DEVELOPMENT OF THE COMPOSITION OF HARD CAPSULES WITH ANTIHELMINTIC ACTIVITY BASED ON PRAZIQUANTEL

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Abstract

Introduction. Helminthiasis remains one of the most important global health problems, especially in regions with low sanitation and limited access to quality medical care.

On April 28, 2017, the Order of the Ministry of Health of Ukraine No. 1422 dated December 29, 2016, which allows the use of international treatment protocols in Ukraine, came into force. In particular, the Ministry of Health of Ukraine signed an agreement with the Finnish medical scientific society Duodecim Medical Publications Ltd, specializing in comprehensive solutions in the field of evidence-based medicine. Among the many clinical protocols proposed for discussion and use, there are recommendations for the treatment of gastrointestinal helminthiasis [7-13].

Among the numerous anthelmintic drugs, praziquantel is the main drug for the treatment of schistosomiasis and other parasitic infestations caused by trematodes and some types of cestodes.

Praziquantel rapidly increases the permeability of helminth cell membranes to calcium ions, which in turn leads to muscle contraction, which progresses to persistent paralysis and death. In addition, praziquantel causes vacuolization and subsequent damage to the helminth epithelium, which makes them vulnerable to the host's immune system and its digestive enzymes. [1-5].

The side effects of praziquantel are listed on fig. 1.

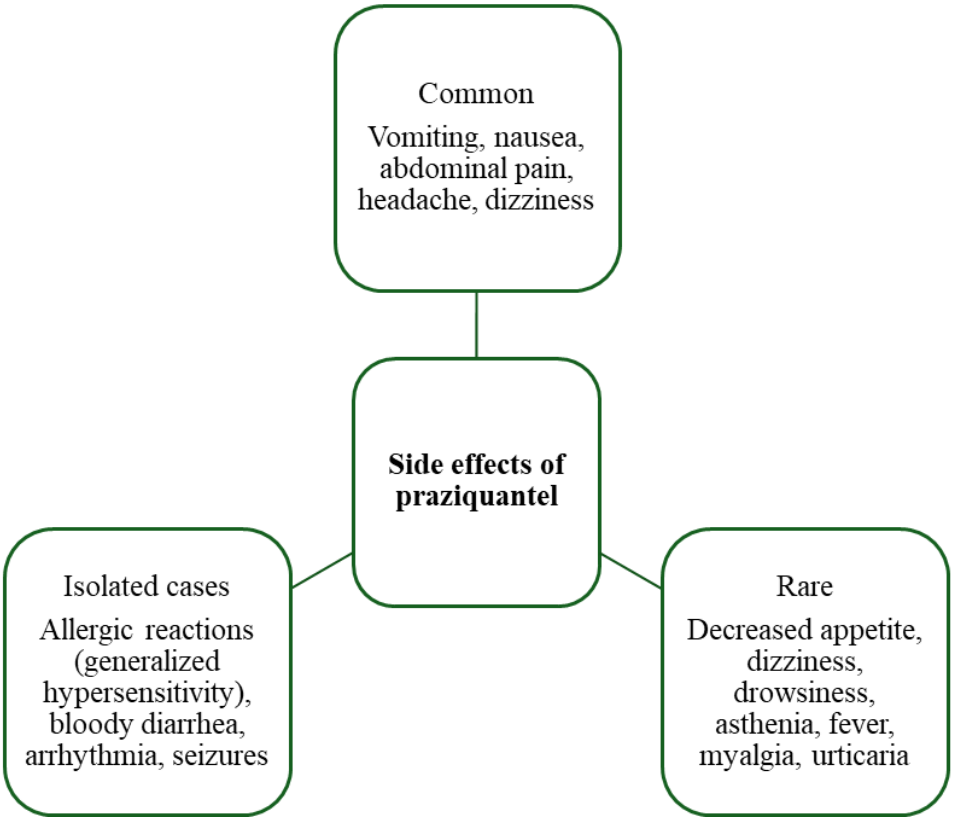

Fig. 1 Side effects of praziquantel

To date, there are no drugs of the ATX group P02BA01 Praziquantel on the pharmaceutical market of Ukraine [6], although there is a need for them, because they are included in the treatment protocols of the relevant groups of antiparasitic diseases and are mentioned in the Guidelines on the principles of evidence-based medicine, which are presented on the website of the Ministry of Health of Ukraine.

Therefore, the development of new anthelmintic drugs based on praziquantel is extremely relevant, as it will increase the effectiveness of treatment, overcome the problem of parasite resistance, and ensure ease of use for all age groups..

The aim of our work is to develop the composition of a solid dosage form, in particular, hard gelatin capsules, based on the active pharmaceutical ingredient praziquantel.

Materials and methods

To achieve the stated research goal, the following research objectives were identified: (fig. 2).

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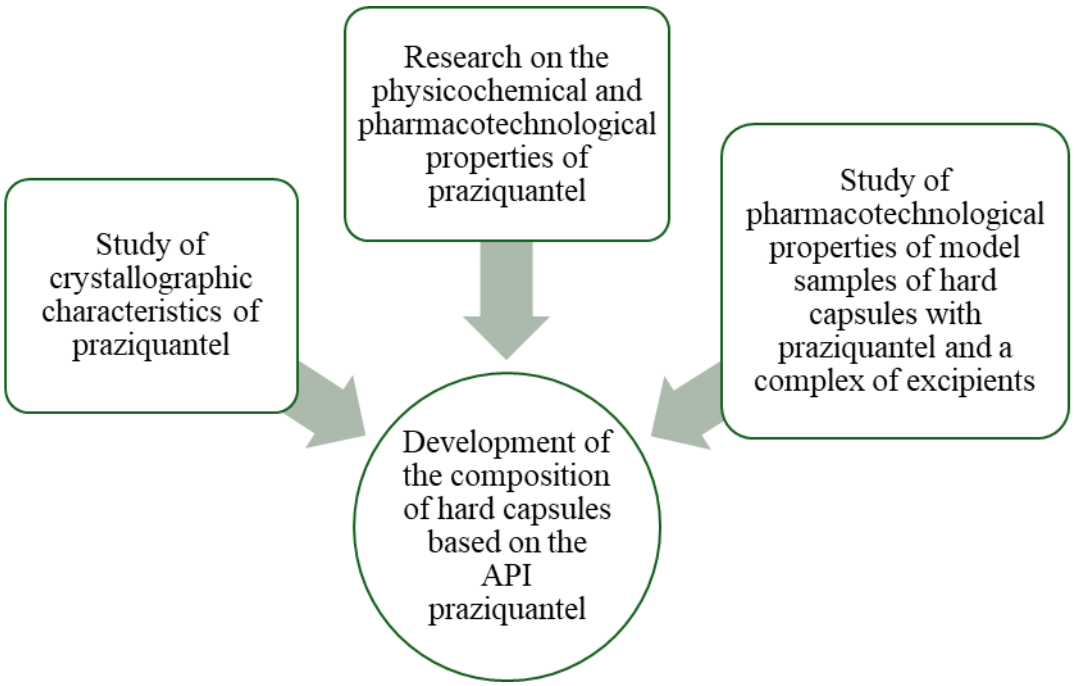

Fig. 2. General research methodology

The object of the study was samples of the substance praziquantel (EF 01/2005:0855). White or almost white crystalline powder. Very slightly soluble in water, freely soluble in alcohol and methylene chloride. Shows polymorphism. The substance used was "Praziquantel Pharm" (China), batch 20240502, May 2024. Mass fraction of the main substance 99.91%.

When choosing doses, we were guided by the recommended treatment doses given in the protocols for the treatment of helminthiasis of the digestive system. Thus, a single therapeutic dose of praziquantel is 5-20 mg/kg. We chose a dose of 350 mg per 1 capsule, which corresponds to 5 mg per 70 kg of body weight.

When developing the composition of the capsule mass, the object of research was samples of capsule mass with the addition of such excipients as lactose, aerosil, talc and magnesium stearate.

The studies used methods of microscopic analysis, determination of bulk density and density after shrinkage, and fluidity..

Microscopic analysis was performed using a Konus-Akademy laboratory microscope (Italy) with a ScopeTek DCM510 eyepiece camera (China) at a total magnification of 90 times. ScopePhoto™ software was used to visualize the images, which allows for measuring linear dimensions in real time and static image mode..

Bulk density and density after shrinkage were determined according to the method of the SPU, 2nd edition, Vol. 1, item 2.9.34, method 1..

The fluidity was determined by the SPU method 2nd edition, Vol. 1, 2.9.36 on the PTG-S3 device (Pharma Test, Germany).

Results and discussion. The goal of pharmaceutical development is to create a drug of appropriate quality with specified quality characteristics. Today, the basis for planning a pharmaceutical experiment is the requirements of Guideline 42-3.1:2004 “Guideline on Quality. Medicinal Products. Pharmaceutical Development” [14].

To develop capsules based on the API praziquantel, the physicochemical and pharmacotechnological properties of the substance were investigated. The studies were conducted on 5 sample batches, the results were evaluated in accordance with the requirements of the SPU.

The crystallographic characteristics of the substance were studied using an Akademia laboratory microscope at a total magnification of 90 times. The results of the study of the substances are shown in Fig. 3.

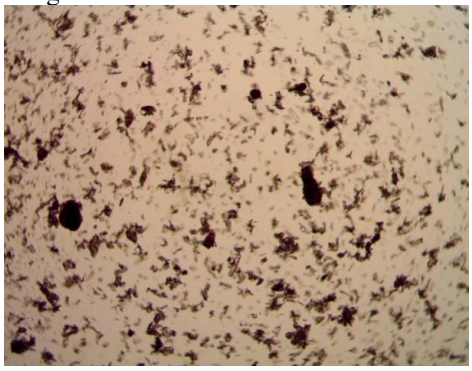

Fig. 3 Praziquantel particles

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As can be seen from Fig. 3, the praziquantel API is a polydisperse powder. The particles are transparent plates of indefinite shape with fragments on the surface capable of agglomeration, their size ranges from 0.15 μm to 2 μm.

Since the encapsulation technology is influenced by such indicators of the capsule mass as: bulk density (this is the mass of a unit volume of freely poured powder, which depends on the density and humidity of the substance, the shape and size of the particles, their mutual arrangement; its value can be used to predict the nature of the excipients used and the volume of the matrix channel of the tablet machines); fluidity (is a complex characteristic determined by the degree of dispersion and shape of the particles, moisture content, particle size distribution, interparticle and external friction coefficient, bulk density), we determined them.

The results of determining the bulk density and density after shrinkage of 3 series of substance samples are given in Table 1. Based on the results obtained, the compressibility index and the Hausner coefficient were calculated for each sample.

Table 1. Determination of bulk density, density after shrinkage, compressibility index and Hausner coefficient of 3 series of samples of praziquantel substance

Indicator	Series		
	1	2	3
Bulk density, g/ml	0,27 ± 0,01	0,27 ± 0,01	0,26 ± 0,01
Bulk density after shrinkage, g/ml	0,418 ± 0,015	0,419 ± 0,015	0,419 ± 0,015
Compressibility index, %	37,21 ± 1,38	37,23 ± 1,38	37,24 ± 1,38
Hausner coefficient	1,59	1,60	1,59

The results obtained (Table 1) show that the substance samples have very poor fluidity (according to the SPU 2.1 fluidity scale, Table 2.9.36.-2).

The fluidity of the substance was additionally assessed by determining the angle of natural slope and the flow velocity through the nozzle (Table 2).

Table 2. Determination of the fluidity of 3 series of praziquantel substance samples

Indicator	Series		
	1	2	3
Natural slope angle, °	39,8 ± 0,5	40,0 ± 0,5	40,0 ± 0,5
Flow rate through the nozzle, кг/с	0,00126 ± 0,00005	0,00125 ± 0,00005	0,00125 ± 0,00005

According to the obtained values of the angle of natural slope (Table 3), the studied samples have satisfactory fluidity (according to the fluidity scale and the corresponding angle of slope SPU 2.1, Table 2.9.36.-1), which is typical for bound materials..

As can be seen from the above results, the substance praziquantel is prone to electrification and agglomeration. The presence of particles with uneven edges and clusters leads to a deterioration in the technological characteristics of the mixture. Therefore, it is advisable to introduce excipients into the mixture to improve the fluidity of the capsule mass.

In order to establish the optimal composition and quantitative content of excipients, we studied the properties of several model samples of capsule masses (Table 3).

The flowability of model samples of capsule mass was assessed by determining the angle of natural slope and the flow velocity through the nozzle (Table 4).

According to the obtained values (Table 5) of the angle of natural slope (according to the flowability scale and the corresponding slope angle SPU 2.1, Table 2.9.36.-1), samples 1 and 5 have satisfactory flowability, samples 2 and 3 have acceptable flowability (the mass may hang), and sample 4 has good flowability.

Table 3. Composition of the capsule mass

Composition of the capsule mass	Quantitative content of ingredients, wt. %				
	Model sample				
	1	2	3	4	5
Praziquantel	83,0	83,0	83,0	83,0	83,0
Lactose	16,5	8,5	13,5	9,5	8,5
Aerosil	–	8,0	–	5,0	4,0
Talc	–	–	3,0	2,0	4,0
Magnesium stearate	0,5	0,5	0,5	0,5	0,5
Total	100,0	100,0	100,0	100,0	100,0

According to the Indicator of the flow rate through the nozzle, the best results are obtained by samples 4 and 5. According to both parameters, the best flow indicators are obtained by model sample 4. Therefore, this composition is rational in the further development of capsules for the treatment of helminthiasis of the digestive system based on the API praziquantel.

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Table 4. Results of the study of the fluidity of model samples of capsule mass

Indicator	Model sample				
	1	2	3	4	5
Natural slope angle, °	38,5 ± 0,5	40,0 ± 0,5	42,0 ± 0,5	31,5 ± 0,5	385,5 ± 0,5
Flow rate through the nozzle, kg/s	0,0077 ± 0,0005	0,0059 ± 0,0005	0,0057 ± 0,0005	0,0129 ± 0,0005	0,0181 ± 0,0005

Conclusions

1. The study of the physicochemical and pharmacotechnological properties of the API praziquantel was conducted. It was found that the API has very poor fluidity in terms of bulk density, density after shrinkage, compressibility after shrinkage, Gaussner coefficient, angle of repose and flow velocity through the nozzle. According to the obtained values of the angle of repose, the samples of the API praziquantel have satisfactory fluidity, which is typical for bound materials.
2. Based on the study of the flowability of five model samples of capsule mass in terms of the angle of natural slope and flow rate through the nozzle, the most rational composition of excipients was determined: lactose 9.5 wt. %, aerosil 5.0 wt. %, talc 2.0 wt. %, magnesium stearate 0.5 wt. %.

Prospects for further research

The next stage of the research is the development of laboratory and industrial technology for the production of hard capsules with praziquantel under the code name “Praziquantel Plus”.

Financing. The study was conducted within the framework of the research project “Development of the composition, technology and biopharmaceutical research of medicinal products based on natural and synthetic raw materials” (state registration number 0114U000945) of the National University of Pharmacy of the Ministry of Health of Ukraine.

Conflict of interest: absent.

Development of the composition of hard capsules with antihelmintic activity based on praziquantel

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Introduction. Helminthiasis is one of the most common forms of parasitosis. To date, the pharmaceutical market still does not offer drugs of the ATX group P02BA01 based on the substance praziquantel, although it is recommended by current clinical protocols for the treatment of schistosomiasis and other parasitic invasions caused by trematodes and some types of cestodes. **The aim of our study** is to develop the composition of a solid dosage form, in particular, hard gelatin capsules, based on the active pharmaceutical ingredient praziquantel.
Materials and methods. The objects of study were samples of the substance praziquantel and model samples of hard capsules with praziquantel and a variable composition of excipients. The studies used methods of microscopic analysis, determination of bulk density and density after shrinkage, and fluidity. **Results.** It was found that praziquantel has very poor fluidity in terms of bulk density, density after shrinkage, compressibility after shrinkage, Gaussner coefficient, angle of repose and flow rate through the nozzle. According to the values of the angle of repose, praziquantel samples have satisfactory fluidity, which is typical for bound materials. The dose of praziquantel per 1 capsule was selected based on the analysis of clinical protocols for the treatment of helminthiasis of the digestive system. Thus, a single therapeutic dose of praziquantel is 5-20 mg/kg. We selected a dose of 350 mg per 1 capsule, which corresponds to 5 mg per 70 kg of body weight.
Conclusions. Based on the study of the fluidity of five model samples of capsule mass in terms of the angle of repose and flow rate through the nozzle, the most rational composition of excipients was determined: lactose 9.5 wt. %, aerosil 5.0 wt. %, wt. 2.0 wt. %, magnesium stearate 0.5 wt. %.
Key words: capsules, solid dosage forms, praziquantel, helminthiasis, technology, composition

References

1. Babes R. M., Selescu T., Domocos D., Babes A. The anthelminthic drug praziquantel is a selective agonist of the sensory transient receptor potential melastatin type 8 channel. Toxicology and applied pharmacology. 2017. Vol. 336. P. 55–65. DOI: https://doi.org/10.1016/j.taap.2017.10.012 (Date of access: 11.12.2024).
2. Garg R. K., Uniyal R., Malhotra H. S. Be careful while using albendazole/praziquantel in neurocysticercosis. *Neurology India*. 2017. Vol. 65, № 4. P. 924–926. DOI: https://doi.org/10.4103/neuroindia.NI_424_16 (Date of access: 11.12.2024).
3. Šagud I., Zanolla D., Perissutti B., Passerini N., Škorić I. Identification of degradation products of praziquantel during the mechanochemical activation. *Journal of pharmaceutical and biomedical analysis*. 2018. Vol. 159. P. 291–295. DOI: https://doi.org/10.1016/j.jpba.2018.07.002 (Date of access: 15.12.2024).
4. Sun Q., Mao R., Wang D., Hu C., Zheng Y., Sun D. The cytotoxicity study of praziquantel enantiomers. *Drug design, development and therapy*. 2016. Vol. 10. P. 2061–2068. DOI: https://doi.org/10.2147/DDDT.S98096 (Date of access: 15.12.2024).
5. Zwang J., Olliaro P. Efficacy and safety of praziquantel 40 mg/kg in preschool-aged and school-aged children: a meta-analysis. *Parasites & vectors*. 2017. Vol. 10, № 1. DOI: https://doi.org/10.1186/s13071-016-1958-7 (Date of access: 15.12.2024).
6. Bratishko Y. S., Semchenko K. V., Tolochko V. M., Zarichkova M. V., Zoidze D. R., Dolzhnikova O. M. (2024) Organizational and economic studies of the circulation of anthelmintic drugs on the domestic pharmaceutical market in the current conditions. *News of Pharmacy*, 2 (108), 50-57. https://doi.org/10.24959/nphj.24.154

7. Guideline 00019. Pinworms (enterobiasis). Duodecim Medical Publications Ltd. 2017. URL: http://guidelines.moz.gov.ua/documents/2918?id=ebm00019&format=pdf (access date: 10.10.2024).
8. Guideline 00020. Ascariasis.URL: http://guidelines.moz.gov.ua/documents/2918?id=ebm00020&format=pdf (access date: 10.10.2024).
9. Guideline 00021. Intestinal cestodes. URL: http://guidelines.moz.gov.ua/documents/2918?id=ebm00021&format=pdf (access date: 10.10.2024).
10. Guideline 01038. Strongyloidiasis. URL: http://guidelines.moz.gov.ua/documents/2918?id=ebm01038&format=pdf (access date: 10.10.2024).
11. Guideline 01039. Nematodoses. URL: http://guidelines.moz.gov.ua/documents/2918?id=ebm01039&format=pdf (access date: 10.10.2024).
12. Guideline 01040. Introduction to the topic of intestinal helminths. *Duodecim Medical Publications Ltd*. 2017. URL: http://guidelines.moz.gov.ua/documents/2918?id=ebm01040&format=pdf (access date: 10.10.2024).
13. Guideline 01043. Trichocephalosis. URL: http://guidelines.moz.gov.ua/documents/2918?id=ebm01043&format=pdf (access date: 10.10.2024).
14. Guideline 42–3.1:2004. Quality guidelines. Medicinal products: Pharmaceutical development / Ministry of Health of Ukraine. Official publication. Kyiv: Morion, 2004. 16 p.

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