Розроблено нову систему міцелярної інактивації активних фармацевтичних інгредієнтів фосфорорганічної природи. Проведено дослідження деструкції метилпаратіону за допомогою міцелярної системи на основі цетилпіридинію хлориду та пероксиду водню, активованого борною кислотою. Запропоновано модельний миючий засіб для очищення технологічного обладнання та проведено оцінювання ризиків для якості при його використанні на фармацевтичному підприємстві

Ключові слова: деконтамінація, міцелярна система, фосфорорганічні сполуки, очищення технологічного обладнання, ризики якості

Разработана новая система мицеллярной инактивации активных фармацевтических ингредиентов фосфорорганической природы. Проведено исследование деструкции метилпаратиона с помощью мицеллярной системы на основе цетилпиридиния хлорида и пероксида водорода, активированного борной кислотой. Предложено модельное моющее средство для очистки технологического оборудования и проведена оценка рисков для качества при его использовании на фармацевтическом предприятии

Ключевые слова: деконтаминация, мицеллярная система, фосфорорганические соединения, очистка технологического оборудования, риски качества

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DEVELOPMENT OF MICELLAR SYSTEM FOR THE DECONTAMINATION OF ORGANOPHOSPHORUS COMPOUNDS TO CLEAN TECHNOLOGICAL EQUIPMENT

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1. Introduction

The problem of environmental protection from the effects of hazardous substances today occupies one of the leading places in the industrial sector, particularly in chemical and pharmaceutical industries. Protection of environment and humans from harmful action of poisonous substances is the main challenge for the government and business leaders. It is also an urgent direction of work of scientists in the fields of chemistry, biochemistry, toxicology and pharmacy. Not the least among others is the problem of disposal of residual organophosphorus compounds (OPC), which are used in pharmaceutical industry (active pharmaceutical ingredients (API)) and in chemical industry (products and intermediate products of fine organic synthesis). This problem is characteristic for agriculture (pesticides) and the military-industrial complex (combat poisonous substances).

At the basis of chemical methods of neutralization of OPC, most often used today [1], is the process of hydrolysis in aqueous solutions of alkalis. However, the effectiveness of these methods often does not lead to the expected results. Taking into account the hydrophobic nature of FOS, optimal decontamination system must provide solubilization and simultaneously contribute to increasing the rate of decomposition of substrates. A promising field of research in the process of creation ecologically safe decontamination compositions is the application of micellar solutions [2]. Concentration of reagents occurs in them and favorable conditions for nucleophilic attack on electrophilic centers of OPC are created. Hydrogen peroxide can be considered a universal agent when creating formulas of "soft" and environmentally safe decontamination systems [3–5]. Therefore, the search for new efficient, ecologically safe systems of OPC decontamination appears to be relevant.

2. Literature review and problem statement

Phosphor organic compounds are widely used in protecting cultivated plants from pests within selective

toxicity, based on differences in the structure of the cholinesterase of the warm-blooded and insects. Features of interaction of OPC with cholinesterase of both irreversible and reversible inhibitors are studied and used in toxicology and pharmacology. These effects are used to produce therapeutic effect in those cases when you need to adjust the transmission of nerve impulse to the controlling element.

Pesticides are known to have been used as early as at the beginning of the 20th century. In the world practice approximately 200 pesticides have become wide spread, especially in agriculture [6].

At the same time, numerous data indicate the occurrence of chromosomal aberrations in lymphocytes of residents of the territories adjacent to the agricultural areas that are exposed to the POS treatment. The same effect is observed in people who were involved in the production and application of FOS [6].

A vivid example of OPC is methylparathion, which is not only a pesticide agent, but also a model of phosphorus anti-cholinesterase ecotoxicants. Methylparathion is considered to be an analog of nervous-paralytic poisons that are used in the studies on disposal of residues of chemical weapons. Methylparathion is produced around the world and is registered for the treatment of many cultures [6].

Poisoning with organophosphorus compounds is known to be the cause of death of 200 thousand people in the world annually [6]. However, despite the Convention on the prohibition of chemical weapons [7], the threat of the use of nervous – paralytic agents and other OPC during military actions and terrorist acts remains.

Under the control of the Congress of the United States, the program of alternative technologies (Chemical Stockpile Disposal Program) [8] was developed. The purpose of this program is to develop effective process of degradation of products and media (reaction mass), formed during chemical destruction of OPC [9].

Today, the most common method of chemical decomposition of OPC is alkaline hydrolysis. In the course of hydrolysis of methylparathion, 4-nitrophenol and dimethylteophosphite acid, paraoxonium – 4-nitrophenol and dimethylphosphate acid [10], 4-nitrophenylphosphate – 4-nitrophenol and phosphate acid [11] are formed.

Another proposed system of OPC neutralization is based on the fact that reactionary masses, obtained in chemical destruction of VX substances, are treated with oxidants for decomposition of esters of methylphosphonic acid. Released acid is precipitated by solution of ferric chloride in the form of insoluble complex compounds. Technology of decomposition of poisonous substances provides for 95–97 % removal of phosphonates [9].

Methods of alkaline hydrolysis of OPC display varying effectiveness. As one of the options, the method of recycling [1] of highly toxic pesticide preparation dimetoat was described. This method involves treatment of pesticide preparation by aqueous-alkaline solution of a substance in the mole ratio of pesticide preparation: NaOH=1:7. As a result of the reaction, the output of soduim ortophosphate is 91.1 %, indicating fairly high effectiveness of this method of disposal.

Methods of hydrolysis with hydrogen peroxide are rather effective [4]. Hydroperoxide-anion HOO^- is one of the most active α-nucleophiles, while H_2O_2 is a rather weak oxidant [2]. To enhance oxidative properties of H_2O_2, different activators of acid nature, which turn it into peroxoacid, are used [2]. With regard to the problem of degassing of OPC, the method of activation of H_2O_2 under the influence of hydrocarbonate-ion HCO_3^- is of interest [4]. However, the use of this method in water systems is limited by extremely low solubility of OPC, which are viscous oils. Therefore, methods of hydrolysis in micro emulsions require special attention [3, 5].

Research into the area of influence of surfactants (SAS) on the kinetics of organic reactions in aqueous solutions has recently formed an independent section of physical and organic chemistry. This particular interest is caused by the fact that they open up new opportunities for adjusting the rates of chemical reactions and studying their mechanism [12, 13].

In the presence of SAS, as a rule, 10–100 multiple acceleration of reaction occurs: in some cases the rate of reactions increases by 10^3–10^4 times [12, 13]. These effects are finally found to have been caused by existence of not individual molecules, but rather of associates of a large number of SAS molecules – micelles. It was found that aqueous solutions containing hydrogen peroxide, cation detergent and activator, within pH values of (8–9) provide a high degree of solubilization of the substrate, increase reactivity of oxidizers and nucleophiles (compared to aqueous solutions), are easy to prepare and environmentally friendly [13].

One of the priority tasks facing producers of medical preparations based on API of organophosphorus nature is to maintain cleanliness of technological equipment before and after production of a series of preparation. The proof that equipment cleaning is performed properly is a conducting validation of cleaning process. The applied agents should be certified and permitted for using in pharmacy.

Validation establishes that the developed system of quality evaluation meets expectations and needs of consumer and requirements of the system. One of the main documents, regulating the validation procedure, is the Validation Master Plan, the document that describes philosophy, strategy and methodology of an enterprise in conducting validation.

Validation objects include facilities, equipment, technological process, analytical methods, and computerized systems. The process validation (PV) includes validation of a technological process, validation of analytical methods, and validation of cleaning processes.

The need of providing high quality of products was the reason for creation of a large number of detergents and disinfectants. Depending on production needs, detergents vary in composition: SAS-based, quaternary ammonium salts, alkaline, acidic, neutral, disinfectants; in addition, there are intensifiers of cleaning ability, etc. (Table 1).

A comparative analysis of the composition showed that commercially available cleansers, which are now used at pharmaceutical enterprises, do not guarantee effective equipment cleaning from OPC. Therefore, development of a new composition of cleanser that effectively decontaminates OPC from the surfaces of equipment is a relevant problem for organization of ecologically safe manufacturing products containing OPC.

Table 1

Commercially available cleansers for technological equipment

No. of entry	Cleanser name	Characteristic		Composition	Manufacturer
1	Cosa CIP 92	Liquid alkaline cleanser (pH of 1 % solution is 11,5–12,5)	Removes organic contaminations: fats in cream residues, ointments, emulsions and carbopol	Non-ionic SAS, sodium salts of organic acids and phosphonates, water	Ecolab GmbH, Germany
2	TEA-salt ABSA	Viscous brown liquid (pH of 35 % solution is 6,0 – 9,0)	Effectively removes fat and mechanical contamination	Triethanolamine salt, alkilbenzolsulphoacids, water	"Nova-Chim" (Ukraine)
3	DDM ECO	Disinfectant liquid alkaline cleanser (pH of 1 % solution is 11,7)	Well dissolves and removes protein at room temperature protein and fat contamination, residues of blood, medicines, etc.	Dodecyldimethyl-ammonium chloride, SAS, water	Laboratoires ANIOS (France)
4	Microbacforte	Disinfectant liquid cleanser (pH of 1 % solution is 8,5)	Has bactericidal, fungicidal, tuberculocidal, virulocidal properties	Benzalkonium chloride, dodecylbis propylene triamin, glycerin oil, SAS, foam regulators, inhibitors of corrosion, flavors, water	BODE CHEMIE GmbH, Germany
5	Socrena	Disinfectant liquid alkaline cleanser (pH of 1 % solution is 12,5)	Bactericidal, fungicidal, dissolves fats	Ammonium dodecylmethyl chloride, SAS, corrosive inhibitors, complexing agents, foam regulators	BODE CHEMIE GmbH, Germany

3. The aim and tasks of the study

The main goal of present study is to develop a model composition of a new cleanser for cleaning technological equipment based on the micellar system of OPC inactivation.

The set aim implies solving some interrelated problems:

– development of the system of micellar inactivation of API-OPC;

– design of a model composition of detergent for cleaning production equipment from the residues of API of organophosphorus nature;

– risk analysis for the quality of production station and cleaning process of the reactor using the chosen system of inactivation of the residues of organophosphorus API.

4. Materials and methods of examining kinetics of decomposition of methylparathion under conditions of micellar catalysis

4. 1. Materials and equipment used in the experiment

In the study we used methylparathion (Sigma-Aldrich, Inc., Germany), hydrogen peroxide (Alfa Aesar, Germany), boric acid and potassium hydroxide (Sigma-Aldrich, Inc., Germany), cetylpyridine chloride (Dishman Pharmaceuticals & Chemicals Limited, India), 1.4-dioxane (Alfa Aesar, Germany).

To carry out kinetic studies, the following equipment was used: pH meter "pH-150 MI" (Russian Federation); scanning UV-spectrophotometer "OPTIZEN POP" (Mecasys, South Korea); laboratory plant of water preparation systems RO-4 (Werner, Germany); plant for obtaining first-class high-purity water Sartorius Stedim biotech Arium H2O pro DI-T (Sartorius, Germany); analytical balance AccuLab ALC 110.4 (Sartorius, Germany); water thermostat Brookfield TC-200 with cooling system Brookfield TC-350 (Brookfield, United States of America). In addition, we used the following auxiliary materials:

– cuvettes made of optical glass with thickness of optical layer 1 cm;

– single-channel automatic dispensers 5–50 ml, 100–1000 ml;

– disposable rubber gloves;

– first-class and third-class water;

– a waste bin;

– a timer.

4. 2. Preparation of source and resulting solutions of reagents

Preparation of source aqueous solutions was carried out based on cetylpyridine chloride (CPC), H_2O_2, KOH. Preparation of working solutions was carried out by pouring the source solutions in equal quantities. The necessary pH level was achieved by adding concentrated solution of KOH.

Preparation of solution of methylparathion was carried out by dissolving the weighed portion in 1.4-dioxane, which was preliminary purified by the method of double distillation.

4. 3. Carrying out kinetic measurements of the process of decomposition of methylparathion

The volume of the sample of kinetic solution made 1515 ml, in which the volume of methylparathion was 15 ml. Kinetic solutions were prepared by pouring working solutions. During the study, a comparison of rates of the reaction of alkaline and peroxide hydrolysis of methylparathion in micellar medium of CPC was conducted. In addition, reactions using the activator of peroxyanion $B(OH)_3$, were studied. The measurement of optical density of 4-nitrophenol, formed during the reaction, was conducted by spectrophotometry at wavelength 400 nm; during measurement, temperature of the solution was 25±0.1 °C.

Constants of rates of first-order reactions were calculated by formula (1):

$$k_{ob}^1 = \frac{1}{t} \cdot \ln \frac{D_\infty - D_0}{D_\infty - D_t}, \quad (1)$$

where t is the time of reaction; D_∞ is the value of optical density after the end of the reaction; D_t is the value of optical density at a certain moment of time; D_0 is the value of optical density at the beginning of the reaction.

$$k^2 = \frac{k_{ob}^1}{[H_2O_2]_o} = \frac{k^2 + (k^2 / V)K_S K_{HOO^-} D_n}{(1 + K_S D_n)(1 + K_{HOO^-} D_n)}, \quad (2)$$

where K_{HOO^-} and K_S are the constants of micellar binding by peroxyanion and substrate; $[H_2O_2]$ is the concentration of solution of hydrogen peroxide; k_{ob}^1 is the constant of rate of the first-order reactions; V is the molar volume of SAS; k_B^2 is the constant of rate of the second-order reactions for aqueous solution; D_n is the concentration of SAS at a moment of time, D_n=[SAS]–CCM (critical concentration of micellar formation).

5. Results of studying destruction of methylparathion under conditions of micellar catalysis

5. 1. A system of micellar inactivation of API of organophosphorus nature

Studies of inactivation of OPC were conducted based on the techniques, presented in the articles [3–5]. The study of degradation of methylparathion was held by the kinetic spectrophotometric method using organized nanodimensional systems – micellar solutions. Concentration of reagents takes place at the separation border between the micellar phase (oil drop) and water. Additionally, favorable conditions for the nucleophilic attack on electrophilic centers of OPC are created.

Hydrogen peroxide was used as a nucleophile. It has a dual nature (an effective oxidizer in relation to OPC analogues of yperite and reactive α-nucleophile in reactions of nucleophile replacement in phosphorus organic ethers). Therefore, it may be considered as a universal agent in creating formulas of "soft" and environmentally safe degassing systems. Cationic cetylpyridine chloride (CPC) was used as a detergent, because anionic detergents slow down the processes in the studied systems.

At relatively high reactive capacity in relation to paraoxone, yprite and their analogues, micellic water systems based on peroxides and peroxyacids are extremely unstable. In alkaline medium (pH>10) OPC are rapidly destroyed as a result of nucleophilic attack of hydroperoxide and hydroxydions on a phosphorus atom to form peroxyacids, which irreversibly decompose to phosphonic acids [4].

Peroxoanions are mostly active at values of pH≤9. For successful flow of nucleophilic reactions involving HOO^- ion, one should use more alkaline media. This is due to the fact that the constant of ionization of hydrogen peroxide has the value of pK_a=11.6. Thus, at pH≤9.0 only 0.03–0.3 % of hydrogen peroxide is located in the ionic reactive form HOO^-.

Conversion of methyparathion in solution H_2O_2–HO^- in all the studied media occurs mainly in two ways: perhydrolysis with generated HOO^--anion (H_2O_2+HO–H_2O+HOO^-) and alkaline hydrolysis with the help of HO^--anions (Fig. 1).

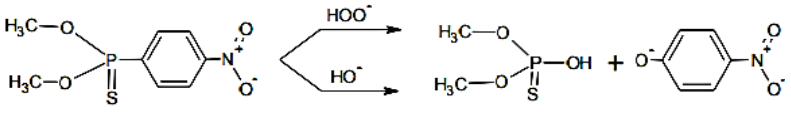

Fig. 1. Chemical scheme of converting methylparathion into H_2O_2–HO^- solution

In this case, contribution of alkaline hydrolysis is minimal and does not exceed 1–5 % of the total rate of substrate decomposition [13].

Hydrogen peroxide in micellar systems in a neutral form is known to be a weak oxidizing agent. Therefore, it is activated using hydrocarbonates, molybdates, phthalates, nitrites and other compounds that form highly active peroxyacids in the reaction with H_2O_2 [2].

Boric acid ($B(OH)_3$) may serve a perspective activator, which during the interaction with hydrogen peroxide forms perborates:

$$B(OH)_3 + H_2O \leftrightarrow B(OH)_4^- + H^+; \quad (1)$$

$$B(OH)_4 + H_2O_2 \leftrightarrow B(OH)_3(OOH)^- + H_2O; \quad (2)$$

$$B(OH)_3(OOH) + H_2O_2 \leftrightarrow B(OH)_2(OOH)_2^- + H_2O; \quad (3)$$

$$B(OH)_2(OOH)_2^- + H_2O_2 \leftrightarrow B(OH)_2(OOH) + H_2O. \quad (4)$$

Reactions involving HCO_4^--anions proceed by more than two orders of magnitude faster in comparison with oxidizing hydrogen peroxide. While in reaction with monoperborate and dipeborate, at pH 8–9, the rate is 3–8 times as high. In a more alkaline medium, constants of rates of second-order reactions of substrates with monopeborate and diperborate are about 2.5 and 100 times higher than with hydrogen peroxide [2].

To determine the optimal detergent concentration, at which the rate of reaction of hydrolysis of methylparathion under conditions of micellar catalysis is the highest, the study of dependences of values of rate constants of first-order reactions on the concentration of OPC was carried out (Fig. 2).

Determined mean values of rate constants of second-order reaction k_{ob}^2 for the studied systems of inactivation of methylparathion made: for decontamination systems CPC/H_2O_2/H_2O – 0.07 $M^{-1} \cdot s^{-1}$, for decontamination systems $B(OH)_3$/CPC/H_2O_2/H_2O – 0.17 $M^{-1} \cdot s^{-1}$, respectively.

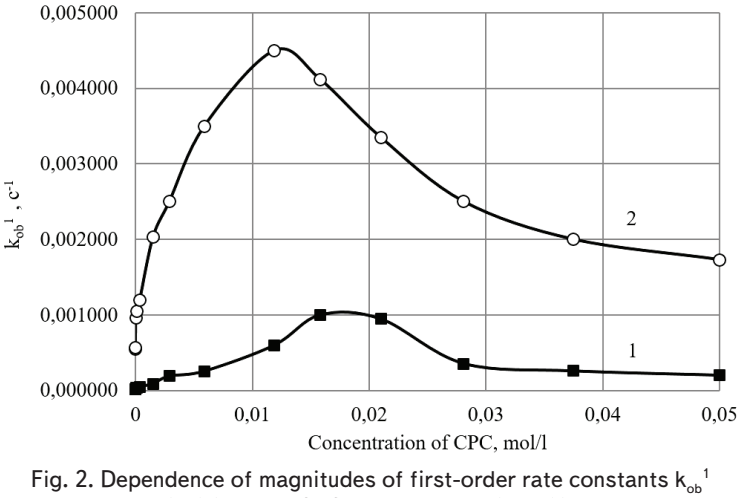

Fig. 2. Dependence of magnitudes of first-order rate constants k_{ob}^1 (1/c) on the CPC concentration (mol/l): 1 – k_{ob}^1 (OH^-); 2 – k_{ob}^1 (HOO^-)

Data on the performed study show that progress of the reaction occurs much faster when adding boric acid as an activator. Therefore, it is possible to propose the presented decontamination system as a model of cleaning solution with the following composition: cetylpyridine chloride, H_2O_2, water, boric acid, pH=12 (KOH).

5. 2. Evaluation of internal risks for quality of production stations when manufacturing medicinal preparation in the form of eye drops based on OPC as a model

An important issue in the organization of pharmaceutical production in accordance with GMP is to create and maintain a mutual national system of inspections of production [14]. One of the factors that provides for effectiveness of the system's operation, is assessment of internal risk for quality of production areas, processes and pharmaceutical production.

Evaluation of internal risk for production areas, its processes and products is determined based on the dossier of production station during repeated planned inspections. It can be additionally performed based on the reports of the latest inspection, based on complexity assessment of the production area. Accordingly, three possible scores are distinguished: 1, 2 and 3 [14].

Evaluation of the internal risk factors for quality was conducted at the example of production station of eye drops based on POC.

The production process of eye drops includes the following stages: preparation of raw material; obtaining a sterile solution; pouring solution in bottles; labeling and packing of bottles in packs. The stages of preparation of solution and packing are the most critical for product quality.

To prepare the solution, it is necessary to use a reactor, equipped with an airtight lid and placed in the class C (D) purity zone. The design and materials of the reactor must comply with GMP. Filling bottles with a sterile solution and sealing should be done in aseptic conditions (class A zone) or pass final sterilization in vials. Depending on the design of machines for filling and sealing containers and bottles capping, materials should pass preliminary stages of washing and sterilization.

Therefore, having examined basic technological processes at the stations for production of eye drops with API of organophosphorus nature, it was found that the nature of work during sterile manufacturing has a very high degree of risk for quality. In this regard, it is important to carry out constant monitoring of the process, as well as to give the station of eye drops production the highest score of the internal risk – 3.

6. Discussion of results of risk analysis for the quality of process to clean reactor using the chosen system of inactivation of the organophosphorus API residues

The obtained experimental results of determination of optimum model structure of a detergent for cleaning production equipment from residues of API of organophosphorus nature and assessment of internal risks for the quality of production stations during manufacturing medicinal preparation in the form of eye drops based on OPC as a model are of great practical importance. They allow conducting a risk analysis for the quality of the reactor cleaning process when using the chosen system of inactivation of residues of organophosphorus API.

The most critical parameter in terms of production of several kinds of products is cross-contamination. One of the main factors that directly influences contamination is equipment. Providing the necessary level of equipment cleanliness within its entire operation period is a prerequisite for conducting validation of cleaning.

Carrying out validation of equipment cleaning includes the following stages [15]:

– organizing the process of equipment cleaning in accordance with standard operating procedures (SOP);

– visual check of equipment cleanliness to detect the lack of visible contamination;

– sampling;

– transmission of samples to a chemical or microbiological laboratory of the quality control department;

– filling in the validation protocol;

– analysis of two more series of product;

– analysis of the obtained results and comparison them with criteria of acceptance;

– drafting the report on validation.

There are two main aspects in the cleaning process. The first one is actually the chemistry of cleaning while the other one includes technical aspects of cleaning, including methods of cleaning and different parameters of the process [16].

The chemistry of cleaning is based on some mechanisms of interaction of the detergent with residues of components of a medicinal preparation on the surface of equipment that is in contact with them. Understanding the mechanism of cleaning can help in choosing an appropriate cleaning agent and, what is more, to help in setting up the whole process. The processes of equipment cleaning may include: solubility, dissolution, dispersion, emulsifying, wetting, hydrolysis, oxidation, physical removal, and antimicrobial action [16].

It is worth paying attention to the process of hydrolysis because the decontamination system, chosen in present work, is directly associated with the hydrolysis of OPC in micellar medium. An important factor in cleaning process is the method of cleaning. Methods of cleaning are usually categorized according to the degree of disassembly required for cleaning equipment and by the means in which a chemical agent contacts with the surface:

– CIP (cleaning in place);

– dynamic immersion;

– static immersion (soaking);

– automatically washing parts;

– ultrasonic cleaning;

– cutting under high pressure;

– manual cleaning.

Special attention should be paid to CIP, it provides safety of operators (staff), time saving – reduction of downtime for sanitary treatment (rinsing, cleaning) [17]. The existence of CIP system provides for the reproducibility of results of cleaning and reduces the risk of cross contamination in the production.

During validation, one determines hard to clean places of the equipment construction, the surface of which are stained with a special indicator. Effectiveness of work is determined visually, in the visible and ultraviolet spectrum. Critical parameters of cleaning process are temperature, fluid pressure (flow rate) and cleaning period, concentration of cleaning agents and quantity of washing.

As part of the work, we developed a concept of validation of cleaning equipment in the production of medicinal preparation in the form of eye drops, which includes OPC. It includes developing standard operating procedures and risk analysis during equipment cleaning.

As a model of equipment for production of eye drops based on OPC, we selected the reactor ArtLife-Techno RVD-630 (Russian Federation) with the built-in CIP system [17]. A brief description of the equipment, selected in this work, is presented in Table 2.

Table 2

Characteristics of reactor RVD-630 [17]

Name	Parameters
Total volume, l	630
Working volume, l	500
Material for producing reactor	AISI 316L
Roughness of internal surface of reactor, Ra	≤0.63
Range of rates of stirrer, rev/min	from 0 to 1000
Pressure in reactor, MPa	from 0.1 to 0.4
Pressure in shirt, MPa	up to 0.4
Heating by heating elements (heat carrier – water), °C	up to 90 °C
Heating by vapor, °C	up to 140 °C
Elliptic bottoms	
Dimensions, mm Length (L) Width (W) Height (H)	 1050 950 1800
Additionally equipped reactor:	–
– with device for sampling;	– control of the product composition in the process of its preparation, possibility of sterilization before and/or after each sampling;
– control and measuring equipments;	– temperature sensors, manometers with separating membrane sensors pH, etc.;
– registers;	– allow registering current parameters of the technological process in electronic and/or paper copy;
– membrane valve;	– provides minimization or absence of stagnant zones in the process of stirring and unloading of product;
– cleaning heads (CIP system);	– provide high quality cleaning of reactor in CIP system (clean in place);
– magnetic stirrer	– is made in bottom performance, torque from the drive shaft to the stirrer is transferred by magnetic field

A concept, which includes the basic stages of conducting validation of cleaning reactor RVD-630, was developed. Based on the equipment characteristics, we developed SOP for conducting validation and cleaning process of the reactor and analyzed the risks when cleaning the equipment.

Risk analysis is a procedure of identifying risk factors and assessing their significance, that is, an analysis of probability that certain undesirable events will take place and will negatively affect the achievement of the objectives of the project. Risk analysis includes an assessment of risks and methods of risks reduction or decreasing adverse effects, associated with them.

During risk analysis, several stages are distinguished:

– risks identification;

– assessment of probability of occurrence of adverse events;

– determining the structure of possible harm;

– assessment of scale of risk;

– identification and evaluation of possible methods of reducing risks;

– making decision on the definition of risk management;

– control of effectiveness and results of implementation of risk-reducing measures.

There are quantitative and qualitative risk analysis methods for using in pharmaceutical production. The choice of a particular method for risk assessment is determined by different circumstances, associated with available information about the product and the process and experience in manufacturing the product. At the initial stage, when there is not enough information about the product and the process (in this case cleaning process), it is advisable to use qualitative methods of analysis, namely, Ishikawa diagram. Ishikawa diagram is a cause-effect diagram, used for the graphic image of relationships between the problem to solve and the factor that caused it. Conclusions about consequences are made on the basis of an analysis of problems. The diagram shows the work on improving the quality of production processes (in this case the process of cleaning) and makes it possible to identify key relationships between various factors and to understand the studied process more clearly.

Results of the risk analysis conducted are presented in Fig. 3, and the assessment of risks for the process of cleaning the reactor RVD-630 is presented in Table 3.

It was found that a significant risk for cleaning procedures is associated with the following:

– presence of stagnant zones (accumulation of residues of the product at the bottom of the reactor);

– failures of automated CIP process (failure of stirrers, cleaning heads, pipes, filters, sensors of temperature, pressure, etc.).

A safety measure aimed at reducing these risks is operating the equipment according to instructions.

Table 3

Risk assessment during procedure of cleaning reactor RVD-630

Component of system	Possible deviations	Existence of risk (+/–)	Explanations	Control/measures	Risk assessment
Equipment	Stagnant zones, process failure	+ +	Accumulation of material at the bottom of the reactor; failures of: stirrers, cleaning heads, pipes, filters, sensors of temperature and pressure, etc.	Operation of equipment according to instructions	Considerable Considerable
Personnel	Failure to meet appropriate SOP	+	Unskilled staff, random mistakes caused by carelessness or other factors	Training and selecting personnel	Considerable
Safety	Toxicity of OPC, washing agents	+	OPC – toxic compounds	Compliance with s afety regulations when working with toxic substances	Considerable
Sampling	Procedures, auxiliary materials	+ +	Inefficient methods of sampling or analysis, substandard materials	Experimental study and selection of the best option	Considerable, inconsiderable
Washing agent	Concentration, effectiveness	+ –	Inappropriate concentration, ineffective against contamination		Considerable, inconsiderable
Documentation	Correct SOP	+	Incorrectly designed SOP of cleaning	Documentation check	Considerable

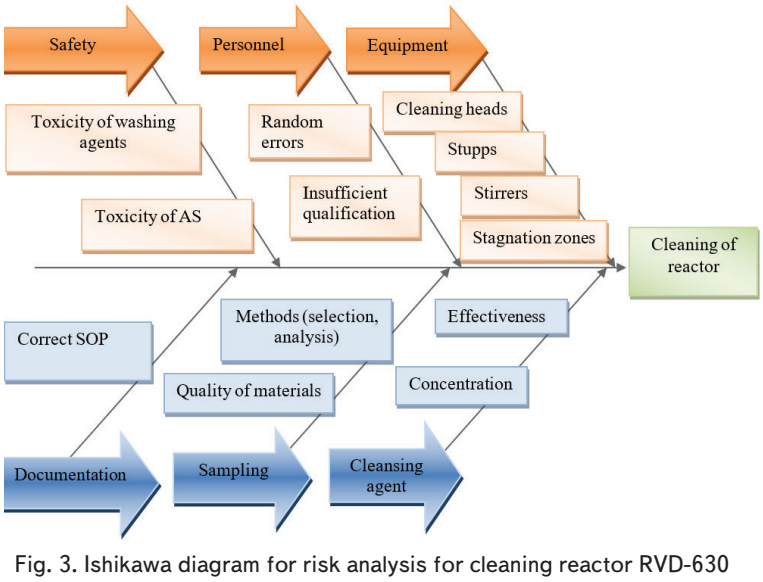

Fig. 3. Ishikawa diagram for risk analysis for cleaning reactor RVD-630 (SOP – standard operating procedures, AS – auxiliary substances)

7. Conclusions

1. The system of micellar inactivation of API of organophosphorus nature was developed. Its essence lies in application of alkaline aqueous solution of CPC as a micelloagent, hydrogen peroxide as a nucleophile and boric acid as an activator of hydrogen peroxide. With the example of destruction of methylparathion, it was shown that the characteristic feature of adding boric acid as an activator is an increase in the reaction rate by 2.5 times. It is due to such activation of hydrogen peroxide, that the decomposition process of OPC with the use of this system is faster in comparison with other methods of decontamination.

2. A model cleaning agent based on the developed system of micellar inactivation was proposed. Using this agent for cleaning technological equipment from the residues of API of organophosphorus nature will improve the quality and reduce the time for performing standard operating cleaning procedures. This positive effect is caused by the appropriate composition of a cleaning agent that is targeted directly to the destruction of molecules of OPC. High efficiency of the agent is based on the use of micellar catalytic system and application of an activator.

3. We performed evaluation of internal risks for quality of production stations when manufacturing medicinal preparation on the basis of organophosphorus compounds in the form of eye drops. The production station was given the highest rate of internal risk – 3.

4. We conducted an analysis of risks for cleaning reactor RVD-630 in case of using developed micellar system for decontamination from residues of API of organophosphorus nature. It was shown that a significant risk of cleaning procedures is associated with existence of stagnant zones and failures in automated CIP process of cleaning the reactor.

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