MATHEMATICS METHODS AND INFORMATION SYSTEMS IN CHEMICAL TECHNOLOGY

МАТЕМАТИЧЕСКИЕ МЕТОДЫ И ИНФОРМАЦИОННЫЕ СИСТЕМЫ В ХИМИЧЕСКОЙ ТЕХНОЛОГИИ

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RESEARCH ARTICLE

Quality management of the chemical-technological process for continuous synthesis of pharmaceutical substances of medicinal compounds in flow microreactors

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Abstract

Objectives. *The introduction of digital tools for the development of medicines, intelligent management systems, and quality control is stipulated not only by modern requirements for the chemical and pharmaceutical industry but also by strict regulatory requirements for manufactured products. This principle ensures the release of a quality product on the first attempt. The aim of this study is to develop information support for the intelligent quality management system for the production of active pharmaceutical substances (APSs) for medicines using a fundamentally new technology: continuous synthesis in flow microreactors. To develop the necessary information support, we developed appropriate systemic, informational, and mathematical models; algorithms for the online management of the experiment; and techniques and algorithms to qualitatively assess whether the product meets official regulatory documents.*

Methods. *System analysis techniques, information and mathematical modeling techniques with multireference regression models, and online optimization using the Hook–Jeevs algorithm (a method of expert evaluation based on the concordance factor) were used to solve the problems formulated.*

Results. *To manage the quality of the process of continuous APS synthesis in the flow microreactor, we developed theoretic multiple system models that were designed to build the digital information environment for the process of experimental research. We developed algorithms for mathematical modeling and optimization of the control process based on multiresponse regression models and*

an online optimization algorithm that allows the process to be managed step by step, taking into account the limitations. Our results show that the degree of conversion is higher in reactions that contain bromodiphenylmethan.

Conclusions. *Based on mathematical modeling method algorithms for the quality control of the process of continuous APS synthesis on a fundamentally new microreactor system, Qmix were developed. The applicability of the proposed methods and algorithms in the production of the drug diphenhydramine from chlorobenzohydrol and bromobenzohydrol as initial substances was proven by an experimental study. The built models were statistically adequate and valid.*

Keywords: *continuous synthesis in flow microreactors, active pharmaceutical substance, theoretic multiple system models, multicell regression models, online optimization, Hook–Jeeves method, expert evaluation, concordance factor, diphenhydramine drug*

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НАУЧНАЯ СТАТЬЯ

Управление качеством химико-технологического процесса непрерывного синтеза активной фармацевтической субстанции лекарственных соединений в проточных микрореакторах

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Аннотация

Цели. *Внедрение цифровых инструментов в разработку лекарственных препаратов, интеллектуальных систем управления и контроля качества обусловлено не только современными требованиями к химико-фармацевтической отрасли, но и строгими регламентированными требованиями к выпускаемой продукции. При этом повышение эффективности разработки и производства лекарственных средств на всех этапах их жизненного цикла опирается на системное применение принципа Quality-by-Design (QbD) – «качество, запланированное при разработке». Это системный подход к разработке лекарственных препаратов, который начинается с четко определенных целей и оканчивается получением лекарственного препарата, с учетом понимания его процесса изготовления и стратегии контроля, основываясь на надежных научных данных и оценке рисков, связанных с качеством. Применение этого принципа позволяет гарантировать выпуск качественного продукта «правильно с первого раза». Это достигается применением на всех стадиях новых технологий цифровизации всех систем сбора, обработки и хранения информации. Целью работы является разработка информационной поддержки интеллектуальной системы управления качеством получения активных фармацевтических субстанций (АФС) лекарственных средств с помощью принципиально новой технологии непрерывного синтеза на микрореакторах проточного типа. Использование этих микрореакторов имеет ряд серьезных преимуществ по сравнению с традиционными периодическими процессами. Среди них возможность подключения аналитического оборудования*

в проточном режиме, что позволяет обеспечить высокий уровень компьютеризации управления синтезом. Для разработки необходимого информационного обеспечения были разработаны соответствующие системные, информационные и математические модели, алгоритмы online управления экспериментом, методики и алгоритмы оценки качества продукта на основе официальных регламентных документов.

Методы. *Для решения поставленных задач были использованы методы системного анализа, методы информационного и математического моделирования с построением многоотказных регрессионных моделей и online оптимизации по алгоритму Хука-Дживса, метод экспертного оценивания на основе коэффициента конкордации. Приведенное алгоритмическое обеспечение реализовано с помощью программной среды SciLab.*

Результаты. *Для управления качеством процесса непрерывного синтеза АФС на проточном микрореакторе построены теоретико-множественные системные модели, служащие для построения цифровой информационной среды процесса экспериментальных исследований. Разработаны алгоритмы математического моделирования и оптимизации процесса управления на основе многоотказных регрессионных моделей и online алгоритма оптимизации, позволяющие осуществлять пошаговое управление процессом с учетом ограничений. Разработан алгоритм экспертного оценивания качества процесса синтеза на основе анализа эффективности и риска разрабатываемого лекарственного средства. Проведены тестовые испытания системы управления на микрореакторной системе Qmix на примере получения АФС дифенгидрамина при применении в качестве исходных веществ хлордифенилметана и бромдифенилметана. Показано, что степень конверсии выше в реакции, где участвует бромдифенилметан. В этом случае в полученной реакционной массе не остается примесей исходных реагентов.*

Выводы. *На основе методов математического моделирования разработаны алгоритмы управления качеством процесса непрерывного синтеза АФС с использованием принципиально новой микрореакторной системе Qmix. Экспериментальными исследованиями доказана работоспособность предложенных методов и алгоритмов в производстве лекарственного средства димедрола из исходных веществ хлорбензогидрола и бромбензогидрола, показана статистическая адекватность и состоятельность построенных моделей.*

Ключевые слова: *непрерывный синтез на проточных микрореакторах, активная фармацевтическая субстанция, системные теоретико-множественные модели, многоотказные регрессионные модели, online оптимизация методом Хука-Дживса, экспертное оценивание, коэффициент конкордации, лекарственное средство димедрол*

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INTRODUCTION

The standard methodology for developing and manufacturing a new medicinal product (MP) usually takes 11–12 years (Fig. 1) [1]. An obvious method to increase the efficiency of drug development is to reduce the duration of the full life cycle, i.e., from development to industrial production, of a drug.

Ensuring that the drug is effective and causes minimal side effects is laid in the development stage, and these factors are tested at the stages of preclinical and clinical testing. It is possible to divide the entire life cycle of drug production into four stages:

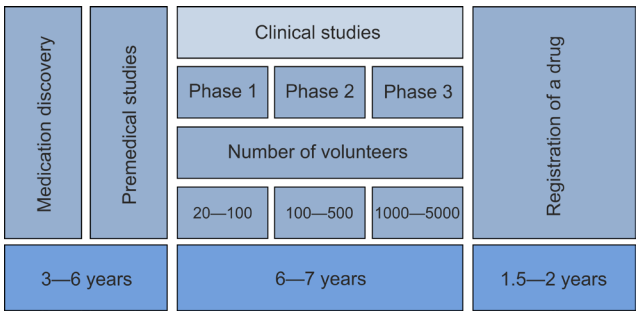

Fig. 1. Development and research of the drug over time.

– nanoscale or computer modeling and screening of molecules;

– microscale—composition (formulation) creation—the stage of pharmaceutical development;

– preclinical and clinical studies and drug registration [2].

An obvious way to significantly reduce total production time is to decrease the time it takes to conduct preclinical and clinical studies. However, it should be noted that reducing the length of preclinical and clinical trials will not be effective if there is an error in the development stage, especially if said error is not identified until the stage of clinical testing. In this case, it will be necessary to return to the stage of pharmaceutical development (microlevel) because it is during that stage that the mean active pharmaceutical substance found at the nanoscale is finally selected, a technological platform for obtaining a ready-made drug form is developed, and the necessary equipment and instrumentation are selected[1] [3].

METHODS

In this study, at the stage of drug development, a relatively new approach was used based on the widespread use of the quality by design (QbD) principle [4, 5]. Applying this principle guarantees the release of a quality product on the first attempt. This is achieved by applying a systematic approach to the development of quality management systems at each stage of the drug's life cycle. It is worth noting that, according to Demming's definition [6], the projected product quality management system will be optimal from a systematic point of view if its constituent links are optimal. In this particular case, these are the stages of a drug production's life cycle. To date, all the stages, with the exception of the pharmaceutical development stage, are certified and have quality management systems.

The pharmaceutical development stage consists of two substages that are fairly autonomous, i.e., they are usually developed by different research teams who are often part of separate organizations.

A systematic approach to the pharmaceutical development stage of a new drug includes [7–10]:

– the application of new innovative technologies for obtaining high-quality products in the form of active pharmaceutical ingredients (APIs) and ready-made drugs;

– the creation of a digital environment for research, including the analysis of information flow at the stage of pharmaceutical development (from the standpoint of system integration—the identification of interrelations between basic concepts and terms);

– the construction of systematic and functional models to determine solutions in the information environment; digitalize information acquisition, processing, and storage; develop databases and knowledge bases; and create intelligent information systems;

– mathematical modeling and software development for research planning and management, the estimation of the relationship between controlled parameters, and the quality of manufactured products.

Analysis of the development of information support for the second substage—the development of a finished product—is fully described in the literature [11]. Therefore, below, we will consider a systematic approach to building a quality management system for the substage of the synthesis of an active pharmaceutical ingredient since, to date, it is in that stage that innovative solutions regarding the synthesis of APIs have been found. A multistage scheme of set-theoretic models described in the form of tuples was chosen as the system model (Fig. 2).

Tuples of the third level and up are constructed in a similar way.

One of the main obstacles to successfully applying the QbD approach at all stages of drug development and production is forming an effective strategy to control the quality of the manufactured product.

The main principle of the QbD concept is that the main development goal is the finished product and its consumer (patient). This is primarily due to the risk assessment of applying a new engineering design for consumers. All possible production hazards associated with the raw materials and the process technology are eliminated only in reverse order during development. Therefore, the quality of the developed medicinal product is ultimately determined during the production stage despite the fact that quality assessment is performed at each stage[2].

In its most general form, the formation of the criterion is based on the following postulates. Each variant of control solution X is evaluated by a set of criteria K characterizing the quality of the found solution: $K = \{ki\}$, where $i = 1,\ldots, n$, where n is the number of criteria. The goal of research is described by the integral criterion G characterizing, from the viewpoint of the chemical–pharmaceutical development of drugs, the quality of the obtained drug, the risk of its use, and its commercial efficacy.

[1] On the approval of the Rules for the organization of production and quality control of medicines: Order of the Ministry of Industry and Trade of Russia of June 14, 2013, No. 916 (Registered at the Russian Ministry of Justice on September 10, 2013, No. 29938).

[2] On the circulation of medicines with additions and changes of 2015: Federal Law of the Russian Federation of 12.04.2010, No. 61-ФЗ.

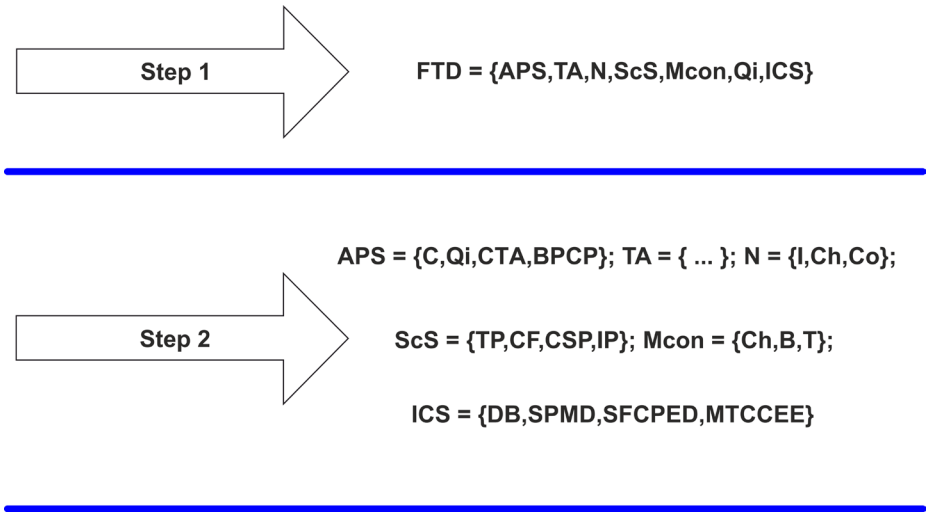

Fig. 2. The structure of the set-theoretic model used to form a task for the development of a system for medication synthesis control.

***Abbreviations*:**
FTD – forming a task to develop a system for medication synthesis control;
APS – active pharmaceutical suspension;
C – composition;
Qi – quality indicators according to regulatory documents;
TA – technical assignment for the development of an APS of a medication;
CTA – compliance with TA;
BPCP – basic physical and chemical properties;
N – name of the medication;
I – international;
Chm – chemical;
Co – commercial;
ScS – scheme of synthesis;
TP – technological process;
CF – control of the feedstock;
CSP – critical stages of the process;
IP – intermediate products;
Mcon – control methods;
Ch – chemical;
B – biotechnological;
T – technological;
ICS – intellectual control systems;
DB – databases;
SPMD – system for preparing management decisions;
SFCPED – subsystem for collecting and processing experimental data;
MTCCEE – means of telecommunication for communication with the external environment.

Let us formulate in general terms the quality criterion of a drug under development:

$$OptimG \rightarrow G\{Q;R;C\}, \quad (1)$$

where Q, R and C indicate the efficiency, risk, and commercial value of the developed drug, respectively.

By "the optimum of the global criterion" we mean the optimal assessment, made by an expert community, of the highest efficiency, lowest risk, and commercial component of a drug being developed in some uncertainty under external conditions. The indicators of the effectiveness of drug use and commercial assessment are quantitative, and the risk criterion is qualitative, i.e., it determines the conditions of drug inapplicability (allergic reaction, patient conditions such as colds, pressure, etc.), side effects, etc. The uncertainty of external conditions lies in the fact that when clinically testing a drug, it is not possible to identify all pathologies in which it should not be used. Only on the basis of long-term use would it be possible to more accurately assess the effectiveness a drug used under various conditions.

Criterion (1) is formed by experts after clinical trials and pilot industrial production. However, at each stage of the development life cycle, a range of conditions is set under which research is to be carried out. With regard to each condition, the quality of the drug obtained is assessed based on a local criterion, which is in turn assessed by its own group of experts.

The value of each of the local criterion K^j_{exp} assessing the quality of the product at each stage of the drug's development and production life cycle is evaluated by a group of experts according to the methodology approved by the Ministry of Health of the Russian Federation[3]. In addition, each stage has its own (technological or environmental–technological) criterion D^m_j, which serves to select the optimal parameters in the technological process.

Thus, the scheme of a criteria-based approach to qualitatively assess the stage of APS synthesis is as follows (2):

$$D \subset K \subset G, \quad (2)$$

where $G\{(R;Q;C)_{TA}; S^j_{exp}; W; \text{IES}\}$ is a global criterion for evaluating a drug under development; $(R;Q;C)_{TA}$ are the components of the global criterion, which are assessed by experts on the basis of quantitative and qualitative indicators of the drug under development according to the work request (R is risk, Q is quality [efficiency], and C is the commercial component); S^j_{exp} is a local criterion for assessing the quality of APS at stage j of the drug development life cycle according to experts; W is the concordance coefficient estimating the degree of agreement among experts; and IES is an intelligent expert system for assessing risk, efficiency, and commercial expediency according to the TA. This system is determined by experts during development and clinical trials as follows:

$$K^j_{exp.}\{E^j_i, W, D\} \subset S^j_{exp.}. \quad (3)$$

In (3), K^j_{exp} is the local criterion for assessing quality at stage j. The criterion is determined by the opinion of each ith expert E and depends on a particular technological criterion D. $D(Y,X,Z)$ is a particular technological criterion assessing the dependence of the objective function of the synthesis process Y on the vector of control parameters X and the constraint vector Z.

Typically, particular criteria include economic, environmental, and technological criteria. For example, at the substage of APS synthesis, the maximum value of the resulting mixture conversion degree Y is used as such a technological criterion along with control parameters X and constraints on the composition Z.

It should be noted that the method of expert evaluation is used to evaluate both the results of a complete drug preparation assessment during the entire life cycle and the quality of products at individual stages.

A fraction of the indicators for the expert assessment of a stage of drug APS synthesis is presented in the table below.

Figure 3 shows an algorithm for the formation of a private criterion of obtaining a drug with the use of the expert assessment method according to the expert tasks seen in the table[4].

RESULTS AND DISCUSSION

The solution to the problem of controlling APS synthesis is explored through a specific drug, diphenhydramine (dimedrol). This drug is well known in the field of pharmacy, and its synthesis is used to demonstrate the development of control algorithms [12]. Currently, in Russia, as in the rest of the world, the synthesis of active pharmaceutical ingredients found in drugs is carried out in capacitive reactors [13]. Only in the last few years have innovative continuous synthesis plants emerged. Figure 4 shows a general view and technical characteristics of the Qmix microreactor system (*Wingflow AG*, Switzerland), and Fig. 5 shows an instrumental scheme for the synthesis of diphenhydramine at this microreactor.

The characteristics of the Qmix system are as follows: the power supply unit is one Qmix Base module with a power of 600 W. The unit includes four neMESYS MPM precision medium-pressure syringe pump modules for generating two continuous streams with pressures up to 200 bar; one microreactor module Qmix Q+2MR with two separate thermostatic zones for two microreactors (temperature range from 20 to 250°C, pressure up to 20 bar); one Qmix P pressure

[3] Appendix No. 3 to the Order of the Ministry of Health of the Russian Federation of August 24, 2017, No. 558н "On the approval of the Rules for the examination of medicines for medical use and the special aspects of the expertize of certain types of medicines for medical use (reference medicines, generic medicines, biological medicines, bioanalog (biosimilar) medicinal products (bioanalogs), homeopathic medicinal products, herbal medicinal products, combinations of medicinal products), forms of expert committee findings" (Conclusion of the expert commission on the results of the examination of the proposed methods for controlling the quality of the medicinal product and the quality of the submitted samples of the medicinal product using these methods, examination of the ratio of the expected benefit /form/).

[4] Order of the Ministry of Health of the Russian Federation of August 24, 2017 No. 558н.

Table. Expert assessment and conclusions on the indicators of the medication submitted for the quality examination

Assessment number according to the Order of the Ministry of Health of the Russian Federation	Designation in the algorithm	Index content
4.1.1.2.	C_1	Assessment of the chemical scheme of synthesis, of the description of the technological process for the production of a pharmaceutical substance and its development including the control of raw materials, critical stages of production and intermediate products and the assessment of the production processes validation.
4.1.1.3.	C_2	Evaluation of the methods proposed by the applicant to explain the chemical and pharmaceutical properties of a pharmaceutical substance.
4.1.1.4.	C_3	Evaluation of the choice of quality indicators of a pharmaceutical substance and standards.
4.1.1.5.	C_4	Evaluation of profiles of a pharmaceutical substance impurities (organic, inorganic, biological).
4.1.1.6.	C_5	Assessment of the standard samples selection.
4.1.1.7.	C_6	Assessment of the methods of quality control of pharmaceutical substances proposed by the applicant.
4.1.1.8.	C_7	Evaluation of the materials submitted by the applicant for the validation of analytical methods for quality control of a pharmaceutical substance.
4.1.1.9.	C_8	The presence or absence of correspondence between the results of laboratory analysis submitted by the applicant for examination of samples of a pharmaceutical substance and the quality indicators included in the regulatory documentation.

Table. Continued

Assessment number according to the Order of the Ministry of Health of the Russian Federation	Designation in the algorithm	Index content
4.1.1.10.	C_9	Evaluation of the data provided by the applicant on the stability of the pharmaceutical substance in all declared types of primary packaging of data according to the pharmaceutical substance shelf life establishment by the applicant for all the declared types of primary packaging, assessment of the justification of the pharmaceutical substance storage conditions established by the applicant.

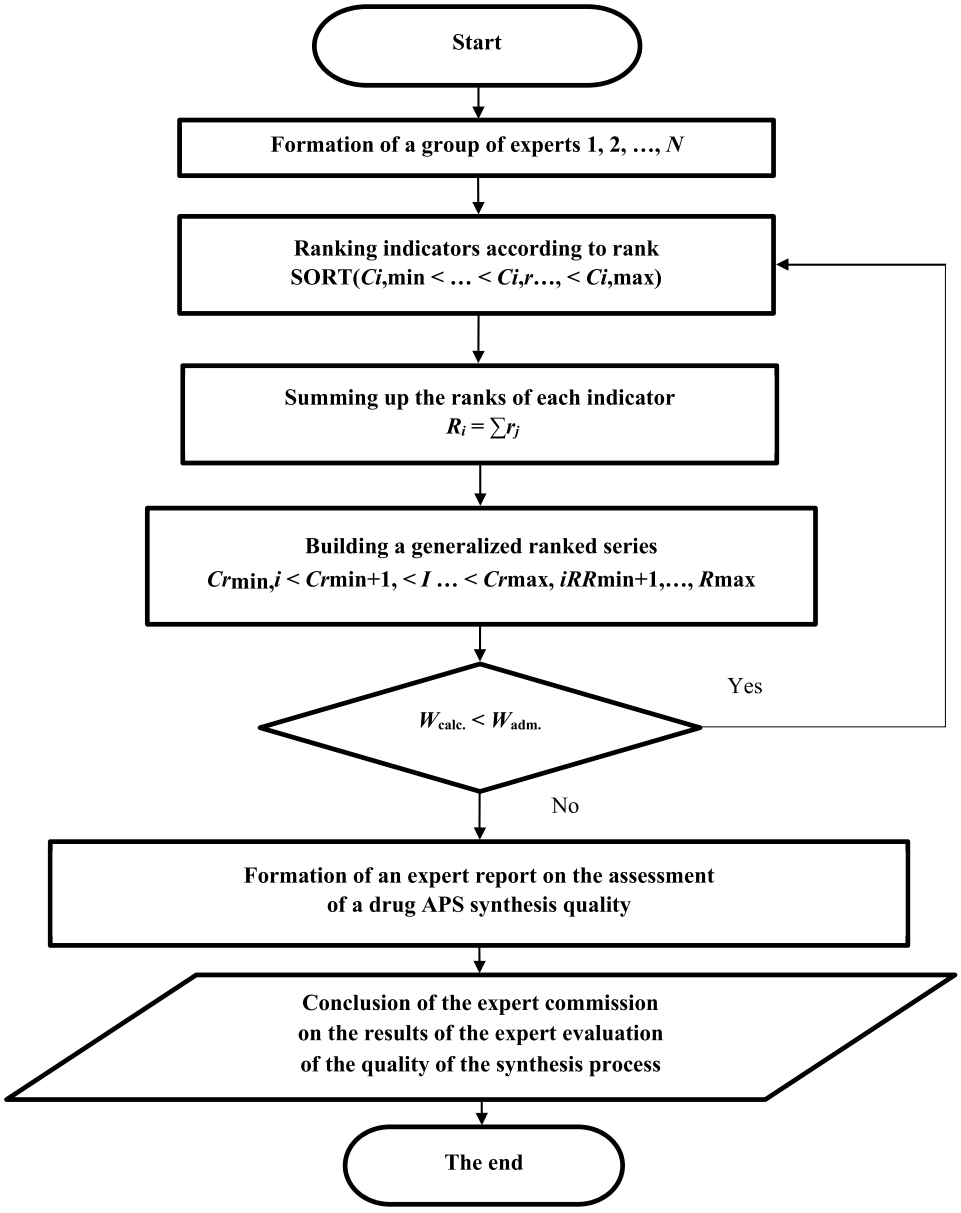

Fig. 3. Block diagram of the algorithm for forming a particular criterion.

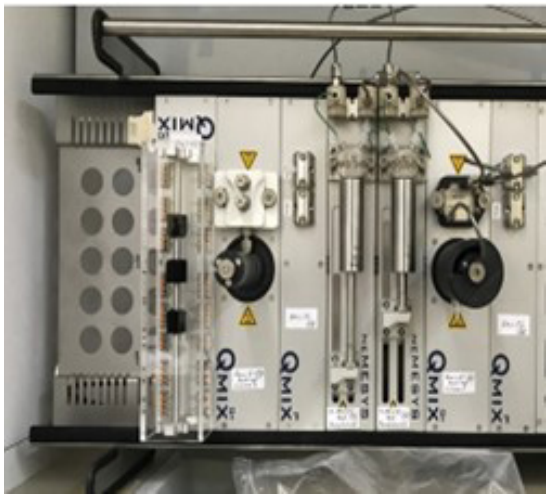

Fig. 4. Appearance of the Qmix microreactor system.

control module for two channels (pressure up to 200 bar); x-Factory microchips measuring 35 × 35 × 3.3 mm; 2-, 5-, 10-, and 50-mL syringes made of special steel; and 1-, 10-, and 50-mL syringes made of borosilicate glass. Capillary material: special 3.175-mm steel. The set of capillaries consists of 6.35-mm fittings (28UNF), 6.35-mm ferrules (28UNF), and 6.35-mm tees (28UNF). Qmix Elements software was used.

Diphenhydramine synthesis technology is described in detail in [13]. A brief description is given below. Using syringe pumps, chlorodiphenylmethane (2.0 M) and pure dimethylaminoethanol are fed into a 19.5-μL microfluidic reactor. Mixing occurs in the first section of the reactor. Immediately after the reactants are mixed, the reactor sections create a turbulent flow to ensure fast and efficient mixing.

Before the mixture enters the second section, it is diluted with acetonitrile.

The mixture is then fed to a pressure transducer and back pressure regulator through the reactor outlet connected to a 2-liter injection valve. The reactor is used to carry out reactions at pressures ranging from 10 to 20 bar.

The outlet is connected to a valve capable of dividing the flow between collection, waste, and an air using a split flow crystallizer.

Since the material exiting the reactor has a concentration of approximately 1.0 M, dilution with acetonitrile is performed in the stream. For the rapid delivery of droplets from the reactor to the mass spectrometer, segmented N_2 (g) droplets were obtained using an electronic pressure regulator. This made it possible to increase the data collection rate and reduce the amount of material consumed during the mass spectrometer data collection. The control system includes a phototransistor, a video microscope, and an optical sensor. Mass spectrometer analysis was performed using an inductive electrospray ionization source (iESI-MS) [14–17].

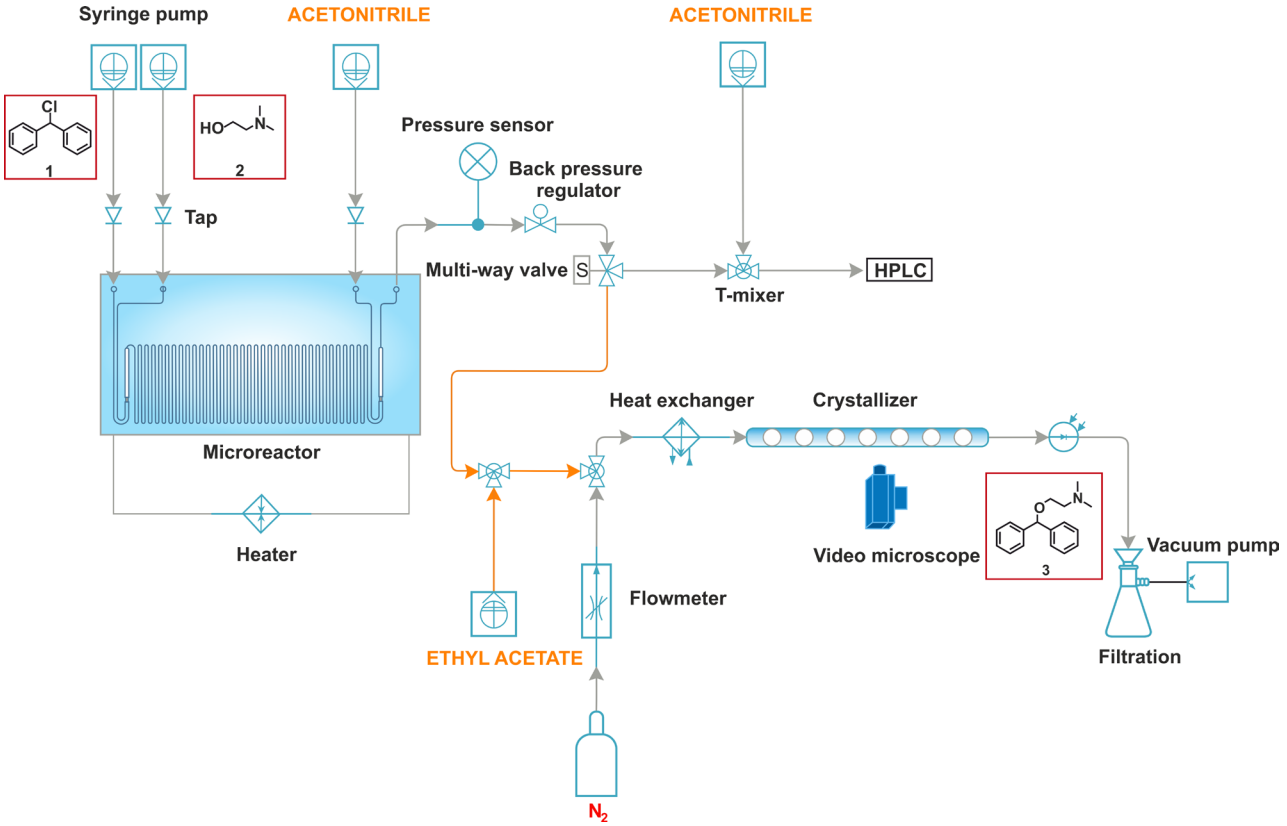

Fig. 5. Apparatus scheme for the synthesis of diphenhydramine.

An information model of the synthesis process in a flow microreactor was considered in [7–9].

When describing the criteria for assessing the quality of the synthesis process, it is indicated that the structure of the particular criterion includes the technological criterion $D(Y,X,Z)$. This criterion estimates the dependence of the objective function of the synthesis process Y on the control parameters vector X and the constraint vector Z.

The task is formulated as follows: it is necessary to construct a step-by-step algorithm to optimize the process of diphenhydramine synthesis in a flow reactor by searching for the maximum target product conversion degree by varying the following control variables x_1 is (t, °C), x_2 is time (min), and x_3 is the substituent in the ingredients Br or Cl with constraints to the permissible composition values. The permissible values of the composition components are as follows: z_1 is benzhydrol (Cl), z_2 is benzhydrol (Br), z_3 is diphenylmethyl (Cl), and z_4 is bis-diphenylmethyl (Br).

To study the dependence of the maximum conversion degree $Y(x_1,x_2,x_3)$ on the control parameters, i.e., x_1, x_2, and x_3, the simplest linear regression model of the criterion $Y(x_1,x_2,x_3)$ dependent on the controlled parameters x_1, x_2, x_3 was chosen (4).

$$Y(x_1,x_2,x_3) = b_1 \times x_{i1} + b_2 \times x_{i2} + b_3 \times x_{i3} (i = 1,2,3,...,n) \quad (4)$$

To solve the optimization problem using this model, it was necessary to formulate equations for the constraints, which are the composition values measured with a chromatograph [18].

For this purpose, we used a system of linear regression multiresponse equations interrelating the control variables x_1, x_2, and x_3 with the composition indices Z_j.

$$Z_j(x_{i1},x_{i2},x_{i3}) \le Z_{\text{adm}}, \quad (5)$$

where x_1, x_2, and x_3 are temperature t (°C), time (min), and the substituent in the ingredients, Br or Cl, respectively, and $Z_{j\text{adm}}$ consists of the admissible values of the composition components: z_1, z_2, z_3, and z_4.

Accordingly, regression equations (5) for assessing the conversion degree and describing constraints in matrix form are as follows:

$$A = (X \times X^t)^{-1} \times (X^t \times Y) \quad (6)$$

$$B = (X \times X^t)^{-1} \times (X^t \times Z) \quad (7)$$

In (6) and (7), A is the column vector of regression coefficients of dimension (1:N); X is the matrix of controlled parameters x_1, x_2, and x_3 of dimension (N:3); Y is the column vector of the values of the objective function of dimension (N:1); N is the number of experiments; $Z(z_1,z_2,z_3,z_4)$ is the matrix of the values of composition components of dimension (N:4); and B is the matrix of regression coefficients of dimensions (3:4).

The regression equations constructed during the first stage via a passive experiment made it possible to solve the optimization problem during the second stage considering the constraints. The purpose of the third stage is to build an online optimization algorithm: at each step j, a plan for changing the controlled variables x_1, x_2, and x_3 is determined such that the values of $D(x_1,x_2,x_3)$ (1) increase in the course of the synthesis, and the constraints (5) do not exceed the admissible limits $Z_j(x_{1j},x_{2j},x_{3j}) \le Z_{j\text{adm}}$.

One of the modifications of the coordinate-wise search for the optimum, the Hook–Jeeves algorithm [19], was chosen as the optimization algorithm. It is important to note that the new values of the objective function for a new point j, $Y(x_{1j},x_{2j},x_{3j})$, are not determined experimentally: they are found as predicted values according to model (1). After determining the maximum value of the objective function $Y_j(x_1,x_2,x_3)$ at this step using the Hook–Jeeves algorithm, the values of $Z_j(x_{1j},x_{2j},x_{3j})$ are calculated using model (2) and transmitted to the researcher, thus allowing them to make the final decision of the synthesis control.

Figure 6 shows the block diagram of an algorithm for optimizing control over the continuous synthesis of diphenhydramine in a Qmix microreactor system using an online optimization algorithm and regression models.

Figure 7 shows the partial results of a study carried out using the suggested algorithms in a Qmix microreactor system. Chlorobenzohydrol and bromobenzohydrol were used as starting components at temperature T = 100–180°C and reaction time t = 2–20 min. The resulting mixture composition was measured using high-performance liquid chromatography.

This graph shows that the conversion degree is higher in the reaction that contains bromodiphenylmethane. In this case, no impurities remain in the resulting reaction mass as starting reagents. Thus, when choosing dimedrol from two starting materials for the synthesis of APS, bromodiphenylmethane is preferred at this stage.

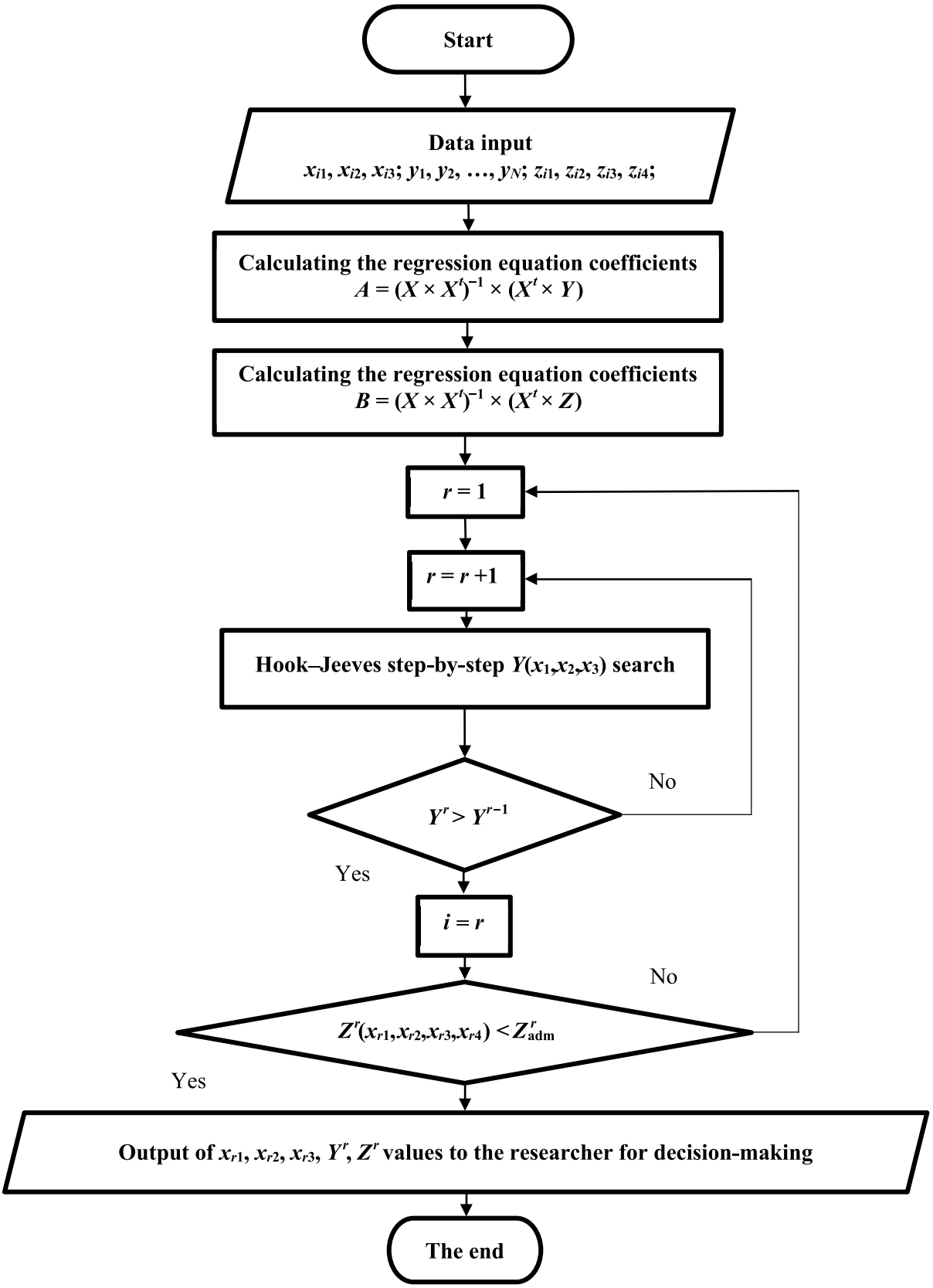

Fig. 6. Block diagram for optimizing the algorithm of control over the continuous synthesis of diphenhydramine in a Qmix microreactor system.

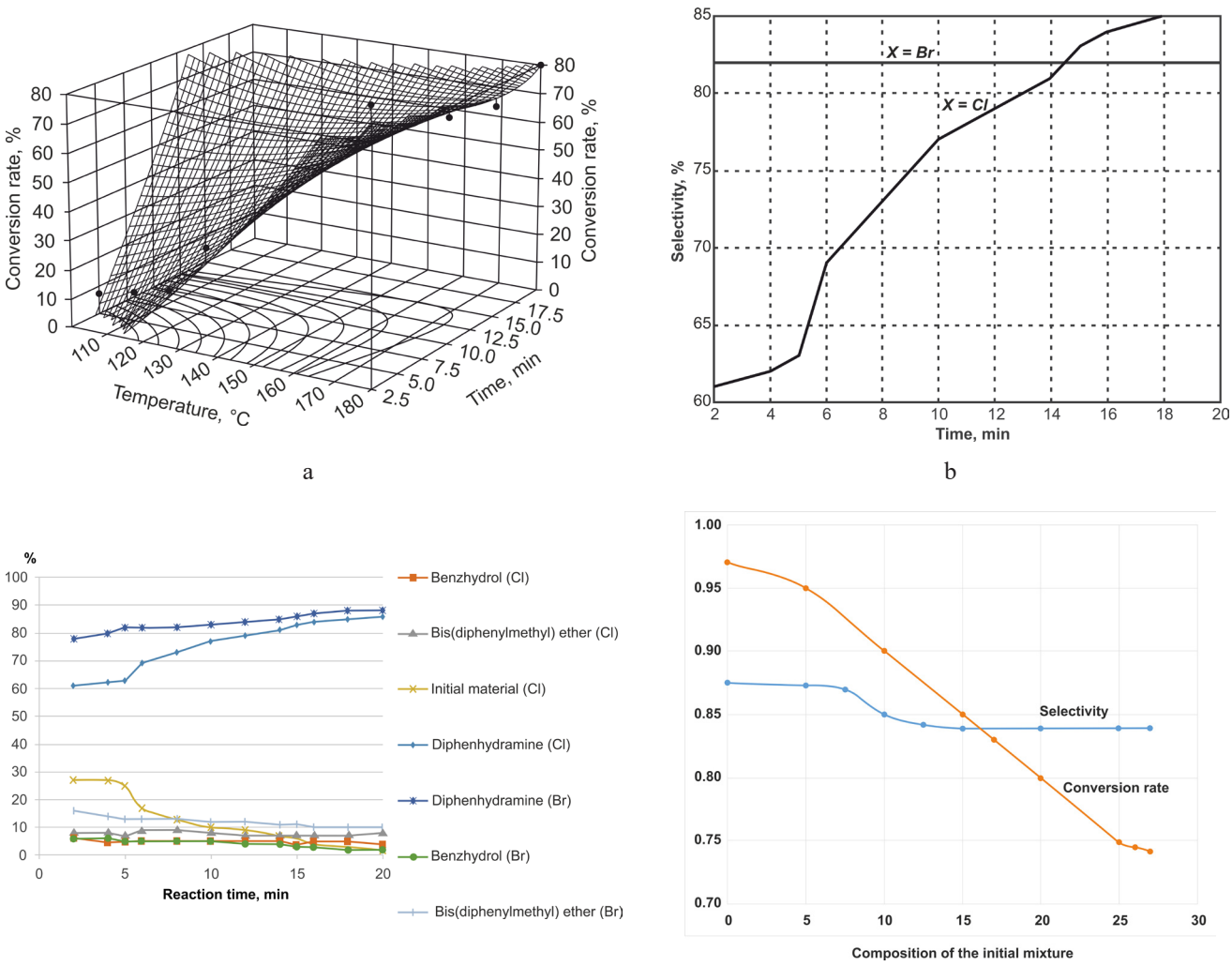

Fig. 7. Graph of the change in the degree of conversion during the synthesis of diphenhydramine APS: (a) dependence of conversion on the reaction temperature and treatment time; (b) selectivity of the process vs. the time of treatment with bromobenzohydrol and chlorobenzohydrol, respectively; (c) product yield vs. processing time; (d) degree of conversion and selectivity of the process vs. the initial mixture composition.

CONCLUSIONS

1. A systematic analysis of a quality management system for the substage of active pharmaceutical ingredient synthesis was carried out in this study because, to date, it is in this stage that innovative solutions in the synthesis of APS have been found. A multistage scheme of set-theoretic models described in the form of tuples was chosen as the system model.

2. The tasks of the criterial approach for assessing the quality of the drug under development were formulated. A methodology and an algorithm for calculating global and local quality assessment criteria based on regulatory documents of the Ministry of Health of the Russian Federation were suggested.

3. A description of the innovative process of the synthesis of an active pharmaceutical substance of a medicinal product in a flow microreactor system Qmix was given. It was found that the system significantly increases the efficiency of the synthesis process.

4. Mathematical modeling of the continuous synthesis process in a flow microreactor based on regression analysis was carried out.

5. The block diagram of an online optimization algorithm for continuous synthesis in a Qmix microreactor system was developed. The synthesis of the active pharmaceutical substance diphenhydramine was used to test the algorithm.

Authors' contribution

All authors equally contributed to the research work.

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