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Cleaning level acceptance criteria and a high pressure liquid chromatography procedure for the assay of Meclizine Hydrochloride residue in swabs collected from pharmaceutical manufacturing equipment surfaces☆

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Abstract

A method using pharmacologically based and visual limit of detection criteria to determine the acceptable residue level for Meclizine Hydrochloride (MH) on pharmaceutical manufacturing equipment surfaces after cleaning is described. A formula was used in order to determine the pharmacologically safe cleaning level for MH. This level was termed as specific residual cleaning Level (SRCL) and calculated to be 50 μg 100 cm^{-2}. The visual limit of detection (VLOD) was determined by spiking different levels of MH on stainless steel plates and having the plates examined by a group of observers. The lowest level that could be visually detected by the majority of the observers, 62.5 μg 100 cm^{-2}, was considered as the VLOD for MH. The lower of the SRCL and VLOD values, i.e. 50 μg 100 cm^{-2}, was therefore chosen as the cleaning acceptance criterion. A sensitive reversed-phase HPLC method was developed and validated for the assay of MH in swabs used to test equipment surfaces. Using this method, the mean recoveries of MH from spiked swabs and '180-Grit' stainless steel plates were 87.0 and 89.5% with relative standard deviations (RSD) of ± 3.3 and ± 2.4%, respectively. The method was successfully applied to the assay of actual swab samples collected from the equipment surfaces. The stability of MH on stainless steel plates, on cleaning swabs and in the extraction solution was investigated.

Keywords: Meclizine Hydrochloride; Cleaning validation; Swab analysis; HPLC

1. Introduction

MH is commercially available both as branded and generic 12.5, 25, and 50 mg tablet dosage forms. It is indicated in the management of nausea and dizziness associated with motion sickness

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[1]. The chemical name of MH is 1-(*p*-chloro-α-phenyl-benzyl)-4-*m*-methylbenzyl) piperazine dihydrochloride monohydrate. It is practically insoluble in water, freely soluble in chloroform and pyridine, and slightly soluble in dilute acids [2]. Due to its poor solubility, it is difficult to remove MH residue from production equipment. Good manufacturing practice dictates that it is necessary to prove that the equipment is clean prior to using the equipment after MH tablet production for the manufacture of other products. The chemical structure of MH is presented in Fig. 1. A variety of analytical methods for MH including spectrophotometry [3–6], conductometry [7], GC/MS [8] and HPLC [9] have been cited in the literature. The tablet assay method included in the MH monograph in the current USP [10] is a cation-exchange HPLC method using a strong cation exchange column. The current USP method lacks the sensitivity and specificity needed for the determination of low levels of MH in test swabs from manufacturing equipment. The main objectives of this project were 2-fold: (1) to propose a residual acceptance criteria based on sound scientific rationale; (2) to develop a simple, sensitive, accurate, linear, precise and rugged cleaning validation method for the determination of residual MH in swabs collected by swabbing equipment surfaces.

The subject of cleaning validation is an important issue faced by the pharmaceutical industry today. In recent years, it has become the subject of greater scrutiny on the part of the FDA. Cleaning validation is a requirement mandated by 1963 GMP regulations (Part 133.4) and by 1978 cGMP regulations (Section 211.6). The main objective of a thorough cleaning validation program is to prevent contamination or adulteration of drug products [11]. Visual inspection alone to ensure cleanliness leading to the conclusion 'no residue detected' is no longer acceptable to the regulatory agencies [12]. Visual inspection of the equipment supported by chemical residue data, obtained by using a validated analytical technique, is required in order to ensure lack of cross-contamination between products [13,14].

Because of the broad spectrum of products manufactured by the pharmaceutical industry using a wide variety of equipment, it is difficult for the FDA and other regulatory agencies to establish clear guidelines for setting acceptance specifications. A single set of acceptance criteria can not be applied to all products and types of equipment. Therefore, companies are expected to establish acceptance criteria based on logical and scientific rationale. Several acceptance criteria have been proposed in the literature [15–17].

In this article, an approach is proposed using MH as the model compound for which the visual limit of detection (VLOD) is compared with a criterion based on phamacological acitivity of MH. The lower of the two values was established as the residual acceptance criterion for MH. The pharmacologically based residual acceptance criterion for MH was designed on the premise that not more than 1/10 000th of the labeled amount of active present in the dosage form should be available for carryover to a dose of the next product produced in the equipment train. The amount of the residue allowed on the total equipment train is termed a residual acceptance level (RAL). The smallest RAL or the lowest allowable residue level based on pharmacological activity is achieved by using the smallest dosage of the current product and the smallest batch size manufactured using the equipment train. The formula used for the calculation of the RAL value is shown:

$$\mathrm{RAL} = \frac{D}{\mathrm{SF}} \times \text{smallest batch size} \qquad (1)$$

Where: D, lowest dosage strength of the current product; SF, Safety factor = 10 000; smallest batch size of any product manufactured using the equipment train.

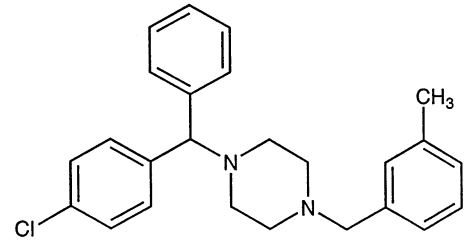

Fig. 1. Structure of Meclizine.

Table 1
Swabbing pattern used for collecting Meclizine Hydrochloride residue from the actual equipment surfaces and from the spiked plates in the cleaning validation studies

1.	Use 4 × 4 inch Absorbond (polyester) swabs. (Note: vinyl, powder free, gloves must be worn to avoid interferences)
2.	Place the swabs in methanol (swabbing solvent) contained in a suitable container insuring that the swabs are completely immersed in the liquid
3.	Fold the swab diagonally in half. Fold the swab again diagonally, splitting the 'right triangle'. The resulting swab is also a right triangle
4.	Squeeze the excess swabbing solvent removing as much excess as possible. (Excess solvent dilutes the collected drug residue and could render artificially low results)
5.	Hold the folded swab between the thumb and second finger using the first finger to apply pressure on the surface to be cleaned
6.	Swab the surface in a horizontal manner insuring that the total surface is wiped, starting from the outside towards the center. Overlapping the same surface is acceptable. Fold the exposed surface of the swab internally, resulting in a triangle one-half its original size. Expose a fresh swab surface and swab vertically, or 90° from the original direction
7.	Repeat steps 3, 4, 5, and 6 using a second Absorbond swab premoistened in methanol, placing the resulting swab in the same container
8.	Cap the sample container securely and label properly indicating drug substance, swab type, swab solvent, operator's name, the date and detailed swabbed location

If the RAL is divided by the surface area of the entire equipment train used in the manufacture of the drug product, a concentration value in mass per unit surface area is obtained and is termed as specific residual cleaning level (SRCL). The formula used for the calculation of the SRCL is shown:

$$\mathrm{SRCL} = \frac{\mathrm{RAL}}{\mathrm{SA}} \quad (2)$$

Where: SA, surface area of the entire equipment train used in the manufacturing of the product.

The SRCL for MH using Eq. (2) was calculated to be 50 μg 100 cm^{-2}.

The VLOD of MH was detemined by spiking five separate 10 × 10 cm 316 stainless-steel plates with known amounts of MH. The lowest level of MH residue that could be visually detected by a majority of associates ($n = 5$) was 62.5 μg 100 cm^{-2}. Since the SRCL value of 50 μg 100 cm^{-2} is lower than VLOD, it was therefore considered as the residual acceptance criterion for MH.

On the basis of the SRCL, the analysis concentration range of interest was determined. In this article, a sensitive reversed-phase HPLC method is described for the determination of trace levels of MH in cleaning validation swab samples obtained from testing the equipment train. The results from recovery studies of MH from polyester swabs (Absorbond) and stainless-steel surfaces are presented. Also, results from the investigation of the stability of MH on stainless-steel surfaces, in undiluted swabs and from swabs stored in the extraction solvent are discussed.

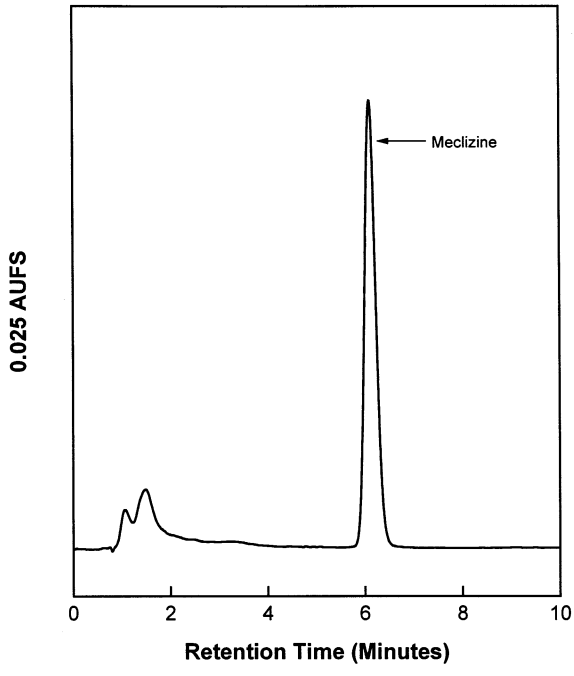

Fig. 2. Chromatogram obtained for a Meclizine Hydrochloride standard solution (10 μg ml^{-1}).

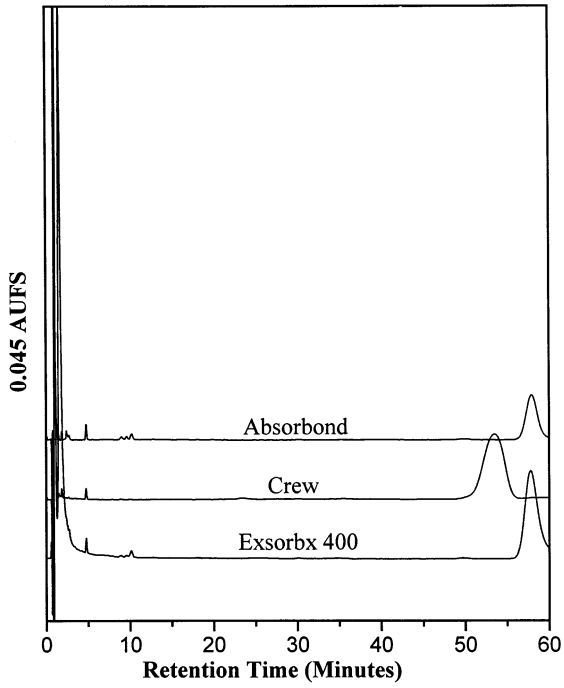

Fig. 3. Representative chromatograms for the blank extracts of Absorbond, Crew, and Exsorbx 400 swabs.

2. Experimental

2.1. Apparatus

The HPLC system used in this study consisted of a Hitachi Model L-6000 pump and a Hitachi 655A-40 Autosampler (Hitachi, Japan). Separation was performed on a Waters Symmetry C_8 column, 5 μm particle size, 3.9 mm (id) × 150 mm column (Waters Associates, Milford, MA, USA). Detection was achieved using an ABI 759A Absorbance Detector (Applied Biosystems, Foster City, CA).

Table 2
Linearity of Meclizine Hydrochloride by regression analysis (Meclizine Hydrochloride vs. peak area)

Meclizine Hydrochloride (μg ml^{-1})	Peak area response (mV sec^{-1})[a]
1.057	46.083
5.283	230.792
10.57	457.384
26.411	158.295
52.832	320.642
Correlation coefficient	0.99999
Slope (mV-sec/(μg ml^{-1}))	43.97
y-intercept (peak area)	−2.837

[a] Average of two replicates

2.2. Chemicals and materials

Methanol and acetonitrile were HPLC grade (Fischer Scientific, Pittsburgh, PA), and were used as supplied. MH was an in-house qualified standard. All other chemicals used were of reagent grade. Absorbond (Texwipe 404), Exsorbx 400 (Berkshire), and Crew (Kimberly–Clark) swabs were obtained from Baxter Products Division, McGaw Park, IL.

2.3. High pressure liquid chromatography conditions

The mobile phase was 0.1 M citrate buffer/acetonitrile/water/triethylamine, 50/400/550/0.5 (v/v/v/v). The buffer was prepared by dissolving 21.09 g of citric acid monohydrate and 1.76 g of sodium citrate dihydrate in 750 ml water in a 1 l volumetric flask, then bringing to volume with water. The mobile phase was degassed prior to use, employing vacuum filtration through a 0.7 μm glass microfiber filter (Whatman, type GF/F). The flow rate was set at 1.5 ml min^{-1}. Column temperature was ambient. The injection volume was 50 μl, and the detection wavelength was set at 230 nm.

2.4. Preparation of calibration standards

A MH stock solution was prepared by accurately weighing 50 mg of a MH standard and transferring it into a 100 ml volumetric flask. It was dissolved in the mobile phase, mixed, then made up to volume with mobile phase. A series of five calibration standards were prepared by transferring appropriate aliquots of the MH stock solution, or dilutions there of, into separate 100 ml volumetric flasks. The concentrations of MH in these calibration standards were 1.000, 5.00, 10.00, 25.00, and 50.0 μg ml^{-1}, respectively.

2.5. Sample preparation

2.5.1. For recovery studies of Meclizine Hydrochloride from Absorbond swabs and '180-Grit' stainless steel plates

The surfaces tested were '180-Grit' stainless steel 10 × 10 cm plates prepared in-house. A spiking solution was prepared by dissolving ≈50 mg of MH into 100 ml of methanol. Using appropriate glass micro syringes, aliquots ranging from 40–1000 μl of the spiking solution were transferred onto four sets of five plates each. The spiked plates thus contained either ≈20, 50, 100, or 500 μg of MH. The solutions on the test surfaces were allowed to evaporate. The plates were then successively swabbed with two Absorbond swabs which were previously moistened with methanol, wringing out the excess. All the swabbings followed a prescribed wiping pattern (Table 1). The swabs from each sample were placed into high density polyethylene (HDPE) bottles. A 10.0 ml aliquot of the mobile phase was added to each bottle. Each bottle was capped and shaken vigorously for ≈1 min. The extract was collected using a 10 cc disposable syringe and transferred to an autosampler vial. In the study for the recovery of MH from Absorbond swabs, aliquots ranging from 40–1000 μl of the spiking solution were deposited directly into separate HDPE bottles (five bottles per concentration level) containing two Absorbond cleaning swabs pre-moistened in methanol. This resulted in spiked levels of 20, 50, 100, and 500 μg, respectively. The same extraction procedure as described earlier was used.

2.5.2. For actual samples collected from the equipment train

A 10 ml aliquot of the mobile phase was pipetted directly on top of the sample swabs contained in HDPE bottles. Each bottle was capped and shaken vigorously for ≈1 min. The extract was collected using a 10 cc disposable syringe and transferred into an autosampler vial.

2.5.3. For stability studies

A series of '180-Grit' stainless-steel plates were spiked with 100 μg of MH in methanol solution, sets of which were allowed to sit undisturbed for up to four days. Other sets of the spiked plates were swabbed immediately, the swabs then placed in HDPE bottles, capped securely, and allowed to sit undisturbed. These were labeled as 'dry' swabs. The remaining sets were swabbed immediately, placed in HDPE bottles, the extraction solvent added and then, the bottles were capped securely. These were labeled as 'wet' swabs.

Table 3
Results obtained for the recovery of Meclizine Hydrochloride from spiked Absorbond swab samples

Meclizine Hydrochloride spiked (μg)	Meclizine Hydrochloride recovered (μg)	% recovery
20.04	17.61	85.9
	17.07	85.2
	16.79	83.8
	17.39	86.8
	17.15	85.6
50.09	42.63	85.1
	43.13	86.1
	43.58	87.0
	43.53	86.9
	43.13	84.1
100.2	94.49	94.3
	93.89	93.7
	94.09	93.9
	91.38	91.2
	93.39	93.2
500.9	476.9	95.2
	473.9	94.6
	477.9	95.4
	475.9	95.0
	480.9	96.0
	Mean	90.0%
	RSD	±5.1%
	n	20

2.6. Chromatographic procedure

For the samples and the calibration standard solutions, 50-μl aliquots were injected separately into the HPLC with the aid of the autoinjector using the operating conditions described in Section 2.3. The amount of residual MH was determined by comparing the MH peak area response

obtained for the sample to a linear calibration curve obtained from the calibration standard solutions.

3. Results and discussion

3.1. Development of the analytical method

One of the objectives of this project was to develop a sensitive, accurate, precise, linear and rugged cleaning validation method for the assay of trace levels of residual MH collected by swabbing various manufacturing equipment surfaces. An initial attempt using a C_{18} bonded phase column resulted in an asymmetric MH peak. The peak asymmetry may be attributed to the interaction of MH with residual silanol sites on the stationary phase. The peak symmetry was improved by using an end-capped Waters Symmetry® C_8 column and by the addition of a competing base (triethylamine) into the mobile phase. A chromatogram obtained by injecting a standard solution is presented in Fig. 2.

3.2. Determination of proper swabbing material

Two swabs of Absorbond, Exsorbx 400 and Crew types were placed in separate beakers containing methanol. The excess methanol was eliminated from the swabs by wringing out the swabs. Then the swabs were transferred into separate HDPE bottles. Ten milliliters of the mobile phase solution was pipetted into each bottle. The bottles were manually shaken for 1 min. The extracts were transferred with the aid of disposable plastic syringes into autosampler vials. The swab extracts were injected into the HPLC using the chromatographic conditions. Absorbond was chosen as the swabbing material because it was free of any interfering peaks which would co-elute with Meclizine, where as Crew and Exsorbx both exhibited extraneous peaks which could potentially interfere. The chromatograms obtained from the extracts of the three swab materials are presented in Fig. 3.

3.3. Assay validation

The validation of the method was carried out by determining the linearity, accuracy, repeatability, intermediate-precision and limit of quantitation of the method.

3.3.1. Linearity

A linearity study was performed in order to determine the linearity of the system response for MH over a concentration range of 1.057–52.83 μg ml^{-1} in mobile phase. The resulting solutions were chromatographed using the described HPLC conditions. A correlation coefficient [r] of 0.99999 was obtained from the linear regression analysis of the data (peak area vs. concentration of MH). This demonstrates that the MH peak area re-

Table 4
Results obtained for the recovery of Meclizine Hydrochloride from spiked '180-Grit' stainless steel plates

Meclizine Hydrochloride spiked (μg)	Meclizine Hydrochloride recovered (μg)	% recovery[a]
20.14	17.80	88.4
	17.78	88.3
	17.80	88.4
	18.61	92.4
	16.49	81.9
50.36	45.02	89.4
	45.42	90.2
	44.37	88.1
	44.77	88.9
	45.02	89.4
100.7	91.23	90.6
	90.43	89.8
	91.54	90.9
	91.64	91.0
	90.93	90.3
503.6	452.2	89.8
	460.3	91.4
	458.3	91.0
	447.7	88.9
	456.8	90.7
	Mean	98.2%
	RSD	±2.4%
	n	20

[a] Uncorrected for recovery factor used in the method.

Table 5
Repeatability results obtained from five replicate injections of a Meclizine Hydrochloride calibration standard on two different days (intermediate precision)

Day 1 Replicate	Meclizine Hydrochloride concentration (μg ml^{-1})	Peak area (mV sec^{-1})	Day 2 Meclizine Hydrochloride concentration (μg ml^{-1})	Peak area (mV sec^{-1})
1	10.11	305.747	10.12	307.908
2		308.232		307.973
3		308.139		306.954
4		308.122		306.984
5		305.94		308.449
Mean		307.236		307.654
RSD		±0.41%		±0.21%
n		5		5

sponse is linear over the concentration range examined. The results of the linearity study are tabulated in Table 2.

3.3.2. Accuracy

The accuracy of the method was determined by spiking both swabs and '180-Grit' stainless steel plates with known amounts of MH and analyzing the spiked samples. The accuracy was then calculated as the % spiked (swabs or swabs obtained from swabbing the spiked plates) of MH recovered from the spiked samples. Independent of this study, the visual limit of detection for MH was determined to be ≈62.5 μg 100 cm^{-2}. The SRCL, calculated based on the formula described in the introduction, was 50 μg 100 cm^2, slightly lower than the visual limit of detection. Recovery studies were carried out in the range of 20–500 μg 100 cm^{-2}, thereby bracketing the visual limit of detection as well as the calculated SRCL level.

A mean recovery of 90.0%, with RSD of ± 5.1% ($n = 20$) was obtained for the recovery of MH from the Absorbond swab material. A swab recovery of approximately 90% was expected as a result of the dilution effect of the methanol contribution from the wetted swabs. The data are contained in Table 3. The data demonstrate that the method is sufficiently accurate and precise for the recovery of MH from Absorbond cleaning swabs.

Table 6
Stability results obtained for Meclizine Hydrochloride spiked onto '180-Grit' stainless steel plates (stability of Meclizine Hydrochloride on dry plates) [a,b,c]

	% Recovery of Meclizine Hydrochloride			
Sample	Initial day	Day 1	Day 2	Day 4
1	89.9	68.2	66.6	79.9
2	88.1	89.1	68.0	82.8
3	91.0	83.6	68.5	85.6
Mean	87.9	80.3	67.7	82.8
RSD	1.6	±13.5	±1.5%	±3.5%
n	3	3	3	3

[a] Uncorrected for recovery factor used in the method.
[b] Sample stored dry on plates at ambient room temperature.
[c] 100.7 mg Meclizine Hydrochloride spiked per 100 cm^2.

Table 7
Stability results obtained for Meclizine Hydrochloride in 'dry' swabs obtained by swabbing spiked '180-Grit' stainless steel plates [a,b,c]

	% Recovery of Meclizine Hydrochloride			
Sample	Initial Day	Day 1	Day 2	Day 4
1	89.9	88.4	89.5	90.0
2	88.1	89.9	91.8	89.2
3	91.0	90.0	91.2	89.3
Mean	87.9	89.4	90.8	89.5
RSD	1.6	±1.0	±1.3%	±0.4%
n	3	3	3	3

[a] Uncorrected for recovery factor used in the method.
[b] Undiluted swab samples, after swabbing stored in HDPE bottles at ambient roomtemperature.
[c] 100.7 mg Meclizine Hydrochloride spiked per 100 cm^2.

Table 8
Stability results obtained for Meclizine Hydrochloride in 'wet' swabs obtained by swabbing spiked '180-Grit' stainless steel plates [a,b,c]

	% Recovery of Meclizine Hydrochloride			
Sample	Initial Day	Day 1	Day 2	Day 4
1	89.9	69.8	72.9	70.6
2	88.1	81.4	73.1	66.7
3	91.0	75.2	78.5	97.4
Mean	87.9	75.5	74.8	78.2
RSD	1.6	±7.7	±4.2	±21.4
n	3	3	3	3

[a] Uncorrected for recovery factor used in the method.
[b] Swab samples, after swabbing, diluted with 10 ml of the internal standard solution in HDPE bottles and stored at ambient room temperature.
[c] 100.7 mg Meclizine Hydrochloride spiked per 100 cm^2.

An overall mean recovery of 89.5% with an RSD of ±2.4% ($n = 20$) was obtained for the recovery of MH from '180-Grit' stainless steel plates. The data are contained in Table 4. In order to correct for the low recovery of MH from the stainless steel plates, a recovery correction factor of 1.1 has been included in the method.

3.3.3. *Repeatability, intermediate precision and limit of quantitation*

Assay repeatability was calculated from the data presented in Table 4. At the 50 μg level, the recovery of MH from five separate stainless steel plates was 89.2% with an RSD of ±0.86%. The overall RSD ($n = 20$) for the recovery of MH at levels ranging from the LOQ of 20–500 μg was only 2.4%.

Injection repeatability and intermediate precision of the method were investigated by making five consecutive injections of a standard solution on two different days. On both days the means and RSDs were calculated for peak area responses obtained for the MA peaks. The data from this study are tabulated in Table 5. The data suggest that the method exhibits acceptable intermediate precision and repeatability with less than 2% RSDs for a MH standard solution when analyzed on two different days.

The smallest level at which the recovery of MH was determined, 20 μg 100 cm^{-2} was conservatively defined as the limit of quantitation (LOQ). Therefore, all the swab results lower than 20 μg 100 cm^{-2} were reported as less than 20 μg 100 cm^{-2}. This LOQ level is significantly lower than the calculated SRCL value of 50 μg 100 cm^{-2} for MH.

3.3.4. *Stability of Meclizine Hydrochloride on stainless steel surface and in the swabs*

In order to study the stability of MH on surfaces and in the swabs prior to analysis, at the initial day, Day 1, Day 2 and Day 4 time intervals, a set of three MH spiked stainless steel plates were swabbed and the extracted residue analyzed for MH using the proposed method. At the same time intervals, a set of three bottles containing 'dry' swabs which had been used on the initial day to swab test plates, were extracted, the solutions then analyzed for MH. Similarly, a set of three bottles containing 'wet' swabs used to test spiked plate on the initial day, then stored with extraction solvent, were also analyzed for MH. The MH peak purity was determined using a diode array detector. The spectral analysis did not indicate co-elution of interfering peaks.

The spiked dry plate stability information is included in Table 6. The spiked plate stability study indicated the length of time the active, MH, can be left on the manufacturing equipment prior to initiation of the swabbing process. The results from the 'dry' swab stability study presented in Table 7, indicate the length of time the submitted swabs can set prior to analysis. The results from the 'wet' swab stability study are included in Table 8, indicate the length of time the swabs can be extracted and allowed to set prior to analysis. The results indicate that MH is stable on swabs in the unextracted 'dry' form for at least 4 days, but is less stable in the swabs in the extracted 'wet' form or on the surfaces of the process equipment. Therefore, it is recommended that the equipment be swabbed immediately after the completion of the cleaning process and the extracted swabs be analyzed immediately.

Table 9
Stability results for a set of Meclizine Hydrochloride calibration standards

Standard	Meclizine Hydrochloride concentration (μg ml^{-1})	% Remaining[a]		
	Initial day	Day 1	Day 2	Day 4
1	25.30	96.6	90.9	92.9
2	50.50	94.3	92.1	92.6
3	101.0	100.2	96.4	88.9
4	202.0	96.2	93.4	91.0
5	303.0	98.0	92.4	91.1
	Mean	97.1	93.0	91.3
	RSD	±2.3	2.2	±1.7
	n	5	5	5

[a] Standard solution stored left on a desk-top away from sunlight at ambient conditions.

3.3.5. Stability of Meclizine Hydrochloride standard solutions

A set of standard solutions were prepared and analyzed by following the procedure in the proposed method. These standard solutions were placed on a bench-top at ambient conditions away from direct sunlight. After 1, 2, and 4 days, these aged solutions were re-analyzed against freshly prepared standard solutions. The initial concentrations of MH in the standard solutions and the % remaining in these solutions at Day 1, Day 2 and Day 4 time intervals are presented in Table 9. The data suggest that the standard solutions are stable for at least 24 h.

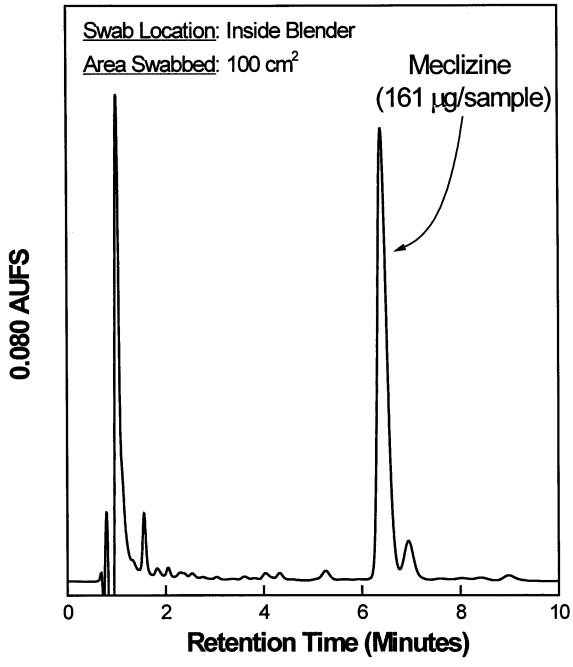

Fig. 4. Chromatogram obtained for a representative swab sample from the equipment train.

3.4. Assay of swab samples collected from different locations within the equipment train

Swab samples from different locations within the manufacturing equipment train were submitted to the laboratory for the analysis of residual MH. These samples were prepared and analyzed by the proposed method. A typical chromatogram obtained for a MH cleaning validation swab sample obtained from a location within the equipment train is presented in Fig. 4. The results obtained for these samples are presented in Table 10.

4. Conclusions

A sensitive high performance liquid chromatographic cleaning validation method for the determination of trace levels of MH in swab samples collected by swabbing pharmaceutical manufacturing equipment surfaces has been developed and found to be accurate and precise. A systematic protocol for setting the allowed residual limit and validating the analytical method was utilized. This protocol can be easily adopted for ensuring the

Table 10
Results obtained for the determination of Meclizine Hydrochloride in actual swab samples collected from different locations within the equipment train

Equipment swabbed	Location swabbed	Area swabbed (cm^2)	Meclizine Hydrochlorolide detected (mg)
Drying racks	Left tray guide	100	102
Drying racks	Right tray guide	100	150
Drying racks	Right tray guide	100	55
Drying racks	Individual tray	100	<20
Blender	Inside wall near top	100	161
Blender	Inside wall near bottom	100	42
Blender	Lid gasket	586	<20
Blender	Discharge valve gasket	260	28
Fitzmill	Grinding chamber	100	70
Fitzmill	Hub of blades	305	170
Fitzmill	Blade surface	100	32
Mixer	Mixer bowl	100	<20
Mixer	Trunion	44	<20
Mixer	Shaft seal	102	113

cleanliness of equipment used in the manufacturing of a majority of the pharmaceutical dry products. This protocol emphasizes the need to demonstrate the stability of the drug substance on the equipment surfaces as well as on the swabs and in solution. In the absence of such stability data, it is possible to under-estimate the amount of drug residue remaining on the equipment surfaces or on the swabs prior to analysis.

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