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Development of the oral solution «Maglycimet» composition based on the magnesium salts with glycine and methylcobalamin

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Abstract

Magnesium deficiency is a fairly common and underestimated problem of modern society. A lack of this element is not resulted in clinical symptoms and, therefore, is not easily recognized. Despite this fact, an insufficient amount of magnesium in the body is the cause and starting mechanism of many diseases. The aim of the presented research is to develop the composition of the domestic drug – an oral solution based on magnesium salts with high bioavailability, effectiveness and quality named «Maglycimet». In order to achieve the goal, physical, physico-chemical, pharmaco-technological, microbiological methods, corresponding to the world pharmacopoeias, were used. As a result of research the oral solution composition based on theoretical and experimental data was developed. Its active pharmaceutical ingredients are represented by magnesium aspartate and magnesium glutamate, together with the amino acid glycine and vitamin B_{12} – methylcobalamin. The developed composition will serve as the basis for a new effective medicine with stress-protective activity.

Keywords: magnesium deficiency, magnesium salts, oral solution, stress-protective activity

INTRODUCTION

Magnesium is one of the most important nutrients of the human body. It is a co-factor and takes part in more than 300 biochemical reactions. Magnesium deficiency leads to a wide range of health problems and serious disorders of all organs and systems [1-3]. This problem is a topical issue of science and can be mastered by taking magnesium-containing drugs.

Magnesium-containing medicines include two types of magnesium salts: formed by magnesium and an inorganic or organic compound. The inorganic salts are represented by: chloride, sulfate, salicylate etc; the organic salts are acetate, citrate, glutamate, gluconate, orotate etc. [4].

Organic derivatives of magnesium and amino acids from a chemical point of view are special compounds, which are called chelate complexes. The term ‘chelate’ was introduced in 1920 by M. Drew. It comes from the Greek word ‘chelle’, which means ‘claw’. The English term ‘chelator’ also has the same origin. Chelators are organic compounds that can interact with ions of metals and capture them into ‘claws’ by two different chemical functional groups. In this case, between the ‘chelator’ and the metal two types of bonds are formed – covalent and coordination [5-6]. In chelate complexes the activity of elements often increases thousands of times compared to the activity of the metal in the ionic state. Chelate complexes have low toxicity, they are mostly well soluble in water, are not destroyed by microorganisms, stay stable in a wide range of pH values, and also they increase the bioavailability of metal captured inside [7].

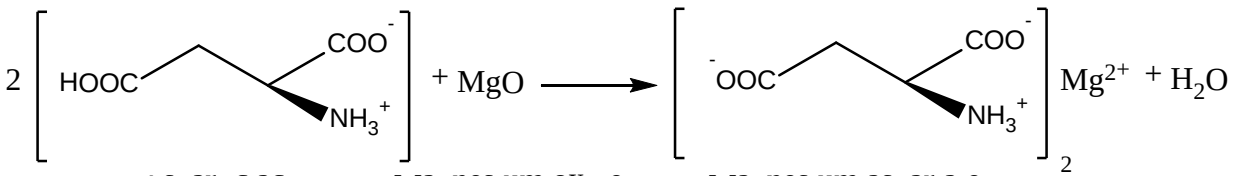
The developed medicine contains two active pharmaceutical ingredients (API) – magnesium aspartate and magnesium glutamate as chelated complexes of magnesium and amino acids.

The aim of this work is to develop the composition of the domestic drug – an oral solution based on magnesium salts, glycine and methylcobalamin with high bioavailability, effectiveness and quality.

MATERIALS AND METHODS

The objects of the research were the obtained series of the medicine with different content of auxiliary substances. The composition includes the following API: magnesium aspartate, obtained from L-aspartic acid and magnesium oxide; magnesium glutamate derived from L-glutamic acid and magnesium oxide; glycine. All substances meet the requirements of the State Pharmacopoeia of Ukraine (SPhU) [8] and the European Pharmacopoeia (EP) [9]; as well as methylcobalamin met the requirements of the Japanese Pharmacopoeia [10]. As auxiliary substances antioxidants, sweeteners, and preservatives that are generally accepted in the technology of oral solutions preparing were used. Their quality meets the requirements of the EP [9]. Food flavoring agents ‘cherry’, ‘raspberry’, ‘peach’ were used to improve the taste of the oral solution, according to the requirements of TU U 15.8-23788752-001-2001. Purified water was utilized as a solvent (according to the requirements of SPhU [11], it was obtained in the Scientific and Research Laboratory of Parenteral and Oral Liquid Medicines of the National University of Pharmacy). Experimental series of the «Maglycimet» oral solution were obtained in the Scientific and Research Laboratory of Parenteral and Oral Liquid Medicines of the National University of Pharmacy.

Pharmacopoeian physical, physico-chemical, pharmaco-technological, microbiological methods were used in the course of investigation [8-9]. The processing of experimental data was performed using the methods of mathematical statistics.



Aspartic acid M·m· 133·10 | Magnesium oxide M·m· 40·31 | Magnesium aspartate M·m· 288·51

Figure 1. – The formation of magnesium aspartate

Table1: The composition of oral solution «Maglycimet»

Compound	Quantity, g/100 ml	Role
Magnesium L-aspartate	8.3132	Active substance
Magnesium L-glutamate	3.9322	Active substance
Glycine	1.0	Active substance
Methylcobalamin	0.00025	Active substance
Sodium metabisulphite	0.15	Antioxidant
Saccharin sodium	0.10	Sweetener
Potassium sorbate	0.15	Preservative
Cherry flavoring	0.60	Flavoring
Purified water	Up to 100 ml	Solvent

RESULTS AND DISCUSSION

The developed medicine is a combined solution for oral application with stress-protective activity. As APIs it contains magnesium aspartate, magnesium glutamate, glycine and methylcobalamin. The key task during the research was to choose the most effective main active ingredients, which together with auxiliary substances will provide an opportunity to obtain a domestic drug with high efficiency, safety and quality. In order to achieve this goal scientific literature has been studied and analyzed. The most bioavailable and effective magnesium salts of amino acids were selected based on the explored pharmacological studies for competitive and high-quality domestic drug obtaining [9-10]. The determination of the magnesium cation quantitative composition was made comparing to the imported drug «Magne-B_6», a solution for internal use in 10 ml ampoules, which contains magnesium (Mg^{2+}) 100 mg per dose (10 ml). Also in the composition development the maximum daily dose of the element recommended by world organizations was taken into account [14].

In order to increase the stress-protective effect of the future medicine and according to the literature data two more active ingredients – the amino acid glycine and vitamin B_{12} in the form of methylcobalamin – were selected.

Magnesium aspartate and magnesium glutamate are chelate complexes of magnesium and proteinogenic amino acids. The formation of chelate complexes with ions of metals is a common property of amino acids. Such compounds provide high bioavailability of magnesium. The mechanism of this process is associated with the fact that metals in chelate complexes have a lower reactivity compared to free ions, which reduces the possibility of unabsorbable or poorly digestible compounds formation and provides more active engagement of magnesium in the human body cycles.

Glycine belongs to proteinogenic amino acids, therefore, is one of the most important amino acids for the human body [15]. This amino acid readily penetrates inside body tissues (including brain tissue) and is well metabolized. It acts as a neurotransmitter in the brain and spinal cord, participates in reflex coordination, sensory signal processing and pain, normalizes and activates the inhibition processes in the central nervous system, improves the metabolic processes in tissues, has an antioxidant, anti-toxic effect, reduces psycho-emotional stress, improves mood, etc.

Vitamin B_{12} (cobalamin) is the most chemically complicated among all vitamins. Cyanocobalamin is the most commonly used one in the cobalamin group. However, scientific studies have shown that cyanocobalamin, as a form of cobalamin, has a number of disadvantages (toxicity, ability to accumulate in cells, difficulty in use due to the several stages of transformation into the active form) [16-18]. Another option is B_{12} derivative – methylcobalamin – which is the bioavailable and metabolically active coenzyme form of this vitamin. It can be used directly by the human body and does not need to be converted, unlike the other form, cyanocobalamin, which first needs to be converted to methylcobalamin in three separate steps. Since this transformation is also partially dependent on other vitamins and coenzymes presence, it leads to a loss of body resources, which is an obvious disadvantage. [19-20]. Therefore, we have chosen methylcobalamin as an API in the developed medicine due to its valuable properties, and because it has the ability to regenerate and protect nervous tissue.

One of the main points in the oral solution «Maglycimet» preparation is that magnesium aspartate and magnesium glutamate are obtained directly in the reactor from magnesium oxide and aspartic acid and magnesium oxide and glutamic acid, respectively. This feature helps to avoid several technological steps (crystallization,

separation from solution, filtration, drying, packaging) and significantly reduce production costs.

As a result of the research the qualitative composition and amounts of the corresponding substances in order to obtain salts (magnesium aspartate and magnesium glutamate) were determined. The calculations were made according to the expected salt formation reactions taking into account the stoichiometric coefficients (Figure 1).

As can be seen in Figure 1, magnesium oxide reacts with aspartic acid in a ratio 1:2. It was considered in the calculations of the initial quantities of substances for the magnesium aspartate formation. The reaction of the magnesium glutamate formation proceeds similarly.

One of the potential factors of instability of magnesium salts of aspartic and glutamic acids in the aquatic environment is exposure to atmospheric oxygen. Due to the presence of highly reactive groups in the amino acids structure and the possibility of their participation in redox processes [15.21], we have provided studies on the choice of antioxidants. The mechanism of the stabilizing action of antioxidants involves the ability of the latter to oxidize faster than API. The stabilizer, quickly reacting with oxygen, prevents the oxidation of the active substance [22].

To prevent the oxidation of magnesium salts in solution we chose a salt of sulfurous acid – sodium metabisulphite. The use of a salt of a sulfurous acid is based on the fact that its redox potential is lower than in oxidizing substances that are presented in the system. It also belongs to direct antioxidants. Moreover, sodium metabisulphite as an antioxidant is widely used in various dosage forms both in Ukraine and abroad in a concentration of 0.05-0.15% [23].

The optimal concentrations of sodium metabisulphite in the combined oral solution «Maglycimet» was found put after studying of 5 prepared model mixtures. Based on the experimental data, we selected the optimal concentration of sodium metabisulphite in an amount of 0.15%.

The developed medicine – the oral solution «Maglycimet» – possesses a bitter, specific flavor that is inherent for the salts of amino acids, therefore, an important role in the composition elaboration was given to its taste.

Corrective substances are used in pharmaceutical technology to give the solution pleasant organoleptic characteristics. These include auxiliary substances that correct taste, color and smell of medicines. We turn our attention to the correctives of the taste and smell, since these properties play a significant role for oral solutions.

For the selection of correctives and their optimal quantities were used the A.I.Tentsova method (determination of numerical indices) and the method of taste evaluation using alphabetic and numerical indices (the method of I.A. Egorov) [22] were used.

Sorbitol, sodium cyclamate, saccharin sodium are the most commonly used sweeteners in order to correct the taste of oral dosage forms. That is why they were used for further research in the composition development. In current pharmaceutical practice the most common sweetener is sorbitol, which belongs to traditional sweeteners. But due to its low potential of sweetness, sorbitol is added to the dosage forms in large quantities, which causes certain difficulties in industrial production. Therefore, for our investigation we also used intensive sweeteners: saccharin sodium and sodium cyclamate. The selection of concentrations was based on the determination of the correction potential of the basic taste and taste in relation to the taste of the solution taken as a standard.

Samples for research were prepared (9 series of oral solution), and various sweeteners were added, namely: saccharin sodium in an amount of 0.05%, 0.1%, 0.15%; a combination of saccharin sodium and sorbitol in a quantitative ratio of 0.1% and 5%, 0.1% and 8.5%, 0.15% and 10%; sodium cyclamate in the amount of 0.05%, 0.1%, 0.15%.

Thus, based on the findings of a volunteers group, it was proved that the best sweetener for an oral combined solution is saccharin sodium in an amount of 0.1%. This choice in the dosage form also allows us to expand the possibilities of its use in the treatment of patients with diabetes.

It is necessary to add food flavorings such as ‘raspberry’, ‘peach’, ‘cherry’, ‘orange’, ‘strawberry’ etc. to mask the specific smell inherent for amino acids. The selection of a specific flavoring and its concentration was established experimentally. As a result of research, based on the findings of a group of 20 volunteers, the sample of the oral solution with the addition of cherry flavoring in the amount of 0.6% had shown the best taste.

Selection of preservative is necessary to ensure microbiological stability of the medicine. The effectiveness of antimicrobial preservatives is one of the important points in ensuring the quality and safety of a multi-dose oral solution.

The study of the antimicrobial preservative action effectiveness was carried out in accordance with the requirements of the general SPhU article [24]. We have developed four series of oral combined solution with various preservatives in order to select the most effective one.

The effectiveness of preservatives was studied on samples of oral solutions containing as antimicrobial preservatives: 0.1% sorbic acid, 0.1% potassium sorbate, 0.1% sodium benzoate, 0.15% potassium sorbate.

Studies have shown that the effectiveness of the antimicrobial conserving action of sorbic acid at a concentration of 0.1% in an oral solution meets the requirements of the pharmacopoeial article by criterion A [24]. Moreover, it is more pronounced against yeast and mold strains of fungi. The antimicrobial preservative effect of 0.1% potassium sorbate and sodium benzoate against the fungal test strains was at the same level.

The effectiveness of the preservative effect of 0.15% potassium sorbate significantly exceeds the requirements of criterion A [24], and also provides a more intensive death of test strains of bacteria and fungi in oral solution than potassium sorbate and sodium benzoate at a concentration of 0.1%.

Thus, potassium sorbate in an amount of 0.15% was chosen as the most acceptable preservative for our oral solution.

The results of the studies allowed us to choose the optimal composition of the developed oral solution, which is shown in Table 1.

CONCLUSIONS

The conducted research allowed us to determine the qualitative and quantitative composition of the oral solution based on magnesium salts named «Maglycimet». The active pharmaceutical ingredients of the drug are magnesium aspartate, magnesium glutamate, glycine and methylcobalamin. The literature data was studied and analyzed, which allowed us to substantiate theoretically the composition and the ratio of the main active substances. In the course of research data on the physicochemical properties of all the proposed components, their stability and compatibility were worked out. Based on theoretical and experimental studies, auxiliary substances were selected to maintain the stability of the solution during storage. Correctives were chosen to give pleasant organoleptic characteristics to the medicine. As antioxidant in order to prevent the oxidation of magnesium salts sodium metabisulphite (0.15%) was experimentally selected. The correctives of taste and smell were determined, namely: saccharin sodium as sweetener, in an amount of 0.1% and the cherry flavoring agent, in an amount of 0.6%. To ensure microbial stability, a preservative — potassium sorbate — was chosen, in an optimal amount of 0.15%. Due to the development and implementation of the new domestic oral solution «Maglycimet», the Ukrainian market will be replenished with a high-quality, effective, stable medicine drug with stress-protective activity.

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