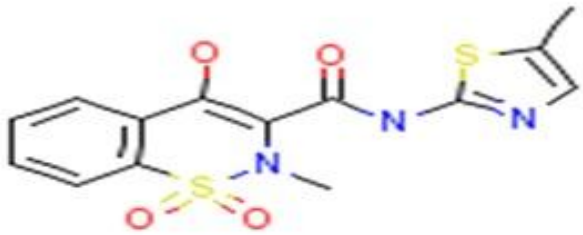


Fig 2. Liquid Chromatography Mass Spectroscopy

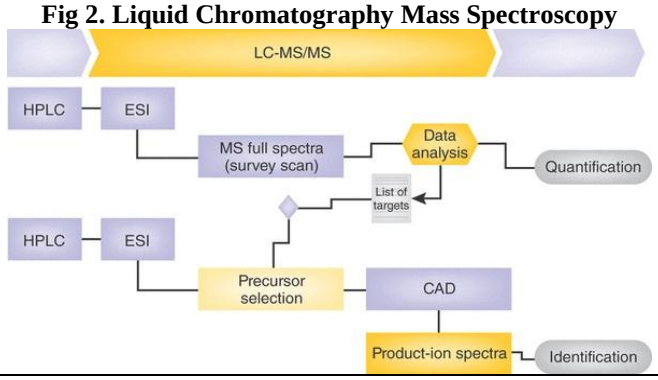
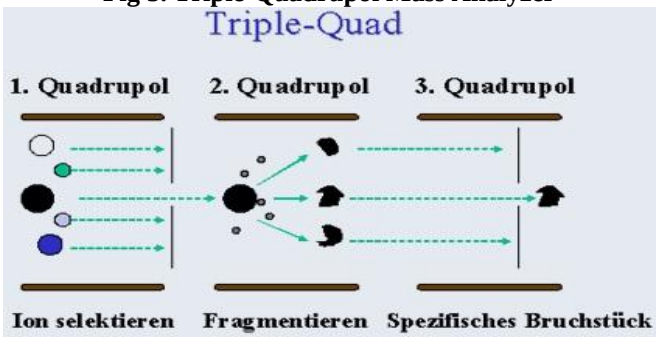


Fig 3. Triple-Quadrupol Mass Analyzer



respectively. The LOD and LOQ were 23.20 and 70.30 ng/spot respectively. Statistical evaluation proved that the established method was accurate, specific, precise, repeatable and robust for the estimation of MLX. The degradation products were well resolved from the pure drug with significantly different Rf values and thus can be used to monitor stability. Being simple and economical, the method can be employed for the routine quality control analysis of MLX in bulk and pharmaceutical dosage forms [7].

A simple, precise and accurate isocratic RP-HPLC method was developed and validated for determination of Meloxicam in bulk drug and tablets. Isocratic RP-HPLC separation was achieved on a LiChrospher RP-18 column (250 x 4.6 mm id, 5 micron particle size) using the mobile phase 'A' 0.1 M dipotassium hydrogen phosphate pH 4.0 with orthophosphoric acid and mobile phase 'B' Methanol . Mobile phase 'A': mobile phase 'B' premixed in the ratio of 65:35 v/v were used as mobile phase at a flow rate of 1.0 mL/min and the column oven temperature was 35 °C good. The retention time of Meloxicam (2H-1, 2-benzothiazine- 3-carboxamide, 4-hydroxy-2-methy-N-(5-methyl-2-thiazolyl)-, 1, 1-dioxide) was about 4.31 min and its known impurity-B (5-methylthiazole-2ylamine) was about 2.26. The photodiode array detector was used to test the purity of the peaks, and the chromatograms were extracted at 254 nm. The method was validated for linearity, precision, accuracy, robustness, solution stability, and specificity. The method was linear in the concentration range of 150-450 µg/ml with a correlation coefficient of 0.999. The limit of detection (LOD) and limit of quantification (LOQ), respectively were 5 and 50 µg/mL for Meloxicam. The accuracy (recovery) was found to be in the range of 98.57%-101.69%. The drug was subjected to the stress conditions hydrolysis, oxidation, photolysis, and heat. Degradation products produced as a result of the stress conditions did not interfere with detection of Meloxicam; therefore, the proposed method can be considered stability-indicating [8].

A simple and rapid method for separation and determination of meloxicam and its degradation products by thin-layer chromatography with densitometric detection in pharmaceutical preparations was described. The method employed TLC F254 plates as the stationary phase. The solvent system consisted of ethyl acetate : toluene : butylamine (2:2:1, v/v/v). Densitometric analysis was carried out in absorbance mode at wavelength of 297 nm. The method was validated for linearity, precision and accuracy. The limits of detection and determination were 0.96 µg per spot and 2.90 µg per spot, respectively. The drug was degraded in acidic and basic environment, at different temperatures. The degradation products were well resolved from the active substance. The HPLC-MS/MS method for the identification of degradation products of meloxicam (i.e. 5-methylthiazol- 2-ylamine and 5-(dioxide-l6 -sulfanylidene)-6-methylidenecyclohexa-1,3-diene) was investigated. Because the presented method allows the efficient separation of the drug from some of its degradation products, so it can be used as a stability-indicating analysis [9-13].

A sensitive, specific, precise and cost effective RP-High-Performance Liquid Chromatographic method of analysis for meloxicam in presence of its impurities was developed. The method employed Hypersil Gold C18 (250 mm x 4.6 mm) column as stationary phase. The mobile phase consisted of 0.65% potassium dihydrogen orthophosphate (pH 6) and methanol in a ratio of 45: 55 v/v. This system was found to give good resolution of

meloxicam and its impurities A, D, C (retention time 4.18, 5.32, 7.21, 9.13 min respectively). Method was validated as per ICH guidelines, in the concentration range of 5-25 µg/ml at 361nm [14-17].

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