DEVELOPMENT OF THE COMPOSITION AND TECHNOLOGY FOR THE PRODUCTION OF ENCAPSULATED DRUGS BASED ON 3,7-DIAZABICYCLO[3.3.1]NONANE

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DESENVOLVIMENTO DA COMPOSIÇÃO E TECNOLOGIA PARA A PRODUÇÃO DE DROGAS ENCAPSULADAS COM BASE EM 3,7-DIAZABICICLO[3.3.1]NONANO

DEVELOPMENT OF THE COMPOSITION AND TECHNOLOGY FOR THE PRODUCTION OF ENCAPSULATED DRUGS BASED ON 3,7-DIAZABICYCLO[3.3.1]NONANE

РАЗРАБОТКА СОСТАВА И ТЕХНОЛОГИИ ПОЛУЧЕНИЯ КАПСУЛИРОВАННОГО ЛЕКАРСТВЕННОГО СРЕДСТВА НА ОСНОВЕ 3,7-ДИАЗОБИЦИКЛО[3.3.1]НОНАНА

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RESUMO

Os seguintes fatores biológicos e farmacêuticos influenciam a eficácia terapêutica e a bioequivalência de medicamentos: propriedades físico-químicas de uma substância farmacêutica, biodisponibilidade, meio de dosagem, via de administração, natureza dos excipientes, sua compatibilidade, bem como condições tecnológicas de produção, incluindo a preparação de formulários de medicamentos. Antes da produção em massa de um medicamento, os parâmetros e características tecnológicas da substância farmacêutica devem ser cuidadosamente estudados e comprovados cientificamente. Este trabalho é dedicado ao estudo das propriedades tecnológicas de uma substância farmacêutica original baseada no derivado de 3,7-diazabiciclo [3.3.1]nonano com o nome químico IUPAC 6-[4metoxi-3-(1H-pirazol-1-ilmetil)benzil]-1,11dimetil-3,6,9-triazatriciclo[7.3.1.1]tetradecano-4,8,12-trion, usado como substância ativa para o desenvolvimento da composição e tecnologia para a preparação de formas de dosagem orais em forma de cápsula. O artigo apresenta os resultados do desenvolvimento e teste de um medicamento sob a forma de cápsulas da substância farmacêutica original da ação nootrópica do 3,7-diazobiciclo[3.3.1]nonano, que é praticamente insolúvel em água. O estudo identificou e avaliou as propriedades tecnológicas e biológicas de uma substância farmacêutica que podem afetar a atividade farmacológica na produção de uma forma de dosagem. O estudo examinou os principais indicadores: solubilidade, tamanho de partícula, fluidez, densidade aparente. As características tecnológicas da substância farmacêutica são estudadas não apenas por certos valores das características indicadas, mas também pelos valores dos índices de Hausner e Carr. Os dados obtidos sugerem o conteúdo e o progresso de outras etapas do desenvolvimento farmacêutico. A presença da fase de atraso na dissolução de cápsulas de hipromelose em meio com pH de 1,2 e taxas de desintegração relativamente baixas em meios com pH de 1,2, pH 4,5 e pH 6,8 serviu de base para a escolha de cápsulas de gelatina. A forma farmacêutica desenvolvida atende aos modernos requisitos farmacopéicos, incluindo a cinética de dissolução: de acordo com os resultados obtidos, em 45 minutos (77,6 ± 2,5)% da substância passa para o meio de dissolução com um pH de 4,5. Os resultados do estudo são utilizados para desenvolver um esquema tecnológico para a obtenção da forma de dosagem de 3,7-diazobiciclo [3.3.1] nonano, seus indicadores e padrões de qualidade.

Palavras-chave: *ampaquinas, drogas nootrópicas, derivados do 3,7-diazabiciclo[3.3.1]nonano, desenvolvimento farmacêutico de formas farmacêuticas, cápsulas*.

ABSTRACT

The following biological and pharmaceutical factors influence the therapeutic efficacy and bioequivalence of drugs: physicochemical properties of a pharmaceutical substance, bioavailability, type of dosage form, route of administration, nature of excipients, their compatibility, as well as technological conditions of production, including the preparation of drugs forms. Before mass production of a drug, the technological parameters and characteristics of the pharmaceutical substance must be carefully studied and scientifically substantiated. This work is devoted to the study of the technological properties of an original pharmaceutical substance based on the derivative of 3.7-diazabicyclo[3.3.1]nonane with the chemical name IUPAC 6-[4methoxy-3- (1H-pyrazol-1-

ylmethyl) benzyl] -1,11dimethyl-3,6,9-triazatricyclo[7.3.1.1]tetradecane-4,8,12-trion, used as an active substance for the development of the composition and technology for the preparation of oral dosage forms in capsule form. The article presents the results of the development and testing of a drug in the form of capsules of the original pharmaceutical substance of the nootropic action of 3,7-diazobicyclo[3.3.1]nonanane, which is practically insoluble in water. The study identified and evaluated the technological and biological properties of a pharmaceutical substance that can affect the pharmacological activity in the production of a dosage form. The study examined the key indicators: solubility, particle size, flowability, bulk density. The technological characteristics of the pharmaceutical substance are studied not only by certain values of the indicated characteristics but also by the values of the Hausner and Carr indices. The data obtained suggest the content and progress of further stages of pharmaceutical development. The presence of the lag phase when dissolving hypromellose capsules in a medium with a pH of 1,2 and relatively low disintegration rates in media with a pH of 1,2, pH 4,5, and pH 6,8 served as the basis for the choice of gelatin capsules. The developed dosage form meets modern pharmacopoeial requirements, including the dissolution kinetics: according to the results obtained, in 45 minutes (77,6 ± 2,5)% of the substance passes into the dissolution medium with a pH of 4,5. The results of the study are used to develop a technological scheme for obtaining the dosage form of 3,7-diazobicyclo[3.3.1]nonane, its indicators, and quality standards.

Keywords: *ampakines, nootropic drugs, derivatives of 3,7-diazabicyclo[3.3.1]nonane, pharmaceutical development of dosage forms, capsules*.

АННОТАЦИЯ

На терапевтическую эффективность и биоэквивалентность лекарственных средств влияют следующие биологические и фармацевтические факторы: физико-химические свойства фармацевтической субстанции, ее биодоступность, вид лекарственной формы, путь введения, природа вспомогательных веществ, их совместимость, а также технологические условия производства, в том числе при получении лекарственных форм. Перед серийным производством лекарственного средства должны быть тщательно изучены и научно обоснованы технологические параметры и характеристики фармацевтической субстанции. Настоящая работа посвящена изучению технологических свойств оригинальной фармацевтической субстанции на основе производного 3.7-диазабицикло[3.3.1]нонана с химическим названием IUPAC 6-[4метокси-3-(1Н-пиразол-1-илметил)бензил]-1,11диметил-3,6,9-триазатрицикло[7.3.1.1]тетрадекан-4,8,12-триона, используемую в качестве действующего вещества для разработки состава и технологии получения лекарственной формы для перорального применения в форме капсул. В статье приведены результаты разработки и испытаний лекарственного средства в форме капсул оригинальной фармацевтической субстанции ноотропного действия 3,7-диазобицикло[3.3.1]нонанана, обладающей низкими технологическими характеристиками, практически нерастворимой в воде. В исследовании были определены и оценены технологические и биологические свойства фармацевтической субстанции, способные оказать влияние на фармакологическую активность при производстве лекарственной формы. В исследовании были изучены ключевые показатели: растворимость, размер частиц, сыпучесть, насыпную плотность. Технологические характеристики фармацевтической субстанции исследованы не только по определенным значениям указанных характеристик, но и по величинам индексов Хауснера и Карра. Полученные данные позволили предположить содержание и ход дальнейших этапов фармацевтической разработки. Наличие лаг-фазы при растворении гипромелозных капсул в среде с pH 1,2 и относительно низкими показателями распадаемости в средах с pH 1,2 pH 4,5 и pH 6,8 послужило основанием выбора желатиновых капсул. Разработанная лекарственная форма отвечает современным фармакопейным требованиям, в том числе по кинетике растворения: согласно полученным результатам за 45 минут в среду растворения с pH 4,5 переходит (77,6±2,5) % субстанции. Результаты исследования используются для разработки технологической схемы получения лекарственной формы 3,7-диазобицикло[3.3.1]нонана, ее показателей и норм качества.

Ключевые слова: *ампакины, ноотропные лекарственные средства, производные 3,7-диазобицикло[3.3.1]нонана, фармацевтическая разработка лекарственных форм, капсулы.*

1. INTRODUCTION

In the last 15 years, stroke remains one of the leading causes of death in the world. According to WHO statistics, in 2015, the death rate in the world from stroke amounted to 6,24 million people, which is exceeded the same indicator in 2000 (5,41 million) by 15,3% (World Health Organization, 2019; Powers, *et al.*, 2018; Hui *et al*., 2020).

Expanding the possibilities of treating patients who suffered acute brain hypoxia or other cerebrovascular diseases is a crucial task of

pharmaceutical development (Clarkson *et al*., 2011; Schitine *et al*., 2012; Su *et al*., 2016; Gudasheva *et al*., 2016; Pyatigorskaya *et al.,* 2018). In recent years, tricyclic derivatives of 3,7-diazabicyclo[3.3.1]nonane- ampakines - which are positive allosteric modulators of glutamate AMPA receptors (PAM-AMPA), have attracted the attention of researchers. Drugs of a similar structure provide the production of neutrophilic factors and have a nootropic effect (Rumyantseva *et al*., 2014; Selyavko, Tsvetkova, 2016; Sernov, Gatsura, 2000).

As a result of the studies carried out by the project developers, computer modeling and optimization of over 200 new structures of the PAM-AMPA receptor - derivatives of 3,7-diazabicyclo[3.3.1]nonane, potentially possessing positive modulatory activity to AMP receptors, was carried out, and the synthesis of the most promising of them was performed (selected by simulation results). Approaches to the synthesis of 3,7-diazabicyclo[3.3.1]nonane derivatives have been developed, which, according to docking data, bind well to the AMPA receptor modulator sites. Based on the analysis of the spatial structure of the AMPA receptor, its complexes with the known PAM AMPA receptor, and the results of their molecular docking, it was shown that compounds of derivatives of 3,7-diazabicyclo[3.3.1]nonane can be highly effective AMPA receptor modulators with pronounced physiological effect (Lavrov, 2011; Zapolski *et al*., 2018).

Physiological researches of the synthesized derivatives of 3,7-diazabicyclo[3.3.1]nonane (bispidine) showed high positive modulation activity against AMPA receptors in vitro tests performed by electrophysiological method, and in vivo tests showed pronounced neuroprotective properties, a significant improvement in memory and cognitive functions in animals (Zefirov *et al.,* 2013).

It is assumed that indications for the use of the obtained compounds, positive AMPA receptor modulators, will include acceleration and improvement of the quality of convalescence after cerebral catastrophes since the acute phase and the phase of convalescence are provided by various pathogenetic mechanisms (Hebert *et al*., 2016; Zakharov, 2014; Skrebitsky *et al*., 2008; Denisov *et al*., 2013).

The section “Pharmaceutical development” in the application for registration of the drug makes possible to present information obtained by applying scientific approaches and managing quality risks in the development of a product and production process. Pharmaceutical development includes comprehensive experimental studies aimed at the scientific justification of the composition of the drug in a particular dosage form, the technological process and its control, the choice of packaging materials, and also contains a study of the physicochemical, biological and microbiological properties of the product. The methodological approach of the pharmaceutical development, currently adopted in the world, is standardized in ICH Q8 Guidelines “Pharmaceutical Development” (Pharmaceutical Development Q8(R2), 2009).

The aim of this work was to develop the drug “3,7-diazabicyclo[3.3.1]nonane” of appropriate quality and justification of the production process with specified functional characteristics.

2. MATERIALS AND METHODS

Pharmaceutical substance based on the derivative 3.7-diazabicyclo[3.3.1]nonane with the chemical name IUPAC 6-[4methoxy-3- (1H-pyrazol-1-yl-methyl) benzyl] -1,11 dimethyl-3,6, 9-triazatricyclo[7.3.1.1]tetradecane-4,8,12-trione, synthesized in the Department of Chemistry, Lomonosov Moscow State University.

Excipients.

Protanal CR 8133® sodium alginate, manufactured by FMC BioPolymer, USA, having a viscosity of 100-300 centipoise (2% solution), with a particle size (0,104-0,125 mm) and an M / G block ratio of 30-40 / 60-70.

Partially pregelatinized Lycatab PGS® corn starch from Roquette, France. The particle size is 100 microns. Sodium Starch Glycolate Colloidal silicon dioxide (Aerosil) with a surface area of 200 m^2/g. Calcium chloride is used as a granulating substance.

Gelatin capsules / HPMC № 3 CAPSUGEL. Capsules filling were performed using a Profiller 2007 manual capsule filling machine (Capsuleconnection, LLC, USA). The solvents and reagents used in the work corresponded in quality to the requirements of Russian Pharmacopeia.

Determination of the particle size of the powder of the substance and the granulate was carried out on the installation for the sieve test of ERWEKA PSS, Germany. Determination of tap density was carried out on a tester "SVM 121" company Erweka GmbH, Germany. Determination of low-ability and angle of repose was carried out on a low-ability tester ERWEKA GTB, Germany,

the size of the outlet of the funnel - 10 and 25 mm; Determination of moisture load was determined using a laboratory instrument AND MS-70 Moisture Analyzer. Drying temperature - 105 °C. Accuracy of determination – 0,01% / min. Granulation was carried out on a laboratory mixer-granulator with a high shear force. The determination of the decay rate was carried out on a “swing basket” type ZT 220 from Erweka GmbH, Germany.

Three media were used: 0,1 M hydrochloric acid solution with pH = 1,2; acetate buffer with pH = 4,5; and phosphate buffer with pH = 6,8. Additionally, 1% of Tween 80 was added to each medium. The medium temperature was (37 ± 0,5) ° C. The volume was 800 ml, and the experiment was carried out without using caps.

The study of the comparative dissolution kinetics was carried out using instrument “arm mixer” at a rotation speed of the stirrer of 50 rpm.

The kinetics of dissolution was studied in three buffer media: with pH = 1,2 (0,1 M hydrochloric acid solution); with pH = 4,5 (acetate buffer) and with pH = 6,8 (phosphate buffer), according to the design of Product specification file the dissolution medium is 0,1 M hydrochloric acid. Since the substance is insoluble in water, 1% Tween-80 was added to the medium. Samples were taken after 5, 10, 15, 30, and 45 minutes in 10 ml portions. The same volume of the corresponding buffer solution was added to the dissolution medium to maintain the volume. The obtained samples were cooled at room temperature, filtered through a blue ribbon paper filter, discarding the first 5 ml of filtrate. The content of the substance in each sample was determined by HPLC.

To obtain statistically reliable results, the study was performed on 6 capsules. The dissolution medium was prepared in accordance with general monograph 1.3.0003.15 "Buffer solutions" (State Pharmacopoeia XIV of Russian Federation). Method of quantitative determination of the released substance. The conditions of the analysis are shown in Tables 1 and 2.

3. RESULTS AND DISCUSSION

The great significance of the dosage form in ensuring the therapeutic performance of drugs has been seriously proven, and today there is no doubt (Zefirov *et al.,* 2013; Demina, 2017; Menshikov, 1986). The rationale of the composition and technology of the dosage form of the original pharmaceutical substance was carried out by taking into account technological and physic and chemical characteristics.

The substance of 3,7-diazabicyclo[3.3.1] nonane is a white, odorless, amorphous powder. It is well soluble in chloroform, acetonitrile, methylene chloride, acetone, dimethylsulfoxide, dimethylformamide, ethyl alcohol, and methyl alcohol. Slightly soluble in diethyl ether, dioxane. Almost insoluble in purified water. Solubility data allow the substance to be classified in the II / IV class of the Biopharmaceutical classification system. The low solubility of the substance will serve as a factor limiting the absorption. To improve the therapeutic performance of such substances, various technologies have been developed to increase both solubility and dissolution rates (Demina, 2015). The results characteristics of the substance of 3,7-diazabicyclo[3.3.1]nonane are shown in Table 3.

Table 3. *Averaged results of determining the technological characteristics of the substance of 3,7-diazabicyclo[3.3.1]nonane, obtained from measurements of 6 samples*

Indicator, unit of measure	Magnitude
Particle size	Less than 100 microns
Flowability, g / s	1, 7±0,2*
Tap density before compaction, g / ml	0,15±0,03
Tap density after compaction, g / ml	0,24±0,02
Angle of repose, degrees	45±3
Humidity,%	0,22±0,3
Carr Index	37,4±0,2
Haussner index	1,59±0,2

*The obtained value is the hole diameter of the funnel - 10 mm.

The results indicate low technological properties of the substance (low-ability, angle of repose single, tap density). Moreover, the powder is dusty and electrified. Based on the calculated values of the Carr and Haussner indices, the low-ability of the substance was rated as "very bad."The obtained information on the characteristics of the substance of 3,7-diazabicyclo[3.3.1]nonane served to choice dosage form - capsules. In the production of capsules, compared to tablets, the active substance is not subjected to stressful technological effects (moistening, drying, pressing), which can adversely affect on release from the dosage form and, possibly, later on,

bioavailability (Demina, 2015).

The experimentally established dosage of 3,7-diazabicyclo[3.3.1]nonane was 15 mg, which is fully consistent with the selected dosage form but justifies the inclusion of excipients. Excipients substances were selected based on their compliance with modern standards of quality, safety and manufacturing. The main filler was sodium alginate. Alginates are high-molecular polysaccharides obtained by extraction and subsequent precipitation with sodium chloride or potassium chloride from Phaeophyceae brown algae, capable of gelation, which is widely used in various dosage forms: pastes, gels, and creams, as well as a release regulator from solid dosage forms. Alginates have mucoadhesive properties that have a positive impact on the efficiency of the insoluble medicinal substance (Kirzhanova *et al.,* 2016). Pregelatinized corn starch is included in the powder mixture as a universal filler and disintegrant, as well as to increase flowability. Sodium starch glycolate was used as a disintegrant to ensure the disintegration of the compacted contents of capsules. As a result, to ensure the release of the active substance in normalized values when conducting an analysis on the “Dissolution” indicator. Aerosil was used as a glidant. The small size of the particles and a large specific surface area prevent the caking of powdered materials and contribute to the redistribution of moisture in the material during granulation. Calcium chloride served as a granulating agent. The composition of 3,7-diazabicyclo[3.3.1]nonane capsules is shown in Table 4.

The powder mixture was granulated before filling into capsules. Perforce to granulating was justified by obtaining a homogeneous composition of the bulk product for the preparation of the contents of the capsules. Due to the low solubility of the substance, not traditional viscous solutions of bonding agents were used as the granulating liquid, but purified water and 95% ethyl alcohol, in which the substance is soluble. Excipients: sodium alginate, pregelatinized starch, and sodium starch glycolate were mixed. The substance was added and again thoroughly mixed, granulated, powdered with aerosil and calcium chloride, previously sifted through a sieve with 0,315 mm holes. The mixture left to distribute moisture in a closed bin for 10-12 hours. It was found during the experiment that the formation of granules when the powder mixture is moistened with purified water, in which the substance is insoluble, proceeds only through pregelatinized corn starch and partially sodium alginate. The resulting product is represented by particles of irregular shape, among which both granules and free particles of substance were present (Swarbrick, 2016; Qualicaps, 2011;Technical Reference File Hard Gelatin Capsules, 2010; Hojava *et al.*, 2013, Gad *et al.*, 2013; Bykovsky *et al.*, 2015; Knitter *et al.,* 2014; Harmonized tripartite guidance ICH Q6A, 2000). Using 95% ethanol as a granulating liquid, in which the substance is well soluble, the granules have a more rounded shape and a smooth surface, there are no particles of the substance in the product. In this case, not only fillers but also pharmaceutical substances take part in the formation of granules due to their dissolution in 95% ethanol. The technique used made it possible to ensure uniformity of dosing, which is extremely important in the manufacture of dosage forms with a low dosage of the substance. The amount of moisturizing liquid used in the granulation process was exactly determined during the experiment for each composition and did not exceed 5% of the total mass of the powder mixture. Averaged results of the determination of the characteristics of the technological granules, obtained as a result of measurements of 6 samples, are given in Table 5.

Table 5. *Averaged results of determining the technological characteristics of the granulate, obtained as a result of measurements of 6 samples*

Indicator, unit of measure	Magnitude
Particle size	100 to 315 microns
Flowability, g / s	5,91±0,04
Tap density before compaction, g / ml	0,44±0,03
Tap density after compaction, g / ml	0,51±0,03
Angle of repose, degrees	35±2
Humidity,%	0,22±0,04
Carr Index	13,72±0,02
Haussner index	1,16±0,02

The results indicate good technological properties of the granulate: the flowability compared with the substance increased from 1,7 to 5,9 g / s, the tap density before compaction increased from 0,15 to 0,44 g / ml, the tap density after compaction - from 0,24 to 0,51 g / ml. Based on the calculated values of the Carr and Haussner indices, the flowability of the substance was rated as “good”. The averaged results of the release of the substance from the hypromelloid capsules into the medium with pH = 1,2 (0,1 M hydrochloric acid

solution, 1% Tween 80), obtained on the basis of the study of 6 samples, are shown in Table 6 and in Figure 1.

The lack of release at the first 5 minutes is caused by the dissolution of the HPMC capsule shell, which is confirmed visually. In general, the results of the determination of the kinetics of dissolution show a significant improvement in the solubility of the insoluble substance as a result of the granulation technology used: in 45 minutes, 64,75 ± 3,0 substances pass into the dissolution medium pH 1,2. However, the result obtained is below the pharmacopeial standards. The lag phase in the kinetics of dissolution in the first 5 minutes may be the reasons for that, due to the solubility of HPMC capsules and the limited solubility of the substance in the medium, as evidenced by the plateau phase of the dissolution curve at 20-45 minutes. As such the presence of the lag phase during releasing of the substance from the hypromellose capsules, a comparative study of their disintegration with disintegration from gelatin capsules in dissolution media was carried out, the results are presented in Table 7.

Table 7. *Averaged results of determining the disintegration of gelatin and hypromellose capsules obtained on 6 samples*

Capsules material	Disintegration time, min		
	pH 1,2	pH 4,5	pH 6,8
HPMC	5 min	13 min 30 seconds	5 min 7 seconds
Gelatin	1 min 45 seconds	2 min 25 seconds	4 min

It can be seen from the data in the table that the gelatin capsules disintegrate faster than the hypromelose capsules, and therefore in the further experiment, gelatin capsules were used. Based on the results of studying the dissolution kinetics in a medium with a pH of 1,2, the volume of the medium was increased to 800 ml, which is recommended for poorly soluble substances. The kinetics of the dissolution of 3,7-diazabicyclo[3.3.1]nonane from gelatin capsules into the medium with pH = 4,5 is shown in Table 8 and in Figure 2.

The release of a substance in the medium with a pH of 4,5 is more intense than in the medium with a pH of 1,2. 37,8 ± 2,1 of the substance was already found at the 5 minutes in the medium with pH 4,5, at the 15 minutes - (72,6 ± 2,5) %. In an acidic medium, during this time, 1% and (50,15 ± 2,20) of the substance are released from the dosage form, respectively. In just 45 minutes, (77,6 ± 2,5) % of the substance passes into the dissolution medium, and this corresponds to the pharmacopeial standards. The slowing down of dissolution after 15 minutes is obviously related to the achievement of the limit of solubility of the substance. It is shown that the developed technology provides the necessary indicators for the release of a substance from the dosage form, which will have a positive impact on the bioavailability of the drug. Table 9 and Figure 3 show the results of studying the kinetics of the dissolution of 3,7-diazabicyclo[3.3.1]nonane from gelatin capsules to a medium with a pH of 6,8.

In the medium with a pH 6,8, as well as in the medium with a pH 4,5, there is an intensive release of the substance in the first 5 minutes, which is ensured by the rapid solubility of gelatin capsules. In general, the dissolution of the substance is somewhat slow, by the 45th minute (63,32 ± 2,3) % was found in the medium.

4. CONCLUSIONS

The results of the determination technological characteristics of the pharmaceutical substance 3,7-diazabicyclo[3.3.1] nonane served as a justification for the development of the composition of the dosage form - a capsule. The developed dosage form corresponds to modern requirements for pharmacopoeial quality levels, including release kinetics: according to obtained results, in 45 minutes (77,6 ± 2,5) % of the substance passes into the dissolution medium with a pH of 4,5, which corresponds to the pharmacopeial standards. It should be noted that the substance is very little soluble in water, increasing its solubility is achieved as a result of the proposed technology for obtaining the dosage form. The results of the study served as the basis for the development process map of obtaining the dosage form of 3,7-diazabicyclo[3.3.1]nonane, indicators, and quality standards. Thus, as a result of the granulation technology used, selection of excipients and the dosage form, it was possible to obtain the standard dosage form “3,7-diazabicyclo[3.3.1]nonane capsules 15 mg”, which corresponds to the pharmacopoeial requirements.

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Table 1. *Chromatographic conditions of analysis*

Chromatographical column:	**POROSHELL 120 EC-C18, 2.1*50mmID, 2.7µm**
Eluent A:	0,1 % TFAinMeCN (0.1 % trifluoroacetic acid in acetonitrile)
Eluent B:	0,1 % TFAinH_2O (0.1 % trifluoroacetic acid in water)
Sample quantity:	20 µL/ Needle wash with MeCN
Flow rate:	1,0 mL/min
Chromatography time:	12 мин
Column Temperature:	25°C
Autosampler temperature:	4 °C
Detectors wavelength:	233nm/Bw4nm; Ref:400nm/Bw100nm.

Table 2. *Elution mode*

Gradient elution		
Time, min	**Eluent A, %**	**Eluent B, %**
0	0.0	100.0
1.0	0.0	100.0
7.0	100.0	0.0
9.0	100.0	0.0
9.1	0.0	100.0
12.0	0.0	100.0

Table 4. *Excipients in the composition of the drug "3,7-diazabicyclo[3.3.1]nonane, 15 mg capsules", their qualifications and purpose*

No	**Component Name**	**Method of control**	**Purpose**
1.	Sodium alginate	Eur. Ph.	Filler
2.	Pregelatinized corn starch	Eur. Ph	Filler, granulometry substance
3.	Sodium starch glycolate	Eur. Ph.	Disintegrant
4.	Colloidal silicon dioxide	Eur. Ph.	Sliding, moisture distributor
	Calcium chloride	Pharmacopoeial monograph 42-2567-00	Granulating substance
	Gelatin capsules	CAPSUGEL, USA	
5.	Gelatin		Capsule material
6.	Titanium Dioxide (E171)		Dye
7.	Triacetin		Plasticizer
8.	Polysorbate 80		Plasticizer
	Hypromelous Capsules (HPMC) Hydroxypropylmethylcellulose Plasticizer (internal standard of the manufacturer)	CAPSUGEL, USA	

Table 6. *Dissolution of 3,7-diazabicyclo[3.3.1]nonane from hypromellose capsules into the medium with a pH 1.2*

Test sample	Release substance,%					
	5 min	10 min	15 min	20 min	30 min	45 min
3,7-diazabicyclo[3.3.1]nonane 15 mg, capsules	1±1	35,9± 1,8	50,15± 2,20	61,87± 2,15	63,36± 1,98	64,75± 3,0

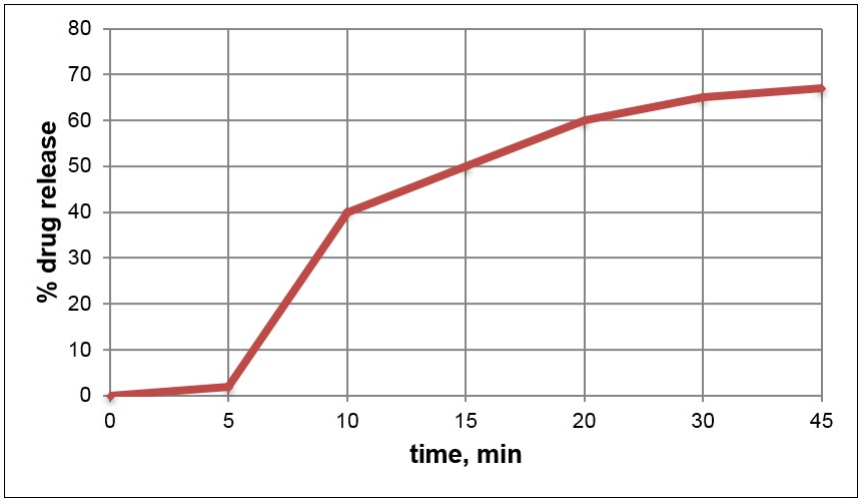

Figure 1. *The average dissolution profile of the drug "3,7-diazabicyclo[3.3.1]nonane 15 mg capsules". Dissolution medium - hydrochloric acid buffer solution with a pH 1,2*

Table 8. *Dissolution of 3,7-diazabicyclo[3.3.1]nonane from gelatin capsules into the medium with pH = 4.5*

Test sample	Release substance,%					
	5 min	10 min	15 min	20 min	30 min	45 min
3,7-diazabicyclo[3.3.1]nonane 15 mg, capsules	37,8± 2,1	64,5± 1,5	72,6± 2,2	73,7± 2,5	75,6± 1,9	77,6± 2,5

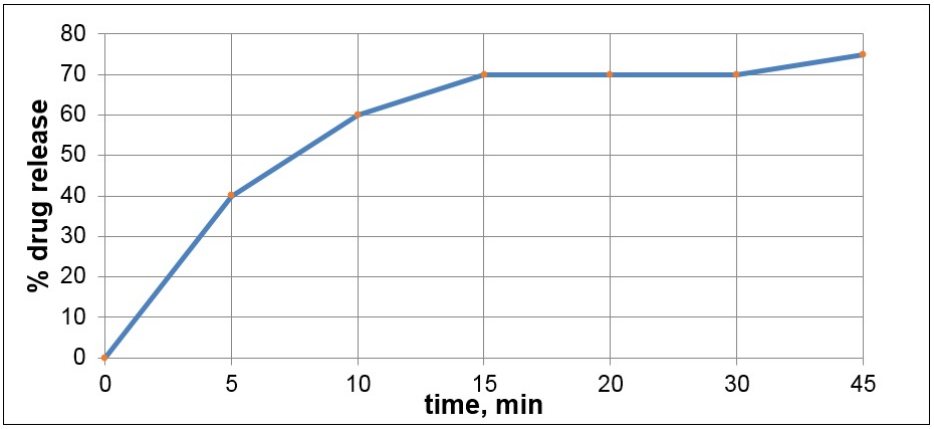

Figure 2. *Averaged dissolution profile of the drug "3,7-diazabicyclo[3.3.1]nonane 15 mg capsules". Dissolution medium - acetate buffer solution with pH 4.5*

Table 9. *Dissolution of 3,7-diazabicyclo[3.3.1]nonane from gelatin capsules into the medium with pH 6,8*

Test sample	Release substance,%					
	5 min	10 min	15 min	20 min	30 min	45 min
3,7-diazabicyclo[3.3.1]nonane 15 mg, capsules	35,54±2,2	44,23±3,0	54,40±2,87	58,71±2,0	60,10±3,1	63,32±2,3

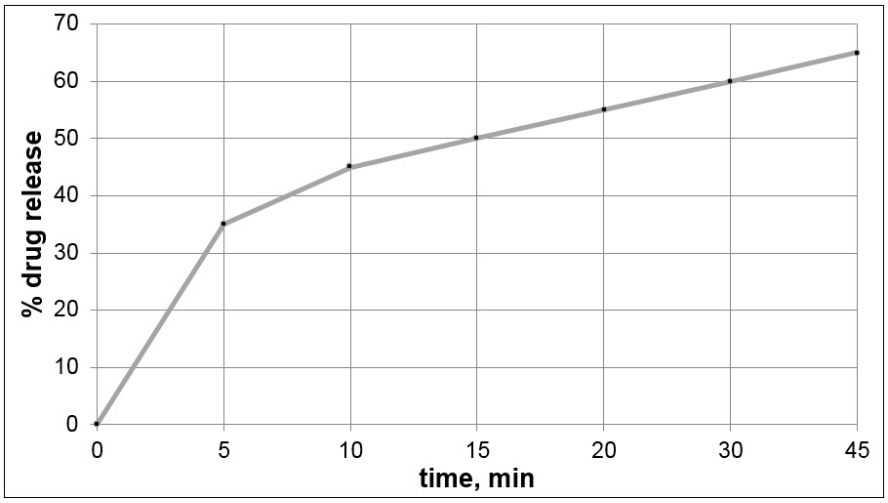

Figure 3. *The average dissolution profile of the drug "3,7-diazabicyclo[3.3.1]nonane 15 mg capsules". The dissolution medium is a phosphate buffer solution with pH 6,8*