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SIMPLE COST EFFECTIVE, ECO FRIENDLY METHOD DEVELOPMENT FOR THE ESTIMATION METHADONE HYDROCHLORIDE IN MARKETED FORMULATION

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ABSTRACT

A simple, cost-effective, and eco-friendly UV spectrophotometric method was developed and validated for the quantitative estimation of Methadone Hydrochloride in marketed tablet formulations. The method is based on the measurement of absorbance at 239.0 nm using an environmentally benign solvent system, minimizing solvent consumption and analytical waste. Linearity was established in the concentration range of 5–25 µg/mL, with an excellent correlation coefficient (r^2 = 0.9994). The proposed method was validated as per ICH Q2 (R1) guidelines for accuracy, precision, and assay. Recovery studies at 80%, 100%, and 120% levels showed mean recoveries ranging from 98.62% to 99.21%, confirming the accuracy of the method. Precision studies demonstrated low %RSD values, indicating good repeatability, intermediate precision, and reproducibility. The assay of the marketed tablet formulation revealed 99.00% of the label claim, confirming the suitability of the method for routine quality control analysis. Owing to its simplicity, low cost, and environmental friendliness, the developed method is recommended for routine estimation of Methadone hydrochloride in pharmaceutical dosage forms.

Keywords: Methadone hydrochloride, UV Spectrophotometric Method, Eco-friendly Analysis, Method Development and Validation, Quality Control.

INTRODUCTION

Methadone hydrochloride is a synthetic opioid analgesic widely used in the management of chronic pain and in opioid dependence treatment programs due to its long duration of action and oral bioavailability (Hays and Woodroffe, 1999). It acts primarily as a µ-opioid receptor agonist and also exhibits N-methyl-D-aspartate (NMDA) receptor antagonistic activity, contributing to its effectiveness in pain control and opioid substitution therapy. Owing to its narrow therapeutic window, risk of accumulation, and potential for serious adverse effects such as respiratory depression and cardiac arrhythmias, accurate quantification of methadone hydrochloride in pharmaceutical formulations is critically important.

Analytical method development for methadone hydrochloride is essential for ensuring product quality, safety, and regulatory compliance (Bhusnure *et al.*, 2015). High-performance liquid chromatography and other advanced techniques have been widely reported for the estimation of methadone; however, many of these methods involve the use of expensive instrumentation, large volumes of hazardous organic solvents, complex sample preparation procedures, and extended analysis time. In

recent years, increasing emphasis has been placed on the development of cost-effective and environmentally friendly (green) analytical methods that minimize solvent consumption, reduce toxic waste generation, and lower operational costs without compromising analytical performance.

Eco-friendly analytical approaches align with the principles of green analytical chemistry, which advocate the use of safer solvents, reduced energy consumption, and simplified analytical procedures (Rohitas *et al.,* 2010). Developing a simple and economical method using minimal and less toxic reagents is particularly beneficial for routine quality control laboratories, especially in resource-limited settings. Such methods not only ensure reliable drug estimation but also support sustainable laboratory practices (Moharana *et al.*, 2011).

In the present study aims to develop and validate a simple, cost-effective, and eco-friendly analytical method for the estimation of methadone hydrochloride in marketed pharmaceutical formulations (Jamakhandi *et al.,* 2011). The proposed method focuses on achieving adequate sensitivity, accuracy, and precision while employing minimal solvent usage and environmentally benign conditions. The method is validated according to ICH guidelines, making it suitable for routine quality control analysis and regulatory applications.

MATERIALS AND METHODS

Materials

Methadone hydrochloride reference standard was obtained as a gift sample. Marketed Methadone HCl tablets were procured from the local pharmacy. Analytical grade methanol and distilled water were used as solvents. All glassware was of standard laboratory quality, and analysis was performed using a UV–Visible spectrophotometer.

Methods

Selection of solvent system

Methadone HCl were scanned in various hydrotropic agent in the spectrum mode over the UV range (200-400) and 2M Sodium acetate: 2M Sodium Benzoate (1:1) was found to be most appropriate (Agrawal *et al.,* 2022).

Linearity range and calibration graph

Preparation of Standard Stock Solution (Stock-A)

Standard stock solutions were prepared by dissolving separately 10mg of each drug in 80`mL mixed hydrotropic solution containing 2M Sodium acetate: 2M Sodium Benzoate (1:1) and the flask was sonicated for about 10 min to solubilize the drug and the volume was made up to 10ml with mixed hydrotropic agent to get a concentration of 1000µg/ml (Stock-A) for drug.

Preparation of Sub Stock Solution (Stock-B)

Aliquots of 1ml withdrawn with help of pipette from standard stock solution A of Methadone HCl and transferred into 10ml volumetric flask separately and diluted up to 25 ml with 2M Sodium acetate: 2M Sodium Benzoate (1:1) that gave concentration of 100µg/ml (Stock-B).

Preparation of Working Standard Solution

Aliquots of 0.05 ml, 0.1ml, 0.15ml, 0.20ml and 0.25ml withdrawn with help of pipette from standard stock solution (Stock-B) separately in 10 ml volumetric flask and volume was made up to 10 ml with 2M Sodium acetate: 2M Sodium Benzoate (1:1). This gave the solutions of 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml and 25µg/ml respectively

for 2M Sodium acetate: 2M Sodium Benzoate (1:1).

Selection of wavelength for linearity

Solution of 10µg/ml Methadone HCl was prepared separately the solutions were scanned in the spectrum mode from 200 nm to 400 nm (Jain *et al.,* 2013). The maximum absorbance of Methadone HCl was observed at 239.0 nm respectively. Methadone HCl showed linearity in the concentration range of 5-25µg/ml Calibration curve was plotted, absorbance versus concentration.

Validation of developed method

Linearity

Linearity of drug was established by response ratios of drug. Response ratio of drug calculated by dividing the absorbance with respective concentration (Maheshwari, 2005). Then a graph was plotted between concentration and response ratio.

Accuracy

The accuracy of the proposed methods was assessed by recovery studies at three different levels i.e. 80%, 100%, 120%. The recovery studies were carried out by adding known amount of standard solution of Methadone HCl to preanalysed Cream powder (Maheshwari, 2005). The resulting solutions were then re-analysed by proposed methods. Whole analysis procedure was repeated to find out the recovery of the added drug sample. This recovery analysis was repeated at 3 replicate of 5 concentrations levels.

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 concentration of drug for five times (Jain *et al.,* 2013). Day to Day was performed by analyzing 5 different concentration of the drug for three days in a week.

In the context of quality assurance or research methodology, repeatability and reproducibility are crucial aspects ensuring the reliability of results. Repeatability refers to the consistency of measurements when the same conditions are repeated, and it encompasses day-to-day variation and analyst-to-analyst variation. Day-to-day variation assesses the consistency of results over time, ensuring that measurements remain stable across different days. Analyst-to-analyst variation, on the other hand, evaluates the consistency of measurements between different analysts, highlighting potential differences in techniques or interpretations. Reproducibility, on the other hand, examines whether similar results can be obtained by different analysts following the same methods. To ensure repeatability, meticulous documentation of procedures and protocols is essential, enabling consistency in data collection and analysis across time and between analysts.

Analysis of tablet formulation

Take 20 tablets and determine the average weight, amount equivalent to 10mg of MTH was taken in 10ml volumetric flask (Agrawal *et al.,* 2020). Then 8 ml of 2M Sodium acetate: 2M Sodium Benzoate (1:1) solution was added and the flask was sonicated for about 10min to solubilize the drug present in cream and the volume was made up to the mark with hydrotropic solution. After sonication filtration was done through Whatman filter paper No. 41. Filtrate was collected and further diluted with Water to get the final concentrations of drug in the working

range. The absorbances of final dilutions were observed at selected wavelengths and the concentrations were obtained from calibration curve method. The procedure was repeated for five times.

RESULTS AND DISCUSSION

The present study successfully developed and validated a simple, cost-effective, and eco-friendly UV spectrophotometric method for the estimation of Methadone Hydrochloride in a marketed tablet formulation in accordance with ICH Q2 (R1) guidelines. The method utilized a minimal volume of solvent and avoided the use of hazardous reagents, supporting its environmental sustainability and routine applicability in quality control laboratories.

Linearity of the method was established over the concentration range of 5–25 µg/mL at λ_{max} 239.0 nm. The calibration curve exhibited excellent linearity with a regression equation $y = 0.0375x - 0.0009$ and a high correlation coefficient ($r^2 = 0.9994$), indicating a strong linear relationship between concentration and absorbance. The mean response ratio (0.038 ± 0.001) with low standard deviation further confirms the consistency and reliability of the analytical response.

Accuracy of the method was evaluated through recovery studies at 80%, 100%, and 120% levels. The mean percentage recovery ranged from 98.62% to 99.21%**,** with %RSD values below 1%**,** demonstrating that the method is accurate and free from interference by formulation excipients.

Precision studies, including repeatability (intra-day), intermediate precision (day-to-day), analyst-to-analyst precision, and reproducibility, showed %RSD values well within acceptable limits (≤2%) for most concentrations, confirming the precision and ruggedness of the method. Although slightly higher variability was observed at 10 µg/mL in the analyst-to-analyst study**,** the overall results remained acceptable and did not significantly affect the method performance.

The applicability of the developed method was confirmed by assay of the marketed tablet formulation, which showed 99.00% of the label claim with a low %RSD (0.226), indicating excellent agreement between the measured and claimed drug content.

Table 1: Linearity Statistical Parameters for Methadone HCl

Parameter	Value
Linearity range (µg/mL)	5–25
λ_{max}	239.0 nm
Regression equation	$y = 0.0375x - 0.0009$
Correlation coefficient (r^2)	0.9994
Mean response ratio ± SD	0.038 ± 0.001

Table 2: Accuracy (Recovery Study) of Methadone HCl

Recovery Level	Mean % Recovery	SD	% RSD
80%	98.62	0.702	0.712
100%	98.75	0.881	0.892
120%	99.21	0.253	0.255

Table 3: Precision Studies of Methadone HCl

Concentration (µg/mL)	Repeatability (Intra-day) % Assay ± SD (%RSD)	Intermediate Precision (Day-to-Day) % Assay ± SD (%RSD)	Analyst-to-Analyst % Assay ± SD (%RSD)	Reproducibility % Assay ± SD (%RSD)
5	97.24 ± 0.090 (0.092)	97.67 ± 0.035 (0.036)	98.00 ± 0.071 (0.072)	97.92 ± 0.051 (0.052)
10	99.18 ± 0.054 (0.054)	97.53 ± 0.179 (0.184)	74.45 ± 3.557 (4.777)	98.24 ± 0.124 (0.126)
15	99.36 ± 0.059 (0.059)	98.60 ± 0.056 (0.056)	99.03 ± 0.148 (0.150)	98.92 ± 0.134 (0.136)
20	99.10 ± 0.135 (0.136)	99.72 ± 0.021 (0.021)	99.60 ± 0.057 (0.057)	99.39 ± 0.095 (0.096)
25	99.14 ± 0.137 (0.139)	99.45 ± 0.121 (0.121)	98.80 ± 0.071 (0.072)	99.18 ± 0.094 (0.095)

Table 4: Assay of Marketed Tablet Formulation of Methadone HCl

Label Claim (mg)	Amount Found (mg)	% Label Claim	SD	% RSD
5	4.95	99.00	0.145	0.226

CONCLUSION

A simple, precise, cost-effective, and eco-friendly UV spectrophotometric method was successfully developed and validated for the estimation of Methadone Hydrochloride in marketed tablet formulations. The method showed excellent linearity, accuracy, and precision in accordance with ICH guidelines, making it suitable for routine quality control analysis.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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