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RESEARCH ARTICLE

# Study of inhalation micropowders obtained by spray drying

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## Abstract

**Objectives.** To study the influence of the type of matrix-forming material and excipients concentration, spray drying parameters on the characteristics of the powder for inhalation, as well as to investigate the inhalation compositions for stability under stressful conditions.

**Methods.** Spray drying was used to obtain powder compositions with the required characteristics for inhalation therapy. Microscopic and analytical studies of powders were carried out. Statistical analysis made it possible to estimate the influence of factors on the powder characteristics and rank them by importance. The stability of spray dried powders was studied.

**Results.** The optimal parameters for obtaining powders for inhalation were found by means of mathematical statistics: air flow rate was 37 $m^3$/h; compressed air flow rate — 601 L/h; inlet air temperature — 150°C; solution flow rate — 45% of the power of the peristaltic pump (16.3 g/min for this composition); L-leucine concentration — 10 wt %; ratio of components of the matrix polyvinylpyrrolidone K-30/D-mannitol = 1 : 3. Under these conditions, as well as by means of 2 experiments additionally selected from the research design, a composition with isoniazid as an active substance was spray dried. The resulting powders were analyzed, in order to confirm the correctness of the recommended parameters.

**Conclusions.** The selection of compositions and spray drying conditions involves multiple criteria. The characteristics of the powder for inhalation may deteriorate significantly during long-term storage. The optimal parameters were determined using statistical analysis and confirmed by experimental data.

## Keywords

spray drying, active pharmaceutical ingredient, micropowders, inhalation, experiment planning methods, optimization

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НАУЧНАЯ СТАТЬЯ

# Исследование ингаляционных микропорошков, полученных методом распылительной сушки

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**Аннотация**

**Цели.** Исследовать влияние типа материала, формирующего каркас частицы, концентрации вспомогательных веществ и параметров распылительной сушки на характеристики порошка для ингаляций. Проверить ингаляционный состав на стабильность в стрессовых условиях.

**Методы.** Для получения порошковых композиций с требуемыми характеристиками для ингаляционной терапии использовалась распылительная сушка. Были проведены микроскопические и аналитические исследования частиц сухого порошка. Статистический анализ позволил оценить влияние факторов на характеристики получаемого порошка для ингаляций и проранжировать их по значимости. Было проведено исследование стабильности порошков, полученных после распылительной сушки.

**Результаты.** Методами математической статистики удалось установить оптимальные параметры получения порошков для ингаляции: расход сушильного агента составил 37 м$^3$/ч; расход сжатого воздуха, подаваемого на форсунку — 601 л/ч; температура сушильного агента на входе в камеру — 150°С; расход раствора — 45% от мощности встроенного насоса (16.3 г/мин для данного состава композиции); концентрация L-лейцина — 10 мас. %; соотношение компонентов матрицы поливинилпирролидон К-30/маннитол = 1 : 3. При данных условиях, а также при условиях 2-х экспериментов дополнительно выбранных из плана исследований, была проведена наработка композиции с изониазидом в качестве активного вещества и проведен анализ полученных порошков, что позволило подтвердить корректность рекомендованных параметров.

**Выводы.** Подбор состава композиций и условий распылительной сушки является многокритериальной задачей. Характеристики порошка для ингаляций могут значительно ухудшиться при длительном хранении. Оптимальные параметры были определены с применением статистического анализа и подтверждены экспериментальными данными.

**Ключевые слова**

распылительная сушка, активный фармацевтический ингредиент, микропорошки, ингаляция, методы планирования эксперимента, оптимизация

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## INTRODUCTION

Pulmonary drug delivery is a promising non-invasive method of active pharmaceutical ingredient (API) delivery for the local treatment of lung diseases [1]. This delivery promotes rapid drug absorption and bypasses the first-pass metabolism effect [2].

Studies have shown that for the purposes of targeted drug delivery to the lungs, the particle size should be in the range of 1 to 5 μm [3]. Obtaining particles in the specified size range is possible using spray drying. This technology has such advantages as high product yield (up to 70%), high drying rate, no API overheating, and the ability to obtain a relatively narrow size distribution of powder particles. This factor is especially important in the development of new inhalation drug delivery systems [4, 5]. Drying parameters and the composition of stock solutions have a crucial influence on the release rate, physical characteristics and the stability of powder compositions. Such parameters need to be carefully investigated, in order to ensure the delivery of high doses of drug substance to the lungs. The dispersion composition of the composition also plays an important role in its stability and aerodynamics.

In addition to the aerodynamic diameter requirements, the powder should have a good level of aerosolization, depending on flowability and dispersibility [6]. Flowability (friability) is an important property of inhalation powders, since it determines their behavior when an emitted dose of drug is inhaled from a powder inhaler [7].

The addition of amino acids to powder compositions can improve the solubility of the powder, its aerodynamic characteristics and increase the yield of the product. The introduction of such an amino acid as leucine can reduce the surface tension and reduce the size of droplets formed during atomization [2]. This results in finer particles, preferred for pulmonary drug delivery, and reduces agglomeration of the powder during storage [1].

Due to their non-toxicity, affordability and water solubility, disaccharides such as lactose, trehalose and mannitol are widely used in the manufacture of inhalation powders. The introduction of carbohydrates in inhalation powders should take into account their hygroscopicity, glass transition temperature and possible interaction with other components and APIs. Hygroscopicity affects the ability of the powder to absorb moisture, as well as drug stability and caking. Studies have shown that the addition of non-hygroscopic mannitol to powder composition improves its dispersibility and prevents particle caking [8].

Biocompatible polymers of synthetic and natural origin can be used as carriers in the creation of inhaler compositions [9, 10]. One widely used polymer in the pharmaceutical industry is polyvinylpyrrolidone (PVP). PVP grade K-30 is widely used in pharmaceutical technology as solution stabilizer, filler and binder.

Isoniazid (widely used for the treatment of tuberculosis) which acts on pathogens located extra- and intracellularly [11] was selected as an API. Using a powder composition consisting of isoniazid, mannitol, leucine and PVP, a stable and easy to use dosage form, can be obtained.

Fillers play an important role in dry inhalation powders. They provide the necessary aerodynamic characteristics and stability of physical properties of the composition [12].

Studies on the stability of pharmaceuticals were conducted, in order to study the degradation of drug substances, as well as to preserve the characteristics of the composition under the influence of stress factors (increased values of temperature and humidity) [13]. This is necessary, in order to develop the optimal composition of the drug product, as well as to determine the basic requirements for the creation of primary packaging. Based on the results of studies, specific storage parameters for drug substances were established [14]. In the present work, the stability of powders obtained after spray drying was investigated at temperature $T$ = 40°C and humidity $W$ = 70%.

The aim of the present study was to research the effect of composition and spray drying parameters upon the properties of the obtained powder inhalation composition and its stability during storage.

## MATERIALS AND METHODS

**Materials.** The experimental work for preparation of placebo powders used mannitol, D(-)-mannite E 421 (hereinafter D-mannite) grade (*Merck,* Germany); amino acid L-leucine (*Suzhou Vitajoy Bio-Tech Co.*, China); PVP K-30 grade (*NEO Chemical,* Russia). Mannitol together with PVP K-30 are used as the matrix-forming agents. Isoniazid was used as the API. The pharmaceutical substance was synthesized at the Department of Organic Chemistry, D.I. Mendeleev Chemical University of Russia. The high quality of isoniazid was confirmed by high-performance liquid chromatography.

**The experimental design.** In order to improve the efficiency of the experiment and obtain reliable results, the experimental design is advisable. Due to the large number of influencing factors and available limitations on the number of experiments, a full factorial experiment combined with two Latin squares was constructed (Table 1).

The most significant controlled parameters were identified: L-leucine concentration (10, 15, 20, and 25%); PVP K-30/D-mannite ratio = 1 : 3 and PVP K-30/D-mannite = 3 : 1. These parameters were varied at four levels. The parameters: drying agent flow rate (32 and 37 $m^3$/h); compressed air flow rate supplied to the nozzle (473 and 601 L/h); drying agent temperature at the chamber inlet (150 and 180°C); liquor flow rate (45 and 55% of the capacity of the built-in pump)—were varied at two levels.

The design of experiment is presented in Table 2. Sixteen experiments were conducted, with experiments No. 8 and No. 9 conducted in three repetitions to assess the homogeneity of variance and reproducibility variance.

**Preparation of dry powder compositions.** The composition of solutions is presented in Table 3. In order to prepare the solutions, 219.3 g of distilled water were measured into a glass beaker and the required weights of L-leucine, D-mannite, PVP K-30 were added one by one. Then everything was stirred with a magnetic stirrer until the formation of a translucent solution and complete dissolution of these substances. The solutions obtained were dried on a spray dryer Mini Spray Dryer B-290 (*Buchi*, Switzerland). Drying parameters were set according to the planning matrix (Table 2).

**Characterization of the obtained dry powder compositions.** The yield and the following characteristics were determined for all samples obtained: bulk density, friability, residual moisture content and the angle of repose. The characteristics were measured immediately after filling and after 2 weeks of storage at $T$ = 40°C, $W$ = 70%.

*The product yield* was determined as follows: the ratio of the mass of powder obtained after the spray drying process to the total mass of solid added to prepare the stock solution (1):

**Table 1.** Variable factors and their acceptable values

| No. | Parameter | Values | |
|---|---|---|---|
| | | (+) | (−) |
| $X_1$ | Air flow rate, $m^3/h$ | 37 | 32 |
| $X_2$ | Compressed air flow rate, L/h | 601 | 473 |
| $X_3$ | Inlet air temperature, °C | 180 | 150 |
| $X_4$ | Power of peristaltic pump, %* | 55 | 45 |
| Factors varying at four levels | | | |
| $X_5$ | Matrix-forming material | A | B | C | D |
| | | PVP K-30 | D-Mannitol | PVP K-30/D-Mannitol = = 1 : 3 | PVP K-30/D-Mannitol = = 3 : 1 |
| $X_6$ | L-Leucine concentration, % | 10 | 15 | 20 | 25 |

**Note:* since the compositions of the solutions were different, their density and viscosity varied accordingly, therefore, for each experiment, the flow rate of liquid supplied for drying at a given power was measured individually during the drying process.

**Table 2.** Design of experiment

| No. | $X_1$ | $X_2$ | $X_3$ | $X_4$ | $X_5$ | $X_6$ |
|---|---|---|---|---|---|---|
| 1 | − | − | − | − | A | 10 |
| 2 | + | − | − | − | B | 15 |
| 3 | − | + | − | − | C | 20 |
| 4 | + | + | − | − | D | 25 |
| 5 | − | − | + | − | B | 25 |
| 6 | + | − | + | − | A | 20 |
| 7 | − | + | + | − | D | 15 |
| 8 | + | + | + | − | C | 10 |
| 9 | − | − | − | + | C | 15 |
| 10 | + | − | − | + | D | 10 |
| 11 | − | + | − | + | A | 25 |
| 12 | + | + | − | + | B | 20 |
| 13 | − | − | + | + | D | 20 |
| 14 | + | − | + | + | C | 25 |
| 15 | − | + | + | + | B | 10 |
| 16 | + | + | + | + | A | 15 |

**Table 3.** Composition of solutions

| No. | PVP, g | D-Mannitol, g | L-Leucine, g | $H_2O_{dist}$, g |
|---|---|---|---|---|
| 1 | 12.6 | 0 | 1.4 | 219.3 |
| 2 | 0 | 11.9 | 2.1 | 219.3 |
| 3 | 2.8 | 8.4 | 2.8 | 219.3 |
| 4 | 7.9 | 2.6 | 3.5 | 219.3 |
| 5 | 0 | 10.5 | 3.5 | 219.3 |
| 6 | 11.2 | 0 | 2.8 | 219.3 |
| 7 | 8.9 | 3.0 | 2.1 | 219.3 |
| 8 | 3.2 | 9.5 | 1.4 | 219.3 |
| 9 | 3.0 | 8.9 | 2.1 | 219.3 |
| 10 | 9.5 | 3.2 | 1.4 | 219.3 |
| 11 | 10.5 | 0 | 3.5 | 219.3 |
| 12 | 0 | 11.2 | 2.8 | 219.3 |
| 13 | 8.4 | 2.8 | 2.8 | 219.3 |
| 14 | 2.6 | 7.9 | 3.5 | 219.3 |
| 15 | 0 | 12.6 | 1.4 | 219.3 |
| 16 | 11.9 | 0 | 2.1 | 219.3 |

$$\eta = \frac{m_{\text{after drying}}}{m_{\text{total}}} \times 100\%, \quad (1)$$

wherein η is a product yield.

*Determination of particle size distribution.* Using Micros MCX-100 Crocus optical microscope (*Micros*, Austria) with hundredfold magnification, particle sizes were determined. In order to study each powder obtained, a small amount of sample was taken and placed on a Goryaev chamber (*Minimed*, Russia). The images of micropowders were processed using ImageG software[1]. In order to characterize the dispersion composition of the samples, the median diameter as well as the quantile of $D_{10}$ and $D_{90}$ were used. Scanning electron microscopy (JEOL 1610LV scanning electron microscope JEOL 1610LV (*JEOL*, Japan)) was performed, in order to visualize the diameter, structural and surface morphology of the microparticles.

*The residual moisture content* of the samples was determined using an Axis AGS500 moisture analyzer (*Axis,* Sweden) at 40°C in automatic mode.

*Bulk density measurement.* In order to establish the bulk density values, the powder was placed in a 1-mL microtube (*Eppendorf*, Germany). The bulk density was determined by the formula as to be the ratio of the mass of the bulk material to the volume occupied by it, including the pores between the particles (2):

$$\rho = \frac{m}{V}, \quad (2)$$

wherein ρ is the bulk density of the powder; $m$ is the mass of the powder; $V$ is the volume of the powder.

*The angle of repose* is a constant three-dimensional angle relative to the horizontal surface formed by a cone-shaped pyramid of material. The angle of repose value was measured in at least three repetitions using an ADA AngleMeter 40 electronic angle meter (*ADA Instruments,* China) in three planes and expressed in angular degrees.

*Investigation of powder stability under stress conditions.* The process of testing powder samples for caking was carried out in the following way. First, sample preparation was carried out. For each sample, two gelatin capsules of 0.25 g of powder were filled. The powder was obtained as a result of the spray drying process. Each pair of capsules was placed in a small filter paper envelope and sent to a Memmert heat-cold-moisture climate chamber HPP110eco, 108 L (*Memmert*, Germany). Powder caking determination tests were performed at 40°C and 70% humidity. After 14 days of keeping the capsules in the climatic chamber, the powder samples were evaluated, checked for caking or sticking. Then the following characteristics were determined: residual moisture content, particle size distribution and angle of repose.

**Statistical analysis of the results.** In order to determine the intensity of the influence of the studied factors on the characteristics of micropowders, statistical analysis of the results was carried out in accordance with [15]. During the analysis, the effects of all factors were calculated and their significance was assessed.

Since multi-criteria problems may not have a local optimum, this case required a transition to a single-criteria problem (convolution of criteria), for example, by the utopian point method [15]. For this purpose, the criteria are normalized in accordance with formula (3):

$$f_j^{\text{norm}} = \frac{f_j}{\text{opt } f_j}, \; j = 1, 2, \ldots, 16, \quad (3)$$

wherein $f_j^{\text{norm}}$ is the normalized value of the criterion; opt $f_j$ is the optimal value of the criterion, $j$ is the ordinal number of the criterion.

The position of the utopian point in the space of vector estimates was determined by equations (4) and (5):

$$F^* = (f_1^*, f_2^*, \ldots, f_m^*), \; m = 1, \ldots, 6, \quad (4)$$

$$f_j^* = \text{opt } f_j^{\text{norm}}, \quad (5)$$

wherein $F^*$ are coordinates of the ideal point in the $f_m^*$ criterion space, since no criterion can obtain a higher value; opt $f_j^{\text{norm}}$ is the optimal value of the normalized criterion, $m$ is the ordinal number of the criterion.

For each experiment, we calculated the distance to the utopian point in space by formula (6):

$$d_j = \sqrt{\sum (f_m^* - f_m^{\text{norm}})^2}, \; m = 1, \ldots, 6, \quad (6)$$

wherein $d_j$ is the distance to the utopian point, $m$ is the ordinal number of the criterion.

The optimal conditions were determined by minimizing the distance to the utopian point.

## RESULTS AND DISCUSSION

According to the methodology and experiment plan, 16 experiments were carried out at different values of varying factors. Analytical studies were carried out for each obtained sample, the results of which are presented in Table 4.

Analytical studies of the micropowders obtained showed that the product yields ranged from 29.5 to 73%, with high yields (more than 60%) obtained in experiments Nos. 6, 7, 8, 11, 12, 15, and 16.

[1] https://imagej.net/. Accessed May 10, 2023.

**Table 4.** Analysis of the obtained powders

| No. | Product yield, % | Residual moisture content, % | Angle of repose, ° | Bulk density, g/cm$^3$ | $D_{10}$, μm | $D_{50}$, μm | $D_{90}$, μm |
|---|---|---|---|---|---|---|---|
| 1 | 36.6 | 0.36 | 43 | 0.45 | 2.2 | 4.0 | 6.9 |
| 2 | 40.3 | 0.12 | 50 | 0.54 | 2.5 | 4.4 | 7.1 |
| 3 | 31.3 | 0.25 | 34 | 0.50 | 2.1 | 2.8 | 4.9 |
| 4 | 29.5 | 0.32 | 36 | 0.42 | 2.4 | 3.1 | 8.5 |
| 5 | 31.9 | 0.32 | 24 | 0.38 | 2.0 | 3.8 | 6.1 |
| 6 | 66.1 | 0.65 | 27 | 0.39 | 2.3 | 3.6 | 6.4 |
| 7 | 61.4 | 0.60 | 36 | 0.48 | 3.9 | 5.1 | 6.9 |
| 8 | 60.3 | 0.45 | 23 | 0.52 | 2.7 | 3.8 | 4.9 |
| 9 | 47.4 | 0.18 | 37 | 0.61 | 2.3 | 3.2 | 4.6 |
| 10 | 44.4 | 0.57 | 37 | 0.51 | 2.1 | 2.8 | 3.6 |
| 11 | 64.3 | 0.60 | 33 | 0.43 | 1.3 | 1.7 | 2.3 |
| 12 | 73.3 | 0.19 | 32 | 0.50 | 2.5 | 3.4 | 4.5 |
| 13 | 36.8 | 0.22 | 33 | 0.39 | 6.4 | 8.8 | 12.7 |
| 14 | 31.4 | 0.15 | 34 | 0.41 | 1.6 | 2.5 | 3.6 |
| 15 | 72.8 | 0.12 | 33 | 0.59 | 2.4 | 3.0 | 5.1 |
| 16 | 70.9 | 0.18 | 38 | 0.40 | 5.2 | 6.2 | 8.2 |

The samples studied retain a small percentage of residual moisture content (range from 0.12 to 0.65 wt %).

The angle of repose is in the range of 23–50° (except for powder No. 2). Bulk density for all samples is less than 0.6 g/cm$^3$, indicating a high level of fluidity of the obtained dry powder compositions. The particle sizes in samples Nos. 3, 8–12, 14, and 15 fall within the range of 1–5 μm, which makes them suitable for inhalation application.

Statistical analysis revealed that the residual moisture content in the studied range is not affected by any of the factors. With regard to the remaining criteria, analysis showed the contradictory nature of the influence of the factors. The optimal conditions for spray drying were obtained and established that the distance to the utopian point should be minimal: $X_1$ is the drying agent flow rate (+) 37 m$^3$/h; $X_2$ is the compressed air flow rate supplied to the nozzle (+) 601 L/h; $X_3$ is the drying agent temperature at the chamber inlet (−) 150°C; $X_4$ is the solution flow rate (−) 45 (g/min); $X_5$ is the matrix material (0.621) = $C$ (PVP K-30/D-mannite = 1 : 3), where $C$ is the concentration; $X_6$ is the L-leucine concentration (0.626 g) = 10%.

Figure shows scanning electron microscope photographs of samples Nos. 2 and 10. The images shows that the particles have a regular spherical shape. The particle size of sample No. 2 has greater uniformity.

After storage of pharmaceutical substances under stress conditions, analytical studies were performed (Table 5).

After a two-week storage period of the samples under stress conditions, it was visually determined that powders Nos. 1 and 7 lost their bulkiness (i.e., stuck together). In this way further analysis of these samples became

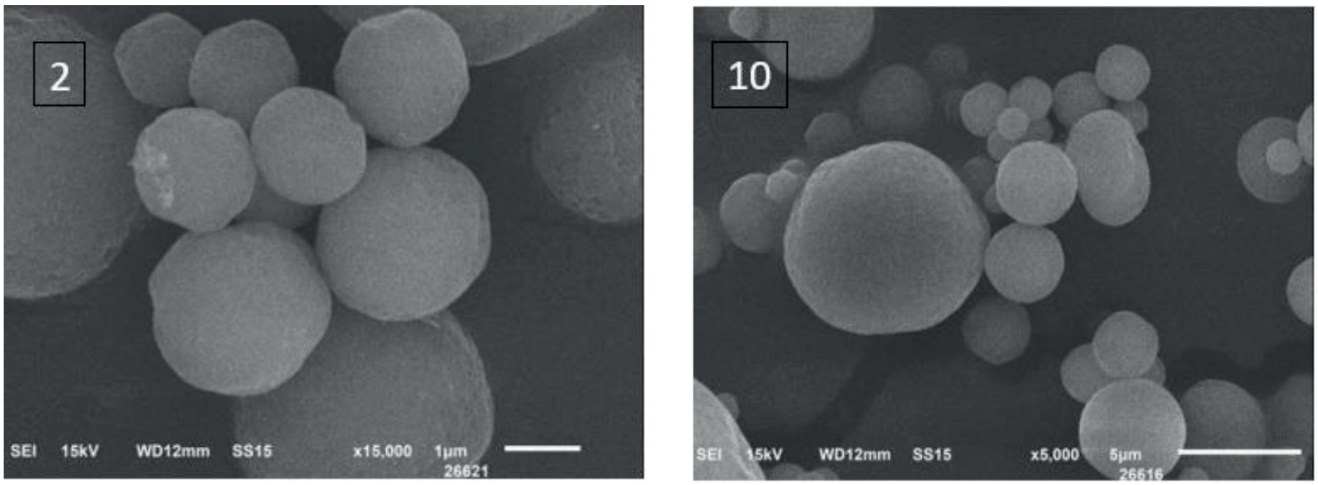


**Fig.** Scanning electron microscope photographs of samples No. 2 and No. 10. Photographs of the samples were made on the equipment of the Central Research Center of the D.I. Mendeleev University of Chemical Technology of Russia

**Table 5.** Analysis of powders after storage under stress conditions

| No. | Residual moisture content, % | $D_{10}$, μm | $D_{50}$, μm | $D_{90}$, μm | Angle of repose, ° |
|---|---|---|---|---|---|
| 1 | – | – | – | – | – |
| 2 | 0.41 | 3.8 | 5.59 | 8.1 | 38 |
| 3 | 0.63 | 4.3 | 5.90 | 8.7 | 35 |
| 4 | 1.15 | 2.9 | 4.90 | 7.1 | 23 |
| 5 | 0.28 | 4.0 | 5.70 | 8.5 | 36 |
| 6 | 2.25 | 4.1 | 6.00 | 8.6 | 40 |
| 7 | – | – | – | – | – |
| 8 | 0.95 | 3.6 | 5.80 | 8.6 | 27 |
| 9 | 0.81 | 4.5 | 6.40 | 9.2 | 51 |
| 10 | 2.07 | 3.6 | 6.30 | 8.6 | 32 |
| 11 | 2.08 | 4.1 | 5.90 | 8.0 | 30 |
| 12 | 0.30 | 3.5 | 5.30 | 7.8 | 30 |
| 13 | 1.40 | 2.4 | 3.60 | 5.7 | 27 |
| 14 | 0.54 | 3.2 | 5.00 | 6.7 | 41 |
| 15 | 0.12 | 3.4 | 4.95 | 7.6 | 35 |
| 16 | 2.32 | 5.0 | 7.28 | 10.0 | 32 |

impossible. All other samples had a small angle of repose. Comparing the parameters obtained in Tables 4 and 5, we can see that after stress tests the residual moisture content and particle size increased insignificantly.

Based on the above, the conclusion can be drawn that not all powders are suitable for long-term storage under stress conditions. In experiments Nos. 8 and 12, the best parameters were obtained, meeting the requirements for inhalation powders.

**Preparation of powder compositions with API.** In order to obtain solutions with API (isoniazid), the conditions obtained as a result of criteria convolution (Table 6, sample 3), as well as the parameters of experiments Nos. 8 and 12 (Table 6, samples 1 and 2, respectively) were used. These samples of placebo compositions showed the best characteristics.

Spray drying conditions for these samples are given in Table 7. The results of the study of the samples of compositions are presented in Table 8.

Table 8 shows that in all experiments, a high product yield (more than 60%) was obtained. Since all powders have a small angle of repose and low bulk density, the aerodynamic properties of these samples can be considered good. The particle sizes have narrow particle size distribution, which makes them suitable for inhalation application.

The samples were investigated for stability under stress conditions for a period of two weeks ($T$ = 40°C; $W$ = 70%). After this time interval, the characteristics of the samples did not change significantly (Table 9).

Thus, the found optimal conditions ensure the achievement of the stated result.

## CONCLUSIONS

The series of studies showed the contradictory influence of composition components and spray drying conditions upon the different characteristics

**Table 6.** Composition of solutions

| No. | PVP, g | D-Mannitol, g | L-Leucine, g | Isoniazid, g | $H_2O_{dist}$, g |
|---|---|---|---|---|---|
| 1 | 1.6 | 4.75 | 0.7 | 0.5 | 109.65 |
| 2 | 0 | 5.60 | 1.4 | 0.5 | 109.65 |
| 3 | 1.6 | 4.75 | 0.7 | 0.5 | 109.65 |

**Table 7.** Parameters of experiments

| No. | $X_1$ | $X_2$ | $X_3$ | $X_4$ | $X_5$ | $X_6$ |
|---|---|---|---|---|---|---|
| 1 | 37 | 601 | 180 | 45 | C | 10 |
| 2 | 37 | 601 | 150 | 55 | B | 20 |
| 3 | 37 | 601 | 150 | 45 | C | 10 |

*Note:* $X_1$ is the flow rate of spray gas, $m^3/h$; $X_2$ is the flow rate of compressed air per nozzle, L/h; $X_3$ is the temperature of spray gas at the spray cylinder inlet, °C; $X_4$ is the power of peristaltic pump, %; $X_5$ is the matrix material; $X_6$ is the L-leucine concentration, %; B is D-Mannitol; C stands for PVP K-30/D-Mannitol = 1 : 3.

**Table 8.** Analysis of the resulting API powders

| Sample | Product yield, % | Residual moisture content, % | Angle of repose, ° | Bulk density, $g/cm^3$ | $D_{10}$, μm | $D_{50}$, μm | $D_{90}$, μm |
|---|---|---|---|---|---|---|---|
| 1 | 68.6 | 3.8 | 15 | 0.5 | 3.5 | 4.6 | 6.5 |
| 2 | 66.6 | 3.8 | 16 | 0.3 | 3.5 | 4.7 | 5.8 |
| 3 | 68.6 | 3.6 | 21 | 0.4 | 2.7 | 3.7 | 4.8 |

**Table 9.** Analysis of resulting API samples after storage under stress conditions

| Sample | Residual moisture content, % | Angle of repose, ° | $D_{10}$, μm | $D_{50}$, μm | $D_{90}$, μm |
|---|---|---|---|---|---|
| 1 | 4.3 | 18 | 3.2 | 4.5 | 5.9 |
| 2 | 4.0 | 17 | 2.1 | 3.0 | 4.3 |
| 3 | 4.6 | 20 | 3.1 | 4.2 | 6.1 |

of the dry powder compositions obtained. The utopian point method was used in order to determine the optimal conditions. For the established parameters, a dry powder composition containing isoniazid was produced. This composition included a mixture of PVP K-30/D-mannite = 1 : 3 and L-leucine with a mass loading of 10% as matrix material. Analysis of the characteristics of the product obtained immediately after drying and after two weeks of storage in conditions of high humidity and temperature confirmed that the required values of quality indicators had been achieved: product yield 68.6%; moisture content less than 5%; angle of repose less than 20°; average particle diameter 4.2 μm.

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## Authors' contributions

**L.A. Shcherbakova, A.I. Saitgareeva**—conducting experiments and analytical research, statistical processing of results, and writing the text of the article.

**M.G. Gordienko, R.R. Safarov**—formulating the problem and research design, analysis of the obtained results, and revising the article.

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