Development of technology for the manufacture of capsules of madder dyeing M.V. Rybalko1, V.A. Kurkin2A.A. Shmygareva1, A.N. Sankov1

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Development of technology for production Rubia tinctorum L. capsules MV Rybalko1, VA Kurkin2, AA Shmygareva1, AN Sankov1 1Orenburg State Medical University, Ministry of Health of the Russian Federation (Orenburg, Russia), 2Samara State Medical University, Ministry of Health of the Russian Federation (Samara, Russia)

#### SUMMARY

A new method of obtaining an extract of madder (Rubia tinctorum L.) using the method of modified maceration and ultrasound for the production of a dosage form - a capsule is described. When using this method, the maximum yield of anthracene derivatives from raw materials is observed, while the content of the sum of anthracene derivatives in the capsule in terms of ruberitric acid is 8.5 mg. The use of madder dye extract in encapsulated form (with the introduction of indifferent excipients into the composition) allows to reduce the frequency of taking the drug, and to use this drug for people suffering from diabetes mellitus.

Keywords:madder dye, Rubia tinctorum L., rhizome withroots, anthracene derivatives, ruberitric acid, capsules, spectrophotometry.

#### RESUME

This article describes a new method of obtaining extract of Rubia tinctorum using the method of modified maceration and ultrasound for the production of dosage forms - capsules. When using this method, the maximum yield of anthracene derivatives from the raw materials is observed. The content of total anthracene derivatives in a capsule calculated on ruberythric acid is 8.50 mg. The proposed possibility of the using extract of Rubia tinctorum in a encapsulated form, with the introduction of indifferent auxiliary substances, reduces the frequency of administration, and this drug can be used for people suffering from diabetes.

Keywords: Rubia tinctorum L., rhizome with roots, anthracen derivatives, ruberythric acid, standardization, spectrophotometry, capsules.

#### INTRODUCTION

Currently, the pharmaceutical market has a wide range of different dosage forms (DF) from medicinal plant materials (MPR). Solid LF (tablets, capsules) are more popular among the population than liquid ones.

Madder dye has a nephrolytic effect due to the presence of a sufficiently large amount of anthracene derivatives of the alizarin series [5, 13]. The following medicinal products are registered in the Russian Federation based on madder raw materials: "Marelin", "Madder dye extract in tablets" [1]. An extract is a concentrated extraction from medicinal plant raw materials, from which the solvent is partially or completely removed [3, 4].

These tablets have the following disadvantages. The tablet does not have a protective shell, therefore it is exposed to the acidic environment of the stomach, which reduces the bioavailability of the active ingredients. As a result, an increase in the frequency of administration of the drug is required, as well as a restriction of the drinking regimen in order to achieve a concentration of anthracene derivatives in the blood plasma sufficient for the desired pharmacological effect. In the production of tablets, excipients such as lactose (milk sugar) are used, which makes it impossible for this Lf to be used by patients with diabetes mellitus.

Therefore, it is urgent to develop an effective method for obtaining an extract of the rhizome and roots of madder dye (Rubia tinctorum L.) for new DF, in particular, capsules with a high content of active ingredients in combination with excipients that reduce the level of allergenicity and make it possible to use this drug in patients with diabetes mellitus. Also, an urgent task is the development of an easy-to-use DF with high bioavailability and the possibility of reducing the frequency of taking capsules, in comparison with tablets, due to the enteric coating.

## MATERIALS AND METHODS

The object of the study was the rhizomes and roots of madder (LLC "Slavyanskaya zdravnitsa", Russia, Saransk, 2017; LLC "Ortilia", Russia, Novosibirsk, 2018). Enteric capsules (CapsulCN International CO., LTD) were also used. Electronic spectra were measured on a UNICO 2800 UV spectrophotometer. We also used a Vilitek VBS ultrasonic bath and an MSH 300 magnetic stirrer.

### **RESULTS AND DISCUSSION**

Madder extract is obtained in production in several ways: by the method of maceration and percolation (from Latin percolatio - filtering), i.e. filtering the extractant through the plant material. In the second case, to increase the yield of the final product, multiple repeated percolation of the raw material (repercolation) is used [6–8]. As a result of our research, we were able to show that the method of modified maceration turned out to be the most effective method for obtaining the extract. Therefore, for further research (making capsules), we obtained madder extract by this method.

The modified maceration method consists in the extraction of madder rhizomes and roots dyeing in the ratio "raw material-extractant" - 1:10 (extractant - 80% ethyl alcohol); infusion for 2 days; extraction in a water bath for 30 min and 15 min using ultrasound; filtering the extraction [9–11]. This method showed the maximum yield of anthracene derivatives, in comparison with other methods of obtaining the extract, which was confirmed by studying the UV spectra of a thick extract of madder rhizomes and roots in an alkaline ammonia medium (Fig. 1). To determine the quantitative content of anthracene derivatives in the extract, and then in capsules, we have developed the appropriate methods (given below in the text).



Rice. 1. Electronic spectrum of an alkaline-ammonia solution of aqueous-alcoholic extraction (extract), obtained by the method of modified maceration from rhizomes and madder roots

The content of the sum of anthracene derivatives in the thick extract of madder dye obtained by the method of modified maceration, in terms of ruberitric acid, was 1.55 mg. The results of the quantitative content of anthracene derivatives in the thick extract are presented in table. 1.

Table 1

Results of quantitative determination of the amount of anthracene derivatives in a thick extract rhizomes and roots of madder dye on ethyl alcohol 80% (1:10)

No.	Extraction method	The content of the sum of anthracene		
p/p		derivatives in terms of ruberitric acid, mg		
1	Maceration	0.61 ± 0.02		
2	Modified maceration	1.55 ± 0.01		
3	Percolation	0.87 ± 0.02		
4	Repercolation	0.55 ± 0.02		

Quantitative determination procedure

anthracene derivatives in thick extract of madder dye

An exact weighed portion of the thick extract (0.2000 g) was placed in a 100 ml volumetric flask, 15 ml of 80% ethanol was added. The flask was connected to a reflux condenser and heated in a boiling water bath for 15 minutes. After cooling to room temperature, the solution was filtered through a paper filter (red ribbon) into a 50 ml volumetric flask, avoiding the capsule powder getting onto the filter. The procedure was repeated twice, each time filtering the extract into the same volumetric flask through the same filter. Then the volume of the solution was brought to the mark with 80% alcohol and thoroughly mixed (solution A).

1.0 ml of solution A was placed in a 50 ml volumetric flask and the volume of the solution was brought to tags with an alkaline ammonia solution prepared in accordance with the requirements of the State Pharmacopoeia of the Russian Federation XIV edition, and heated in a boiling water bath for 15 min. After cooling, the optical density of the test solution was measured on a spectrophotometer at an analytical wavelength of 520 nm in a cuvette with a layer thickness of 10 mm. Purified water was used as a reference solution [12].

The content of the sum of anthracene derivatives in terms of ruberitric acid in a thick extract of rhizomes and madder roots in mg was calculated by the formula:

, where

D is the optical density of the test solution;m is the mass of the sample of the contents of the capsule, g;

520 - specific absorption index (acid A at  $\mathcal{E}_{1cm}^{1\%}$ ) alkaline-ammonia solution RSO ruberitrin 520 nm.

Metrological specifications method quantitative definitions sums anthracene derivatives in madder dye extract obtained by the method of modified maceration are presented in table. 2.

table 2

Metrological characteristics of the quantitative determination procedure the amount of anthracene derivatives in a thick extract of madder dye

f		S	P,%	t (P, f)	-X	E,%
ten	1.52	0.02756	95	2.23	± 0.06	± 4.04

The results of statistical processing show that the error of a single determination of the amount of anthracene derivatives in the madder dye extract obtained by the method of modified maceration with a confidence level of 95% is  $\pm$  4.04%.

## Obtaining capsules of madder dye extract

The obtained aqueous-alcoholic extract of roots with rhizomes of madder dye was evaporated to a thick extract with a moisture content of no more than 25%. Talc and potato starch were used as auxiliary substances for encapsulating the madder dye extract. Talc (3%) was initially added to the uncooled thick extract; after cooling, starch was added in a ratio of 1: 0.75.

Method for the quantitative determination of anthracene derivatives in capsules of madder dye

An exact weighed portion of the contents of the capsule (0.47 g) was placed in a flask with a ground section

with a capacity of 100 ml, 15 ml of 80% alcohol was added. The flask was connected to a reflux condenser and heated in a boiling water bath for 15 minutes. Then, after cooling to room temperature, the solution was filtered through a paper filter ("red" strip) into a 50 ml volumetric flask, avoiding the tablet powder getting onto the filter. Then the solution was brought to the mark with 80% alcohol and mixed thoroughly.

1 ml of the obtained extract was placed in a volumetric flask with a capacity of 50 ml and the volume of the solution was brought to the mark with an alkaline ammonia solution prepared in accordance with the requirements of the State Pharmacopoeia of the Russian Federation XIV edition. After cooling, the optical density was measured on a spectrophotometer at a wavelength of 520 nm (Fig. 2). A solution prepared as follows was used as a reference solution: 0.5 ml of the extract was placed in a 25 ml volumetric flask and the volume of the solution was brought up to the mark with water [12].



Rice. 2. Electronic spectrum of an alkaline-ammonia solution of aqueous-alcoholic extraction from madder dye capsules

The content of the sum of anthracene derivatives in the capsule of madder dye in terms of ruberitric acid in mg was calculated by the formula:

, where

D is the optical density of the test solution;m is the mass of the sample of the contents of the capsule, g; Pc - average weight of one capsule;

520 - specific absorption index (acid A at  $\mathcal{E}_{less}^{i\infty}$ ) alkaline-ammonia solution RSO ruberitrin 520 nm.

The content of the sum of anthracene derivatives in the capsule of madder dye obtained by the method of modified maceration in terms of ruberitric acid was  $8.50 \pm 0.02$  mg.

The metrological characteristics of the method for the quantitative determination of sums anthracene derivatives in capsules of madder are presented in table. 3.

The results of statistical processing of the experiments carried out show that the error of a single determination of the sum of anthracene derivatives in capsules of madder dye with a confidence level of 95% is  $\pm 4.20\%$ .

Table 3

Metrological characteristics of the quantitative determination procedure the amount of anthracene derivatives in capsules of madder dye

f		S	P,%	t (P, f)	-X	E,%
ten	8.15	0.1557	95	2.23	± 0.34	± 4.20

Dissolution test

After the capsules of the madder dye extract were made, a comparative study was carried out on the solubility of the tablets "Marena dye extract" and the obtained capsules in an environment similar in acidic properties to gastric juice. Conditions similar to those in the stomach were simulated: pH 1.5–1.8, as well as tonic and peristaltic movements. The experiment time was 30 minutes, which corresponds to the average duration of the stay of drugs in the stomach. As a result, after 30 minutes, the tablet was completely dissolved in hydrochloric acid, while the capsule remained intact. Presumably, part of the anthracene derivatives of the tablet in the course of a chemical reaction with hydrochloric acid in gastric juice was inactivated due to the addition of hydrogen to the keto group,

Thus, enteric capsules madder dyeing are more preferred over tablets due to the absence of irritating effect on the walls of the stomach and targeted delivery of anthracene derivatives to the intestine. The advantages of capsules also include the possibility of their use in patients with diabetes mellitus due to the replacement of lactose with talc and starch.

### CONCLUSIONS

1. A method of obtaining an extract for the manufacture of capsules by the method of modified maceration.

2. A technology has been developed for the manufacture of enteric capsules of madder dye extract with the content of the sum of anthracene derivatives in terms of ruberitric acid 8.5 mg.

3. As auxiliary substances for the manufacture of capsules, it is proposed to use talc and starch, which allows the use of this Lf in patients with diabetes mellitus.

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