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The assessment of the quality parameters of inulin active pharmaceutical ingredients according to physicochemical characteristics

Aim. To assess the quality parameters of plant active pharmaceutical ingredients (API) in accordance with the requirements of modern normative documents by such physicochemical characteristics as "Description", "Solubility", "Hygroscopy", "Microscopy", as well as identification of the structural components of fructan in order to involve the data obtained in development of the national normative documents on the substance of inulin.

Results. The study of nine plant API of inulin obtained from chicory, agave and Jerusalem artichoke, as well as the reference standards of fructan from chicory and dahlia has been conducted by such physicochemical characteristics as "Description", "Solubility", "Hygroscopy", "Microscopy". According to the British Pharmacopoeia 2010 (BP) the chemical reactions of identification confirmed the presence of fructose and glucose after hydrolysis of the substance. According to the United States Pharmacopeia 36 – NF 31 (USP) it has been found by the identification reaction that the substances analyzed (in addition to the standard substances) contain impurities of sugars with the properties of reducing agents. By appearance the samples under study are loose, amorphous powders of practically white and pale yellow color, they are hygroscopic and very hygroscopic, readily soluble and very soluble in hot water. By the microscopic study they are completely or partially fragmented spherical or ovoid fractions with the expressed central micelles and peripheral semi-transparent shells, as well as small parts separated from the main pseudocrystalline formations.

Conclusions. The results of studying the substances of inulin by such physicochemical characteristics as "Description", "Solubility", "Hygroscopy", "Microscopy", as well as identification of the structural components of fructan according to the requirements of the BP and USP, can be used for the input quality control of plant API of inulin to confirm the structure and determine the purity of the substance. The results of studying the physicochemical characteristics of plant API of inulin can be used when developing the national normative documents on the substance of inulin.

Key words: inulin; description; solubility; hygroscopy; microscopy; identification; quality control

Н. М. Смєлова, О. А. Євтіфєєва, С. М. Губарь

Оцінка показників якості активного фармацевтичного інгредієнта інуліну за фізико-хімічними характеристиками

Метою роботи є оцінка показників якості рослинних активних фармацевтичних інгредієнтів інуліну згідно з вимогами сучасної нормативної документації за такими фізико-хімічними характеристиками як «Опис», «Розчинність», «Гігроскопічність», «Мікроскопія», а також ідентифікація структурних складових фруктану з метою залучення одержаних даних при розробці національної нормативної документації на субстанцію інуліну.

Результати. Проведено дослідження дев'яти рослинних АФІ інуліну, одержаних з цикорію, агави та топінамбуру, а також стандартних зразків фруктану з цикорію та жоржини за фізико-хімічними характеристиками «Опис», «Розчинність», «Гігроскопічність», «Мікроскопія». Хімічними реакціями ідентифікації згідно з Британською фармакопеєю 2010 підтверджено наявність фруктози та глюкози після гідролізу субстанції. За реакцією ідентифікації за Американською фармакопеєю 36 – NF 31 встановлено, що аналізовані сполуки (окрім стандартних речовин) містять домішки цукрів, що мають властивості відновників. За зовнішнім виглядом наведені зразки представляють собою сипкі, аморфні порошки білого, майже білого та блідо-жовтого кольору, гігроскопічні та дуже гігроскопічні, легко та дуже легко розчинні у гарячій воді. За мікроскопічним дослідженням – це повністю або частково фрагментовані сферичні чи яйцеподібні частки, для яких виражені центральні міцели і периферичні напівпрозорі оболонки, а також невеликі частки, що відділяються від основних псевдокристалічних утворень.

Висновки. Результати дослідження субстанцій інуліну за такими фізико-хімічними характеристиками як «Опис», «Розчинність», «Гігроскопічність», «Мікроскопія», а також ідентифікація структурних складових фруктану за вимогами Британської та Американської фармакопей можуть бути використані для вхідного контролю якості рослинних активних фармацевтич-

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них інгредієнтів інуліну як для підтвердження структури, так і з метою визначення чистоти субстанції. Результати вивчення фізико-хімічних характеристик рослинних активних фармацевтичних інгредієнтів інуліну можуть бути використані при розробці національної нормативної документації на субстанцію інуліну.

Ключові слова: інулін; опис; розчинність; гігроскопічність; мікроскопія; ідентифікація; контроль якості

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Оценка показателей качества активного фармацевтического ингредиента инулина по физико-химическим характеристикам

Целью работы является оценка показателей качества растительных АФИ инулина согласно требованиям современной нормативной документации по таким физико-химическим характеристикам как «Описание», «Растворимость», «Гигроскопичность», «Микроскопия», а также идентификация структурных составляющих фруктана с целью привлечения полученных данных при разработке национальной нормативной документации на субстанцию инулин.

Результаты. Проведено исследование девяти растительных АФИ инулина, полученных из цикория, агавы и топинамбура, а также стандартных образцов фруктана из цикория и георгины по физико-химическим характеристикам «Описание», «Растворимость», «Гигроскопичность», «Микроскопия». Химическими реакциями идентификации согласно Британской фармакопее 2010 подтверждено наличие фруктозы и глюкозы после гидролиза субстанции. По реакции идентификации согласно Американской фармакопее 36 – NF 31 установлено, что рассматриваемые соединения (кроме стандартных веществ) содержат примеси сахаров, обладающие свойствами восстановителей. По внешнему виду приведенные образцы представляют собой сыпучие, аморфные порошки белого, почти белого и бледно-желтого цвета, гигроскопичны и очень гигроскопичны, легко и очень легко растворимые в горячей воде. По результатам микроскопических исследований – это полностью или частично фрагментированные сферические или яйцевидные частицы, для которых выражены центральные мицеллы и периферические полупрозрачные оболочки, а также небольшие частицы, отделяющиеся от основных псевдокристаллических образований.

Выводы. Результаты исследования субстанций инулина по таким физико-химическим характеристикам как «Описание», «Растворимость», «Гигроскопичность», «Микроскопия», а также идентификация структурных составляющих фруктана по требованиям Британской и Американской фармакопей могут быть использованы для входного контроля качества растительных АФИ инулина как для подтверждения структуры, так и с целью определения чистоты субстанции. Результаты изучения физико-химических характеристик растительных АФИ инулина могут быть использованы при разработке национальной нормативной документации на субстанцию инулин.

Ключевые слова: инулин; описание; растворимость; гигроскопичность; микроскопия; идентификация; контроль качества

STATEMENT OF THE PROBLEM

One of the valuable API having a high biological activity and a specific effect on the organism is the polysaccharide inulin. It has found its application for stabilizing therapeutic proteins, enhancing dissolution of lipophilic drugs, as a filler of tablets, in the form of methacrylate hydrogels for transporting biologically active compounds to the distal segments of the gastrointestinal tract [1]. Inulin is also used as a diagnostic agent in determining the glomerular filtration rate in renal diseases. In addition, this polysaccharide has a prebiotic effect (stimulates the growth and the metabolic activity of bifidobacteria), affects the metabolism of carbohydrates and lipids, participates in the process of elimination of salts of heavy metals, etc., from the body [2, 3].

Inulin is a polyfructose chain, in which the molecules of fructose are connected to the β-(2→1)-glycoside bond, usually there is also one molecule of glucose connected with α-D-glucopyranosyl bond (Fig. 1) [1, 4-6].

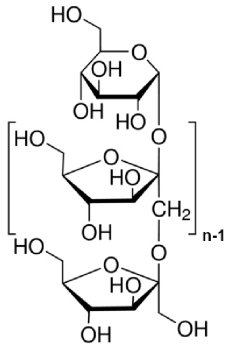

Fig. 1 *The chemical structure of inulin (GFn, n = 2-60) where G corresponds to the glucosyl part, F – is the fructosyl part, and n – is the degree of polymerization*

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Table 1

THE QUALITY REQUIREMENTS FOR PLANT API OF INULIN BY THE MONOGRAPHS "INULIN" ACCORDING TO THE BRITISH AND UNITED STATES PHARMACOPEIAS

Parameters	BP	USP
Description		
Appearance	An amorphous, granular, white powder	An amorphous, odorless, white powder, friable like chalk
Properties		
Hygroscopy	Hygroscopic	–
Solubility	Sparingly soluble in water; readily soluble in hot water; sparingly soluble in organic solvents	Soluble in hot water; sparingly soluble in cold water and in organic solvents
Microscopy	When studying in absolute ethanol it looks like large, very irregular masses that are completely or partially fragmented, sometimes with smaller spherical or ovoid particles	–
Identification		
Seliwanoff's test (a qualitative reaction for keto group – fructose)	A red color must appear	–
The reaction with Fehling's reagent (a qualitative reaction for aldehyde group)	After hydrolysis of the substance to the structural components – fructose and glucose a red precipitate must appear	The reaction is carried out without hydrolysis of the substance to confirm the absence of reduced sugars. The reaction does not proceed at room temperature, a slight reaction maybe in 1 min of boiling

The properties of inulin depend primarily on the degree of polymerization (DP), i.e. the number of monomeric fructose links in the polysaccharide macromolecule. The length of the fructose chain of the plant inulin varies from 2 to 60. Under the action of acids and specific enzymes fructan can be hydrolyzed to the structural monomers [1, 6].

A high-molecular inulin, which number of fructose residues is more than 10, is of interest for use in medical practice since its pharmacological activity is higher [7].

The raw material base for obtaining fructan has been significantly extended; its largest amount is stored in representatives of *Asteraceae*, *Liliaceae* and *Poaceae* families [5, 7, 8].

However, a significant number of plant sources and variability of production conditions determine the presence of substances of the polysaccharide at the market today; they differ in the number of fructose residues, the degree of purification from impurities, and by their physicochemical properties.

ANALYSIS OF RECENT RESEARCHES AND PUBLICATIONS

The description of physicochemical properties of API of inulin is given in the works of many researchers. Thus, according to the literature sources, inulin is an amorphous, granular, hygroscopic, practically odorless white powder, under the microscope it has the appearance of ribbed irregular particles, does not reduce Fehling's reagent. It is poorly soluble in cold water and readily soluble in hot water. Depending on the method of obtaining and polyfructan as the starting material it can be in the form of an amorphous powder and in the form of crystals [2, 3, 5, 9].

Pharmacopoeial requirements for the quality control of inulin are presented in the monographs "Inulin" of the BP and USP (Tab. 1) [10, 11]. In the State Pharmacopeia of Ukraine (SPhU) the appropriate normative documents for the substance of inulin are absent.

IDENTIFICATION OF ASPECTS OF THE PROBLEM UNSOLVED PREVIOUSLY

The primary task of quality control of the substances to be analyzed in standardization is to identify a compound and study its critical characteristics. The particle size and morphology, hygroscopicity, and solubility of substances are incomplete list of indicators that determine the physicochemical and technological properties of substances, and this, in turn, is directly related to bioavailability and efficacy of the finished drug, its safety and stability when using [5-9].

Therefore, determination of the physicochemical characteristics of API of inulin and its identification are the initial, but not the less important stage of the input quality control of the object to be analyzed, it allows, if necessary, either to detect adulteration or to prove the quality of the substance.

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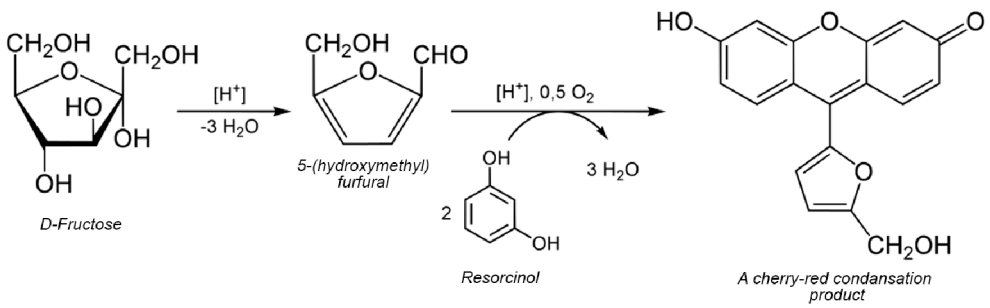

Fig. 2 *The chemistry of the reaction of identification B (Seliwanoff's test)*

OBJECTIVE STATEMENT OF THE ARTICLE

The aim of this fragment of complex studies is the quality control of plant API of inulin in accordance with the requirements of modern normative documents by such physicochemical characteristics as "Description", "Solubility", "Hygroscopy", "Microscopy", as well as identification of the structural components of fructan in order to involve the data obtained in development of the national normative documents on the substance of inulin.

PRESENTATION OF THE MAIN MATERIAL OF THE RESEARCH

As the study objects the API of inulin were chosen from such plant sources as chicory (batch 01, 04, 05, 06, 07, 09), agave (batch 02, 08) and Jerusalem artichoke (batch 03). The physicochemical characteristics of standard substances of *inulin with chicory* (batch 10; Sigma-Aldrich, PN: I2255, BN: SLBQ7169V) and *with dahlia* (batch 11; Sigma-Aldrich, PN: I3754, BN: SLBN1201V) were also taken into account.

The analysis of the objects was carried out in accordance with the requirements of the BP and USP by the following parameters: "Description", "Hygroscopy", "Microscopy", "Solubility in *water R,* in *hot water R*, in organic solvents" and by chemical reactions of identification: the reaction with copper tartrate reagent (Fehling's reagent) and with the alcoholic solution of resorcinol (Seliwanoff's test). The comparative characteristics of requirements regarding the quality of API of inulin according to these pharmacopoeias are given in Tab. 1.

The solubility and the degree of hygroscopicity of the substances were studied according to the requirements of the monograph of the State Pharmacopeia of Ukraine (SPhU, 5.11) [12]. The solubility of substances was studied in *water R*, in *hot water R* (80-90 °C) and in organic solvents (*chloroform R*). Determination of the degree of hygroscopicity was assessed in 24 hours, keeping the substances over the saturated solution of *ammonium chloride*.

The morphological characteristics (shape and size of the powder) for all API of inulin was studied by the method of microscopy according to the SPhU, 2.9.37, using an "Opton" microscope by "West Germany" company (the magnification range – x 100 – x 200). On a glass slide a small amount of the substance powder uniformly distributing on the surface was placed (approximately 0.01 g) in the mixture with *ethanol (96 %) R* [12].

Identification of inulin was carried out according to the methods of the BP and USP:

Identification B (BP). Dissolve 10 mg of the substance in 2 ml of *hot water R*, add 3 ml of 0.15 % *alcoholic solution of resorcinol*, then 3 ml of *hydrochloric acid R*, mix and heat at 80 °C. A red color must appear (Fig. 2).

Preparation of 0.15 % alcoholic solution of resorcinol: place 0.15 g of *resorcinol R* in a 100 ml volumetric flask, add a small amount of *ethanol R* (96 %), dilute to the volume with the same solvent, and mix [11].

Identification C (BP). Boil 5 ml of 10 % aqueous solution of inulin with 0.5 ml of *hydrochloric acid R* for 2 min, cool and neutralize with *sodium hydroxide solution R* by litmus paper. Add 0.5 ml of *copper tartrate solution R1* prepared according to the requirements of the BP. A red precipitate must appear (Fig. 3).

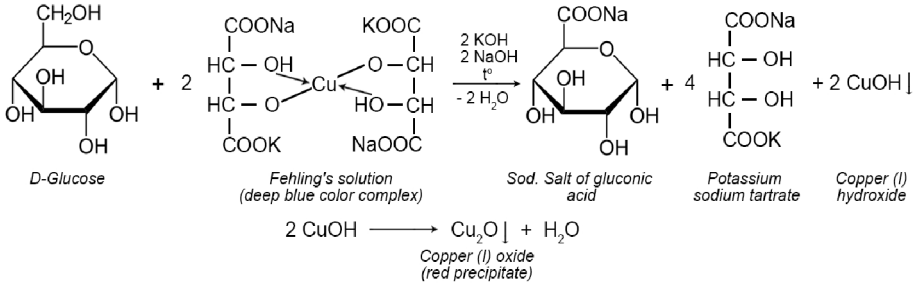

Fig. 3 *The chemistry of the reaction of identification C (reaction with Fehling's reagent)*

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Table 2

CHARACTERISTICS OF THE STUDY OBJECTS

Batch No.	Description
01	A loose, amorphous, odorless, white powder
02	A loose, amorphous, odorless, pale yellow powder
03	A loose, amorphous, odorless, practically white powder
04	A loose, amorphous, odorless, white powder
05	A loose, amorphous, odorless, pale yellow powder
06	A loose, amorphous, odorless, white powder
07	A loose, amorphous, odorless, white powder
08	A loose, amorphous, odorless, practically white powder
09	A loose, amorphous, odorless, white powder
10 (Standard substance of *inulin with chicory*)	A loose, amorphous, odorless, white powder, friable like chalk
11 (Standard substance of *inulin with dahlia*)	A loose, amorphous, odorless, white powder, friable like chalk

Preparation of copper tartrate solution R1 (by the requirements of the BP):

Solution A. Dissolve 34.6 g of *copper (II) sulfate R* in the mixture of 0.5 ml of *sulfuric acid R* and *water R*, dilute the solution to the volume of 500 ml.

Solution B. Dissolve 176 g of *potassium sodium tartrate R* and 77 g of *sodium hydroxide R* in *water R*, dilute the solution to the volume of 500 ml with the same solvent.

Mix the equal volumes of solutions A and B immediately before use [11].

Identification (*USP*). Dissolve 10.0 g of inulin in 20 ml of *hot water R* in a 100 ml volumetric flask, cool, dilute the solution to the volume with *water R* and mix (*solution S*). To 2 ml of *solution S* add 5 ml of *copper tartrate solution* prepared according to the requirements of the USP: the reaction does not proceed at room temperature, a slight reaction maybe in 1 min of boiling (Fig. 3).

Preparation of copper tartrate solution (by the requirements of the USP):

Solution A. Dissolve 34.6 g of *copper (II) sulfate R* in *water R*, dilute the solution to the volume of 500 ml with the same solvent.

Solution B. Dissolve 173 g of *potassium sodium tartrate R* and 50 of *sodium hydroxide R* in 400 ml of *water R*. Heat to boiling, cool, dilute the solution obtained to the volume of 500 ml with *water R* that is free of carbon dioxide.

Table 3

THE DEGREE OF HYGROSCOPY

Batch No.	The degree of hygroscopy, %	Compliance
01	14.31 ± 0.01	Hygroscopic
02	15.94 ± 0.29	Very hygroscopic
03	14.54 ± 0.04	Hygroscopic
04	21.19 ± 0.05	Very hygroscopic
05	16.03 ± 0.12	Very hygroscopic
06	15.11 ± 0.21	Very hygroscopic
07	11.41 ± 0.07	Hygroscopic
08	9.40 ± 0.23	Hygroscopic
09	11.09 ± 0.24	Hygroscopic
10 (Standard substance of *inulin with chicory*)	12.10 ± 0.10	Hygroscopic
11 (Standard substance of *inulin with dahlia*)	11.90 ± 0.17	Hygroscopic

Mix the equal volumes of solutions A and B immediately before use [10].

The reagents used in the analysis meet the requirements of the SPhU. All tests were performed in several replicates.

According to the BP when carrying out chemical reactions of identification the substances of inulin studied (batches 01-09) and standard substances of inulin with chicory and dahlia (batches 10, 11) had a red color in Seliwanoff's test (identification B), confirming the presence of fructose, and an orange-red / dark-red precipitate in the reaction with Fehling's reagent after hydrolysis (identification C), indicating the presence of glucose.

According to the USP [10] by the reaction with copper tartrate reagent performed without prior hydrolysis of the substances the reaction did not proceed at room temperature, however, when heated for 1 min the appearance of an orange-red precipitate in the compounds analyzed was observed (batches 1-9). This indicates the presence of sugars with the properties of reducing agents in the substances studied and requires further research. In the samples of batches 10, 11 a blue coloration after heating did not change.

In the experiment it has been found that the API of inulin studied (batches 01-09) and the standard substances of inulin with chicory and dahlia (batches 10, 11) are loose, amorphous, powders of white, practically white and pale yellow color by the "Description" [10, 11] parameter (Tab. 2).

According to Tab. 3 the test samples are hygroscopic (increase in mass is from 2 % to 15 %) and very hygroscopic (increase in mass is more than 15 %).

By the parameters of "Solubility" [11] in *water R* (the temperature was 25 °C) the substances analyzed

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Table 4

SOLUBILITY OF API OF INULIN

Batch No.	In water (at 25 °C)	In hot water (at 90 °C)	In organic solvents
			Chloroform R
01	Slightly soluble	Readily soluble	Insoluble
02	Soluble	Very soluble	
03	Readily soluble	Readily soluble	
04	Soluble	Very soluble	
05	Readily soluble	Very soluble	
06	Slightly soluble	Readily soluble	
07	Soluble	Readily soluble	
08	Readily soluble	Very soluble	
09	Slightly soluble	Readily soluble	
10 (Standard substance of *inulin with chicory*)	Slightly soluble	Readily soluble	
11 (Standard substance of *inulin with dahlia*)	Practically insoluble	Readily soluble	

were readily soluble, soluble and sparingly soluble in *water R*, while by the solubility in *hot water R* (its temperature was 80-90 °C) all samples were very soluble or readily soluble (Tab. 4).

It is known from the literature sources that the less the number of fructose residues in the inulin structure is, the greater is the solubility of the substance [1, 2, 4]. In this regard, high parameters of solubility in water at the temperature of 25 °C indicate the potential presence of low molecular weight inulin fractions in the test samples.

The solubility of substances was also checked in *chloroform R*. It has been experimentally confirmed that in *chloroform R* all samples are insoluble.

The next step was to study the structure of plant API of inulin by the method of microscopy

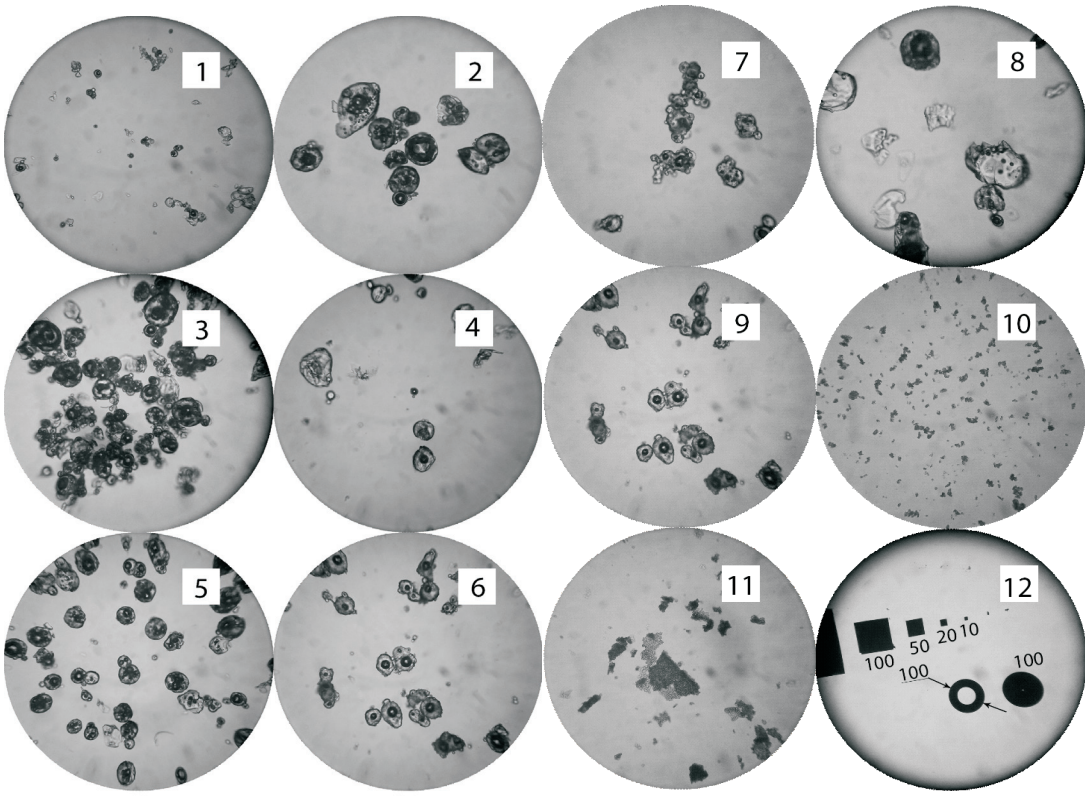

Fig. 4 *The photomicrographs of API of inulin in ethanol (96 %) R obtained with a light microscope in 200-fold magnification: the substances of inulin of batch 01-09 (1-9); standard substance of inulin with chicory (10); standard substance of inulin with dahlia (11); a calibrated stage micrometer (12)*

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in *ethanol (96 %) R* [11]. The photomicrography is given in Fig. 4.

The study of morphology of API of inulin by light microscopy shows that the samples (batches 02-09) look like masses with large spherical or ovoid particles that are completely or partially fragmented. As noted in the works [2], these formations can be described as pseudomorphic or pseudocrystalline with the expressed central micelles looking like black cores and peripheral semi-transparent shells, as well as small parts of inulin (in the form of dark points) separated from the main pseudocrystalline formations.

The samples of batches 01, 10, 11 in this magnification are also completely or partially fragmented spherical or ovoid particles; however, the substances have a smaller size due to the greater degree of fineness.

CONCLUSIONS AND PROSPECTS FOR FURTHER RESEARCH

1. According to the BP the presence of the structural components – fructose and glucose after hydrolysis of the main substance can be confirmed by the chemical reactions of identification of plant API of inulin. According to the USP the identification reaction can confirm the presence of inulin as a substance that does not reduce Fehling's reagent, as well as determine the presence of impurities of sugars with the properties of reducing agents.
2. The results of studying the physicochemical characteristics of plant API of inulin according to such parameters as "Appearance", "Solubility", "Hygroscopy", "Microscopy" can be used for the input quality control of API of inulin to confirm the structure and determine the purity of the substance.
3. The results of studying the physicochemical characteristics of plant API of inulin can be used when developing the national normative documents on the substance of inulin.

Conflict of Interests: authors have no conflict of interests to declare.

ABBREVIATIONS

API, plant active pharmaceutical ingredients; BP, the British Pharmacopoeia; USP, the United States Pharmacopeia.

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