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ANALYSIS

STABILITY-INDICATING HPLC METHODS FOR DETERMINATION OF ASSAY AND RELATED SUBSTANCES IN NOVEL ORODISPERSIBLE MECLIZINE HYDROCHLORIDE TABLET

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Abstract: Orodispersible tablets (ODT) constitute an innovative dosage form that provides a patient-friendly option that enhances compliance and therapeutic convenience, particularly for pediatric and geriatric populations with swallowing difficulties. Meclizine ODT (6.25 mg and 12.5 mg) were developed at F1 Pharma S.A., packaged in blisters and designed for stability studies. This study reports the development and full validation in compliance with ICH Q2(R1) guidelines of two HPLC methods for the quantification of meclizine hydrochloride and its related impurities in the 6.25 mg ODT formulation. Both methods proved highly specific, precise, accurate, and robust, with validated working ranges suitable for routine quality control and stability testing. Forced degradation experiments identified impurities C and H as the primary degradation products. Long-term stability studies conducted under ICH Zone II and III conditions confirmed the chemical stability of the formulation, with assay values consistently within ± 5% of the label claim and impurity levels within acceptable limits. The developed novel ODT formulation meets all regulatory requirements, while validated HPLC methods ensure reliable routine analysis, supporting quality control and stability studies of this innovative dosage form, which enhances patient comfort and treatment effectiveness.

Keywords: orodispersible tablets (ODT), meclizine hydrochloride (MEC), stability studies, method validation.

The development of orodispersible tablets (ODTs) has provided a patient-friendly alternative to conventional solid dosage forms, as the incorporation of superdisintegrants enables rapid dispersion directly in the oral cavity. This dosage form has attracted increasing attention in recent years as a convenient and effective drug delivery platform, particularly for pediatric and geriatric populations, who often experience difficulties swallowing traditional tablets or capsules [1–7]. Addressing these needs, novel meclizine hydrochloride ODT formulations (6.25 mg and 12.5 mg) were developed at F1 Pharma S.A. to enhance patient compliance and improve therapeutic accessibility. These innovative formulations combine the advantages of rapid oral disintegration with reliable dose delivery, offering a valuable solution for vulnerable patient groups and expanding the clinical utility of meclizine in the prevention of motion sickness.

Meclizine is a first-generation antihistamine drug commonly prescribed for the prevention and treatment of motion sickness and vertigo. It works primarily by blocking H1 histamine receptors in the central nervous system. In addition to its antihistaminic effects, meclizine exhibits mild anticholinergic activity, which contributes to its ability to reduce nausea and dizziness.

According to the European Pharmacopoeia (Ph. Eur.) [8], six impurities of meclizine hydrochloride are specified: B, C, D, E, F, and H (Table 1). Most of these impurities are related to the manufacturing process of the active substance, while only impurity H is recognized as a degradation product of the API.

Several analytical methods for the determination of meclizine hydrochloride have been reported in the literature, including thin-layer chromatographic (TLC) [9], spectrophotometric [10–15],

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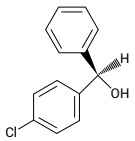
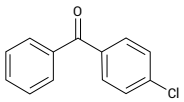
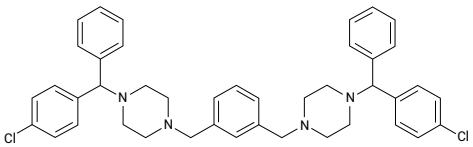
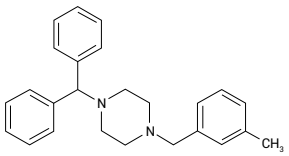
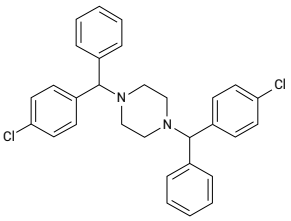
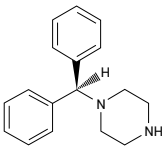
Table 1. List of meclizine hydrochloride impurities according to Ph. Eur.

IMP	Name	Structure	Origin
B	(RS)-(4-chlorophenyl) phenylmethanol		**Synthesis** By-product of synthesis
C	(4-chlorophenyl) phenylmethanone		**Synthesis** Key starting material
D	1,1′-(1,3-phenylenebis(methylene))bis[4-(4-chlorophenyl) phenylmethyl]piperazine		**Synthesis** By-product of synthesis
E	1-(diphenylmethyl)-4-[(3-methylphenyl)methyl] piperazine		**Synthesis** By-product of synthesis
F	1,4-bis[(4-chlorophenyl) phenylmethyl]piperazine		**Synthesis** By-product of synthesis
H	1-[(RS)-(4-chlorophenyl) phenylmethyl]piperazine		**Synthesis** Intermediate product **Degradant** Dealkylation

GC/MS [16] or LC/MS/MS [17] methods. Meclizine has also been described in major pharmacopoeias, including the British Pharmacopoeia (BP), United States Pharmacopeia (USP), and European Pharmacopoeia (Ph. Eur.), which provide potentiometric and chromatographic procedures. The impurity profile of meclizine hydrochloride is most commonly determined by high-performance liquid chromatography (HPLC) [18–24].

This study aimed to develop and validate novel stability-indicating HPLC methods in accordance with ICH Q2(R1) guidelines [25], enabling the reliable determination of meclizine hydrochloride and its related impurities, suitable for testing new formulations during the drug development process. A new orally disintegrating tablet (ODT) formulation was prepared and characterized, and the validated HPLC procedures were applied to monitor its stability under accelerated, intermediate, and long-term conditions. The results demonstrate that the formulation meets all regulatory requirements, highlighting both the methodological novelty and practical significance of this work for quality control and stability assessment. The developed tablets

are currently the subject of a patent application in the Republic of Poland.

Additionally, in line with the growing importance of Green Analytical Chemistry, the developed methods were evaluated using the AGREE tool to assess their environmental sustainability.

EXPERIMENTAL

Materials, Chemicals, and Reagents

All chemicals used in this study were of analytical reagent grade, and all solvents were of HPLC grade. Acetonitrile was obtained from Supelco (Merck Life Science Sp. z o.o, Poland) and methanol from Baker (Avantor Performance Materials S.A., Poland). Hydrochloric acid (35 – 38%), hydrogen peroxide (30%), sodium hydroxide, and concentrated phosphoric acid (85%) were purchased from Chempur (Poland). Sodium dihydrogen phosphate dihydrate was obtained from Supelco (Merck Life Science Sp. z o.o, Poland).

Meclizine hydrochloride working standard and active substance were supplied by Symed Labs Limited. The following impurity standards were purchased from Sigma-Aldrich (Merck Life Science Sp. z o.o., Poland): 4-chlorobenzhydrol (Meclizine Impurity B), 4-chlorobenzophenone (Meclizine Impurity C), and 1-(4-chlorobenzhydryl)piperazine (Meclizine Impurity H). Ultra-pure water for all analyses was produced in-house using a Direct-Q Water Purification System Millipore (Merck Life Science Sp. z o.o., Poland).

The orodispersible tablets with meclizine were developed and supplied by F1 Pharma S.A (Poland).

Instrumentation and Chromatographic Conditions

High-performance liquid chromatography (HPLC) was used for the determination of assay, identification, and related substances of meclizine hydrochloride in tablet formulations. Analyses were performed on Hitachi Primaide (Merck) and Hitachi Elite LaChrom (Merck) HPLC systems equipped with a diode-array detector (DAD). For assay determination, a Waters Spherisorb SCX column (5 µm, 250 × 4.6 mm) was used, while for impurity profiling, a Hypersil Phenyl column (5 µm, 250 × 4.6 mm) was employed. Chromatographic data were recorded at a detection wavelength of 230 nm.

Additional laboratory equipment included an analytical balance (Mettler Toledo MS105), ultrasonic bath (Polsonic), laboratory shaker (Julabo SW22), and pH meter (inoLab pH 730P). Filtration was performed using 0.45µm syringe filters (25 mm, LLG LabWare, Nylon (PA) and RC yellow) and PVDF membrane filters (Durapore, 0.45 µm) with a vacuum pump (AGA LABOR). A centrifuge (OHAUS FC5515) was used during sample preparation.

Standard Solution Preparation

The diluent used throughout the analysis consisted of methanol and water mixed in a 50 : 50 (v/v) ratio.

- Assay Determination

Approximately 25 mg of meclizine hydrochloride (MEC) analytical standard was accurately weighed and quantitatively transferred into a 50 mL volumetric flask. The diluent was added, and the mixture was sonicated to dissolve the substance completely. The solution was then made up to volume with the same diluent. Subsequently, 5 mL of this solution was transferred into a 20 mL volumetric flask and diluted to volume with diluent, resulting in a final concentration of approximately 0.125 mg/mL of MEC in the standard solution. An exemplary chromatogram of the standard solution used for assay determination is presented in Figure 1.

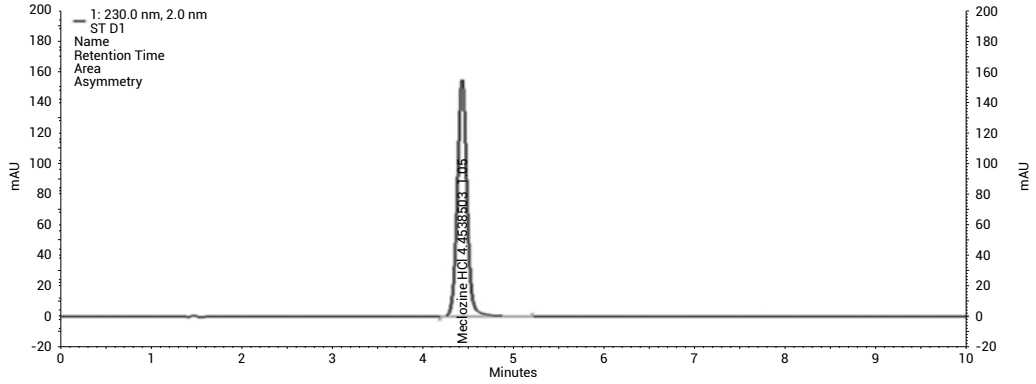


Figure 1. Chromatogram of the standard solution (assay determination). The x-axis shows retention time (RT, min) and the y-axis shows absorbance (mAU). Next to the peak, the retention time (RT), peak area, and asymmetry factor are indicated.

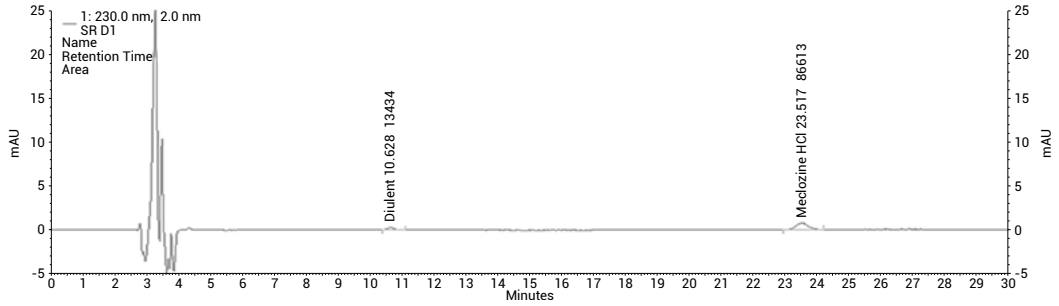


Figure 2. Chromatogram of standard solution (impurity determination). The x-axis shows retention time (RT, min) and the y-axis shows absorbance (mAU). Next to the peaks, the retention time (RT) and peak area are indicated.

• Impurity Determination

Approximately 25 mg of MEC analytical standard was accurately weighed and transferred into a 50 mL volumetric flask. The diluent was added, and the mixture was sonicated to dissolve the standard completely and then made up to volume with the diluent to obtain Solution A. An aliquot of 1 mL of Solution A was transferred into a 20 mL volumetric flask and diluted to volume with diluent to obtain Solution B. Then, 1 mL of Solution B was transferred into a 100 mL volumetric flask and again diluted to volume with the diluent, yielding Solution C. The final concentration of MEC in Solution C was approximately 0.00025 mg/mL, corresponding to 0.2% of the assay concentration of the active substance in the sample solution. An exemplary chromatogram of the standard solution used for impurity analysis is shown in Figure 2.

Sample Solution Preparation (for Assay and Impurity Determination)

The same diluent used for the preparation of the standard solutions, consisting of methanol and water in a 50 : 50 (v/v) ratio, was employed for the preparation of the sample solutions. Twenty tablets containing 6.25 mg of MEC were randomly selected and weighed to determine the average tablet mass. A portion of the powdered tablets equivalent to the average tablet mass was accurately weighed and transferred into a 50 mL volumetric flask. Diluent was added, and the mixture was sonicated for 15 minutes to ensure complete dissolution. The solution was then made up to volume with diluent and filtered through a 0.45 µm syringe filter prior to HPLC analysis. Representative chromatograms of the sample solution used for the assay and impurity determinations are shown in Figures 3 and 4, respectively.

Chromatographic Conditions

• Assay Determination

The HPLC analysis for assay determination was performed under the following conditions: the flow rate was set at 2.0 mL/min, the column temperature was maintained at 25°C, and the total run time was 10 minutes. The injection volume was 10 µL. The mobile phase consisted of a pH 4.0 phosphate buffer, acetonitrile, and methanol mixed in a 25 : 45 : 30 (v/v/v) ratio.

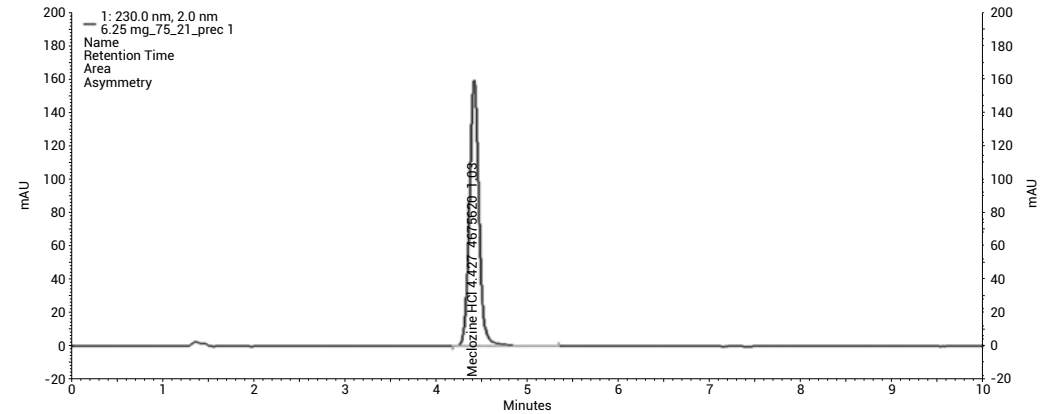


Figure 3. Chromatogram of sample solution—meclizine hydrochloride tablets 6.25 mg (assay determination). The x-axis shows retention time (RT, min) and the y-axis shows absorbance (mAU). Next to the peak, the retention time (RT), peak area, and asymmetry factor are indicated.

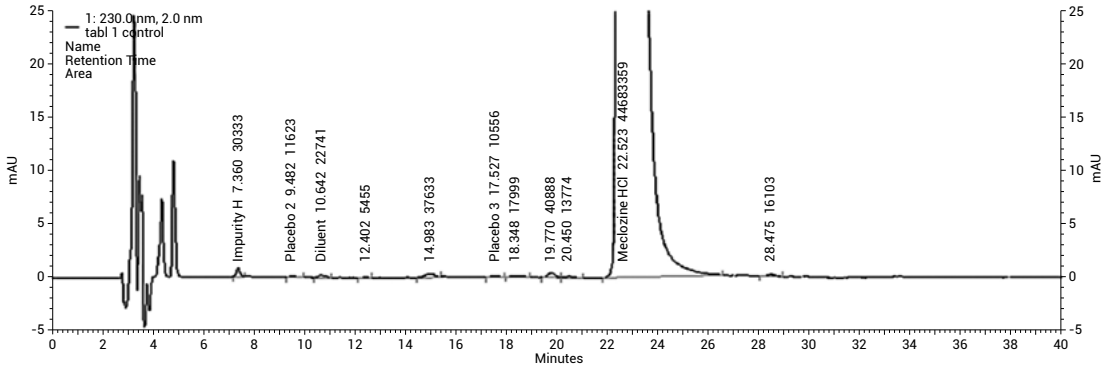


Figure 4. Chromatogram of sample solution—meclizine hydrochloride tablets 6.25 mg (impurity determination). The x-axis shows retention time (RT, min) and the y-axis shows absorbance (mAU). Next to each peak, the retention time (RT) and peak area are indicated.

- Impurity Determination

For the analysis of related substances, the flow rate was set at 1.0 mL/min, and the column temperature was maintained at 35°C. The injection volume was 50 µL. The total analysis time was 40 minutes for the sample solutions and 30 minutes for the standard solutions. The mobile phase consisted of a pH 4.0 phosphate buffer, acetonitrile, and methanol in a 60 : 35 : 5 (v/v/v) ratio.

RESULTS AND DISCUSSION

Assay Validation and Active Substance Identification Method in Meclizine Hydrochloride Tablets

The validated analytical method for the assay of meclizine hydrochloride (MEC) in tablets containing 6.25 mg of the active substance demonstrated adequate specificity, precision, linearity, and accuracy. The procedure was confirmed to be specific, as no interference was observed at the retention time of MEC from excipients present in the placebo matrix. Precision was demonstrated by analyzing six independently prepared samples of the finished product. The relative standard deviation (RSD) for the assay results was 0.5% for both analysts, and the difference between their mean results was 0.2%. The linearity of the method was confirmed over the tested concentration range, with a correlation coefficient (R) of 0.9999, indicating a strong linear relationship between concentration and response. Accuracy was assessed by recovery studies at three concentration levels: 70%, 100%, and 150% of the target assay level, through spiking placebo with known quantities of MEC. The recovery values ranged from 98.0% to 102.0%, confirming the accuracy of the method.

The method was also found suitable for identification purposes. The retention time of MEC in the sample solutions matched that of the reference standard, and the UV spectra of the sample and standard solutions were comparable in the range of 200–300 nm.

Stability studies demonstrated that standard solutions of MEC were stable for at least 14 days when stored at room temperature and 4°C, ensuring sufficient time to perform routine analyses. Sample solutions were shown to be stable for up to 48 hours under the same storage conditions.

The validated method covered a concentration range of 0.0875 mg/mL to 0.1875 mg/mL, with a nominal sample concentration of 0.125 mg/mL, confirming the suitability of the method for routine quality control of meclizine hydrochloride in orodispersible tablet formulations.

Standard and placebo solutions spiked with known impurities (impurity B, impurity C, and impurity H) were filtered using different types of 0.45 µm syringe filters (nylon, RC, and PTFE). Based on the obtained impurity recovery values, only PTFE syringe filters were found to be suitable for the determination of related substances in the tablets.

Validation of Impurity Determination Method for Meclizine Hydrochloride Tablets

The validation parameters included: specificity, selectivity, linearity, limit of detection (LOD), limit of quantification (LOQ), recovery, precision, accuracy, and robustness.

To assess the specificity and selectivity of the method, the following solutions were prepared and analyzed according to the validated procedure: diluent, standard, placebo, active substance, sample (meclizine hydrochloride tablets 6.25 mg), and standard solutions spiked with impurities B, C, and H at 0.5%. No peaks corresponding to meclizine hydrochloride or the known impurities were detected in the diluent and placebo chromatograms. All

peaks of meclizine hydrochloride and impurities were resolved, as illustrated in Figure 5. The relative retention times (RRT) and relative response factors (RRF) for the known impurities are shown in Table 2.

Table 2. Relative retention times (RRT) and relative response factors (RRF) for individual impurities.

Name	RRT	RRF
Impurity B	~0.61	1.77
Impurity C	~0.88	0.67
Impurity H	~0.33	1.53
Unknown impurities	–	1.00

The limits of detection (LOD) and quantification (LOQ) were determined based on signal-to-noise ratios calculated from blank chromatograms, with the LOD corresponding to S/N = 3 and LOQ to S/N = 10. Six replicate injections of a standard solution were performed at both the LOD and LOQ concentrations to confirm the detection and quantification limits. The method showed sufficient sensitivity, with the following limits of detection (LOD) and quantification (LOQ):

- LOD for meclizine hydrochloride: 2.5×10^{-5} mg/mL (equivalent to 0.02% impurity content);
- LOD for impurity B and impurity H: 2.1×10^{-5} mg/mL (0.02%);
- LOD for impurity C: 3.3×10^{-5} mg/mL (0.03%);
- LOQ for meclizine hydrochloride: 8.75×10^{-5} mg/mL (0.07%);
- LOQ for impurity B and Impurity H: 6.25×10^{-5} mg/mL (0.05%);
- LOQ for impurity C: 1.0×10^{-4} mg/mL (0.08%).

The linearity of the method was evaluated over a concentration range from the limit of quantification (LOQ) up to 500% of the specified impurity limit (0.2%) for meclizine hydrochloride. Calibration curves were constructed by preparing solutions at multiple concentration levels using accurately weighed portions of the standard substance, followed by appropriate dilution to achieve the desired concentrations. All solutions were analyzed under the chromatographic conditions defined in the validated analytical procedure. The resulting peak areas were plotted against the corresponding concentrations, and linear regression analysis was performed using the equation $y = ax + b$. The method exhibited excellent linearity across the tested range, with a correlation coefficient (R) of 0.9998, confirming the strong linear relationship between the analyte concentration and detector response.

The accuracy of the method was evaluated by performing recovery studies at three concentration levels: LOQ, 100% (0.2%), and 500% (1.0%) of the specified impurity limit for meclizine hydrochloride. At each level, three individual solutions were prepared by spiking independently weighed placebo with the appropriate amount of Meclizine hydrochloride standard substance, following the sample preparation procedure described in the analytical method. Each solution was injected onto the column twice. The recorded chromatograms were used to calculate the recoveries of meclizine hydrochloride by comparing the measured concentrations to the theoretical concentrations. The results are summarized in Table 3.

The results demonstrated that the average recovery values at all tested concentration levels were within the established acceptance criteria. The

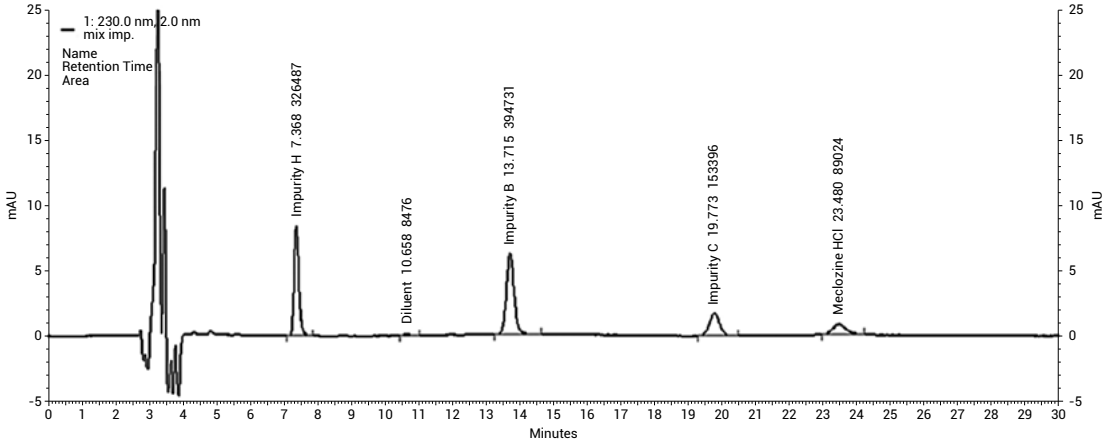


Figure 5. Chromatogram of standard solution spiked with known impurities B, C, and H at 0.5% concentration. The x-axis shows retention time (RT, min) and the y-axis shows absorbance (mAU). Next to each peak, the retention time (RT) and peak area are indicated.

Table 3. Accuracy of meclizine hydrochloride determination.

Concentration level	Impurity level	Solution no.	Concentration theoretical [mg/mL]	Concentration calculated [mg/mL]	Recovery [%]	Average recovery [%]	RSD [%]
LOQ (35%)	LOQ (0.07%)	1	0.0000861	0.0000934	108.5	106.3	2.5
		2	0.0000877	0.0000937	106.8		
		3	0.0000863	0.0000893	103.5		
100%	0.2%	1	0.0002460	0.0002524	102.6	101.9	0.7
		2	0.0002507	0.0002537	101.2		
		3	0.0002465	0.0002511	101.9		
500%	1.0%	1	0.0012300	0.0012515	101.8	101.4	0.3
		2	0.0012533	0.0012697	101.3		
		3	0.0012324	0.0012477	101.2		
General recovery limit: 90% – 110%, recovery limit at QL level: 75% – 125%							

method showed satisfactory accuracy from the quantification limit up to 500% of the acceptable impurity limit (where 0.2% represents 100% of the specified limit). All criteria for accuracy as per the validation guidelines were successfully met.

To determine the precision of the method, six sample solutions spiked with known impurities at the 0.5% concentration level were analyzed. Calibration standard solutions were prepared in accordance with the analytical procedure. Intermediate precision was assessed by performing six chromatographic purity tests on similarly spiked samples, carried out by a second analyst using different equipment, reagents, and a column from another batch. The results are presented in Table 4.

The impurity profiles obtained in the repeatability and intermediate precision studies were comparable. The differences between the average concentrations for all individual quantified impurities from the six (6) test solutions prepared by the two analysts were within the acceptance criteria:

– for impurities at the quantitation limit (QL, 0.1%): ≤ 60%,
– for impurities above 0.1%: ≤ 40%.

To evaluate stability, standard solutions were prepared in accordance with the validated method and divided into two portions. One portion was stored at 2°C – 8°C, and the other at ambient temperature. Analyses were performed after 24 hours, 5 days, 9 days, and 14 days, and the results were compared with freshly prepared standard solutions. For meclizine hydrochloride, recoveries at all time points ranged from 99.1% to 101.0%, meeting the acceptance criterion (95.0% – 105.0%). The results confirmed that the standard solution is stable for up to 14 days when stored either refrigerated (2°C – 8°C) or at ambient temperature.

Stability of Sample Solutions

Two sample solutions of meclizine hydrochloride tablets 6.25 mg were prepared according to the validated method and divided into two portions: one stored at 2°C – 8°C and the other at ambient temperature. The relative differences in the content of any individual impurity between the initial measurement and subsequent time points met the acceptance criterion for impurities above the quantitation limit (QL) and ≤ 0.5% (≤ 25% relative difference,

Table 4. Summary of method precision results (repeatability and intermediate precision) for meclizine hydrochloride tablets 6.25 mg.

Name	**Repeatability precision** First analyst **Average content [%]**	**Intermediate precision** Second analyst **Average content [%]**	**Relative difference of average values [%]**
Impurity H (RRT ≈ 0.33)	0.512	0.490	4.3
Impurity B (RRT ≈ 0.61)	0.519	0.487	6.3
Impurity C (RRT ≈ 0.88)	0.626	0.620	1.0
Unknown impurity (RRT ≈ 0.67)	<LOQ	<LOQ	-
Total impurities	**1.657**	**1.597**	**4.0**

calculated against a freshly prepared standard solution). The impurity profiles remained comparable throughout the study. The results demonstrated that the sample solutions are stable for up to 72 hours when stored at either ambient temperature or refrigerated (2°C – 8°C).

Robustness

Robustness was evaluated by introducing small, deliberate variations to critical chromatographic parameters that could influence impurity determination, including the column batch, mobile phase flow rate, buffer pH, column temperature, buffer concentration, and mobile phase composition. Parameter adjustments were made in accordance with the European Pharmacopoeia (EP) general chapter 2.2.46 *Chromatographic separation techniques* [26], as follows:

- flow rate: 0.9 and 1.1 mL/min (nominal: 1.0 mL/min);
- buffer pH: 3.8 and 4.2 (nominal: 4.0);
- column temperature: 32°C and 38°C (nominal: 35°C);
- buffer concentration: ±10% from nominal (8.9 g/1000 mL);
- mobile phase composition: adjusted within allowable EP limits from nominal ratio (buffer pH 4.0 : ACN : MeOH – 60 : 35 : 5, v/v/v).

System suitability, standard solutions, and placebo solutions spiked with known impurities were analyzed before and after each parameter change. Under all modified conditions, system suitability requirements were met (RSD for meclizine hydrochloride peak area from six injections ≤ 5.0%), and impurity as well as placebo peaks remained baseline resolved. The results, when compared to those obtained under nominal conditions, confirmed that small variations in the method parameters did not affect chromatographic performance.

Stress Testing (Forced Degradation Studies)

Stress testing, also referred to as forced degradation, is a critical element of drug development. It facilitates the identification of potential degradation products, elucidates degradation pathways, and supports the development of stability-indicating analytical methods. In this study, samples of the active pharmaceutical ingredient (API), placebo, and meclizine hydrochloride (MEC) orodispersible tablets were subjected to various stress conditions to assess chemical stability under extreme physicochemical environments. The applied stress conditions included: acidic hydrolysis (0.5 M hydrochloric acid), alkaline hydrolysis (0.5 M sodium hydroxide), oxidative stress (10% hydrogen peroxide), photolysis **(**exposure to ultraviolet light for 24 h), temperature (exposure at 60°C for one week), ACC stability **(**40°C, 75% relative humidity for one month). Following stress exposure, the impurities were quantified using a validated high-performance liquid chromatography (HPLC) method. The results are shown in Table 5.

No peaks corresponding to the retention times of meclizine hydrochloride or any known impurities were observed in the placebo chromatograms before or after the forced degradation experiments, confirming the specificity of the method. Among the tested stress conditions, the tablets were most susceptible to oxidative degradation, while exhibiting lower sensitivity to UV/Vis light exposure.

Degradation under oxidative, alkaline, and acidic conditions primarily resulted in the formation of impurity C (RRT ≈ 0.88). In addition, the formation of and impurity H (RRT ≈ 0.33). was observed specifically under oxidative conditions.

A time-dependent increase in impurity levels was noted, with significantly higher concentrations after 120 minutes of oxidative treatment compared to 20 minutes. Specifically, exposure to hydrogen peroxide for 120 minutes resulted in impurity C at 0.44% and impurity H at 0.30%, compared with 0.16% and 0.05%, respectively, in the control sample (Table 5).

Several unknown degradation products were also detected under oxidative stress, with relative retention times of 0.52 (0.28%), 0.66 (0.23%), 0.81 (0.16%), and 1.21 (1.09%). These findings indicate that oxidative conditions significantly accelerate the degradation of meclizine hydrochloride, promoting the formation of both known and previously unidentified impurities.

Stability Studies

Evaluation of the influence of environmental factors such as temperature, humidity, and light on the stability of the active pharmaceutical ingredient (API) provides essential data for defining appropriate storage conditions, retest intervals, and shelf-life of the drug product. ICH-compliant stability studies [27] were conducted under long-term, intermediate, and accelerated storage conditions:

- long-term (LT): 25°C/60% RH, 36 months.
- intermediate (INT): 30°C/65% RH, 12 months.
- accelerated (ACC): 40°C/75% RH, 6 months.

Laboratory stability studies were conducted for meclizine hydrochloride 6.25 mg tablets packaged in polyvinyl chloride/polyvinylidene chloride (PVC/PVdC) blisters. The stability data for two pilot batches (A and B), along with the release results, are presented in Figure 6.

Table 5. Summary of degradation studies for meclizine tablets.

	RRT	Impurity [%]							
		Control sample	**UV Vis light**	**60°C 7 days**	**45°C 75%RH 7 days**	**0.5 M HCl 2 h/60oC**	**0.5 M NaOH 2 h/60oC**	**10% H2O2 RT 20 min**	**10% H2O2 RT 120 min**
Unknown imp.	0.25	ND	ND	<LOQ	ND	ND	0.07	ND	<LOQ
Unknown imp.	0.31	ND	ND	ND	ND	ND	<LOQ	ND	<LOQ
Impurity H	**0.33**	**0.05**	**0.05**	**0.11**	**0.05**	**0.07**	**0.08**	**0.11**	**0.30**
Unknown imp.	0.52	ND	ND	<LOQ	ND	ND	ND	0.10	0.28
Unknown imp.	0.55	ND	ND	<LOQ	ND	ND	ND	<LOQ	0.09
Impurity B	0.61	ND	ND	ND	ND	<LOQ	ND	<LOD	<LOQ
Unknown imp.	0.66	0.09	0.09	0.11	0.07	0.08	0.10	0.11	0.23
Unknown imp.	0.81	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0.08	0.08	0.16
Impurity C	**0.88**	**0.16**	**0.14**	**0.23**	**0.15**	**0.20**	**0.34**	**0.25**	**0.44**
Unknown imp.	0.91	<LOQ	<LOQ	0.08	<LQO	<LOQ	<LOQ	0.07	0.17
Unknown imp.	**1.21**	**ND**	**ND**	**ND**	**<LOQ**	**ND**	**ND**	**0.44**	**1.09**
Unknown imp.	1.26	<LOQ	<LOQ	<LOQ	ND	<LOQ	ND	ND	ND
Unknown imp.	1.34	ND	ND	ND	<LOQ	ND	ND	ND	ND
Sum of impurities	/	**0.30**	**0.28**	**0.53**	**0.27**	**0.35**	**0.67**	**1.16**	**2.88**

ND – not detected, LOD for meclizine HCl = 0.02%, LOQ for meclizine HCl = 0.07%, LOD for impurity B and H = 0.02%, LOQ for impurity B and H = 0.05%, LOD for impurity C = 0.02%, LOQ for impurity C = 0.08%.

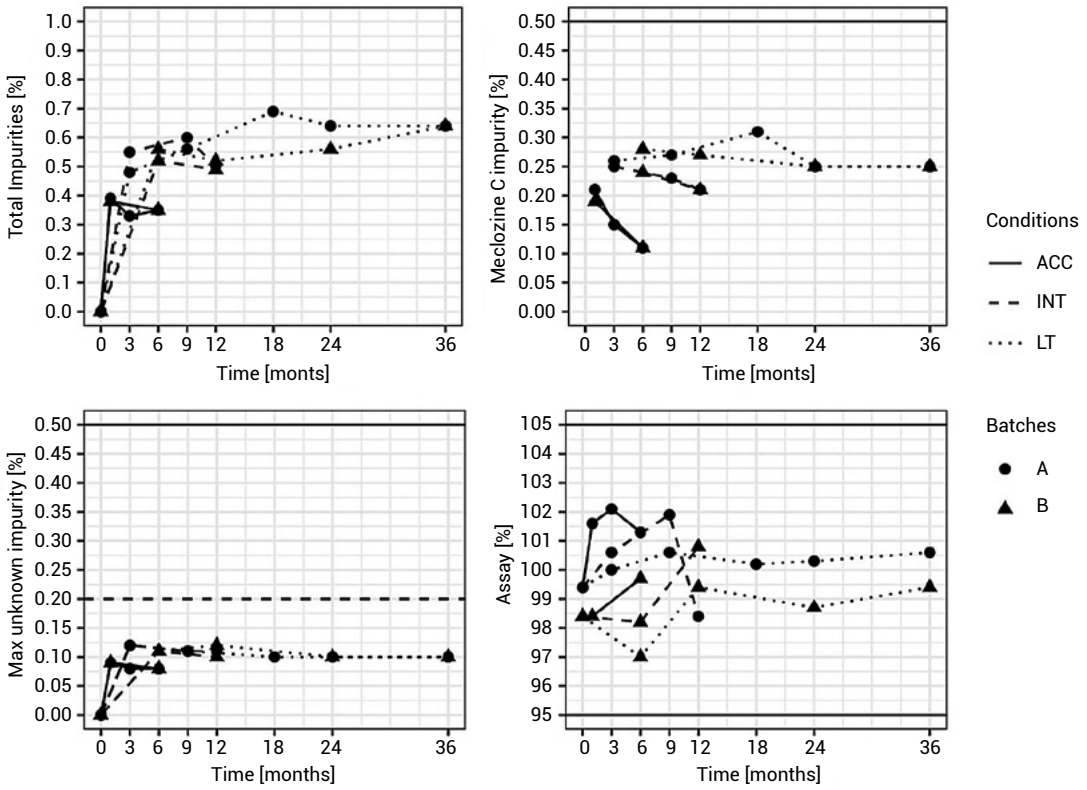


Figure 6. Stability study of MEC tablets [%] in time in accelerated, intermediate and long-term conditions.

The assay of meclizine hydrochloride remained stable under all tested conditions throughout the entire study period, with values ranging from 97.0% to 102.1%. Stability testing demonstrated an increase in the maximum unknown single impurity to 0.12% and in the total impurities to approximately 0.69% over the study period. As impurities C and H had been identified as the main degradation products, their presence was monitored throughout the study. No significant increase in impurity H was observed, with levels rising from not detected (ND) at the initial testing to 0.13% after 36 months under LT conditions. Impurity C reached a maximum of 0.31% after 18 months under LT conditions.

Stability studies demonstrated that the tested batches of meclizine hydrochloride orodispersible tablets (ODT) remain stable over a period of three years and meet the predefined acceptance criteria. The assay acceptance criterion for meclizine hydrochloride was established at ± 5% of the label claim at the time of release and ± 10% at the end of the shelf life, reflecting relatively low active substance content per tablet. Limits for related substances were specified in accordance with ICH guidelines for identification and qualification thresholds, with unknown impurities not exceeding 0.2% and known impurities limited to a maximum of 0.5%. The limits for the total impurities were set as follows: NMT 1.0% at the release and NMT 2.0% during the shelf life.

Assessment of Green Profile of Method

In analytical chemistry, environmental considerations play a crucial role in the design of laboratory procedures. From the very beginning, it is important to evaluate not only the general principles of green chemistry (GC) but also the specific aspects of green analytical chemistry (GAC). The increasing relevance of GAC in the work of analytical chemists emphasizes the need for consistent, objective, and standardized tools to assess the environmental impact of analytical procedures, as well as to facilitate direct comparisons between different methods. Several tools exist to assess the greenness of analytical methods (e.g., LCA, NEMI, Eco-Scale, GAPI, ComplexGAPI, RGB/WAC models, hexagon-CALIFICAMET, AGREE/AGREEprep) [28–31].

In this study, the environmental profile of the developed method was specifically evaluated using the AGREE metric, and the results are presented with representative pictograms. The AGREE tool provides a single numerical value representing the

overall greenness of an analytical method. It employs a radial diagram divided into 12 sections, each corresponding to a specific principle of green analytical chemistry: sample pretreatment activities, sample size (mg or μL), instrumental position, number of steps in the analytical process, level of automation and miniaturization, derivatization status, amount of waste, number of analytes per hour, amount of energy per sample, toxicity, use of biobased reagents, and environmental threats. Each section is scored from 0 to 1, and the average value gives the final AGREE score, with higher values indicating a more environmentally friendly procedure [31]. In this study, the AGREE tool (available at: https://mostwiedzy.pl/pl/wojciech-wojnowski,174235-1/AGREE) was employed.

The analysis of the developed methods using the AGREE tool showed that they have almost identical index values [Figure 7], indicating a moderate level of greenness. The methods comply with the principles of green chemistry to a moderate extent; however, several aspects still require improvement (marked in red on the diagram), such as sample size, positioning of the analytical device, toxicity, and the amount and use of toxic reagents.

CONCLUSIONS

Innovative orodispersible tablet (ODT) formulations of meclizine hydrochloride were developed to improve patient compliance, particularly for pediatric and geriatric populations, who often struggle with swallowing conventional tablets. These ODTs rapidly disintegrate in the oral cavity, offering a convenient and patient-friendly dosage form without compromising dose accuracy.

For routine quality control and regulatory compliance, HPLC methods for both assay and impurity analysis in meclizine hydrochloride ODTs were successfully developed and validated, demonstrating high specificity, precision, accuracy, and linearity. Both methods serve as dependable and practical analytical approaches for the continuous evaluation and long-term monitoring of these important orally disintegrating tablet formulations.

The obtained AGREE score of approximately 0.5 confirms the moderate greenness of the developed analytical methods, indicating partial compliance with the principles of Green Analytical Chemistry.

According to the European Pharmacopoeia, the monograph for meclizine hydrochloride lists six related substances (B, C, D, E, F, and H), of which only impurities C and H were detected in the drug product. Extensive stability studies conducted under ICH Zone II and III conditions confirmed that the developed formulations remain chemically stable for the entire period, with assay values consistently within ± 5% of the label claim and impurity levels, including the principal degradation product (impurity C), remaining within acceptable limits.

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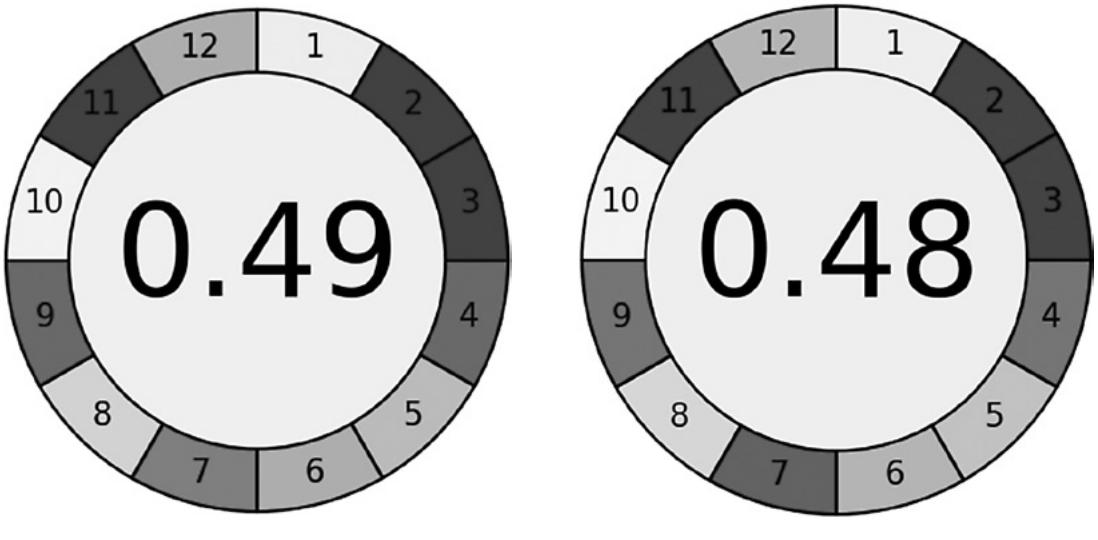

Assay determination Impurity determination

Figure 7. Greenness evaluation of the developed HPLC methods (AGREE assessment).

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Conflict of Interest

The authors declare no conflicts of interest.

Author's Contribution

Research concept and design: Mg.S. and M.S.;
Collection and/or assembly of data: Mg.S.;
Data analysis and interpretation: Mg.S.;
Writing the article: Mg.S.;
Critical revision of the article: M.S.;
Final approval of the article: M.S.

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