თა სხვადასხვა ასაკობრივ ჯგუფებში - ასაკოვანი თაგვები უფრო რადიორეზისტენტული აღმოჩნდა. ასაკთან დაკავშირებული რადიორეზისტენტობა განსაკუთრებულ როლს ასრულებს პოსტრადიაციული აღდგენის ადრეულ სტადიაზე. თუმცა, გვიანი რადიაციული დაბერების ეფექტის ფორმირება განსაკუთრებით გამოხატულია ახალგაზრდა ცხოველებში.

DEVELOPMENT OF FORMULATION AND TECHNOLOGY OF FOAMING AGENT FROM MASTIC (PISTACIA LENTISCUS L.) GUM

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Helicobacter pylori (H. pylori) and its eradication problem is the subject of intensive research. Since its discovery (1982), this gastropathogen has been considered a serious public health problem due to its association with dyspepsia, gastritis, gastric and duodenal ulcers, and gastric carcinoma. Helicobacter pylori is detected in 50-80% of Asia's population, 70-90 percent of Africa, 30% of USA, 70% of Eastern Europe, 30-50 percent of Western Europe, and 20% of Australia's population. H. pylori infection is influenced by age, ethnicity, gender, region, and socioeconomic level [1,5,10].

Numerous investigations on the efficient eradication of H. pylori have been conducted in vitro and in vivo trials since its discovery. Proton pump inhibitors, several antibiotics, bismuth salts, and other substances were investigated. However, research show that these medication regimens are ineffective. The increase of H. Pylori antibiotic resistance is the most significant issue impeding successful therapy. Among the difficulties are the following:

- side effects of proton pump inhibitors and antibacterial drugs - cytotoxicity to the intestinal flora and general toxicity to the body [3,4,10];
- negative attitude towards taking tablets and capsules by patients and the prescription's vulnerability [2].

As a consequence, it is critical to develop local antibacterial, targeted delivery formulations for H. pylori eradication that offer extended action and are characterized by high bioavailability up to H. pylori's localization in the stomach mucosa based on the biologically active ingredient [6].

The evergreen plant Mastic gum (Pistacia lentiscus L., family Anacardiacae, genus Pistacis L.) was discovered to exhibit bactericidal effect against 11 strains of Helicobacter pylori. The European Medicines Agency (EMA) certified Pistacia lentiscus L. gum as a herbal medicine in 2015 for two therapeutic indications: moderate dyspepsia and skin inflammation/minor wound healing. Poor solubility and biological permeability, on the other hand, greatly decrease its healing capability [7].

As a result, the present challenge is to create a mechanism that allows for enhanced medication penetration across the epithelial barrier in the stomach. In this aspect, foams are very interesting.Foams are light systems, unlike solid medicinal forms, they do not swell, on the contrary, they grow in volume, completely covering the mucous membrane. Foams are considered as an alternative to solid and liquid therapeutic forms, they do not require taste correction, are designed for delivery a healing substance through the skin and mucous membranes, and for effective treatment [2,8,9].

The aim of the research was to determine the formulation of the innovative medicinal form - foam system from Mastic gum and to develop the technology.

- To achieve is the goal we have to solve the following tasks:
- Determining the formulation of the foaming powder composition containing Mastic gum based on biopharmaceutical studies;
- Development of foaming powder technology containing Mastic gum;
- Study of physico-chemical and technological characteristics of foaming powder;

Material and methods. Mastic gum, foaming agents, foam stabilizing agents, foaming structure - polyol group substances.

Biopharmaceutical, physico-chemical and technological methods of analysis were used in the research process.

Results and discussion. In the first stage, the foaming substances and their optimal concentration were determined. Surfactants were used for this purpose: (surfactants) sodium lauryl sulfate (SLS), lecithin, egg white protein, sodium dodecyl sulfate (SDS). During the research, the ability of the above substances (foaming agents) to foam, both individually and in combinations, was studied. The results are shown in Figs 1 and 2.

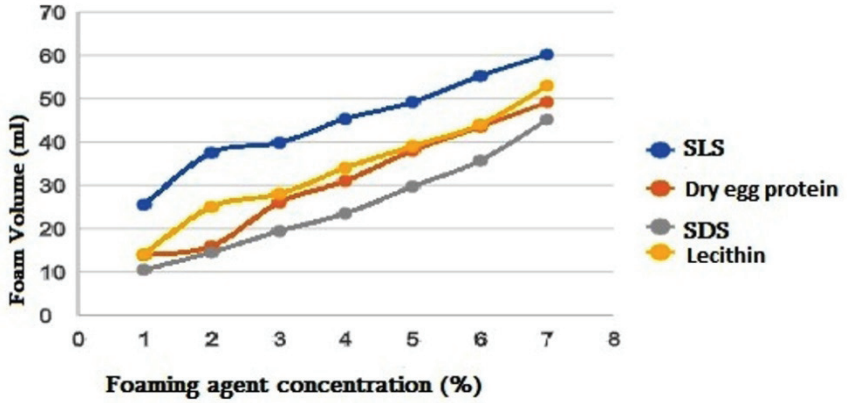

Fig. 1. Foaming ability of Sodium lauryl sulfate (SLS), Dry egg protein, Sodium dodecyl sulfate (SDS) and Lecithin

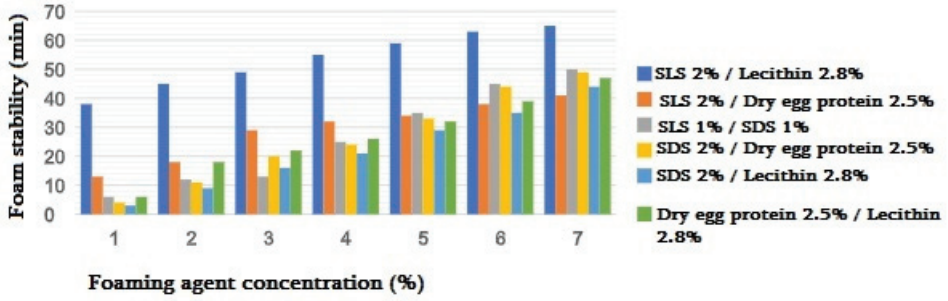

Fig. 2. Results of the combination of foaming agents sodium lauryl sulfate (SLS), dry egg protein, sodium dodecyl sulfate (SDS) and lecithin foam forming ability

1%: Foam quality 74% | **2%: Foam quality 96%** | **3%: Foam quality 94%** | **4%: Foam quality 92%**

Fig. 3. Quality of foams prepared in 1%, 2%, 3%, 4% xanthan and gelatin ratio 1: 1

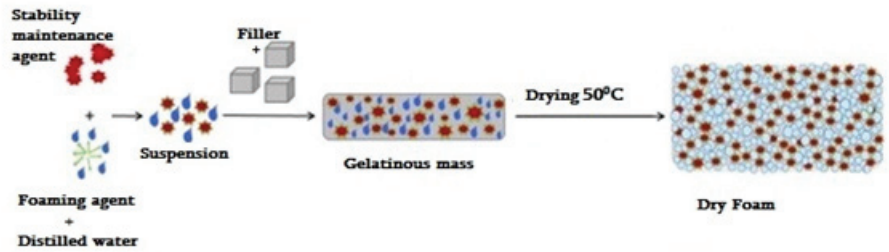

Fig. 4. Dry foam preparation scheme

According to the obtained results (Fig. 1,2), the combination of sodium lauryl sulfate (SLS) and lecithin, 2: 2.8%, was selected considering the foam volume and foam stability.

After the selection of foaming agents, studies were continued to select the agents that maintain the foam stability and to determine the appropriate concentration. The quality of foams prepared in 1: 1 ratio of 1, 2, 3 and 4% xanthan and gelatin was studied (Fig. 3). When the foam quality is from 0% to 52%, the air bubbles do not interact with each other and are spherical in shape. The viscosity of the foam is also low because there is a lot of free fluid in the system, which in turn affects the possibility of fluid

loss. When the foam quality is between 52% and 96%, the air bubbles are in contact with each other and as a result, the viscosity also increases. Foams with 52% and 60% quality do not have the ability to hold air bubbles. When the foam quality is more than 96%, the foam has a higher viscosity and is better able to hold air bubbles, which in turn ensures long-term stability of the foam.

Based on the obtained results, a combination of 2% xanthan and gelatin in a 1: 1 ratio was selected as the foam stabilizing agent and the desired concentration.

In the next phase of the research, the influence of fillers and their concentrations on the formation of the structure of a multilayer, dry foam system was studied. Isomalt, sorbitol and maltodextrin were used as fillers. The foams were prepared using the technological scheme shown in Fig. 4. 12 foam formulations were prepared.

The foams prepared with sorbitol and maltodextrin after drying had an uneven soft-sticky structure, with a smooth surface. The resulting foam compositions are not subject to granulation. Foam formulations prepared with isomalt have produced dry foams with an even, funnel-like structure that are suitable for granulation. Further studies were therefore continued on foam systems prepared using isomalt.

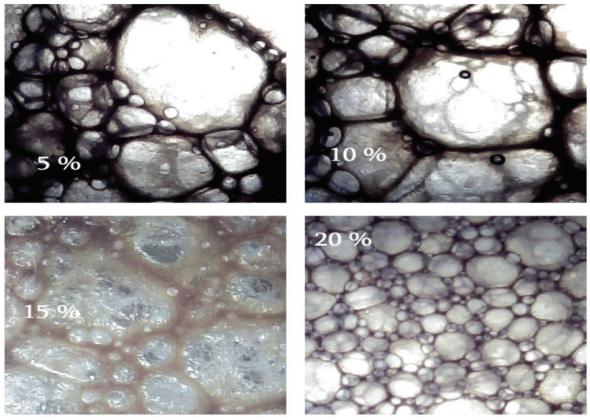

Fig. 5. Microscopic analysis of isomalt foams

In the next stage of the research, a microscopic study of dry foam prepared using isomalt was performed (Fig. 5). Fig. 5 shows that the foam containing 20% isomalt is characterized by small air bubbles of less liquid mass that adhere tightly to each other; in 15% of cases, the air space of the foam bubbles is slightly increased. As for the 10% and 5% cases, the spatial forms of foam bubbles with a large amount of liquid mass are increased.

To finally determine the optimal amount of isomalt, in the next stage of the study we studied the effect of its concentration and active pharmaceutical ingredient (Mastic gum 0.25 g, quantity determined on the basis of preliminary pharmacological studies) on foam stability, quality and density. The results are presented in Table 1.

It can be observed from the results (Table 1) that the foam density, stability, and quality improve in direct proportion to the filler-isomalt concentration. The appropriate concentration of foam filler - isomalt - was determined to be 20% based on the results. Mastic gum, on the other hand, has been determined to have no detrimental impact on the foam quality.

At the next stage of the research, the physicaland technological properties of the dry foam system were determined. The results are presented in Table 2.

The results in Table 2 show that the powder looseness of the foam system including Mastic gum is low, with extremely tiny particles and a high degree of particle density, which is most likely attributable to hygroscopicity.

The final stage of the research was devoted to determine the formulation of capsules with containing a foaming powder of mastic gum and development of the technology. In order to improve the physical-technological properties, the following substances were selected as excipients: dry egg protein, metocell group substances - metocell K100, metocell K15, metocell M102, as well as sodium hydrocarbonate, citric acid, talc and calcium stearate. To ensure the foaming ability of the capsules, gas-forming agents were added to them: sodium bicarbonate and citric acid.

Table 1. Results of the study of the influence of isomalt concentration and Mastic gum on the stability, quality and density of foam

Izomalt concentration	**Foam density, (g/sm³)**	**Foam stability (min), ml**	**Foam quality, (%)**
	Permissible limits according to NTD		
	0.2-0.7 g/sm³	**45 min, 0-10 ml**	**96-100%**
5%	0.36	45 min, 23 ml	66% (low)
10%	0.39	58 min, 16 ml	78% (low)
15%	0.48	73 min, 10 ml	85% (medium)
20%	0.67	90 min, 0 ml	96% (high)
Mastic gum, 0,25g	0.67	90 min, 0 ml	97% (high)

Table 2. Results of determination of physical and technological characteristics of the foam system containing Mastic gum

Physical and technological characteristics	Results
Description	Yellowish, brown amorphous powder
Particle shape and size	Spherical crystals, measuring 131.34-189.28 μm
Flow rate g/s	2,19
Angle of difference, ^{0}	15,1±1,23
Bulk density, g/sm^3	0,64±0,05
Tapped density g/sm^3	0,77±0,12
Moisture content, %	0,82±0,20

Table 3. Foam capsules formulations containing Mastic gum

Substances name	Formulation code and content of substances in capsules, mg											
	A1	A2	A3	A4	B1	B2	B3	B4	C1	C2	C3	C4
Mastic gum	250	250	250	250	250	250	250	250	250	250	250	250
SLS	9	9	9	9	9	9	9	9	9	9	9	9
Lecithin	12,6	12,6	12,6	12,6	12,6	12,6	12,6	12,6	12,6	12,6	12,6	12,6
Xanthan	4,5	4,5	4,5	4,5	4,5	4,5	4,5	4,5	4,5	4,5	4,5	4,5
Gelatine	4,5	4,5	4,5	4,5	4,5	4,5	4,5	4,5	4,5	4,5	4,5	4,5
Isomalt	90	90	90	90	90	90	90	90	90	90	90	90
Dry egg protein	38	35	32	34	24	22	41	30	25	32	20	39
Sodium-bicarbonate	18	21	24	30	27	33	21	26	31	28	31	21
Citric acid	6	7	9	10	9	11	6	10	8	7	10	7
Metocell K100	9	-	-	-	12	-	-	-	12	-	12	-
Metocell K15	-	9	-	-	-	7	-	8	-	9	-	-
MetocellM102	-	-	9	10	-	-	10	-	-	-	-	8
Talc	3,4	3	5,4	2,4	4	-	1,4	2,4	1	-	2,4	1,4
Calcium stearate	5	4,4	-	3	3,4	6,4	-	3	2,4	3,4	4	3
Average mass	450	450	450	450	450	450	450	450	450	450	450	450
Features	**Results of biopharmaceutical evaluation**											
Foaming start time, No more than 5 minutes	4,21	4,24	7,41	5,31	4,42	5,17	3,48	5,71	4,31	5,64	4,43	4,38
Foam volume, ml. Not less than 45 ml	34,2	31,3	39,4	36,2	34,1	30,1	41,1	36,3	38,1	35,3	34,6	35,8
Foam half-life time, min. Notless than 40 minutes	38,1	44,3	42,7	45,4	42,1	46,4	51,5	47,1	49,3	46,2	44,5	46,1

Interaction of sodium bicarbonate with citric acid and solubility area (hydrochloric acid) results in the formation of carbon dioxide (CO2) bubbles; as a consequence the release of a significant portion stimulates the formation of foam. Using selected excipients, 12 formulations for the powder-capsule of the foam system containing Mastic gum were compiled. The compositions are listed in Table N3. Based on biopharmaceutical studies, was evaluated Mastic gum containing capsules foam forming ability in artificial gastric juice and their stability. The results are presented in Table 3.

Formulation B3 (Table 3) is optimal according to the onset of foaming, foam volume and foam half-life of Mastic gum capsules.

Conclusions:Based on biopharmaceutical studies, the formulation of capsules containing a foaming powder composition was determined, mg: Mastic gum 250.0; Sodium lauryl sulfate (SLS) - 9.0; Lecithin - 12.6; Xanthan 4.5; Gelatin 4.5; Isomalt 90.0; Dry egg whites - 41.0; Sodium bicarbonate - 21.0; Citric acid - 6.0; Metocell M102 - 10.0; Talc - 1,4.

The technology of preparation of Mastic gum foaming powder containing capsules has been developed.

Foaming capsules containing Mastic gum, in artificial gastric juice, with foam-forming ability and foam stability meet the standard requirements for foam systems.

REFERENCES

1. Verma A, Dubey J, Hegde RR, Rastogi V, Pandit JK. Helicobacter pylori: past, current and future treatment strategies with gastroretentive drug delivery systems. // J Drug Target. 2016 Dec;24(10):897-915. doi: 10.3109/1061186X.2016.1171326. Epub 2016 Apr 19. PMID: 27027827.
2. Farkas D., Kallai-Szabo N., Antal I. Foams as carrier systems for pharmaceuticals and cosmetics. // Acta Pharmaceutica Hungarica. 10.33892/aph.2019.89.5-15.
3. Ierardi E, Losurdo G, Fortezza RF, Principi M, Barone M, Leo AD. Optimizing proton pump inhibitors in Helicobacter pylori treatment: Old and new tricks to improve effectiveness. // World J Gastroenterol. 2019 Sep 14;25(34):5097-5104. doi: 10.3748/wjg.v25.i34.5097. PMID: 31558859; PMCID: PMC6747288.
4. Jung YS, Lee SH, Park CS, et al. Trends in the eradication rates of Helicobacter pylori infection in Daegu and Gyeongsangbuk-do, Korea: multicenter study over 13 years. // Korean J Gastroenterol 2014; 63:82–9
5. Peleteiro B, Bastos A, Ferro A, et al. Prevalence ofHelicobacter pylori infection worldwide: a systematic reviewof studies with national coverage. // Dig Dis Sci 2014; 59:1698–709.
6. Parreira P, Fátima Duarte M, Reis CA, Martins MC. Helicobacter pylori infection: A brief overview on alternative natural treatments to conventional therapy. // Crit Rev Microbiol. 2016;42(1):94-105. doi: 10.3109/1040841X.2014.892055. Epub 2014 Mar 10.
7. Pachi VK, Mikropoulou EV, Gkiouvetidis P, Siafakas K, Argyropoulou A, Angelis A, Mitakou S, Halabalaki M. Traditional uses, phytochemistry and pharmacology of Chios mastic gum (Pistacia lentiscus var. Chia, Anacardiaceae): A review. // J Ethnopharmacol. 2020 May 23;254:
8. Karakashev SI, Grozdanova MV. Foams and antifoams. // Adv Colloid Interface Sci. 2012 Aug-Sep;176-177:1-17. doi: 10.1016/j.cis.2012.04.001. Epub 2012 Apr 13. PMID: 22560722.
9. Chandrasekar V., Swamy GJ, Kannan K., Sangamithra A. Effect of foaming agent concentration and drying temperature on physiochemical and antimicrobial properties of foam mat dried powder. // Asian J. Dairy & Food Res., 34 (1) 2015: 39-43.
10. Hu Y, Zhu Y, Lu NH. Novel and Effective Therapeutic Regimens for Helicobacter pylori in an Era of Increasing Antibiotic Resistance. // Front Cell Infect Microbiol. 2017 May 5;7:168. doi: 10.3389/fcimb.2017.00168.

SUMMARY

РАЗРАБОТКА РЕЦЕПТУРЫ И ТЕХНОЛОГИИ ПЕНООБРАЗОВАТЕЛЯ ИЗ МАСТИЧНОЙ (PISTACIA LENTISCUS L.) КАМЕДИ

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An acid fraction derived from the evergreen plant of Mastic gum(Pistacia lentiscus L., family Anacardiacae, genus Pistacis L.) has been found to have bactericidal activity against 11 strains of Helicobacter pylori. However its healing potential is significantly reduced by poor solubility and low biological penetration. Therefore, the current problem is to develop a system that provides increased penetration of the drug into the stomach through the epithelial barrier. Foams are especially interesting in this regard.

Foams are light systems, they do not swell, on the contrary, they grow in volume, completely covering the mucous membrane. The foams do not require taste correction and are designed to deliver a therapeutic substance from the skin and mucous membranes and provide an effective treatment.

The aim of the research was the determination of formulation and development of technology of innovative medicinal form from Mastic gum.

Based on biopharmaceutical studies, the formulation of capsules containing a foaming powder composition was determined: Mastic gum 250.0; Sodium lauryl sulfate (SLS) - 9.0; Lecithin - 12.6; Xanthan 4.5; Gelatin 4.5; Isomalt 90.0; Dry egg whites - 41.0; Sodium bicarbonate - 21.0; Citric acid - 6.0; Metocell M102 - 10.0; Talc - 1,4.

The technology of preparation of Mastic gum foaming powder containing capsules has been developed.Foaming capsules containing Mastic gum, in artificial gastric juice, with foam-forming ability and foam stability meet the standard requirements for foam systems.

Keywords: Helicobacter pylori, eradication, biologically active substances, Mastic gum (Pistacia lentiscus Linn.) and Foams.

РЕЗЮМЕ

РАЗРАБОТКА РЕЦЕПТУРЫ И ТЕХНОЛОГИИ ПЕНООБРАЗОВАТЕЛЯ ИЗ МАСТИЧНОЙ (PISTACIA LENTISCUS L.) КАМЕДИ

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Кислая фракция, полученная из вечнозеленого растения мастиковой камеди (Pistacia lentiscus L., семейство Anacardiacae, род Pistacis L.), обладает бактерицидной активностью в отношении 11 штаммов *Helicobacter pylori*. Однако ее целебный потенциал значительно снижается ввиду плохой растворимости и низкой биологической проникающей способности. Поэтому актуальной задачей является разработка системы, обеспечивающей повышенное проникновение препарата в желудок через эпителиальный барьер. Особенно интересны в этом отношении пены.

Пены – это легкие системы, они не набухают, а наоборот, увеличиваются в объеме, полностью покрывая слизистую оболочку. Они не требуют коррекции вкуса и предназначены для доставки лечебного вещества с кожи и слизистых оболочек и обеспечения эффективного лечения.

Цель исследования - определение рецептуры и разработка технологии инновационной лекарственной формы из мастиковой камеди.

На основании биофармацевтических исследований определена рецептура капсул, содержащих состав пенообразующего порошка: мастиковая камедь - 250,0; лаурилсульфат натрия (SLS) - 9,0; лецитин - 12,6; ксантан - 4,5; желатин - 4,5; изомальт - 90,0; сухие яичные белки - 41,0; гидрокарбонат натрия - 21,0; лимонная кислота - 6,0; метоцелл M102 - 10,0; тальк - 1,4.

Разработана технология приготовления пенообразующего порошка мастиковой камеди и её содержащих капсул. Пенообразующие капсулы, содержащие мастиковую камедь в искусственном желудочном соке, обладающие пенообразующей способностью и стабильностью пены, соответствуют нормативным требованиям к пенным системам.

რეზიუმე

დანამასტაკის (Pistacia lentiscus L.) გუმფისისაგან ქაფწარმომქმნელი ფხვნილის რეცეპტურის განსაზღვრა და ტექნოლოგიის დამუშავება

[1]რ. ზაზაძე, [1]ლ. ბაკურიძე, [1]ლ.ჩაველაშვილი, [2]ნ. გონგაძე, [1]ა. ბაკურიძე

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, [1]ფარმაცევტული ტექნოლოგიების დეპარტამენტი; [2]სამედიცინო ფარმაკოლოგიის დეპარტამენტი, საქართველო

მარადმწვანე მცენარის, დანამასტაკის (Pistacia lentiscus L., ოჯახი Anacardiacae, გვარი Pistacis L.) ხის გუმფისისგან მიღებულ მჟავა ფრაქციას, აღმოაჩნდა ჰელიკობაქტერია პილორის (Helicobacter Pylori) 11 შტამის მიმართ ბაქტერიციდული მოქმედება. თუმცა მის სამკურნალო პოტენციალს მნიშვნელოვნად ამცირებს ცუდი ხსნადობა და დაბალი ბიოლოგიური შეღწევადობა. აღნიშნულიდან გამომდინარე, აქტუალურ პრობლემას წარმოადგენს ისეთი სისტემის შემუშავება, რომელიც უზრუნველყოფს კუჭში სამკურნალო ნივთიერების შეღწევადობის გაზრდას ეპითელური ბარიერის გავლით. ამ მხრივ განსაკუთრებით საინტერესოა ქაფები.

ქაფები – მსუბუქი სისტემებია, ისინი არ გამოილექებიან, პირიქით იზრდებიან რა მოცულობაში, სრულად ფარავენ ლორწოვან გარსს. ქაფები არ საჭიროებს გემოს კორექციას და განკუთვნილია კანიდან და ლორწოვანი გარსიდან სამკურნალო ნივთიერების მიწოდებისა და ეფექტური მკურნალობისთვის.

კვლევის მიზანს წარმოადგენდა დანამასტაკის გუმფისისაგან ინოვაციური სამკურნალწამლო ფორმის – ქაფოვანი სისტემის, რეცეპტურის განსაზღვრა და ტექნოლოგიის დამუშავება.

ბიოფარმაცევტული კვლევების საფუძველზე განისაზღვრა ქაფწარმომქმნელი ფხვნილის კომპოზიციის შემცველი კაფსულების ფორმულაცია: დანამასტაკის გუმფისი 250,0; ნატრიუმის ლაურილსულფატი (SLS) – 9,0; ლეციტინი - 12,6; ქსანტანი - 4,5; ჟელატინი - 4,5; იზომალტი - 90,0; მშრალი კვერცხის ცილა - 41,0; ნატრიუმის ჰიდროკარბონატი - 21,0; ლიმონის მჟავა - 6,0; მეტოცელ M102 – 10,0; ტალკი - 1,4.

დამუშავებულია დანამასტაკის გუმფისის შემცველი ქაფწარმომქმნელი ფხვნილის და მისი შემცველი კაფსულების მომზადების ტექნოლოგია. დანამასტაკის გუმფისის შემცველი ქაფწარმომქმნელი კაფსულები, ხელოვნური კუჭის წვენში, ქაფწარმოქმნის უნარით და ქაფის სტაბილურობით აკმაყოფილებს ქაფოვანი სისტემების მიმართ სტანდარტის მოთხოვნებს.