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Investigation of the Influence of Formulation Method on Technological Parameters of Gramicidin S and β-cyclodextrin Inclusion Complexes

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Abstract

Introduction. Gramicidin S is a peptide antibiotic that has been widely used for more than 70 years. Gramicidin S is available in the form of tablets with a low dosage, which leads to possible deviations in the "Uniformity of dosage" parameter during manufacturing. Another limitation is the presence of lactose and sucrose in the formulation, which limits the drug application by patients demonstrating intolerance. As an alternative, we propose inclusion complexes of gramicidin S with β-cyclodextrin.

Aim. The work aims to describe the influence of the methodology to prepare the inclusion complex on the characteristics and properties of the final product.

Materials and methods. The gramicidin S – β-cyclodextrin inclusion complex has been prepared by dry mixing, paste complexation, co-precipitation and fluid-bed complexation. The complex formation has been confirmed by ^{1}H NMR spectroscopy, differential scanning calorimetry and thermogravimetry while the morphology and size by scanning electron microscopy for the solid and dynamic light scattering for the solution. The flowability, slope angle, bulk density of the obtained powders were estimated using the methods described in Russian Pharmacopoeia of the XIV edition.

Results and discussion. In the present work, we prepared a set of gramicidin S and β-cyclodextrin inclusion complexes by various approaches. The thermal analysis demonstrated a significant change in the peak referring to phase transition of the substances, indicating the interaction between the components. The ^{1}H NMR spectroscopy reveals that the L-ornithine amino group is the part of gramicidin S involved in the complexation. Evaluating the technological properties of gramicidin S and β-cyclodextrin inclusion complexes significant variability, which is associated with the particle morphology. Complexes obtained using co-precipitation and fluid-bed complexation methods are more suitable for producing gramicidin S tablet production by direct compression technology.

Conclusion. Herein, we demonstrate that the formation of the gramicidin S and β-cyclodextrin inclusion complex occurs through the L-ornithine amino group in the gramicidin S. In addition, depending on the method significant differences in the particle size and shape have been observed. The obtained results could provide valuable information for the development of new gramicidin S buccal formulations, which are more consistent in the "Uniformity of dosage" and allow to avoid the use of lactose and sucrose as excipients.

Keywords: gramicidin S, antibiotic, β-cyclodextrin, inclusion complex

Conflict of interest. The authors declare that they have no obvious and potential conflicts of interest related to the publication of this article.

Contribution of the authors. Aleksandr A. Drannikov, Ivan S. Vatlin developed the experimental design, held the experiment. Aleksandr A. Drannikov, Sergei V. Krivoshchekov analyzed the obtained results. Mikhail V. Belousov, Marina E. Trusova were supervisors of this work. Aleksandr A. Drannikov, Ivan S. Vatlin, Sergei V. Krivoshchekov, Artem M. Guriev Antonio Di Martino prepared the manuscript. All authors took part in the discussion.

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Исследование влияния способа получения комплексов включения грамицидина С и β-циклодекстрина на их технологические показатели

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Резюме

Введение. Антибиотик пептидной природы грамицидин С находит широкое применение протяжении более чем 70 лет. Грамицидин С выпускается в форме таблеток, которые имеют низкую дозировку, что обуславливает риск отклонения по показателю «Однородность дозирования». Содержание в таблетках лактозы и сахарозы, ограничивает применение препарата пациентами с непереносимостью данных компонентов. В качестве альтернативы предлагается образование комплексов включения грамицидина С с β-циклодекстрином.

Цель. Исследовать влияние способов получения комплексов включения грамицидина С и β-циклодекстрина на их технологические показатели

Материалы и методы. Получение комплекса включения грамицидина С и β-циклодекстрина проводили с применением методов сухого смешивания, затирания в пасте, соосаждения, комплексообразования в псевдоожиженном слое. Подтверждение образования комплекса проводили, используя ^{1}H ЯМР-спектроскопию, дифференциальную сканирующую калориметрию и термогравиметрию. Морфологию определяли с применением методов сканирующей электронной микроскопии, динамического рассеяния света. Сыпучесть, угол откоса, насыпную плотность полученных порошков определяли с применением методик, указанных в Государственной фармакопее РФ XIV издания.

Результаты и обсуждение. В ходе работы получен ряд комплексов грамицидина С и β-циклодекстрина с использованием различных способов. Термограммы комплексов включения демонстрируют значительное изменение пика в области, соответствующей фазовому переходу веществ, что явно свидетельствует о наличии взаимодействия между компонентами комплекса включения. Результаты ^{1}H ЯМР-спектроскопии позволили сделать вывод о комплексообразовании по аминогруппе L-орнитина в молекуле грамицидина С. При исследовании технологических свойств комплексов включения грамицидина С и β-циклодекстрина, установлена значительная вариабельность их технологических параметров, что связано, в том числе, с морфологией частиц. Комплексы, полученные с использованием методов соосаждения и комплексообразования в псевдоожиженном слое, могут быть использованы в производстве таблетированных лекарственных форм грамицидина С по технологии прямого прессования.

Заключение. В рамках настоящего исследования установлено, что образование комплекса включения грамицидина С и β-циклодекстрина проходит по аминогруппе L-орнитина в молекуле грамицидина С. Обнаружены существенные различия размеров и формы частиц, что сказывается на значениях технологических параметров комплексов включения, получаемых с использованием различных подходов. Полученные результаты могут быть использованы при разработке новых буккальных форм грамицидина С, обладающих меньшей вероятностью несоответствия по показателю «Однородность дозирования» и исключающих содержание лактозы и сахарозы.

Ключевые слова: грамицидин С, антибиотик, β-циклодекстрин, комплекс включения

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Вклад авторов. А. А. Дранников, И. С. Ватлин разработали дизайн исследования, провели исследование. А. А. Дранников, С. В. Кривощеков провели анализ полученных данных. М. В. Белоусов, М. Е. Трусова осуществляли научное руководство исследованием. А. А. Дранников, И. С. Ватлин, С. В. Кривощеков, А. М. Гурьев, А. Ди Мартино подготовили текст статьи. Все авторы участвовали в обсуждении результатов.

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INTRODUCTION

Peptide antibiotic gramicidin S is widely used in the treatment of infections caused by gram-positive and gram-negative bacteria, as well as some fungi [1] for more than 70 years of industrial production of the antibiotic without resistance formation [2].

At the same time, fillers such as lactose and sucrose are often used in the composition of gramicidin S lozenges[1], which promotes a potential risk when using the drug by patients with individual intolerance to those excipients.

An additional problem of all tableted dosage forms of gramicidin S is the low dosage of the active ingredient (up to 0.55 wt. % per 1 tablet), which carries high risk of production deviations of the uniformity of dosage parameter meaning. During the manufacturing, the problem is being solved by introducing of an active pharmaceutical ingredient (API) into the composition of the humidifier during the stage of wet granulation of the tablet mixture [3].

One of the possible ways to solve these problems is the formation of inclusion complexes with cyclodextrins – starch derivatives, which form a structure with a hydrophilic outer and hydrophobic inner surface, which polarity is close to that of ethanol. Due to this, poorly soluble substances are incorporated completely or partially into the cavity of cyclodextrin, changing their properties without chemical modification [4].

[1] State register of medicines. Gramicidin S. Available at: https://grls.rosminzdrav.ru/grls.aspx?s=%D0%B3%D1%80%D0%B0%D0%BC%D0%B8%D1%86%D0%B8%D0%B4%D0%B8%D0%BD&m=mnn. Accessed: 24.11.2021. (In Russ.)

It was previously shown that the drug encapsulation into β-cyclodextrin cavity improves parameters such as flowability, slope angle and bulk density, as well as increases the API solubility in water [5].

Within this work, we analyzed the influence of various approaches to prepare the inclusion complex of gramicidin S and β-cyclodextrin on the technological properties of the resulting product.

MATERIALS AND METHODS

Gramicidin S dihydrochloride (TS 9348-023-47509455-2012, JSC «PFK Obnovlenie», Russia) was used as an object of this research, excipients – β-cyclodextrin, EP/USP (Roquette Frères, France), ethanol 95 % (Russian Pharmacopeia XIV ed, FS.2.1.0036.15) and purified water (Russian Pharmacopeia XIV ed, FS.2.2.0020.18).

To prepare the gramicidin S and β-cyclodextrin inclusion complex we applied following approaches:

1. Dry mixing method.

500.0 g of β-cyclodextrin, 50.0 g of gramicidin S dihydrochloride and grinding bodies were loaded in the drum of a ceramic ball mill MShK-50 (LLC "Slavyanskaya ceramic company", Ukraine). The resulting mixture was micronizing for 8 hours while maintaining the drum rotation at 20 rpm.

2. Paste complexation.

10.0 g of gramicidin S dihydrochloride was dissolved in 200.0 ml of 95 % ethyl alcohol, obtaining a 5 % solution. The drug solution was filtered through a syringe filter with a pore size of 0.45 μm (Gluvex, Russia). The filtrate was slowly added to 100.0 g of β-cyclodextrin with stirring, and then the solvent was removed by evaporation. To remove the residual ethanol content, we dried the resulting mixture was dried at room temperature under a vacuum of 0.1 bar in a VAC-24 drying oven (Stegler, China).

3. Co-precipitation method.

2.0 g of gramicidin S dihydrochloride was dissolved in 40.0 ml of ethanol, resulting a 5 % solution. Separately, 20.0 g of β-cyclodextrin was dissolved in 1000 ml of purified water. The drug solution was added to the β-cyclodextrin solution with stirring on a magnetic stirrer. The resulting solution was sonicated with ODA-M30 (ODA Service, Russia) for 2 minutes to complete the components dissolution, and then filtered through a filter with a pore size of 0.45 μm (Gluvex, Russia). The filtrate was cooled to 2–8 °C for 16 hours to obtain the finished complex in the form of a crystalline precipitate, which was then separated by decantation.

4. Fluid-bed complexation.

The complex was obtained in a Glatt GPCG1 Fluid Bed Dryer Granulator (Glatt GmbH, Germany). The value of the volumetric flow rate of the inlet air flow parameter varied in the range from 0 to 100 m^3/h and was regulated by opening or closing the damper. The product temperature was maintained at 60 ± 2 °C by the inlet air to the chamber, which was set at 80 °C. The pressure applied to the spray nozzle was 2 bar. Water in an amount of 400.0 ml, mixed with gramicidin S to obtain a concentration of 0.05 g/L, was used as a humectant for the granulation process. The feed rate of the granulation mixture was 8 g/min. The loading weight of β-cyclodextrin was 200.0 g.

Confirmation of gramicidin S encapsulation in the β-cyclodextrin cavity was carried out using ^{1}H NMR spectroscopy using a Bruker BioSpin 500 MHz NMR spectrometer (Bruker Corporation, USA) at a 400 MHz frequency. The chemical shifts value was determined in ppm; tetramethylsilane (Russian Pharmacopeia XIV ed, OFS.1.3.0001.15) was used as a standard.

Additionally, the formation of the complex was confirmed using thermal analysis methods – differential scanning calorimetry (DSC) and thermogravimetry (TGA). An STD Q600 V20.9 Build 20 synchronous thermal analyzer (TA Instruments, USA) was used for the analysis.

The morphological features of the obtained samples of the complex of gramicidin S and β-cyclodextrin were determined using a NOVA NANOSEM 450 microscope (FEI Czech Republic s.r.o., Czech Republic) equipped with a vacuum detector. The measurement was carried out at a 5 kV voltage and a pressure of 90 Pa. Images were acquired at an approximation of 10 kx9 with a dot size of 50 nm.

The determination of the particle size of the inclusion complexes was carried out using the method of dynamic light scattering. A Zetasizer Nano ZS device (Malvern Instruments, Great Britain) was used for the work. The particle sizes of the complex were detected in hexane, which is chemically inert with respect to the complex components. Flowability, slope angle, bulk density for the obtained powders were determined using the methods specified in the State Pharmacopoeia of the Russian Federation of the XIV edition using a flowability tester GT (ERWEKA GmbH, Germany), a funnel diameter of 10 mm, and a tester for determining the bulk density of powders SVM 102 (ERWEKA GmbH, Germany).

RESULTS AND DISCUSSION

During this work, we obtained a number of gramicidin S and β-cyclodextrin inclusion complexes using various approaches: dry mixing, paste complexation, co-precipitation and fluid-bed complexation. As a result, we obtained 4 samples, which were further analyzed by DSC-TGA (figure 1) and ^{1}H NMR spectroscopy (figure 2) in order to confirm the encapsulation and the interaction sites of the API and β-cyclodextrin. Thermograms of the obtained complexes demonstrate identical character, confirming the interaction of gramicidin S and β-cyclodextrin independently on the complex preparation method.

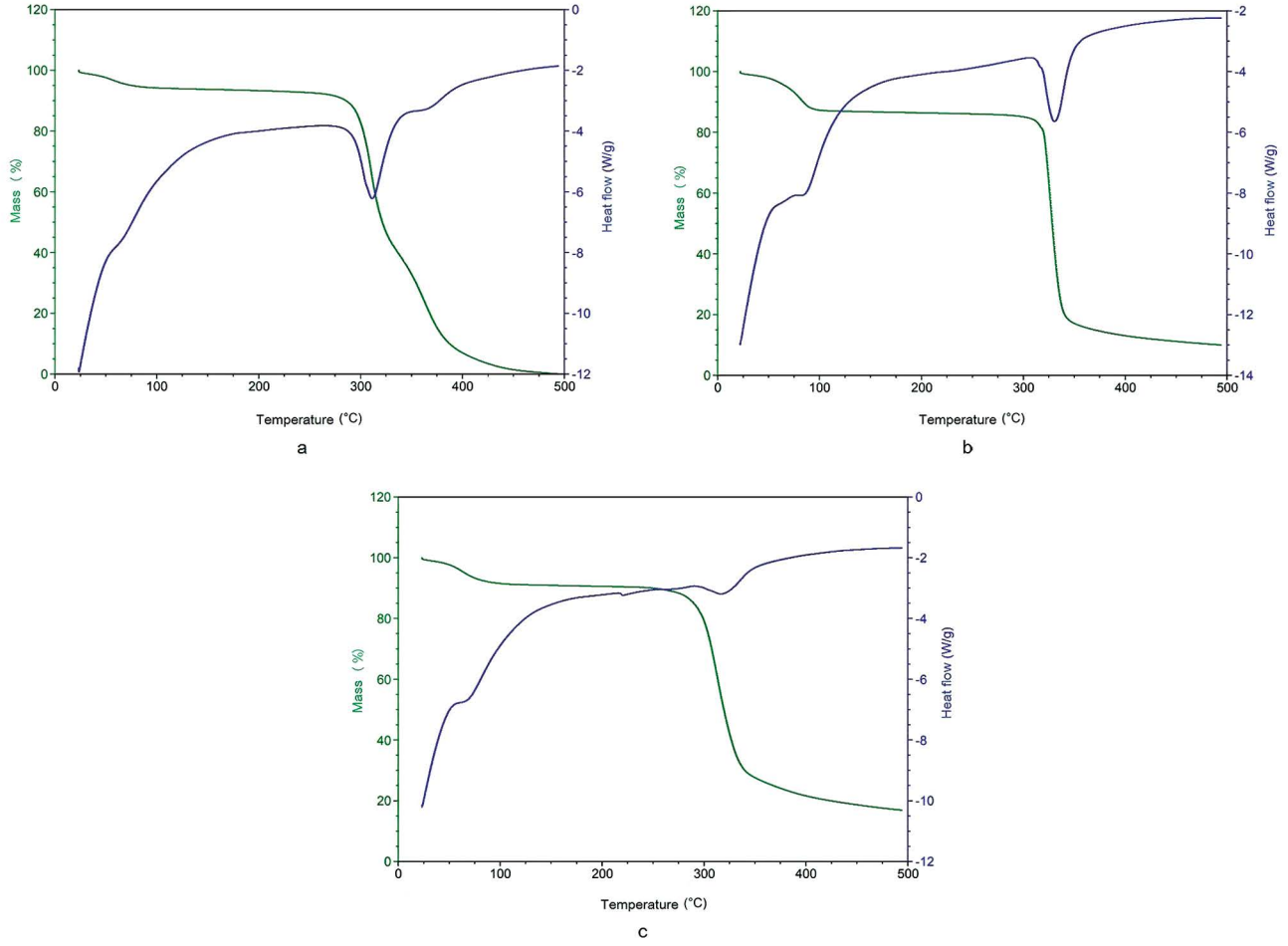

Figure 1. DSC-TGA thermograms of
a – gramicidin S dihydrochloride; b – β-cyclodextrin; c – inclusion complex of gramicidin S and β-cyclodextrin

In the region of 75–115 °C on the thermogram of β-cyclodextrin (figure 1 b) one can observe the 15 % mass sample decrease is observed, which is associated with the evaporation of residual moisture from the surface of cyclodextrin (85–100 °C) and water molecules located in the polysaccharide cavity (100–115 °C). Further, starting from 300 °C, an endothermic peak is observed, indicating the melting of β-cyclodextrin with its subsequent destruction, which correlates by a significant decrease in the weight of the test sample [6].

On the thermogram of gramicidin S dihydrochloride (figure 1 a), the only endothermic peak is observed starting from 280 °C, which corresponds to the melting point of the peptide. Further heating leads to the sample decomposition.

Comparing the obtained data with the inclusion complex thermogram (figure 1c), a significant change of the peak in the region of 300–340 °C definitely proves the interaction between the drug and polysaccharide, and supposing indicates the complex formation energy.

In order to identify the sites of encapsulation, we analyzed the obtained samples applying ^{1}H NMR spectroscopy method. Currently it is known that the inclusion complex formation results in changes of chemical shifts of the encapsulated groups protons [7].

Comparing the chemical shifts of the initial compounds and the final product, a significant change in the chemical value from 7.91 to 7.69 was found for the protons of L-ornithine amino group (figure 2), so we conclude that complexation of gramicidin S molecule takes place.

Summarizing the obtained data, we suggest the following structure of the inclusion complex of gramicidin S and β-cyclodextrin (figure 3).

The ^{1}H NMR spectra for all the samples obtained via different approaches were identical to that shown in figure 2, so we conclude that the encapsulation of gramicidin S into β-cyclodextrin occurs within the same mechanism following by encapsulation of the same part of the API molecule, regardless of the solvent removal method.

Studying the technological properties of the gramicidin S and β-cyclodextrin inclusion complex mixtures obtained using different approaches we revealed the variability of the parameter meanings (table 1).

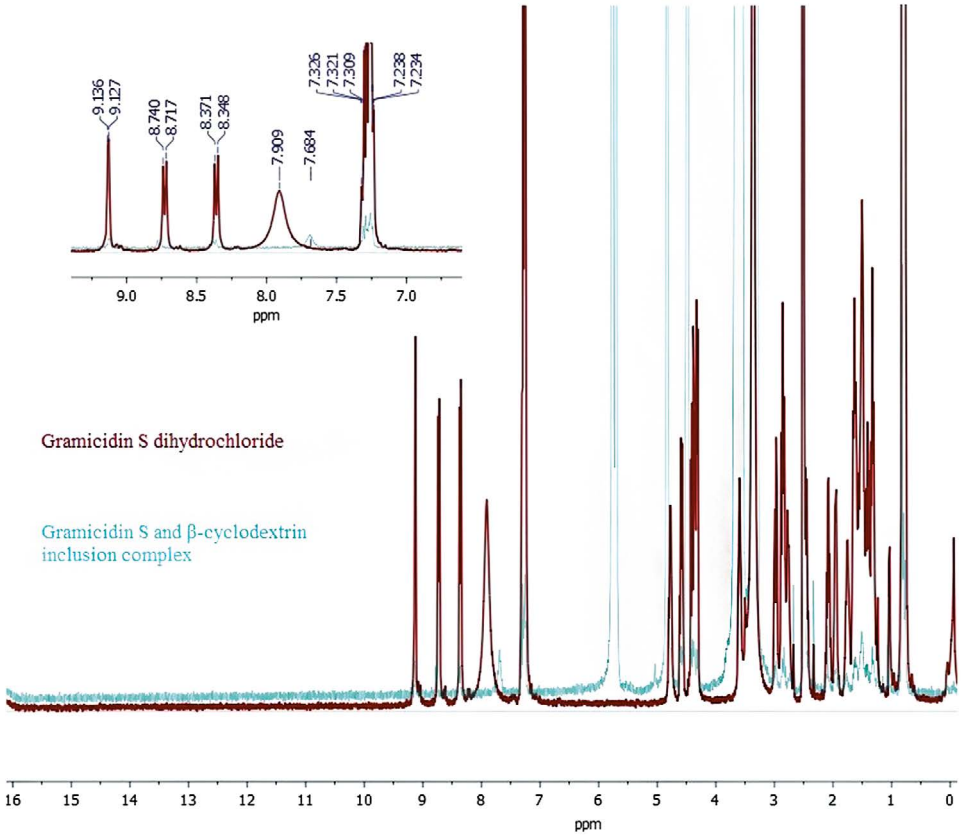

Figure 2. **^{1}H NMR spectra of gramicidin S dihydrochloride and inclusion complex of gramicidin S and β-cyclodextrin**

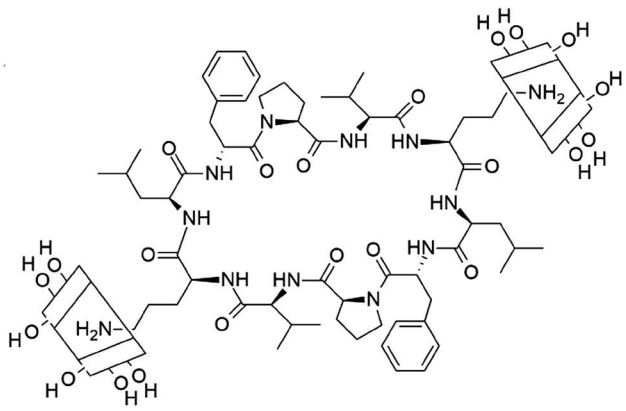

Figure 3. **Supposed structural formula of the inclusion complex of gramicidin S and β-cyclodextrin**

Table 1. **Technological parameters of gramicidin S and β-cyclodextrin inclusion complexes obtained applying different approaches**

Inclusion complex formation method	Flowability, s/100 g	Angle of repose, deg.	Bulk density, g/cm³
Gramicidin S dihydrochloride	–*	–	0,475 ± 0,05 0,593 ± 0,01 (c*)
Co-precipitation	10,4 ± 0,01	17,5 ± 0,3	0,735 ± 0,05 0,896 ± 0,05 (c)
Dry mixing	–	–	0,755 ± 0,05 0,880 ± 0,05 (c)
Paste complexation	–	–	0,790 ± 0,05 0,900 ± 0,05 (c)
Fluid-bed complexation	19,1 ± 0,01	43,0 ± 0,3	0,600 ± 0,05 0,698 ± 0,05 (c)

Note. «c» – in compressed state.
«-» – can't be determined (no flow).

According to table 1, it can be seen that agglomerates of inclusion complexes obtained using co-precipitation and fluid-bed complexation methods demonstrate good flowability and a slope angle less than 45 degrees, which is a rare property for inclusion complexes of cyclodextrins and poorly soluble substances [8]. The observed variability of technological parameters of products obtained using different approaches can be explained by different particle morphology (figure 4, 5).

Figures 4 and 5 show that the application of co-precipitation and fluid-bed complexation methods makes it possible to achieve more uniform distribution of particle size in the resulting inclusion complex mixture reducing the role of internal friction forces, which prevent the flow [9]. The flow is a critical parameter, guaranteeing the uniformity of the granulometric composition of the tablet mixture, uniform filling of the matrices and entry into the compression zone during tableting, ensuring the uniformity of the mass of the dosage form and the stability of its physicochemical properties [10].

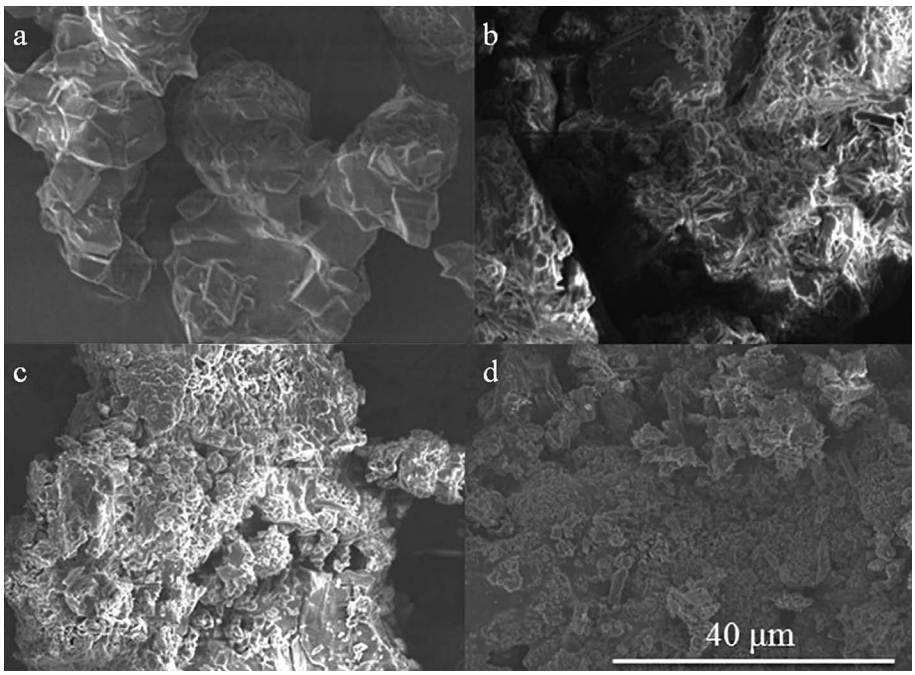

Figure 4. **Micrographs of complexes particles for obtained by the method:**
a – fluid-bed complexation; b – co-precipitation; c – paste complexation, d) dry mixing

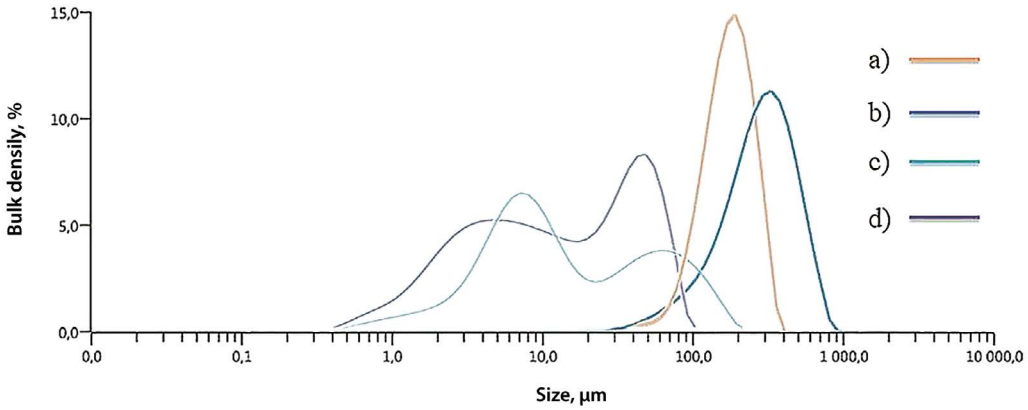

Figure 5. **Particle size distribution for inclusion complexes obtained by:**
a – fluid-bed complexation; b – co-precipitation; c – paste complexation, d) dry mixing

Due to that, inclusion complexes obtained via these approaches can be used in the production of tablet dosage forms of gramicidin S applying direct compression technology, which is the most suitable for tablet production for buccal application [11]. The transition to this type of technology will significantly reduce costs by simplifying the technology and reducing the production time.

Moreover, use of β-cyclodextrin makes it possible to abandon such fillers as lactose or sucrose that will reduce the risk of using the drug for patients with individual intolerance to these components. Also formation of agglomerates containing inclusion complexes of gramicidin S and β-cyclodextrin can reduce the risk of incompatibility of the finished drug with the indicator "Uniformity of dosage", which is critical for low-dosage drug formulations [12].

CONCLUSION

Within this work we revealed the influence of methods for obtaining gramicidin S and β-cyclodextrin inclusion complexes on the technological parameters of the final product. We determined that using various approaches allows to obtain inclusion complexes identical in chemical structure, while the complexation proceeds at the L-ornithine amino group in the gramicidin S molecule.

At the same time, we found significant differences in the particle morphology of the inclusion complexes obtained using various approaches, which explains the significant variability of technological parameters of the resulting products, such as flowability, slope angle, bulk density.

Applying the obtained results for the development of new buccal dosage forms of gramicidin S will decrease the risk of inconsistency of the uniformity of dosage indicator, allowing also excluding the use of lactose and sucrose as fillers.

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