# STUDY OF STABILITY WHEN STORING OF TABLETS UNDER THE CONDITIONAL NAME "AP-HELMIN" AS ONE OF THE FACTORS OF PHARMACEUTICAL DEVELOPMENT

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## Introduction

According to the World Bank, economic losses from helminthiasis of the digestive system rank fourth in the overall structure of diseases and injuries of the world's population [1].

We proposed a complex anthelmintic drug in the form of coated tablets under the conditional name "AP-helmin", the active ingredients of which are albendazole and praziquantel in the ratio (1:4) [2-4].

In the development of coated tablets under the conditional name "AP-helmin" we relied on the requirements of Guideline 42-3.1:2004 [5].

One of the main indicators of drug quality is the stability of its physicochemical, pharmacological and consumer characteristics. The shelf life of the drug depends on many factors, and the deterioration of any of them during the shelf life indicates the negative processes occurring in the drug.

In accordance with the requirements of the State Pharmacopoeia of Ukraine (SPhU) coated tablets are under control by such basic quality indicators as appearance, average weight, weight homogeneity, identification, quantification of active substances, resistance to crushing, disintegration, microbiological purity [6].

The purpose of this work is to study stability during the storage of coated tablets under the conditional name "AP-helmin" on the basis of compliance of quality indicators with the requirements of SPhU and the developed project of quality control methods.

## Materials and methods

The object of the study were 5 series of coated tablets for the treatment of helminthiasis of the digestive system under the conditional name "AP-helmin".

The researched tablets contain active substances albendazole and praziquantel in the ratio of (1:4). The conducted study of the anthelminthic activity and acute toxicity showed that this drug has a high level of specific pharmacological activity with low toxicity [8].

Based on previous research of physical and chemical, pharmacotechnological and microbiological properties of the pure substances, their mixture in the ration (1:4) and coated tablets with them, we have developed a project of quality control methods (QCM) for investigated coated tablets (Table 1).

**Table 1. Quality indicators of coated tablets under the conditional name "AP-helmin"**

| Indicator (SPhU method) | QCM project requirements |
|---|---|
| Appearance (SPhU 2.0, pp. 1121-1125) | Tablets are oblong, white, homogeneous, without chips and cracks |
| Average weight, g | 0.80 |
| Uniformity of mass, % (SPhU 2.0, 2.9.5) | Not more than ± 5 % |
| Identification:<br>• albendazole (SPhU 2.0, 2.2.24)<br>• praziquantel (SPhU 2.0, 2.2.24) | <br>IR absorption spectrophotometry. The spectrum obtained must be identical to the standard sample of the substance albendazole<br>IR absorption spectrophotometry. The spectrum obtained must be identical to the standard sample of the substance praziquantel |
| Quantitative determination of active substances:<br>• albendazole<br>• praziquantel | <br>From 0.09 to 0.11<br>From 0.36 to 0.44 |
| Resistance to crushing, N (SPhU 2.0, 2.9.8) | Not less than 50 |
| Disintegration (SPhU 2.0, 2.9.1) | No more than 30 minutes |
| Microbiological purity (SPhU 2.0, 5.1.4) | The total number of viable aerobic microorganisms should not exceed $10^3$ CFU/g and yeast and mold fungi $10^2$ CFU/g. There should be no bacteria *Escherichia coli* |

To assess the quality the SPhU techniques listed in table 1 were used.

To quantify albendazole in tablets the method of spectrophotometry in the ultraviolet region (SPhU 2.0, 2.2.25) was used. Class A measuring vessels, reagents meeting the requirements of State Pharmacopoeia of Ukraine (SPhU), harmonized with the relevant European Pharmacopoeia techniques, analytical balance AXIS ANG200 (Poland), spectrophotometer Evolution 60s (USA) were used in the experiment. Albendazole was extracted from tablets with ethyl alcohol when heated, 0.1 M sodium hydroxide solution was added and the obtained sample was evaluated spectrophotometrically in the ultraviolet light at a wavelength of 308 nm. The samples comply with the Bouguer-Lambert-Behr law in the concentration range $1 \times 10^{-3}$ - $1.2 \times 10^{-2}$ mg/mL, correlation coefficient – ≥ 0.9998. The investigated method for quantifying albendazole in the drug meets the eligibility criteria for the range of determination ± 5.0 % for validation characteristics: specificity, linearity, precision, accuracy – within 80-120 % of the nominal content. It was experimentally established that praziquantel did not affect the obtained results.

DOI: 10.5281/zenodo.4038951

Liquid chromatography (SPhU 2.0, 2.2.29) was used to quantify praziquantel tin coated tablets. Chromatography was performed on a liquid chromatograph Agilent 1200 m. It was experimentally established that albendazole did not affect the results obtained.

The drug batch was stored for 27 months. The samples were stored at room temperature (15.0-25.0 °C) in a dry dark place (because the active substances albendazole and praziquantel are recommended to be stored in a dark place) [7].

Studies on the compliance of the drug with the requirements of the QCM project were performed at the beginning of the experiment and at a set interval of 3 months - during the 1st year and 6 months - during the 2nd year.

Statistical processing of the results of the research was carried out in accordance with the requirements of the SPhU, 2 ed., section 5.3 and the national part 5.3.N.2.

**Results and discussion**

The results of the analysis of samples of the investigated drug, laid in storage, are given in table 2.

As it can be seen from the above results, the samples of coated tablets under the conditional name "AP-helmin", laid down for storage (storage mode: at room temperature in a dry dark place), have satisfactory quality indicators according to the studied indicators in accordance with the QCM project. Yet, there is a tendency to reduce the resistance to crushing and reduce the quantitative content of active substances.

Thus, the obtained findings allow recommending the following shelf life of the investigated coated tablets: in a dry dark place at room temperature for at least 24 months.

**Conclusions**

1. There were 5 series of coated tablets for the treatment of helminthiasis of the digestive system under the conditional name "AP-helmin", laid down for storage for 27 months at the room temperature (15.0-25.0 °C) in a dry dark place.
2. It is experimentally proven that the studied samples of coated tablets remain stable throughout the shelf life.
3. As after 27 months of storage there is a tendency to reduce the resistance to crushing and reduce the quantitative content of active substances, the most rational is to set a shelf life of no less than 24 months in a dry dark place at room temperature.

**Study of stability when storing of tablets under the conditional name "Ap-helmin" as one of the factors of pharmaceutical development**

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**Introduction.** According to the World Bank, economic losses from helminthiasis of the digestive system rank fourth in the overall structure of diseases and injuries of the world's population.To meet the existing needs of the population of Ukraine in effective anthelmintic drugs, there were developed a complex anthelmintic drug in the form of coated tablets under the conditional name "AP-helmin", the active ingredients of which are albendazole and praziquantel in the ratio (1:4). One of the main ways to assess the quality of the drug is to maintain its stability during storage. Thus, the purpose of this work is to study stability during the storage of coated tablets under the conditional name "AP-helmin" on the basis of compliance of quality indicators with the requirements of SPhU and the developed project of quality control methods.
**Materials & methods.** As the object of the study there were investigated 5 series of coated tablets for the treatment of helminthiasis of the digestive system under the conditional name "AP-helmin". The well-known SPhU methods were used to assess the stability of the established indicators. **Results & discussion.** The proper quality and stability of the drug is confirmed throughout the study period. Yet, there is a tendency to reduce the resistance to crushing and reduce the quantitative content of active substances after 27 months of storage.
**Conclusion.** It was found that throughout the study period of storage samples of the drug met the requirements of the project MCYA and HFC. Therefore, the most rational is to establish the shelf life of coated tablets under the conditional name "AP-helmin" for at least 24 months in a dry dark place at room temperature.

**Keywords**: tablets; stability; pharmaceutical development; Ap-helmin; albendazole; praziquantel

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Received: 18.06.2020
Published: 21.09.2020

Table 2. Results of the study of the stability of coated tablets under the conditional name AP-helmin" (n = 5)

| **Indicator by QCM project** | Shelf life, months | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Start | 3 months | 6 months | 9 months | 12 months | 18 months | 24 months | 27 months |
| Appearance | Tablets are oblong, white, homogeneous, without chips and cracks | | | | | | | |
| Average weight, g | 0.81 ±0.0032 | 0.80 ±0.0032 | 0.81 ±0.0033 | 0.81 ±0.0033 | 0.80 ±0.0032 | 0.80 ±0.0029 | 0.80 ±0.0032 | 0.79 ±0.0029 |
| Uniformity of mass, % | ±3.9 | ±4.1 | ±4.1 | ±4.1 | ±4.1 | ±3.6 | ±4.1 | ±4.2 |
| Identification:<br>• albendazole<br>• praziquantel | <br>Responds<br>Responds | <br>Responds<br>Responds | <br>Responds<br>Responds | <br>Responds<br>Responds | | | <br>Responds<br>Responds | <br>Responds<br>Responds |
| Quantitative determination of active substances:<br>• albendazole<br>• praziquantel | <br>0.10±0.004<br>0.42±0.020 | <br>0.11±0.005<br>0.42±0.021 | <br>0.10±0.004<br>0.42±0.021 | <br>0.10±0.004<br>0.41±0.020 | <br>0.10±0.005<br>0.41±0.020 | <br>0.10±0.005<br>0.40±0.021 | <br>0.09±0.004<br>0.39±0.020 | <br>0.09±0.004<br>0.39±0.020 |
| Resistance to crushing. N | 96±0.02 | 96±0.02 | 95±0.02 | 95±0.02 | 96±0.02 | 95±0.02 | 94±0.02 | 90±0.02 |
| Disintegration, min. | 28 min 27 sec ±18sec | 28 min 17 sec ±21sec | 27 min 32 sec ±22sec | 26 min 04 sec ±18sec | 27 min 13 sec ±15sec | 28 min 19 sec ±16sec | 28 min 11 sec ±19sec | 29 min 11 sec ±21sec |
| Microbiological purity | Responds | Responds | Responds | Responds | Responds | Responds | Responds | Responds |

DOI: 10.5281/zenodo.4038951