

## ТЕХНОЛОГІЯ ЛІКАРСЬКИХ ПРЕПАРАТІВ

*Recommended by Doctor of Pharmacy, professor T.G.Yarnykh*

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### METHODOLOGY OF CREATING AN ENCAPSULATED DOSAGE FORM WITH BEE PRODUCTS. REPORT II

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*Key words: bee products; granules; capsules; antiulcer effect*

*On the basis of experimental studies the authors have demonstrated that a topical issue of the pharmaceutical science today is development of the rational therapeutic dosage forms based on standardized biologically active substances of bee products that have specific chemical and pharmacological properties for new domestic, natural, highly effective drugs for prevention and treatment of ulcer diseases of the human gastroduodenal area. The pharmaceutical market of drugs with the antiulcer activity of different dosage forms has been analyzed. It has been found that dosage forms produced in a small range are economically and socially efficient for further development of a completely new drug based on bee products. Today science has proven that encapsulated dosage forms are promising. This dosage form is a cost effective, and allows to encapsulate various drugs from substances in the solid state to liquid and pasty ingredients. Research in recent years has confirmed that the choice of a rational dosage form of drugs in combination with excipients provide the optimal pharmacological effect of drugs under development, which production is possible both in industrial and pharmacy conditions.*

The study of natural medicinal resources of our country in order to seek new sources of biologically active substances and creation of national drugs on their basis is a topical issue of pharmacy.

Continuing the experiments with the results presented in the publication [2] the aim of this study was to develop an optimal composition and the rational technology of a solid dosage form – capsules for treating ulcerative gastroduodenal diseases.

As for this problem, bee products (pollen, propolis, honey, bee venom, royal jelly, bee bread) are of particular interest as sources of the raw material. Volumes of their procurement in Ukraine (the data of 1995) are: propolis – 20 tons, pollen – 100 tons, bee venom – 200 kg, honey – 40,000-60,000 tons, royal jelly – 100 kg and wax – 800 tons. This amount is sufficient for industrial production of drugs, besides it is a domestic raw material that is always at hand, and its transport costs are negligible.

Since ancient times bee products are widely used in folk medicine to treat various diseases [19]. Fundamental research of domestic and foreign scientists has proven their high biological value and versatile pharmacological activity (anti-inflammatory, antimicrobial, anesthetic, antioxidant, immune-stimulating, antiradiation, antiulcer, hepatoprotective, etc.). Moreover, they are practically harmless to the human body [2, 3, 4, 8, 10, 15, 18].

Today specialized companies of Romania, Germany, France, Spain, Canada, Japan, Czech Republic and

others produce a rich variety of bee products. In addition, analysis of the literary data has shown that a lot of publications are devoted to the research concerning the use of apidrugs in medical practice: in dermatology, surgery, gynecology, otolaryngology, dentistry and especially gastroenterology [3]. For example, in the treatment of stomach ulcers disappearance of heartburn, pain, improvement of appetite and the patients' general state are observed from the first days of administration of a combination of propolis with rosehip oil and vitamin E [3, 8, 10].

In treatment of chronic gastritis with low acidity of the gastric juice a good result is achieved when using honey and kalanchoe emulsions with propolis and aloe juice. This treatment promotes regeneration of the mucous membrane of the stomach, improves the blood circulation and stimulates the gastric secretion. In cases when intake of honey causes heartburn, propolis and oil solution with vitamin E is used.

The advantage of apidrugs is the fact that they (unlike, for example, antibiotics) do not damage the normal intestinal microflora, and only inhibit pathogens (this treatment does not lead to dysbiosis) [8]. Moreover, if antibiotics inhibit the body's defenses, on the contrary, drugs with propolis stimulate them. They also have other pharmacological properties that are very useful in the treatment of peptic ulcer and other gastrointestinal diseases [8, 19].

Propolis drugs are multi-component systems of biologically active substances. They contain more than 50 sub-

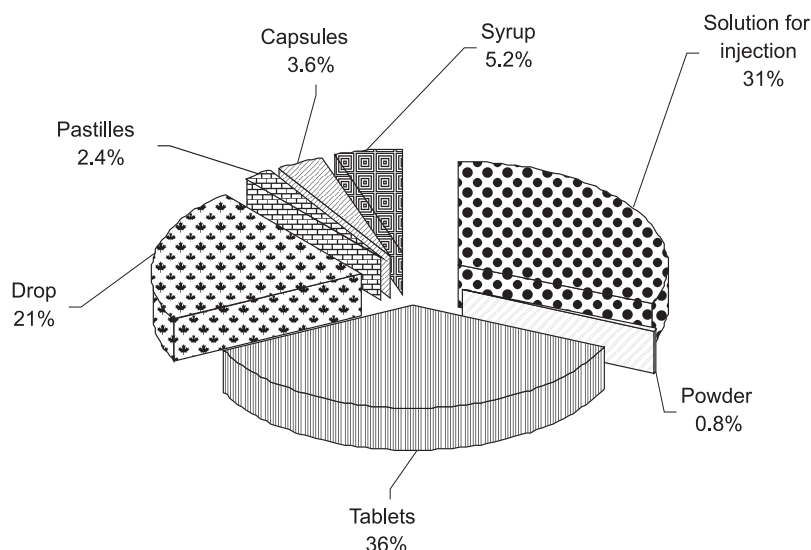


Fig. 1. The share of capsules at the pharmaceutical market compared to other dosage forms for internal administration.

stances of different chemical poisons. The main groups are resins, balms, essential oils and wax, as well as minerals, vitamins, amino acids (from 8 to 17) and others. It has been found that flavonoids are more than 25% of all components of propolis.

Investigations of such researchers as S.A.Popravko, O.I.Tikhonov, V.I.Litvinenko and others have shown that flavones (luteolin, apigenin, etc.), flavonols (quercetin, kaempferol, etc.), flavanones, phenolic acids (caffeic, coumaric, ferulic, etc.) are in the composition of propolis. The presence of terpenoids, such as acetoxybetulenol, bisabolol, aromatic aldehyde, isovanillin, benzoic acid has been also found. In this regard, academician Tikhonov O.I. developed waste-free processing of the raw propolis, and it allowed to offer the Ukrainian healthcare a number of purified biologically active standardized substances of propolis and apidrug created on their basis [4, 5, 6, 7, 8].

Taking into consideration the abovementioned, we have studied almost all types of dosage forms, which are the most optimal for development of drugs, have a high therapeutic efficacy, bioavailability, and are currently being developed in a small range. As can be seen from Fig. 1, the most interesting is the dosage form in the form of capsules.

Capsules are a very common dosage form in developed countries. For example, in the USP XXIII there are more than 220 articles on capsules, in the BP 1993 they are over 50. This dosage form allows to encapsulate various drugs: hard capsules filled with substances in the solid state (powders, granules, microcapsules, etc.), soft capsules filled with liquid and pasty ingredients. Pure substances, without any additives (e.g. antibiotics) are often used as the content of capsules. In the pharmaceutical industry a direct filling of capsules with medicinal substances is quite common. But some of them do not meet the technological requirements of industrial equipment by their physical and chemical characteristics and can not be filled to the capsular shell without using the special methods to eliminate their technological disadvantages. For example, granulation, introduction of excipients, etc., are widely used.

Capsules are a dosage form; they are often intended for internal use, more rarely for vaginal, rectal, and other routes of administration. There are two types of capsules: soft gelatin capsules (*Capsules molles*) and solid ones with caps (*Capsules dure averculatae*).

Recognition of a capsule dosage form and the growing interest to it is explained by a high bioavailability and a number of advantages. They have a good appearance, can eliminate a bitter taste, an unpleasant appearance or odour of medicinal substances, and many peculiarities such as:

**Stability.** In the manufacture of capsules medicinal substances are not exposed to heat, encapsulation of drugs can be intact (without wet granulation, pressure). Sealed capsule keeps medicinal substances from microbial contamination, exposure to air, light, moisture, dust, mechanical external actions, fluctuations in temperature. Furthermore, the capsule shell provides protection of the mucous membranes from the irritant action of certain medicines, and the latter, in turn, from the destructive effect on digestive enzymes.

**A high bioavailability.** Gelatin capsules are readily soluble, permeating for digestive juices, and the pharmacological action of the medicinal substance reveals rather quickly (in an average of 4-8 min).

Rather high bioavailability of encapsulated dosage forms is explained by the fact that the composition of the shell includes gelatin – the product of partial hydrolysis of the collagen-containing raw material. Collagen is the main protein component of fibrous connective tissues of mammals. In the basis of its protein molecule there is a polypeptide chain formed by twelve amino acids, most of which are essential to the human body. The main acids are glycine (27%), proline (16%), oxyproline (14%), lysine (5%) and others. Gelatin is easily and rapidly absorbed even in severe disorders of the gastrointestinal tract; moreover, it is indifferent and non-toxic.

**Ease of use.** Gelatin capsules are odourless and tasteless, and thanks to their shape and surface properties they are easy to use. As mentioned above, the basic ma-

Table

Classification of hard capsules by size

Number	000	00	0	1	2	3	4	5
Average capsule size, cm <sup>3</sup>	1.37	0.95	0.68	0.5	0.37	0.3	0.21	0.13

terial of the shell is gelatin, which is a natural protein that is easily digestible by the body. In oral administration the gelatin shell is wetted with saliva in the mouth, glides well, thus, a capsule slips easily even with a slight gulp. The shell quickly swells and dissolves in the gastrointestinal tract. Capsules can be transparent or opaque, painted in different colours (to prevent photochemical reactions of photosensitive substances, giving capsules a good marketable appearance).

When encapsulating the undesirable effects of moisture (as in wet granulation) or pressure (as in pressing tablets) for some labile substances can be avoided. The content of capsules may be solid or pasty (for gelatin capsules with caps) and consists of one or more medicinal substances with a possible introduction of various excipients approved for medical use.

*Focus of the therapeutic action.* The ability to provide a medicinal product specific properties is achieved by introduction of excipients to the walls of the capsule, their tanning or coating with special films. Due to it, to obtain capsules with different release rates and localization of drug action is possible.

*Physiological inertness.* Modern production of capsules is fully mechanized. With the automated method of filling a high accuracy of dosing (with standard deviation of  $\pm 3\%$ ) and the minimal loss of drugs are guaranteed.

The advantages of gelatin capsules listed provide them a wide distribution in medicine. The disadvantages of capsules include their hygroscopicity, which prevents encapsulation of aqueous solutions, and the need to satisfy certain conditions of storage.

Medicinal substances used to fill gelatin capsules should be dosed at temperatures not exceeding 35°C in order to prevent softening and destruction of capsules. In addition, they should not dissolve the capsule shell, do not have any negative impact, do not evolve gaseous substances, do not increase in volume in order not to cause tearing of capsules, as well as not to cause tanning of capsules from the inside and reduction of their solubility in the gastrointestinal tract.

In industry, to fill gelatin capsules the automated complete production lines equipped with elements of robotics, electronics and microprocessor technology with efficiency of several hundred thousand capsules per shift are used. In addition to the main technological processes in manufacturing capsules there are auxiliary processes associated with regeneration of wastes, sorting and packing capsules, etc. On the automated lines capsules closed with caps are delivered automatically from the storage drum, substandard and nonstandard capsules are rejected, other capsules are oriented in a position comfortable for filling, caps are opened, capsules are filled with a powdered or granulated medicinal

substance, then they are closed, substandard and empty capsules are rejected and collected in special containers. The filled capsules are delivered for dispensing and packing. Dosing on such automatic lines is carried out by volume using piston-type, vacuum, screw or vibration dosing devices (accuracy of dose  $\pm 2\%$ ).

Hard capsules (see their classification in Table) have the shape of a cylinder with hemispherical ends and consist of two parts: a shell and a cap; both parts must be free to enter one another without forming gaps. The inner diameter of the cap should match the outer diameter of the shell. They have special grooves and projections for the "lock" that prevents opening the capsule during transportation. When connecting two parts they form a standard-size container. Capsules should have a smooth surface with no visible damage and mechanical or air inclusions. For coloration of capsules such dyes as tartrazine, indigo, titanium dioxide, and their various mixtures, which are permitted for medical application, are used.

Gelatin is a favourable medium for the growth and reproduction of microorganisms; in its composition there are stabilizing and preserving agents such as sodium metabisulphate, benzoic acid, sodium benzoate, etc. To prevent dissolution of capsules in the stomach acetophthalate cellulose (4%) is also introduced to the composition of the capsule mass. Sometimes flavouring agents are added into the capsule mass to give a pleasant odour, and sugar as a sugar syrup is added to improve the flavour of the capsule when swallowing. In some cases, medicinal substances that have the local anesthetic action (benzocaine) are introduced to the composition of the gelatinous mass to form a capsule shell [15, 16, 17].

Humidity and temperature are the factors that affect the gelatin capsule quality. For their best storage it is desirable to keep temperature within 15-20°C and humidity should be 30-40%.

Wide possibilities of prescribing drugs in the form of capsules caused an increase in their production and use around the world. After starting the use of antibiotics that have an unpleasant bitter taste in medical practice there was a growing interest of manufacturers to encapsulated dosage forms. Over the past decades (from the 1950-s) there has been production of modern automatic machines for manufacturing gelatin capsules in industrial-scale volumes, and it has become possible to manufacture encapsulated drugs of different pharmacological groups (anticonvulsants, antiarrhythmic agents, hypnotics, sedatives, anthelmintic agents, laxatives, diuretics, hypocholesterolemic agents, tranquilizers and drugs with the antiulcer action) [7, 9].

The growth rate of manufacturing drugs in capsules is far ahead of other similar indicators concerning solid dosage forms (Fig. 2).

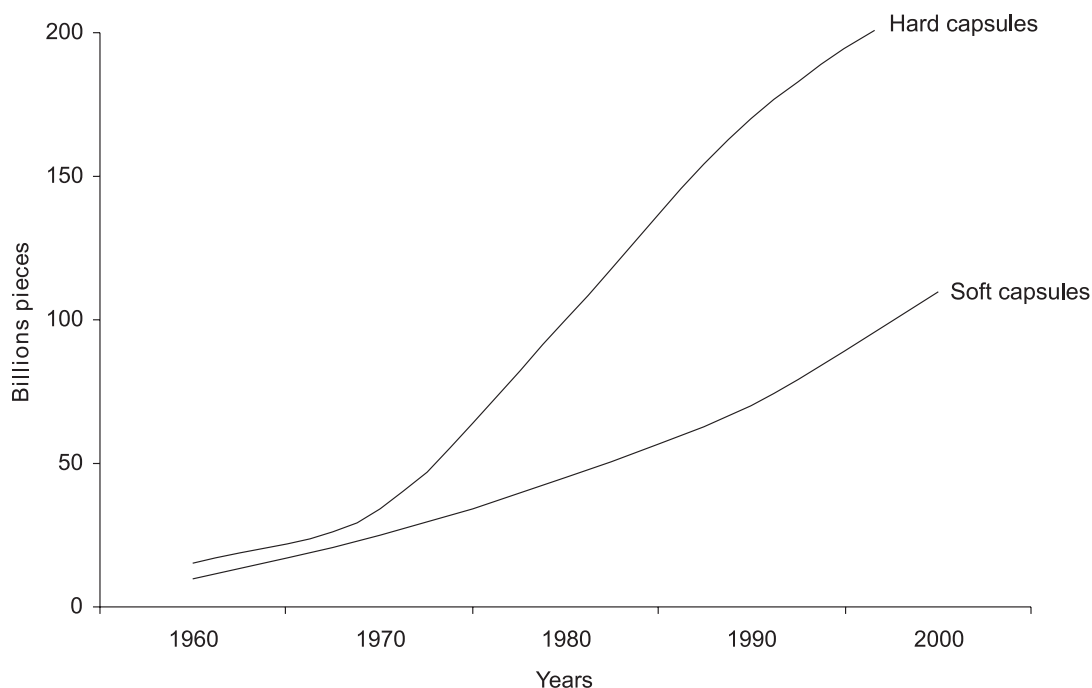


Fig. 2. Production of capsules in the world for the whole period.

But along with this, the nomenclature of encapsulated drugs is small in our country and it is at the stage of development.

Taking into account the abovementioned, we conclude that Ukraine has all the necessary conditions (raw material, research and development, scientific personnel, etc.) for manufacture of domestic solid (capsules) dosage forms from bee products (both in the conditions of a chemist's shop and pharmaceutical factories) and for further development of one of the areas of medicine – apitherapy.

In terms of the above, to solve this problem we have conducted the research on selection and use not only of biologically active substances, but excipients as well.

The term “excipients” summarizes a large group of substances, both of natural and synthetic and semi-synthetic origin. Their use in pharmaceutical technology is always based on the following prerequisites: be indifferent towards the macroorganism; to active ingredients; have forming properties.

In terms of the classical drug technology the latter feature was dominant when choosing and assessing excipients for drug manufacture since a dosage form as the final result is estimated as the form that is the most suitable for application, transportation and storage [17].

With the introduction of the biopharmaceutical concept (G.Levy, J.Wagner) in the pharmaceutical technology in the early 60-s the assessment of excipients as those that provide the creation of a dosage form was changed. At present excipients are considered to be potential carriers of definite biological effects revealed in their combination with medicinal substances. They are an independent integral part of drugs, a component that forms chemical bonds with the active medicinal substance – inclusion compounds. Therefore, introduction of a certain type of excipients in a particular dosage form requires special

studies (biopharmaceutical ones) in terms of their interaction with drugs.

In this respect, science-based application of excipients is one of the objectives of biopharmaceutics – creation of a dosage form with an optimal composition, rational technology and high biological availability [1].

If medicinal substances provide the therapeutic effect of drugs, then excipients serve a dual function: firstly, they help to form the easily dosed mass, and secondly, they provide release of a medicinal substance from the dosage form [11].

The content of excipients should be minimized, or more specifically, it should be optimal, so that their influence reduces to facilitating technology and providing physiological availability. In this regard, the number of some excipients is regulated by certain limits. Thus, the total number of excipients should not exceed 20% of the mass of medicinal substances (excluding diluents, their number is not subjected to limitation). The amount of talc should not exceed 3%, stearic acid, calcium stearate or magnesium, Tween-80 should be 1% of the total mass.

All excipients must be chemically indifferent, do not have a negative effect on the quality of mixtures in their preparation, transportation and storage, should maximize the assimilation of active ingredients by the body. Depending on their purpose they are divided into the following groups: diluents, disintegrating agents lubricants, adhesives, adsorbents, corrigents.

The group of diluents include substances that are used to produce the required weight of capsules when a medicinal substance is in their composition in small doses (0.01-0.001 g). The main substances used for this purpose are beet and milk sugar, glucose, sodium chloride, urea, calcium sulphate, basic magnesium carbonate, calcium hydrogen phosphate, etc. Mannitol, sorbi-

tol, bentonite, sodium bicarbonate, dextrose, starch can be used as a diluent. Recently the arsenal of fillers has been replenished with such substances as cellulose derivatives, modified starches and others. Numerous studies have demonstrated the possibility of using cellulose derivatives, including microcrystalline cellulose, etc., as fillers [8, 14].

The USP also recommends such diluents as calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, microcrystalline cellulose, powdered cellulose, dextrates, dextrin, dextrose, fructose, kaolin, lactose, mannitol, sorbitol, starch, gelatinous starch, sucrose, pressed sugar, confectioner's sugar.

The role of diluents in the manufacture of capsules is rather significant: they largely determine stability of a drug, the extent and rate of its digestion.

Lubricants are substances that improve the flowability of the powder mixture when filling of capsules, as well as reduce adhesion of the mass to machine parts, collectors, etc. Improved flowability of the material is needed for fast, accurate and uniform filling of capsules. As a result of good lubricity of the mass, the continuous operation of the encapsulation system and uniform dispensing of drugs are achieved.

Substances that enhance lubricity include calcium stearate, glycerol behenate, clarified mineral oil, polyethylene glycol, stearine sodium fumarate, purified stearic acid, talc, hydrogenated vegetable oil, zinc stearate, starch, fat-free milk powder, aerosil, calcium silicate, magnesium silicate, colloidal silica. Recently the use of talc is limited because it is not indifferent [19].

To reduce sticking of the material to machine parts the substances, which are often called antiadherent substances or adhesives such as stearic acid, its calcium and magnesium salts, hydrocarbons (ceresin, liquid and solid paraffin) silicon carbon, are used.

By the mechanism of the lubricity action lubricants are divided into three groups:

- substances that improve the flowability of granules (starch, talc, polyethylene glycol, aerosil);

- antiadhesive substances (stearic acid, paraffin, silicone lubricants);
- substance of the mixed type (calcium, magnesium, and aluminum stearate).

Adsorbents are substances added to the powder mixture in cases where it is composed of oils, fats and hygroscopic components. Absorbing the excessive moisture adsorbents provide flowability of the mass, that is why they are also called hydrostats. Bentonites, kaolin, aerosil, magnesium oxide and basic carbonate, aluminum oxide hydrate are also used as adsorbents.

There is no sense to use corrigents in the manufacture of capsules because the gelatin shell masks the taste and odour of medicinal substances; in addition, they do not require introduction of a binder if the manufacturing process does not include the stage of preliminary granulation [7, 14].

Analyzing the abovementioned, the next stage of our research will be to identify physical, chemical and technological properties and characteristics of standardized biologically active substances of bee products, excipients and their mixtures for creating an encapsulated dosage form, i.e. fluidity, the angle of repose, bulk weight, bulk density, moisture content and moisture absorption, selection of the number of capsules by the known methods.

#### CONCLUSIONS

1. It has been shown that a topical issue of the pharmaceutical science today is development of the rational therapeutic dosage forms for prevention and treatment of ulcer diseases of the human gastroduodenal area.

2. The pharmaceutical market of drugs with the anti-ulcer activity of different dosage forms has been analyzed.

3. Research in recent years has confirmed that the choice of a rational dosage form of medicinal substances in combination with excipients provide the optimal pharmacological effect of drugs under development. Today encapsulated dosage forms are promising; their production is possible both in industrial and pharmacy conditions.

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### **МЕТОДОЛОГІЯ СТВОРЕННЯ КАПСУЛЬОВАНИХ ЛІКАРСЬКИХ ФОРМ З ПРОДУКТАМИ БДЖІЛЬНИЦТВА. Повідомлення II**

**Н.С.Богдан, О.І.Тихонов**

**Ключові слова:** продукти бджільництва; гранули; капсули; противиразкова дія

На основі експериментальних досліджень авторами показано, що актуальною темою фармацевтичної науки сьогодення є розробка раціональних терапевтичних лікарських форм на основі біологічно активних стандартизованих субстанцій продуктів бджільництва, які мають специфічні хімічні і фармакологічні властивості для створення нових вітчизняних, природних, високоефективних лікарських засобів для профілактики та лікування виразкових захворювань гастродуоденальної зони людини. Проаналізовано фармацевтичний ринок лікарських препаратів противиразкової активності різних лікарських форм і з'ясовано, що лікарські форми, які виробляються в незначному асортименті, є економічно і соціально доцільними для подальшої розробки нового лікарського препарату на основі продуктів бджільництва. На теперішній час наукою доведено, що перспективними у даних дослідженнях є капсульовані лікарські форми. Досліджувана лікарська форма економічно вигідна та дозволяє капсулювати різноманітні лікарські засоби: від речовин, які знаходяться в твердому стані, до рідких і пастоподібних інгредієнтів. Науковими дослідженнями останніх років підтверджено, що вибір раціональної лікарської форми лікарських речовин у комплексі з допоміжними сполуками забезпечує оптимальну фармакологічну дію розроблюваних препаратів, виготовлення яких можливе як у промислових, так і в аптечних умовах.

### **МЕТОДОЛОГІЯ СОЗДАНИЯ КАПСУЛИРОВАННЫХ ЛЕКАРСТВЕННЫХ ФОРМ С ПРОДУКТАМИ ПЧЕЛОВОДСТВА. Сообщение II**

**Н.С.Богдан, А.И.Тихонов**

**Ключевые слова:** продукты пчеловодства; гранулы; капсулы; противоязвенное действие

На основе экспериментальных исследований авторами показано, что актуальной темой фармацевтической науки сегодня является разработка рациональных терапевтических лекарственных форм на основе биологически активных стандартизованных субстанций продуктов пчеловодства, которые имеют специфические химические и фармакологические свойства для новых отечественных, природных, высокоэффективных лекарственных средств для профилактики и лечения язвенных заболеваний гастродуоденальной зоны человека. Проанализированы фармацевтический рынок лекарственных препаратов противоязвенной активности различных лекарственных форм и выяснено, что лекарственные формы, которые производятся в незначительном ассортименте экономически и социально целесообразны для дальнейшей разработки нового лекарственного препарата на основе продуктов пчеловодства. Сегодня наукой доказано, что перспективными в данном исследовании являются капсулированные лекарственные формы. Данная лекарственная форма экономически выгодна и позволяет капсулировать различные лекарственные средства, начиная с веществ, которые находятся в твердом состоянии, до жидких и пастообразных ингредиентов. Научными исследованиями последних лет подтверждено, что выбор рациональной лекарственной формы лекарственных веществ в комплексе со вспомогательными соединениями обеспечивает оптимальное фармакологическое действие разрабатываемых препаратов, изготовление которых возможно как в промышленных, так и в аптечных условиях.