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SUBSTANTIATION OF THE CHOICE OF EXCIPIENTS OF "CORVALOL" IN THE FORM OF SUBLINGUAL TABLETS

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Based on the study of the physical properties of the tableting mass the choice of excipients for "Corvalol" sublingual tablets by the method of direct compression has been substantiated. Three model mixtures for tablet formulations have been analyzed. It has been found that the optimal excipients are β -cyclodextrin, lactose monohydrate 80, potassium acesulfame, magnesium stearate. It has been demonstrated that the conclusions made when analysing physical parameters of the tablet formulations are confirmed by actual results of compression.

Sublingual tablets are convenient for the elderly and patients with swallowing problems. This form is also indispensable in emergency situations when it is necessary to take the drug immediately, and drinking liquids are not available. Usually the small volume of saliva is enough to dissolve such tablets completely. Active substances of the tablet enter the blood flow, sucked by the sublingual mucosa directly, or can be swallowed as a solution, followed by absorption in the mucosa of the gastrointestinal tract. By sublingual administration of active substances the therapeutic effect is faster than by oral administration because the drug enters the blood flow by avoiding the primary metabolism in the patient's liver [1-3].

"Corvalol" drops are indispensable for more than 50 years for the functional disorders of the nervous system, disorders of the autonomic nervous system, diseases of the cardiovascular system, spastic pain [4]. In the modern world solid dosage forms have become increasingly popular by displacing liquid forms. This makes development of a drug in tablets similar to "Corvalol" drops promising.

There are many ways for obtaining fast dissolving or fast disintegrating tablets [5, 6]. One of them is the direct compression method, which requires introduction of an effective disintegrator in the tablet formulation or the use of fast dissolving components. The method does not require the use of water or heating during formulation, and it is optimal for active substances that are unstable in water or thermolabile ingredients. However, this method is very sensitive to the type and proportion of excipients in the tablet composition [7].

The aim of this work was to carry out the experimental studies on choosing excipients and their amounts for obtaining "Corvalol" in the form of sublingual fast dissolving tablets by the method of direct compression.

Materials and Methods

The following components were used: β -cyclodextrin ("ISP" GmbH, Switzerland), ethyl ester of α -bromo-isovaleric acid ("Farmak" PJSC, Ukraine), mint oil ("Frey + Lau" GmbH, Germany), phenobarbital ("Harman Finocem" Ltd., India), potassium acesulfame ("Nutri-nova" GmbH, Germany), magnesium stearate ("Trialon"

Research and Production Company, Ukraine), lactose monohydrate 80 ("Merck" GmbH, Germany), lactose monohydrate 200 ("Merck" GmbH, Germany) and sorbitol ("Merck" GmbH, Germany). All substances corresponded to the SPhU requirements and were used without further purification.

Samples preparation: Complexes of β -cyclodextrin with ethyl ester of α -bromo-isovaleric acid and β -cyclodextrin with mint oil were prepared according to the procedure described in [8]. Tablet formulations were prepared using a mixer by stepwise mixing of the components in the container.

Samples of tablet formulations were prepared by using a Glatt CML-10 mixer. Fluidity, the angle of repose and the bulk density of the samples obtained were measured by an Erweka instrument. Compression of tablet formulations was carried out on a Korsch XL100 press.

Results and Discussion

Special attention was paid to the choice of fast dissolving components in the aqueous medium, the use of which would make it possible to obtain a tablet formulation that is suitable for obtaining tablets by direct compression. Fluidity of such tablet formulation must be higher than three grams per second; otherwise, the tablet formulation will stay in the product pipeline of the press. The tablet obtained should have smooth edges and a surface without roughness. The bulk density and the angle of repose are informative values.

Ethyl ester of α -bromo-isovaleric acid and mint oil under normal conditions were converted to a solid form by forming the complexes of inclusion with β -cyclodextrin. Potassium acesulfame was selected as a sweetener to correct the organoleptic properties of tablets. Magnesium stearate was used as a lubricant to avoid sticking of the mixture for tableting to the punches of the press. The weight of the active ingredients in a tablet was chosen in such a way that one tablet corresponded to ten drops of "Corvalol". The content of the components of the model mixtures for tablet formulations are shown in Tab. 1.

By stepwise mixing of the components three variants of mixtures for tableting were obtained, in which fluidity, the angle of repose and the bulk density were determined. The results are shown in Tab. 2.

Table 1

Model mixtures for tablet formulations of "Corvalol" sublingual tablets

The name of the component	The content of the components in the mixture, %		
	Mixture 1	Mixture 2	Mixture 3
Ethyl ester of α -bromo-isovaleric acid	3.10	3.10	3.10
Mint oil	0.22	0.22	0.22
Phenobarbital	2.83	2.83	2.83
β -cyclodextrin	21.44	21.44	21.44
Lactose monohydrate	71.31	–	–
Lactose monohydrate	–	71.31	–
Sorbitol	–	–	71.31
Potassium acesulfame	0.10	0.10	0.10
Magnesium stearate	1.00	1.00	1.00

The results obtained demonstrate that tablet formulations 1 and 3 are suitable for preparing a tablet by direct compression, and the tablet formulation 2 is not suitable because of its low fluidity.

For further selection the compression of all three tablet formulations obtained was conducted. The compression of the tablet formulation 1 was good; the tablets obtained were smooth with no visible chips and roughness.

Table 2

Physical parameters of tablet formulations

Tablet formulations	Fluidity, g/s	Bulk density, g/cm ³	The angle of repose, degrees
Tablet formulation 1	3.8	0.15	32
Tablet formulation 2	1.8	0.09	35
Tablet formulation 3	3.0	0.16	31

The tablet formulation 2 was poorly supplied to the product pipelines of the press and, as a result, tablets were obtained with no visible chips and roughness, but their mass was not homogeneous. Tablets obtained by compression of the tablet formulation 3 had visible chips. These observations confirm the conclusions made when analysing physical parameters of the tablet formulations.

CONCLUSIONS

1. The experimental substantiation for the choice of excipients of "Corvalol" drug for obtaining the fast dissolving sublingual tablets by direct compression has been carried out.

2. The technological parameters of three variants of tablet formulations for tableting have been studied. It has been demonstrated that the optimal excipients are β -cyclodextrin, lactose monohydrate, potassium acesulfame, magnesium stearate.

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ОБҐРУНТУВАННЯ ВИБОРУ ДОПОМІЖНИХ КОМПОНЕНТІВ ПРЕПАРАТУ «КОРВАЛОЛ» У ФОРМІ СУБЛІНГВАЛЬНИХ ТАБЛЕТОК

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Ключові слова: Корвалол; таблетки сублінгвальні; пряме пресування

На основі вивчення фізичних властивостей маси для таблетування обґрунтований вибір допоміжних речовин для отримання сублінгвальних таблеток «Корвалол» методом прямого пресування. Були проаналізовані три модельні суміші для таблетування. Встановлено, що оптимальними допоміжними речовинами є β -циклодекстрин, лактози моногідрат 80, ацесульфам калію, магнею стеарат. Показано, що висновки, зроблені під час аналізу фізичних параметрів сумішей, підтверджуються фактичними результатами пресування.

ОБОСНОВАНИЕ ВЫБОРА ВСПОМОГАТЕЛЬНЫХ КОМПОНЕНТОВ ПРЕПАРАТА «КОРВАЛОЛ» В ФОРМЕ СУБЛИНГВАЛЬНЫХ ТАБЛЕТОК

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Ключевые слова: Корвалол; таблетки сублингвальные; прямое прессование

На основе изучения физических свойств массы для таблетирования обоснован выбор вспомогательных веществ для получения сублингвальных таблеток «Корвалол» методом прямого прессования. Были проанализированы три модельные смеси для таблетирования. Установлено, что оптимальными вспомогательными веществами являются β -циклодекстрин, лактозы моногидрат 80, ацесульфам калия, магния стеарат. Показано, что выводы, сделанные при анализе физических параметров смесей, подтверждаются фактическими результатами прессования.