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INVESTIGATIONS WITH THE AIM OF OBTAINING A MASS FOR PRESSING MEDICATED CHEWING GUMS "LYSODENT C"

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Розробка якісних пресованих гумок жувальних лікувальних «Лізодент С» з лізоциму гідрохлоридом і аскорбіновою кислотою як активними фармацевтичними інгредієнтами та композицією Health in Gum® марки PWD-01 як жувальною основою, передбачає одержання однорідної маси для пресування. З метою запобігання розширювання маси для пресування через її полідисперсність, необхідним виявилось проведення попередньої грануляції субстанції лізоциму гідрохлориду, яка характеризується дрібнодисперсністю, гігроскопічністю та недостатніми для здійснення прямого пресування фармакотехнологічними властивостями.

Мета роботи – проведення фізико-хімічних та фармакотехнологічних досліджень з метою одержання однорідної маси для пресування гумок жувальних лікувальних «Лізодент С».

Матеріали та методи. Об'єкти досліджень – гранулят лізоциму гідрохлориду (Bouwhuis Enthoven, Нідерланди) з інтенсивним підсолоджувачем сукралозою (Solo Sucralose-Non Micronised NF, V.B. Medicare PVT. LTD., Індія) і смаковою добавкою (Nat Apple Flavor Wonf, Kerry Inc., Малайзія) та маса для пресування, одержана шляхом змішування грануляту, композиції Health in Gum® марки PWD-01 (Cafosa, Іспанія) і аскорбінової кислоти (Foodchem, Китай). Як зволожувач при грануляції використано етанол 96 %. У ході виконання експерименту використано фізико-хімічні (вологосорбційна здатність), фармакотехнологічні (оптична мікроскопія, текучість, насипна густина та густина після усадки, визначення гранулометричного складу аналітичним просіюванням) та статистичні випробування згідно з вимогами ДФУ 2.0.

Результати. Кристалографічним аналізом встановлено подібність за своїм розміром та формою одержаних гранул лізоциму гідрохлориду до гранул композиції HiG марки PWD-01, що також підтверджено дослідженням фракційного складу – їх основну фракцію складають частинки з розміром $1,0 > n \geq 0,7$. Крім того, перетворення порошку лізоциму гідрохлориду у гранулят покращило його фармакотехнологічні характеристики. Однак, гранулят, як і чиста субстанція лізоциму гідрохлориду, характеризується гігроскопічністю, що вимагає, відповідно, зниження його вологосорбційної здатності. Кристалографічний аналіз суміші, одержаної змішуванням грануляту та композиції HiG марки PWD-01 з преміксінгом аскорбінової кислоти, встановив її дисперсну однорідність, а дослідження її технологічних характеристик – хорошу текучість, що забезпечить отримання якісних пресованих гумок. Втім, вологопоглинаюча здатність утвореної маси для пресування не знизилась, а навпаки збільшилась, що пов'язано з наявністю у суміші таких гігроскопічних компонентів, як лізоциму гідрохлорид та жувальна основа.

Висновки. Встановлено, що використання попередньої грануляції лізоциму гідрохлориду призвело до однорідності одержаної маси для пресування. Однак гігроскопічність суміші вимагає введення до її складу вологопоглинаючих агентів або дотримання 40 % відносної вологості навколишнього середовища у процесі виготовлення препарату

Ключові слова: гумки жувальні лікувальні, гранулят лізоциму гідрохлориду, маса для пресування, фізико-хімічні та фармакотехнологічні дослідження

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1. Introduction

One of the most important trends in modern pharmaceutical technology is the development of drugs in the form of medicated chewing gums (MCGs), which are well perceived by patients, are convenient in use and are characterized by high bioavailability [1, 2]. MCGs under the conventional name "Lysodent C" for use in dental practice developed at the Industrial Technology of Drugs Department of NUPh as APIs containing lysozyme hydrochloride (Bouwhuis Enthoven, Netherlands) and ascorbic acid (Foodchem, China). The proposed gum is obtained by pressing on a tablet machine using the composition Health in Gum® PWD-01 (Cafosa, Spain) as a chewing gum base [3, 4]. In order to provide good taste properties for the developed medicinal product, an intensive sweetener sucralose (Solo Sucralose-Non Mi-

cronised NF, VB Medicare PVT. LTD., India) and a flavouring agent "Green Apple" (Nat Apple Flavor Wonf (Kerry Inc., Malaysia), which were selected on the basis of preliminary organoleptic and microscopic studies, were also added [5].

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues

It is known that a great importance in the pharmaceutical development of any medicinal product is the study of properties of its components according to the methods of SPhU. Physicochemical and pharmacotechnological characteristics of the components of the drug directly affect the choice of the method for obtaining the dosage form, the way of addition of the API, as well as

the mode of technological process and its consumer attributes [6, 7].

3. Analysis of recent studies and publications in which a solution of the problem are described and to which the author refers

Today MCGs have become widely known and used in European countries and the USA, but currently are not being manufactured by the pharmaceutical industry in Ukraine [8]. However, in recent years, scientists in Ukraine [5, 9] have been conducting research on the development of drugs in the form of medicated chewing gums, which can serve as a delivery system for many APIs and be used to treat various diseases by providing both local and systemic action [1, 2, 10, 11].

4. The field of research considering the general problem, which is described in the article

In the development of compressed MCGs "Lysodent C", it was found that a mixture of APIs with a chewing gum base is a polydisperse system, which may lead to its segregation during the pressing process. Therefore, the main task was to obtain a homogeneous blend for pressing. This, in turn, requires preliminary granulation of the substance of lysozyme hydrochloride, which is characterized by fine dispersion, hygroscopicity and insufficient pharmacotechnological properties for direct compression method [6, 12]. Taking into account the satisfactory technological characteristics of ascorbic acid and in order to avoid its oxidation in contact with a moisturizer, it is rationally to include this substance into a premixing mixture with granulate of lysozyme hydrochloride and a gum base.

5. Formulation of goals (tasks) of article

Thus, the purpose of the work was to obtain granulate of lysozyme hydrochloride and a homogeneous mass for pressing and to study their physicochemical and pharmacotechnological properties in order to develop high-quality compressed MCGs "Lysodent C".

6. Presentation of the main research material (methods and objects) with the justification of the results

The research objects are granulate obtained from lysozyme hydrochloride (Bouwhuis Enthoven, Netherlands), intensive sweetener sucralose (Solo Sucralose-Non Micronised NF, VB Medicare PVT. LTD., India) and a flavouring agent (Nat Apple Flavor Wonf, Kerry Inc., Malaysia) and also a mass for pressing, obtained by mixing granulate, composition Health in Gum® PWD-01 (Cafosa, Spain) and ascorbic acid (Foodchem, China). As a granulating agent, 96 % ethanol was selected.

In the process of experiment, the following research methods were used:

- physicochemical:
 - moisture absorption capacity – sample weight was 1.0 g; carried out at room temperature at values of relative humidity of 40, 60 and 75 % for 24 hours; increase of moisture content was determined gravimetrically [6, 7, 13];
 - pharmacotechnological:
 - optical microscopy (SPhU 2.0, Vol. 1, p. 2.9.37) [11] – carried out using a laboratory microscope Konus-

Academy (Italy) equipped with a ScopeTek camera; the photos were taken in reflected light; photo processing was carried out in Scope Photo software (version 3.0.12.498);

- flowability (SPhU 2.0, Vol. 1, p. 2.9.36) [11] – determined by the time of pouring of powders (granulates) through the funnel on the laboratory device model VP-12A (MZTO); determination of the angle of repose was carried out on the scale of the angle protractor and on the basis of $\tan(\alpha)$;

- bulk density and tapped density (SPhU 2.0, Vol. 1, p. 2.9.34) [11] – were measured on a device for determining the bulk volume of PT-TD1 type "PharmaTest" (Germany) using a 250 ml graduated cylinder;

- granulometric composition by analytical sifting (SPhU 2.0, Vol. 1, p. 2.9.38) [11] – were determined on the device with vibration shaker model VEB MLW Labortechnik Ilmenau (Germany) using a set of laboratory sieves SLM-200 with a cell size of 1.0, 0.7, 0.5, 0.355, 0.25 and 0.09 mm;

- mathematical:
 - statistical processing of results (SPhU 2.0, Vol. 1, p. 5.3) [11] – carried out with the help of Microsoft Excel software.

In order to exclude the negative influence of auxiliary substances on the tissues of the oral cavity, granulation of lysozyme hydrochloride was decided to be carried out using 96 % ethanol, which allows the rapid production of high quality granules. To obtain MCGs, the amounts of lysozyme hydrochloride, sucralose and powdered flavouring agent were mixed in a mixer and wetted with 96 % ethanol. The mixture was granulated through a sieve with a cell size of 2.0 mm, dried at room temperature, and calibrated through a sieve with a cell size of 1.0 mm. The crystallographic analysis of the resulting granulate and its mixture with the chewing base is shown in Fig. 1.

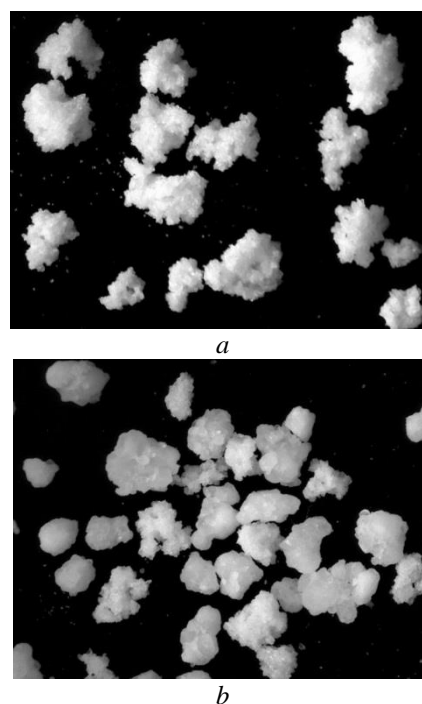


Fig. 1. Crystallographic analysis: *a* – granulate of lysozyme hydrochloride; *b* – a mixture of lysozyme hydrochloride granulate with a composition HiG PWD-01

The results shown in Fig. 1 indicate that the resulting granulate of lysozyme hydrochloride is similar in its size and shape to the granules of HiG PWD-01 composition. The shape factor of both samples is close to 1, which indicates the isodiametric form of the particles of the studied samples. The homogeneity of the resulting mixture is also confirmed by studies of the fractional

composition – the main fraction of HiG PWD-01 and the resulting granulate are particles with a size of $1.0 > n \geq 0.7$ (Fig. 2).

Since it has been previously established that the substance of lysozyme hydrochloride is a hygroscopic substance, our next task was to study the moisture absorption capacity of its granulate (Fig. 3).

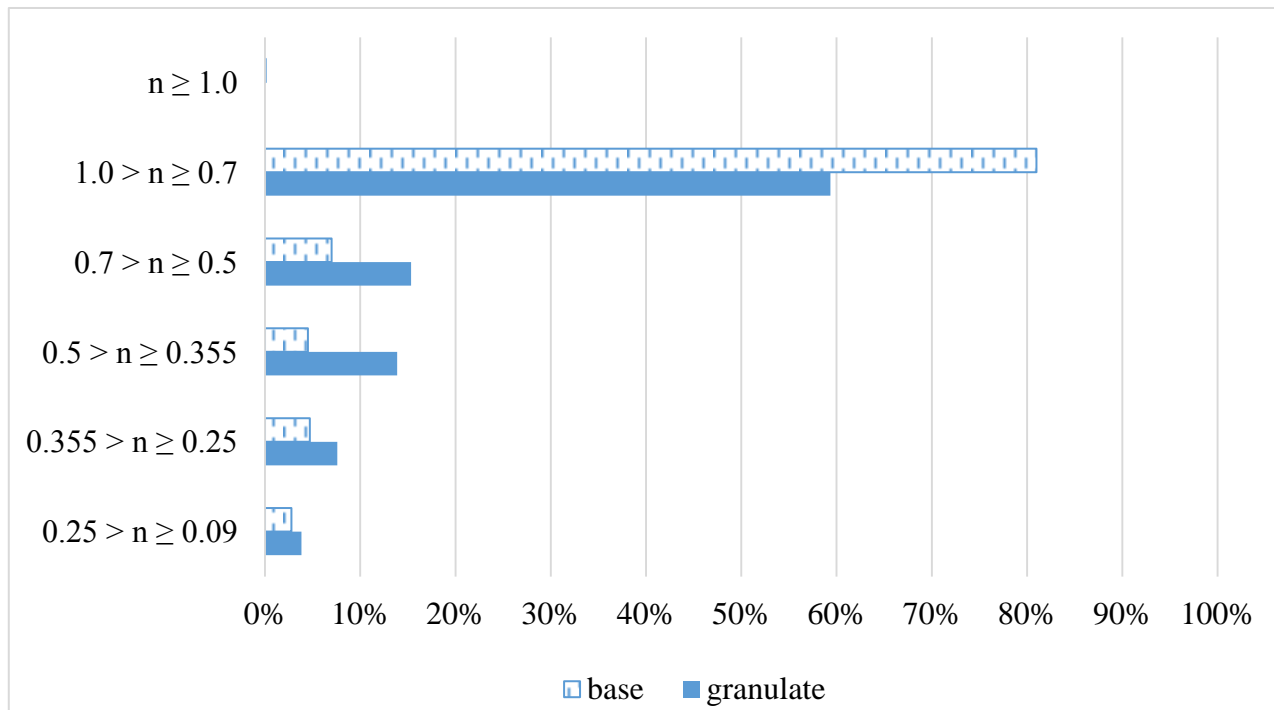


Fig. 2. The fractional composition of the granulate and the composition HiG PWD-01

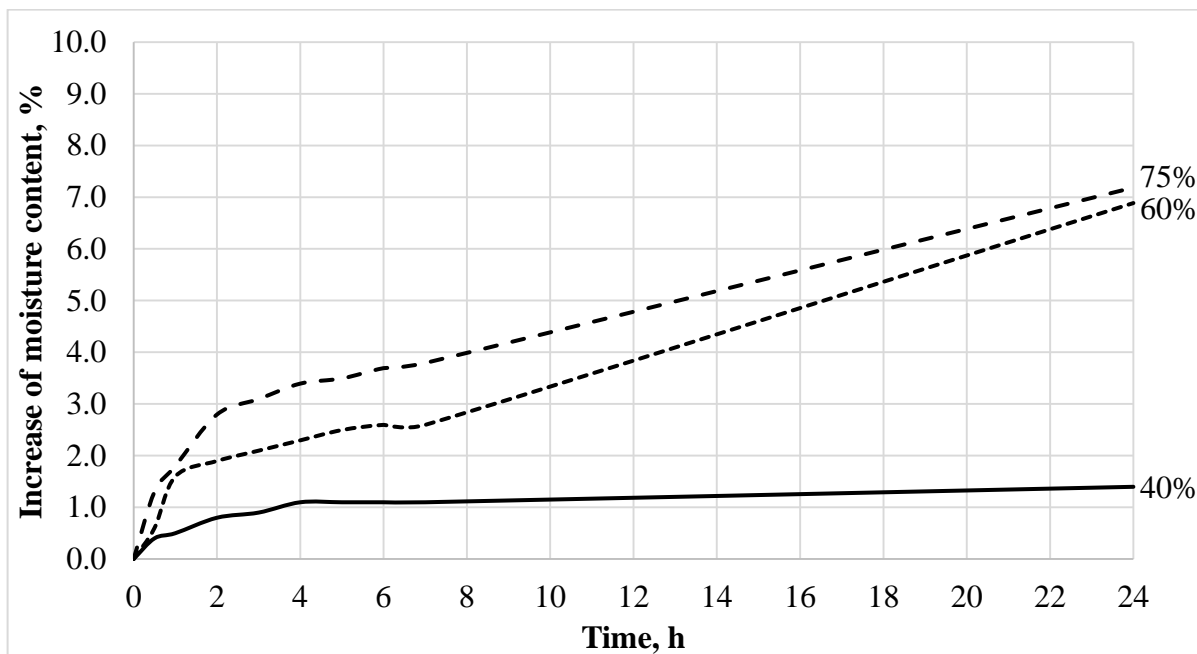


Fig. 3. Moisture absorption of granulate

As the results of moisture absorption show (Fig. 3), lysozyme hydrochloride granulate is also characterized by hygroscopicity – at values of relative humidity of 40, 60 and 75 %, the mass increments of samples for 24 h were 1.40, 6.89 and 7.19 % respectively, which exceed data on the moisture absorbing capacity of the pure substance of lysozyme hydrochloride by 0.10, 0.70 and 0.40

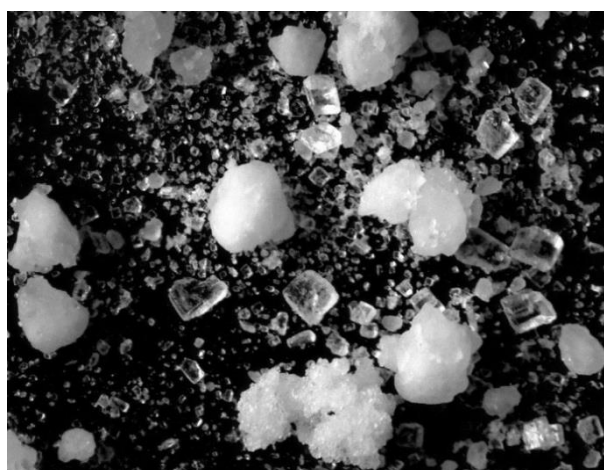
%, respectively. Consequently, the issue that needs to be taken into account in the development of MCGs "Lysodent C" is to reduce the moisture absorption capacity of the granulate by adding the moisture absorbing agent into the composition or maintenance of 40 % relative humidity of the environment in the process of manufacturing chewing gums.

Research of pharmacotechnological properties of lysozyme hydrochloride granulate has been performed according to the requirements of SPhU 2.1 [11]. The results are shown in Table 1.

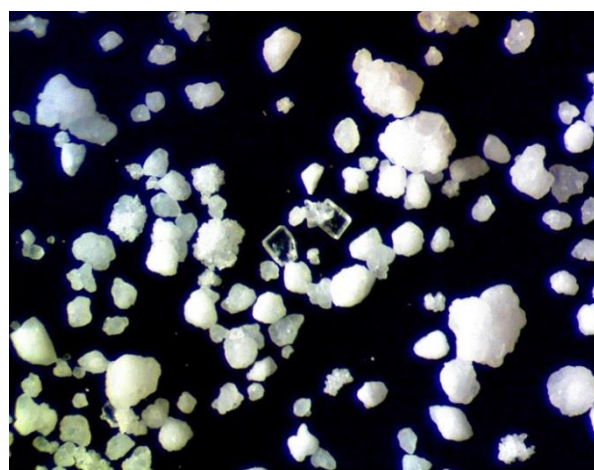
Table 1
Pharmacotechnological properties of lysozyme hydrochloride granulate

Pharmacotechnological indicators	Results
Flowability, s/100 g of sample	8.01±0.62
Angle of repose tan(α), deg. protractor, deg.	34.47±1.48 35.33±1.43
Bulk volume, V_0 , ml	234.0±1.0
Tapped volume, V_{1250} , ml	198.6±0.5
Bulk density, $\frac{m}{V_0}$ g/ml	0.401±0.001
Tapped density, $\frac{m}{V_{1250}}$ g/ml	0.475±0.006
Compressibility index, %	15
Hausner index	1.18

Note: $n=5$, $P = 95\%$



a



b

Fig. 4. Comparative crystallographic analysis of two MCG blends: *a* – mass for pressing I; *b* – mass for pressing II

As shown in the results (Fig. 4), the mixing of lysozyme hydrochloride granulates, ascorbic acid and the chewing base HiG PWD-01 resulted in a homogeneous distribution of APIs in mass for pressing, which would not lead to its segregation in the compression process and, in turn, would contribute to obtaining high-quality medicinal product. This is also confirmed by studies of fractional composition – the main fraction of mass for pressing II is a particle with a size of $1.0 > n \geq 0.5$ (Fig. 5).

The moisture absorption capacity of the formed mass for pressing did not decrease, but on the contrary increased with relative humidity of 60 and 75 % to 7.88 and 9.08 % respectively (Fig. 6), which is due to the presence in the mixture of such hygroscopic components

as lysozyme hydrochloride and chewing gum base. In this case, moisture absorption of the mixture at 40 % relative humidity was approximately at one level – 0.30 % for 24 hours of observation. This confirms the preliminary findings regarding the maintenance of appropriate conditions for obtaining MCG, namely 40 % of relative humidity of the environment.

According to the results (Tab. 1), the conversion of lysozyme hydrochloride powder into granulate improved its pharmacotechnological characteristics. This, first of all, made it possible to exclude the use of the vibrating device in the study of the flow of granulate and to speed up its flow to 8 s/100 g, which differs from the flowability of the substance lysozyme hydrochloride with 14 s/100 g. By the angle of repose value, as well as the values of the compressibility index and the Hausner index, the flowability of the granulate is also characterized as good.

So, in Fig. 4 is shown a comparative crystallographic analysis of two MCG blends obtained in different ways:
a) by simple mixing of the API substances with the composition of HiG PWD-01 (mass for pressing I);
b) by mixing lysozyme hydrochloride granulates and composition HiG PWD-01 with premixing of ascorbic acid (mass for pressing II).

The performed pharmacotechnological studies of the resulting mass for pressing (Table 2) also showed better results compared with the indicators of the individual components that compose this mixture. For all investigated properties, the produced mass for pressing has a good flowability, which would provide dose homogeneity and obtaining high-quality compressed MCGs.

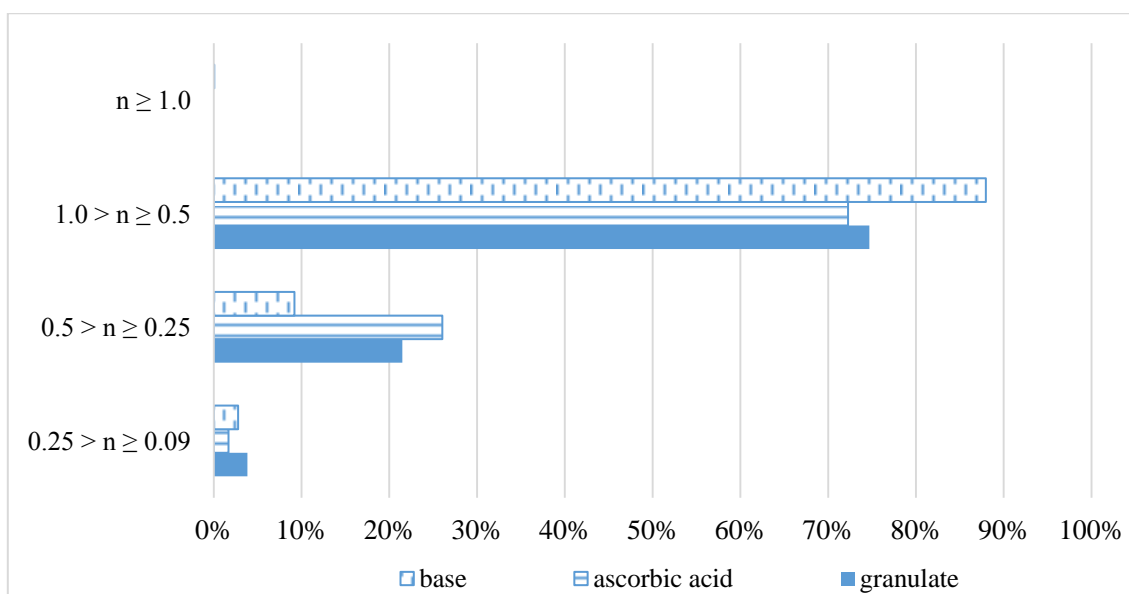


Fig. 5. The fractional composition of the resulting mass for pressing

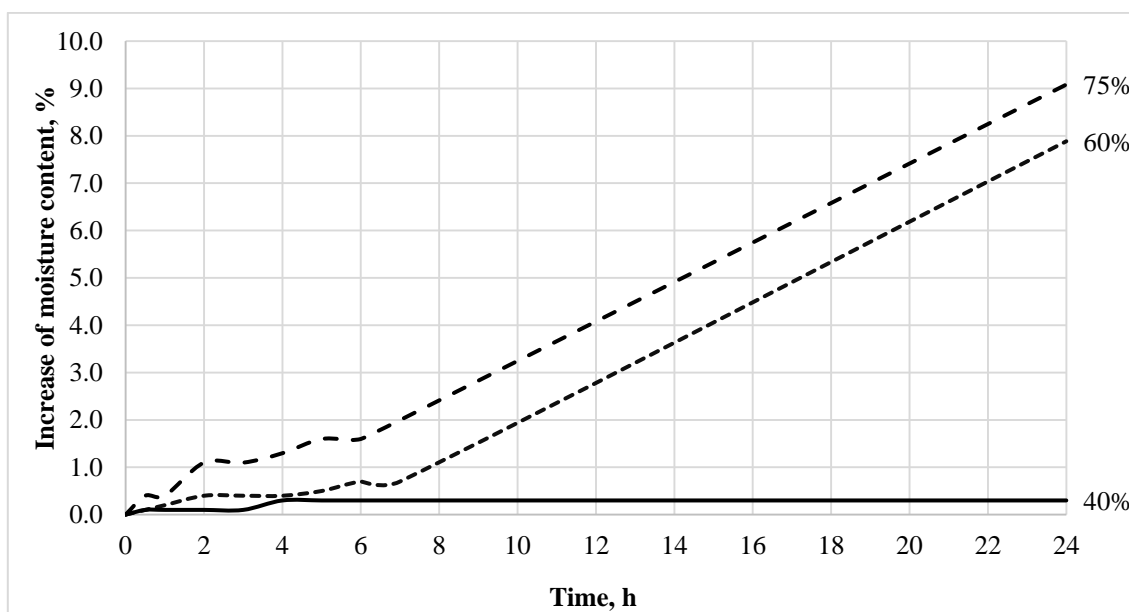


Fig. 6. Moisture absorption of a mixture of granulate lysozyme hydrochloride with ascorbic acid and a composition HiG PWD-01

Table 2
Pharmacotechnological properties of the resulting mass for pressing

Pharmacotechnological indicators	Results
Flowability, s/100 g of sample	7.43±0.65
Angle of repose $\tan(\alpha)$, deg.	30.65±1.70
protractor, deg.	31.25±2.72
Bulk volume, V_0 , ml	154.3±0.6
Tapped volume, V_{1250} , ml	135.0±0.4
Bulk density, $\frac{m}{V_0}$, g/ml	0.648±0.003
Tapped density, $\frac{m}{V_{1250}}$, g/ml	0.740±0.002
Compressibility index, %	13
Hausner index	1.14

Note: $n=5, P=95\%$

7. Conclusions from the conducted research and prospects for further development of this field

1. It has been established that the use of preliminary granulation resulted in a more homogeneous distribution of active substances in the chewing gum mass and improved their technological properties in comparison with simple mixing of substances.

2. The investigated mass for pressing of MCGs, formed by mixing granulate of lysozyme hydrochloride and chewing base with premixing of ascorbic acid, is characterized by hygroscopicity, which requires the addition into it moisture absorbing agents.

3. Based on the results of the moisture absorption capacity of the resulting mass for pressing, it is proposed to perform a process for obtaining MCG at 40 % relative humidity of the environment.

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