Biopharmaceutical study of general tonic capsules by in vitro method

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Abstract. One of the main indicators of the quality of modern drugs are biopharmaceutical indicators, in particular, the "Dissolution" test - for solid dosage forms, as well as theoretical and experimental justification for the creation of new drugs and improvement of existing ones, taking into account the increase in their therapeutic effect and the reduction of side effects on organism. The article presents the results of research on the development of the "Dissolution" test for Indian ginseng, conducted at the Tashkent Pharmaceutical Institute. Determination of the dissolution rate of drugs from solid dosage forms is carried out on the device "Rotating basket". To study the release rate of active substances from the analyzed encapsulated dosage form, the generally accepted method "Rotating basket" included in the XIV edition of the State Pharmacopoeia (SP XIV) was used. Based on the results of the experiments, the following conditions for determining the bioavailability of the analyzed capsules by the in vitro method were selected: to determine the dissolution profile, two dissolution media are used in succession - a 0.1 M solution of hydrochloric acid (capsules should not dissolve within 60 minutes) and - a phosphate buffer solution with pH 7.4 (at least 75% of the active substances should be released within 45 minutes), the volume of the medium is 1000 ml, the rotation speed of the basket is 100 rpm, the temperature regime is 37±10°C.

1 Introduction

Biopharmacy is a relatively recent branch of pharmaceutical science, the subject of which is the interaction of drugs in dosage forms, due to their physical and chemical properties; the relationship between the dosage forms themselves and the therapeutic effect. Due to the fact that the pharmacotherapeutic efficacy of drugs is determined by the processes of their absorption, distribution and elimination (removal) from the macroorganism, biopharmacy pays special attention to the study of these processes, as well as the influence of the physicochemical properties of dosage forms on them. The main task of biopharmacy is to increase the effectiveness of medicinal substances and minimize possible undesirable side reactions. Accordingly, in the pharmaceutical complex of knowledge, where previously the only criteria for the quality of drugs were their physicochemical constants, new provisions

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are introduced that have a biological, medical justification. According to modern biopharmaceutical concepts, the processes of obtaining (isolation) of medicinal substances, methods of their purification, drying, grinding, obtaining dosage forms, methods of introduction into the body, etc., can significantly affect the therapeutic effect. A rigorous and detailed study of all aspects of obtaining and prescribing drugs is the main content of a biopharmaceutical study. Based on the foregoing, biopharmacy can be defined as a science that studies the influence of pharmaceutical factors on the therapeutic efficacy of drugs.

A huge role in the technology of dosage forms is played by the correct choice of excipients. No pharmaceutical factor has such a significant and complex effect on the action of the drug. Excipients are a large group of substances of natural and synthetic origin that help to obtain certain dosage forms with the necessary physicochemical and therapeutic properties.

A feature of the encapsulated dosage form is its ease of use, which does not require any special skills from the patient (compared to injections). A number of advantages make capsules an attractive form for drug manufacturers. Capsules can be used during the entire process of drug efficacy study without the need to transfer them to another form for patients to take [1-3].

Despite the lower profitability of the production of capsules in comparison with tablets, this dosage form still has a relatively low cost and provides high stability to the encapsulated active substances [4-5].

Capsules are easy enough to develop their production technology, since the main requirement for the encapsulate material is only to ensure dosing uniformity, which allows manufacturers to bring new products to market faster. A number of advantages make capsules an attractive form for drug manufacturers [6-7].

Studies conducted in recent years by a number of scientists have shown that the lack of a pressing process in encapsulated dosage forms in most cases is the reason for a decrease in the disintegration time compared to tablets and dragees, and, accordingly, more complete absorption in the body. In this regard, there is currently a tendency to expand the range of medicines by developing both tableted and encapsulated dosage forms. Capsules can be used throughout the entire drug efficacy study process. Despite the lower profitability of capsule production compared to tablets, this dosage form still has a relatively low cost and provides high stability to the encapsulated active ingredients [2-3, 6-8].

To date, there are capsules with a general tonic effect on the pharmaceutical market. Taking into account the positive aspects of the encapsulated dosage form, the composition was selected at the Tashkent Pharmaceutical Institute and the technology of capsules with adaptogenic action was developed.

The objective of these studies was to determine the bioavailability of the developed dosage form (DF) in in vitro studies with a preliminary scientifically based selection of the conditions for the "Dissolution" test. The "Dissolution" test is intended to determine the amount of the active substance, which, under the conditions specified in the monograph or regulatory documentation, for a certain period of time should be released into the dissolution medium from the solid dosage form and it is possible to determine the amount of the drug substance, which, under the conditions specified in private pharmacopoeial article, for a certain period of time should be released into the dissolution medium from solid dosed DF.

2 Materials and methods

To study the rate of active substances release from the analyzed encapsulated dosage form, the commonly method “Rotating Basket” included in SP XI was used [7, 9].
According to the literature data, when using the above method, the release of active substances influenced by various factors such as the rotation speed of the basket, the volume and pH of the dissolving medium, etc. In view of the above, the studies to select the optimal rotational speed of the basket in the “Dissolution” test for Indian ginseng capsules were carried out.

This method is also official in our Republic. The main reasons for the wide use of the “Rotating Basket” method are the high correlation of the research results in many cases with the results of in vitro experiments, the simplicity of the method, the ease of implementation and the low cost.

In this method, mixing is provided by a propeller agitator located in the center at a speed of 60 rpm. To prevent the specimen from changing its position, insertion of the specimen into a handle or basket has been proposed. In another version, the fixation of the sample is carried out with plates adapted for attaching a tablet or capsule. The plates are made of organic glass or Teflon and allow you to attach six capsules or tablets. When using such a device, the difficulties associated with the evaluation of capsules, which tend to float on the solvent or stick to the wall, disappear [4-5, 10-11].

The main working part of the device is a cylindrical mesh with a diameter of 0.25 mm, which filled with a test tablet of up to 1 liter, rotating 50-200 times per minute and maintaining a temperature of 37 °C ± 10°C. Do not shake any part of the instrument. Water or other solvents (hydrochloric acid, buffer solutions with different pH) are used as a solvent medium. Capsules were dissolved at the following rotation speeds of the basket: 50, 100, 150, 200 rpm. The studies were conducted at a temperature of 37±10°C. Every 15 minutes from the beginning of the experiment samples were taken to quantify diclofenac sodium and paracetamol transferred to the dissolution medium, after which the dissolution medium was replenished in the same volume.

To determine the quantitative content of active substances, the spectrophotometry method was used: the optical density of the obtained solution was measured at a wavelength of 510 nm (Indian ginseng).

The content of active substances (Indian ginseng) in one capsule, in percentage was calculated by the formula:

\[ X = \frac{D_1 \times a_0 \times 1000 \times V_2 \times 100 \times P}{D_0 \times V_1 \times a_1 \times 50 \times 100} = \frac{D_1 \times a_0 \times V_2 \times 20 \times P}{D_0 \times a_1 \times V_1} \]  

\[ (1) \]

\( D_1 \) – optical density of the tested solution; \( D_0 \) – optical density of the SS solution of active substances; \( a_0 \) – the mass of the active substance SSS sample, in mg; \( a_1 \) – the content of active ingredients in one capsule, in mg; \( V_1 \) – volume of the aliquot, ml; \( V_2 \) – volume of the second dilution, ml; \( P \) – content of active substances in SSS, %.

Conversion coefficient of optical density of aescin at wavelength 0.925-510 nm for panaxosides.

In all experiments, the studies were conducted on six units of the dosage form.

### 3 Results and Discussion

The results of Indian ginseng release studies are shown in Figure 1. According to the results obtained, at a basket rotation speed of 50 r/min, the release of dry extract of Indian ginseng was 75% less than it is required by the XIV edition of the State Pharmacopoeia, and amounted to 60.7%, and this speed excluded from the subsequent study.

When the basket rotation speed was 100 r/min, 28.7% of the dry Indian ginseng extract extracted in 15 minutes, 58.6% of the dry Indian ginseng extract in 30 minutes, 65.2% in 45 minutes, and 75.9% in 60 minutes. At the following basket rotation speed (150 rpm), 31.5%
of the dry ginseng extract was extracted in 15 minutes, 63.2% of the dry ginseng extract - in 30 minutes, 71.4% - in 45 minutes, and 82.8% - in 60 minutes.

Fig. 1. Research results on the release of Indian ginseng.

According to the data in Figure 1, similar results for dry extract of ginseng at a rotation speed of 150 rpm were 31.5%, 63.2%, 71.4 and 82.8%. Consequently, in all cases, more than 75% of the active substances were released into the dissolving medium in 45 minutes, which meets the requirements of SP XI.

At 200 r/min, 52.6% of the dry ginseng extract was extracted in 15 minutes, 72.1% of the dry ginseng extract was extracted in 30 minutes, 84.2% - in 45 minutes, and 90.1% - in 60 minutes. Thus, at speeds of 100 r/min, 150 r/min, 200 r/min basket released more than 75% of the active ingredient required in 45 minutes.

The antilogarithms of the obtained results calculated scientifically justify the chosen rotational speed of the basket.

The results obtained shown in Figure 2.

Fig. 2. Antilogarithm of dissolution of capsule based on dry extract of Indian ginseng.

For the scientific substantiation of the rational speed of the basket rotation, the antilogarithms of the values of the quantitative content of the active substance for 100, 150 and 200 revolutions of the basket were calculated.

The results of further research aimed at choosing one of the three speeds of rotation of the basket, presented in Figure 2, indicate that the dry extract of ginseng falls under the first order equation at a basket rotation speed of 100 rpm.
Based on the foregoing, for further research on the quality of ginseng dry extract capsules from a biopharmaceutical point of view, the following conditions for conducting in vitro experiments are recommended.

Based on the results obtained, the following conditions for the experiments to assess the quality of the finished product from a biopharmaceutical point of view were determined:
- solvent medium: purified water,
- volume of the solvent medium: 1000 ml,
- speed of basket: 150 r/min,
- temperature: 37 ± 10 °C.

4 Conclusion

Based on the above, for further study of the quality of general tonic capsules from the biopharmaceutical point of view, the following conditions of in vitro experiments are recommended: the experiments were conducted at 4 different basket rotation speeds: 50, 100, 150, 200 r/min. For the scientific substantiation of the chosen basket rotation speed, the antilogarithms of the obtained results were calculated. The following conditions were determined for the in vitro experiments: the solvent medium was purified water, the volume of the solvent medium was 1000 ml, the rotation speed of the basket was 100 rpm, and the temperature was 37 ± 10 °C.

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