DEVELOPMENT OF COMPOSITION OF HARD CAPSULES WITH ANTIHYPERTENSIVE ACTION

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Introduction. Considerable spreading of hypertension, myocardial infarction and angina pectoris requires a medicinal correction. About 50–75 % of patients with hypertension require combination therapy. A combination of two drugs from any two groups of antihypertensive medicines helps to reduce blood pressure levels more than an increase in the dosage of the drug used as monotherapy [2, 4]. Therefore, the creation of effective combined medicinal preparations is topical.

The combination of bisoprolol fumarate and hydrochlorothiazide is beneficial. The different types of antihypertensive medicines are used in conjunction. Their antihypertensive effect is better than the blood pressure-lowering effect of a certain medicine of alone dose. The compound preparation increases patient's toleration, improves compliance.

The aim of the study. The objective of our work was a development of hard capsules with bisoprolol fumarate and hydrochlorothiazide. Both active pharmaceutical ingredients are used in the treatment of hypertension and heart failure [1, 3]. Both are administered orally and may be used alone or in combination, but there is no such single dosage form as capsules currently on the market of Ukraine containing both bisoprolol and hydrochlorothiazide.

Methods of research. The technological properties (bulk density, fractional composition) of the active ingredients and mixtures for encapsulation have studied according to the methods described in the State Pharmacopoeia of Ukraine. The substances, excipients, mixtures for encapsulation and prepared capsules on their basis were research subject.

Main results. Bisoprolol fumarate is a synthetic $beta_1$-selective (cardioselective) adrenoceptor blocking agent. It is a white powder, which is readily soluble in water and ethanol. Hydrochlorothiazide is a thiazide-type diuretic and antihypertensive. Hydrochlorothiazide is a white, or practically white, crystalline powder with slightly bitter taste, which is slightly soluble in water and soluble in ethanol.

The recommended single dose of bisoprolol fumarate and hydrochlorothiazide was used, which according to the instructions for medical use is 10 mg and 25 mg respectively.

The pharmacotechnological properties analysis of the tested substances have shown that the substances had insufficient values of flowability. The bulk density of the substances mixture was small (0.41 g/ml). That is predetermined application of a dry granulation technology. Dry granulation is superior to wet granulation in terms of stability, cost efficiency and productivity. The dry granulation process was used to form granules without using a liquid solution because the temperature had a significant effect on the stability of bisoprolol fumarate.

The following auxiliary matters were studied: starch 1500 (partially pregelatinized starch) as filler-disintegrant, aerosil as glidant with the purpose of a mixture components choice for capsules filling.

Partially pregelatinized corn starche starch 1500 are free-flowing and self-disintegrating powder. Its physico-chemical properties are well adapted to the use as filler-disintegrant in two-piece hard gelatin capsules. The mixtures for encapsulation with content of starch 1500 from 5 to 12 % were investigated. It was determined that optimum was 65 % of starch 1500 for the obtaining of contents of the capsule with the mass 0.11 g.

The research of a dependence of the encapsulation mass bulk density from the size of granules were investigated. The bulk density of granules is increased with decrease of granule size due to their best compression. The optimum bulk density is within the limits of (0.55 – 0.65) g/ml. Therefore we chose a fraction of granules with the particles size within the limits of (950 – 1000) μm.

Aerosil was included to the composition of the developed medicinal form with the aim of improvement of granules gliding properties. Aerosil has a large specific surface and homogeneity of particles of spherical form, and provides the improvement of granules flowability in an optimum amount. It is favourable to the diminishing of a piston friction of a metering device in the capsule filling process. Necessary amount of aerosil was determined by an experimental way. At the increase of the aerosil content in the encapsulation mass to 1 % its flowability increases, and then begins to diminish slowly. It is explained that the smoothing of rough particles surfaces of encapsulation mass components takes place due to a large aerosil dispersion. Thus a friction diminishes between particles at their motion, flowability of granules increases as a result. The increase of aerosil concentration in the composition more than 1,5 % results in the considerable increase of particles bulk density. An optimum amount of aerosil in the encapsulation mass is 1 %.

Dry granulation was conducted on a laboratory tablet press using slugging tooling. When the product was compacted properly, then it was passed through a sieve size 16 (1000 μm) to produce the required uniform size of granules.

Researches on a stability of capsules showed that properties of capsules remained stable during 6 months (observation time).

Conclusions. Thus, the composition of capsules with bisoprolol fumarate and hydrochlorothiazide was suggested.

References

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