
ТЕХНОЛОГІЯ ЛІКАРСЬКИХ ПРЕПАРАТІВ

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THE STUDY OF STABILITY OF THE COMBINED ANTIHYPERTENSIVE TABLETS DURING STORAGE

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Key words: combined tablets; amlodipine; indapamide; lisinopril; shelf life; stability

Creation of drugs for treating hypertension, namely the combined tablets based on antihypertensive agents of different pharmacological groups, is very important for domestic pharmaceutical science and practice. According to the results of the previous studies the composition and technology of the combined tablets "Amlopamide" for treating hypertension have been developed. As active ingredients these tablets contain amlodipine besylate, lisinopril dehydrate and indapamide. The excipients are microcrystalline cellulose, lactose monohydrate, potato starch and calcium stearate. The aim of this work was to study the physical and chemical, pharmaceutical and technological parameters, as well as microbiological purity of the combined tablets during storage. The modern methods of testing are used to determine stability of "Amlopamide" tablets obtained by direct compression in accordance with the State Pharmacopoeia of Ukraine. To determine the shelf life of the combined antihypertensive tablets "Amlopamide", as well as to study their stability, different batches of the drug were kept in different containers at a temperature of $(20\pm 5)^{\circ}\text{C}$. The control of the drug stability was performed according to all parameters: appearance, the average tablet weight, disintegration time, dissolution, uniformity of dosage units, identification, the assay content of active substances and microbiological purity. The results of the experimental studies have shown that during storage for 27 months at a temperature of $(20\pm 5)^{\circ}\text{C}$ the samples of the combined tablets "Amlopamide" in all containers used by all parameters meet the requirements of normative documents and State Pharmacopoeia of Ukraine (SPhU). It has been determined that the shelf life of the tablets is 2 years while storing at room temperature.

Despite the obvious progress in development of drug therapy for treating hypertension this pathology is the most common cardiovascular risk factor in developed countries, including in Ukraine. One of the key links in achieving the target level of blood pressure (BP) in patients with hypertension is creation of fixed drug combinations, which considerably facilitate the process of achieving target BP, increase the activity of each drug compared to monotherapy, reduce the probability of side effects, increase compliance of patients to treatment and simultaneously reduce the cost of it [6, 9, 10]. According to the results of the previous studies together with employees of "CPP "Red Star" PJSC (Kharkov) the composition and technology of the combined three-component tablets under the conditional name "Amlopamide" for treating hypertension have been developed. As active ingredients these tablets contain amlodipine besylate (calcium channel blocker), lisinopril dehydrate (ACE inhibitor) and indapamide (thiazid-like diuretic). The excipients are microcrystalline cellulose, lactose monohydrate, potato starch and calcium stearate [4]. In the abovementioned context, creation of domestic com-

bined drugs for treating hypertension is rather relevant for domestic pharmaceutical science and practice.

The quality control carried out in the technological processes of production of drugs guarantees the efficiency and safety of their use. At the present stage of development of domestic pharmaceutical industry and with introduction of the rules of good manufacturing practice (GMP) in the pharmaceutical enterprises of Ukraine the approaches to the quality control of drugs change. Standardization of the medicines developed, as well as determination of stability, conditions and the shelf life are important stages of their introduction into production [1, 5].

The aim of this work was to study the physical and chemical, pharmaceutical and technological parameters, as well as microbiological purity of the combined tablets during storage.

Experimental Part

To determine the stability of "Amlopamide" tablets obtained by direct compression the methods of physical and chemical (high performance liquid chromatography), pharmaceutical and technological, biological

studies were used in accordance with the State Pharmacopoeia of Ukraine (SPhU) by standard practice [1]. The quality control was performed according to the following parameters: appearance, identification, the average tablet weight, the loss on drying, friability, microbial purity, etc.

For identification and quantitative determination of active substances of the combined tablets "Amlopamide" the method of high performance liquid chromatography (HPLC) was used. This method allows determining compounds in very low concentrations. Determination of active ingredients – amlodipine besylate, lisinopril dehydrate and indapamide in the composition of drugs are mainly carried out by chromatographic and spectrophotometric methods [7, 8]. The presence of three active substances in the drug studied has determined the need for development of identification and quantitative determination methods, which allow to identify all active ingredients in tablets. Chromatographic analysis was performed on an Agilent 1100 liquid chromatograph with an UV-detector. To determine lisinopril in "Amlopamide" tablets the buffer solution with pH 7.0: acetonitrile *R* – water of chromatographic grade *R* (20:15:65) was used as a mobile phase; to determine amlodipine and indapamide the buffer solution with pH 7.0: acetonitrile *R* – water of chromatographic grade *R* (20:28:52) was used [2].

To provide the uniformity of dosage units (UDU) the content of active substances in a dosage unit in the batch must be within the narrow limits of the label claim. The UDU was studied by the method of direct determination according to the method of the SPhU for the presence of the labeled amount of active substances in the composition of the combined drugs [1]. Statistical processing of the results obtained was performed according to the SPhU ($n = 5$).

Results and Discussion

To determine the shelf life of the combined antihypertensive tablets "Amlopamide", as well as to study their stability, different batches of the drug were kept in different containers at room temperature (20 ± 5)°C. The following types of containers were used: polymer jars for packaging of drugs with the first opening (TU U 00481318.001-98); blisters based on PVC film (GOST 25250-88) and printed lacquered aluminium foil (TU 48-21-270-88); amber glass jars of BDS-10-27.5-OC-1 type (TU 64-2-239-79) with stretched lids of type 1,2 (OST 64-2-87-81). The control of the drug stability was performed according to all parameters: appearance, the average tablet weight, disintegration time, dissolution, uniformity of dosage units, identification, the assay content of active substances and microbiological purity.

By appearance "Amlopamide" tablets are round, biconvex tablets of a white colour to white colour with a yellow tint. The observations showed the absence of such phenomena as stratification tablets, split edges, change of the tablet surface in colour. Determination of average tablet weight of the samples was conducted according to the requirements of the SPhU (of 20 tablets). Deviations in determining the average weight were not

more than $\pm 7.5\%$. It corresponds to the existing requirements.

The experimental results of studying the quality indicators of "Amlopamide" tablets developed are given in Table.

The results given in Table have shown that the combined tablets "Amlopamide" developed during storage at the temperature of (20 ± 5)°C studied in all containers give positive results by all parameters. It should be noted that at room temperature the tablets tend to increase in disintegration time. It is related to the fact that in the course of time the frame of the coat is thickened, and the penetration time of water through the capillaries of the micropores of the porous body increases, but during storage for 2 years and 3 months this parameter corresponds to the requirements of the SPhU.

Identification of active substances of the tablets was carried out using HPLC. The studies conducted have shown that on the chromatogram peaks and the retention times of the test solution were the same as peaks and retention times of standard solutions. While studying the quantitative content of the active substances of the combined tablets "Amlopamide", namely lisinopril dehydrate (calculated with reference to lisinopril), amlodipine besylate (calculated with reference to amlodipine) and indapamide (calculated with reference to 100% substance), varies within the permissible limits ($\pm 10\%$) during the whole period of storage [2].

The "Dissolution test" is the most important parameter in the study of kinetics of the active substances release from tablets. To study the release of active substances from "Amlopamide" tablets dissolution test for solid dosage forms was applied using a device with the blade [1]. Quantitative determination of active ingredients every 10 min for 60 min was performed using HPLC, water *R* was used as the dissolution medium. The studies have shown that release of lisinopril dehydrate (calculated with reference to lisinopril), amlodipine besylate (calculated with reference to amlodipine) and indapamide (calculated with reference to 100% substance) regardless of the shelf-life occurs within 80-95% for 45 min, and it meets the requirements of the SPhU [1].

The experimental data obtained on studying UDU of "Amlopamide" tablets indicate that by the quantitative content of active substances this dosage form stand the test for "Uniformity of dosage units" in accordance with the SPhU.

The microbiological purity test has shown that there are no bacteria of *Enterobacteriaceae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* families in the tablets. The viable aerobic microbial count of bacteria and fungi complies with the requirements of the SPhU for drugs for internal use [1, 3].

The results of the experimental studies have shown that during storage for 27 months at a temperature of (20 ± 5)°C the samples of the combined tablets "Amlopamide" in all containers used by organoleptic, pharmaceutical and technological parameters, as well as microbiological purity meet the requirements of normative documents and SPhU.

Table

The results of studying the stability of "Amlopamide" tablets during storage at the temperature of (20±5)°C

The name of parameters by QCM	The norm by QCM	Shelf life, months											
		Polymer jars			Blister			Amber glass jars of BDS type					
		12	24	27	12	24	27	12	24	27			
Appearance		White, round, biconvex tablets											
Identification Lisinopril Amlodipine Indapamide		On the chromatogram of the test solution obtained under the conditions of quantitative determination the retention times of peaks for lisinopril, amlodipine and indapamide are the same as the retention times of peaks for lisinopril, amlodipine and indapamide on the chromatogram of the standard solution with the accuracy of ±3%											
Average tablet weight	from 0.133 to 0.147 g	0.1385±0.0266	0.1405±0.0040	0.1401±0.0132	0.1403±0.0093	0.1395±0.0095	0.1400±0.0090	0.1403±0.0092	0.1390±0.0181	0.1393±0.0193			
Disintegration	not more than 15 min	3.2±0.3	4.5±0.2	5.1±0.3	4.0±0.4	4.3±0.2	5.0±0.4	3.9±0.3	4.5±0.2	5.3±0.2			
Uniformity of dosage units	The acceptance value for the first 10 units should be not more than 15	Satisfied	Satisfied	Satisfied	Satisfied	Satisfied	Satisfied	Satisfied	Satisfied	Satisfied			
Dissolution	for 45 min at least 75%	93.2±1.5	89.7±2.2	85.6±2.7	93.7±1.4	90.9±1.0	86.8±1.5	91.9±0.5	85.8±0.8	84.6±1.3			
Microbiological purity	bacteria not more than 1000 fungi not more than 100	< 1000 < 100	< 1000 < 100	< 1000 < 100	< 1000 < 100	< 1000 < 100	< 1000 < 100	< 1000 < 100	< 1000 < 100	< 1000 < 100			
The quantitative content: Lisinopril	in a tablet from 0.0045 to 0.0055 g	0.0050±0.0001	0.0049±0.0002	0.0051±0.0001	0.0048±0.0002	0.0049±0.0001	0.0050±0.0001	0.0048±0.0002	0.0051±0.0001	0.0050±0.0001			
Amlodipine	from 0.0045 to 0.0055 g	0.0048±0.0002	0.0050±0.0001	0.0049±0.0002	0.0050±0.0001	0.0049±0.0001	0.0050±0.0001	0.0049±0.0001	0.0050±0.0001	0.0051±0.0001			
Indapamide	from 0.00225 to 0.00275 g	0.00249±0.00001	0.00252±0.00001	0.00248±0.00001	0.00251±0.00001	0.00260±0.00001	0.00258±0.00001	0.00251±0.00001	0.00262±0.00001	0.00250±0.00001			

Note: n = 5. P = 95%.

CONCLUSIONS

The influence of storage conditions and types of containers on the quality of the combined antihypertensive tablets "Amlopamide" has been studied. The stability of organoleptic, pharmaceutical and technological, as well

as microbiological parameters of tablets during storage for 27 months in amber glass jars, polymer jars and blisters at room temperature (20±5)°C has been experimentally proven. It has been determined that the shelf life of the tablets is 2 years while storing at room temperature.

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ВИВЧЕННЯ СТАБІЛЬНОСТІ КОМБІНОВАНИХ АНТИГІПЕРТЕНЗИВНИХ ТАБЛЕТОК У ПРОЦЕСІ ЗБЕРІГАННЯ

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Ключові слова: комбіновані таблетки; амлодипін; індапамід; лізиноприл; термін придатності; стабільність

Створення лікарських засобів для лікування артеріальної гіпертензії, а саме комбінованих таблеток, на основі антигіпертензивних речовин різних фармакологічних груп є вельми актуальним для вітчизняної фармацевтичної науки і практики. За результатами попередніх досліджень було розроблено склад і технологію комбінованих антигіпертензивних таблеток «Амлопамід». У якості діючих речовин таблетки мають амлодипіну безилат, лізиноприлу дигідрат та індапамід. У складі допоміжних речовин – мікрокристалічна целюлоза, лактози моногідрат, крохмаль картопляний і кальцію стеарат. Мета роботи – вивчення фізико-хімічних, фармако-технологічних показників та мікробіологічної чистоти комбінованих таблеток в процесі зберігання. Для визначення стабільності таблеток «Амлопамід», отриманих методом прямого пресування, були використані сучасні методи досліджень у відповідності до вимог ДФ України. Для встановлення терміну придатності таблеток та вивчення стабільності серії препарату були закладені на зберігання в різних упаковках при температурі (20±5)°C. Контроль стабільності препарату проводили за наступними характеристиками: зовнішній вигляд, середня маса таблеток, час розпадання, розчинення, однорідність дозованих одиниць, ідентифікація та кількісний вміст діючих речовин, мікробіологічна чистота. Результати досліджень показали, що в процесі зберігання протягом 27 місяців при температурі (20±5)°C зразки комбінованих таблеток «Амлопамід» в усіх використаних упаковках за всіма показниками відповідають вимогам нормативної документації та ДФУ. Встановлено термін придатності таблеток – 2 роки при зберіганні при кімнатній температурі.

ИЗУЧЕНИЕ СТАБИЛЬНОСТИ КОМБИНИРОВАННЫХ АНТИГИПЕРТЕНЗИВНЫХ ТАБЛЕТОК В ПРОЦЕССЕ ХРАНЕНИЯ

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Ключевые слова: комбинированные таблетки; амлодипин; индапамид; лизиноприл; срок хранения; стабильность

Создание лекарственных средств для лечения артериальной гипертензии, а именно комбинированных таблеток, на основе антигипертензивных веществ разных фармакологических групп является очень актуальным для отечественной фармацевтической науки и практики. За результатами предыдущих исследований были разработаны состав и технология комбинированных антигипертензивных таблеток «Амлопамид». В составе действующих веществ таблетки содержат амлодипина безилат, лизиноприла дигидрат и индапамид. В составе вспомогательных веществ – микрокристаллическая целлюлоза, лактозы моногидрат, крахмал картофельный и кальция стеарат. Цель работы – изучение физико-химических, фармако-технологических показателей и микробиологической чистоты комбинированных

таблеток в процессе хранения. Для определения стабильности таблеток «Амлопамид», полученных методом прямого прессования, были использованы современные методы исследований в соответствии с требованиями ГФ Украины. Для установления срока хранения таблеток и изучения стабильности серии препарата были заложены на хранение в разных упаковках при температуре $(20\pm 5)^\circ\text{C}$. Контроль стабильности препарата проводили по следующим характеристикам: внешний вид, средняя масса таблеток, время распада, растворения, однородность дозированных единиц, идентификация и количественное содержание действующих веществ, микробиологическая чистота. Результаты исследований показали, что в процессе хранения на протяжении 27 месяцев при температуре $(20\pm 5)^\circ\text{C}$ образцы комбинированных таблеток «Амлопамид» во всех используемых упаковках по всем показателям соответствуют требованиям нормативной документации и ГФУ. Установлен срок хранения таблеток – 2 года при хранении при комнатной температуре.