UDC 661.122:615.453.62:615.284
DOI: 10.15587/2519-4852.2020.198411

SUBSTANTIATION OF PRODUCTION TECHNOLOGY OF TABLETS "AP-HELMIN"

K. Semchenko, L. Vyshnevska, Ie. Gladukh, A. Sichkar

Мета. *Метою даної роботи є обґрунтування технології виготовлення таблеток «АП-гельмін» та встановлення можливих критичних параметрів виробничого процесу.*
Матеріали та методи. *У процесі проведення досліджень використовували такі об'єкти як суміш чистих субстанцій альбендазол та празиквантел у співвідношенні (1:4), таблеткова маса та зразки таблеток-ядер на їх основі. У роботі використовували загальноприйняті фізико-хімічні та фармакотехнологічні методи Державної фармакопеї України, а саме проводили оцінку зовнішнього вигляду, фізичних параметрів, насипної густини, показника стисливості, текучості, сили роздавлювання, визначення середньої маси, однорідності маси, стійкості до роздавлювання та часу розпадання.*
Результати. *Експериментально встановили, що суміш діючих речовин має незадовільну текучість, що вказує на необхідність уведення стадії вологого гранулювання при розробці технології таблеток з ними.*
Стадію вологого гранулювання проводили із додаванням таких допоміжних речовин як крохмаль кукурудзяний, целюлоза мікрокристалічна 101 (МКЦ-101) та повідон (у вигляді 10 %-го розчину).
Дослідження 4х зразків таблеткової маси дозволили встановити найбільш раціональний склад для утворення таблеток-ядер – зразок № 4. Зразки за складом № 4 являють собою таблетки-ядра білого кольору, однорідні, без сколів і тріщин, та за стійкістю до роздавлювання та часом розпадання відповідають вимогам ДФУ (96 N та 8 хв 27 сек, відповідно).
Наступним етапом дослідження була розробка загальної технології приготування таблеток «АП-гельмін». Для забезпечення належних споживчих характеристик ввели стадію нанесення покриття плівковою оболонкою Opadry II ®YS-1-7027 White («Colorcon») білого кольору.
Висновки. *На основі отриманих результатів складено технологічну схему виробництва з урахуванням критичних параметрів та прогнозованих методів контролю на різних стадіях*
Ключові слова: *технологія, таблетки, протигельмінтні препарати*

1. Introduction

Helminthiasis of the digestive system is a socially significant problem that is relevant to many countries in the world. Active migration of the population, including for tourism purposes, contributes to the spread of atypical pathogens of this group of diseases.

In Europe, it is believed that one in three people have helminth disease. The incidence of helminthiasis increases significantly in the autumn months (this is related to the life cycle of most pathogens and the return of children to children's collectives) [1].

In Ukraine parasitic diseases, including helminthiasis of the digestive system, are recognized as a nationwide problem due to the high level of their spread (the incidence of helminthiasis is equal to the incidence of SARS and ARI combined) and the degree of economic losses in their treatment [2]. In our country, the most recorded cases are related to enterobiasis, ascariasis and trichocephalosis: respectively, 458.5:138.01:21.4 cases per 100 thousand people. According to random studies, the prevalence of children with parasitosis is: 8.5 % of children who attend preschools; 11 % of students; 20 % of boarding school children with part-time and 100 % with full-time stay; 6.9 % of preschool children (up to 7 years old) [3].

For the most part, the symptoms of helminthiasis are so non-specific and varied that often the affected are not even aware of their condition.

In 75.3 % of cases, helminthiasis is accompanied by disorders of the gastrointestinal system: pain in the right hypochondrium, nausea, impaired appetite, dyspeptic phenomena, decreased acidity of gastric juice, etc. [4].

The existing range of anthelmintic drugs in Ukraine does not fully meet the needs of the population. Thus, as of February 5, 2020, there are no drugs of the group P02B (drugs used for trematodoses) in the State Register of Medicinal Products, which complicates the treatment of some groups of helminthiasis of the digestive system, in particular, intestinal cestodes [5].

In view of the above, the development of the newest domestic drugs for the treatment of helminthiasis is an urgent task of pharmacy. We offered a drug containing albendazole and praziquantel in the ratio (1:4) as active ingredients in the dosage form tablets under the conditional name "AP-helmin" [6, 7].

The aim of the research. The aim of this work was to substantiate the technology of production of tablets "AP-helmin" and to establish the possible critical parameters, in accordance with the requirements of the Guidelines 42-3.1:2004 "Guidelines for quality. Medicines. Pharmaceutical Development".

2. Planning (methodology) of the research

To meet the said purpose, we have identified the following tasks of the study:

– to study the physicochemical properties of a mixture of active pharmaceutical ingredients;

– to establish the need for the introduction of an additional technological stage of wet granulation;

– to investigate the properties of tablet mass of different composition and to choose the most rational for further development of the tablet-core;

– to reason the rational technology of obtaining tablets-cores of the selected composition and method of coating them;

– to develop the technological scheme of production of "AP-helmin" tablets, to establish the critical parameters of production and to forecast the possible types of quality control at different stages of production.

3. Materials and methods

The objects of the study were a mixture of substances albendazole and praziquantel (1:4), tablet mass and tablet core samples based on them.

Pharmacotechnological parameters of the mixture of substances, tablet mass and obtained samples of tablet cores were studied in the development and justification of the production technology of "AP-helmin" tablets. The studies were carried out in accordance with the requirements of the State Pharmacopoeia of Ukraine (SPhU) by conventional methods [8].

4. Results of the research

The first step in the development of "AP-helmin" tablet technology was to study the technological parameters of the mixture of substances albendazole and praziquantel (1:4) (Table 1).

As can be seen from the results in Table 1, the mixture of active substances albendazole and praziquantel in the ratio (1:4) has poor flowability (according to the flowability scale of SPhU 2.1, Table 2.9.36.-2), indicating the need to introduce the stage of granulation in the development of technology tablets with these substances.

The methods of dry and wet granulation were investigated. During dry granulation, a strong dispersion of the mass and its sticking to the technological parts of the equipment were observed, while using the wet granulation method, the resulting mass had satisfactory technological characteristics.

Table 1

Technological properties of substances albendazole and praziquantel (1:4) mixture

Indicator	Value
Bulk density before shrinkage, g/ml	0.32
Bulk density after shrinkage, g/ml	0.46
Compressibility index	30.77
Hausner ratio	1.44
Flowability, g/sec	1.190
K_{comp}	0.086
Force of crushing, N	141

The wet granulation step was carried out with the addition of such excipients as corn starch, microcrystalline cellulose 101 (MCC-101) and povidone (as a 10 % solution).

The choice of excipients was carried out on the basis of well-known data on the technology of tablets, and also the economic affordability of these substances was taken into account.

Corn starch acts as a filler and loosening agent, giving the tablet mass of the necessary physical and chemical properties.

MCC-101 is used in the composition of tablet masses for wet granulation and in the amount of 5–20 % contributes to the rapid adsorption and uniform distribution of moisture, improving the efficiency of drying the tablet mass and improve the mechanical characteristics of the finished tablets [9, 10].

As a binder and wetting agent, povidone was used in the form of a 10 % solution at a standard concentration in the tablet mass of not more than 5 %.

Granulation was performed by wetting the tablet mass with 10 % solution of povidone, the formation of granules, drying the granules at a temperature of 50.0±2.0 °C for 2 h.

The obtained granules were dusted with magnesium stearate, which acts as an antifriction agent, in the amount of 1 %.

The composition of the samples of tablets-cores obtained by the above technology are given in Table 2.

Table 2

Composition of tablets-cores

Ingredient	Content, mass. %			
	Sample 1	Sample 2	Sample 3	Sample 4
Mixture of albendazole and praziquantel (1:4)	62.5	62.5	62.5	62.5
Corn starch	25	24	23.5	23
MCC-101	8.5	8.5	8,5	8.5
Povidone	3	4	4.5	5
Magnesium stearate	1	1	1	1
Total:	100.0	100.0	100.0	100.0

According to the results of the studies in Table 2, the tablet mass of sample 1 is not sufficiently moist, that is, the formation of the granules will be impossible. Tablets-cores of tablet masses 2 and 3 have chips and cracks, which indicates their poor quality. The tablets-cores of sample 4 were homogeneous, which is why we conducted further studies with them.

The results of pharmaco-technological studies of tablets-cores of sample 4 are given in Table 3. Studies were conducted in five series of sample tablets.

Table 3

The results of the study of the quality of tablets-cores of sample 4

Indicator (SPhU method)	Value	Requirements of SPhU
Appearance (SPhU 2.0, pp. 1121-1125)	Tablets oblong white, homogeneous, without chips and cracks	Responds
Physical parameters	Length 19 mm (oblong) Width 8 mm Height 6 mm Rib height 3 mm	–
Average mass, g	0.80±0.0032	–
Uniformity of mass, % (SPhU 2.0, 2.9.5)	±4.1	Responds
Resistance to crushing, N (SPhU 2.0, 2.9.8)	96±0.02	Responds
Disintegration (SPhU 2.0, 2.9.1), average	8 min 27±18 sec	Responds
Friability (SPhU 2.0, 2.9.7), %	0.7±0.03	Responds

As can be seen from the results of the studies in Table3, model sample 4 is a white core tablet, homogeneous, free from chips and cracks, and with a resistance to crushing and disintegration time, meet the requirements of SPhU (96 N and 8 min 27 sec, respectively).

The technology of production of tablets of the selected composition was developed taking into account the physicochemical and pharmacotechnological properties of active pharmaceutical ingredients. Critical stages and critical parameters of production, as well as predicted methods of control in the production process, were determined during the development of stages of the technological process [11, 12].

In order to ensure proper consumer characteristics (including the correction of the bitter taste of active substances and facilitating swallowing of the tablet due to smoothing of the roughness of the tablet and the sliding effect) and protect selected active pharmaceutical ingredients from environmental influences, a white coat Opadry II ®YS-1-7027 White ("Colorcon") was introduced. The indicated coating was used in the form of a 2 % suspension applied to the surface of the core tablets (with the use of laboratory equipment Unilab-05-TJ BWI Huttlin GmbH).

Based on the researches, the technological scheme of production of "AP-helmin" tablets was developed (Fig. 1).

We identified the critical parameters of each stage of the manufacturing process of tablets, which can affect the quality of the finished product, reproducibility of production technology, including various series, and functional characteristics.

The obtained series of tablets according to the proposed technology is stored for the purpose of determining the shelf life of the drug.

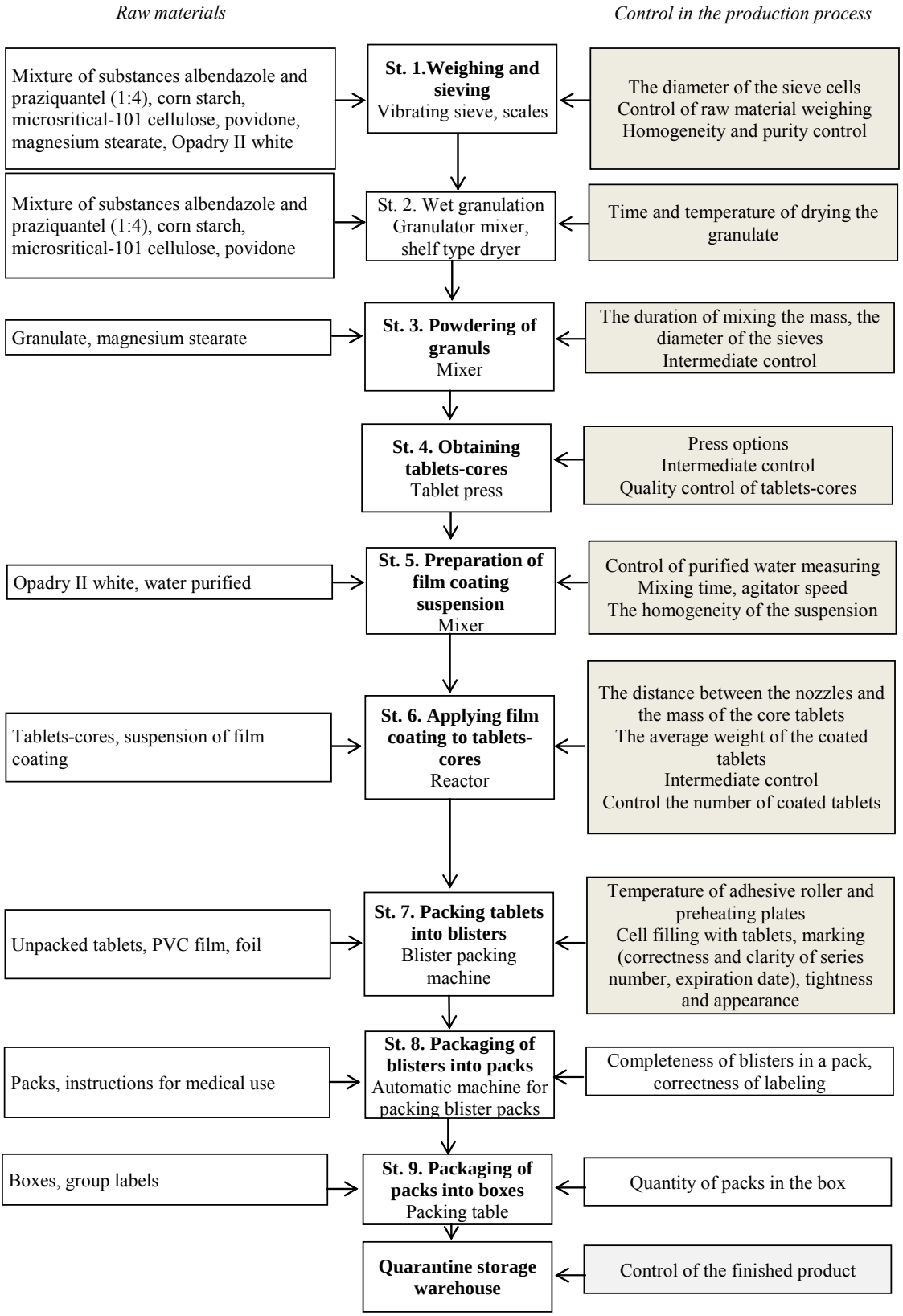

Fig. 1. Technological scheme of production of tablets "AP-helminth"

5. Discussion

The results show that the physicochemical properties of the selected active pharmaceutical ingredients do not provide the proper flow characteristics. Therefore, it is advisable to introduce into the process the stage of wet granulation.

It is advisable to carry out the stage of wet granulation with the addition of such excipients as corn starch, MCC-101 and povidone (in the form of a 10 % solution). The number of selected excipients is experimentally justified. Physical parameters, average mass, uniformity of mass, resistance to crushing and disintegration time

were determined for the tablets-cores of the selected composition.

To ensure the proper consumer characteristics of "AP-helmin" tablets, a coating step with the Opadry II ®YS-1-7027 White ("Colorcon") white film coat was introduced.

Thus, the technological scheme for the production of "AP-helmin" tablets has 9 main stages.

Study limitations. The studies conducted are based on the development of tablet technology in the laboratory conditions and do not fully reflect the possible risks of manufacturing this dosage form under industrial conditions. The critical parameters of quality control in the manufacturing process are described as predicted and require confirmatory research.

The prospects for the further research. The article describes the reasoning of the production of "AP-helmin" tablets and identifies the critical stages of the production process and the possible critical control parameters in the production process. The next stage of research is the testing of technology in the conditions of small-scale production, clarification of critical parameters of the production process and quality control, adaptation of technology to the conditions of industrial production.

6. Conclusions

The production technology of "AP-helmin" tablets based on the mixture of substances albendazole and praziquantel in the ratio (1:4) is substantiated and the rational introduction of the technological stage of wet granulation of the tablet mass is proved.

The technological scheme of production of "AP-helminth" tablets was presented.

Critical parameters of technological process and quality control in the production process are determined.

Conflict of interests

Authors declare no conflict of interest.

References

1. Osin i helmintoz: zviazok isnuie (2015). Farmatsevt Praktyk, 10, 29. Available at: http://nbuv.gov.ua/UJRN/farmpr_2015_10_19

2. Stankevych, V. V., Tarabarova, S. B. (2015). Sanitarno-hihiienichna problema zabrudnennia helmintamy obiektiv navkolyshnoho seredovyshcha v Ukraini (ohliad). Hihiiena naselenykh mists, 66, 85–89. Available at: http://nbuv.gov.ua/UJRN/gnm_2015_66_14

3. Koziarin, I. P., Ivakhno, O. P., Chorna, V. V., Makhniuk, V. M. (2015). Helmintozy v Ukraini. Suchasnyi stan problemy. Hihiiena naselenykh mists, 66, 268–272. Available at: http://nbuv.gov.ua/UJRN/gnm_2015_66_44

4. Shadrin, O. H., Kovalchuk, A. A., Diukareva, S. V., Polkovnychenko, L. M. (2015). Stan shlunkovo-kyshkovoho traktu ta shliakhy korektsii yoho porushen pry helmintozakh u ditei. Sovremennaia pedyatryia, 8, 88–91. Available at: http://nbuv.gov.ua/UJRN/Sped_2015_8_17

5. Nastanova 00021. Kyshkovi tsestodozy. Available at: http://guidelines.moz.gov.ua/documents/2918?id =ebm00021&format=pdf

6. Semchenko, K. V., Vyshnevska, L. I. (2019). Pat. UA. Antyhelmintnyi zasib na osnovi albendazolu ta prazykvantelu. MPK (2019.1): A61K 31/4184, A61K 31/47, A61P 33/00. No. u201910233; declareted: 07.10.2019.

7. Semchenko, K. V., Vyshnevska, L. I. (2019). Pat. UA. Antyhelmintnyi zasib na osnovi albendazolu ta prazykvantelu. MPK (2019.1): A61K 31/4184, A61K 31/47, A61P 33/00. No. a201910236; declareted: 07.10.2019.

8. Derzhavna Farmakopeia Ukrainy. Vol. 1 (2014). Kharkiv: Derzh. p-vo «Naukovo-ekspertnyi farmakopeinyi tsentr yakosti likarskykh zasobiv», 1128.

9. Lenchyk, L. V., Sichkar, A. A., Gladukh, Ye. V., Kyslychenko, V. S. (2016). Development of the composition of tablets with the extract of bird cherry and their standardization. News of Pharmacy, 3, 39–42. doi: http://doi.org/10.24959/nphj.16.2123

10. Sherif, S. Z. H. (2017). Microcrystalline cellulose: the inexhaustible treasure for pharmaceutical industry. Nanoscience and Nanotechnology Research, 4 (1), 17–24.

11. Lyapunov, N. A., Zagoriya, V. A., Georgievskii, V. P., Bezuglaya, E. P. (Eds.) (2001). Nadlezhashchaya proizvodstvennaya praktika lekarstvennyh sredstv. Aktivnye farmacevticheskie ingredienty. Gotovye lekarstvennye sredstva: Rukovodstvo po kachestvu. Rekomendacii PIC/S. Kyiv: Morion, 472.

12. Nastanova ST-N MOZU 42-4.0:2011. Likars'ki zasobi. Nalezhna virobnicha praktika. Kyiv: MOZ Ukraini, 252.

Received date 13.03.2020
Accepted date 14.04.2020
Published date 30.04.2020

Kateryna Semchenko, PhD, Associate Professor, Department of Pharmaceutical Technology of Drugs, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: tolochko.kv@gmail.com

Liliia Vyshnevska, Doctor of Pharmaceutical Sciences, Professor, Head of Department, Department of Pharmaceutical Technology of Drugs,, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: atl@nuph.edu.ua

Ievgenii Gladukh, Doctor of Pharmaceutical Sciences, Professor, Department of Technologies of Pharmaceutical Preparations, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: prom_farm@nuph.edu.ua

Antonina Sichkar, PhD, Associate Professor, Department of Technologies of Pharmaceutical Preparations, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: tfp@nuph.edu.ua