Kislinskaya Alina Yurievna

The micronization process using rapid expansion of a supercritical fluid (using salicylic acid, erythromycin, and favipiravir as examples)

Abstract

According to the Decree of the Government of the Russian Federation of 15.04.2014 N 328 (as amended on 02.08.2025) "On approval of the state program of the Russian Federation "Development of industry and increasing its competitiveness", aimed at the implementation of innovative, resource-saving and environmentally friendly technologies and equipment, the introduction of new methods for obtaining nano- and microparticles is promising. The production and use of nano- and micro-sized materials is of interest to various industries. In the chemical industry, when obtaining particles of paints and varnishes, polymers, fertilizers; in the pharmaceutical industry, to reduce the particle size of active pharmaceutical ingredients (API) in order to increase their surface area, dissolution rate and, as a result, bioavailability. In addition, a promising direction is the production of thin films and coatings with improved functional and structural properties. However, micronization methods common in industry are characterized by a number of limitations, such as obtaining particles of non-uniform size and shape, the use of toxic solvents, carrying out the process at high temperatures, which excludes the production of particles heat-labile substances.

Among the promising modern micronization methods, based on the use of supercritical fluids (SCF) stand out. Processes using SCF, such as rapid expansion of supercritical solutions (RESS), do not require toxic solvents. The size and shape of the resulting particles can be controlled by varying the solubility of the SCF depending on the process parameters and the phase transition rate.

This dissertation presents a developed setup for the RESS process and presents the results of experimental studies of the micronization of salicylic acid, favipiravir, and erythromycin, which are poorly water-soluble substances with known solubility in supercritical carbon dioxide (SC-CO_2). During the experimental studies, the dependence of the main characteristics of the resulting particles on

various process parameters was established; mathematical models were developed for calculating the movement of carbon dioxide (CO_2) in a hydraulic nozzle and an expansion chamber for calculating temperature, pressure, density, and velocity profiles; and a software module was developed for calculating the size of particles formed during the process in the expansion chamber.

This work was carried out under Agreement No. 075-03-2025-355/4 of April 29, 2025, between the D.I. Mendeleyev University of Chemical Technology of Russia and the Ministry of Science and Higher Education of the Russian Federation for the performance of work on the topic "Hierarchical Porous Materials for Personalized Implants and Medical Devices" (unique identifier: FSSM-2025-0007).

The aim of the study was to investigate and mathematically model the micronization process using the rapid expansion of a supercritical fluid, using salicylic acid, erythromycin, and favipiravir as examples.

Tasks:

1. Design a laboratory setup and create a process flow diagram for implementing the process of rapid expansion of a supercritical solution.

2. Identify patterns in the influence of temperature and pressure near the crossover point on the formation of nano- and micro-sized particles of salicylic acid, erythromycin, and favipiravir; develop a technology for producing thin polycaprolactone-based coatings using the rapid expansion of a supercritical solution.

3. Conduct comprehensive analytical studies of the resulting particles and coatings and evaluate the influence of process parameters on their characteristics.

4. Mathematical modeling of the process of rapid expansion of a supercritical solution to determine the pressure, temperature, density, and flow velocity profiles in the nozzle and expansion chamber; predict the size of particles formed in the expansion chamber.

Scientific novelty.

Patterns in the influence of temperature and pressure near the crossover point on the size of nano- and micro-sized particles of salicylic acid, erythromycin, and favipiravir obtained during the RESS process were identified.

It was established that the RESS process produces particles of salicylic acid, erythromycin, and favipiravir with an amorphous structure.

Mathematical models of the motion of SC-CO_2 in a hydraulic nozzle and gaseous CO_2 in an expansion chamber were developed to determine the velocity, pressure, and temperature distribution profiles.

Mathematical models were developed to predict the size of particles formed during the RESS process.

Theoretical and practical significance.

A laboratory setup equipped with control and measuring instruments was designed, and a process flow diagram for the RESS process (RU Patent No. 237116) was created, enabling the production of nano- and microparticles, thin films, and coatings.

A technology for producing nano- and microparticles of salicylic acid, erythromycin, and favipiravir using RESS was developed. Microparticles of salicylic acid, favipiravir, and erythromycin nanoparticles were obtained using the designed RESS setup. The dependences of the particle sizes of salicylic acid, erythromycin, and favipiravir on temperature, pressure, and expansion chamber height during the RESS process were determined. Comparative studies of the dissolution rates of the original and micronized favipiravir particles in a phosphate buffer solution were conducted in Franz flow cells.

A software module was developed for calculating the particle size distribution depending on the process pressure and temperature during the RESS process. The presented calculations will reduce the number of experimental studies and the costs of their implementation.

The main provisions for the defense.

1. Design of a RESS system for producing micro- and nanoparticles (Utility Model Patent No. 237116).

2. Micronization of salicylic acid, erythromycin, and favipiravir using RESS. Results of experimental studies of the effect of thermodynamic micronization parameters (temperature, pressure) on the size and degree of crystallinity of salicylic acid, erythromycin, and favipiravir. Results of comparative studies of the solubility of initial and micronized favipiravir particles in a phosphate buffer solution, performed using flow cells. The process of producing thin polycaprolactone-based coatings. Results of a study of the thickness and structure of the resulting coatings depending on the nozzle diameter and the distance from the nozzle to the substrate.

3. Mathematical model of carbon dioxide movement in a hydraulic nozzle and expansion chamber, used to calculate pressure, temperature, density, and flow velocity.

4. Software module for calculating the particle size obtained during the RESS process.