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# SOLID-PHASE METHOD FOR PRODUCING POLYMER COMPLEX OF ROUTINE

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## ABSTRACT
In this paper we discuss problems of obtaining a polymer complex of routine with polyvinylpyrrolidone, optimization of technological parameters of solid-phase synthesis and study obtained complexes.

**KEYWORDS**: routine, polivinylpyrrolidone, solid-phase reaction, vitamin P.

## INTRODUCTION
Routine (vitamin P) is related to bioflavonoids. It is entering the body and acting as anti-ulcer, anti-inflammatory, anti-allergic, radioprotective, choleretic agent is angioprotector and corrector of microcirculation [1-3].

However routine is practically insoluble in water and in physiological solutions, which greatly reduces its bioavailability. In this regard, the creation of new forms of preparation that enhance its solubility, is of particular interest, as it allows to reduce the concentration of the input routine and improve its pharmacological properties.

## MATERIALS AND METHODS
For obtaining the complex of routine a planetary mechanical reactor activator "AGO-2U" (firm Gefest, Russia) has been used. It was established that the formation of complexes is fulfilled with proton-donor hydroxyl group (OH) of the aromatic ring of routine with proton-acceptor lactam group (> N-C = O) PVP [4]. It was established that a substance of rutipol on the pharmacological action more effective (26 to 60%) than routine [5].

## RESULTS AND DISCUSSION
Main stages of solid-phase method for producing a substance of rutipol are the followings: routine and PVP are mixed, loaded into mehanical reactor, carry out mechanical activation and unload the resulting substance.
To simplify technological scheme of the process for producing substance of rutipol and in order to avoid the use of flammable and explosive organic solvents and reducing the total time of the process, we have developed a one-step flexible technology (Figure 1).
In order to identify the optimal conditions for obtaining the complex of routine optimization by the Box-Wilson mathematical experiment planning method has been carried out. On the basis of prior information, as the main factors influencing the process of policomplexformation were selected:
$X_1$- time of grinding - components activation (min.)
$X_2$- value of the influencing force (g),
$X_3$- weight ratio of the starting components (g / g).
The following main levels and varying intervals have been established.

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**Tables:**

***Table 1. Levels of factors and intervals of variation***

| № | Parameters of factors | $X_1$ (min) | $X_2$ (g) | $X_3$ (g:g) |
|---|---|---|---|---|
| 1 | Main level | 7,5 | 40 | 1:2 |
| 2 | Interval variation | 2,5 | 20 | 1:1 |
| 3 | Upper layer | 10 | 60 | 1:3 |
| 4 | Lower level | 5 | 20 | 1:1 |

Optimization parameter of the process for obtaining of the product was taken polycomplex concentration in a solution of 0.1 N HCl, defined spectrophotometrically.

***Table 2. Planning matrix and the results of experiments***

| № | $X_1$ | $X_2$ | $X_3$ | $X_1 X_2$ | $X_1 X_3$ | $X_2 X_3$ | $Y_1$ | $Y_2$ | $Y_{average}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | - | - | + | + | - | - | 50,30 | 51,74 | 51,02 |
| 2 | + | - | + | - | + | - | 36,95 | 38,61 | 37,78 |
| 3 | - | + | + | - | - | + | 54,97 | 57,17 | 56,07 |
| 4 | + | + | + | + | + | + | 46,4 | 47,92 | 47,16 |
| 5 | - | + | - | - | + | - | 66,32 | 68,2 | 67,26 |
| 6 | + | - | - | - | - | + | 35,01 | 36,03 | 35,52 |
| 7 | - | - | - | + | + | + | 40,07 | 41,67 | 40,87 |
| 8 | + | + | - | + | - | - | 76,60 | 79,08 | 77,84 |
| Σ | | | | | | | | | 51,69 |

To optimize the process of the full factorial experiment $2^3$ was used. On the basis of findings was found a mathematical model of the process of mechanic-chemical policomplexformation "Rutipol", which is expressed by the following equation:

**Formulae:**

$$\mathbf{Y=51.69-2.11X_1+10.39X_2-3.68X_3+2.53X_1X_2-3.42X_1X_3-6.78X_2X_3}$$

The results of statistical analysis have showed that the mathematical model is adequate and all coefficients are significant. The high solubility of the resulting complex can be explained by the formation of "entropy-frozen" solution, which contributes to a sharp increase in solubility.
The results of statistical analysis showed that:
a) dispersion is homogeneous (Cochran's criterion): $G_{tab.} = 0.68> = 0.24\ G_{exp.}$
b) model is adequate (Fisher criterion): $F_{tab.} = 6.59> = 5.33\ F_{exp.}$
c) the confidence interval has value: $b_i = 1.37$
Comparing the confidence interval with the regression coefficients of the equation, we conclude that all factors have maximum impact to optimization parameter. Due to technical limitations of the grinder (factor $X_2$) the fulfillment of the experiments on the steep scaling was not possible.
Thus, we have optimized the mechanic-chemical technology of producing complex of routine, made the mathematical model of the process, the solid-phase interaction of routine with polyvinylpyrrolidone, found influencing factors to the process. Optimal conditions for obtaining the complex of routine are:
• grinding time 10 min .;
• energy intensity 60g;
• ratio of starting components 1:1.
In optimal conditions of the experiment has been shown that by mechanical processing routine with PVP the solubility of routine can be increased from 35% to 78%.
According to the results of the researches has been developed the basic technological scheme of producing the complex preparation of routine, with P-vitamin action.

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Figure:

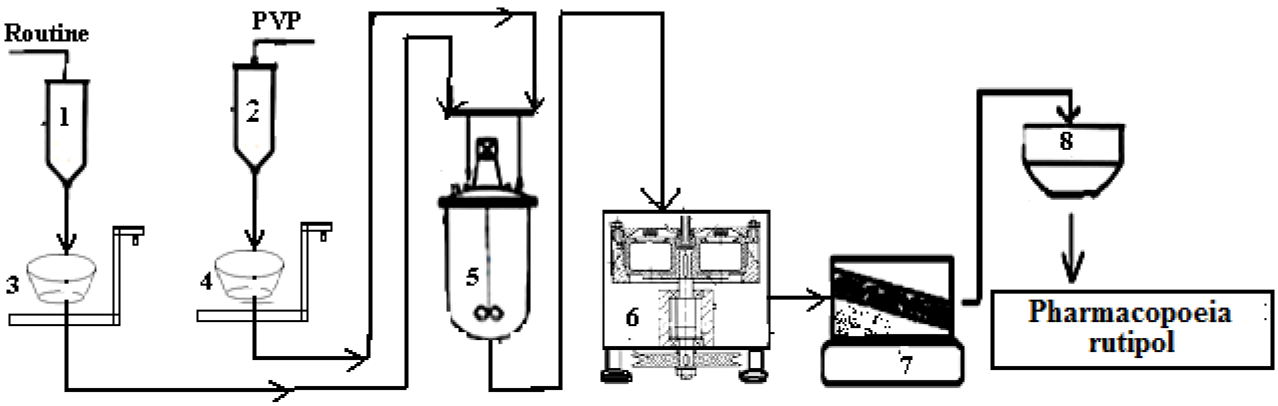


***Figure 1. Solid-phase technological scheme of producing the complex of routine***
***1,2-bunkers; 3 4- scales; 5-mixer; 6- mechanical reactor; 7- vibrating screen; 8- collector.***

Conducting optimization of the technological process, as well as the study of the process of dissolution dynamics showed that the activation of a mixture of routine: PVP = 1: 1 (weight ratio) with the force 60 g for 10 minutes leads to the synthesis of polycomplex of rutipol in which the solubility of routine is increased up to 77, 8% (Figure 2).

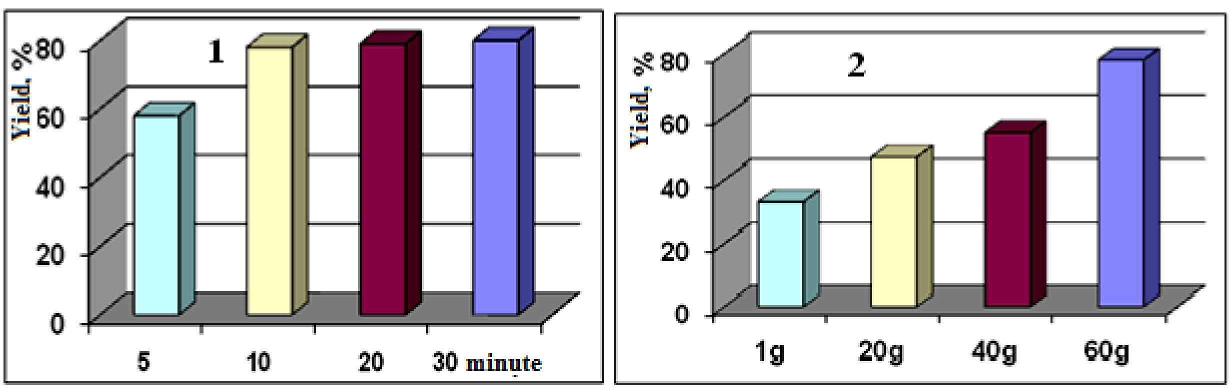


***Figure 2. Effect of mechanosynthesis time (1) and power density of the reactor (2) on the dynamics of solubility of complexes of routine: PVP = 1: 1 (weight ratio)***

Study dialysis of synthesized complexes in different mediums (H2O and 0.1N HCl) showed little dynamics of the complex release, resulting in energy intensity of mechanical reactor 60 g, which indicates the formation of a relatively strong complex of routine with PVP (fig.3).

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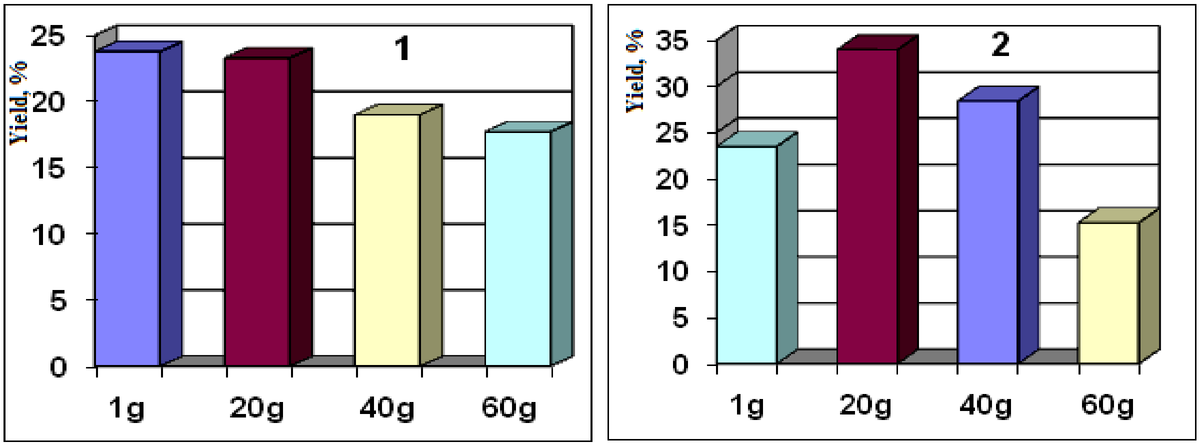


*1-water; 2-solution 0.1 N HCl.*

***Figure 3. Effect of reactor power density to the dynamics of the release of routine complexes: PVP = 1: 1 (weight ratio)***

The change dependence in the molecular weight of PVP (12000 ± 1500) on the value of power density of mechanic reactor and the ratio of routine: PVP (Figure 4) has been studied. In the use of intensive mode of mechanic processing and an increase of routine amount occurs a significant reduction of the molecular weight of the PVP macromolecules (up to 8000 ± 500). A strong decrease of the molecular weight is due to the tension of PVP macromolecules.

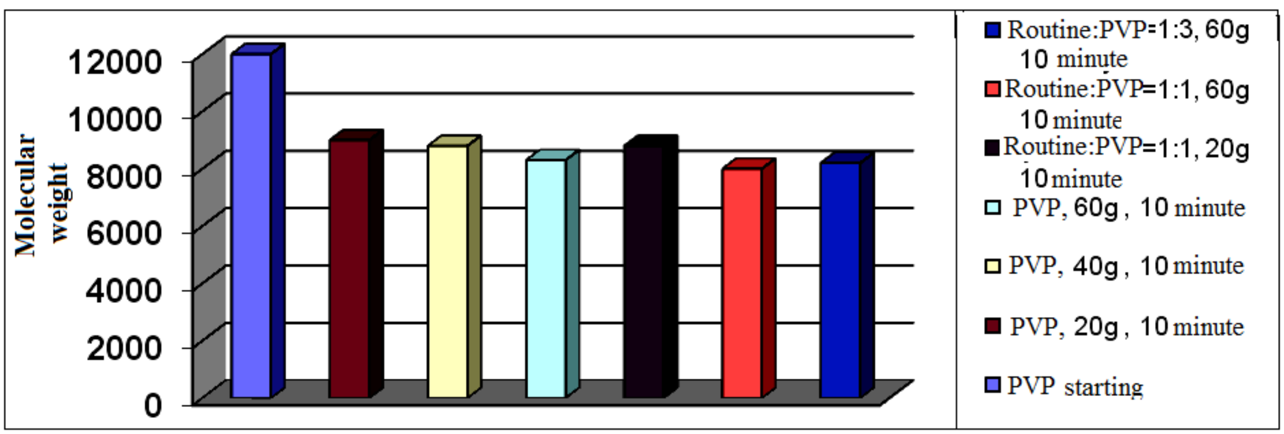


***Figure 4. Dependence of the molecular weight of PVP and complexes on the conditions of mechanical activation***

## CONCLUSION

Thus, the solid-phase reactions of routine with PVP were studied, obtained the complexes with prolonged and enhanced bioavailability. The optimal conditions for the process have been found by the Box-Wilson mathematical experiment planning method. The mathematical model of the process was used and revealed the main factors (weight ratio of the starting materials - 1: 1, the duration - 10 minutes, the energy intensity – 60 g), affecting the process of obtaining the rutipol preparation substance. A reduction in the molecular weight of PVP during mechanical processing has been established.

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