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Research Article

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Study of technological properties of the active pharmaceutical ingredients for developing the combined medicine for neuropathy complex treatment

Almakaiev M. S.

Research Laboratory of Parenteral and Oral Liquid Medicines, National University of Pharmacy, 53, Pushkinska str., Kharkiv, Ukraine

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ABSTRACT

Based on the analysis of literature data about modern state of solving the problem of treatment of diabetic and alcoholic neuropathy it has been grounded the necessity of application of the combined medicine on basis of pyrimidine nucleotides salts in combination with vitamins B complex, thioctic acid and magnesium lactate dihydrate in therapeutic practice. At the first stage of pharmaceutical development the technological properties of the initial active pharmaceutical ingredients and their combination (morphological properties of substances and their granulometric composition, flowability, density of bulk product and density of settled product, repose angle) have been studied. From the results of determination of technological properties of the substances it has been found that magnesium lactate dihydrate has the most optimal properties of density and flowability. It has been found that the model mixture of active pharmaceutical ingredients has unsatisfactory technological properties (flowability, density of bulk product and density of settled product, repose angle). Therefore for providing of cost-efficient manufacturing process it is necessary to optimize the investigated technological characteristics of the mixture of active pharmaceutical ingredients and enter auxiliary substances, which improve flowability of the mixture, distribution of the active pharmaceutical ingredients when capsulation, prevent balling, into its composition.

Keywords: pyrimidine nucleotides salts, magnesium lactate dihydrate, capsulation, thioctic acid, pyridoxine hydrochloride.

INTRODUCTION

The problem of administering the effective and safe pharmacotherapy of neuropathy various types (diabetic, alcoholic) is one of the main problems in modern clinical practice of physicians. To prescribe not only antihyperglycaemic medicines, but also drugs decreasing the intensity of oxidative stress and insulin resistance, improving the blood rheological properties, reducing the symptoms of hypoxia manifestations in the treatment regimens is recognized as the modern trend in the complex therapy of diabetes mellitus [1, 2]. Great many new medicines and dosage forms, creation of medicines of new generation complicate significantly the choice of optimal medicine for treatment of certain pathology and individual patient. As a result, the cases of simultaneous prescription up to 5 – 10 or more different groups of medicines with various action mechanisms for one patient are fixed very often that leads to a number of negative consequences including:

– risk of increase in the number of side effects and uncontrolled clinical responses;
– significant rise in cost of the treatment process, especially when realizing the long-term therapy, which is the most common in neurological practice [3, 4].

Therefore application of combined neurotropic medicines containing the components, which influence on the various links of pathogenesis of this syndrome and complement each other pharmacodynamically and clinically is topical.

The aim of our investigation is to examine the technological properties of a number of active pharmaceutical ingredients (APhIs) and their combinations for creation of polycomponent medicine in solid dosage form for the complex treatment of neuropathy.

EXPERIMENTAL SECTION

The objects of the investigation are such active substances as salts of pyrimidine nucleotides produced in China, pyridoxine hydrochloride produced by «DSM Nutritional Products GmbH» (Germany), thioctic acid produced by «Shanghai Modern Pharmaceuticals» (China), magnesium lactate dihydrate produced by «Moehs Cantabria S.L.» (Spain).

The technological properties of the active substances and their combinations have been studied, namely morphological properties of substances and their fraction composition, flowability, density of bulk and settled product, repose angle.

The study of morphological properties (forms and sizes of crystals) for all APhIs has been carried out by microscopic technique according to State Pharmacopoeia of Ukraine (SPhU) [5] using the microscope «Opton» produced by «West Germany». Determination of granulometric composition has been carried out by the method of analytical sieving; density of bulk product (poured density) and density of settled product (tapped density) have been set as the mass of freely poured powder per volume unit before and after settling; flowability has been investigated by the method of «immobile funnel» according to the procedures described in SPhU [5].

RESULTS AND DISCUSSION

Qualitative composition and quantitative content of the main ingredients of the dosage form has been chosen on the basis of the literature data and preliminary pharmacological researches. Pyrimidine nucleotides salts, pyridoxine hydrochloride (vitamin B_6), thioctic acid and magnesium salt have been chosen as the active substances in the ratio that it is possible to influence on many leading links of pathogenesis of diabetic and alcoholic neuropathy by one medicine [6].

Application of nucleotides for treatment of neuropathy accelerates regeneration of nerve tracts after traumatic tissue destruction significantly [7]. It is known that any therapy of diabetic complications is accompanied by prescribing the vitamin medicines; the vitamins of B-group (or neurotropic vitamins) occupy the main place among them [8]. Vitamins B complex are involved in the processes of neuron axonal transport, neurotransmission along motor and sensory fibres, regulate the balance of nociceptive and antinociceptive systems [8, 9].

Magnesium is a vital element, which is found in all body tissues and necessary for normal function of cells, it is involved in most reactions of metabolism. In particular, it is involved in the regulation of neurotransmission and muscle contraction. Magnesium lactate has been chosen as organic salt of magnesium. This salt has the properties which are peculiar to organic lactate-anion and inorganic magnesium-cation [10].

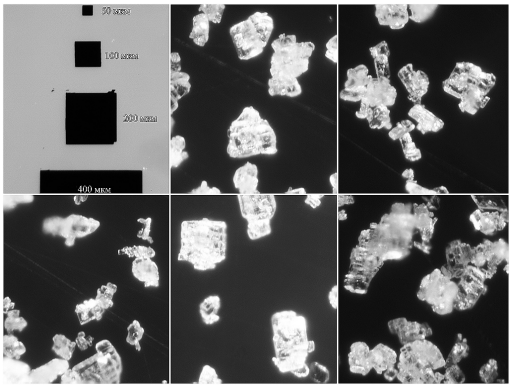
Thioctic acid is associated with autooxidative glycosylation. It affects on hyperglycaemia caused by oxidative stress and plays a significant role in prevention of glycation and hypoxia of nerve tissue [11 – 12].

It is necessary to study the technological properties of APhIs at the first stage of pharmaceutical development and apply them for substantiation of composition and development of technology for preparation of the medicine in capsules. The technological properties of the APhIs and their combinations have been studied to evaluate the processability of powder-like substances and also to predict the behaviour of free-flowing powder mass under the production conditions.

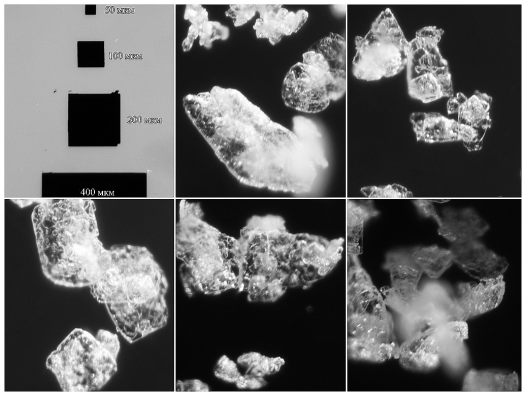
The shape and size of particles, granulometric composition, flowability, density of bulk product (poured density) and density of settled product (tapped density), repose angle belong to the technological properties of free-flowing materials [13].

It is necessary to investigate all APhIs of the medicine to obtain objective presentation. Analysis of the quantities of active substances and their percentages has showed that the technological properties of the mass for capsulation containing the mixture of APhIs in therapeutic concentrations are conditioned by the properties of magnesium lactate, because its amount is more than 70% of the total amount of APhIs. Salts of pyrimidine nucleotides enter into the medicine composition in small quantities and it can be neglected by their influence on the technological properties of the APhIs mixture. The technological properties of the powders are conditioned by their dispersity and

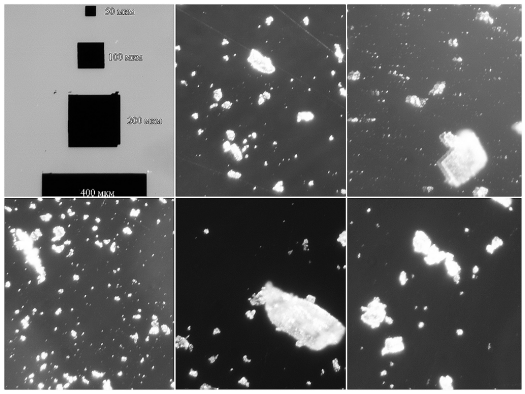
crystals shape, therefore we have assessed the size and form of crystals of pyridoxine hydrochloride, thioctic acid and magnesium lactate dihydrate. The photos of crystals are presented on Pictures 1 – 3.



Picture 1. The photos of particles of pyridoxine hydrochloride



Picture 2. The photos of particles of thioctic acid



Picture 3. The photos of particles of magnesium lactate dihydrate

The research results of the technological properties of active substances of developed combined dosage form are presented in Table 1.

From the results presented on Picture 1 and in Table 2 we can see that the substances chosen by us have different crystals form. The research of granulometric composition of the APhIs has showed that all APhIs are crystalline (thioctic acid) or fine-crystalline (magnesium lactate dihydrate, pyridoxine hydrochloride) powders with the size of the main fraction of particles, which is less than 0.4 mm and 0.2 mm respectively. The APhIs have particles both of isometric form (magnesium lactate dihydrate, pyridoxine hydrochloride) and anisometric form (thioctic acid).

Table 1 The research results of the technological properties of the APhIs for the developed dosage form of capsules

Parameter, dimension units (acceptability criterion)	APhI		
	magnesium lactate dihydrate	thioctic acid	pyridoxine hydrochloride
Flowability, g/s (3.0 – 10.0)	0.500	–	0.275
Density of bulk product (poured density), g/cm^3 (0.4 – 0.5)	0.695	0.407	0.486
Density of settled product (tapped density), g/cm^3 (0.5 – 0.6)	0.893	0.500	0.634
Repose angle, º (25 – 35)	41 – 45	–	46 – 55
Granulometric composition, %			
– particles with the size less than 0.4 mm	100.0	96.0	100.0
– particles with the size of 0.2 – 0.25 mm	4.0	96.0	5.0
– particles with the size less than 0.2 mm	96.0	4.0	95.0
Particles shape	round crystals and their aggregates	cubic and round crystals and their aggregates	cubic and scaly crystals and their fragments

The form and size of the particles condition such technological characteristics of substances as flowability, density of bulk product (poured density) and density of settled product (tapped density), repose angle etc. Thioctic acid with anisometric form of particles has low flowability. From the substances with isometric form of particles pyridoxine hydrochloride has low flowability because of high dispersivity of powder – 95% of powder mass has particles with the size less than 0.2 mm. Magnesium lactate dihydrate with the round form of particles has high value of flowability as compared with other APhIs. From the obtained data such conclusion has been made the substances of active compounds individually have different technological characteristics, some of them do not pour well and electrify, some substances are also inclined to formation of agglomerates. Active substances have different particles size that also affects the technological properties of their mixture.

From the results of determination of the technological properties of substances it follows that magnesium lactate dihydrate has the most optimal properties of density and flowability as compared with other ingredients that can allow to obtain the good technological mass when mixing with powders with unsatisfactory characteristics. To obtain a stable dosage form it has a great importance because its amount is more than 70% of the mass for capsulation. Capsulated dosage form, as distinct from other ones, does not require compulsory introduction of auxiliary substances if APhIs have satisfactory technological characteristics. In the composition of the developed medicine not all substances of active compounds have technological properties provided obtaining the mass for capsulation of high quality but its main component (magnesium lactate dihydrate) has good technological properties as compared with other APhIs and may theoretically condition the properties of the APhIs mixture. Therefore the purpose of our further researches is the study of structural and technological properties of the model mixture containing all APhIs in therapeutic concentrations. The model mixture has been obtained for further researches and its technological properties have been studied.

The research results of the technological properties of the model mixture of APhIs are presented in Table 2.

Table 2 The research results of the technological properties of the model mixture of APhIs

Parameter	Dimension unit	Acceptability criterion	Value
Flowability	g/s	3.0 – 10.0	0.450
Density of bulk product (poured density)	g/cm^3	0.4 – 0.5	0.630
Density of settled product (tapped density)	g/cm^3	0.5 – 0.6	0.763
Repose angle	º	25 – 35	43 – 47

From the data obtained it is obviously that the model mixture of APhIs has unsatisfactory technological characteristics (flowability, density of bulk product and density of settled product, repose angle). Therefore for providing of cost-efficient manufacturing process it is necessary to optimize the investigated technological characteristics of the APhIs mixture and enter auxiliary substances, which improve flowability of the mixture, distribution of the APhI when capsulation, prevent balling, into its composition.

CONCLUSION

Based on the analysis of literature data about modern state of solving the problem of treatment of diabetic and alcoholic neuropathy it has been grounded the necessity of application of the combined medicine on basis of pyrimidine nucleotides salts in combination with vitamins B complex, thioctic acid and magnesium lactate dihydrate in therapeutic practice.

The technological properties of the initial APhIs and their combination (morphological properties of substances and their granulometric composition, flowability, density of bulk product and density of settled product, repose angle) have been studied.

It has been found that the model mixture of APhIs has unsatisfactory technological properties (flowability, density of bulk product and density of settled product, repose angle). Therefore for providing of cost-efficient manufacturing process it is necessary to optimize the investigated technological characteristics of the APhIs mixture and enter auxiliary substances, which improve flowability of the mixture, distribution of the APhIs when capsulation, prevent balling, into its composition.

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