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DETERMINATION OF THE OPTIMAL DISSOLUTION TEST CONDITIONS FOR CAPSULES BASED ON DRY EXTRACT OF WALNUT LEAVES (JUGLANS REGIA L.)

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ABSTRACT

Among the biopharmaceutical characteristics of modern pharmaceutical products, the "Dissolution" test occupies a pivotal role, as it enables the evaluation of the release of active constituents from a dosage form and the prediction of their in vitro bioavailability. This study presents the results of the development and scientific substantiation of "Dissolution" testing conditions for capsules containing a dry extract of walnut leaves (Juglans regia L.), the formulation and manufacturing technology of which were developed at the Tashkent Pharmaceutical Institute. Based on the experimental findings, the optimal in vitro dissolution testing conditions for evaluating the release of biologically active constituents were ascertained as follows: purified water - 500 ml was selected as the dissolution medium; the basket rotation speed was set at - 50 r/pm; the temperature of the dissolution medium was maintained at 37±1°C; and the test duration was - 45 minutes.

ОПРЕДЕЛЕНИЕ ОПТИМАЛЬНЫХ УСЛОВИЙ ПРОВЕДЕНИЯ ТЕСТА «РАСТВОРЕНИЕ» ДЛЯ КАПСУЛ НА ОСНОВЕ СУХОГО ЭКСТРАКТА ЛИСТЬЕВ ГРЕЦКОГО ОРЕХА (JUGLANS REGIA L.)

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ABSTRACT

Среди биофармацевтических показателей современных лекарственных препаратов тест «Растворение» занимает одно из ключевых мест,

грецкий орех (Juglans regia L.), сухой экстракт, капсулы, биофармацевтические исследования, биологическая эффективность, in vitro.

поскольку позволяет оценить высвобождение действующих веществ из лекарственной формы и прогнозировать их биодоступность in vitro. В настоящей работе представлены результаты исследования по разработке и обоснованию условий проведения теста «Растворение» для капсул на основе сухого экстракта листьев грецкого ореха (Juglans regia L.), состав и технология которых разработаны в Ташкентском фармацевтическом институте. На основании результатов экспериментальных исследований для оценки высвобождения биологически активных веществ методом in vitro были определены оптимальные условия проведения испытания: в качестве среды растворения использовали очищенную воду объёмом - 500 мл; скорость вращения корзинки составляла - 50 об/мин; температура среды поддерживалась на уровне 37±1 °C; продолжительность испытания - 45 минут.

Ease of use, wide standardization possibilities, low side effects, and the over-the-counter dispensing of herbal preparations expand the prospects for the production of medicines and dietary supplements based on plant components. Improper nutrition is identified by experts as one of the primary causes of various diseases. A violation of the diet leads to various changes in the functioning of body systems and a decrease in protective properties. One of the most optimal ways to solve this problem is the use of biologically active supplements (BAS) in combination with food products. The use of natural medicines is scientifically and economically substantiated, and the amount of biologically active substances in them is significantly higher than in traditional food products. [1-6].

As a result of the development of high technology, the isolation of BAS from plant raw materials is one of the urgent tasks of modern pharmaceuticals. Due to their low toxicity, good tolerance, safety, the possibility of long-term use, and the fact that they do not cause serious complications, natural medicinal products are widely used to preserve and restore health, as well as to prevent and treat many serious diseases. [2,5-8].

One of the most relevant and widespread dosage forms today is gelatin capsules. Their production began in the second half of the 20th century and is still used in medicine due to a number of advantages. Capsules possess high bioavailability due to rapid swelling and dissolution in the gastrointestinal system. The breakdown of capsules is understood as the complete decomposition of a pressed body into its constituent parts (granules, powder, or a soft mass). The time it takes for all components to decompose depends on its type. Any form of biologically supplement passes through the stomach and gastrointestinal tract upon ingestion, so the breakdown parameter is important. Active substances must be released during the passage of tablets or

capsules through the gastrointestinal tract. The biopolymer coat of the gelatin capsules allows the active drug to be absorbed more quickly. [8,10-12].

In view of the above, research is being conducted at the Tashkent Pharmaceutical Institute to develop a dietary supplement in capsule form from a dry extract obtained from walnut (*Juglans regia*.L.) leaves. Various excipients were used to select the composition of the biologically active additive in capsule form based on the obtained dry extract. Based on the dispersion density of the dry extract, the use of gelatin capsules with a size of "1" was deemed appropriate.

The pharmacotechnological parameters of the encapsulated masses prepared as a model were determined according to the methods presented in State Pharmacopoeia of the Republic of Uzbekistan edition I and State Pharmacopoeia of the Russian Federation edition XIV [13,14] and a specific composition was selected.

Subsequent studies were aimed at determining the conditions for conducting the "Dissolution" test, which is one of the main quality indicators of the capsule dosage form.

Objective of the research. The objective of the next research was to scientifically substantiate the conditions for conducting the "Dissolution" test for the developed capsules based on a dry extract obtained from walnut leaves (*Juglans regia* L.).

Experimental part

Materials and methods

Capsules obtained on the basis of dry extract from walnut leaves (*Juglans regia*.L.) were selected as the object for these studies.

The disintegration and dissolution of a solid dosage form directly affect the absorption of its active ingredients. Therefore, during the production of new medicinal products and biologically supplements in these forms (tablets, capsules, dragees), their level of biological effectiveness is determined by the "Dissolution" test, which is one of the main quality indicators. Conducting the "Dissolution" test makes it possible to determine the rate and extent of release of the active substance from the solid dosage form into the dissolution medium under specified conditions. This, in turn, simulates to a certain degree the behavior of the dosage form within the human gastrointestinal tract. [15-18].

The development of "Dissolution" test methods for modern drugs is a complex process, where the conditions and scope of research are determined by the physicochemical and pharmacokinetic properties of the active substance. When selecting research methods, the results of experiments on animals must be taken into account, i.e., the main pharmacokinetic parameters of the medicinal substance obtained in the experiment, primarily the test conditions and the dissolution medium. The technology and composition of the dosage form allow for the selection of instrument and hydrodynamic test parameters (rotation speed) [16,18].

Solubility is important for drug forms intended for enteral administration, as the maximum rate of passive movement of the drug through biological membranes depends on the membrane permeability of the drugs and the absorption of the solution/solubility concentration. Given that 40% of the manufactured medicinal substances are classified as insoluble substances, and 85% of the best-selling drugs in the USA and Europe are taken orally, the relevance of research in this direction is evident.

Research conducted by us: I edition of the State Pharmacopoeia of the Republic of Uzbekistan, 2.9.3. The "Dissolution" test for solid dosage forms

was performed using the method described in the article. Six capsules and the following equipment were used:

- Electronic analytical scales QUINTIX 224-10RU (Sartorius, Germany);
- Liquid chromatograph "Agilent 1200 series" (Agilent Technologies, USA);
- Agilent DS-708 solubility tester model G7911A (Agilent Technologies, Germany).

To develop a scientifically grounded "Dissolution" test for "Yugelm-mal" capsules, the influence of the basket rotation speed and pH on the release rate of the active substances in the capsule was studied.

To conduct these studies, purified water was used as the dissolution medium, and its volume was set at 500 ml. In accordance with the requirements of the first edition of the State Pharmacopoeia of the Republic of Uzbekistan, the studies were conducted at a temperature of 37±1°C and at the following rotation speeds of the "rotating basket": 50, 100, 150, and 200 r/pm. To determine the amount of sulfate transferred to the dissolution medium, medium samples were taken at 5, 10, 15, 30, 45, and 60 minutes after the start of the experiment. In this case, the aliquot volume was 10 ml. Aliquot was taken from the middle of the device's container and filtered through a "Millipor" filter with a diameter of 0.45 μm. After sampling the medium, its volume was filled with an equal amount of solvent. [13,14]

Preparation of the juglone standard sample solution for comparison. 15 mg of the juglone standard sample was weighed and dissolved in a 100 ml volumetric flask with methanol. Then, the volume of the solution was brought to the mark.

The amount of juglone released into the dissolution medium is calculated using the following formula:

$$X = \frac{S_{in} * a_{st} * 500 * P}{S_{st} * 100 * V * b}$$

Here:

S_{in} – the area of the juglone peak on the chromatogram of the test solution, mAU;

Sst - area of the main peak on the chromatogram of the juglone standard solution, mAU;

$a_{ст}$ – juglone standard solution weight, mg;

b – the amount of juglone in one capsule, mg

V – aliquot volume, ml

P - juglone content in the standard sample, %.

Results and discussion. Table 1 shows the amount of juglone released into the dissolution medium at specified time intervals and various rotation speeds of the basket.

Table 1

The amount of juglone released into the aqueous medium at various rotation speeds of the basket

Basket rotation speed, rpm	The amount of juglone released into the aqueous medium, %					
	5 min	10 min	15 min	30 min	45 min	60 min
50	11.3	35.3	58.5	74.7	83.6	89.2
100	24.0	41.6	60.1	77.8	85.9	90.1
150	30.8	46.7	63.2	81.9	88.5	91.2
200	40.3	49.2	68.9	85.4	90.8	93.3

According to the results presented in Table 1, as the basket rotation speed increases, the amount of juglone contained in the capsules released into the melting medium also increases. For example, 5 minutes after the start of the experiment, 11.3%, 24.0%, 30.8%, and 40.3% of the main biologically active substance were released at speeds of 50, 100, 150, and 200 rpm, respectively.

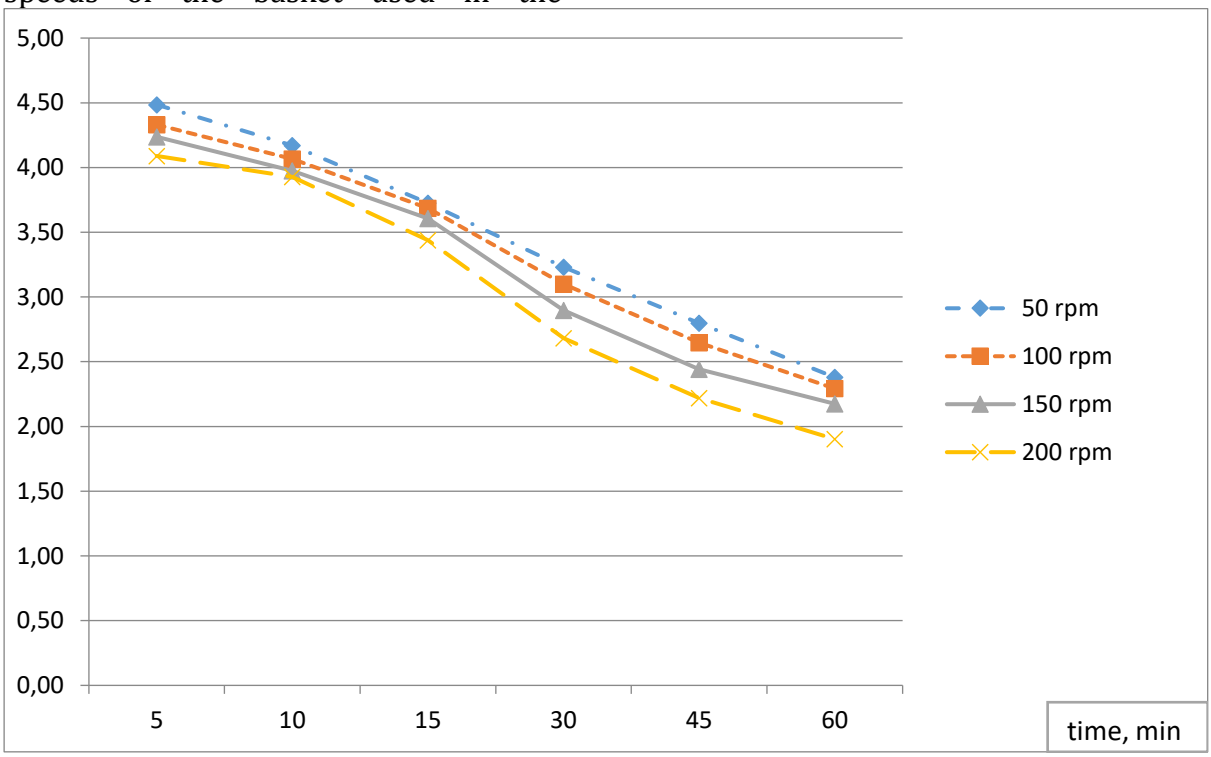
After 30 minutes, these indicators were 74.7%, 77.8%, 81.9%, and 85.4%. In accordance with the requirements of the State Pharmacopoeia of the Republic of Uzbekistan and other current regulatory documents, at all basket rotation speeds over 45 minutes, 75% more oil was released into the melting medium, amounting to 83.6% (50 rpm), 85.9% (100 rpm), 88.5% (150 rpm), and 00.8% (200 rpm).

In To select one of the four rotation speeds of the basket used in the experiments and to scientifically substantiate it, the antilogarithm indicator of the amount of excretion was calculated and presented in the form of a diagram in Figure 1.

Based on the results obtained, the first-degree equation corresponds to a basket rotation speed of 50 rpm.

Based on the above, the following conditions were ascertained for conducting the "Dissolution" test for "Yugelm-mal" capsules on the "Rotating basket" equipment: the melting medium is purified water, its volume is 500 ml, the basket rotation speed is 50 rpm, the temperature is 37±1°C, and the experimental time is 45 minutes.

The developed "Dissolution" test was tested in the quality control department of "MALIKA LABORATOPIES" LLC.



Picture 1. Antilogarithmic release curves of juglone from capsules containing dry walnut leaf extract

Conclusion: For "Yugelm-mal" capsules prepared on the basis of a dry extract obtained from walnut (*Juglans regia* L.) leaves, the following conditions

were ascertained for conducting the "Dissolution" test on the "Rotating basket" equipment: the melting medium is purified water, its volume is 500 ml, the rotation speed of the basket is 50 rpm, the temperature is 37±1°C, and the experimental time is 45 minutes.

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