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A validated stability-indicating HPLC assay method for Meclizine HCl in bulk drug

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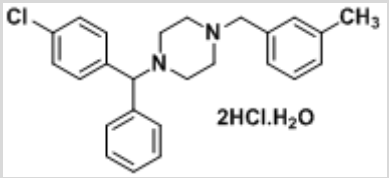
Abstract

An isocratic reversed phase stability-indicating high-performance liquid chromatographic (HPLC) assay method was developed and validated for quantitative determination of Meclizine HCl in bulk drugs. The developed method separated the drug from the degradation products, using a Water Nova Pack C18 (250 x 4.6) mm, 5µ column and the mobile phase containing 1.0gm Sodium dihydrogen phosphate and 1.0 gm 1-octaneSulfonic acid salt in 1000ml water filter and mixed. The detection was carried out at wavelength 264 nm. The developed method was validated with respect to linearity, accuracy (recovery), precision, system suitability, selectivity, robustness prove the stability indicating ability of the method.

Keywords: HPLC, Meclizine HCl, Degradation, Chromatographic Column.

1. Introduction

Meclizine [1], is antihistamine, considered to be antiemetic it is used as an anti vertigo or antiemetic agent,-specifically in the prevention and treatment of nausea, vomiting and dizziness associate with motion sickness [2]. Meclizine works by blocking a chemical messenger in the brain, it helps to reduce or prevent vomiting and dizziness caused by motion sickness. It also used for vertigo caused by certain inner ear problems. Meclizine should be taken with caution in the elderly because of increased risk of confusion and amnesia [3]. The drug is safe in pregnancy [4]. Several methods have been reported for Meclizine in pharmaceutical preparations such as HPLC UV and capillary zone electrophoresis, were also developed and validated to detect Meclizine in pharmaceutical preparations, but the sensitivity is too low [5-9].



Molecular formula	$C_{25}H_{27}ClN_2O$
Molecular weight	390.9
IUPAC Nomenclature	1-((4-chlorophenyl)(phenyl)methyl)-4-(3-methylbenzyl)piperazine dihydrochloride hydrate
Colour	white powder
Therapeutic Category	Anti-vertigo or Anti-emetic agent

1.1 Literature survey

Available literature states few HPLC methods for the estimation of Meclizine HCl at 254 nm. Though HPLC method is highly sensitive and accurate but not cost effective. Thus there is need to develop a simple rapid and economical method for routine analysis of Meclizine HCl. The objective of present study was to develop and validate simple, sensitive, accurate, precise, rapid and economical method for estimation of Meclizine HCl in bulk and in pharmaceutical formulations as per ICH guidelines [10, 11].

In continuation of our previous work, **[**12**],** present study involves development of RP-HPLC method using simple mobile phase which was sensitive and rapid for quantification Meclizine HCl in tablet samples as well as subsequent validation of developed method according to ICH guide lines. [13].

2. Experimental

2.1 Material and reagents

Meclizine HCl bulk drug was made available from Lupin Ltd. India (purity 99.8%). Sodium dihydrogen phosphate, 1- octane Sulfonic acid was obtained from Qualigens fine chemicals, India Limited. Acetonitile and methanol were obtained from Rankem laboratories, India. All chemicals and reagent were used as HPLC grades; Milli-Q-Water was used throughout the experiment.

2.2 Chromatographic Conditions

The chromatographic system (Systronic) consists of quaternary solvent delivery pump, a degasser, an auto- injector, column oven and UV detector. The chromatographic column of 250 mm length and internal diameter of 4.6 mm filled with Octadecylsilane Water

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Nova Pack C_{18} (250 x 4.6) mm, 5µ stationary phase with particle size 5 micron and pore size 100A° was used. The instrumental settings were a flow of 1 ml/min, the injection volume was 10 µl. and wavelength 264 nm.

2.3 Mobile Phase

The mobile phase containing 1.0gm Sodium dihydrogen phosphate and 1.0 gm 1-octane Sulfonic acid salt in 1000ml was water filter and mixed. Prepared a homogenous mixture of buffer, methanol and acetonitile (50:20:30, v/v/v).

2.4 Preparation of Standard stock solutions

Standard stock solutions of 500ppm of Meclizine HCl in acetonitile and water (25:75) were prepared in volumetric flasks.

2.5 Sample solution

500 ppm of Meclizine HCl in 100ml calibrated flask containing acetonitile and water mixture (25:75).The desired concentration for the drug was obtained by accurate dilution and the analysis was followed up as in the general analytical procedure [14, 15].

2.6 Selectivity

Selectivity is the ability of the method to assess unequivocally the analyte in the presence of components, which may be expected to be present. Typically, these might include degradants, and matrix etc. The selectivity of the developed LC method for Meclizine HCl was carried out in the presence of its degradation products. Stress studies were performed for Meclizine HCl bulk drug to provide an indication of the stability indicating property and selectivity of the proposed method. Intentional degradation was attempted to stress condition exposing it with acid (0.25 N Hydrochloric acid), alkali (0.25N NaOH) hydrogen peroxide (10%) heat (60°C) to evaluate the ability of the proposed method to separate Meclizine HCl from its degraded products. For heat, study period was 3 days, for acid, oxidation it was 48 hr, and for base 2 hour. Assay studies were carried out for stress samples against Meclizine HCl reference standard and the mass balance (% assay + % sum of all impurities + % sum of all degraded products) was calculated.

3. Results and discussion

3.1 Optimization of chromatographic conditions

The main target for the development of chromatographic method was to get the reliable method for the quantification of Meclizine HCl from bulk drug and which will be also applicable for the degradable products. Initially, we took the effort for the development of HPLC method quantification of standard Meclizine HCl from bulk. Satisfactory results were obtained when used, Water nova pack C18 (250mm x 4.6) mm, 5µ gave the graph with better Gaussian. For optimization of this method various solvents-buffer combination have been tried such as 0.1M KH_2PO_4 and Acetonitile (60:40,v/v), 0.01M Ammonium acetate *p*H-5.9 and acetonitile (20:80,v/v), Acetonitile and water (80:20, v/v), K_2HPO_4, Methanol and water (10:70:20,v/v/v), 1.0gm KH_2PO_4 and 0.45gm 1-Hexa sulphonic acid sodium salt and Ortho phosphoric acid with methanol (25:75, v/v) all these combination were not satisfactory. The solvent buffer combination for quantification of Meclizine HCl was found with 2.0gm Sodium dihydrogen phosphate and 1.0 gm 1-octaneSulfonic acid salt in 1000ml water filter and mixed.

3.2 Method Validation

The validation of analytical procedures is based on the four most common types of analytical procedures: Identification tests, Quantitative tests for impurities' content, Limit tests for the control of impurities, Quantitative tests of the active moiety in samples of drug substance or drug product or other selected component in the drug product.

In the present study the developed method was validated, as described below, for various parameters like linearity and range, accuracy, precision, ruggedness, system suitability, specificity, LOQ, and LOD.

3.3 System suitability

For system suitability studies, five replicate injections of acid, base and oxidative degraded solutions were used and the RSD of peak area ratio, resolutions, tailing factor and number of theoretical plates of the peak were calculated. The system suitability results are shown in **Table 1.**

Table 1: System stability study

Working Standard	Wt. of Standard (mg)	Area
Injection-1	**25.29 mg**	11885.60
Injection-2	------	11890.10
Injection-3	------	11876.50
Injection-4	------	11882.40
Injection-5	------	11868.70
Injection-6	------	11876.00
AVG	------	11879.88
SD	------	7.68
%RSD	------	0.06

3.4 Precision

The precision of the method was studied by determining the concentrations of the drug Meclizine HCl in the tablet for six times. The results of the precision study (**Table 3**) indicate the reliability of the method (RSD %< 2).

Table 2: Results of system precision as is basis

Sample No.	Wt. of sample (mg)	Area	Assay (as is basis)	Assay (on dried basis)
1	25.06	11648.80	95.65	99.54
2	25.01	11620.80	95.61	99.50
3	24.95	11589.40	95.58	99.47
4	25.08	11662.60	95.69	99.58
5	25.75	11968.60	95.64	99.53
6	24.96	11593.00	95.57	99.46
AVG	----	----	95.62	99.51
SD	----	----	0.04	0.05
%RSD	----	----	0.05	0.05

Table 3: Results of Intermediate system precision (Standard)

Working Standard	Wt. of Standard (mg)	Retention time	Area
Injection-1	25.01	10.61	10500154.00
Injection-2	25.01	10.61	10509628.00
Injection-3	25.01	10.60	10500217.00
Injection-4	25.01	10.60	10500103.00
Injection-5	25.01	10.61	10509909.00
Injection-6	25.01	10.61	10511842.00
AVG	25.01	10.61	10505308.83
SD	25.01	0.01	5693.83
%RSD	25.01	0.05	0.05

Table 4: Results of Intermediate system precision (Sample)

Sample No.	Wt. of sample (mg)		Area	Assay (as such basis)	Assay (on dried basis)
1	25.27	10.61	10509774.00	95.71	99.60
2	25.31	10.61	10511791.00	95.57	99.46
3	25.22	10.61	10490796.00	95.72	99.62
4	25.18	10.61	10470694.00	95.69	99.58
5	25.18	10.60	10468665.00	95.67	99.57
6	25.17	10.60	10453450.00	95.57	99.46
AVG	----	10.61	----	95.66	99.55
SD	----	0.01	----	0.07	0.07
%RSD	----	0.05	----	0.07	0.07

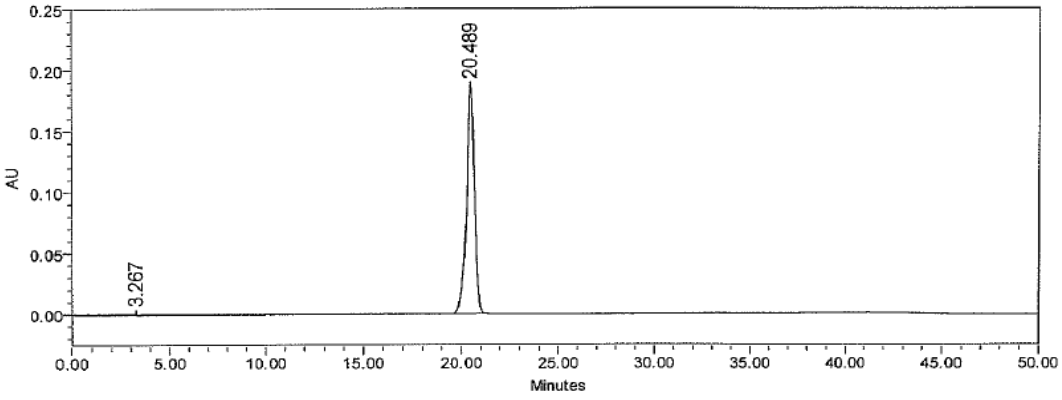


Figure 1: A typical chromatogram of Meclizine HCl Standard

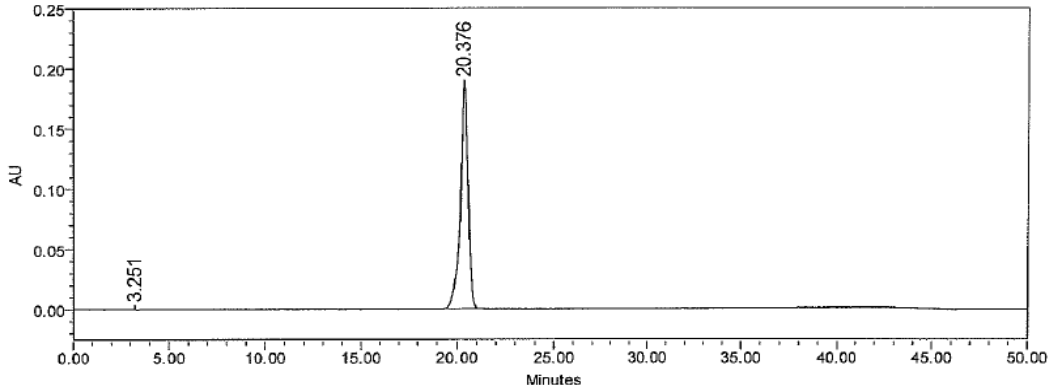


Figure 2: A typical chromatogram of Meclizine HCl Sample

3.5 Accuracy (Recovery test)

The accuracy of an analytical procedure expresses the closeness of agreement between the value, which is accepted either as a conventional true value or an accepted reference value and the value found. This is sometimes termed trueness.[19, 20]

Accuracy, sometimes also referred to as recovery is an indicator of the trueness of the test measurements.[20] To determine the accuracy of the method three quality control samples were used. The samples chosen were such to represent the entire range of the standard curve i.e. lower, middle and higher concentration of the range.[21]

The recovery experiments were carried out by the standard addition method. The recoveries obtained by the RP-HPLC method for Meclizine HCl are depicted in Table 5.

Table 5: Results of the recovery tests for the Meclizine HCl

Level of Addition (%)	Amount added (n=3) ppm	% Recovery *	% Average recovery†
80	50	98.11	98.14
100	100	99.22	99.44
120	150	99.70	99.65

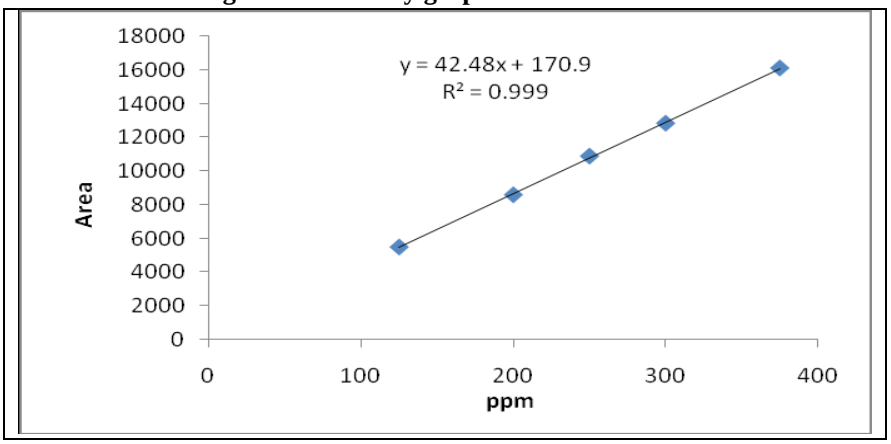
3.6 Calibration and linearity

Linearity test solutions for the method were prepared from Meclizine HCl stock solutions at six concentrations levels from tested from 80% to 120% of the targeted level of the assay concentration Meclizine HCl. Standard solutions containing 80-120 µg/ml of Meclizine HCl in each linearity level were prepared. Linearity solutions were injected in triplicate. The calibration graphs were obtained by plotting peak area verses the concentration data was treated by least-squares linear regression analysis, the calibration graphs were found to be linear in the mentioned concentrations the slopes and correlation coefficients are shown in Table 6. The standard curve found to be linear over the concentration range of 125-375 ppm. The equation of the standard curve relating the peak area to the Meclizine hydrochloride concentration in this range was y = 42.48x + 170.9. The present study reveals that, the drug showed good linearity in the range of 125-375 ppm with coefficient of correlation value 0.9999 for peak area.

Table 6: Results of the LOD and LOQ

Name	% LOD	%LOQ
Meclizine HCl	0.11	0.43

Figure 2: Linearity graph of Meclizine HCl



3.7 Robustness

To determine the robustness of the developed method experimental condition were purposely altered and the resolution between Meclizine HCl and acid degraded product were evaluated. The flow rate of the mobile phase was 1.0 ml/min. To study the effect of flow rate on the resolution, it was changed by 0.2 units from 0.8 to 1.2ml/min while the other mobile phase component was held as stated in chromatographic conditions. The effect of percent organic strength on resolution was studied by varying acetonitrile from –10 to +10 % while other mobile phase components were held constant as stated in chromatographic condition. The effect of column temperature on resolution was studied at 25 and 35°C instead of 30°C while the other mobile phase components were held constant stated in chromatographic condition. The results are shown in Table-6

Table 6: Results of robustness study

Sr.No.	Parameters	Standard parameter	Changes studied	
1	Flow rate	1.4 ml/min.	1.3 ml/min.	1.5 ml/min.
2	pH of Phosphate buffer	6.50	6.40	6.60
3	Mobile phase composition	Water : ACN : Phosphate buffer: Sulphate buffer250 : 750 : 50 :50	Water : ACN :Phosphate buffer :Sulphate buffer 230 : 770 : 50 : 50	Water : ACN :Phosphate buffer :Sulphate buffer 270 : 730 : 50 :50

3.8 LOD and LOQ (Sensitivity)

A series of solutions in the range 0.2–1.1% of the assay concentration (40 μg mL−1) were prepared by dilution of the standard solutions. Each solution (20 μL) was injected five times, the areas were measured for the drug peak, and the standard deviation for the five injections was calculated for each concentration. On the basis of data obtained, the standard deviation at concentration 0 was calculated and this value was used for calculation of the LOD and LOQ.

3.9 Stability of analytical solution

The stability of the standard solutions and the sample solutions was tested at intervals of 24, 48 and 72 h. The stability of solutions was determined by comparing results of the assay of the freshly prepared standard solutions. The RSD for the assay results determined up to 72 h for Meclizine HCl was 0.35 %. The assay values were within + 2 % after 72 h. The results indicate that the solutions were stable for 72 h at ambient temperature.

4. Conclusion

The method developed for quantitative determination of Meclizine HCl is rapid, precise, accurate and selective. The method was completely validated showing satisfactory data for all method-validated parameters tested. The developed method is stability indicating and can be used for assessing the stability of Meclizine HCl as bulk drugs. The developed method can be conveniently used for the assay determination of Meclizine HCl in bulk drugs and pharmaceutical dosage form.

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