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Research Article

QUANTITATIVE ESTIMATION OF MELOXICAM: A NOVEL APPROACH USING HYDROTROPIC SOLUBALIZATION TECHNIQUE

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ABSTRACT

Objective: Analysis of drug utilized the organic solvent which are costlier, toxic, and causing environment pollution. Hydrotropic solution may be a proper choice to preclude the use of organic solvents so that an attempt has been made to develop simple, accurate, novel, safe and precise spectrophotometric method for estimation of poorly-water soluble drug meloxicam. **Methods:** Solubility of meloxicam is increased by using 8% phenol and 25% sodium benzoate solution as hydrotropic agent. There was more than 32 fold solubility enhanced in hydrotropic solution as compare with distilled water. The meloxicam shows the maximum absorbance at 362 nm. At this wavelength hydrotropic agent and other tablet excipients do not shows any significant interference in the spectrophotometric assay. **Results:** The developed method was found to be linear in the range of 15-75 µg/ml with correlation coefficient (r^2) of 0.9994. The mean percent label claims of tablets of meloxicam in two marketed, formulation-I and formulation-II estimated by the proposed method were found to be 98.35±0.76 to 98.53±0.94 respectively. The developed methods were validated according to ICH guidelines and values of accuracy, precision and other statistical analysis were found to be in good accordance with the prescribed values. **Conclusion:** As hydrotropic agent used in the proposed method so this method is eco-friendly and it can be used in routine quantitative analysis of drug in bulk drug and dosage form in industries.

Keywords: Meloxicam, Phenol, Sodium Benzoate, Eco-Friendly, Hydrotropic Solubilizing Agents.

INTRODUCTION

Meloxicam (MCM) is chemically, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1, 2-benzothiazine-3-carboxamide-1, 1-dioxide (Figure 1), an oxicam derivative with non-steroidal anti-inflammatory drugs (NSAIDs) with analgesic and antipyretic properties. Prostaglandins are substances that contribute to inflammation of joints. Meloxicam inhibits prostaglandin synthetase (cylooxygenase 1 and 2) and leads to a decrease of the synthesis of prostaglandins; therefore, inflammation is reduced [1, 2]. The drug is official in IP [3], BP [4], USP [5] and EP [6]. Literature survey revealed few spectrophotometric and fluorimetric method [7], high performance liquid chromatography method [8-10], high performance thin layer chromatography method [11], LC [12] and liquid chromatography - MS method [13] has been reported for the determination of Meloxicam. All the reported method used the costly organic solvents. As the environmental pollution it is necessary to preclude the use of organic solvents for analysis of drug. Various techniques have been employed to enhance the aqueous solubility and hydrotropy is one of them. Hydrotropic solubilization is the phenomenon by which aqueous solubility of poorly water soluble drugs and insoluble drugs increases. Maheshwari and Jain et al has used sodium salicylate, sodium benzoate, urea, nicotinamide, sodium citrate and sodium acetate are the most common examples of hydrotropic agents utilized to increase the water solubility of drug [14-25]. Some drug like diacerein [26] and sildenafil citrate [27] estimated spectrophotometrically by hydrotropic technique. Organic solvents have disadvantage of their higher cost, toxicity and pollution. Hydrotropic solution may be a proper choice to preclude the use of organic solvents. Therefore, it was thought worthwhile to employ this hydrotropic solution to extract out the MCM from fine powder of tablets to carry out spectrophotometric estimation.

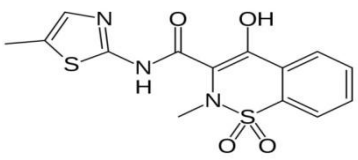

Figure1: Chemical Structure of Meloxicam

MATERIALS AND METHODS

Instrument

UV-Visible double beam double detector spectrophotometer, Shimadzu model-1700 having spectral bandwidth 3 nm and of wavelength accuracy ±1 nm, with 1cm quartz cells was used.

Reagents and chemicals

Analytical pure sample of MCM was supplied as gift sample from Intas Laboratories Pvt. Ltd phenol and sodium benzoate obtained from Merck Chemical Division, Mumbai. Reverse Osmosis Water was used throughout the study. Tablet formulation M -Cam7.5mg (Unichem Lab. Ltd.) and Movac 7.5mg (Alkem Lab. Ltd) purchased from the local market.

Preliminary solubility studies

A definite amount of drug was added to a screw capped 25 ml of volumetric flask containing different aqueous systems viz. distilled water, different combination of hydrotropic agent. The volumetric flasks were shaken mechanically for 12 hrs at 25±1°C in a mechanical shaker. These solutions were allowed to equilibrate for next 24 hrs and then centrifuged for 5 min at 2000 rpm. The supernatant liquid was taken for appropriate dilution after filtered through whatman filter paper #41 and analyzed spectrophotometrically against corresponding solvent blank. After analysis, it was found that the enhancement in the solubility of MCM was to be more than 32 folds in mixture of 8% phenol and 25% sodium benzoate solution as compared to solubility studies in other solvents.

Selection of hydrotropic agent

MCM was scanned in hydrotropic agent in the spectrum mode over the UV range (200-400) and mixture of 8% phenol and 25% sodium benzoate solution as hydrotropic agent were found to be most appropriate because:

- MCM is soluble in it (32 fold enhancement of solubility)
- MCM is stable in hydrotropic agent (as shown in Figure 2**)**

- MCM exhibit good spectral characteristics in it.
- Phenol and sodium benzoate solution has no interference with the λ_{max} of MCM i.e. 362 nm

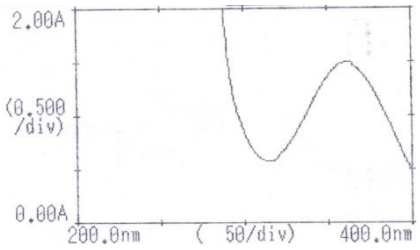

Figure 2: Spectra of MCM in Mixed Hydrotropic Agent

Establishment of stability profile

Stability of MCM was observed by dissolving in mixture of phenol and sodium benzoate solution (8%:25%W/W) as hydrotropic agent. Solution of MCM was prepared in the conc. of 45 µg/ml and scanned under time scan for 30 min. Spectra of drug under time scan shows that drug are stable in hydrotropic solution.

Linearity range and calibration graph

Preparation of standard stock solution (Stock-A)

Accurately weighed 100 mg of the MCM was transferred in to 100 ml volumetric flask containing 80 ml of hydrotropic agent and the flask was sonicated for about 10 min to solubilize the drug and the volume was made up to the mark with mixed hydrotropic agent to get a concentration of 1000 µg/ml (Stock-A).

Preparation of working standard solution

The standard solution (1000 µg/ml) was further diluted with distilled water to obtain 15, 30, 45, 60 and 75µg /ml solution and absorbance were noted at 362 nm against distilled water as blank.

Analysis of Tablet Formulation

Two marketed formulation M –Cam (Unichem Laboratories Ltd.), Movac (Alkem Laboratories Ltd) were selected for tablet analysis, i.e. containing 7.5 mg MCM. Twenty tablets were accurately weighed, average weight determined and ground to fine powder. An accurately weighed quantity of powder equivalent to 100 mg of MCM was transferred into 100 ml volumetric flask containing 80 ml of hydrotropic solution. The flask was sonicated for about 20 min to solublize the drug; volume was adjusted to mark with hydrotropic agent and filtered through whatman filter paper no. 41. The Absorbance of sample solutions was analyzed on UV spectrophotometer at 362 nm against R.O. water as blank. Drug content of tablet formulation were calculated using calibration curve.

VALIDATION OF METHOD

The developed methods for quantitative estimation of MCM were validated as per ICH guidelines (Linearity, Accuracy and Precision) [28].

Linearity

Linearity of MCM was established by response ratios of drug. Response ratio of drug was calculated by dividing the absorbance with respective concentration

Accuracy

To check the degree of accuracy of the method, recovery studies were performed in triplicate by standard addition method at 80%, 100% and 120%. In pre-analyzed tablet solution, a definite amount of drug was added and then its recovery was studied. These studies were performed in by adding fixed amount of pure drug solution to the final dilution while varying the concentration of tablet sample solution in the final dilution

Precision

Precision of the methods was studied at three level as at repeatability, intermediate precision (Day to Day and analyst to analyst) and reproducibility.

Repeatability was performed by analyzing same 5 concentrations of drug for 5 times. Day to Day was performed by analyzing 5 different concentration of the drug for three days in a week.

Reproducibility was performed by analyzing same concentration of drugs for five times in different lab.

RESULT AND DISCUSSION

Based on the solubility, stability and spectral characteristics of the drug, mixture of 8% phenol and 25% sodium benzoate solution was selected as hydrotropic agent. There was more than 32 fold solubility enhanced in mixed hydrotropic solution as compare with distilled water. After solubilizing the Meloxicam in selected hydrotropic agent, it was scanned in spectrum mode and the working wavelength for the estimation, considering the reproducibility and variability was found to be 362 nm. The developed method was found to be linear in the range of 15-75 µg/ml with linear equation was Y=0.0247X + 0.0068 and correlation coefficient (r^2) of 0.9994. Calibration curve was plotted between concentrations versus absorbance Figure 3. Observation of linearity data has been reported in the Table 1. The Result of their optical characteristics has shown in Table 2.

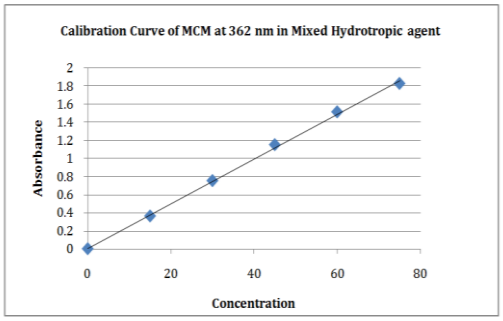

Figure 3: Calibration Curve of MCM at 362 nm in Mixed Hydrotropic Agent

Table 1: Linearity of MCM at λ_{max} =362 nm in Mixed Hydrotropic Agent

Standard Conc. (µg/ml)	Rep-1	Rep-2	Rep-3	Rep-4	Rep-5	Mean
0	0	0	0	0	0	0
15	0.357	0.362	0.351	0.369	0.372	0.3622
30	0.751	0.754	0.762	0.742	0.758	0.7534
45	1.119	1.123	1.112	1.21	1.189	1.1506
60	1.51	1.531	1.498	1.521	1.508	1.5136
75	1.823	1.824	1.822	1.845	1.824	1.8276
Correlation Coefficient (r^2)						0.9994
Slope (m)						0.0247
Intercept (c)						0.0068

Table 2: Optical Characteristic and Linearity Data of MCM in Mixed Hydrotropic Agent

S. No.	Parameter	Mixed Hydrotropic Agent
1	Working λ	362 nm
2	Beer's law limit (µg/ml)	15-75
3	Correlation Coefficient (r^2)*	0.9994
4	Slope (m)*	0.0247
5	Intercept (c)*	0.0068
6	Number of samples (n)	25

***Average of 5 determination of 5 concentrations**

The mean percent label claims of tablets of MEL in formulation-I and formulation-II estimated by the proposed method were found to be 98.35±0.76 to 98.53±0.94 respectively. These values are close to 100, indicating the accuracy of the proposed analytical method. The statistical evaluation of tablet analysis is reported in Table 3 and Table 4.

Table 3: Results and Statistical Parameters for M –Cam7.5mg Tablet Analysis Using Mixed Hydrotropic Agent

Drug	Label Claim (mg)	Amount Found (mg)	% MEAN*	S.D.*	%COV*	Std. Error*
M –Cam7.5mg	**7.5**	7.32	97.60	1.02	1.045	0.186
M –Cam7.5mg	**7.5**	7.39	98.53	0.84	0.853	0.154
M –Cam7.5mg	**7.5**	7.42	98.93	0.43	0.435	0.079
Mean		**7.38**	**98.35**	**0.76**	**0.778**	**0.140**

***Average of five in 3 replicates determination**

Table 4: Results and Statistical Parameters for Movac -7.5mg Tablet Analysis Using Mixed Hydrotropic Agent

DRUG	Label Claim (mg)	Amount Found (mg)	% MEAN*	S.D.*	%COV*	Std. Error*
Movac -7.5mg	7.5	7.41	98.80	1.01	1.022	0.185
Movac -7.5mg	7.5	7.36	98.13	0.94	0.958	0.172
Movac -7.5mg	7.5	7.4	98.67	0.87	0.882	0.159
Mean		**7.39**	**98.53**	**0.94**	**0.954**	**0.172**

***Average of five in 3 replicates determination**

Linearity was established in the range of 15-75 µg/ml and it was reported as response ratio; Table 5. Then a graph was plotted between concentration and response ratio (Figure 4).

Table 5: Response Ratio of MCM in Mixed Hydrotropic Solution

S. No.	Mixed Hydrotropic Agent		
	Conc.(µg/ml)	ABS	Response Ratio
1.	15	0.352	0.090
2.	30	0.749	0.090
3.	45	1.117	0.090
4.	60	1.511	0.090
5.	75	1.831	0.090

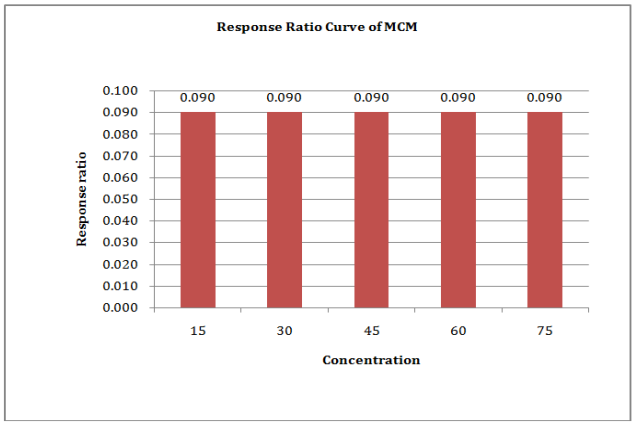

Figure 4: Response Ratio Curve of MCM in Mixed Hydrotropic Agent

The percentage recovery and percentage relative standard deviation of the recovery were calculated and reported in Table 6.The values of mean percent recoveries were also found to show variability in ranging from 97.39±0.47 to 98.85±0.95%. Low values of standard deviation, percent coefficient of variation and standard error further validated the proposed method.

Table 6: Result of Recovery Studies of Tablet Formulation with Statically Evaluation

Drug	QC Conc. (µg/ml)	Recovery Level % (Amount Drug Added)	Amount of Drug Found (Mean±SD)*	% RSD
MCM	**10**	**80**	97.39±0.47	0.483
		100	97.98±0.73	0.745
		120	97.83±0.67	0.684
MCM	**12**	**80**	98.41±0.81	0.823
		100	98.73±1.02	1.033
		120	98.85±0.95	0.961

***Average of five determination**

Result of precision at different level were found be within acceptable limits (RSD<2). The results have been reported in Table 7. Presence of hydrotropic agent do not shows any significant interference in the spectrophotometric assay thus further confirming the applicability and reproducibility of the developed method.

Table 7: Result of Precision of MCM

	Validation Parameter	Percentage Mean ± S.D*. (n=6)	Percentage RSD
Mixed Hydrotropic Agent	Repeatability	98.77±1.09	1.10
	Intermediate Precision		
	Day to Day	98.42±1.05	1.06
	Analyst to Analyst	98.53±0.84	0.852
	Reproducibility	98.49±1.02	1.031

*** Mean of fifteen determinations (3 replicates at 5 concentrations level)**

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