ТЕХНОЛОГІЯ ЛІКАРСЬКИХ ПРЕПАРАТІВ

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SOME ASPECTS OF DEVELOPING THE PRODUCTION TECHNOLOGY FOR COMBINED TABLETS BASED ON B VITAMINS

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Key words: technology; B vitamins; flowability; slope angle; tapped density; compressibility; benfotiamine; pyridoxine hydrochloride

The studies in selecting the optimal technology for obtaining a combined dosage form – tablets based on B vitamins, namely selection of the rational tableting method and the method of introduction of the active substances and excipients into the tableting blend, as well as the optimal drying mode for the pyridoxine hydrochloride granulate, have been performed. For this purpose the properties of active pharmaceutical ingredients, which precondition the technological characteristics of individual powders affecting the functional characteristics of the drug, have been studied. The studies of the technological properties of the active substances of the combined tablets such as flowability, slope angle, tapped density, and compressibility have been conducted. The benfotiamine substance has a good flowability, which indicates the possibility of applying the method of the direct compression. The pyridoxine hydrochloride powder has a poor flowability as indicated by the results of studies of flowability, slope angle, compressibility and density. Such different structure of powders of the active ingredients indicates additional difficulties in choosing the optimal technology of introduction of the active ingredients into the formulation. Three batches of the tableting blend with different methods of introduction of the active ingredients and excipients have been tested. It has been determined that when wetting the tableting blend containing benfotiamine and pyridoxine hydrochloride the increase of the quantitative content of thiamine o-monophosphate impurity is observed. Therefore, removal of benfotiamine from the mixture at the lubrication stage or the use of the technology of obtaining two individual granulates with the active substances eliminated the issue of formation and increase of thiamine o-monophosphate impurity. The optimal mode of drying of the pyridoxine hydrochloride granulate has been chosen; it is 55-65°C for 60-70 min, and it allows to obtain the pyridoxine hydrochloride granulate with the optimal moisture content (not more than 5.0%).

Vitamins of B group: B_1, B_6 and B_{12} are crucial for functioning of the nervous system; their sufficient concentrations in the body are required for maintenance of its normal function. It has been found that in various diseases of the nervous system the exogenous intake of these vitamins has a pronounced pharmacological effect favouring the regeneration of the nervous tissue, improvement of its blood supply and optimizing its intracellular metabolism [2, 6, 7, 9, 11].

Combined drugs containing B vitamins (especially B_1, B_6 and B_{12}) have long been used in the treatment of various disorders of the nervous system, including neuropathies of the various origin. The clinical experience accumulated shows the effectiveness of aqueous solutions of B vitamins (thiamine, pyridoxine and cobalamin) in the formulation of injections, but the bioavailability of traditional medicines of thiamine in oral administration remains low [2, 6, 7].

The known drug Milgamma® (Wörwag Pharma, Germany) is film-coated tablets containing two active ingredients – benfotiamine and pyridoxine. Benfotiamine is a fat-soluble derivative of thiamine. When taken orally benfotiamine (unlike water-soluble form of vitamin B_1) has almost 100% bioavailability due to the ability of the substance to penetrate passively the lipophilic cell membrane. Due to its specific properties benfotiamine is retained in the tissues (especially in the nervous tissue) for a longer period providing the prolonged therapeutic effect. Pyridoxine is also involved in the protein metabolism and partly in the fat metabolism. Both vitamins potentiate the action of each other [1, 8, 9, 10, 12, 13].

In terms of the abovementioned facts the issue of developing of a combined domestic drug in the form of tablets based on a fat-soluble benfotiamine and pyridoxine hydrochloride for treatment of diseases of the nervous system of various the origin is of vital importance.

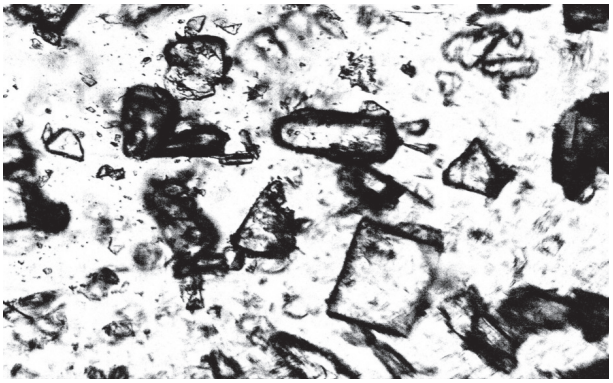

Fig. 1. The shape of benfotiamine particles.

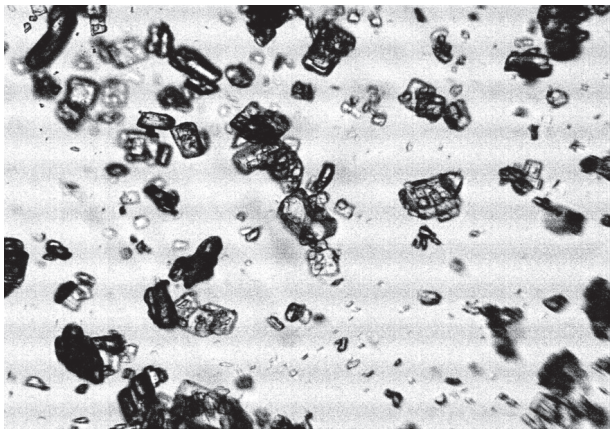

Fig. 2. The shape of pyridoxine hydrochloride particles.

Materials and Methods

In the study the benfotiamine substance manufactured by Yonezawa Hamari Chemicals Ltd., Japan and pyridoxine hydrochloride manufactured by DSM Nutritional Products GmbH, Germany were used.

Physicochemical and technological properties of active ingredients such as morphological properties, particle size distribution, flowability, slope angle, tapped density, and compressibility were studied. The study of the size and shape of the crystals for all active ingredients was performed by the microscopy method according to the State Pharmacopeia of Ukraine (SPhU) with a Motic microscope by "Fisher Bioblock Scientific" company. In order to estimate the particle size distribution the screen analysis was used according to the requirements of the SPhU using a Retsch AS 200 screen analysis instrument by "Fisher Bioblock Scientific". Determination of flowability and the natural slope angle of powder was performed using an ERWEKA instrument type GT/GTB with a vibrating funnel in accordance with methods described in the SPhU [3]. Qualitative and quantitative testing of the drug samples was conducted in the course of the study. The moisture content, impurities, and the quantitative content of the active ingredients were studied as indicators characterizing the quality of the product [3].

Results and Discussion

At the first stage of the experimental studies taking into account the large number of suppliers of drug substances, which in some cases differ by their crystallographic, physicochemical and technological parameters, first of all, it would be appropriate to study these properties and use them to substantiate the composition and development of the technology for tablet production.

The technological parameters of powders are mainly preconditioned by their dispersion and shape of crystals, therefore, the size and shape of the crystals of benfotiamine and pyridoxine hydrochloride were assessed [3, 5]. Based on the results of crystallographic studies (Fig. 1, 2) it has been found that the substance of benfotiamine under study is a coarse crystalline powder with a volumetric structure. Pyridoxine hydrochloride is a powder with the crystalline structure and its particles are transparent plates.

The study of the particle size distribution of the active substances has shown that the benfotiamine substance consists of large crystals (90-355 μm), and it is about 90% of the total number indicating a good flowability of the powder. The pyridoxine hydrochloride powder, on the contrary, is composed mainly of the microcrystalline fraction (10-40 μm). Such particle size distribution of pyridoxine hydrochloride confirms a low flowability of the powder and may complicate the tableting process. The technological properties of the drug substances determine the rational tableting technology. Of all the technological parameters such parameters as flowability, tapped density, and compressibility of the substance are the most likely to affect the process of formulation [3, 4, 5]. The study of these technological parameters was performed using the methods given in the SPhU [3]. The results of the study of the technological properties of the drug substances of the active ingredients of the combined dosage form of tablets are shown in Table 1.

Analysing the results obtained we can conclude that the benfotiamine substance has a good flowability; it indicates the possibility of using the direct compression method for tableting. The pyridoxine powder has a poor flowability as evidenced by the results of the flowability test, natural slope angle, tapped density and

Table 1

The results of the study of technological properties of benfotiamine and pyridoxine hydrochloride substances

Parameters, unit of Measurement	Acceptance criterion	Name of the active pharmaceutical ingredient (API)	
		Benfotiamine	Pyridoxine hydrochloride
Flowability, g/sec	3.0-10.0	9.44	0.96
Slope angle, deg.	25-35	35.9	45.4
Tapped density, g/ml	0.5-0.6	0.698	0.586
Compressibility, g/ml	0.55-0.65	0.54	0.31

Table 2

Quality parameters of the tableting blend with different methods of introduction of the active substances and excipients into the tableting blend

Name of the parameter, unit of measurement	Acceptance criterion	The results obtained		
		Batch 1	Batch 2	Batch 3
Flowability, g/sec	3.0-10.0	10.0	10.0	10.0
Tapped density, g/ml	0.5-0.6	0.575	0.605	0.605
Compressibility, g/ml	0.55-0.65	0.52	0.55	0.55
Moisture content, %	4.0-5.0	4.3	4.1	4.0
Related substances:				
Benfotiamine:				
Thiamine hydrochloride,%	NMT 0.5	0.2	0.2	0.2
Thiamine o-monophosphate, %	NMT 0.5	0.7	0.3	0.3
Benzoic acid, %	NMT 0.5	0.1	0.1	0.1
Unspecified impurity, %	NMT 1.0	0.7	0.4	0.5
Total unspecified impurities, %	NMT 1.0	0.7	0.4	0.5
Sum of impurities, %	NMT 2.5	1.17	1.04	1.50
Pyridoxine hydrochloride:				
Pyridoxal hydrochloride, %	NMT 0.5	0.2	0.3	0.2
Unspecified impurity, %	NMT 1.0	0.3	0.2	0.4
Total unspecified impurities, %	NMT 1.0	0.3	0.4	0.4
Sum of impurities, %	NMT 1.5	0.8	0.9	1.0
Assay, mg/tab.:				
Benfotiamine	95.0-105.0	99.0	101.0	100.0
Pyridoxine hydrochloride	95.0-105.0	99.7	102.0	101.0

compressibility. Such different structure of powders of the active ingredients indicates additional difficulties in choosing the optimal technology for introduction of the active ingredients into the formulation. In addition, when choosing the technology it should be considered that the dosage form selected is film-coated tablets, and such factors as flowability and compressibility of the tableting blend are the critical parameters in production of high-quality tablet cores. The physicochemical and technological characteristics of the active substances obtained indicate that both the granulation method (pyridoxine hydrochloride) and the direct compression method (benfotiamine) should be employed in order to produce tablets of the appropriate quality.

At the stage of development of the drug production technology the selection of the mode of introduction of the active substances and excipients into the tableting blend was performed. Model mixtures of the tableting blend with different methods of introduction of the active substances and excipients into the tableting blend were prepared and tested: **Method 1** (Batch 1) – introduction of the ingredients into the tableting blend prior to wetting; **Method 2** (Batch 2) – introduction of pyridoxine hydrochloride into the tableting blend prior to wetting, introduction of benfotiamine at the stage of lubrication of the tableting blend; **Method 3** (Batch 3) – benfotiamine and pyridoxine hydrochloride were granulated separately and then mixed. The results of the study are presented in Table 2.

The method of introduction of the basic active ingredients into the tableting blend did not have a negative effect on the technological characteristics and the quantitative content of the active substances, but when wetting the tableting blend containing benfotiamine and pyridoxine hydrochloride **(Batch 1)** the increase in the quantitative content of thiamine o-monophosphate impurity was observed. This negative factor indicates that the interaction of benfotiamine with aqueous solution of K 29/32 povidone in the presence of pyridoxine hydrochloride is accompanied with the partial transformation of benfotiamine into thiamine, and it promotes the increase of thiamine o-monophosphate impurity. Therefore, removal of benfotiamine from the mixture at the lubrication stage or the use of the technology of obtaining two individual granulates with the active substances eliminated the issue of formation and increase of thiamine o-monophosphate impurity. Considering that the method of benfotiamine introduction is more efficient during lubrication stage (significantly reduces the manufacturing process and is more cost-effective), it was decided to focus on the latter method of the substance introduction.

The studies on choosing the optimal drying temperature of pyridoxine hydrochloride granules obtained by wet granulation were also conducted. When selecting the optimal drying mode for the granulate the following factors were considered: the drying method should ensure the achievement of a certain level of moisture in the tableting blend without destruction of components and changes in physicochemical properties of the active ingredients. The optimal drying temperature for granules was determined by physicochemical parameters (mois-

Table 3

Selection of the drying mode for the pyridoxine hydrochloride granulate

Batch number and the drying mode	Quality indicators for pyridoxine hydrochloride granulate				
	Mositure content, % (4.0-5.0)	Related substances**		Assay, mg/tab.	
		benfotiamine	pyridoxine hydrochloride	Benfotiamine, mg/tab (95.0-105.0)	Pyridoxine hydrochloride, mg/tab. (95.0-105.0)
Batch 3 (30-40°C – 60-70 min)	7.0	complies	complies	101.0	100.0
Batch 4 (55-65°C – 60-70 min)	4.0	complies	complies	99.8	99.9
Batch 5 (70-80°C – 60- 70 min)	4.0	does not comply	does not comply	99.8	99.9

** **Related substances: benfotiamine**: thiamine hydrochloride – not more than 0.5; thiamine o-monophosphate – not more than 0.5%; benzoic acid – not more than 0.5%; unspecified impurity – not more than 1%; the sum of unspecified impurities – not more than 1%; the sum of all impurities – not more than 2.5%; **pyridoxine hydrochloride:** pyridoxal hydrochloride – not more than 0.5%; unspecified impurity – not more than 1%; the sum of unspecified impurities – not more than 1%; the sum of all impurities – not more than 1.5%.

ture in the tablet mass, impurities, potency, flowability). Data on selection of the drying mode for the pyridoxine hydrochloride granule are presented in Table 3.

Based on the results of the tests performed the optimal drying mode was chosen for the granulate. Application of the granulate drying mode in the range of (55-65)ºC for 60-70 min (Batch 4) allows to obtain the pyridoxine hydrochloride granulate with the optimal moisture content of not more than 5.0%. Drying of the granulate at lower temperatures (30-40)ºC (Batch 3) results in the high moisture content in the granulate. Drying of the granulate at higher temperatures of (70-80)ºC (Batch 5) leads to destructive changes in the active substances and appearance of impurities.

CONCLUSIONS

1. At the stage of the pharmaceutical development the comprehensive study on choosing the optimal production technology for combined tablets based on B vitamins has been conducted.

2. The physicochemical and pharmacotechnological properties of the active substances of benfotiamine and pyridoxine hydrochloride have been studied; it allows to choose the best method of the tablet formulation: the granulation method – for pyridoxine hydrochloride and the direct compression method – for benfotiamine.

3. Based on the results of the experimental studies the rational method of introduction of the active ingredients into a tableting blend has been proposed: for pyridoxine hydrochloride – prior to wetting, for benfotiamine – at the stage of the tableting blend lubrication.

4. Selection of the optimal temperature for drying of pyridoxine hydrochloride granules obtained by wet granulation has been confirmed by controlled quality indicators.

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ДЕЯКІ АСПЕКТИ РОЗРОБКИ ТЕХНОЛОГІЇ ОТРИМАННЯ КОМБІНОВАНИХ ТАБЛЕТОК НА ОСНОВІ ВІТАМІНІВ ГРУПИ В

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Ключові слова: *технологія; вітаміни групи В; плинність; кут укосу; насипна густина; ущільненість; бенфотіамін; піридоксину гідрохлорид*

Проведено дослідження з вибору оптимальної технології отримання комбінованої лікарської форми таблеток на основі вітамінів групи В, а саме, вибір раціонального способу таблетування та способу введення діючих та допоміжних речовин у таблеткову масу, а також оптимального режиму висушування грануляту піридоксину гідрохлориду. З цією метою вивчені властивості активних фармацевтичних інгредієнтів, які обумовлюють технологічні характеристики індивідуальних порошків, що впливають на функціональні характеристики лікарського препарату. Проведені дослідження технологічних властивостей діючих речовин комбінованих таблеток: плинності, кута укосу, насипної щільності, пресуємості. Субстанція бенфотіаміну має добру плинність, що вказує на можливість застосування методу прямого пресування. Порошок піридоксину гідрохлориду має погану плинність, про що свідчать результати дослідження плинності, кута природного укосу, щільності і пресування. Така різна структура порошків діючих речовин вказує на додаткові складності при виборі оптимального способу введення діючих речовин у лікарську форму. Досліджено 3 серії таблеткової маси з різними способами введення до неї діючих та допоміжних речовин. Встановлено, що при зволоженні таблеткової маси, до складу якої входили бенфотіамін і піридоксину гідрохлорид, спостерігалось збільшення кількісного вмісту домішки тіаміну о-монофосфату. Тому виведення бенфотіаміну із суміші на стадії опудрювання або застосування технології отримання двох окремих гранулятів діючих речовин зняло питання появи і зростання величини домішки тіаміну о-монофосфату. Визначено оптимальний режим висушування грануляту піридоксину гідрохлориду – 55-65°С протягом 60-70 хвилин, що дозволяє отримати гранулят піридоксину гідрохлориду з задовільною плинністю (10 г/с) та оптимальною вологістю (не більше 5,0%).

НЕКОТОРЫЕ АСПЕКТЫ РАЗРАБОТКИ ТЕХНОЛОГИИ ПОЛУЧЕНИЯ КОМБИНИРОВАННЫХ ТАБЛЕТОК НА ОСНОВЕ ВИТАМИНОВ ГРУППЫ В

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Ключевые слова: *технология; витамины группы В; сыпучесть; угол откоса; насыпная плотность; прессуемость; бенфотиамин; пиридоксина гидрохлорид*

Проведены исследования по выбору оптимальной технологии получения комбинированной лекарственной формы таблеток на основе витаминов группы В, а именно, выбор рационального способа таблетирования и способа введения действующих и вспомогательных веществ в таблеточную массу, а также оптимального режима сушки гранулята пиридоксина гидрохлорида. С этой целью изучены свойства активных фармацевтических ингредиентов, которые обусловливают технологические характеристики индивидуальных порошков, влияющие на функциональные характеристики лекарственного препарата. Были проведены исследования технологических свойств действующих веществ комбинированных таблеток: сыпучести, угла откоса, насыпной плотности, прессуемости. Субстанция бенфотиамина имеет хорошую сыпучесть, что указывает на возможность применения метода прямого прессования. Порошок пиридоксина гидрохлорида имеет плохую сыпучесть, о чем свидетельствуют результаты исследования сыпучести, угла естественного откоса, плотности и прессуемости. Такая разная структура порошков действующих веществ указывает на дополнительные сложности при выборе оптимального способа введения действующих веществ в лекарственную форму. Были исследованы 3 серии таблеточной массы с разными способами введения в нее действующих и вспомогательных веществ. Установлено, что при увлажнении таблеточной массы, в состав которой входили бенфотиамин и пиридоксина гидрохлорид, наблюдалось увеличение количественного содержания примеси тиамина о-монофосфата. Поэтому выведение бенфотиамина из смеси на стадии опудривания или применение технологии получения двух отдельных гранулятов действующих веществ сняли вопрос образования и увеличения объема примеси тиамина о-монофосфата. Выбран оптимальный режим сушки гранулята пиридоксина гидрохлорида – 55-65°С в течение 60-70 минут, что позволяет получить гранулят пиридоксина гидрохлорида с хорошей сыпучестью (10 г/с) и оптимальной влажностью (не более 5,0%).