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Analytical Method Validation of Meloxicam and Paracetamol Tablet in Combination by HPLC Method

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ABSTRACT

The objective of this study is to validate a simple and accurate method for the analysis of Meloxicam and Paracetamol in combination in tablet form simultaneously by High Performance Liquid Chromatography method. Analysis of these two drugs in combination is not available in any pharmacopoeias. Thus, HPLC method is developed using C18, 250mm X 4.6mm (Internal Diameter) column using Buffer (0.2gm trimethylamine dissolved in water and volume made up to 100ml and pH adjusted to 6.60 with orthophosphoric acid): Acetonitrile in the ratio 38:62 as mobile phase in isocratic system. 20 microliter of sample was injected and column temperature was adjusted to 25 degree Celsius using 310nm wavelength in PDA detector. The optimized method was then validated as per ICH guidelines Q2 [R1]. Paracetamol was eluted first followed by Meloxicam. The resolution between Meloxicam and Paracetamol was found to be 2.792. The recovery percentages of Meloxicam were found to be 100.25%, 99.84% and 99.63% for 80%, 100% and 120% respectively and similarly for Paracetamol recovery percentages were 99.38%, 99.43% and 99.75 for 80%, 100% and 120% respectively. Limit of detection when using this method was found to be 0.1744 for Meloxicam and 4.3083 for Paracetamol. Similarly, limit of quantification was found to be 0.5286 for Meloxicam and 13.0556 for Paracetamol. Robustness test was carried out by varying mobile phase, flow rate, pH of buffer, column temperature and wavelength. No significant change in assay of API was notice while varying those parameters. The proposed method can be used for evaluation of Meloxicam and Paracetamol in combination in tablet by using HPLC.

Keywords*: Analytical Method Validation, HPLC*

INTRODUCTION

Validation is defined as a demonstration of giving that any procedure, strategy, process, instrument, materials, action, frame work or analyzer proceed as planned following predetermined arrangement of criteria. The validated procedure guaranteed reliability and consistency in the planned outcome [1].

Further, it focuses on the compliance of the product and analysis of the final product. It is significant thing in the pharmaceutical industry. The validation of the analytical method aims for the consistency accuracy and reliability of the results of the testing sample. Any method can show the problems, limitation and interference by external materials during performing the testing. Hence, such problems should be resolved. It has a significant job in accomplishing such objectives [2-6].

Reasons for Validation

1) It is mandatory condition for enrollment of any pharmaceutical item or pesticide plan.

2) It supports to accomplish the scope of "legitimate/reference technique" endorsed by administrative offices.
3) It ensures high caliber of the outcomes.
4) It improves the money related main concern of the research facility.
5) It is obligatory necessity for accreditation of the research center by ISO 17025 rules.
6) It helps in arriving at acknowledgment of the drugs by worldwide organizations.

The process of confirming the analytical testing strategy utilized for a particular test which is reasonable for its expected use is referred to the method validation. The results which are gained by the process of validation of method are utilized for passing a judgment on the consistent outcomes of analysis. This ensure for the quality and reliable product. For the reliable testing procedure, well-developed method is regarded as the fundamental process [7-9]. The requirement of testing method is characterized by this. The reliability for the requirement of process is affirmed by the performance capacities of considered method. Analytic testing processes are proposed for the insurance of the identification, purification and potential action of medicine. The physical characteristics are also studied in this process. A stability studies for longer time is assured by well-developed method. It also confirms the quality of the drug during the manufacturing of drug. Likewise, the developed process may bolster evaluation of performance of drug. It ensures the safety parameters and the study of physical characters [10-14].

For creating the trustworthy analytical data from the competent laboratory, a proper standard method should be set up. It can only be possible from validation of analytical method [15-20]. The total information about chemical should be studied for the set-up of the method and its validation. Reproducible data should be given by the analytical procedure even when performed by different analyst in various lab centers utilizing distinctive reagent, different instruments and equipment. For the validation of the analytical method, certain parameters should be followed such as linearity, accuracy, precision, specificity and reproducibility of the result of the sample. The number of medication presented for consumers has been increasing every day at higher rate. These medications might contain totally fresh element that is not yet seen in the market or there might be small basic alteration or modification in the structure from current medication [21-27].

Essential measures for method validation of drug analysis are given below:

1) For biological fluids, assay may be difficult to perform by using analytical method.
2) There is presence of many excipients in the formulation which can interfere with the formulated drug and expected results are difficult to gain.
3) For the combine product of two or more active pharmaceutical ingredient, analytical method may not be found.
4) The complete literature about the analytical methods of the drug cannot be gained because of the patient guidelines.
5) Requirement of costly reagents and solvents in the existing analytical procedures may not be suitable. It may likewise include difficult extraction and separation procedures which is not suitable.
6) Absence of the drug or drug combination in any pharmacopoeias.

Validation of analytical procedure is the legal requirement and is mandatory to perform. ICH guidelines [Q2 (R1)] have set the guidelines for the validation of analytical method. They are listed below.

Types of Analytical Methods to be validated

The validation of the analytical methods must be performed for the following test:

a) Identification tests
b) Analysis of the impurities for its quantification and its limit test
c) Analysis of active pharmaceutical ingredient for is quantification

a) Identification Tests: For the identity of chemical or ingredient, identification testis planned. It can be done by various type of analytical method. Examination of various properties such as reaction with other substances, spectral evaluation, properties of chromatogram and so on. In this test, comparison of sample is done with the reference standard.

b) Analysis of the impurities for its quantification and its limit test: Impurities can be quantified and identified. Almost all raw materials contain the impurities. Total removal of the impurities is very difficult task. So regulatory body has set certain criteria for the limit in the presence of the impurities. Percentage purity of the chemicals is reflected by this test. Following the various parameters of the validation in limit test is less essential whereas it is utmost criteria for quantification analysis.

c) Analysis of API for its quantification: Quantification of API or other chemical is the most essential part of the analytical test. It reflects the accurate presence and proper action of the API in the drug product. With regard to such archive, assay can be defined as estimation of active pharmaceutical ingredient in the product quantitatively. The quantification of API should follow certain procedure which has same parameters of validation. In the same way, dissolution which also deals with the release of API should follow the same guidelines of the validation.

The validation ICH guidelines have set certain criteria for the validation of analytical method. The parameters are listed below:

- Specificity
- Accuracy
- Precision
  - ✓ Repeatability
  - ✓ Intermediate Precision
  - ✓ Reproducibility
- Detection Limit
- Quantification Limit
- Linearity
- Range
- Robustness

Besides, revalidation may be essential for the following conditions:

- Alteration in the process of product manufacturing
- Alteration in the ingredients in the final product of drug
- Alteration in the steps of analytical method(ICH harmonized tripartite guideline, 2005)

MELOXICAM

Meloxicam *i.e.* an oxicam derivative and a non-steroidal anti-inflammatory drug (NSAID) having the characters of anti-inflammatory, antipyretic and analgesic actions. In contrast to conventional nonselective NSAIDs, Meloxicam specially

restrains the action of cyclo-oxygenase II (COX-II), bringing about a diminished transformation of arachidonic acid into prostaglandin precursors. Consequently, prostaglandin synthesis inhibited. The resulting decrease in prostaglandin synthesis. This is known as the therapeutic effects of Meloxicam. (Pubchem) Meloxicam is indicates for the relieve of the symptoms of arthritis, primary dysmenorrhea, fever; and for an analgesic, particularly where there is an inflammatory component [28-32].

Paracetamol

Paracetamol/acetaminophen is one of the most well known and most regularly utilized pain relieving and antipyretic medications around the globe, accessible as over the counter drug. When the use of non-steroidal anti-inflammatory drugs (NSAID) is problematic Paracetamol is preferred in the patients [32-34].

The patent of bronchial asthma, peptic ulcer disease, haemophilia, pregnantor breastfeeding women, salicylate-sensitized people, children under 12 years of age Paracetamol is preferred than other NSAID. Patients related to osteroarthritis a first-line treatment drug for the pain is suggested for Paracetamol [35-38].

Paracetamol is mostly used over the counter drug for fever and mild-to-moderate pain. At less does it has almost no side effect but at higher dose it shows direct hepatotoxic effect. Acute livery injury can show fatal effect [39-40].

MATERIALS AND METHODS

Instrument

The HPLC analysis was carried out using HPLC instrument of shimadzu with C18, 250mm X 4.6mm (Internal Diameter) column.

Chemicals and Materials

Meloxicam and Paracetamol were gifted from MDH Pharmaceutical Pvt. Ltd. (Bhaktapur, Nepal). Tablets containing 100mg Meloxicam and 1500mg Paracetamol (Melox-P) which is used for veterinary purpose was also gifted from MDH Pharmaceuticals Pvt. Ltd. Analytical grade chemicals and reagents were used.

Selection of Wavelength

The standard solution of Meloxicam, Paracetamol and sample solution of tablet were prepared. All three solutions were scanned separately in the UV range of 200-400 nm with the help of UV-Visible Spectrophotometer. According to UV spectrum, it showed that standard solution of Meloxicam had maximum wavelength at 365nm. Similarly, the standard solution of Paracetamol had maximum wavelength 248 nm. The sample solution of tablet showed maximum wavelength at 365nm and 248nm. By comparing UV spectrum of sample with that of standard solution of Meloxicam and standard solution of Paracetamol, 365 was the maximum wavelength of Meloxicam and 248nm was maximum wavelength of Paracetamol. As Meloxicam and Paracetamol had two different wavelengths, suitable wavelength had to be selected. So, 310nm wavelength was selected which lies between two wavelengths of Meloxicam and Paracetamol.

Chromatographic Condition

Column: C18, 250mm X 4.6mm (Internal Diameter)
Column Temperature: 25°C
Wavelength: 310nm
Flow Rate: 0.8ml/min
Detector: PDA

Injection Volume: 20µl
Mobile Phase: Buffer: Acetonitrile (38:62)

Preparation of Buffer
0.2 gram (gm) of trimethylamine was weighed in an electronic balance and dissolved it with the help of water in 100 ml volumetric flask. The volume was made upto 100ml with same solvent. The pH of the final solution was adjusted to 6.60 by using orhtophosphoric acid. The buffer was mixed with acetonitrile in the ratio of 38:62 for the preparation of mobile phase. Then the mobile phase was filtered through 0.45µm filter paper by using vacuum filter and then sonicated for 5 minutes prior use.

Preparation of Standard Solution of Meloxicam
16mg of Meloxicam was weighed. It was then dissolved with Acetonitrile in 100ml volumetric flask and then diluted to the mark with the same solvent. Then 1ml of the stock solution was pipetted out in 25ml volumetric flask and diluted with the mobile phase up to the mark of volumetric flask. It was then filtered through 0.22µm then sonicated for 5 min.

Preparation of Standard Solution of Paracetamol
1gm of Paracetamol was weighed. It was then dissolved with Acetonitrile in 100ml volumetric flask and then diluted to the mark with the same solvent. Then 1ml of the stock solution was pipetted out in 25ml volumetric flask and diluted with the mobile phase up to the mark of volumetric flask. It was then filtered through 0.22µm then sonicated for 5 min.

Preparation of Sample Solution
The sample was provided by MDH Pharmaceuticals Pvt. Ltd. The sample has following composition:

Each tablet contains:
Meloxicam: 100mg
Paracetamol: 1500mg

As the concentration of Meloxicam was relatively lesser than that of Paracetamol in the sample tablet, sample equivalent to 16mg of Meloxicam was weighed. It was then dissolved with acetonitrile in 100ml volumetric flask and then diluted to the mark with the same solvent.

Then 1ml of the stock solution was pipetted out in 25ml volumetric flask and diluted with the mobile phase up to the mark of volumetric flask. It was then filtered through 0.22µm then sonicated for 5 min. The resulting solution consists of 6.4µg/ml of Meloxicam and 105.6µg/ml of Paracetamol.

Method Validation and Results
The RP-HPLC method was validated with reference to ICH guidelines [Q2 (R1)].

System Suitability
Six replicates injections of same concentration of standard solution were injected and the system suitability parameters. The result shows the theoretical plates of both drugs; Meloxicam and Paracetamol were above 2000 i.e. 4787 and 4165 respectively, resolution between Paracetamol and Meloxicam was 2.792 and % RSD of peak area of Meloxicam and Paracetamol were 0.07015 and 0.07783 respectively.

Specificity
The chromatograms of the blank, standard and sample solution were compared. There were no any interfering peaks in the blank and also the retention time of test solution matches to that of respective standards in the standard solution.

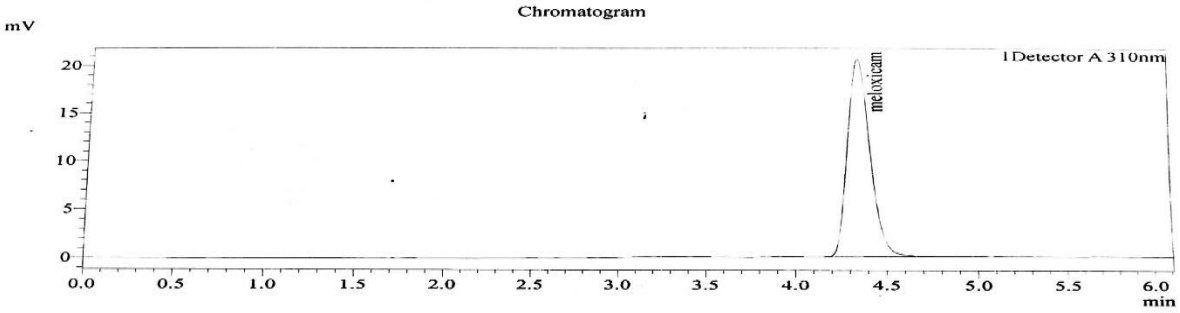

Fig 1. Chromatogram of Meloxicam

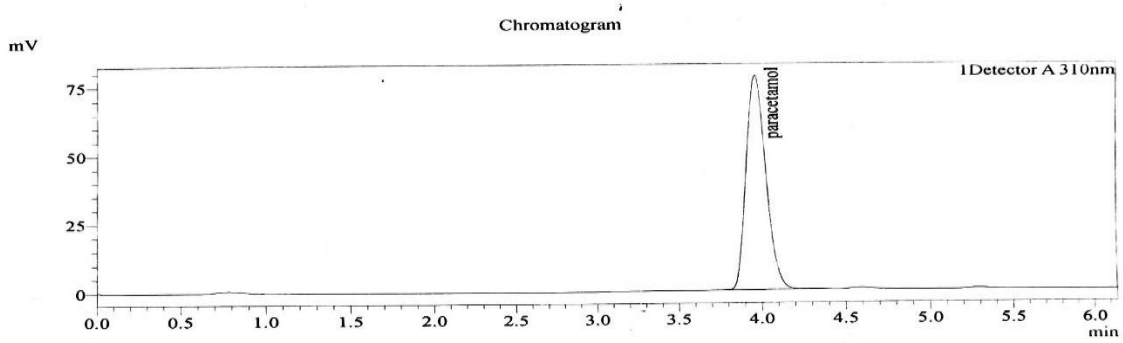

Fig 2. Chromatogram of Paracetamol

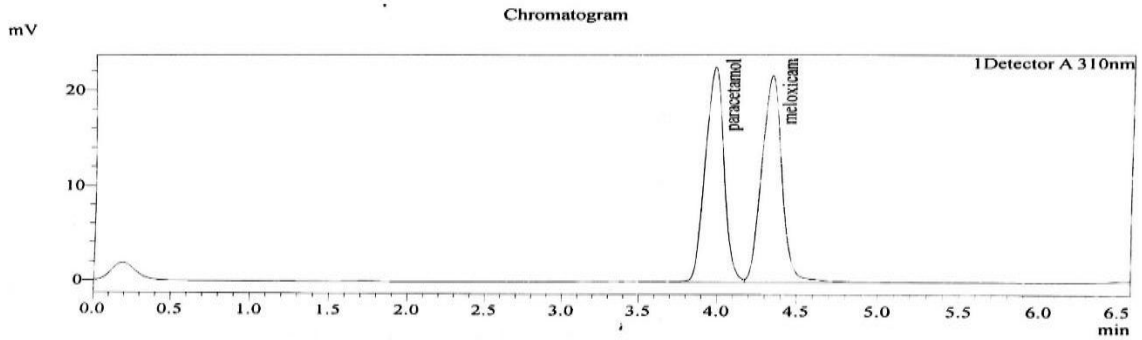

Fig 3. Chromatogram of Sample Solution

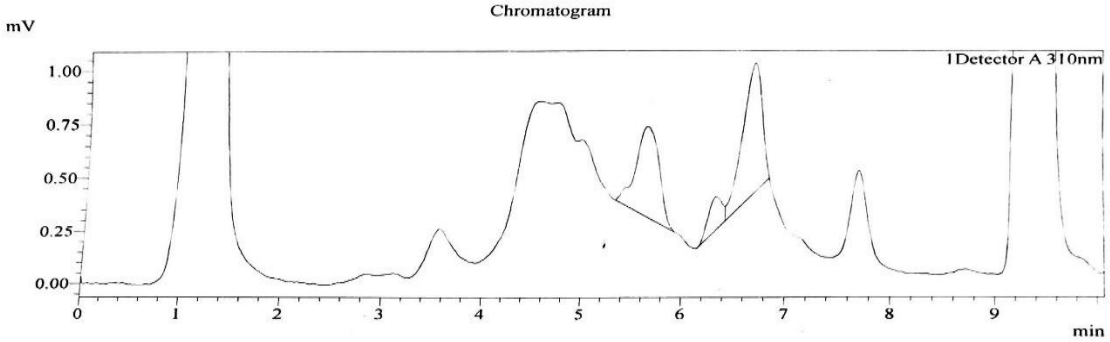

Fig 4. Chromatogram of Blank Solution

Linearity

Linearity was assessed at six different concentrations. The linearity of Meloxicam was evaluated from 2.8µg/ml to 8.8µg/ml and that of Paracetamol was evaluated from 51.6µg/ml to 141.6µg/ml. The calibration curve was plotted against drug concentrations.

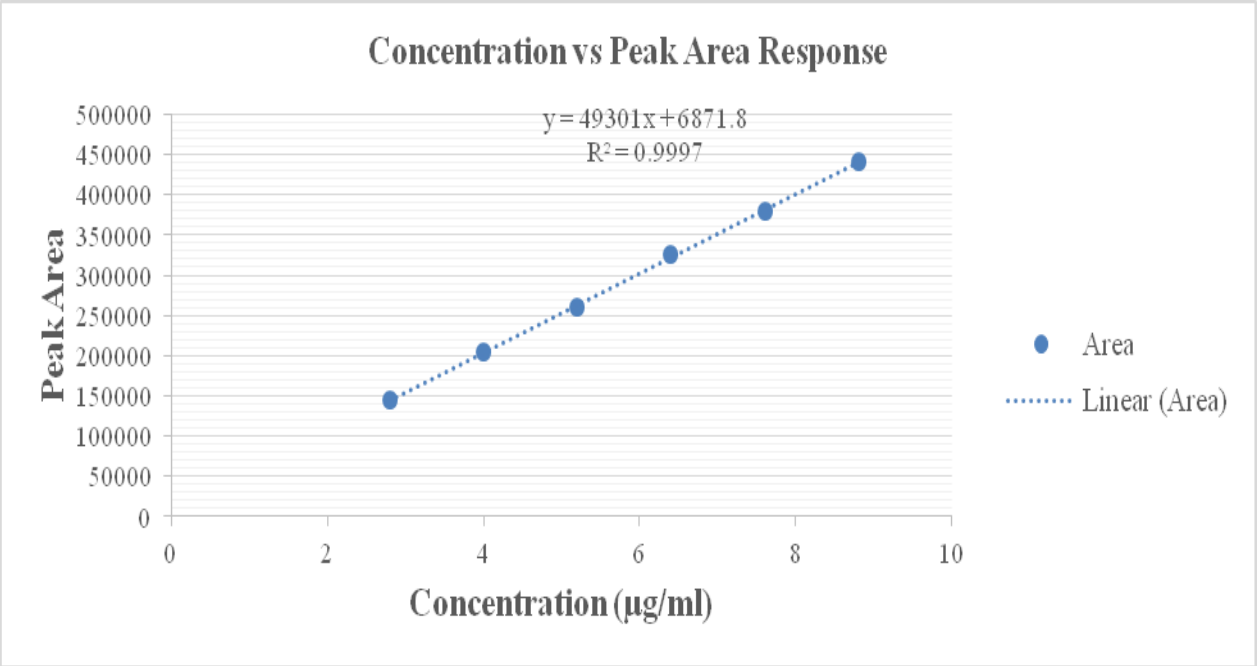

Fig 5. Calibration Curve of Meloxicam

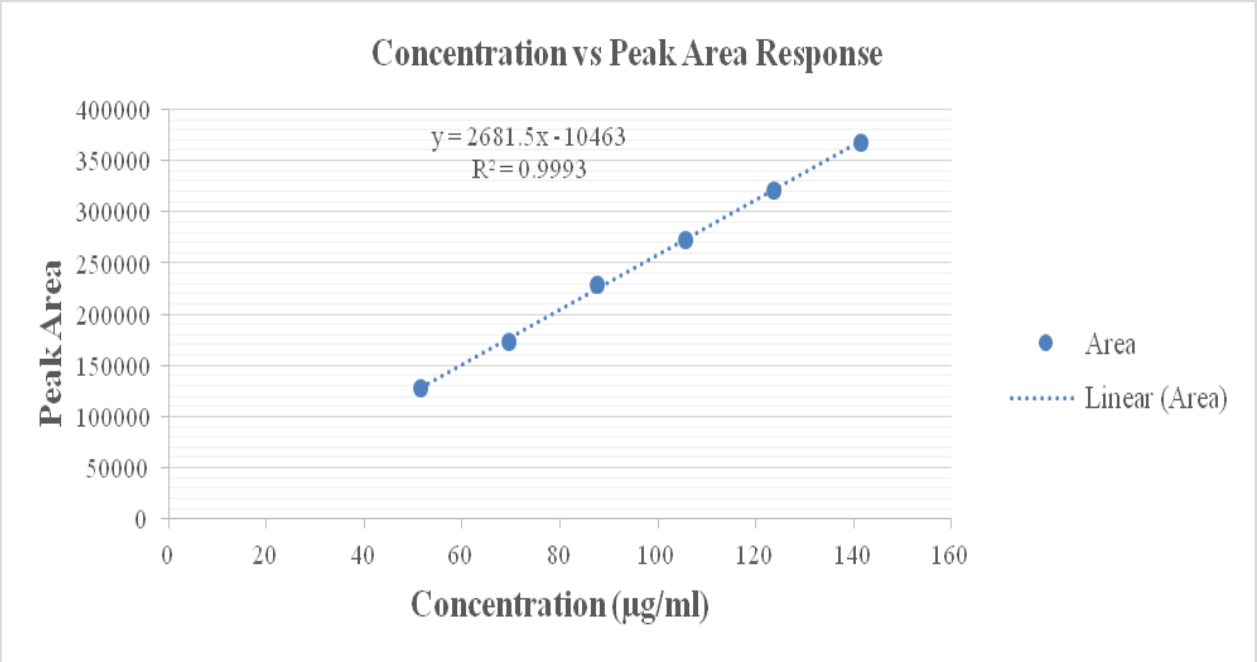

Fig 6. Calibration Curve of Paracetamol

Accuracy
Accuracy was carried out in the sample solutions in the range of 80%, 100% and 120% where the known amount standard solution was spiked on those samples. The content of Meloxicam was found within the limit of ±2% and the mean of the recovery percentage was found to be 100.25% for 80%, 99.84% for 100% and 99.63 for 120%. The RSD was 0.55%, 0.27% and 0.45% respectively. The content of Paracetamol was found within the limit of ±2% and the mean of the recovery percentage was found to be 99.38% for 80%, 99.43% for 100% and 99.75 for 120%. The RSD was 0.2%, 0.41% and 0.22% respectively.

Range
Range was carried out in the 80 to 120% of the test solutions. The solution was weighed and diluted such that the concentration is 80%, 90%, 100%, 110% and 120%. The concentration of Meloxicam in the test solution was found to be 99.57%, 99.41%, 100.04%, 99.26% and 99.08% for 80%, 90%, 100%, 110% and 120% respectively. The %RSD was 0.55%, 0.39%, 0.49%, 0.17% and 0.0706% respectively.

The concentration of paracetamol in the test solution was found to be 100.49%, 100.52%, 98.88%, 98.35% and 98.67% for 80%, 90%, 100%, 110% and 120% respectively. The %RSD was 0.21%, 0.81%, 0.85%, 0.26% and 0.0101% respectively. The concentration was found to be with the limit of ±2% and also %RSD was not more than 2%.

Precision
Repeatability Precision and Intermediate Precision were carried out.

Repeatability was assessed in the six sample solution of 100% concentration. The peak area of six determinations of meoxicam were found to be 99.79%, 100.03%, 99.98%, 99.83%, 100.96% and 100.48% which show the mean of 100.17%. the %RSD was 0.45. The mean of six determinations of paracetamol was found to be 99.92% with the %RSD of 0.65.

In Intermediate Precision, variation due to different analyst and different day were carried out to know the effect on the precision of the analytical procedure. The mean of peak area of meloxicam was found to be 99.36% with the %RSD 0.45 for the analysis carried out by analyst 1 and 100.27% with %RSD 0.96 for the analysis carried out by analyst 2 on day 1. Similarly, the mean of peak area of meloxicam was observed as 99.29% with %RSD of 0.16 for analysis carried out by analyst 1 and 100.39% with %RSD 0.44 for the analysis carried out by analyst 2 on day 2.

The mean of peak area of paracetamol was found to be 100.23% with the %RSD 0.64 for the analysis carried out by analyst 1 and 99.62% with %RSD 0.66 for the analysis carried out by analyst 2 on day 1. Similarly, the mean of peak area of paracetamol was observed as 100.22% with %RSD of 0.25 for analysis carried out by analyst 1 and 99.59% with %RSD 0.46 for the analysis carried out by analyst 2 on day 2.

Limit of Detection (LOD) and Limit of Quantification (LOQ)
The LOD of meloxicam was found to be 0.1744µg/ml and LOQ was found to be 0.5286 µg/ml whereas, the LOD of paracetamol was found to be 4.3083µg/ml and LOQ was found to be 13.0556 µg/ml.

Robustness
Robustness was carried out by varying the mobile phase, flow rate of mobile phase, pH of buffer, temperature of column and wavelength. There was no significant

difference in the result of assay, thus the method was robust.

CONCLUSION

A simple and precise method was validated for the simultaneous determination of Meloxicam and Paracetamol in tablet form by reverse phase high performance liquid chromatography. The method was non-tedious, less time consuming and economical.

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