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SELECTION OF FLAVOUR ADDITIVES AND METHOD OF THEIR INTRODUCTION IN THE COMPOSITION OF COMPRESSED MEDICATED CHEWING GUMS

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Abstract

An important characteristic of oral medicines, which include medicated chewing gums, is their pleasant taste. This can be achieved by adding taste coregents to their composition.

The aim: to choose rational flavour additives and justify the method of their introduction to the compressed medicated chewing gums that are being developed.

Materials and methods: mint (Natural Mint Flavor SD, Kerry Inc., Malaysia), apple (Nat Apple FlavorWonf, Kerry Inc., Malaysia) and banana (Banana FLV, Kerry Inc., Malaysia) have been used as powdered flavour additives. As flavourings – oil solutions: Peppermint Natural WonfFlavor, Kerry Inc., Malaysia), Apple (Nat Apple FlavorWonf, Kerry Inc., Malaysia), Strawberry (Strawberry FlavorWonf, Kerry Inc., Malaysia), Melon (Chemical-Food Aromatic PlantLLC, Russian Federation) and Lemon (Chemical-Food Aromatic Plant LLC, Russian Federation). Aerosil brand 380 (Evonik Resource Efficiency GmbH, Germany), Syloid® 244FP (Grace Discovery Sciences, USA) and Neusilin® ULP 2 (Fuji Chemical Industry Co. Ltd, Japan) have been taken as carriers. The choice of flavour additives and flavourings was made using organoleptic methods of coregents evaluation according to A. I. Tentsova and I. A. Yegorov. The technological and physicochemical properties of the samples were studied according to conventional methods of the State Pharmacopoeia of Ukraine.

Results and discussion. In determining the taste of medicated chewing gums samples with different coregents, the combination of powder additive and liquid flavouring "Apple" has got the highest mark. In order to substantiate the rational method of liquid flavouring introduction in the composition of the compressed chewing gums, it is proposed to introduce the adsorbents Aerosil 380, Syloid® 244FP and Neusilin® ULP 2, which also play the role of moisture regulators and glidants. Microscopic analysis of adsorbents mixtures with flavouring, as well as physicochemical and technological investigations of the mass for pressing have revealed that the best adsorbing, moisture-regulating and flow properties has Syloid® 244FP.

Conclusions. As a coregent in medicated chewing gums was selected a combination of powdered (2.0 %) and liquid (0.6 %) flavours "Apple". The method of introducing the oil flavouring into the composition of the compressed gums has been chosen – by spraying on the adsorbent with subsequent mixing. Based on the studies, Syloid® 244FP at a concentration of 1.0 % was chosen as the rational carrier.

Keywords: medicated chewing gums, flavours, adsorbents, organoleptic methods of coregents evaluation, physicochemical and technological research.

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1. Introduction

During the development of drugs for oral use, great attention is paid to their taste characteristics. Dosage forms (DF) of that type of drugs include medicated chewing gum (MCG), the release of APIs from which occurs in the mouth in the process of chewing. Therefore, in substantiating the composition of drugs in this DF, the main issue remains to give them a pleasant taste [1, 2].

It is known that the organoleptic properties of drugs are perceived by man comprehensively and represent a combination of taste and smell [3]. So not only sweeteners but also flavour additives are referred to corrective substances – they mask the unpleasant smell of APIs or complement the sweetener taste [4, 5].

As groups of excipients, sweeteners and flavours are listed in foreign pharmacopoeias – European, British and National formulary of USA Pharmacopoeia [6, 7]. In the national documentation, these groups of substances are described in DSTU-H CODEX STAN 192: 2014 Nutritional Supplements. Nomenclature and general requirements [8].

The object of our research is compressed MCGs for the treatment and prevention of diseases of the hard and soft tissues of the oral cavity containing lysozyme hydrochloride and ascorbic acid as APIs, as a chewing base –composition Health in Gum®(HiG) PWD-01 [9]. This combination gives the gum a sour-sweetish taste with a short aftertaste (about 1 minute). Therefore, based on previous studies of the MCG composition, as the optimal intensive sweetener sucralose has been introduced, as it has good corrective properties, a safe, low-calorie and non-carious substance, which is especially important for dental drugs [4, 10]. The introduction of this excipient gave the gum an intense sour-sweet taste with a longer (about 7 minutes) pleasant sweet aftertaste [11].

However, according to the recommendation of Cafosa (Spain), in order to improve the taste characteristics of MCGs, in addition to an intense sweetener, they must additionally contain flavours, both powder and liquid. In this case, the powder additive should contain as little sugar or polyols (preferably be arabic gum-based) as possible, the liquid additive should be water insoluble (triacetin or oil-based) to provide the gum with a prolonged taste. In addition, the oil flavouring additionally acts as a plasticizer, improving the sensitive properties of MCG during chewing [12, 13].

The main issue with the introduction of the flavouring into the compressed MCGs is the choice of a carrier capable of converting the liquid component into powder form and homogeneously distributing it in the mass for compression.

The aim of the work was to choose flavouring additives and the way of their introduction into the compressed MCGs, which are being developed.

2. Materials and methods

The objects of the study are specimens of compressed MCGs, which had different combinations of powder and liquid flavours.

Mint (Natural Mint Flavor SD, Kerry Inc., Malaysia), apple (Nat Apple FlavorWonf, Kerry Inc., Malaysia) and banana (Banana FLV, Kerry Inc., Malaysia) have been used as powdered flavour additives.

As flavourings – oil solutions: Peppermint (Natural WonfFlavor, Kerry Inc., Malaysia), Apple (Nat Apple FlavorWonf, Kerry Inc., Malaysia), Strawberry (Strawberry FlavorWonf, Kerry Inc., Malaysia), Melon (Chemical-Food Aromatic PlantLLC, Russian Federation) and Lemon (Chemical-Food Aromatic Plant LLC, Russian Federation).

Aerosil brand 380 (Evonik Resource Efficiency GmbH, Germany), Syloid® 244FP (Grace Discovery Sciences, USA) and Neusilin® ULP 2 (Fuji Chemical Industry Co. Ltd, Japan) have been taken as carriers.

The choice of flavour additives and flavourings was made using organoleptic methods of coregents evaluation according to A. I. Tentsova and I. A. Yegorov with the involvement of 20 volunteers. In the Tentsova A. I. method, numerical (point) gradation is used to quantify the intensity of only the basic taste. In the method of Yegorov I. A. a double assessment of the intensity of taste and aftertaste is used, which provides a better approach to the choice of corrective substances [14, 15]. Characteristics of these methods are given in **Table 1**.

The choice of the adsorbent was based on physicochemical (optical microscopy, moisture absorption capacity) and technological (flowability, angle of repose, bulk density and tapped density, compressibility index, Haussner ratio) studies according to the requirements of SPhU 2.1 [16]:

– Moisture absorption capacity: weight of the sample – 1.0 g; carried out at room temperature at relative humidity values of 40, 60 and 75 % for 24 h; the increase in moisture content was determined gravimetrically;

– Optical microscopy: was performed using a laboratory microscope Konus-Asademy (Italy) equipped with ScopeTek camera; the photographing was made in transient light; photo processing was done in Scope Photo software (version 3.0.12.498);

– Flowability and angle of repose have been determined by the time of the flow of powders (granules) through the funnel on a laboratory device model VP-12A (Mariupol factory of technological equipment, Ukraine); determination of the angle of repose was carried out on the scale of the angle gauge and calculated as the inverse tangent (arctan) of the ratio of cone maximum height to its radius;

– Bulk density and tapped density: determined on a Pharma Test tap density tester model PT-TD1 (Germany) using a 250 ml graduated cylinder;

– Statistical processing of results: was carried out using Microsoft Excel 2016 software.

Table 1

Characteristics of organoleptic methods of coregents evaluation

Taste evaluation by A. I. Tentsova	Taste evaluation by I. A. Yegorov	
	letter indexes taste and aftertaste	numerical indexes of taste
– "sweetness": 1 – sweet, 5 – very sweet; – "the presence of aftertaste": 1 – absent, 5 – strong; – "aftertaste character": 1 – unpleasant, 5 – very pleasant; – "compatibility of flavours and medicinal substance tastes": 1 – incompatible, 5 –compatible; – "taste in general": 1 – unpleasant, 5 – very pleasant	– "K" – sour; – "O" – sweet; – "B" – bitter; – "S" – salty; or combinations thereof, e. g., "KO" – sweet and sour, BKO – bitter-sour-sweet, etc., where the first letter indicates a dominant taste	– 1 – devoid of taste, the standard of which is purified water; – 2 – weak taste shades (for which reference solutions are prepared: B2 – 0.0002 % aqueous solution of quinine hydrochloride; K2 – 0.02 % aqueous citric acid solution; S2 – 0.1 % aqueous sodium chloride and O2 – 0.38 % sucrose solution); – 3 – normal intensity of taste, which is common for a person in everyday life; – 4 – a supersaturated taste that causes irritation
From the obtained data calculate the taste index as the arithmetic mean of all indicators	From the obtained data compose the taste formula	

4. Research results

Because flavour additives and flavourings give the product a special smell and taste, they must be selected based on the basic taste of the masking agent, being its complement. Considering the presence of ascorbic acid in the composition of the studied MCGs, it was rational to add mint and citrus or fruit coregents, which are appropriate to be used in preparations with sour taste [15, 17].

As mentioned above, according to preliminary results for determining the taste of chewing gum, sucralose, which was added to the composition of MCG in the amount of 0.15 %, was chosen as an intensive sweetener for further studies [11]. The number of flavours was selected according to the recommendations of Cafosa: powdered – 2.0 %, liquid – 0.6 % [12, 13]. In **Table 2** the results of the MCG samples taste evaluation are given.

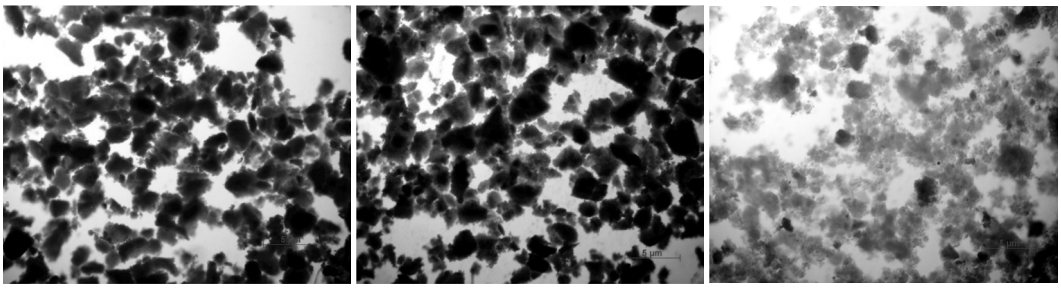
Table 2

Results of taste determination of MCG samples with different flavour coregents combinations

Composition (powdered flavour additive/liquid flavouring)	Evaluation of the basic taste	Formula of taste	General taste
Mint/mint	2.30±0.10	B2K2O2	cooling slightly bitter, slightly sour, slightly sweet
Mint/lemon	2.10±0.12	B3K3	bitter-sour
Apple/apple	4.85±0.05	K2O3	slightly sour and sweet
Apple/melon	4.30±0.10	K3O3	sour-sweet
Apple/strawberry	4.10±0.15	K3O3	sour-sweet
Apple/lemon	3.80±0.15	K3O2	sour, slightly sweet
Banana/strawberry	4.60±0.10	K2O2	slightly sour and slightly sweet

Note: n=3, P=95 %

An important question is the method of the selected flavouring introduction into the composition of the compressed gums. To this end, it has been proposed to use adsorbents that make it easy to convert liquid API into powders with good flowability – Aerosil 380, Syloid® 244FP and Neusilin® ULP 2 [18, 19]. The flavouring solution was sprayed onto the adsorbents tested and mixed until a homogeneous dry mixture was formed. Their choice was based on the degree of adsorption, the quantitative content in 1 gum (the ratio of flavouring:adsorbent as 1:2) and the ability to homogeneous distribution of flavour in the mixture, which, accordingly, will have a significant impact on the technological properties of the mass for pressing. Microscopic analysis of mixtures is shown in **Fig. 1**.



a *b* *c*

Fig. 1. Microscopic analysis of adsorbents mixtures with flavouring:
a – Syloid® 244FP; *b* – Neusilin® ULP 2; *c* – Aerosil 380

Considering the fact that the developed MCGs include hygroscopic substances (lysozyme hydrochloride and chewing base HiG PWD-01) [9], and carriers selected also play the role of moisture regulators, we have investigated their moisture absorption capacity. To avoid changes in the taste characteristics of the MCGs Syloid® 244FP and Neusilin® ULP 2 were introduced into the mass for pressing at a concentration of 1.0 % (according to the recommendations of the Cafosa a concentration of the adsorbent in chewing gum should not exceed 1.5 %) [12, 13]. The studies were carried out for 24 h with a relative humidity (r.h.) of 40, 60 and 75 %. The results obtained are shown in **Fig. 2**.

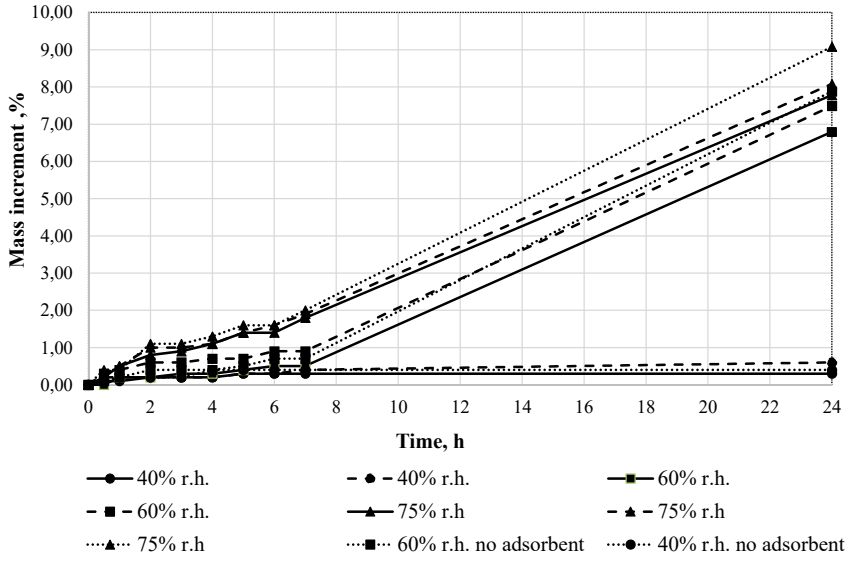


Fig. 2. Moisture absorption capacity of adsorbents at different relative humidity

According to the literature, the adsorbents studied are also capable of influencing the flowability of powders, acting as glidants in the production of solid DFs [20–22]. Therefore, for the final

selection of a rational carrier of oil flavouring in the developed compressed MCGs, we have studied the main technological properties of the mass for pressing with the inclusion of these substances at a concentration of 1.0 %. The results are given in **Table** 3.

Table 3

Technological properties of the mass for pressing with the studied adsorbents

Technological indicators	Results	
	with Syloid® 244FP	with Neusilin® ULP 2
Flowability, s/100 g of sample	5.73±0.21	6.59±0.09
Angle of repose:		
tan (α), deg.	29.76±1.01	30.25±0.54
Goniometer, deg.	31.00±2.91	32.40±0.48
Bulk volume, V_0, ml	147.9±0.5	147.7±0.9
Tapped volume, V_{2500}, ml	126.3±0.7	128.5±0.4
Bulk density, $\frac{m}{V_0}$, g/ml	0.682±0.002	0.677±0.003
Tapped density, $\frac{m}{V_{1250}}$ or $\frac{m}{V_{2500}}$, g/ml	0.790±0.004	0.798±0.003
Compressibility index, %	14	15
Haussner ratio	1.16	1.18

Note: n=5, P=95 %

The next step in our research was the choice of Syloid® 244FP concentration. To this end, the excipient was introduced into the mass for pressing at various concentrations of 0.5, 1.0 and 1.5 %. The effect of the amount of Syloid® 244FP on the moisture absorbency of this adsorbent and the flowability of the mass has been studied. Assessment of moisture absorption capacity was carried out after 24 h of observation at 60 % relative humidity. The results obtained are shown in **Fig. 3**.

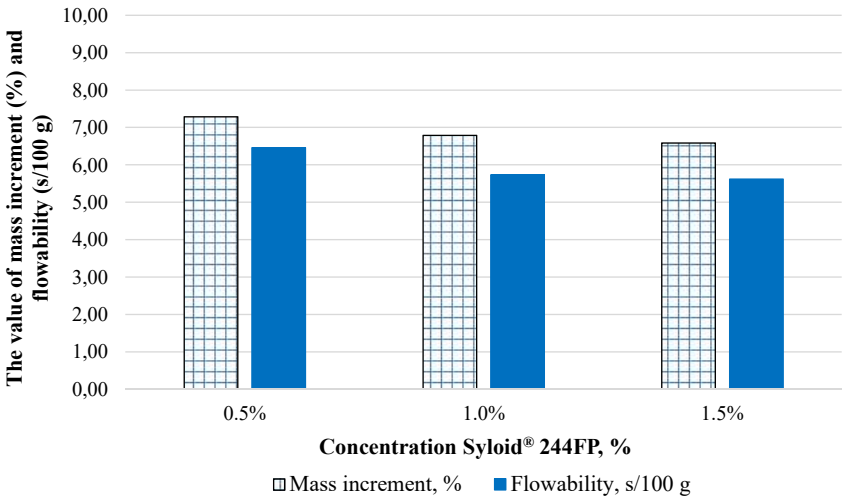


Fig. 3. Effect of concentration Syloid® 244FP on moisture absorption capacity and flowability of mass for pressing

4. Discussion

According to the results of determining the taste of MCG samples (**Table 2**), it has been found that the sample with the combination of powdered flavour additives and liquid flavouring "Apple" has got the highest mark, which became the basis for the choice of these flavours in the composition of MCGs under development.

The results of microscopic analysis of adsorbents mixtures with flavouring (**Fig. 1**) have shown that each excipient adsorbed the flavouring solution very quickly, forming a dry powder mixture. However, when using Aerosil 380, there was an uneven change in the colour of the mass with the formation of agglomerates of size from 0.5 to 2.5 microns, which, respectively, can lead to a heterogeneous distribution of the coregent in the mass for pressing. Microscopic analysis has revealed that the particles of the mixture of flavouring with Syloid® uniformly distributed in the field of view, had the same colour and size (1.5–2.5 μm) unlike the mixture with Neusilin®, where particles different in linear size (from 1.0 to 4.0 μm) were observed.

Therefore, the results obtained have determined the feasibility of further studies of samples of mixtures with Syloid® 244FP and Neusilin® ULP 2.

According to the results of the moisture absorption capacity of adsorbents (**Fig. 2**), during 7 h of study at all values of relative humidity the decrease in mass increment for pressing mass was observed when using Syloid®, with the introduction of Neusilin® sample mass at 60 % r.h. on the contrary, increased slightly. However, at 24 h observation at a relative humidity of 75 % mass increment of the sample with Syloid® was 7.78 %, with Neusilin® – 8.08 %, which reduced the initial value of the humidity of the mass for pressing by 1.3 % and 1.0 %, respectively. At 60 % r.h. the mass increment of the samples with adsorbents was also less than the initial value (7.88 %), namely with Syloid® – 6.79 %, and with Neusilin® – 7.49 %. According to the data presented, 40 % relative humidity practically did not affect the properties of the mass for pressing – statistically significant changes in mass increment during 24 h of the experiment, both with and without the use of adsorbents were not observed. But the best moisture absorption ability also characterized the sample with Syloid® 244FP.

As shown by the results of the study of the technological properties of the mass for pressing (**Table 3**), mixtures with Syloid® 244FP and Neusilin® ULP 2 have good flowability [17]. This is also confirmed by the values of the angles of repose, compressibility indexes and Haussner ratios of the samples studied. However, considering all the results of the studies, Syloid® 244FP was chosen as the rational carrier, which had better adsorbing and moisture-regulating properties.

Results from the study of the Syloid® 244FP concentration effect on moisture absorption capacity and flowability of mass for pressing (**Fig. 3**) indicate that an increase in Syloid® 244FP concentration in mass for pressing leads to an improvement in the studied indicators, but no statistically significant difference in moisture absorption and flowability values is observed when using adsorbent in 1.0 and 1.5 % quantities. This, in turn, allows setting a rational Syloid® 244FP concentration – 1.0 %.

The influence of various adsorbents on the ability to adsorb liquid components and the technological characteristics of solid dosage forms are investigated in the writings of other scientists.

The study by Suhas G. Gumaste and colleagues was devoted to comparing different silicates for their suitability to develop tablets by adsorbing components of liquid lipid-based drug delivery systems. It was found that among various silicates studied, Neusilin® US2 was the only silicate able to produce tablets with acceptable tensile strength in presence of a lipid component at 1:1 w/w ratio due to the fact that the liquid was mostly adsorbed into the pores of the silicate rather than at the surface [23].

Another study by Hentzschel C. M. and colleagues was devoted to the investigation of tableting properties of different silicates. According to their conclusions, tablets with acceptable tensile strength were obtained with all plain silicates except for Aerosil. Therefore, these silicates may be used in tablet formulations, e. g. as carrier materials for liquid or amorphous drugs [24].

Therefore, our studies confirm the results of other scientists on the high ability of the above carriers to adsorb liquid components and their positive impact on the technological characteristics of pressed solid drugs. However, the choice of flavouring and carrier in the composition of the compressed chewing gum took into account, above all, the quantitative recommendations of Cafosa firm for these excipients, since increasing their concentrations may not only reduce the technological properties of the mass for pressing and, accordingly, the finished product, but also adversely affect its taste characteristics.

Our further studies will focus on the effect of the selected adsorbent (Syloid® 244FP) on the kinetics of APIs release from medicated chewing gums.

5. Conclusions

Optimal coregents of taste and smell have been determined and their rational concentrations in the composition of compressed MCGs have been established: sucralose (0.15 %) as an intensive sweetener and a combination of powdered flavour additive (2.0 %) and liquid flavouring (0.6 %) "Apple".

The method of introducing the oil flavouring into the composition of the compressed gums has been chosen – by spraying on the adsorbent with subsequent mixing.

Based on the results of physicochemical and technological investigations as a flavouring carrier, which also plays the role of moisture regulator and glidant in the composition of the studied gums, Syloid® 244FP was selected at a concentration of 1.0 %.

Conflict of interests

The authors declare that they have no conflicts of interest.

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RESEARCH ON THE SELECTION OF EXCIPIENTS AS THE RATIONALE FOR THE COMPOSITION OF THE TABLETS WITH DRY EXTRACT OF *SANGUISORBA OFFICINALIS*

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Abstract

The aim. The aim of the research was to study the effect of different groups of excipients on the pharmaco-technological propertiesof the powder mass for tabletting in the development of the composition of the tablets with dry extract of *Sanguisorba officinalis* for complex therapy of the gastrointestinal tract diseases.

Materials and methods. Objects of study – dry extract *Sanguisorba officinalis*, 25 excipients used in the production of tablets by the method of direct compression, grouped into five groups of factors (fillers based on sugars and microcrystalline cellulose, disintegrants, glidants and lubricants), samples of powder masses. Studies on the determination of pharmaco-technological properties (fluidity, bulk density, bulk density after shrinkage, degree of compressibility, Hausner ratio, and angle of repose) of the obtained powder masses were carried out according to the methods of the State Pharmacopoeia of Ukraine, Second edition. The method of mathematical planning of the experiment was used in the work, the obtained results were subjected to variance analysis, and the ranked series of advantages were placed, in which the excipients were placed in the sequence of their influence on the studied pharmaco-tecnological parameters.

Results and discussion. The influence of excipients (factors) on the pharmaco-technological properties (responses) of the powdered tablet masses with the construction of ranked benefits was studied using a five-factor experiment, a hyper-Graeco-Latin square. The results of the analysis of variance showed that glidants have the greatest influence on the fluidity, the bulk density and the bulk density after shrinkage. Neusilin US 2 significantly affects the fluidity of the powder masses and Hausner ratio, the Talc having the greatest effect on the bulk density and the bulk density after shrinkage of the powder masses. The representative of the disintegrants group – Sodium starch glycolate most influences the compressibility index, the sugar-based filler – Pearlitol 500 DC – on the angle of repose.

Conclusions. The effect of 25 excipients on the pharmaco-technological characteristics of the powdered tablet masses with dry extract of *Sanguisorba officinalis* was studied. It was found that among the sugars-based fillers equally good results were shown