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SUBSTANTIATION OF THE COMPOSITION OF «GLYAKAMF» CAPSULES WITH THE HYPOGLYCEMIC ACTION

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On the basis of a comprehensive study the optimal composition of capsules with the hypoglycemic action has been developed. The research results have shown that kinetics of the active substances release depends on a filler. It has been experimentally proven that the optimal content of a capsule is 500 mg.

Despite the significant advances in the field of diabetology that have been achieved in the last 20 years, the problem of diabetes continues to be relevant. Moreover, type 2 diabetes (D2), which is 85-90% of patients with diabetes, is a serious medical and social problem of the XXI-th century. Medical and social significance of D2 is determined, above all, by its severe cardiovascular and neurological complications leading to early disability and high mortality, reduction in duration and the quality of life [6, 7, 11, 12, 13].

Production technology largely determines the stability of the product, its rate of release from the dosage form, the intensity of absorption – that is, therapeutic efficacy [2, 4, 5].

The choice of the dosage form is important because it promotes the patient's treatment efficiency. Taking this into account, capsules have been chosen as a dosage form for development of a drug with the hypoglycemic action [1, 12].

The aim of our work was to study the hypoglycemic action of some substances and their combinations for further development of a new drug that would have the hypoglycemic effect. As the compounds under research we have chosen four substances, namely, glibenclamide, glysulfaside, metformin and diacamph that differ in their chemical structure and have different mechanisms of influence on pathophysiological chains of D2.

The highest hypoglycemic activity has been shown by the combination of glibenclamide with metformin, glysulphazide with metformin and glysulphazide with diacamph. But having almost identical hypoglycemic activity the combination of glysulphazide-diacamph has shown longer hypoglycemic effect (up to 14 hours). This effect may be due to the fact that the substances used in this combination by the direction of action complement each other, namely, glysulphazide increases insulin secretion and diacamph reduces metabolic manifestations of insulin resistance: increases the tissues sensitivity to insulin, improves tolerance to carbohydrates and inhibits gluconeogenesis [1].

The above results show that diacamph and glysulphazide can complement each other action concerning the work of the body insular apparatus, therefore, on this basis the conclusion can be made about expediency of the combination of these two substances to create a new drug to use for the treatment of D2.

Thus, according to the results of the research as active ingredients for development of the combined product a combination of the following substances have been chosen: glysulphazide and diacamph in the ratio of 0.5 / 0.5 of the maximum effective dose of each substance [1].

Materials and methods

To improve the technological properties of the mixture of glysulphazide and diacamph for encapsulation we have determined the impact of such groups of excipients as diluents and glidants on the technological properties of the mass [5]. The research was carried out based on the fact that one capsule would contain 400 mg of the mixture of the active substances (200 mg of each substance). As excipients the widespread and relatively cheap ingredients applied in pharmaceutical manufacture were used: namely apple pectin, sodium bicarbonate, potato starch, corn starch, lactose and sorbitol were used as diluents, calcium and magnesium stearate and aerosil were used as glidants [5].

Flowability of the mixture was the criteria for evaluation. To provide rhythmical work of the capsule machine and precision of dosing the mixture into the capsule it is necessary that the mass for encapsulation has good indicators of flowability. None of the samples developed has shown satisfactory fluidity. Thus, on the basis of the research conducted one may state that it is not expedient to improve the technological properties of the mixture for encapsulation by introducing only the excipients.

Thus, improving the fluidity of the mixture of glysulfaside and diacamph should be attained by other means, namely, increasing of the particle size by granulation.

Results and discussion

Granulation is necessary to improve the fluidity of the powder mass that occurs as a result of a significant decrease in the total surface of the particles during their adhesion to the granules and thus reducing friction appeared between the particles in motion. The resulting granulate at equal sizes of the granules obtained gains fairly constant bulk density. An important role is also played by resistance of granules: strong granules are less prone to abrasion and have better fluidity.

Among the methods of granulation the most common in pharmaceutical manufacture is the wet granulation method, which is the cheapest and the easiest to use [6, 8].

Table 1

The wetting indicators of the mixture of active substances

Sample	Moisturizer	Δ θ, deg	Cos θ
1	Potato starch paste, 3%	7.32	0.92
2	Potato starch paste, 5%	6.98	0.88
3	PVP solution, 5%	5.20	0.55
4	PVP solution, 10%	5.60	0.68
5	Methylcellulose solution, 5%	9.16	0.72
6	Purified water	8.12	0.96

Table 2

Disintegration of granules with different fillers

Sample	Time, min	
	Purified water	Model gastric juice
№1	3.4±0.5	4.6±0.5
№2	6.8±0.5	7.6±0.5
№3	3.8±0.5	4.6±0.5
№4	10.4±0.5	11.0±0.5

Note: n=5, P=95%

To investigate the wetting of the mixture of glysulfaside and diacamph the following humidifiers have been chosen: 3 and 5% starch paste, 5 and 10% solution of polyvinylpyrrolidone, 5% methylcellulose gel and water [5, 6]. The wetting angle measured immediately after applying a humidifier and during the experiment was chosen as a criterion and its changes Δθ were calculated. The results are shown in Tab. 1.

Due to the fact that in pharmaceutical manufacture the mixing time of the wet mass for simple mixtures (two- and three-component) is usually about 7-10 minutes and for the complex – 15-20 minutes, we have investigated the behavior of the humidifier for 10 minutes. At the beginning of the experiment the contact angle was taken as 100% and its decrease was investigated in 15 sec and 10 min.

Based on the data obtained the conclusion can be made that all humidifiers show the limited wetting. The lowest value has 5% solution of PVP – the wetting angle of 5% PVP solution drop is virtually unchanged although the mass surface gets moistened. Thus, for further studies 5% polyvinylpyrrolidone solution was chosen as a humidifier.

In sources of scientific literature it has been noted by many researchers that when creating drugs to treat diabetes the effect of hydrocarbons, which are introduced into the drug, should be considered. This is due to the fact that the treatment of the disease is long-termed, and sometimes lifelong, and hydrocarbons can directly affect the condition of the organism and the therapeutic effect.

For further research potato starch, lactose, sodium carbonate and microcrystalline cellulose were chosen as fillers. The samples of the granulate were prepared with starch – №1 with lactose – №2 with sodium bicarbonate – №3 and with MCC – №4. To select a filler for the granulate the disintegration rate of the mass for encapsulation was measured. The study was conducted using purified water and model gastric juice as a solvent. The research results are shown in Tab. 2.

The results presented in the Table 2 show that the lowest solubility of granules is provided by microcrystalline cellulose. And the samples of potato starch and sodium bicarbonate have the best indicators, almost the same results.

Therefore, for further research in choosing a filler the dissolution rate of the drug has been studied. The research has been carried out by UV spectroscopy [3, 10]. The results obtained are shown in Fig. 1, 2.

The research results have shown that kinetics of active substances release depends on the filler. Potato starch

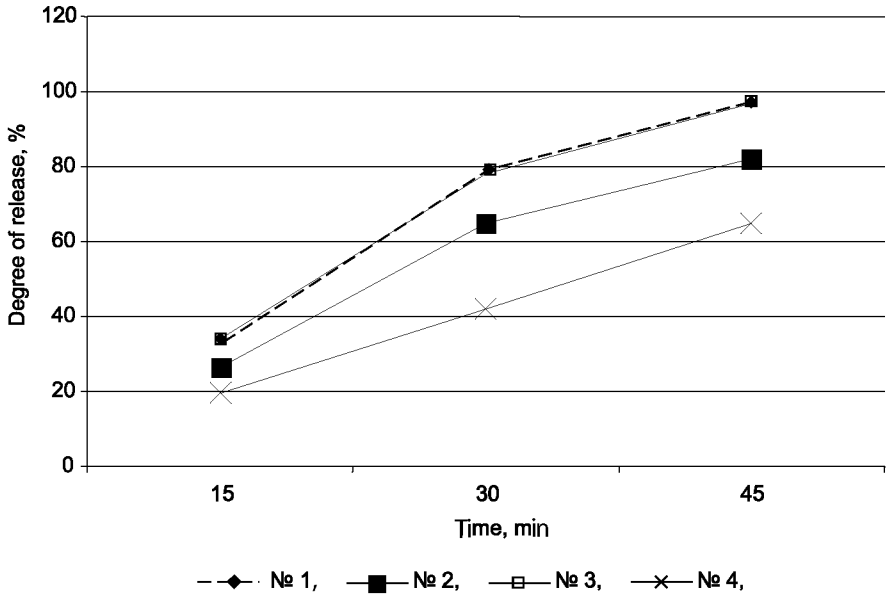

Fig. 1. Kinetics of glysulphazide release.

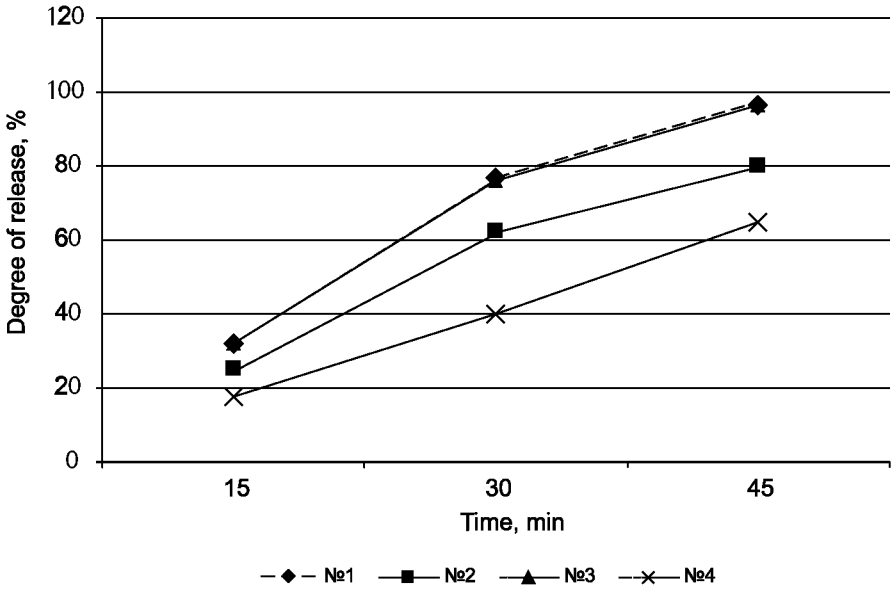

Fig. 2. Kinetics of diacamph release.

and sodium bicarbonate have shown the best results of active substances release.

Considering, according to many sources of literature, the advantages of starch, namely starch is the most often used as an excipient in creating oral hypoglycemic drugs, its contraindications and side effects have not been determined; children patients with diabetes are recommended to use potato starch; starch is a cheap and available product, which is important in industrial production; we have chosen potato starch as a filler for granules in the mixture of glysulphazide and diacamph.

In this regard, we have prepared the granulate with the active substances, potato starch as a filler and 5% solution of polyvinylpyrrolidone as a humidifier. The quantity of the humidifier was determined experimentally before obtaining the mass, which turned into a lump but did not stick to the hands. Granulation was performed by rubbing of a damp and thoroughly mixed mass through a grid with the pore diameter of 2-3 mm. The granulate was then dried, calibrated and powdered by calcium stearate. Calcium stearate was chosen for its technological properties because of its marked sliding properties and the absence of lubricating properties being unnecessary in the production of capsules. The technological characteristics of the resulting granules determined are presented in Table 3.

As Shown by the data, the granulate has satisfactory technological parameters and can be encapsulated by automatic mode capsule machines.

Thus, on the basis of the research when developing granules for encapsulation the optimal composition of capsules under the conditional name «Glyakamf» has been determined.

Table 3

Technological properties of the granules obtained

Indicator	The results obtained
Flowability, sec	19.1±1.1
Natural slope angle, degree	25±1
Bulk density, g/ml	0.60±0.02
Density after settling, g/ml	0.82±0.02
Compaction, g/ml	0.26±0.02

Note: n=5, P=95%

Ingredients per a capsule:

– Glysulphazide – 200 mg
– Diacamph – 200 mg
– Polyvinylpyrrolidone – 25 mg
– Potato starch – 70 mg
– Calcium stearate – 5 mg

The weight of the capsule content – 500 mg.

CONCLUSIONS

1. It has been found that kinetics of release of active substances depends on a filler.

2. On the basis of the research when developing granules for encapsulation the optimal composition of capsules under the conditional name «Glyakamf» has been found to be: glysulphazide – 200 mg, diacamph – 200 mg, polyvinylpyrrolidone – 25 mg, potato starch – 70 mg, calcium stearate – 5 mg.

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ОБОСНОВАНИЕ СОСТАВА КАПСУЛ САХАРОСНИЖАЮЩЕГО ДЕЙСТВИЯ «ГЛИАКАМФ»

М.В.Марченко, Т.В.Крутских

На основании проведенных комплексных исследований разработан оптимальный состав капсул сахароснижающего действия. Результаты исследований показали, что кинетика высвобождения действующих веществ зависит от наполнителя. Экспериментальным путем доказано, что оптимальное содержимое капсулы составляет 500 мг.

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ОБГРУНТУВАННЯ СКЛАДУ КАПСУЛ ЦУКРОЗНИЖУВАЛЬНОЇ ДІЇ «ГЛІАКАМФ»

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На підставі проведених комплексних досліджень розроблено оптимальний склад капсул цукрознижувальної дії. Результати досліджень показали, що кінетика вивільнення діючих речовин залежить від наповнювача. Експериментальним шляхом доведено, що оптимальний вміст капсули складає 500 мг.