Scientific and Methodical approach to developing the formulation of an Innovative Medicinal Product based on a derivative of 3,7-diazabicyclo [3.3.1]nonane (hydrindane)

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ABSTRACT:
Different derivatives of 4-hydroxy-3-methoxy benzoic acid were synthesized and evaluated for their antioxidant, *α-amylase* inhibition and *urease* inhibition ability. Antioxidant evaluation was performed by DPPH radical scavenging assay and the results revealed that compounds 8, 10 and 13 as most active antioxidant agent with IC_{50} values of 43.09µg/ml, 44.59µg/ml and 43.43µg/ml respectively. *α-Amylase* inhibition study was performed using diastase by colorimetric method. Compound 9 showed maximum inhibition with IC_{50} value of 33.26 µg/ml. Compound 4 was found to possess maximum *urease* inhibition ability with IC_{50} value of 35.82µg/ml. Molecular docking study was performed using autodock software.

KEYWORDS: Development of drug composition, derivatives of 3,7-diazabicyclo [3.3.1] nonane, brain-derived neurotrophic factor rehabilitation of patients after brain damage, nootropics, ampakines.

INTRODUCTION:

Nootropic medicinal products are a special group of neuropsychotropic medicinal products, the specific effect of which is characterized by the ability to improve memory and learning ability, intellectual and cognitive functions in healthy individuals and patients with various diseases. A synonym of nootropic medicinal products used in the literature is the term "cognitive enhancer"[1].

The number of registered pharmaceutical forms of the nootropic products determines the priority of creating oral dosage forms of an innovative medicinal product that would have the pro-cognitive effect for restoring dendritic plasticity and cognitive functions after brain damage. Given the fact that this product can be absorbed through the walls of the gastrointestinal tract, and pass through the blood-brain barrier, there are no limitations in developing the peroral dosage form. Also, the peroral dosage form has significant advantages when used for geriatric and pediatric patients.

When choosing the peroral dosage form, one should be guided by the breadth of therapeutic concentrations of the medicinal product, which is determined during nonclinical and clinical studies.

It should be noted that the leader in creating ampakines, pharmaceutical company Respire Rx Pharmaceuticals Inc. (ex-Cortex Pharmaceuticals) develops peroral dosage forms of ampakines in capsules[2].

In the process of patent search, it has been confirmed that there are no foreign and Russian technical facilities with similar emerging technologies, and there are no registered claims that discuss the potential of using 6-[4-methoxy-3-(1H-pyrazole-1-ylmethyl) benzyl]-1,11-dimethyl-3,6,9-triazatricyclo[7.3.1.1]tetradecan-4,8,12-trion as a pharmacologically active pharmaceutical substance or as part of composition dosage forms. No applications have been found either stating the possibility of using tricyclic derivatives of 3,7-diazabicyclo [3.3.1] nonane for restoring the motor and cognitive functions after brain damage. The innovative molecule is protected by the developers of the patent registered in the Russian Federation, the European Union, and the United States[3,4].

METHODS:

Development of the scientific-methodological approach for an unbiased assessment of the pharmaceutical development and the choice of the dosage form of the innovative nootropic medicinal products based on hydrindane derivatives for the rehabilitation of patients after brain damage was performed with the help of the informational and analytical methods. The authors performed a systematic analysis of the range of auxiliary substances introduced into medicinal products for the rehabilitation of cognitive and motor functions after brain damage caused by acute injury and acute ischemia.

RESULTS AND DISCUSSION:

The medicinal agent based on a derivative of 3,7-diazabicyclo [3.3.1] nonane (hydrindane) ensures long-lasting activation of AMPA receptors and production of neurotrophic factors, allowing it to be used for treatment of cognitive disorders and rehabilitation of patients after acute brain hypoxia due to ischemia or another brain injury, such as trauma[5].

According to document ICH Q8, "the first stage (Preformulation studies) of pharmaceutical development is focused on studying individual physicochemical properties of the active substances and additive agents for identifying critical characteristics of the initial materials that affect the quality of the finished product"[6].

The results of this study are used in developing specifications for incoming inspection, and for choosing and assessing suppliers. The importance of such research is determined by the fact that up to 50% of the problems with technology and quality of finished forms (granules flowability, compression process, disintegration and solubility of solid peroral forms, etc.) depend on the components of the dosage form. It is well known that compliance with the pharmacopoeial requirements to active substances and additive agents is not sufficient for ensuring the sustainability of the processes and the desired pharmacokinetic properties of many medicinal forms.

Pharmaceutical substance of hydrindane is innovative in terms of the structure and production process. The quality of and the requirements for pharmaceutical substances are established in the Pharmacopoeia of Russia[7].

The physicochemical and biological properties of the medicinal substance that can influence the pharmacological action of the medicinal product and its production technology, including solubility, particle size, flowability, bulk density, etc., have been experimentally determined and assessed[5].

Currently, the most popular solid peroral dosage forms are tablets and capsules. The technology of producing tableted medicinal products is widely used by manufacturers. However, one should consider its peculiarities: the multistage process, many technological additive agents in the formulations, the effect of stress process conditions on the pharmaceutical substance, such as moisture, high temperature, and pressing that can result in polymorphic transformations, and affect the stability and efficiency of the pharmaceutical substance.

Capsules have distinct marketing, biopharmaceutical, and technological advantages. Apart from the attractive appearance, capsules mask unpleasant taste and odor of the pharmaceutical substance, ensure high dosing accuracy, and most importantly, during the production of capsules, the pharmaceutical substance is not exposed to the severe technological effect, which has a positive effect on the stability and the efficacy of the medicinal product. The biopharmaceutical possibilities of modifying the release of the substance from the capsules make it possible to vary it in a wide range–from fast to phases, and the prolonged one. Manufacturers also point to the economic efficiency of producing capsulated medicinal products compared to the production of tablets by reducing the number of process stages and types of the required production equipment[8].

Currently, capsules made of gelatin, the natural product of hydrolysis of collagen-containing raw materials, which are wastes of the food industry (meat and fish factories), are the most commonly used. Currently, it is widely used in the food industry[9, 10].

A molecule of gelatin is a polypeptide, the peptide skeleton of which consists of polar and nonpolar amino acids, including glycine (about 30%), proline, oxyproline, alanine, glutamic and aspartic acid. Therefore, gelatin has doubtless advantages: it is biocompatible, easily digestible, and does not have adverse reactions. Gelatin amino acids have a pharmacological action on the organism: they improve metabolism, improve mental performance and strengthen the heart muscle, have a beneficial effect on the tissues of the musculoskeletal system, on the mucosa of the gastrointestinal tract in case of erosions and peptic ulcers, and are some main sources of energy for the central nervous system, the muscles, and the brain. Moreover, gelatin is used in medicine as a plasma-substituting medicinal product – "Geoplasma balance"[11].

It should be noted that gelatin, being a natural product, is easily digested, dissolves quickly in the acidic environment of the stomach (due to the presence of stomach protease, pepsin), and releases the contents of the capsules, thus facilitating rapid delivery of a pharmaceutical substance into the bloodstream. The disadvantages of gelatin are the following: the polypeptide structure of gelatin determines its susceptibility to microbial contamination, and the walls of the capsules are very sensitive to changes in the moisture content (both increased and decreased moisture content of the capsules have negative effect on the properties of the medicinal product). Also, gelatin, being the raw material of animal origin, has limitations in the use for certain categories of consumers, such as vegans, as well as religious or ethnic groups (Jews, Muslims, Hinduites, etc.) who observe dietary laws that prohibit the use of certain products of animal origin. As a result of poor processing quality during production, gelatin may create a threat to health due to the onset of serious diseases of animals, such as spongiform encephalopathy, pig influenza, etc.

The drawbacks of gelatin capsules stimulated the search for alternative materials for the pharmaceutical form. The alternative material, apart from the lack of the aforementioned drawbacks of gelatin, should have similar physicochemical properties to make it possible to use the developed technologies and the existing machinery without major redesigning. It must be proven safe and should have permission for pharmaceutical use. Hydroxy propymethy lcellulose (hypromellose) has become a successful alternative material for hard capsules, which have been recently introduced to the market[10].

Hypromellose is obtained by synthetic modification of cellulose and is considered to be safe for humans[12, 13]. It is virtually insoluble in hot water, in acetone, in anhydrous ethanol, and chloroform, but dissolves well in cold water with the formation of a

colloidal solution, and shows reversible temperature saturation by helium. Modification of the molecule of hydroxypropymethyl cellulose by methoxy, hydroxy, and propoxy groups allows obtaining products with variations of many parameters, such as the temperature of saturation by helium, viscosity, elasticity, and hydration. This provides an opportunity to create products with the modified release, and high resistance to the conditions of storage and mechanical processing.

Hydroxypropymethyl cellulose is widely used in the pharmaceutical industry for coating the tablets and as the base for viscoplastic forms: gels and creams. Hydroxypropymethyl cellulose is well compatible with the known additive agents and has gelatin-like properties. The marketing advantage is that hydroxypropymethyl cellulose meets the dietary and cultural needs of all patients. It meets the production needs, as the capsules may be produced and filled using the existing equipment. It is characterized by the proven information about safety and is allowed for pharmaceutical use. Also, it improves characteristics of the capsules, their strength, protection from moisture, from microbial contamination, and high compatibility with products[9,10,12].

Hypromellose capsules are more stable to moisture, compared to gelatin. The humidity of the capsules themselves is 6–7%, which is lower than that of the gelatin capsules, which is 12–13 %. This is extremely important for hygroscopic pharmaceutical substances and the conditions of filling, transportation, storage of both empty capsules, and dosage forms. However, since the hydroxypropymethyl cellulose capsules have appeared in the market of the Russian Federation only recently, there are virtually no publications about their properties and the use in creating medicinal products.

Thus, since hydrindane is very poorly soluble in water, hard capsules were chosen as dosage forms rather than tablets. In the production of tableted medicinal products, the substance is exposed to technological stress factors (hydration, drying, pressing), which may affect its poor enough solubility, and, possibly, further bioavailability. As mentioned above, in the process of manufacturing dosage formulations in the form of hard capsules, the pharmaceutical substance is exposed to sparing processing; this is considered a biopharmaceutical benefit of this dosage form. The absence of the pressing stage in the process scheme is extremely important; it prevents the negative effect on the release of the pharmaceutical substance from the dosage form. This article is devoted to the comparative study of the possible use of gelatin and hypromellose capsules for obtaining the dosage form of hydrindane.

Traditionally, the pharmaceutical substance is placed into hard capsules in the form of powder or granules. In case of low dosage of the pharmaceutical substance for ensuring accuracy of dosing by a capsule-filling machine, fillers (diluents) are introduced in the formulations: mannitol, lactose, microcrystalline cellulose, corn starch and other additive agents that have been approved for pharmaceutical use.

To ensure sliding of the capsulated mass relative to the working parts of the capsule-filling machine, sliding substances are introduced into its composition in small amounts (often 1 – 3 %): magnesium stearate, glyceryl monostearate, stearic acid, talc, aerosil, etc.[13]. During filling, the capsulated mass is compressed, and, therefore, desintegrants are often present in the recipes: croscarmellose, corn starch, crospovidone, starch, alginic acid, sodium glyceryl amylose, etc.

The choice of additive agents was closely associated with the technology of the capsulated mixture preparation for filling; the technological properties of the pharmaceutical substance were first studied for choosing and substantiating the technology of preparation.

Since dosing into the capsules is performed automatically, the powdered content should primarily have good flowability so that the powder moves by gravity from the hopper of the machine into the dosing device. In turn, flowability depends on many characteristics of the powder: the fractional composition, amorphousness, and humidity of the substance, etc., and therefore, flowability is usually determined in two ways: the flow rate from a standard funnel and the angle of friction. The angle of friction characterizes the effect of friction between the particles, and the effect of gravity on the powder mass provides an estimate of the influence of the particle size, the shape, and the electrostatic interaction between them during pouring of the powder from the hopper of the capsule-filling machine [14]. The angle of friction depends on the shape, the dimensions, and the cohesive properties of the particles; it varies in a wide range: 25° to 30° for well-flowing materials, and 60° to 70° for non-free-running materials[8, 14].

Like other characteristics of bulk mass, bulk density is a complex indicator, which depends on many other characteristics: granulometric composition, moisture content, packing density in the layer. It is important that it is not a constant value; it may vary under the influence of vibration, and during storage at the warehouse. Therefore, the distinction is made between the minimum bulk density of powder freely poured, and the maximum bulk density after compaction — for freely poured powder subjected to densification by shaking. Bulk density is closely related to the capacity of the capsule, the number of which is chosen depending on the weight of the capsule content.

Flowability and bulk density, being important characteristics of the powder mass in the pharmaceutical technology, determine the rhythm and operation speed of the capsule-filling machine, and, consequently, its productivity. In addition to the technological conditions, flowability also affects uniformity and density of the capsulated mass. These characteristics are comprehensive, and depend on many parameters, like the shape and the surface of powder particles, particle-size composition, and humidity, and largely determine the bulk density of the powder mass.

The technological characteristics of a pharmaceutical substance can be evaluated not only by certain characteristic values but also by the values of Carr and Hausner indices, which are calculated and assessed by the scale shown in USP 38[15].

The low technological characteristics of pharmaceutical substance hydrindane, its small dosage, small particle size, their amorphous nature, and volatility were the bases for granulation of the capsulated mixture to increase flowability and uniformity of the content of all components in the powder mixture[8,14].
Depending on the consistency of the binder, the currently used granulation methods include or exclude wetting of powder mass. Dry granulation involves the use of considerable compression force or mass melting, which cannot be considered appropriate in the case of a pharmaceutical substance that is insoluble in an aqueous medium due to the possible loss of its pharmacological activity. Out of the methods of wet granulation, the most acceptable is granulation in a granulating mixer with high shearing force. Granules are formed by moistening the powder mixture with a solution of an adhesive substance, which is fed through a nozzle. The resulting agglomerates roll along the surface of the rotating bottom in the shape of a plate. In the process, the granulated mixture builds up layer by layer; at the same time, the surface of the resulting granules is polished. The obtained granules are strong, and have a smooth surface. Side grinders are provided for aligning the fractional composition. In some cases, the still wet granules are calibrated using an external nozzle. The Z-shaped vanes of the disc rotor ensure intensive mixing[8,16].

Compared to the traditional scheme of granulation by forcing through, the use of a granulating mixer reduces the power consumption, the production area, and the cost of the product. With the scientifically substantiated choice of additive agents, the use of this technology allows to minimize the amount of the humidifier, and to remove from the process the stage of granules drying, which is accompanied by the adverse effect of the temperature on the active pharmaceutical ingredients and cumbersome equipment for air handling and cleaning, as well as to reduce the duration and the intensity of mixing the wetted mass[8, 14, 16].

CONCLUSION:

In the framework of the work performed in accordance with the international requirements and approaches, the authors have studied the following elements of pharmaceutical development: the physical and chemical properties of the pharmaceutical substance hydrindane have been determined, the quality indicators and the methods of their determination and norms have been identified; the dosage form has been substantiated — solid bisectional capsules; the promising additive agents for creating capsulated form of hydrindane have been screened; the characteristics of hydrindane have been technologically determined, the need for granulation of the pharmaceutical substance prior to filling into capsules has been shown, and the promising technology of granulation has been substantiated.

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Received on 20.08.2019 Modified on 30.09.2019
Accepted on 18.10.2019

Research J. Pharm. and Tech. 2019; 12(12): 5752-5756.
DOI: 10.5958/0974-360X.2019.00996.X