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Obtaining and research of pharmaceutical properties of antiemetics in a form of powder for inhalation

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ABSTRACT. Samples of antiemetic drugs (ondansetronum, palonosetronum, metoclopramidum) in the form of powder for inhalation have been developed by the method of spray drying. The granulometric composition, hygroscopicity and aerodynamic distribution of aerosol particles of the drugs have been investigated. The dosage form of the powder for inhalation of antiemetics (ondansetronum and palonosetronum) in terms of its particle size distribution, hygroscopicity and content of the agent corresponds to those for inhalation using dry powder inhalers. In the study of the phase-dispersed composition of aerosol, ondansetronum and palonosetronum in the dosage form of powder for inhalation as part of the HandiHaler inhaler (at a flow rate of 60 l/min) showed high rates of the released dose up to 72–76%, respirable particle fraction (up to 5 μm) up to 54–56% and a mass median particle size of about 3 microns. Obtaining the inhaled form of metoclopramide requires optimization of the production method for receiving the product with acceptable pharmaceutical properties.

KEYWORDS: delivered dose, inhalation administration, mass median particle size, lactose, metoclopramidum, ondansetronum, palonosetronum, powder for inhalation, antiemetic drugs, spray drying, respirable fraction

ABBREVIATIONS:

i/m – intramuscular administration;
i/v – intravenous administration;
RF – the Russian Federation;
p/o – per os, oral administration;
DPI – dry powder inhaler.

INTRODUCTION

The relevance of improving the methods of administration of antiemetic drugs is determined by a high prevalence of emetic syndrome both in oncosurgical practice and in cytostatic therapy. Moreover, in the field of disaster medicine, emetic syndrome is considered to be an integral component of a primary response to radiation in case of radiation injuries in high doses, as well as a possible concomitant sign of poisoning by a number of toxicants. Thus, equipping emergency medicine units and the Armed Forces of the Russian Federation with highly effective antiemetics in a convenient form for application is an important practical task.

Antiemetic drugs registered in Russia are represented by the following dosage forms:

– oral (syrup, oral tablets): ondansetron, granisetron, tropisetron, metoclopramide, domperidone, perphenazine, hyoscine butyl bromide, aprepitant, palonosetron + netupitant, trifluoperazine;

– injection (solution for i/m, i/v + i/m administration): ondansetron, metoclopramide, promethazine, hyoscine butyl bromide, trifluoperazine;

– infusion (lyophilisate or concentrate for i/v administration, solution for i/v administration): granisetron, tropisetron, fosaprepitant, palonosetron;

– suppositories: ondansetron, hyoscine butyl bromide;

– buccal forms that do not require drinking with water (lyophilized, dispersible tablets): ondansetron, domperidone.

Among above listed active ingredients, ondansetron and metoclopramide are included in standard kits of medical equipment for civil defense of the Ministry of the Russian Federation for Civil Defence, Emergencies and Elimination of Consequences of Natural Disasters and the Armed Forces of the Russian Federation.

Latran (ondansetron hydrochloride dihydrate) is aimed at prevention and relief of main clinical manifestations of an early radiation reaction in radiation injury and, in the form of tablets for oral administration, is included as a standard medicine in the composition of individual medical civil protection kits, as well as in the composition of first-aid kits for wartime [1, 2].

Metoclopramide in the form of tablets for oral administration (10 mg) and in the form of a 0,5% solution for injection in ampoules of 2 ml is in the list of medicines included in the medical equipment kits for the military units of medical service of the RF Armed Forces [2, 3].

It is obvious that the majority of the existing dosage forms of antiemetic drugs (tablets, infusion solutions) are of little use in the field and in emergency situations, namely in mass casualty situations. In addition, classical oral dosage forms (syrup, solution, tablets and capsules for oral administration) are limitedly suitable for use in case of onset of vomiting.

Promising directions for improving the methods of using antiemetics include the development of injectable forms for quick self-administration in the field (syringes, autoinjectors), modern oral forms (instant, not requiring drinking, sublingual tablets, buccal forms, etc.), as well as inhalation forms [4, 5, 6].

As examples of the implementation of these approaches, one can note ondansetron sublingual tablets and its injectable forms, the development of forms for the intramuscular administration of combined anti-missile therapy drugs, and the study of inhaled forms of ondansetron (nebulizer solution) [7].

It is obvious that the development of drugs for the relief of emetic syndrome or an early radiation reaction in a form suitable for inhalation should be aimed at replacing oral drugs. At the same time, among the advantages of inhalation therapy, one should point out the high rate of the onset of the effect and the possibility of administering drugs with the onset of nausea and vomiting. In addition, the lack of technical means for a self-injection (or within the framework of mutual assistance) of solutions (automatic injectors, antiemetic drugs in the form of syringe-tubes) in the nomenclature of the medical service today practically excludes the possibility of self-administration of antiemetics when vomiting begins at the prehospital stage.

Of the drugs registered in the Russian Federation, ondansetron, metoclopramide (as official antiemetics for federal executive authorities), and palonosetron, one of the most powerful long-acting 5HT3-antagonists (its effective dose for humans is 0,25 mg), can be distinguished as means for creating an inhaled dosage form of drugs for prophylaxis and relief of early radiation reaction.

Among the options for inhalation use of antiemetic drugs, preference should be given to the use of the following dosage form: powder for inhalation in capsules together with an individual portable inhaler. The advantages of this form include the possibility of delivering drugs into the respiratory tract and into the systemic circulation in higher doses than using a nebulizer or metered-dose aerosol inhaler (container). The loading capacity of the dosage form in a DPI can be up to 50-100 mg per 1-2 breaths, which is unachievable with other methods of inhalation. High speed of drug administration, simplicity and ease of use, independence from external energy sources can be an advantage of dry powder inhalers when used in the field and in emergency situations.

The aim of the study is to develop a technology for producing antiemetics in the form of a powder for inhalation using the spray drying method and to investigate the pharmaceutical properties of the resulting drugs.

MATERIALS AND METHODS

The preparation of drugs in the form of a powder for inhalation was carried out by spray drying in an open circuit of Nano Spray Dryer B-90 HP (Buchi, Switzerland). At the first stage, the standard settings of the device were used, in which the concentration of the active principle in the working solution was varied to achieve the required powder particle size and acceptable productivity. The spray drying parameters are presented in Table 1.

Mixtures of the active principle with lactose were dissolved in distilled water to a concentration of 1,0%. The ratios «active principle: lactose» were 1:2,125 and 1:5,25 for ondansetron; 1:1,5, 1:24 and 1:99 for palonosetron; 1:1,5 and 1:0,25 for metoclopramide.

After obtaining powder samples, the particle size distribution (in the range 0,01–3500 μm) was analyzed using a Mastersizer 3000 laser diffraction analyzer (Malvern Instruments Ltd., Great Britain) equipped with an Aero S air dry dispersion system. In the course of grain-size analysis the following indicators were calculated:

Table 1.

Parameters of spray drying process

Табл. 1.

Параметры процесса распылительной сушки

Parameter	Value
Gas flow rate	100–110 l/min
Set temperature	100 °C
Actual temperature: - at the input of the drying cylinder - at the outlet (in the electrostatic collector) - at the outlet from the spraying head	100 °C 85 °C 35–40 °C
Pressure	27–33 hPa
Peristaltic pump capacity	50%
Relative spraying rate	70%
Concentration of the active principle in the working solution	1%

– the width of the distribution of particles in microns;

– standard percentiles of the particle size distribution in microns (Dv(50)), «median volumetric distribution», the size less than 50% of the sample particles; Dv(10), the size less than 10% of the sample particles; Dv(90), the size less than 90% of the sample particles).

The determination of hygroscopicity of obtained drug powders was carried out in accordance with FS 01/2016:51100 Section 5.11. «Properties».

In order to determine optimal parameters of the production process and obtain data on pharmaceutical properties of drugs in the finished dosage form, the delivered dose and the respirable fraction were evaluated. These indicators characterize, respectively, the amount of active substance actually received by the patient (excluding the amount deposited on the constituent parts of the inhaler) and presumably penetrating into the lungs during inhalation.

To study the delivered dose, sampling devices containing a filter were used, and then the extraction of the active substance and its quantitative analysis by HPLC with ultraviolet detection in accordance with the standards of the European Pharmacopoeia (section «Dosage Forms - Preparations for Inhalation <0671>») and Pharmacopoeia United States of America (Section <601>) took place.

To study the aerodynamic distribution of drug particles by size in the finished dosage form «powder for inhalation» and the subsequent calculation of the respirable fraction of the aerosol, the pharmaceutical impactor NGI («Copley Scientific», Great Britain) was used, corresponding to the specifications of the State Pharmacopoeia of the Russian Federation (edition XIV, volume 2, OFS.1.4.2.0001.15), the European Pharmacopoeia («Apparatus E») and the United States Pharmacopoeia («Apparatus 5»). To calculate the mass median size of aerosol particles, delivered dose and respirable fraction, CITDAS 3.1 software (Copley, Great Britain) was used.

As measures of central tendencies for all quantitative characteristics in the compared groups, the arithmetic mean and root mean square (standard) errors of the mean were assessed. Descriptive statistics in the text are presented as M ± SD, where M is the mean, SD is the standard deviation.

RESULTS AND ITS DISCUSSION

Substantiation of dosage compositions of medicines in powder form for inhalation

When developing drugs in a final dosage form «powder for inhalations», one focused on the estimated content of an active principle in a dosage unit of the inhalation agent (capsule, metered powder for inhalation). In general, for a capsule of a standard size 3 (the most common size for inhalation preparations), the maximum powder content (active principle + excipients) is no more than 25 mg. In addition, the ranges of recommended single and daily doses of the considered drugs were taken into account for their non-inhalation administration. It was assumed that in subsequent experiments the content of active and auxiliary substances can be adjusted taking into account the optimization of the phase-disperse composition of the aerosol of the drug. The rationale for the choice of dosage compositions of drugs in the dosage form «powder for inhalation» is presented in Table 2.

Taking into account the doses recommended for clinical use of the drugs under consideration (with their non-inhalation intake), several variants of dose compositions were selected: they correspond to or close to a single and daily dose of drugs for non-inhalation intake (based on 1 capsule, taking into account the addition of up to 25 mg of an auxiliary substances - lactose).

Preparation of powder for inhalation by spray drying and evaluation of its properties

Studies have been carried out on the production of powders for inhalation of antiemetic drugs by the method of spray drying. The results of evaluating the granulometric composition of obtained samples are presented in Table 3.

The target indicator for inhaled dosage forms as powders for inhalation is the median particle size Dv(50) of no more than 5 μm (preferably 2–4 μm), as well as the dispersion index (range of distribution) of particle sizes is no more than 3. The achievement of these parameters allows one to make an indirect conclusion about the production of powder, which granulometric composition reaches acceptable values of deposition in deep parts of the lungs during inhalation. Such samples do not require significant optimization of the preparation procedure and can be studied at subsequent stages as part of devices for inhalation administration. It was noted that the majority of the samples under study, with the exception of metoclopramide, met formulated requirements.

It is known that with a decrease in the particle size (1 μm or less), the adhesion properties of the powder increase significantly. When generating an aerosol in an inhalation device, this leads to difficulty in deagglomeration and a decrease in the released dose. The selection of laboratory operating parameters in order to achieve a powder particle size of 2–4 μm should be considered as a purpose of optimizing the dosage form for such samples.

For ondansetron samples it was shown that with an increase in the content of the active principle in the dosage form, as well as with an increase in its concentration in the working solution, an increase in the Dv(50) index occurs. Optimal parameters for obtaining ondansetron powder with a dose of the active principle of 8 mg and with a particle size Dv(50) 2.90 ± 0.01 μm was the concentration of the working solution of 0,5%. For a sample with a dose of the active principle of 4 mg, the optimal production conditions assumed the use of a working solution at a concentration of 1%.

Table 2.

Rationale for the choice of dose compositions of antiemetic drugs in a dosage form of powder for inhalation

Табл. 2.

Обоснование выбора дозовых составов противорвотных препаратов в лекарственной форме «порошок для ингаляций»

Name of the medicinal product	Recommended doses, mg (route of administration)		Dose of active ingredient in powder for inhalation (per 1 capsule, excipient – lactose, up to 25 mg)
	Single	Daily	
Palonosetron	0,25–6,3 (i/v)	6,3 (i/v)	0,25 1 6,3
Ondansetron	4–8 (p/o, i/m, i/v)	32 (p/o, i/m, i/v)	4 8
Cerucal (metoclopramide)	10 (i/m, i/v)	30 (i/m, i/v)	10 20

Table 3.

Granulometric composition of powder samples of antiemetic drugs obtained by spray drying, M±SD, n=4

Табл. 3.

Гранулометрический состав образцов порошков противорвотных лекарственных средств, полученных методом распылительной сушки, M±SD, n=4

Drug sample (percentage in the working solution)	Dose of an active principle (in 25 mg of the dosage form), mg	Width of particle distribution, μm	Dv(10), μm	Dv(50), μm	Dv(90), μm
Ondansetron (0,5%)	4	2,12±0,18	0,60±0,06	1,45±0,01	3,67±0,25
	8	2,12±0,26	1,20±0,01	2,90±0,01	7,34±0,35
Ondansetron (1,0%)	4	2,43±0,33	0,84±0,02	2,30±0,12	6,44±1,06
	8	2,18±0,11	1,15±0,05	4,53±0,13	11,0±0,20
Palonosetron (0,5%)	0,25	2,53±0,32	0,61±0,07	1,70±0,34	4,21±0,59
	1	2,89±0,42	0,79±0,14	2,21±0,19	6,55±0,28
	6,3	2,39±0,13	1,16±0,03	3,75±0,24	10,13±0,86
Palonosetron (1,0%)	0,25	2,48±0,27	0,75±0,05	2,09±0,23	6,89±1,32
	1	3,03±0,31	0,92±0,05	2,73±0,01	9,17±0,77
	6,3	2,36±0,03	1,8±0,02	4,52±0,10	12,1±0,35
Metoclopramide (0,5%)	10	2,12±0,06	3,96±0,02	6,77±0,06	11,55±1,09
	20	2,92±0,26	2,56±0,32	8,46±0,32	18,35±1,87
Metoclopramide (1,0%)	10	2,48±0,14	4,85±0,41	7,66±0,17	14,47±2,41
	20	3,39±0,31	4,43±0,24	9,37±0,45	21,42±2,18

When evaluating the granulometric composition of samples containing palonosetron as an active principle, we noted previously revealed tendency for the particles to coarse with an increase in the proportion of the active substance in relation to the inert carrier. Achieving the optimal size range of 2–4 μm for palonosetron samples with a dose of 0,25–1 mg of the active principle required the use of a working solution at a concentration of 1%. When a dose of the active principle is 6,3 mg, a concentration of the working solution of 0,5% is required to obtain a sample with a given size.

Samples of micronized metoclopramide powder were characterized by large particle sizes. The Dv(50) parameter was 6–8 μm (when using a 0,5% concentration of the working solution) and 7–9 μm (when using a 1% concentration of the working solution). This indicated the necessity for further optimization of the production procedure in order to obtain a product with acceptable pharmaceutical properties.

When analyzing the content of the active principle and assessing the hygroscopicity of samples (Table 4), it was noted that for the majority of investigated drugs the passage of the spray drying procedure did not lead to a destruction of the active substance. The exception was metoclopramide, for which the content of the active principle was less than 50%. Apparently, for this preparation, the procedure for optimization of production technology should include a decrease in the drying temperature.

Table 4.

The content of the active agent in samples and the hygroscopicity of the powders, M ± SD, n=5

Табл. 4.

Содержание активного начала в образцах и гигроскопичность порошков, M±SD, n=5

Drug sample (percentage in working solution)	Nominal content in a capsule, mg	Actual content (% of nominal)	Hygroscopicity, %
Lactose (control)	25	99,3±0,62	4,5±0,15
Ondansetron (0,5%)	4	99,4±0,27	5,5±0,40
	8	98,7±1,10	7,9±0,47
Ondansetron (1,0%)	4	99,0±0,87	6,7±0,50
	8	98,6±1,14	11,7±0,93
Palonosetron (0,5%)	0,25	97,7±0,71	5,3±0,63
	1	98,2±0,94	5,4±0,57
	6,3	96,4±1,56	6,9±0,34
Palonosetron (1,0%)	0,25	98,8±0,65	5,0±0,42
	1	99,1±0,85	5,2±0,69
	6,3	95,2±2,34	6,7±0,12
Metoclopramide (0,5%)	10	49,8±3,51	diffuses in the air
	20	38,7±4,64	diffuses in the air
Metoclopramide (1,0%)	10	25,4±4,89	diffuses in the air
	20	18,5±3,73	diffuses in the air

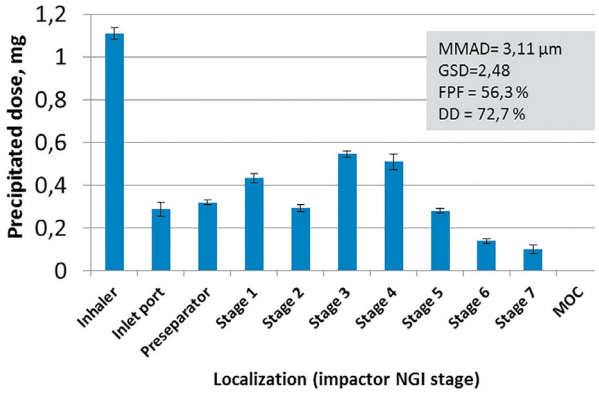

Fig. 1. Results of studying the distribution of the mass-median aerodynamic diameter of aerosol particles after inhalation of the ondansetron sample (M±SD, n=3)
Рис. 1. Результаты исследования распределения масс-медианного размера частиц аэрозоля после ингаляции образца «ондансетрон» (M±SD, n=3)
Note: MMAD – mass-median aerodynamic diameter of particles; GSD – geometric standard deviation; FPF – fine particle fraction; DD – delivered (released) dose

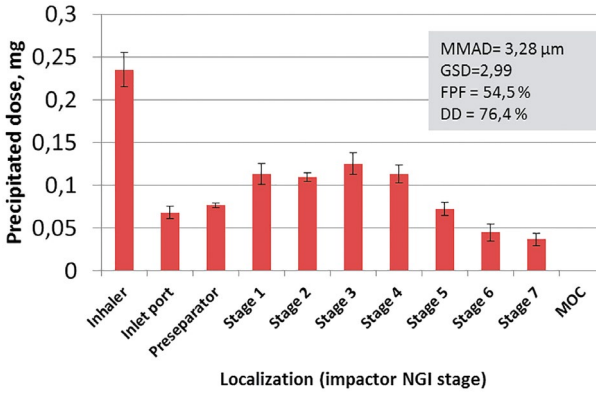

Fig. 2. Results of studying the distribution of the mass-median size of aerosol particles following inhalation of the palonosetron sample (M±SD, n=3)
Рис. 2. Результаты исследования распределения масс-медианного размера частиц аэрозоля после ингаляции образца «палоносетрон» (M±SD, n=3)
Note: MMAD – mass-median aerodynamic diameter of particles; GSD – standard gradient deviation; FPF – fine particle fraction; DD – delivered (released) dose

It was shown that the hygroscopicity of lactose (an inert filler of the dosage form) was 4,5 ± 0,15%, and of other samples – ranging from 5,0 to 11,7%. The highest value of the indicator was observed in the sample of ondansetron with a dose of the active principle of 8 mg, obtained from the working solution with a concentration of 1,0%. In the study of metoclopramide samples, the watering of the powder was noted.

Thus, the use of spray drying without modifications (due to the addition of excipients, changes in operating modes or the composition of the gas mixture) made it possible to obtain samples of some antiemetic drugs (ondansetron, palonosetron), the powders of which, in terms of their particle size distribution, hygroscopicity and active ingredient content, are suitable for inhalation applications using MDI.

The study of aerodynamic distribution of aerosol particles of drugs

To study the aerodynamic distribution of aerosol particles formed upon activation of drugs during inhalation, the samples of ondansetron, where a dose of the active principle was 4 mg (1% in the working solution), and palonosetron, where a dose of the active principle was 1 mg (0,5% in the working solution) were taken for the next stage of the study.

The indicators of the phase-dispersed composition of drug aerosols (particle size, respirable fraction, released dose) were investigated in the HandiHaler inhaler under the following conditions: pressure drop - 4 kPa, flow rate - 60 l/min, inspiratory volume – 4 liters.

The results are shown in Figures 1 and 2.

It was found that the drugs ondansetron and palonosetron were characterized by a high rate of the released dose (up to 72–76%), and a respirable fraction of particles up to 5 microns in size (up to 54–56%). The mass-median size of aerosol particles of the samples was about 3 µm.

CONCLUSION

Directions for improving the methods of using antiemetics in clinical practice and in emergency situations are associated with the development of dosage forms that are practical for application, among which dry powder inhalers deserve the greatest attention due to their advantages (high speed of administration in relatively high doses, simplicity and ease of use, portability and independence from external energy sources [10]).

Taking into account a possible content of the active principle in the dosage unit of the inhalation agent, as well as the value of the clinically recommended doses, palonosetron, ondansetron and metoclopramide were selected for the study. They are currently available on the market in injectable and oral forms and are used in emergency situations. Among the drugs under study, palonosetron had the lowest effective dose (0,25–6,3 mg), which made it possible, if necessary, to use excipients (lactose) to improve pharmaceutical properties of the powder for inhalation.

Powders of palonosetron and ondansetron obtained by spray drying were characterized by their particle size distribution by a median particle size Dv(50) of no more than 5 µm, while for metoclopramide the parameter Dv(50) was 6–8 µm (when using 0,5% concentration of the working solution) and 7–9 microns (when using 1% concentration of the working solution), which indicated the need for further optimization of the production method to obtain a product with acceptable pharmaceutical properties. It was shown that with an increase of the active principle in relation to lactose in the dosage form, as well as with an increase in its concentration in the working solution, an increase in the particle size (Dv(50)) of the samples obtained by spray drying occurs.

It was noted that for ondansetron and palonosetron the spray drying procedure did not lead to the destruction of the active substance, while in the case of metoclopramide, a 50% decrease in the content of the active principle was detected. Apparently, for this preparation, the procedure for optimizing the production technology should include a decrease in the drying temperature. In addition, metoclopramide powder was hygroscopic (diffused in the air).

Thus, the use of spray drying made it possible to obtain powders of antiemetics (ondansetron and palonosetron),

which, in terms of their particle size distribution, hygroscopicity, and active principle content, are suitable for inhalation use with DPI. These assumptions were confirmed by the results of a study of the phase-dispersed composition of the aerosol of the samples of ondansetron and palonosetron in the dosage form powder for inhalation as part of the HandiHaler inhaler. At a flow rate of 60 l/min, the obtained drug samples were characterized by a high release dose rate of up to 72–76%, a respirable particle fraction (up to 5 microns) up to 54–56%, and a mass median particle size of about 3 microns.

These results confirm the possibility of obtaining a powder for inhalation by spray drying methods of palonosetron and ondansetron preparations in a dosage form. In relation to other antiemetics (for example, metoclopramide), optimization of the production technology is required.

As further directions of research, it is necessary to point out the study of the stability of the obtained powders of antiemetics during storage, comparative studies of the pharmacokinetics of ondansetron and palonosetron with inhalation and traditional routes of administration.

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Научная статья

Получение и исследование фармацевтических свойств противорвотных средств в лекарственной форме порошок для ингаляции

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АННОТАЦИЯ. Методом распылительной сушки наработаны образцы противорвотных лекарственных средств (ондансетрон, палоносетрон, метоклопрамид) в форме порошка для ингаляции. Исследованы гранулометрический состав, гигроскопичность и аэродинамическое распределение частиц аэрозоля полученных лекарственных средств. Лекарственная форма «порошок для ингаляции» противорвотных средств (ондансетрон или палоносетрон) по своему гранулометрическому составу, гигроскопичности и содержанию активного начала соответствует показателям для ингаляционного применения с использованием ингаляторов сухого порошка. При исследовании фазово-дисперсного состава аэрозоля образцов ондансетрон и палоносетрон в лекарственной форме «порошок для ингаляции» в составе ингалятора ХандиХалер (при скорости потока 60 л/мин) выявлены высокие показатели высвобождаемой дозы до 72–76%, респирабельная фракция частиц (до 5 мкм) до 54–56% и масс-медианный размер частиц около 3 мкм. Для получения ингаляционной формы метоклопрамида с приемлемыми фармацевтическими свойствами требуется оптимизация методики наработки продукта.

КЛЮЧЕВЫЕ СЛОВА: доставляемая доза, ингаляционное введение, масс-медианный размер частиц, лактоза, метоклопрамид, ондансетрон, палоносетрон, порошок для ингаляции, противорвотные лекарственные средства, распылительная сушка, респирабельная фракция

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