UDC 615.451.1:615.014.8:543.632.514.2:546.46
DOI: 10.15587/2519-4852.2024.302066

RESEARCH FOR THE SELECTION OF TASTE CORRIGENTS, FILTER MATERIALS AND PRIMARY PACKAGING FOR ORAL SOLUTION WITH MAGNESIUM SALTS

Daria Snehyrova, Lyudmila Almakaieva

The aim. *Theoretically and experimentally, justify the choice of excipients for a combined oral solution with organic magnesium salts. Determine the compatibility of filter materials of three types. Select single-dose primary packaging for the developed oral solution and confirm its suitability during the relevant studies.*

Materials and methods. *Organoleptic, physicochemical, and pharmaco-technological methods were used in the investigation. All methods meet the requirements of the State Pharmacopoeia of Ukraine and the European Pharmacopoeia. Organoleptic methods indicated the taste of the medicinal speciality behind the methods of O.I. Tentsova and I.A. Egorov. Physicochemical methods were used to determine pH, colour, density, and quantitative amount of active pharmaceutical ingredients. Pharmaco-technological methods were used to determine the properties of filter materials and primary packaging.*

Results. *A sweetener and a flavouring agent for an oral solution with magnesium salts were selected based on the research. Saccharin sodium was selected as a sweetener in the amount of 0.15 %. «Cherry» in the amount of 0.4 % and «caramel» in the amount of 0.2 % were selected as flavouring agents. As a result of experiments, the suitability of filter materials made of capron, nylon and polyethersulfone was proven. This is determined by the constancy of the main quality indicators of the drug 24, 48 and 72 hours after filtration. The suitability of the single-dose primary packaging in the process of storing the oral solution has been studied and proven. In the work, polymer ampoules of the «Moplen EP 2S 12 B» brand and the «Purell HP 371P» brand were used. The conducted research allows us to create a competitive domestic drug that will be technologically simple and convenient in administration and will also be distinguished by relatively low raw material costs and production.*

Conclusions. *Based on theoretical and experimental studies, auxiliary substances, such as sweeteners and flavouring agents, were selected for the combined magnesium-containing drug. The suitability of filter materials for the combined oral solution was investigated and confirmed. The suitability of single-dose primary packaging of two types was selected and experimentally proven*

Keywords: *oral solution, organic magnesium salts, excipients, single-dose primary packaging*

How to cite:
Snehyrova, D., Almakaieva, L. (2024). Research for the selection of taste corrigents, filter materials and primary packaging for oral solution with magnesium salts. ScienceRise: Pharmaceutical Science, 2 (48), 36–43. doi: http://doi.org/10.15587/2519-4852.2024.302066

1. Introduction

Magnesium plays a fundamental role in the regulation of a number of processes that are necessary for the normal functioning of all human systems and organs. Magnesium is an element that is often forgotten, unlike, for example, calcium, potassium, and sodium. Although, it has been established that about 15 % of the population suffers from hypomagnesemia [1]. This is probably due to the lack of specific symptoms of cation deficiency until the level gets really low and also because of the lack of a good understanding of the element's physiology. This problem leads to several diseases. Also, it worsens the condition and leads to various complications in patients with concomitant diseases. The clinical manifestation of hypomagnesemia varies from an asymptomatic course to severe arrhythmias [2]. Several studies have shown that chronic cation deficiency is associated with many serious diseases or leads to their exacerbation [3].

Nowadays, magnesium salts' different bioavailability remains an issue discussed at the cellular and systemic levels. In different years, a number of authors conducted research on it. Bioavailability studies of a number of salts of the cation show that organic magnesium salts (for example, magnesium citrate) have higher bioavailability than inorganic salts (for example, magnesium oxide) [4]. In a study [5], Firoz M. and Graber M. compared the bioavailability of four commercial drugs with the element. The results showed a higher bioavailability of drugs with organic compounds of the element compared to those with inorganic derivatives. Blancquaert L. et al. analyzed the bioavailability of magnesium salts in vitro and in vivo using 15 commercial drugs. The results confirmed the general pattern, which is that inorganic magnesium compounds are absorbed worse than organic ones. [6]. Coudray C. and co-authors studied the bioavailability of inorganic compounds of the element, such, as oxide, chloride, sulfate, carbonate, and organic compounds, such, as acetate, pidolate, citrate, gluconate, lactate, aspartate. Studies have shown better results when using organic magnesium salts. In particular, the best compounds were pidolate, lactate, gluconate, aspartate [7].

One of the highly effective organic magnesium salts is magnesium pidolate. A number of studies confirms its high bioavailability. For example, the study by Decologne S. et al. compares the magnesium level in blood serum in mice after oral administration of magnesium pidolate, lactate, aspartate. It was found, that after receiving oral magnesium pidolate, the level of the cation in blood serum increased by 100 %, and magnesium lactate – by 50 % (compared to the initial level) [8]. Kyselovič J. and others compared the bioavailability of a number of magnesium compounds: oxide, sulfate, chloride, carbonate, lactate, citrate, pidolate. The study revealed the best intestinal absorption of magnesium pidolate salt [9].

One of the limiting factors of using magnesium for therapeutic purposes is not enough information on the permeability of the element through the blood-brain barrier directly to the nervous system. In experiments, Romeo V. et al. studied the ability of cation-based compounds at the same concentration (5 mmol/l) to penetrate the blood-brain barrier in rat and human models. It was found that all salts reduced the permeability of the blood-brain barrier. Among them, magnesium pidolate and magnesium threonate proved to be the most effective in the human model [10]. The authors also found that using magnesium pidolate increased cation transport through the blood-brain barrier. Thus, it can be concluded that using this compound may lead to a greater penetration of magnesium directly into the nervous system compared to other salts. Therefore, it can be of particular relevance for the treatment of neurological conditions associated with cation deficiency.

Currently, our consumers have access to an imported drug that includes the active pharmaceutical ingredient magnesium pidolate, which is a solution for oral use [11]. Therefore, due to the current situation, it is necessary to create domestic drugs with this salt, which will have high quality and bioavailability and will also be distinguished by simplicity in in technology and low production costs.

To solve this problem, we have developed a technology for obtaining a combined oral solution based on magnesium pidolate and magnesium lactate salts. The novelty of the research is in using techniques that simplify the technology of obtaining an oral solution and, at the same time, make it more economical [12]. Using a dosage form as an oral solution ensures high bioavailability of the active pharmaceutical ingredients in the drug. Also, technology is simple for large-scale production. In addition, such liquid dosage forms are characterized by high compliance, which is especially important in pediatric and geriatric practice. Children cannot swallow large tablets and capsules, and they are not able to use medicines with a bitter or unpleasant taste. In addition to children, a number of elderly and sick adults, for example, after complex surgeries, also cannot use solid dosage forms [13].

The aim. Based on theoretical and experimental studies, we aimed to choose correctors of taste and smell for a combined oral solution based on magnesium salts, to experimentally choose and confirm the suitability of the filtering mode, and to justify the choice of single-dose primary packaging in the form of polymer ampoules of 10 ml for the developed drug.

2. Planning (methodology) of the research

The combined oral drug is a complex system that includes more than one active pharmaceutical ingredient. Therefore, when such medicines are created, great attention to a number of factors should be paid, including the compatibility of active ingredients with each other and with auxiliary substances, the ability to influence the effectiveness of each other, stability during storage, safety of the drug and others. Based on this, during development, it is necessary to conduct appropriate studies to confirm their quality at each stage of the development.

The investigated medicinal product under development includes the active pharmaceutical ingredients of magnesium L-lactate, magnesium L-pidolate. To increase the expected stress-protective effect, pyridoxine hydrochloride (vitamin B_6) was added. This vitamin and magnesium have a synergistic effect [14, 15].

From literature data and previously conducted experimental studies, it is known that magnesium salts have a bitter, salty, sour, and alkaline taste [16]. Therefore, a necessary technological aspect in the development of their oral solutions is the masking of unpleasant organoleptic effects of active pharmaceutical ingredients using, for example, a special group of excipients. Bitter taste is corrected with sweeteners in combination with flavoring agent that causes a feeling of bitterness, for example, orange, cherry, apricot. The sour taste is corrected by adding a sweet compound in combination with a flavouring agent, for example, lemon, or blueberry. The sweet taste is corrected by adding vanilla or caramel [17]. Taking into account the above-mentioned data, the next stage of our research was the selection of taste and smell correctors for the drug.

After the selection of active pharmaceutical ingredients and auxiliary substances, a series of oral solutions were prepared. This process was described in detail in our work [12]. The next stage of our research was the selection and confirmation of the suitability of filter materials because there is a probability of unwanted mechanical impurities entering the pharmaceutical product at any technological stage of production. They can be present in starting substances, solvents, air, process equipment, etc.

The next stage of the work was the selection and confirmation of the compliance of the primary packaging for the drug. As primary packaging, we planned single-dose polymer ampoules of 10 *ml* of two types. During the experiments, the physicochemical features of the combination of active pharmaceutical ingredients and auxiliary substances in the selected primary packaging were investigated. This is due to the fact that none of the materials is definitely stable when interacting with different solvents and substances.

3. Materials and methods

Scientific research carried out in the laboratory of parenteral and oral liquid medicines of the National Univer-

sity of Pharmacy, Kharkiv (2016–2019) and pharmaceutical corporation *«YURiA-PHARM»*, Cherkasy, (2020–2021).

The objects of research were a series of combined oral solutions. The active pharmaceutical ingredients of the drug were magnesium L-lactate, magnesium L-pidolate, pyridoxine hydrochloride. In the work, the antioxidant sodium metabisuphite was used. All substances meet the requirements of the State Pharmacopoeia of Ukraine (SPhU) [18] and the European Pharmacopoeia (EP) [19]. Solvent – purified water – meets the requirements of SPhU [20].

In the research, sodium cyclamate, saccharine sodium, and sorbitol were used as sweeteners. Their quality corresponded to the requirements of the EP [19].

The following flavoring agents were studied: «cherry», «peach», «raspberry», «caramel». All of them corresponded to TU U 15.8-23788752-001-2001.

Organoleptic, physicochemical, and pharmaco-technological methods according to the requirements of SPhU [18] and EP [19] were used. All the laboratory and analytical equipment passed metrological certification. The pH of the medium was measured by a potentiometric method, SPhU, 2.2.20 [18]. Quantitative determination of pyridoxine hydrochloride was performed by the liquid chromatography method, SPhU, 2.2.29 [18]. Quantitative determination of magnesium was performed using the complexometric method, according to SPhU, 2.5.11. [18].

Methods according to A.I. Tentsova (numerical indexes) and I.A. Egorov (alphabetic and number indexes) were used to choose a sweetener and its quantity. The corrector was selected based on the findings of a group of 20 volunteers using a questionnaire. The group's determination of taste characteristics was carried out on the basis of a "blind" method. It assumes that people do not know the name of the active pharmaceutical ingredients, the sweetener and their quantity. During the research, the participants gave up smoking and consumed spicy and sweet foods, such as coffee, which could lead to false results in the experiments. The research was conducted as follows. The volunteer rinsed his mouth with purified water [20] and then tasted the sample. The next tasting was carried out with an interval of at least 10–15 minutes. Each participant recorded their feelings in the rating table using a specially designed scale of numbers and letters.

According to the methodology of O. I. Tentsova [21], each of the tasters evaluated the taste according to a five-point system using the terms given in Table 1. The evaluation of sensations was recorded in the table, and a numerical index of taste was derived from the arithmetic mean value of all indicators. In parallel, the second group of twenty people conducted an organoleptic evaluation of the proposed solution with sweeteners with different points of value from the point of view of evaluating the main taste according to the generally accepted classification (Table 1). Based on these data, the numerical index of the main taste was determined. The larger the index, the higher the masking potential of the corrector.

Next, taste characteristics were determined, and taste maps and taste formulas were compiled.

Table 1

Parameters for evaluating the organoleptic characteristics of an oral solution according to the methods of O. I. Tentsova and I. A. Egorov

The methodology of O. I. Tentsova			
1		2	
Taste sensation	Point	A sense of basic taste	Point
Very pleasant	5	Not tart, not bitter	5
Pleasant	4	Slightly tart or bitter	4
Decent	3	A little tart or bitter	3
Bad	2	Tart or bitter	2
Very bad	1	Very tart or bitter	1
Methodology of I.A. Egorov			
1		2	
Taste sensation	Letter	Taste sensation	Index
Sweet	S	Not sweet, not bitter, not salty, not sour	1
Bitter	B	Slightly sweet, slightly bitter, slightly salty, slightly sour	2
Salt	S	Sweet, bitter, salty, sour	3
Sour	SR	Very sweet, very bitter, very salty, very sour	4

The concentration of the studied flavouring agents was from 0.1 to 1.0 %. Corrigent was selected using the organoleptic evaluation of taste from the point of view of objective sensations according to the following system:

a) 1 – very bad;
b) 2 – bad;
c) 3 – not bad;
d) 4 – pleasant;
e) 5 – very pleasant.

To determine the effect of filter materials on the quality indicators of the drug, the following method was used. A sample of the prepared oral solution and the filter material under study were placed in three flasks with polished stoppers. The ratio was 1 cm^2 of filter material to 1 ml of the solution under study. In the first flask with a polished stopper, a control solution of the drug without filter material was placed. All the flasks were left in a dark place at a temperature of 25±2 °C for a day. At the end of the exposure time, the investigated solution was analyzed according to the following parameters according to SPhU methods [18]: transparency, colour, pH of the solution, and quantitative content of active pharmaceutical ingredients. The filter material was considered suitable if the indicators of 3 parallel experiments coincided with the indicators of the control solution.

Single-dose polymer ampoules of two types for the oral solution based on magnesium salts were chosen: from polypropylene «Moplen EP 2S 12 B» brand according to TU U 24.4-05761614.054-2002 and «Purell HP 371P» brand, following EP requirements [19]. To determine the suitability of the primary packaging, the drug was placed in ampoules. The solution was analyzed according to the main quality indicators according to the project of methods of quality control (MQC) after 3, 6, 9, 12, 18, 24, and 27 months of storage according to the SPhU [18] and EP [19].

The statistical processing of experimental data was carried out in accordance with the requirements of the general monograph of SPhU "Statistical analysis of the results of a chemical experiment" using mathematical statistics methods and the application program package "Microsoft Office Excel" licensed "STATISTICA® for Windows" (StatSoft Inc.).

4. Research results

Research on the selection of taste correctors.

Due to the fact that magnesium salts have an unpleasant taste, research was conducted on the selection of correctors for the taste and smell of the oral solution.

Research on the choice of sweetener was carried out in several steps, with the most positive results being chosen by composition. First, 12 series of solutions were obtained with the active pharmaceutical ingredients magnesium L-lactate, magnesium L-pidolate, pyridoxine hydrochloride and selected antioxidant sodium metabisulfite. Different sweeteners in different concentrations were added to the samples. The following were used: sodium cyclamate in the amount of 0.05–0.15 %; sodium saccharinate in the amount of 0.05-0.15 %; a combination of sodium saccharinate and sorbitol in ratios of 0.1 and 5 %, 0.1 and 8.5 %, 0.15 and 10 %; sorbitol in the amount of 20–30 %. Four samples passed the second stage of research, from which one best sample was selected for the third stage. The results of the final studies are presented in Table 2.

According to the final evaluations, the samples of the oral solution with different sweeteners were similar in terms of taste characteristics. However, the latter had the highest numerical value. That is why, for the oral solution, the sweetener saccharine sodium in the amount of 0.15 % was chosen.

In order to give the drug pleasant organoleptic characteristics, flavouring agents were also studied. To select this corrector, we used the developed series of oral solutions with the selected sweetener saccharine sodium in the amount of 0.15 %. The flavouring agent was selected from those available in our laboratory, as well as those distributed on the pharmaceutical market. The following corrigents were used in the work: «cherry», «raspberry», «peach», «caramel» and their concentrations from 0.1 to 1.0 %. As a result of the research, the flavourings «cherry» and «caramel» in concentrations of 0.4 % and 0.2 % were selected.

Research on the selection and confirmation of the suitability of filter materials.

After selecting active pharmaceutical ingredients and auxiliary substances, the next stage was determining the technological parameters for preparing the solution. The proposed technology's advantage is that magnesium lactate is obtained directly in the reactor for preparing the solution, and magnesium pidolate is added as a concentrate. Our work describes detailed research results [12].

Table 2

Final results of studies on the selection of a sweetener for a combined oral solution

Sample composition (g/100 ml)	Taste evaluation methods			
	A. I. Tentsova		I. A. Egorov	
	Taste sensation (point)	A sense of basic taste (point)	Formula of taste	Overall taste
Magnesium lactate – 1.8600 Magnesium pidolate – 9.3600 Pyridoxine hydrochloride – 0.1000 Sodium metabisuphite – 0.1500 Sorbitol – 20.0000 Purified water up to 100 ml	3.8	3.9	B_2S_2	Slightly bitter, slightly sweet
Magnesium lactate – 1.8600 Magnesium pidolate – 9.3600 Pyridoxine hydrochloride – 0.1000 Sodium metabisuphite – 0.1500 Sorbitol – 10,000 Sodium saccharinate – 0.1000 Purified water up to 100 ml	4.6	4.7	B_1S_3	Not bitter, sweet
Magnesium lactate – 1.8600 Magnesium pidolate – 9.3600 Pyridoxine hydrochloride – 0.1000 Sodium metabisuphite – 0.1500 Saccharine sodium – 0.1000 Purified water up to 100 ml	4.4	4.5	S_3	Sweet
Magnesium lactate – 1.8600 Magnesium pidolate – 9.3600 Pyridoxine hydrochloride – 0.1000 Sodium metabisuphite – 0.1500 Saccharine sodium – 0.1500 Purified water up to 100 ml	4.7	4.8	S_3	Sweet

A possible factor of contamination of finished liquid medicines is unwanted mechanical impurities that enter from the air, raw materials and technological equipment. To prevent this, such a technological stage as filtration is used. An important stage of pharmaceutical development is the selection and determination of the suitability of filter materials. In our research, we used membranes with a pore size of 1.0 μm. Membrane filters from the following materials were studied:

1) capron (type «MIFIL»);

2) nylon (type «Ultipor N 66»);

3) polyethersulfone (type «Bevpor»).

The results of studies after 24, 48 and 72 hours after finishing of filtration are presented in Table 3.

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The results of studies determine the suitability of various membrane filters for oral solution

MQC factors	Duration, hours	Filter material		
		Kapron	Nylon	Polyester sulfone
pH (SPhU/EP, 2.2.3) (5.5-6.5)	24	5.93	5.93	5.93
	48	5.94	5.94	5.93
	72	5.94	5.95	5.94
Appearance (visually) (transparent light brown liquid)	24	C	C	C
	48	C	C	C
	72	C	C	C
Mechanical inclusions (filter particles that have come off)	24	N	N	N
	48	N	N	N
	72	N	N	N
Quantitative content:				
Magnesium (SPhU/EP, 2.5.11) (9.5–10.5 mg/ml)	24	10.15± ±0.01	10.16± ±0.01	10.16± ±0.01
	48	10.18± ±0.01	10.17± ±0.01	10.18± ±0.01
	72	10.18± ±0.01	10.19± ±0.01	10.18± ±0.01
Pyridoxine hydrochloride (SPhU/EP, 2.2.29) (0.95–1.05 mg/ml)	24	0.989± ±0.006	0.989± ±0.007	0.988± ±0.006
	48	0.991± ±0.007	0.991± ±0.006	0.991± ±0.006
	72	0.992± ±0.006	0.992± ±0.006	0.993± ±0.006

Note: C – complies with the requirements; N – none; the number of measurements n=5, indicated confidence intervals for P=95 %

The data presented in the table prove the suitability of kapron, nylon, and polyethersulfone filters, a combined oral solution based on magnesium salts. Studies show the drug's quality indicators are unchanged after filtration.

Research on the selection and confirmation of the suitability of the primary packaging.

Single-dose packaging in the form of polymer ampoules of 10 *ml* for the combined oral solution based on magnesium salts was chosen. In the work, polypropylene ampoules of the «Moplen EP 2S 12 B» and «Purell HP 371P» brands were used. To confirm the stability of the drug, the quality control of the solution in accordance with the MQC after 3, 6, 9, 12, 18, 24, 27 months after bottling in ampoules was carried out. To save space in the article, Table 4 shows in detail only the data of the main results of studies of the stability, namely after storage for 6, 12 and 24 months.

During the literature data, the suitability of polymer ampoules of two types was confirmed. The obtained results show the invariance of the main indicators of the quality of the solution during different periods of storage: 3, 6, 9, 12, 18, 24, 27 months.

Table 4

The results of studies on determining the suitability of various types of primary packaging for oral solution

MQC factors	10 ml ampoules	
	«Moplen EP2S12»	«Purell HP 371P»
Colour (visually) (transparent brown liquid)		
Initial data	C	C
6 months	C	C
12 months	C	C
24 months	C	C
pH (SPhU/EP.,2.2.3.) (5.5–6.5)		
Initial data	5.95	5.95
6 months	5.97	5.98
12 months	5.96	5.98
24 months	5.96	5.97
Density (SPhU/EP, 2.2.5.) (1.050–1.070)		
Initial data	1.061	1.060
6 months	1.060	1.060
12 months	1.061	1.060
24 months	1.061	1.061
Quantitative composition:		
Pyridoxine hydrochloride (SPhU/EP, 2.2.29) (0.90–1.10 mg/ml)		
Initial data	0.979±0.006	0.980±0.006
6 months	0.978±0.007	0.980±0.006
12 months	0.979±0.006	0.979±0.007
24 months	0.978±0.006	0.978±0.006
Magnesium (SPhU / EP, 2.5.11.) (9.00–11.00 mg/ml)		
Initial data	10.37±0.01	10.30±0.01
6 months	10.36±0.01	10.30±0.01
12 months	10.36±0.01	10.29±0.01
24 months	10.36±0.01	10.29±0.01

Note: C – complies the requirements; the number of measurements n=5, indicated confidence intervals for P=95 %

5. Discussion of research results

According to the literature, magnesium salts are conditionally divided into compounds of the first and second generation [22]. The salts of the first generation include inorganic derivatives, for example, oxide, chloride, sulfate. The second-generation salts include structurally more complex organic derivatives of the element, for example, latcate, pidolate, asparaginate, glutamate. Studies carried out by a number of authors in different years showed an advantage in the bioavailability of second-generation salts [23, 24]. Despite this fact, advertised inorganic derivatives occupy a larger share of the domestic pharmaceutical market [11, 25]. Because of this it makes difficult for the consumer to make the best choice.

The goal of our work was to create a domestic drug with high efficiency, bioavailability and quality. At the

same time, this will be distinguished by the simplicity of the technological implementation and the relatively low cost of the input substances. We have created a domestic drug based on magnesium salts of the second generation: lactate and pidolate. The composition of the solution includes magnesium salts in the form of L-isomers. It is known that such isomers have a greater affinity for the human body and, therefore, exhibit higher pharmacological activity than D-derivatives. That was shown in the work [26]. Also, the authors, for example [27], established a high ability of L-pyroglutamic acid to penetrate through the blood-brain barrier. This is evidence that its magnesium salts will also penetrate there well and, as a result, determine the high therapeutic effect of the drug.

Among the reasons that lead to low compliance of patients to treatment, the taste and smell of the drug plays a key role along with the factors of frequency of administration, amount of the drug, duration and cost of therapy [28]. There are a number of ways to mask the unpleasant taste and smell of the drugs. The masking of the bitter taste behind additional flavouring agents can be seen in a number of works. For example, authors by [29] using hydroxypropyl-β-cyclodextrin and sodium saccharin to mask the bitter taste of dental lidocaine HCl. The taste evaluation study indicated that the mentioned compounds (1:1 and 1:2 ratios) significantly improved the bitter taste drug. There are other more sophisticated methods to mask bitter taste using researchers, such as encapsulation, coating, inclusion complexes, extrusion method, ion exchange resins and so on. Cherian, S. and other using encapsulation to mask bitter tasting compounds in order to delay their release. Suppression of bitter taste was accomplished by encapsulating a bitter taste stimulus in erodible stearic acid microspheres, and embedding these 5 μmeter diameter microspheres in pullulan films that contain sucralose and peppermint oil as masking agents [30].

We have chosen an effective, easy-to-implement, and economical method for the manufacturer, which includes adding a sweetener and flavouring agents. The saccharine sodium belongs to the group of synthetic intensive sweeteners and is almost 300 times sweeter than sucrose. It has a long shelf life, is thermally stable, decomposes at low pH values. The main positive factor of using saccharine sodium is the possibility of recommending a medicinal product with it to patients suffering from diabetes. This corrector does not cause damage to tooth enamel, does not contribute to weight gain. Flavoring agents «cherry» and «caramel» to mask the unpleasant smell based on the feedback of a group of volunteers were also selected. Choosing the optimal correctors for the oral solution will increase patient compliance with treatment, which is especially important in pediatric and geriatric practice.

The next stage of research was confirmation of the suitability of filter materials. Such studies are an integral part of ensuring the quality of the finished drug. In works, Mesut, B. Pillai, S. and etc. describe in detail the importance of the correct selection and confirmation of the compatibility of filter materials with active pharmaceutical ingredients and auxiliary substances in the development of drugs [31, 32]. It was described, that the correct use of filters and execution of the process itself ensures that the drug will not contain extraneous impurities. Also, selected concentrations of active pharmaceutical ingredients and auxiliary substances will be preserved, which will ensure the safety of the product. All these factors are checked and confirmed by relevant studies in the development process. In our work, we proved the suitability of filters made of capron, nylon and polyethersulfone, which are widely available in the pharmaceutical market of Ukraine.

The suitability of the primary packaging is a critically important aspect in each individual case, as none of the materials is universal and persistent to all substances and solvents. Bedogni, G. and others conducted long-term stability studies of an optimized solution of praziquantel. Stability studies were conducted at different temperatures (4, 25, and 40 °*C*) for 12 months. There were assessed the effects of pH, storage temperature and light on stability. The authors note the importance of an integrated approach to assessing stability in accordance with the requirements of the relevant documentation [33].

At the final stage of our research, the suitability of single-dose ampoules of 10 *ml* made of polypropylene of two brands was proved. Control studies of samples of the drug after 3, 6, 9, 12, 18, 24, 27 storage according to the project of MQC was conducted.

Using single-dose ampoules of 10 *ml* as the primary packaging for the oral solution allows the addition of a preservative to be excluded, which reduces the cost of raw materials. Besides, the proposed single-dose ampoules increase the convenience of taking the drug since, in some cases, it is not convenient to dose liquid medicine, for example, for a small child or an elderly person. Also, if the liquid medicine has a thick consistency, in many cases, a certain amount of the drug remains on the measuring utensil (spoon, measuring cup). This may lead to a violation of the dosage regimen. The single-dose ampoules made of polymer materials that we offer are safer compared to glass ampoules, which are used by foreign manufacturers. Unahalekhaka, A. conducted a study on the detection of glass microparticles among open glass ampoules. Glass particles were examined using a stereomicroscope. Glass particulates were detected in 65 % of the ampoules [34]. Using single-dose polymer ampoules solves this problem.

Practical relevance. Filtration is an important technological stage in the production of liquid medicines. It ensures the purity of the drug and helps to get rid of various unwanted mechanical impurities. Conducted research on the selection and confirmation of the suitability of filter materials will allow pharmaceutical companies to choose the appropriate type of filter material that is available for large-scale production.

Research on the choice of primary packaging is of great importance for the release of quality drugs by pharmaceutical manufacturers. Primary packaging of drugs has always been and remains relevant at various stages of pharmaceutical production. Only those materials that are approved for use in the pharmaceutical industry, accord-

ing to the requirements of SPhU, should be used. Studies of the stability of the drug in the selected primary packaging have been conducted, taking into account regulatory requirements. This is confirmed by the preservation of the quality of the drug after its storage.

Research limitations. The study of the stability of the developed oral preparation was carried out only in single-dose polymer ampoules. The work also planned to conduct research on the stability of the oral solution in polymer multi-dose vials of 100 ml.

Prospects for further research. Research on the selection of the qualitative and quantitative composition of magnesium-containing liquid medicinal products continues. Methods of improving the technology for obtaining drugs are being studied. Research to study and compare the pharmacological properties of the obtained drugs is planned.

6. Conclusions

1. Based on theoretical and experimental studies, the qualitative and quantitative composition for the combined oral solution based of magnesium salts was selected. The active pharmaceutical ingredients of the drug are bioavailable magnesium salts in the form of L-isomers, as well as vitamin B_6.

2. The conducted research made it possible to choose taste and smell correctors for the drug. Saccharine sodium in the amount of 0.15 % was chosen as a sweetener. A combination of «cherry» and «caramel» was chosen as the flavouring agents in the amounts of 0.4 % and 0.2 %, respectively.

3. The selection of filter materials for the drug was experimentally investigated and substantiated. The suitability of filters of three types, namely kapron, nylon, and polyethersulfone has been proven.

4. Conducted research on the suitability of the primary packaging of two brands of polypropylene. The obtained data made it possible to recommend ampoules of «Moplen EP 2S 12 B» and «Purell HP 371P» brands.

5. The composition and technology of obtaining an oral medicinal product in a single-dose polymer package of 10 ml have been developed. The technology is easy to implement and has relatively low cost. This will allow domestic manufacturers to create a highly effective, competitive medicine.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this paper, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

Funding

The study was performed without financial support.

Data availability

Data will be made available at a reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence.

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Received date 12.12.2023
Accepted date 15.04.2024
Published date 30.04.2024

Daria Snehyrova, Doctor of Philosophy in Pharmaceutical Sciences, Assistant, Department of Commodity science, Safety and Quality Management, State University of Trade and Economics, Kyoto str., 19, Kyiv, Ukraine, 02156

Lyudmila Almakaieva, Doctor of Pharmaceutical Sciences, Professor, Department of Pharmaceutical Disciplines, Uzhhorod National University, Narodna sq., 1, Uzhhorod, Ukraine, 88000

***Corresponding author:** Daria Snehyrova, e-mail: dsnegireva2017@gmail.com*