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Optimization of process parameters and compositions of inhalation powders containing antibiotics

Abstract

In accordance with Decree No. 529 of the President of the Russian Federation dated June 18, 2024, the development of modern medicines and next-generation platforms is included in the List of Essential Science-Intensive Technologies. These include biotechnological and high-tech pharmaceuticals.

The development of inhalation dosage forms and breath-activated dosing device is a priority area. This area facilitates the transfer to advanced design technologies and the creation of high-tech products based on intelligent manufacturing solutions. This corresponds to the Strategy for Scientific and Technological Development of the Russian Federation, approved by Decree No. 145 of the President of the Russian Federation dated February 28, 2024.

Inhalation therapy is a promising non-invasive method for delivery active pharmaceutical ingredients directly to the site of inflammation. Spray drying can be used to produce inhalation powders containing anti-tuberculosis drugs. This method is widely used in the pharmaceutical industry due to the possibility to scale up of drying and to produce particles with desired properties.

The development of inhalation dosage forms and breath-activated dosing device is a difficult multiparameter problem. This is due to the complex interactions between powder component composition, hydrodynamics, and heat transfer during spray drying, as well as the design of the breath-activated dosing device. These factors affect the quality characteristics and stability of the produced formulations, the efficiency of powder release from the breath-activated dosing device, and the pharmacokinetics of the drug. The solution of this problem requires experimental researches, the use of mathematical modeling and optimization methods.

This thesis is devoted to the optimization of technological parameters and compositions of inhalation powders containing antibiotics. The development of breath-activated dosing device design to powder delivery is presented in the thesis too.

This thesis was carried out in the frame of Agreement No. 075-03-2026-347/3 dated May 29, 2026, between Mendeleev University of Chemical Technology and the Ministry of Science and Higher Education of the Russian Federation. The agreement provides for work on the topic "Laboratory for the Development of Innovative Nasal and Inhalation Drugs for the Treatment of Socially Significant Diseases (continued)" (unique project identifier: FSSM-2025-0003).

The aim of the study is to optimize the technological parameters and compositions of inhalation powders containing antibiotics and to develop an breath-activated dosing device for their delivery.

Tasks:

1. Design of experiment development and carrying on a complex of experiments for the production of multicomponent inhalation powders. Identification the specific features of powder formation, taking into account the mutual influence of composition, hydrodynamics, and heat transfer during spray drying. Assessment the impact of these factors on the quality and stability of the produced compositions. Multiparameter optimization.
2. Complex of analytical investigations of multicomponent inhalation powders. Assessment the quality and stability of the produced compositions. Investigation the kinetics of antibiotic release from inhalation powders and their membrane permeability. Assessment the release of the required dose from a breath-activated dosing device, including when an inert carrier is added to the powder.

3. Mathematical modeling of particle hydrodynamics in the proposed breath-activated dosing device. Complex of computational experiments simulating the device's operation at various aeration flow rates.

4. Development of a pharmacokinetic model describing the redistribution of the administered active ingredient between the systemic circulation and the lungs. Development of a pharmacodynamic model to predict effectiveness of therapy.

5. Development of specific chapters of laboratory regulations for the production of multicomponent powders for inhalation.

Scientific novelty

The relationships were established between the composition and formation conditions of inhalation powders and their quality characteristics, powder extraction efficiency, and active pharmaceutical ingredient release rate. The interactions between hydrodynamics and heat and mass transfer during spray drying were taken into account.

The computational experiments were carried out using the mathematics of continuum mechanics and the Euler–Lagrange approach. The possibility of aeration of inhalation powder with a given granulometric composition upon inhalation has been confirmed. The movement of particles through internal channels of complex structure and deagglomeration chambers of a breath-activated dosing device was investigated. The calculations were done at aeration rates ranging from 25 to 60 L/min.

The pharmacokinetic and pharmacodynamic models were developed based on literature and experimental data. The literature data included the information on drug distribution in the human body and their pharmacological effects. The experimental data characterized antibiotic release and its permeability through a membrane. The developed models made it possible to obtain drug distribution profiles in the body and predict the potential therapeutic effect.

Theoretical and practical significance

Recommendations were developed for the inhalation powders compositions with antibiotics and the conditions for their production.

A prototype of a breath-activated dosing device device was developed and tested. The recommendations for the type and amount of inert carrier incorporated into the inhalation powder formulations were developed. Know-how was registered for the combination of the breath-activated dosing device and two inhalation powder formulations.

The specific chapters of laboratory regulations were developed. They include the process flow diagrams, equipment diagrams, material balances, and a list of control points.

Pharmacokinetic and pharmacodynamic models were developed to predict changes in antibiotic concentrations in the lungs and to assess the potential therapeutic effect. The computer program entitled "Software Module for Calculating the Pharmacokinetics and Pharmacodynamics of Isoniazid Following Inhalation Administration" was registered.

The main provisions for the defense

1. Conditions for the formation of fine powders by spray drying, taking into account the mutual effects of hydrodynamics and heat and mass transfer. Relationships between the quality characteristics of inhalation powders, their extraction efficiency from a breath-activated dosing device, and the release rate of the active pharmaceutical ingredient.
2. Results of experimental investigations on the production of inhalation powder formulations by spray drying. Formulations with non-modified and prolong release kinetics were investigated.
3. Results of analytical investigations of the produced powder formulations. Results of stability studies of inhalation powder formulations under stress conditions and studies of antibiotic permeability through a membrane. Results of statistical analysis of experimental data.

4. Mathematical description of particle movement in a breath-activated dosing device. Results of calculations at aeration rates ranging from 25 to 60 L/min. The model accounts for the complex structure of the internal channels and two particle deagglomeration chambers of the breath-activated dosing device.

5. Design of a breath-activated dosing device to ensure the extraction of the required powder dose. Use of an inert carrier in the powder formulation.

6. A prototype of a finished dosage form combining a breath-activated dosing device and two inhalation powder formulations. The formulations are characterized by non-modified and prolong release kinetics.

7. Pharmacokinetic and pharmacodynamic models to predict changes in antibiotic concentrations in the lungs and therapeutic efficacy. The models can be used for preliminary selection of therapeutic doses when planning clinical trials.

8. The chapters of laboratory regulations. Process flow diagrams, equipment diagrams, material balances, and a list of control points.