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Original Article

Quality Control of Hydrochlorothiazide Pharmaceuticals

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ABSTRACT

Background: One of the organisational strategies to ensure the use of relevant good practises for each stage in the life cycle of pharmaceutical products is the market surveillance program, which aims to demonstrate product specification adherence. It uses analytical pharmacopoeial and literature-based approaches primarily to carry out quality control on the chosen pharmaceutical items. **Aim:** Development of a program for analytical control of different medicinal products containing 25 mg hydrochlorothiazide. **Materials and Methods:** European Pharmacopoeia and USP HPLC methods for assay and related substances were applied in prescription medicines. **Results:** The system suitability tests were evaluated for each method, and the results of each generated group of products were compared. The quantitative content values deviation and the quantitative limitations for each impurity were determined. The deviations are in the range 0.76%-4.01%. Calculated RSD values are below 2%. The results obtained by both methods are within the acceptable limits of 95%-105%. In the European Pharmacopoeia method, the limits of three impurities were determined and seven more were found and marked as unknown. The USP method allows identification of only one impurity. **Conclusion:** For the market surveillance program for pharmaceuticals containing hydrochlorothiazide, an analytical control program has been developed. The program combines multiple pharmacopoeial HPLC methods and compares the outcomes with an initial assessment of each method's applicability for all pharmaceuticals containing hydrochlorothiazide.

Keywords: Market Surveillance Program, HPLC, Hydrochlorothiazide, System suitability test.

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INTRODUCTION

During the development of a medicinal product, a risk assessment is made at each stage of the life cycle and the critical stages are defined. The parameters and analytical techniques for this are determined, together with the criteria whose application ensures product quality. These criteria are reflected in the medical product's specification, which is a required component of its registration file.

The control is the manufacturer's commitment throughout the production process, including control over the initial raw materials, the intermediate and crucial production stages, and the finished pharmaceutical product. Applying GMP and ISO quality standards during the production process ensures and creates the pharmaceutical product's high quality.

In order to maintain the quality, efficacy, and safety of the medications during their path from the point of production to the patients, it is essential to adhere to the storage and transportation guidelines set forth by the manufacturer. The quality management system should cover the organizational structure, procedures, processes and resources, as well as the activities necessary to provide assurance that the quality and integrity of the delivered product is maintained and remains within the legal chain of supply during storage and /or transportation.

Market Surveillance (MS) has been introduced in this aspect. It aims to control the quality of medicinal products after they enter the drug supply network. The main goal in its planning is to cover medicinal products from as many different groups as possible, as well as with the greatest possible variety of pharmaceutical forms based on risk assessment according to set criteria. When preparing the MS plan, the rule of not repeating analyzes of medicinal substances analyzed in the last 5 years, both by the national control laboratories EU countries must ensure effective MS. They are required to guarantee that:

- Products placed on the market are monitored.
- The marking and documentation requirements have been respected.
- Products have been designed and manufactured in accordance with EU harmonization requirements.
- MS authorities have the necessary powers, resources and knowledge to perform their functions.

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- Procedures are put in place for following up complaints and monitoring accidents and by the European Group of Control Laboratories (OMCL) are observed.

The Standard Operating Procedure (SOP) is followed when organizing and conducting market surveillance. The Directorate "Analyses of Medicinal Products" receives motivated proposals for products that should be included in the market surveillance plan from the Directorate "Market Surveillance and Inspections", the Directorate "Authorisation for the Use of Medicinal Products", the Directorate "Tracking of Medicinal Products, safety and clinical trials" and the Directorate "Medicinal information and non-international studies". The selection of products is carried out on the basis of risk assessment and collected information, according to the competences of the relevant directorates, subject to specific criteria. The following are considered risky:

- Products that have been imported for the first time on the market.
- Products with non-conformities found by the inspectors according to GMP or GDP.
- Products with a complex synthesis of the active substance or with the risk of the presence of dangerous impurities.
- Products with a new place of production or with a complicated manufacturing.
- Products with detected quality deviations, blocked or withdrawn from the network
- Products with reported adverse reactions.
- Products with potential stability issues
- Products with a new combination of active substances.
- High daily dose or low unit dose products.
- Products with increased usage.
- Products that have been counterfeited or are expected to be counterfeited.

When preparing the MS plan, the rule is observed not to repeat analyzes of medicinal substances carried out in the last 5 years, both by the Bulgarian Official Control Laboratory and by the European Group of Control Laboratories.Analytical control is essential when checking the quality of medicines. It is carried out in two forms-as part of the annual planned supervision of the market and on a signal. Market supervision is regulated by law and is part of state health control. Analytical quality control is also carried out upon a signal of suspected deviation in the quality of a specific medicinal product.[1-9]

MS is based on Market Surveillance Studies (MSS) which are carried out on commercialized medicines, particularly on those having a national marketing authorization. Products are tested according to a common protocol and national sampling procedures. To ensure that the same types of medicines are of comparable quality in the different member states, these studies are multilateral. Several are organized yearly. They look at different types of products for a given active substance and herbal drugs. Where a need is identified, the results of these studies could support revision of the relevant European Pharmacopoeia monographs and/or general chapters and methods. According to the available SOP, from the suggested medicinal products with an assessed risk, groups are formed, and including all authorized medicinal products with the corresponding active substance.

The MS of the European medicinal market is organized by the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe and is carried out within the framework of the OMCL. Every year the secretariat of the OMCL accepts proposals for products to be included in MS from the coordinating group, each network member laboratory or inspectors from the European OMCL Member States. Each submitted proposal is accompanied by a justification, based on a risk study, historical data or in case of suspicion of possible falsification. MS can be conducted on medicinal products containing the same active substance (MSS 052 Repaglinide Tablets) or in the same dosage form (MSS 050 Hyaluronic acid-based Dermal Fillers) or combining to be the test method (MSS 048 Subdivision of tablets; MSS 051 Foreign Matter in Herbal Drug).

A draft program is prepared from the submitted proposals and distributed to the OMCL group for comments and discussion. At the annual meeting of the control laboratories, the program is subject to voting and final approval.The analysis of the market surveillance carried out for the period 2009-2019 showed that the distribution of the analyzed products by pharmacological-therapeutic groups follows the frequency of use of the corresponding drugs, with the largest percentage belonging to the group of antihypertensive medicinal products-31% of all analyzed medicinal products for the period.[8]

Special attention is paid to medicinal products for Arterial Hypertension (AH), which is one of the most common chronic non-communicable diseases in the world, affecting about 20% of the population. In this study Market Surveillance program including comparative tests were performed for assay and quantitative determination of impurities of widely used thiazide diuretic hydrochlorothiazide. This medication is used to treat high blood pressure applied in mono-and combined drug products.

Hydrochlorothiazide is used to treat hypertension, congestive heart failure, symptomatic edema, diabetes, renal tubular acidosis. Hydrochlorothiazide is combined with a number of other antihypertensive agents such as ACE inhibitors and AT1 blockers in double or triple fixed dose combinations for the treatment of hypertension.[10-18]

A number of analytical techniques have been described in the literature for the analysis of HCTZ-monoproducts and in drug combinations. They can be grouped as pharmacopoeial methods and methods from the scientific literature, as well as chromatographic, mainly High-Performance Liquid

Chromatography (HPLC) and UV-spectrophotometry methods.[19-23]

They are used in identification, purity and quantification tests. Most of the methods, regardless of the good indicators of the analytical parameters in the process of their validation, are used for very specific purposes, are difficult to apply to drug combinations and are accompanied by a number of limitations. This leads to complications in their application for analytical control, the need to modify test conditions with subsequent validation or revalidation, incomparability of results from different methods and the resulting difficulties in assessing the quality of antihypertensive products.

MATERIALS AND METHODS

Materials

Deionized water (18.2 μΩ), Methanol (Fisher Scientific), Acetonitrile (Honeywell), Sodium dihydrogenphosphate (Sigma Aldrich), Orthophosphoric acid (Fisher Scientific), Sodium dihydrogenphosphate dehydrate (Fisher Scientific), Tetrahydrofuran (Honeywell).

Commercially available medicinal products were used to fulfill the set goals and objectives of the current study: three products containing 25 mg hydrochlorothiazide and coded as follows: HCTZ1, HCTZ2 and HCTZ3.

Analytical Standards are Hydrochlorothiazide-Sigma-Aldrich, LRAA6504, Chlorothiazide-Sigma-Aldrich, LRAA 899, Benzothiadiazepine related compound A-Sigma-Aldrich, LRAA 9008, Hydrochlorothiazide for peak identification-CRS Bach 3, EDQM.

Methods

Chromatographic System and Conditions

Analyses of the medicinal products were performed on an Agilent 1260 Infinity II chromatographic system; Detector: Diode Array Detector WR; Pump: Quaternary Pump LL. Specialized Open Lab CDS software was used to process the obtained data.Method for Assay and Related Substances of Medicinal Products Containing Hydrochlorothiazide According to European Pharmacopoeia[24]-Method 1 for Assay (M1), Method 2 for Related Substances (M2)Column: 100x4.6 mm, C 18.3 μm (M1 and M2-Waters Spherisorb 100x4.6 mm, C 18. 3 μm); column temperature -25°C; flow rate: 0.8 mL/min; gradient elution; mobile phase A: phosphate buffer (34.8 g/L sodium dihydrogenphosphate dihydrate, pH=3.2 with 10% orthophosphoric acid): methanol: tetrahydrofuran in ratio 940:60:10 v/v and mobile phase B: methanol: phosphate buffer: tetrahydrofuran in ratio 500:500:50 v/v; λ: 224 nm; injection volume: 10 μL; solvent: acetonitrile: methanol in ratio 50:50 v/v; Standard solutions of chlorazide and hydrochlorothiazide for quantification in concentration range 0.06-0.09 mg/mL, solution for System Suitability Test (SST) in concentration range 0.00001125-0.075 mg/mL, solution for peak identification.

Method for Assay and Related Substances of Medicinal Products Containing Hydrochlorothiazide According to USP[25]-Method 3 (M3)

Column: 250x4.6 mm, C 18.5 μm (M3-Intersil ODS, 250x4.0 mm, 5 μm); column temperature -25°C; flow rate: 2.0 mL/min; isocratic elution; mobile phase: acetonitrile: 0.1 M sodium phosphate 1:9 v/v, pH=3.0 with 10% orthophosphoric acid; λ: 254 nm; injection volume: 20 μL;

Standard solutions of Hydrochlorothiazide for quantification in concentration range 0.00075-0.18 mg/mL, solution for SST, and standard solutions of benzothiadiazepine related compound A in concentration range 0.00075-0.0019 mg/mL.

Sample Preparation

The average weight of 10 tablets of the products HCTZ1-HCTZ3 was calculated and the required amount equivalent of 30 mg Hydrochlorothiazide from the fine powder tablet mass was weighed and dissolved in 5 mL solvent in a volumetric flask of 20 mL. The sample was sonicated for 5 min and top up to the mark after cooling and then sonicated for another 15 min. The resulting solution was centrifuged at 6000 rpm for 10 min.

The test solution for the assay was obtained by dilution of 0.5 mL supernatant to 10 mL with buffer and has concentration 0.075 mg/mL.

The test solution for the quantification of related substances is the obtained clear supernatant.

The sample solutions for M3 were prepared as follow: the average weight of 10 tablets of the products HCTZ1-HCTZ3 was calculated and the required amount equivalent of 30 mg Hydrochlorothiazide from the fine powder tablet mass was weighed and dissolved in 20 mL mobile phase in a volumetric flask of 200 mL and sonicated for 5 min. Then 20 mL acetonitrile were added, the sample was sonicated for another 5 min and was top up to the mark with mobile phase. The resulting solution was centrifuged at 6000 rpm for 10 min.

The obtained clear supernatant with concentration 0.15 mg/mL was used as test solution for the assay and for the quantification of related substances.

RESULTS

Quantification of Medicinal Monoproducts of Hydrochlorothiazide according to European Pharmacopoeia (M1)

The implemented method was validated according to European Pharmacopoeia requirements and International Council for

Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). For the purposes analytical parameters repeatability, specificity, linearity and accuracy were determined.

System Suitability Test (SST)

Solutions for SST are as follow-a mixture of chlorothiazide and hydrochlorothiazide in concentration 0.0075 mg/mL. The norm for achieving specificity is Rs chorothiazide/ hydrochlorothiazide≥2.00; standard solution of Hydrochlorothiazide in concentration c=0.075 mg/mL; solutions of Hydrochlorothiazide in concentration range 0.06-0.09 mg/mL.

The obtained results are presented in Table 2 and show that the chromatographic system is suitable for the method, according to the acceptance criteria of the European Pharmacopoeia.

Assay of Hydrochlorothiazide in Medicinal monoproducts HCTZ1-HCTZ3 (M1)

The test solutions of products HCTZ1-HCTZ3 were analyzed for 17 min, as the average retention time for hydrochlorothiazide is 3.04 min with RSD 0.49% and peak symmetry factor As=1.10 (Figure 1).

The hydrochlorothiazide quantity in each product was calculated and the results are presented in Table 3. The amounts range from 99.87 to 104.98%.

Purity Test for Medicinal Products of Hydrochlorothiazide According to European Pharmacopoeia (M2)

In order to restore the system to baseline conditions the gradient elution scheme was modified as two additional steps were added (Table 4).

In order to assess the system suitability the following solutions were used-a mixture of chlorothiazide and hydrochlorothiazide in concentration 0.0075 mg/mL, standard solution of hydrochlorothiazide in concentration c=0.075 mg/mL and solutions of hydrochlorothiazide in concentration range 0.00001125-0.075 mg/mL.

The obtained results are presented in Table 5 and show that the chromatographic system is suitable for the method, according to the acceptance criteria of the European Pharmacopoeia.

Quantification of Related substances in Medicinal monoproducts HCTZ1-HCTZ3, Containing Hydrochlorothiazide Using M2

The quantity of the following impurities in medicinal monoproducts HCTZ1-HCTZ3, was analyzed (Figure 2).

Chlorothiazide-6-Chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1- dioxide; Impurity B-4-Amino-6-chlorobenzene-1,3-disulfonamide and Impurity C-N-[[7-(Aminosulfonyl)-6-chloro-2,3-dihydro-1,1-dioxo-4H-1,2,4-benzothiadiazin-4-yl]methyl]-6-chloro-3,4-dihydro-1,1-dioxo-2H-1,2,4-benzothiadiazine-7-sulfonamide.

The quantity of all the impurities was calculated as a percentage, relative to the area of the main peak. The results are presented in Table 6.

Assay and Quantification of Related Substances in Medicinal Monoproducts of Hydrochlorothiazide According to USP (M3)

As the used column diameter is different from the one described in the pharmacopoeial monograph and in order to achieve the desired peak separation in the system suitability test analyses

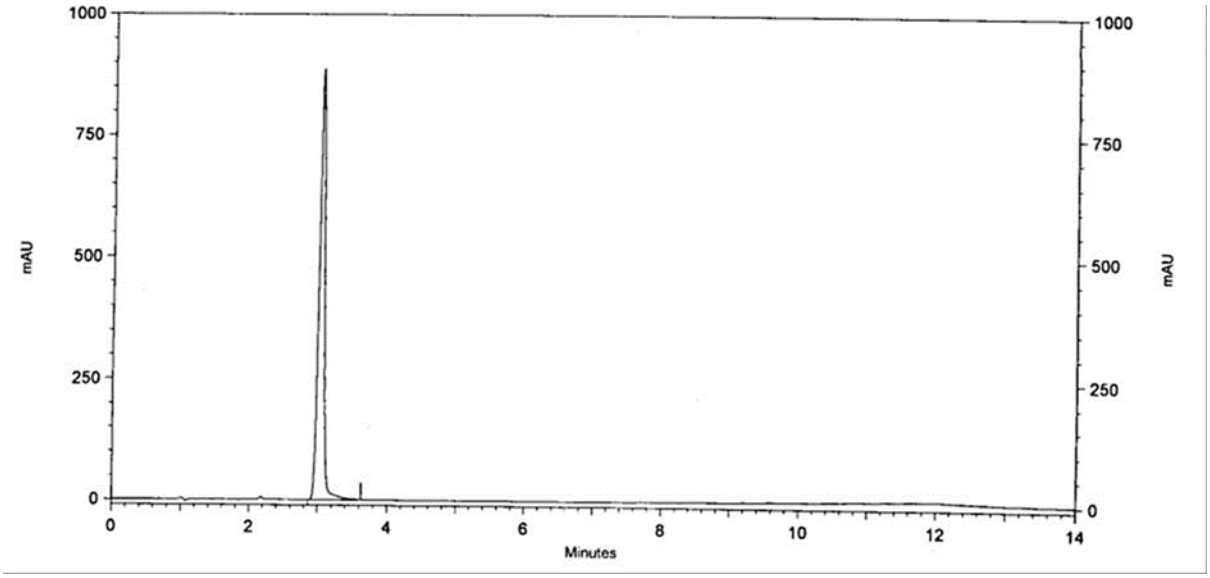

Figure 1: Assay of Hydrochlorothiazide in medicinal product HCTZ1 using M1.

Table 1: Gradient elution scheme M1.

Method	Time, min	Mobile phase A	Mobile phase B
European Pharmacopoeia	0-4	80	20
	4-10	80-20	20-80
M1	0-4	80	20
	4-10	80-20	20-80
	10-14	20-80	80-20
	14-17	80	20

Table 2: Results of SST parameters for M1.

Analytical parameter	Value for hydrochlorothiazide
Repeatability	RFI/RFII=1.00
Specificity	Rs chorothiazide/ hydrochlorothiazide=2.10
Linearity range	0.06-0.09 mg/mL
Linearity correlation coefficient	R^2=1
Accuracy	RSD=0.11%

Table 3: Assay of hydrochlorothiazide in medicinal products using M1.

Method	Analyzed medicinal product					
	HCTZ1		HCTZ2		HCTZ3	
	Assay, %	RSD, %	Assay, %	RSD, %	Assay, %	RSD, %
M1	99.87	1.69	104.98	1.83	100.34	0.39

Table 4: Gradient elution scheme M2.

Method	Time, min	Mobile phase A	Mobile phase B
European Pharmakopoeia	0-17	100-55	0-45
	17-30	55	45
M2	0-17	100-55	0-45
	17-30	55	45
	30-34	55-100	45-0
	34-37	100	0

and to maintain the system working pressure the flow rate was modified to 1 mL/min.

The following solutions for system suitability were used-a mixture of chlorothiazide and hydrochlorothiazide with concentration 0.15 mg/mL. RSD (n=3)≤1.5%; standard solution of hydrochlorothiazide with concentration 0.15 mg/mL; solutions of hydrochlorothiazide in concentration range 0.00075-0.18 mg/mL, solutions of benzothiadiazine Related Compound A in concentration range 0.00075-0.0019 mg/mL.

The obtained results are presented in Table 7 and show that the chromatographic system is suitable for the method M3, according to the acceptance criteria of the USP.

The test solutions of products HCTZ1-HCTZ3 were analyzed for 25 min and the average retention time of Hydrochlorothiazide is 19.59 min with RSD 0.84% and peak symmetry factor As=1.1, as the average retention time of benzothiadiazine Related Compound A is 10,93 with RSD 0.96% and peak symmetry factor As=0.996 (Figure 3).

Assay of Hydrochlorothiazide in Medicinal Monoproducts HCTZ1-HCTZ3 (M3)

The Hydrochlorothiazide quantity in each product was calculated and the results are presented in Table 8. The amounts range from 96.74 to 100.97%.

Quantification of Related Substances in Medicinal mono products HCTZ1-HCTZ3 (M3)

According to USP in HCTZ1-HCTZ3 the quantity of benzothiadiazine related compound A-3-chloroaniline-4, 6-disulfonamide, 4-Amino-6-chlorobenzene-1,3- disulfonamide was analyzed.

The quantity of the impurity was calculated as a percentage, relative to the area of the main peak. The results are presented in Table 9.

For the analysis of medicinal products containing hydrochlorothiazide two different pharmacopoeial methods were applied. They differ significantly in terms of the required impurities and their permissible limits.

In European Pharmacopoeia Method (M2) the limits are as follows: Imp. A, Imp. B and Imp. C≤0.5%; each unidentified impurity≤0.1%; total impurities≤1%.

M2 allows identification of three impurities-Imp. A, Imp. B и Imp. C. In addition another seven impurities were detected and labeled as unidentified. On the other side USP method M3 allows identification only of benzothiadiazine related

Table 5: Results of SST for M2.

Analytical parameter	Value for hydrochlorothiazide
Repeatability	RFI/RFII=1.01
Specificity	Rs chorothiazide/ hydrochlorothiazide=3.21
Linearity range	0.00001125-0.075 mg/mL
Linearity correlation coefficient	R^2=1
Accuracy	RSD=0.04%
LOQ	0.00001125 mg/mL

Table 6: Quantification of related substances in HCTZ1-HCTZ3, using M2.

Impurity	HCTZ1, %	HCTZ2, %	HCTZ3, %
Imp. B	0.55	0.52	1.25
Unk.1	0.02	0.02	0.01
Chlorothiazide	0.06	0.07	0.02
Unk.2	0.02	0.01	
Unk.3	0.01	0.01	0.02
Unk.4	0.02	0.02	0.05
Unk.5	0.01	0.01	0.01
Unk.6	0.01	0.01	0.02
Imp. C	0.31	0.19	0.2
Unk.7	0.02	0.02	0.04
Total	1.03	0.88	1.62

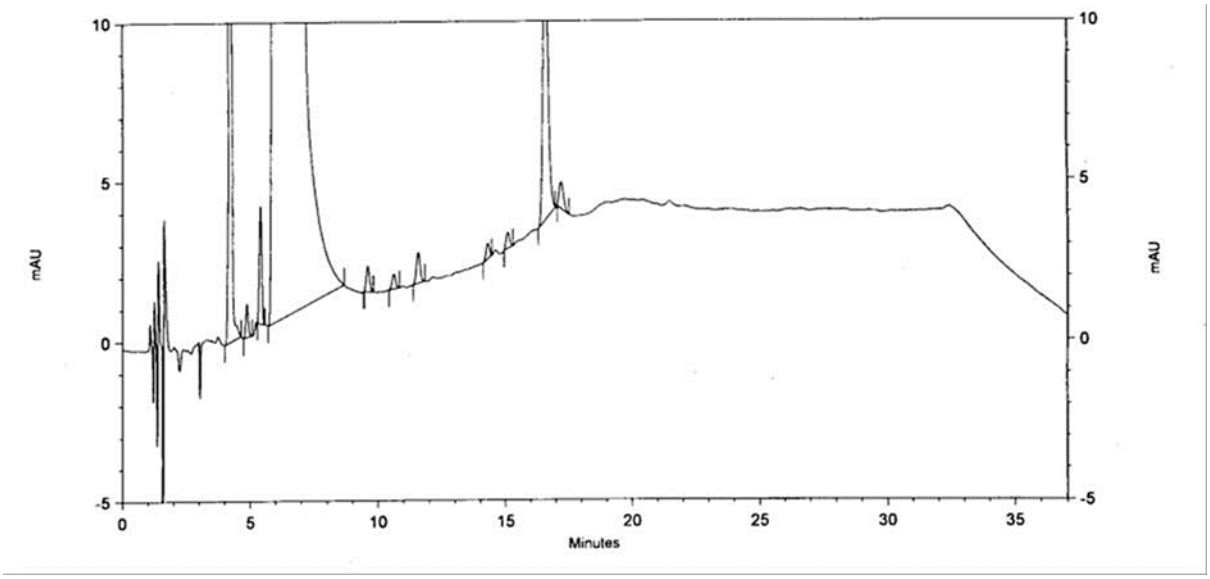

Figure 2: Quantification of related substances in medicinal monoproduct HCTZ1 using M2.

compound A, and also only for it the acceptance criteria are described-benzothiadiazine related compound A≤1%. On the obtained chromatogram only two peaks were detected-peak of Hydrochlorothiazide and of benzothiadiazine related compound A, which is in quantity below LOQ in products HCTZ1 и HCTZ2 and in HCTZ3-0.62% (Table 9).

DISCUSSION

Selection of active substances

After a literature research and analysis of the available information, it was established that in the group of antihypertensive medicinal products there are five pharmaco-therapeutic subgroups, distinguished due to differences in the structure and respectively in the mechanism of action.

Table 7: Results of SST for M3.

Analytical parameter	Value
Repeatability hydrochlorothiazide	RFI/RFII=1.00
Specificity	Rs chorothiazide / hydrochlorothiazide = 3.13 RSD (n=3)≤0.08%
Linearity hydrochlorothiazide Range Correlation coefficient	0.00075-0.18 mg/mL R^2=1
Linearity benzothiadiazine related Compound A Range Correlation coefficient	0.00075-0.0019 mg/mL R^2=0.999
Accuracy hydrochlorothiazide	RSD=0.08%
LOQ hydrochlorothiazide	0.0005 mg/mL

In view of the possibility of statistical processing of the data obtained from the conducted model tests, as well as to prove a trend in the results, and not a random phenomenon, it was necessary to choose three antihypertensive medicinal products that differ in their structure and, accordingly, in their activity, i.e. one representative from three of the pharmacotherapeutic subgroups.

During the literature research, a trend towards the use of combined dosage forms of antihypertensive drugs was highlighted, which provides patient convenience, improves proper use and, accordingly, therapeutic response. It is for this reason that, in terms of the market, combined preparations are becoming more and more important, which inevitably raises the question of the increased need for adequate quality control of these products.

Selection of comparative analytical tests

Four types of analytical methods are most commonly applied in drug quality control:

- Assessment of appearance-at 94.53%;
- Quantification-at 86.65%;
- Identity-85.56%;
- Determination of impurities-61.27%.

The remaining analytical tests were conducted on a significantly smaller part of the analyzed products.

The "Appearance Assessment" analytical test consists of checking the following indicators:

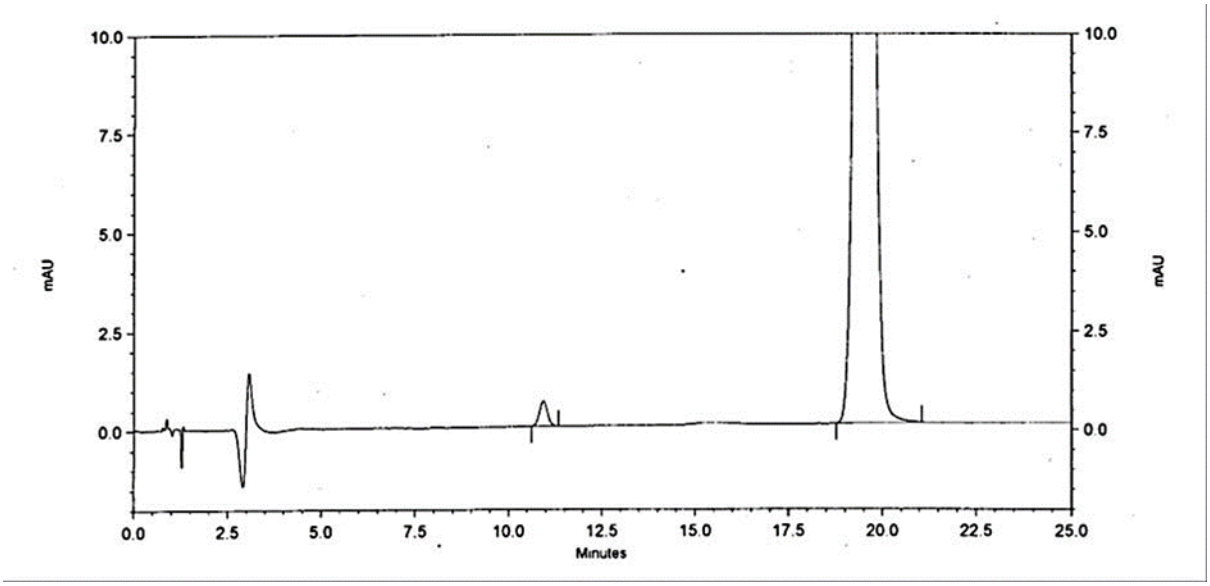

Figure 3: Assay and quantification of related substances in medicinal monoproducts of Hydrochlorothiazide according to USP (M3).

Table 8: Assay hydrochlorothiazide in H1-H3 using M3.

Method	Analyzed medicinal product					
	HCTZ1		HCTZ2		HCTZ3	
	Assay, %	RSD, %	Assay, %	RSD, %	Assay, %	RSD, %
M3	99.11	0.46	100.97	0.25	96.74	0.72

Table 9: Quantification of related substances in medicinal monoproducts HCTZ1-HCTZ3 (M3).

Impurity	HCTZ1 %	HCTZ2%	HCTZ3%
Benzothiadiazine Related Compound A	<LOQ	<LOQ	0.62

- Concurrence of the available data on the primary and secondary packaging with those approved in the dossier of the medicinal product.
- The appearance of the medicinal product must correspond to the approved dossier (type and color of tablet/capsule/liquid, type of packaging, if applicable-for ampoules or vials).
- Availability of a leaflet and matching of the information available in the leaflet with the currently approved part of the drug file.
- In view of the above, the assessment of appearance when performing model tests is not possible, given the need to access the information available in the approved drug file.
- The analytical methods that have been applied are from two main sources:
- Pharmacopoeial monographs of the European Pharmacopoeia and the USP. For analysis, the monographs current at the time of conducting the analyzes are applied. The methods differ in terms of performance and provide sufficiently complete information about the analytical conditions for the method to be applied.

The general conditions of the applied HPLC comparative tests are

The analyzes were carried out in compliance with the requirements of monograph 2.2.29. in the European Pharmacopoeia as the quantitative content of active substance is calculated by the formula:

Assay=Asa x Mst x Dsa x Pst x Av x 100/Ast x Dst x Msa x DC,

where: sa-sample; st-standard; A-peak area (mAU); M-Mass (mg); D-Dilution; P-Purity of the standard; Av-average mass of the tablets (mg); DC-declared content (mg).

The amount of impurities was calculated as a percentage of the area of the peak of the active substance in order to unify the approach to the calculation of impurities and the possibility of comparing the results obtained from different analytical methods.

If the length or diameter of the chromatographic column used in a particular analysis differs from that described in the method, the flow rate of the mobile phase is recalculated.

In order to restore the system to baseline conditions the gradient elution scheme was modified as two additional steps were added (Table 1).

Analysis were carried out for the quantitative determination of medicinal monoproducts containing Hydrochlorothiazide by pharmacopoeial methods. For each method, an evaluation of the suitability of the system was carried out, according to the requirements and methodology of the ICH and the European Pharmacopoeia. Each formed group of products was analyzed with each of the selected quantification methods. The results obtained from each assay were compared and the deviation in the quantitative content values was calculated.

Analysis were also carried out for the quantitative determination of impurities in medicinal monoproducts containing Hydrochlorothiazide. The identifiable impurities, the total detected impurities and the quantitative limits for the respective impurities in the analytical methods were compared, and a discrepancy was found both in the amounts of detected impurities and in the possibility of detecting impurities with two different methods for the same medicinal product.

Aiming to achieve the desired peak separation in the system suitability test analyses and to maintain the system working pressure the following changes of the pharmacopoeial method were applied:

The flow rate was modified to 1 mL/min; the chromatographic columns are in accordance with those recommended for each analytical method, and the analytical tests are carried out according to the conditions described in the source, such as applied minimum corrections concerning the chromatographic column or flow rate are fully compliant with the requirements set out in the HPLC monograph in the European Pharmacopoeia.

As a result of the analyzes carried out, the following recommendations were made:

The methods used must be relevant pharmacopoeial methods or validated methods, according to ICH and European Pharmacopoeia, especially when comparing the results obtained. In the event of a significant discrepancy in the results of the evaluation of the products, it is mandatory to carry out a preliminary assessment of the suitability of the methods for each of the analyzed products included in the analysis group. An assessment of the analytical parameters is required according to the acceptance criteria of the European Pharmacopoeia. When different impurities or related substances are proven in the purity tests or when it is impossible to detect impurities in the analyzed products to refine the control, it is appropriate to use different analytical methods or highly reliable combinations of chromatographic and spectral techniques.

CONCLUSION

To preserve the quality, efficacy, and safety of pharmaceutical products, adequate and precise quality control must be implemented as part of the market surveillance program. The analysis conducted showed that using a single pharmacopeial technique increases the probability of missing data in the results. Combining multiple methods from various pharmacopoeias and comparing the results to the validated method by the manufacturer, if there is one, is the most accurate way to run a market surveillance program.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

MS: Market surveillance; **USP:** United States Pharmacopoeia; **HPLC:** High-performance liquid chromatography; **RSD:** Relative standard deviation; **GMP:** Good manufacturing practice; **ICH:** International Council for Harmonisation; **ISO:** International Organization for Standardization; **OMCL:** Official medicines control laboratory; **AH:** Arterial hypertension; **ACE:** Angiotensin-converting enzyme; **AT1:** Angiotensin II receptor type 1; **HCTZ:** Hydrochlorothiazide; **UV-spectrophotometry:** Ultraviolet spectrophotometry; **SST:** System suitability test; **ODS:** Octadecylsilane; **MSS:** Market Surveillance Studies.

SUMMARY

The development of a programme for the analytical control of various medicinal products containing Hydrochlorothiazide is described in this article. The programme is required for market surveillance and quality assurance. In a previously developed suitability test, pharmacopoeial HPLC methods were used for purity and quantification of each formed group of products. The results of each analysis were compared, and the methods employed were evaluated.

REFERENCES

1. Regulation 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency; 2004. Available from: http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF.
2. Little W, McGivern R. Chapter 19. Introduction to sociology-1st Canadian edition. In: OpenStax college. BC campus; 2014. p. 579-607. Available from: https://my.uopeople.edu/pluginfile.php/57436/mod_book/chapter/37634/SOC1502.Textbook.pdf. In: Health and medicine.
3. Guidelines on good distribution practice of medicinal products for human use; 2013. p. C68/01. Available from: https://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:068:0001:0014:EN:PD.
4. European directorate for the quality of medicines and health care, market surveillance studies. Available from: https://www.edqm.eu/en/market-surveillance-studies-48.htmL.
5. SG. Law on medicinal products in human medicine. 2007;13:31.
6. Executive Agency for Medicines. Planning and monitoring of the national market. Sop. 2019:0008-3.
7. General European OMCL Network (GEON). Risk analysis model for targeting market surveillance by OMCLs. General document. PA: PH/OMCL; 2020;80(6):3-9.
8. Ilieva-Tonova D, Stoimenova A, Pencheva I. Market surveillance and control of medicinal products in Bulgaria 2009-2015. Technol. 2016;6(1):366-73.
9. WHO. Guidelines on the conduct of surveys of the quality of medicines; 2015. Available from: https://www.who.int/docs/default-source/medicines/norms-and-standards/current-projects/guidelines-on-medicines-quality-surveys-qas15-630-30062015.pdf?sfvrsn=4869e295_2.
10. Beermann B, Groschinsky-Grind M, Rosén A. Absorption, metabolism, and excretion of hydrochlorothiazide. Ther. 1976;19(5 Pt 1):531-37. doi: 10.1002/cpt1976195part1531, PMID 1277708.
11. Beermann B, Groschinsky-Grind M. Pharmacokinetics of hydrochlorothiazide in man. Pharmacol. 1977;12(4):297-303. doi: 10.1007/BF00607430, PMID 590315.
12. Diovan HCT- valsartan and hydrochlorothiazide tablet, film coated. DailyMed.
13. Exforge HC. amLodipine valsartan and hydrochlorothiazide tablet, film coated. DailyMed.
14. Diovan HCT- valsartan and hydrochlorothiazide tablet, film coated. DailyMed.
15. Exforge HC. amlodipine valsartan and hydrochlorothiazide tablet, film coated. DailyMed.
16. Hydrochlorothiazide. The American Society of Health System Pharmacists. Archived from 17 the original on 10 May 2017.
17. Duarte JD, Cooper-DeHoff RM. Mechanisms for blood pressure lowering and metabolic effects of thiazide and thiazide-like diuretics. Ther. 2010;8(6):793-802. doi: 10.1586/erc.10.27, PMID 20528637.
18. Musini VM, Gueyffier F, Puil L, Salzwedel DM, Wright JM. Pharmacotherapy for hypertension in adults aged 18 to 59 years. Rev. 2017;8(8):CD008276. doi: 10.1002/14651858.CD008276.pub2, PMID 28813123.
19. El-Gizawy SM, Abdelmageed OH, Omar MA, Deryea SM, Abdel-Megied AM. Development and validation of HPLC method for simultaneous determination of amlodipine, valsartan, hydrochlorothiazide in dosage form and spiked human plasma. Chem. 2012;03(6):422-30. doi: 10.4236/ajac.2012.36055.
20. Ertürk S, Cetin SM, Atmaca S. Simultaneous determination of moexipril hydrochloride and hydrochlorothiazide in tablets by derivative spectrophotometric and high-performance liquid chromatographic methods. Anal. 2003;15;33(3):505-11. doi: 10.1016/s0731-7085(03)00252-8, PMID 14550868.
21. Saglik S, Sagirli O, Atmaca S, Ersoy L. Simultaneous determination of fosinopril and hydrochlorothiazide in tablets by derivative spectrophotometric and high-performance liquid chromatographic methods. . 2001;427(2):253-7. doi: 10.1016/S0003-2670(00)01201-0.

22. Erk N. Spectrophotometric analysis of valsartan and hydrochlorothiazide. Lett. 2002;35(2):283-302. doi: 10.1081/AL-120002530.
23. Satana E, Altinay S, Göğer NG, Ozkan SA, Sentürk Z. Simultaneous determination of valsartan and hydrochlorothiazide in tablets by first-derivative ultraviolet spectrophotometry and LC. Anal. 2001;25(5-6):1009-13. doi: 10.1016/s0731-7085(01)00394-6, PMID 11377086.
24. European pharmacopoeia. ed 9.1; 2016, suppl. 8.
25. United States pharmacopoeia; 2017. p. 41-NF 36.

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