The mixture of acetates of the dimethyl ethers (0.9 g) was deposited on a column (35 × 2 cm) of silica gel and was eluted in the same way as the monomethyl ethers. The yield of the 2,3-di-O-methyl ether was 0.2 g, $[\alpha]D^{20}$–183.8° (c 0.8). The yields of the fractions containing mixtures of the 3,4- and 2,4-di-O-methyl ethers and the 2,4- and 2,3-di-O-methyl ethers were 0.17 and 0.36 g, respectively. The preparative GLC of the first mixture gave in one cycle 23 mg of the 3,4-di-O-methyl with mp 74-75°C $[\alpha]D^{20}$ –182.5° (c 0.5), and 32 mg of the 2,4-di-O-methyl ether, $[\alpha]D^{20}$ –210.1° (c 0.9).

When the second mixture was chromatographed, the yields of 2,4- and 2,3-di-O-methyl ethers were 26 and 30 mg, respectively.

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OPTIMIZATION OF THE PRECIPITATION OF PLANTAGLYUTSID FROM EVAPORATED AQUEOUS EXTRACTS

K. A. Sabirov and A. M. Khagi

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The optimization of one of the stages of the technology of Plantaglyutsid – its precipitation from the evaporated aqueous extract with ethanol – has been optimized by the methods of mathematical statistics. Information has been obtained on the optimum parameters for performing the process with the aim of achieving the maximum yield of preparation and lowering the consumption of raw material.

Plantaglyutsid is the total preparation obtrained from the leaves of Plantago major L. (rippleseed plantain) and it contains a mineralized complex of polysaccharides. It is used in medical practice as an antigastritis agent [1]. The technology of the isolation of Plantaglyutsid was developed by the Khar'kov Scientific-Research Institute of Pharmaceutical Chemistry. In 1978 its production was begun at the Tashkent Pharamecutical Chemical Plant.

There is no information in the literature on the optimization fo the technological stages in the production of Plantaglyutsid.

One of the main stages is the isolation of Plantaglyutsid from the leaves of the rippleseed plantain is its precipitation with ethanol from the evaporated aqueous extract. Hitherto, this process has been performed by treating the still residue after the evaporation of the aqueous extract with ethanol in a ratio of 1:3. The treated solution is kept under static conditions for 3-4 h. The precipitated Plantaglyutsid is separated by filtration, washed with ethanol, and dried.

EXPERIMENTAL

In order to itensify the precipitation stage, to shorten the technological cycle, and to raise the yield of desired product we have studied the main factors affecting the process and have performed its optimization by using the mathematical methods of experimental planning.

On the basis of preliminary experiments we determined as the main factors:

X_1 – the ratio of the volumes of still residue and precipitant;

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TABLE 1. Planning, Results, and Statistical Treatment of the Experiments

The planning matrix of the experiments									Response functions				Levels of the factors and intervals of their variation					
experiment No.	X_0	X_1	X_2	X_3	X_4	X_5	X_{12}	X_{34}	Y_1	Y_2	$\bar{Y}$	$\hat{Y}$	level	X_1, liter/liter	X_3, °C	X_{34}, rpm	X_2, cSt	X_5, min
1	+	−	−	+	+	−	−	−	15.1	15,3	15,2	14,6	Base level	3	60	48	5,5	30
2	+	−	+	−	+	+	+	−	14,2	14.4	14,3	13,4	Interval of variation	0,5	5	12	1 0	10
3	+	+	+	−	−	−	−	−	13.7	14,1	13,9	13 3						
4	+	+	−	+	−	+	+	−	14,4	15,0	14,7	14,5	Upper level	3,5	65	60	6,5	40
5	+	+	−	−	+	+	−	+	12,3	12,8	12,5	13,5	Lower level	2,5	55	36	4,5	20
6	+	−	−		−	−	+	+	14,0	14,6	14,3	13,3						
7	+	−	+	+	−	+	−	+	12 2	13,0	12,6	13,6	Step of steepest ascent	−0,2	−2,3	—	—	—
8	+	+	+	+	+	−	+	+	12,5	11,9	12,2	12,9						

Result of the statistical treatment of the experiments

$S^2\{Y\}$ 0,13	$S^2\{BI\}=0,016$	$S^2_{max}=0,32$	$\sum_{i=1}^{N} S^2\{y\}=$ 1,06	$G_{calc}=0,3019$	$G_{tab}=0,3043$	$b=0,30$	$S^2_R=2,57$	$S_R=5,14$	S_R =5,17	$F_{calc}=2,42$	$F_{tab}=4,46$ $\alpha=0,95$

X_2 – the temperature of the still residue being treated;

X_3 – the dynamic conditions of the precipitation;

X_4 – the viscosity of the still residue;

X_5 – the time of precipitation.

As the optimization criterion we selected the yield of Plantaglyutsid, Y, g.

For optimizing the process we selected the Box–Wilson method and used a fractional factorial design of the 2^{5-2} type [2]. The planning matrix, the levels of the factors and the intervals of their variation, the steps of steepest ascent, and the results obtained (response function), and also the results of a statistical treatment of the experiments and regression equations are given in Table 1.

The results of the experiments are presented in the form of the regression equation:

$$\bar{Y} = 13.71 - 0.39X_1 - 0.46X_2 - 0.38X_3 - 0.16X_4 - 0.19X_5 + 0.16X_{13} - 0.18X_{23}.$$

The significance of the regression coefficients was evaluated from the Student–Fisher t criteria. From a comparison of the values of b with the regression coefficient it follows that the significant factors in this equation are:

X_1 – the ratio of the volumes of the still residue and the precipitant;

X_2 – the temperatures of the still residue.

These factors had coefficients with minus signs in the regression equation, and this means that when a steepest ascent is performed their values must be weakened.

To check of the adequacy of the equation obtained to the true response surface we calculated Fisher's F_p criterion and compared it with tabular values. As can be seen from Table 1, the calculated value of the F criterion was less than the tabular value, which permits us to consider the equation obtained as corresponding to the real process and to perform a steepest ascent along the response surface. The results obtained when experiments were performed according to a steepest ascent program and the conditions of their performance are given below:

Experiment No.	X_1	X_2	X_3	X_4	X_5	Yield $\bar{Y}$
1	3	60	48	5.5	30	15.0
2	2.6	55.4	48	5.5	30	15.4
3	2.4	53.1	48	5.5	30	15.1
4	2.2	48.5	48	5.5	30	14.6

Thus, the optimum regime for the stage of the precipitation of Plantaglyutsid from an evaporated aqueous extracts of the leaves of the rippleseed plantain with ethanol is the treatment of the still residue at a temperature of 55-56°C and a viscosity of 5.5 cSt with ethanol in a ratio of 1:2.6 v/v with stirring at a speed of the stirrer of 48 rpm for 30 min followed by settling for 2 h. The product obtained corresponds to the requirements of the normative-technical documentation [3].

SUMMARY

1. It has been shown that the main factors affecting the precipitation process are the ratio of the volumes of still residue and precipitant, and also the temperature of the still residue subjected to the treatment.

2. An optimization of the precipitation stage has been carried out by the method of mathematical statistics, as a result of which the consumption of ethanol has been decreased by 10-12% and the yield of desired product has been increased by 5-6%.

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