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The research on creation the dosage form based on 3-(4-nitrophenyl)-5-(nonylsulfonyl)-1,2,4-triazol-4-amine

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Key words: Triazoles, Dosage Forms.

Aim. To research the dosage form based on 3-(4-nitrophenyl)-5-(nonylsulfonyl)-1,2,4-triazole-4-amine.

Materials and methods. Based on synthetic, physical-chemical and pharmacological studies of 4-amino-5-(2-,3-,4-nitrophenyl)-1,2,4-triazole-3-thiones, the 3-(4-nitrophenyl)-5-(nonylsulfonyl)-1,2,4-triazole-4-amine has been selected for further study, as in previous research this compound showed high actoprotective, antioxidant, neuroprotective activity and can find its application as a potential drug.

Conclusions. A complex of physical-chemical and pharmaco-technological research have been conducted that allowed to predict the gastrointestinal tract part, where absorption will be after oral administration, and allowed to propose a model dosage form.

Дослідження зі створення лікарської форми на основі 3-(4-нітрофеніл)-5-(нонілсульфоніл)-1,2,4-тріазол-4-аміну

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З метою дослідження зі створення лікарської форми на основі синтетичних, фізико-хімічних і фармакологічних досліджень похідних 4-аміно-5-(2-,3-,4-нітрофеніл)-1,2,4-тріазол-3-тіонів для подальшого вивчення обрали 3-(4-нітрофеніл)-5-(нонілсульфоніл)-1,2,4-тріазол-4-амін. У попередніх дослідженнях виявили, що 3-(4-нітрофеніл)-5-(нонілсульфоніл)-1,2,4-тріазол-4-амін виявляє високу актопротекторну, антиоксидантну, нейропротекторну активність і може застосовуватись як потенційний лікарський засіб. Для цієї речовини здійснили комплекс фізико-хімічних і фармако-технологічних досліджень. Результати дають змогу прогнозувати, в якому відділі шлунково-кишкового тракту відбуватиметься всмоктування при пероральному прийманні, а також запропонувати модельну лікарську форму.

Ключові слова: 1,2,4-тріазол, лікарська форма.

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Исследования по созданию лекарственной формы на основе 3-(4-нитрофенил)-5-(нонилсульфонил)-1,2,4-триазол-4-амин

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С целью исследования по созданию лекарственной формы на основе синтетических, физико-химических и фармакологических исследований производных 4-амино-5-(2-,3-,4-нитрофенил)-1,2,4-триазол-3-тионов для дальнейшего изучения отобрано 3-(4-нитрофенил)-5-(нонилсульфонил)-1,2,4-триазол-4-амин. В предыдущих исследованиях установлено, что 3-(4-нитрофенил)-5-(нонилсульфонил)-1,2,4-триазол-4-амин проявил высокую актопротекторную, антиоксидантную, нейропротекторную активность и может найти свое применение как потенциальное лекарственное средство. Для данного вещества проведен комплекс физико-химических и фармако-технологических исследований. Результаты исследований позволяют прогнозировать, в каком отделе желудочно-кишечного тракта будет происходить всасывание при пероральном приеме, а также предложить модельную лекарственную форму.

Ключевые слова: 1,2,4-триазол, лекарственная форма.

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The design of dosage forms based on new biologically active compounds is one of the priorities of modern pharmaceutical science. Particular attention of researchers is attracted to chemical modification of heterocyclic molecules as perspective direction in the creation of potential drugs. Modern medicine successfully uses 1,2,4-triazoles. Primarily this is the group of antifungal drugs (Fluconazole, Itraconazole), drugs with antidepressant (Trazodone, Alprazolam), hepatoprotective, wound healing and antiviral (Thiotriazolin) effects. Based on this, to keep on the search of biologically active substances among 1,2,4-triazole derivatives is actual both from theoretical and practical point of view.

It should be noted that the pharmacological effect of all medicines based on 1,2,4-triazoles is influenced by presence, nature and position of substituents in 1,2,4-triazole cycle. The search

of pharmacologically active agents among the derivatives of this heterocyclic system is reflected in many works both of our country [1,2] and foreign [3] scientists. But there is almost no information in literature regarding the synthesis and biological properties of 4-amino-5-(2-, 3-, 4-nitrophenyl)-1,2,4-triazole-3-thiones and its derivatives, which may be potential substances that will form the basis for new drugs. It should be also noted that the creation of new pharmaceutical drug involves a whole range of researches, including the creation of potential dosage forms.

Purpose

The main aim of our work was to determine the physical-chemical and pharmacological-technological properties of 3-(4-nitrophenyl)-5-(nonylsulfonyl)-1,2,4-triazole-4-amine, that in previous researches has shown high actoprotective, antioxidant, neuroprotective activity, as well as to develop the technology of model dosage form based on the obtained results.



Experimental part

Working on the search of biologically active compounds among 4-amino-5-(2-, 3-, 4-nitrophenyl)-1,2,4-triazole-3-thiones we have obtained a series of 3-alkylthio-5-(2-, 3-, 4-nitrophenyl)-4-amino-1,2,4-triazoles and explored the reaction of their further oxidation [4]. From the previous study results of pharmacological activity of the synthesized substances most active compound, namely 3-(4-nitrophenyl)-5-(nonylsulfonyl)-1,2,4-triazole-4-amine (fig. 1), has been selected and the development of potential dosage form has been proposed.

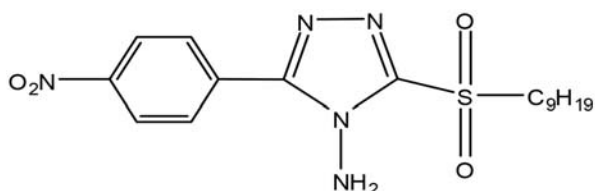


Fig. 1. Structural formula of 3-(4-nitrophenyl)-5-(nonylsulfonyl)-1,2,4-triazole-4-amine.

We should pay attention to the fact that the solubility of substances plays an essential role in the action of drugs, primarily intended for oral administration, as the maximum rate of passive drug transport through biological membranes (which is the main way of absorption) depends on the permeability and solubility. Therefore, to predict the solubility of the synthesized compounds and the part of gastrointestinal tract where absorption will occur, we have found ionization constant.

Calculation of ionization constants for 3-(4-nitrophenyl)-5-(nonylsulfonyl)-1,2,4-triazole-4-amine have been predicted by Speakman and Beyts methods [5,6]. Experimental determination of ionization constants of 3-(4-nitrophenyl)-5-(nonylsulfonyl)-1,2,4-triazole-4-amine has been carried out at the Department of physical-colloidal chemistry at Zaporozhye State Medical University by potentiometric titration of samples in aqueous solution [7]. The point of equivalence has been determined with using device for measuring ions ЭВ-74 using glass (ЕЦІ6307) and silver chloride (ЕВІ1193) electrodes. Measurements have been performed in cell that has been thermostated to the standard (20°C) temperature. To determine the ionization constants 0.01 M solutions of the compounds (1–16, table 1) have been titrated with 0.1 M solution of hydrochloric acid and parallel with solution of 0.1 M potassium hydroxide, every ten portions of 0.25 ml each using a pipette dosing П-1 with measuring pH after each addition of titrant. Constants have been calculated using formula (1) by the average of experiments with deviations not exceeding 0.05 units.

$$pK_a = pH + \lg ([A] / [B]) \quad (1)$$

where [A] is equilibrium concentration of acid, mol/L, [B] is base equilibrium concentration, mol/L.

Calculated and experimentally obtained ionization constant pKa for the 3-(4-nitrophenyl)-5-(nonylsulfonyl)-1,2,4-triazole-4-amine are equal to 1.07 and 1.15 respectively. This allowed us to predict the gastrointestinal tract part where absorption will occur after oral administration, – namely, in the stomach.

Table 1
Physical-technological properties
of 3-(4-nitrophenyl)-5-(nonylsulfonyl)-1,2,4-triazole-4-amine

Investigated parameters	Units of measurement	Indicators
Physical properties		Brown crystalline solid substance, odorless.
Melting point	°C	129
Solubility		Water 1:1000 Ethanol 1:1 0,001 N solution of HCl 1:10
Calculated pKa		1,07
Experimental pKa		1,15
Bulk density before/after shrinkage	g/ml	0,340±0,025/ 0,453±0,021
Fluidity	s/100 g sample or (g/s)	40,0±1,0 (2,5±0,06)
Angle of repose	degree	27,0±0,3
Moisture	%	3,44±0,13

Analysis of know data on the value of dosage forms and the routes of administration in the overall assessment of therapeutic action leads to the conclusion that rationally selected dosage form allows to use maximum medicinal effect of drugs with minimal side effects, substantially change the nature of the substance, to speed up the absorption or excretion, reduce the analgesic action where it is necessary, to improve the organoleptic properties of the drug, etc. [8].

To select rational dosage form we have investigated physical-chemical and pharmacological-technological properties of 3-(4-nitrophenyl)-5-(nonylsulfonyl)-1,2,4-triazole-4-amine, as the main active ingredient. The results are shown in table 1.

Based on the results, and paying to attention the ease of use and affordability, tablet form was offered as the best and the one that best meets the demands of current pharmaceutical market.

While designing the composition and technology of tablets it is advisable to use direct pressing of powders that would eliminate the step of humidifying and drying of tablet weight and would reduce the cost of drugs [8].

Getting the model tablets has been performed by direct compression, in the content of active ingredient in the tablet – 0,015 g.

Excipients that provide optimal technological properties for tableting mass have been used to obtain the model tablets for 0.30 g by using direct compression method [9]. So to provide moisture sorption properties aerosil A-380 has been used. To select optimal content we studied the influence of aerosil concentrations on fluidity of tablet mass with 3-(4-nitrophenyl)-5-(nonylsulfonyl)-1,2,4-triazole-4-amine. The results are shown in fig. 2.

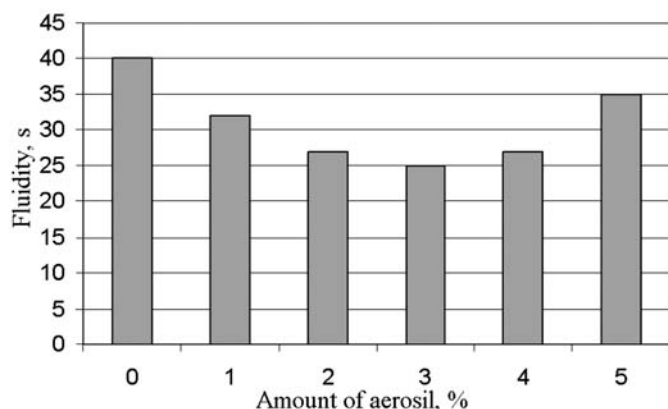


Fig. 2. The influence of aerosil concentrations on fluidity of tablet mass.

Fig. 2 shows that the addition of aerosilin an amount up to 3% of the sample total weight increases fluidity. With further increase of aerosol concentration the fluidity of mixture decreases. Thus, the optimum amount of aerosol in a model formis 3%.

To ensure sufficient adhesion of the particles in tablets and to increase compressibility, a dry binder – microcrystalline cellulose (MCC) was added into tablet. The results of studies on the dependence of resistance to crushing on the number of MCC are shown in fig. 3.

From these data it follows that with the increase of MCC in the tablet the resistance to crushing increases irregularly. The optimal content of MCC in tablet is 4.0–5.0%, which provides the necessary resistance to crushing.

The corn in amount of 15% of tablet weight was injected to the tablet form to ensure the desired disintegration time. In order to reduce the forces for pushing pills from matrix, tablet mass formulations containing such moving substances and lubricants as medical talc in an amount of 5.0% magnesium stearate in amount of 1.0% and combination of 2.0% medical talc and 1.0% magnesium stearate have been studied.

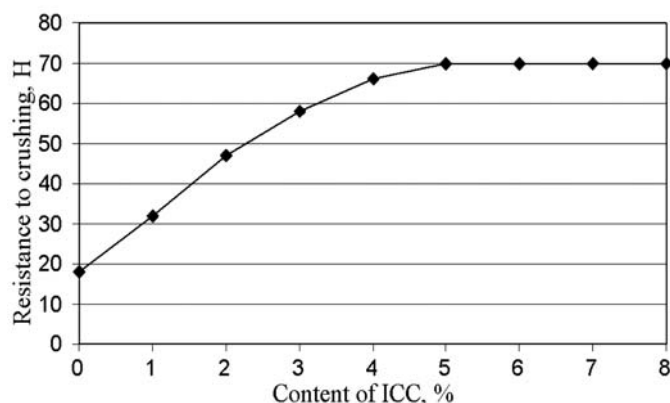


Fig. 3. The dependence of resistance to crushing on the number of MCC.

It is established that it is optimal to use a combination of 2.0% medical talc and of 1.0% magnesium stearate.

It was studied experimentally, that the optimal residual moisture content in weight for tablet must be within $(4,5 \pm 0,5)\%$.

On the basis of these studies technological process of obtaining tablets with 3-(4-nitrophenyl)-5-(nonylsulfonyl)-1,2,4-triazole-4-amine has been created. Modeling dosage form in the form of tablets consists to the requirements of SPU – 1 species [10].

Conclusions

Experimental and theoretical definition of pKa constant for 3-(4-nitrophenyl)-5-(nonylsulfonyl)-1,2,4-triazole-4-amine has been obtained. This allows us to predict the gastrointestinal tract part where absorption will occur after oral administration.

Based on pharmacological and technological research 3-(4-nitrophenyl)-5-(nonylsulfonyl)-1,2,4-triazole-4-amine has been selected for further study in tablet dosage form.

Based on the research technological process for obtaining tablets with 3-(4-nitrophenyl)-5-(nonylsulfonyl)-1,2,4-triazole-4-amine has been developed.

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