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DETERMINATION OF THE CRITICAL PARAMETERS OF THE TECHNOLOGICAL PROCESS OF OBTAINING SOLID DOSAGE FORMS WITH DRY EXTRACT AND CRUSHED ROOTS AND ROOTES OF *SCUTELLARIA BAICALENSIS*

Key words*: Scutellaria baicalensis,* validation, critical parameters, technological process

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ВИЗНАЧЕННЯ КРИТИЧНИХ ПАРАМЕТРІВ ТЕХНОЛОГІЧНОГО ПРОЦЕСУ ОДЕРЖАННЯ ТВЕРДИХ ЛІКАРСЬКИХ ФОРМ ІЗ СУХИМ ЕКСТРАКТОМ І ПОДРІБНЕНИМИ КОРЕНЯМИ ТА КОРЕНЕВИЩАМИ ШОЛОМНИЦІ БАЙКАЛЬСЬКОЇ

Ключові слова: *Scutellaria baicalensis,* валідація, критичні параметри, технологічний процес

Efficiently organized validation of technological processes according to international standards is an integral part of the life cycle of pharmaceutical production, one of the processes in the quality management system of modern pharmaceutical companies, and incorporates the approaches set forth in the rules of Good Manufacturing Practice (GMP) and ISO 9000 series standards [1, 2] Requirements of Good Manufacturing Practice (GMP) are measures to ensure the quality of products through which the appropriate organization of production and quality standards are achieved, taking into account the intended nature of the use of these drugs and requirements. The GMP guideline is that quality is built in in the process of products manufacturing, and not only controlled in the finished product. Validation and qualification are just that section of the GMP rules, which provides control of both the state of technological systems, equipment and processes, and the order of testing, which allows the production of invariably high-quality products [3]. Validation of technological processes in accordance with the requirements of good manufacturing practice is carried out in order to confirm that a process, personnel actions and the functioning of systems that provide this technological process are fully consistent with the purpose and allow obtaining the expected results. Each stage of drugs manufacture should serve as a convincing evidence that the process of its production occurs in accordance with the designed plan. Validation studies should be carried out in accordance with established procedures. Results and conclusions should be logged. If a new production formulation or manufacturing method is being introduced, then actions that demonstrate their suitability for routine (serial) production should be performed. It has to be proven that the established process with the use of specific materials and equipment permits continuous release of products of the required quality. Significant changes in the manufacturing process, equipment or materials must be validated [3].

An important condition for obtaining a high-quality medicinal product is the definition of critical points and parameters of the production process, which is divided into several successive stages.

The purpose is to determine the critical parameters of the technological stages of obtaining tablets based on the dry extract of the *Scutellaria baicalensis* and hard gelatine capsules on the basis of native raw material – roots and rhizomes of *Scutellaria baicalensis*; to establish critical limits when introducing the obtaining technology into industrial production, which will allow obtaining high-quality, effective, safe and affordable preparations with nootropic action.

Materials and methods

The subject of our research was the technological process of obtaining tablets based on dry extracts of roots and rhizomes of *Scutellaria baicalensis*. We have identified the critical parameters of the technological process for each stage. Validation tests were carried out for the determined critical parameters and the eligibility criteria were calculated.

Pharmacological and technological properties of the tablet masses and the finished pharmaceutical form have been studied according to the methods of the SPU [4].

The quality of the resulting tablets and capsules was evaluated by such indicators as: appearance, identification, average mass, homogeneity of mass, decomposition, dissolution, erosion, microbiological purity, quantitative determination. Methods for assessing the quality of the drug were: visual, gravimetry, spectrophotometry.

The ranges of critical parameters have been determined according to the experimental data obtained.

Results and discussion

At the stage of the pharmaceutical development of tablets and capsules, a detailed analysis of each stage of the technological process was conducted to establish parameters to be monitored during the introduction into industrial production and during validation of the manufacturing process. One of the most important are the stages for tableting (encapsulation) mass preparation and the subsequent tabletting (encapsulation), so the parameters and characteristics of these operations are critical.

The development of a method for obtaining preparations in the form of tablets (direct compression or wet granulation method) depends on the crystallographic, physico-chemical and pharmaco-technological properties of active substances, excipients and quality requirements to the final dosage form, which must be stable and have certain therapeutic effect.

Researches conducted on the study of active, auxiliary substances, the determination of the methods for obtaining tablets and capsules are presented in [5, 6], have allowed determining rational compositions and critical parameters.

Active substances, auxiliary substances and materials that are part of tablets and capsules are tested for compliance with the requirements of the SPU or TC (entrance control).

At the stage of raw material preparation in the manufacture of tablets, the control of the size of the holes of the screen was monitored and the quality of screening was evaluated. The weight of each ingredient was loaded according to the production formula. To make the humidifier using measuring tank measure the required amount of water heated to 30 °C and polyvinylpyrrolidone. Mixed to obtain a homogeneous clear solution 10 ± 1 min.

The mixing of the components at the stage of mass moistening and granulation of the dosage form is carried out in a mixer-granulator. Weighed and sieved substances were loaded with Vacuum. Humidifier was added and mixed to a homogeneous distribution of components. The rotation speed of the mixer was 20 rpm, the wetting time 10 ± 2 min. The drying time of the mass was 35–40 min at a drying temperature of 50 ± 5 °C to a residual moisture of granules 3.5 ± 0.5%, which was determined every 15 minutes. Calibration was carried out through a sieve with mesh size 1.5–2.0 mm.

At the stage of granulate powdering, the process was carried out with calculated amount of mixture, containing silica, talc, calcium stearate and sodium croscarmellose for 5 ± 2 min. In the resulting intermediate product, the appearance, quantitative content, homogeneity of the active substance distribution, and the quality of powdering were determined.

At the tabletting and dust control stage, the compression force and the weight of the tablets were monitored and control of the intermediate product of the tablets (description, average weight of tablets, homogeneity of the tablet weight, diameter, height, mechanical strength, friability, quantitative content, disintegration and dissolution) was performed.

At the packing stage, the temperature of the cells formation and the temperature of PVC and foil the rmowelding were monitored. The resulting tablets were controlled for the number of tablets in a blister, the correct labelling, the quality of the packages and their tightness.

At the boxing stage, controlled the number of blisters in a box and the correct marking.

In the production of capsules based on native raw material, the grinding and sieve mesh control 0,500 ± 0,050 mm were performed at the raw material preparation and sifting stage.

Mixing of the components of the dosage form was carried out in a mixer. Loaded with vacuum weighted and sieved materials. The process of mixing the mixture was carried out in a mixer (bin). The loading sequence and mixing time, which was 30 ± 1 min at a rotational speed of 8 rpm, was monitored and the quality of the semi-finished product was controlled by the following parameters: appearance, quantitative content, moisture content in mass for encapsulation.

At the encapsulation stage, the size of the capsule and the weight of the capsule content were monitored. The resulting capsules were subjected to quality control of intermediate products (appearance, average mass, quantitative content).

During the packing of capsules in a cellular package, the parameters of cells formation temperature (120–135 °C) and the temperature of the thermal sticking of PVC and foil (165–175 °C) were controlled. The resulting capsules were controlled for the number of capsules in a blister, the correct labelling, the quality and tightness of the package.

At the boxing stage, control was carried out on the number of blisters in a box and the correct labelling.

The critical parameters of the developed technological processes of production are given in tables 1 and 2. Technological schemes of production of drugs are shown in Fig. 1 and 2.

Table 1

Critical parameters of the technological process of tablets production

Critical parameter	Acceptability criterion
Stage 1. Preparation of materials	
The size of the holes of the screen Sieve № 23 (dry extract of Scutellaria baicalensis, corn starch, sodium croscarmellose, microcrystalline cellulose, granulac 200, polyvinylpyrrolidone, aerosil, talc, calcium stearate)	0,329 ± 0,032 mm
Sieve integrity before and after screening of raw materials	The sieve should be whole, without defects and damage
Quality of raw materials sifting	Homogeneity, absence of lumps
Weight of each ingredient	According to the production formula for serial loading according to the regulated value
Stage 2 Preparation of moisturizer	
Weight of water Weight of polyvinylpyrrolidone	Based on a batch of the drug
The temperature of water heating	30 °C
Humidifier mixing time	(10 ± 1) min
Completeness of dissolution	Until a homogeneous clear solution is obtained
Weight of the received humidifier	According to the production formula
Stage 3. Moistening the mass, drying and obtaining granules	
Sequence of loading, mixing time (active and auxiliary substances	(30 ± 1) min
Speed of rotation of the mixer	20 rpm
Amount of moisturizer	According to the production formula
Moisturizing time	(10 ± 2) min
The quality of the wet mass	Homogeneous in moisture and color mass, absence of lumps
Drying time	35–40 min
Drying temperature	50 ± 5 °C
Residual moisture (of obtained dry granulate)	3.5 ± 0.5%
Size of the mesh for dry granulation openings (calibration)	1.5–2.0 mm
Weight of granulate	Control of the weight conformity with the regulated value

Continuation of table 1

Critical parameter	Acceptability criterion
Stage 4. Granulate powdering.	
Loading of raw materials (aerosil, talc, calcium stearate, sodium croscarmellose)	Correspondence of loading with the calculated regulated value
Time of powdering	(5 ± 2) min
Rotation speed of transporting technological container	20 rpm
Amount of the resulting tablet mass	Conformity of the mass to the regulated value (load of the batch)
Quality of the semi-product:	
Appearance of the mass	Homogeneous mass of light yellow color without extraneous inclusions
Quantitative content	Sum of flavonoids, in terms of baicalin not less than 0.0135 g in 0.32 g sample of tablet mass
Homogeneity of the active substance distribution	Standard deviation not more than 5%
The quality of powdering	Homogeneous mass, without lumps and homogeneous in color
Stage 5. Tableting and dust control	
Rotor speed	60 rpm
The approximate force of pressing	10 kN
The main pressing force	18 kN
Weight of the resulting tablets	Conformity of the mass of received tablets to the regulated value (loading of a batch)
Control of intermediate products	
Description	Tablets of light yellow color, flat-cylindrical shape with a line and a facet
Average weight of tablets	From 0.304 g to 0.336 g (0.32 g ± 5%)
Homogeneity of the weight of tablets	Not more than two individual weights of tablets may deviate from the average weight of the tablet by more than ± 5%.However, no individual weight of a tablet should deviate from the average weight of the tablets by more than ± 10%
Diameter	10.0 ± 0.3 mm
Height	3.2 ± 0.4 mm
Mechanical strength	Not less than 80 N
Friability, %	Not more than 1%
Quantitative content (sum of flavonoids, in terms of baicalin)	Not less than 0.0135 g in one tablet
Disintegration	No more than 15 min
Dissolution	Not less than 75% for 45 min
Stage 6. Packaging of tablets in contour cell packs	
Temperature parameters for the formation of film cells	120–135 °C
Temperature of PVC film and foil thermo sticking	165–175 °C
Control of intermediate products	
Number of tablets in a blister	10 pcs
Correct marking	Correspondence to the original layout, clear application of the batch number and the expiration date
Quality of contour cell packs	Each blister must be of high quality, without visible defects and damage
Tightness of packing	100% of blisters should be hermetically sealed
Stage 7 Packing in boxes	
Number of blisters in cardboard box	1 or 3 pieces
Correct marking	Clear application of the batch number and the expiration date

Table 2

Critical parameters of technological process of capsules production

Critical parameter	Acceptibility criterion
Stage 1. Preparation of raw materials	
Size of holes in the sieve	(0.500 ± 0.050) mm
Stage 2. Screening	
Sieve N 5 (crushed roots and rhizomes of the Scutellaria, calcium stearate)	(0.500 ± 0.050) mm (0.329 ± 0.032) mm
Sieve integrity before and after screening of raw materials	The sieve should be whole, without defects and damage
Quality of raw materials sifting	Homogeneity, absence of lumps
Weight of each ingredient	According to the production formula for batch loading according to the regulated value
Stage 3. Mixing of components	
Sequence of loading, mixing time (active and auxiliary substances	(30 ± 1) min
Container rotation speed	8 rpm
Amount of received mass for encapsulation	Conformity of the weight to the regulated value (load of the batch)
Quality of the semi-product:	
Appearance of the mass	Homogeneous mass of brownish-yellow color
Quantitative content	The sum of flavonoids, in terms of baicalin not less than 0.03 g in the sample of mass for encapsulation
The moisture content of the mass for encapsulation	Not more than 10%
Stage 4. Encapsulation	
The number of empty capsules of the required size	Conformity of mass according to calculated batch, capsules number 1
Mass for encapsulation	Conformity of the mass to the regulated value (load of the batch)
Weight of received capsules	Conformity of the weight of capsules to regulated value (loading of a batch)
Control of intermediate products	
Appearance	Absence of possible defects: – mechanical damage (cracks); – visible air or mechanical inclusions
Average weight of capsules	From 0.277 g to 0.322 g (0.30 g ± 7.5%)
Quantitative content (sum of flavonoids, in terms of baicalin)	Not less than 0.03 g per capsule
Disintegration	Not more than 30 minutes
Stage 5.Packaging of capsules in contour cell packs	
Temperature parameters for the formation of film cells	120–135 °C
Temperature of PVC film and foil thermo sticking	165–175 °C
Control of intermediate products	
Number of capsules in a blister	10 pcs
Correct marking	Correspondence to the original layout, clear application of the batch number and the expiration date
Quality of contour cell packs	Each blister should be of high quality, without visible defects and damage
Tightness of packing	100% of blisters should be hermetically sealed
Stage 6 Packing in boxes	
Number of blisters in cardboard box	1 or 2 pcs.
Correct marking	Clear application of the batch number and the expiration date

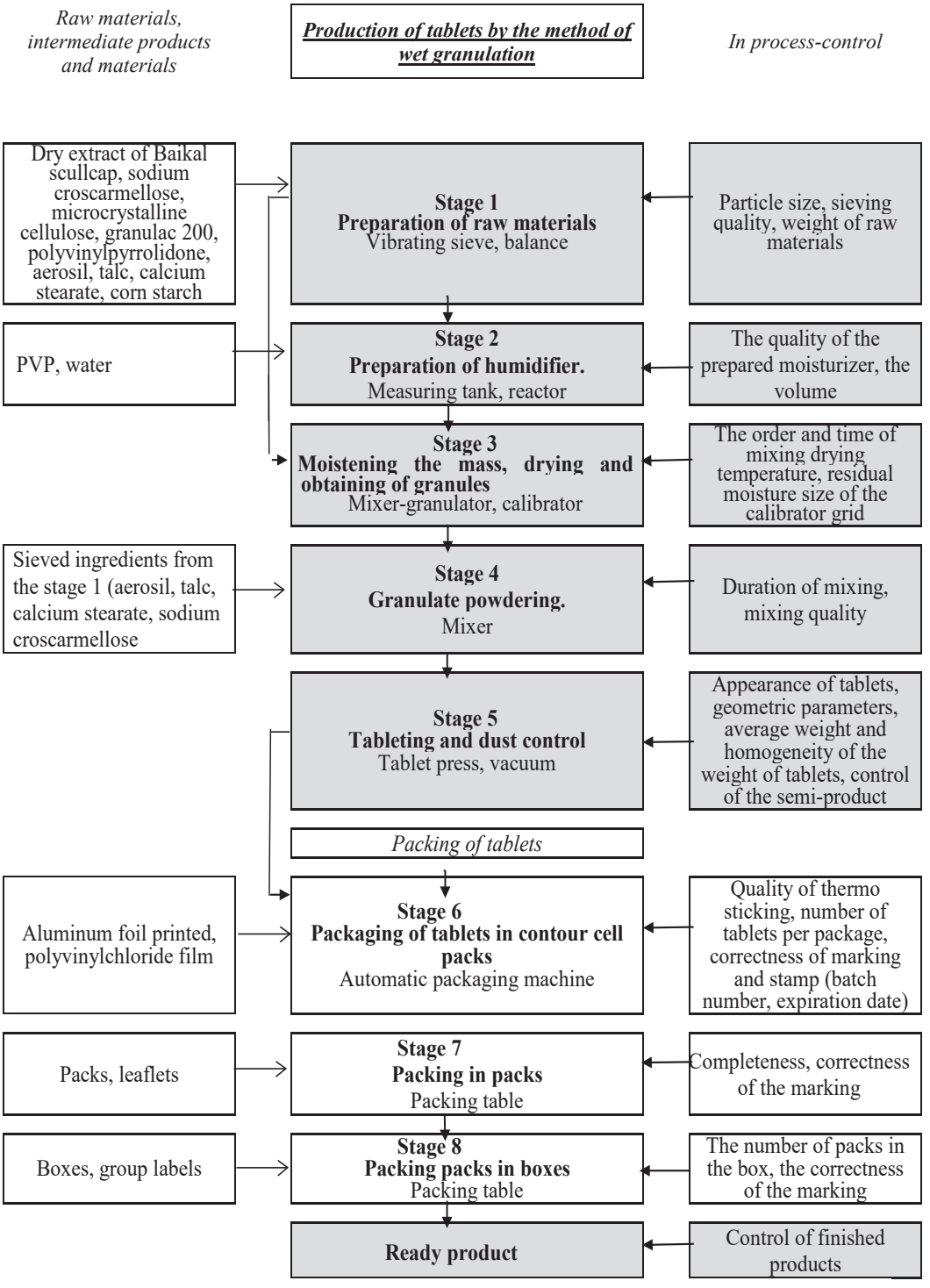

Fig. 1. **Technological flowchart of the tablets production process**

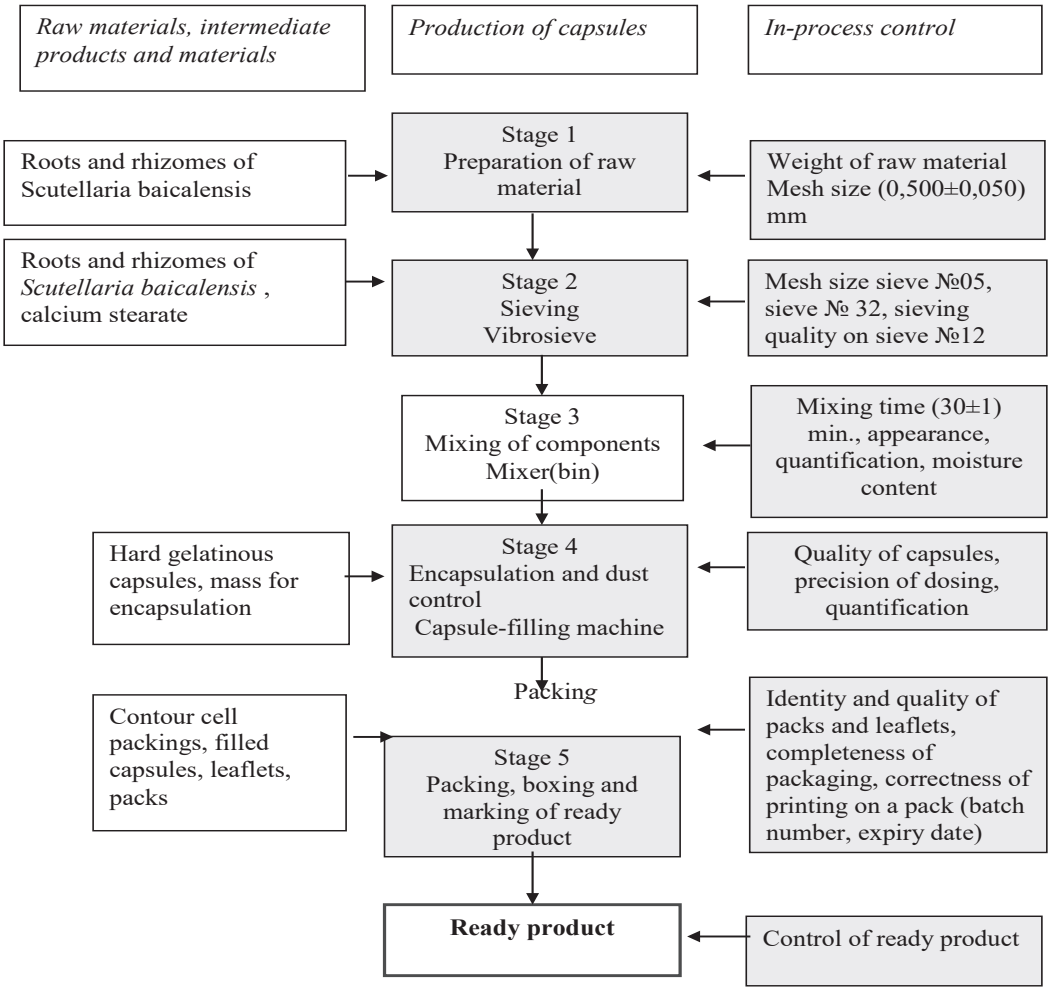

Fig. 2. **Technological flowchart of capsules production**

The proposed technological scheme of drugs production has a high stability of the given characteristics and their low variability, depending on the change in technological and pharmaco-technological characteristics of the intermediates within the limits of the proposed projected field of the final product quality characteristics, which is confirmed by dissolution profiles with repetition of the results.

Taking into account the results of the validation tests, it can be concluded that the established values of the critical parameters of the technological process of producing tablets based on the dry extract of the Baikal skullcap and hard gelatin capsules on the basis of the native raw material and the conditions for their implementation allow stable and guaranteed obtaining of intermediate and finished products meeting the quality parameters according to reference documents. Validation data of experimental and industrial series meet the eligibility criteria, and the developed technology is reproducible and promising for further validation.

C o n c l u s i o n s

1.In the process of production of tablets based on the dry extract of scullcap and solid gelatin capsules on the basis of crushed plant material, critical parameters have been determined that significantly affect the quality of the resulting preparation.

2.The conducted validation research of the technological process allow guaranteeing the quality of the received drugs and the subsequent reproducibility of the technological process.

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Key words*: Scutellaria baicalensis*, validation, critical parameters, technological process

A B S T R A C T

An important condition for obtaining a high-quality drug is the determination of critical points and parameters of the production process, which is divided into several successive stages.

The aim study of the critical parameters of the production of tablets and capsules with vegetable raw materials. For this purpose, validation studies of technological processes were carried out for tablets with dry extract of *Scutellaria baicalensis* and hard gelatin capsules with vegetable raw materials.

The subject of our research was the technological process of obtaining tablets based on dry extract of the roots and rhizomes of Baikal skullcap and hard gelatin capsules based on crushed raw materials. We have identified critical process parameters for each stage. Validation tests were carried out for certain critical process parameters and acceptance criteria were calculated.

Quality control of finished tablets based on dry extract of Baikal skullcap and finished hard gelatin capsules based on crushed roots and rhizomes of Baikal skullcap was performed according to the following indicators: appearance, identification, average weight, mass uniformity, disintegration, dissolution, abrasion, microbiological purity, quantitative determination .

The obtained validation data of experimental-industrial series meet the acceptance criteria, and the developed technology is reproducible and promising for further validation.

On the basis of the obtained results, it can be concluded that the established critical values of the parameters of the production processes and their conditions of carrying out allow for stable and reliable production of semi-finished and finished products that meet the quality standards in accordance with regulatory documents.

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ВИЗНАЧЕННЯ КРИТИЧНИХ ПАРАМЕТРІВ ТЕХНОЛОГІЧНОГО ПРОЦЕСУ ОДЕРЖАННЯ ТВЕРДИХ ЛІКАРСЬКИХ ФОРМ ІЗ СУХИМ ЕКСТРАКТОМ І ПОДРІБНЕНИМИ КОРЕНЯМИ ТА КОРЕНЕВИЩАМИ ШОЛОМНИЦІ БАЙКАЛЬСЬКОЇ

Ключові слова: *Scutellaria baicalensis,* валідація, критичні параметри, технологічний процес

А Н О Т А Ц І Я

Важливою умовою отримання якісного лікарського препарату є визначення критичних точок і параметрів виробничого процесу, який розділяють на кілька послідовних стадій.

Метою досліджень є вивчення критичних параметрів виробництва таблеток і капсул із рослинною сировиною. З цією метою здійснювали валідаційні дослідження технологічних процесів для таблеток із сухим екстрактом *Scutellaria baicalensis* і твердих желатинових капсул із рослинною сировиною.

Предметом нашого дослідження був технологічних процес одержання таблеток на основі сухого екстракту коренів та кореневищ шоломниці байкальської і твердих желатинових капсул на основі подрібненої сировини. Нами було визначено критичні параметри технологічного процесу для кожної стадії. Для визначених критичних параметрів технологічного процесу виконували валідаційні випробовування та розраховували критерії прийнятності.

На етапі фармацевтичної розробки таблеток та капсул було зроблено детальний аналіз кожної стадії технологічного процесу з метою встановлення параметрів, що підлягають моніторингу під час впровадження у промислове виробництво та у разі валідації технологічного процесу виготовлення. Одними із найважливіших є стадії приготування маси для таблетування (капсулювання) і наступне таблетування (інкапсулювання), тому параметри і характеристики цих операцій є критичними.

Контроль якості готових таблеток на основі сухого екстракту шоломниці байкальської та готових твердих желатинових капсул на основі подрібнених коренів та кореневищ шоломниці байкальської виконували за такими показниками: зовнішній вигляд, ідентифікація, середня маса, однорідність маси, розпадання, розчинення, стираність, мікробіологічна чистота, кількісне визначення.

Запропонована технологічна схема одержання препаратів має високу стійкість заданих характеристик і їхню низьку варіабельність залежно від зміни технологічних і фармакотехнологічних характеристик напівпродуктів у межах запропонованого проектованого поля характеристик якості кінцевого продукту, що підтверджується профілями розчинення з повторенням результатів.

Отримані дані валідації дослідно-промислових серій відповідають критеріям прийнятності, а розроблена технологія є відтворюваною та перспективною для подальшої валідації.

На підставі отриманих результатів можна зробити висновок, що встановлені критичні значення параметрів виробничих процесів і умови їх проведення дають змогу стабільно і надійно одержувати напівпродукти і готові продукти, які відповідають нормам якості згідно з нормативними документами.

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ОПРЕДЕЛЕНИЕ КРИТИЧЕСКИХ ПАРАМЕТРОВ ТЕХНОЛОГИЧЕСКОГО ПРОЦЕССА ПОЛУЧЕНИЯ ТВЕРДЫХ ЛЕКАРСТВЕННЫХ ФОРМ С СУХИМ ЭКСТРАКТОМ И ИЗМЕЛЬЧЕННЫМИ КОРНЯМИ И КОРНЕВИЩАМИ ШЛЕМНИКА БАЙКАЛЬСКОГО

Ключевые слова: *Scutellaria baicalensis*, валидация, критические параметры, технологический процесс

А Н Н О Т А Ц И Я

Важным условием получения качественного лекарственного препарата является определение критических точек и параметров производственного процесса, который разделяют на несколько последовательных стадий.

Целью исследований является изучение критических параметров производства таблеток и капсул с растительным сырьем. С этой целью проводили валидационные исследования технологических процессов для таблеток с сухим экстрактом *Scutellaria baicalensis* и твердых желатиновых капсул с растительным сырьем.

Предметом нашего исследования был технологических процесс получения таблеток на основе сухого экстракта корней и корневищ шлемника байкальского и твердых желатиновых капсул на основе измельченного сырья. Нами были определены критические параметры технологического процесса для каждой стадии. Для определенных критических параметров технологического процесса выполняли валидационные испытания и рассчитывали критерии приемлемости.

На этапе фармацевтической разработки таблеток и капсул был осуществлен детальный анализ каждой стадии технологического процесса с целью установления параметров, подлежащих мониторингу при внедрении в промышленное производство и при проведении валидации технологического процесса изготовления. Одними из важнейших являются стадии приготовления массы для таблетирования (капсулирования) и последующее таблетирование (инкапсулирование), поэтому параметры и характеристики этих операций являются критическими.

Контроль качества готовых таблеток на основе сухого экстракта шлемника байкальского и готовых твердых желатиновых капсул на основе измельченных корней и корневищ шлемника байкальского осуществляли по следующим показателям: внешний вид, идентификация, средняя масса, однородность массы, распадаемость, растворение, истираемость, микробиологическая чистота, количественное определение.

Предложенная технологическая схема получения препаратов имеет высокую устойчивость заданных характеристик и их низкую вариабельность в зависимости от изменения технологических и фармакотехнологических характеристик полупродуктов в пределах проектируемого поля характеристик качества конечного продукта, что подтверждается профилями растворения с повторением результатов.

Полученные данные валидации опытно-промышленных серий соответствуют критериям приемлемости, а разработанная технология воспроизводимой и перспективной для дальнейшей валидации.

На основании полученных результатов можно сделать вывод, что установленные критические значения параметров производственных процессов и условия их проведения позволяют стабильно и надежно получать полупродукты и готовые продукты, которые соответствуют нормам качества согласно нормативным документам.

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