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# Quantitative Analysis of Pentamax Tablets by High-Performance Liquid Chromatography

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**Abstract**—A procedure was proposed for quantitative analysis of Pentamax tablets, a new multicomponent drug, by high-performance liquid chromatography. Model mixtures containing all active and auxiliary components of the tablets were analyzed by the introduced/found method; the absence of a systematic determination error was verified. Preproduction tablet samples were analyzed. The results of the analysis match the requirements of normative technical documentation and technologic loads.

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Pentamax is a new original multicomponent cold medication, antipyretic, and spasmolytic, which was developed and prepared for production by OAO Farmstandart-Leksredstva (Kursk). The drug contains the following components: Paracetamol (I), Ibuprofen (II), Caffeine (III), Drotaverine hydrochloride (IV), Phenobarbital (V), and several auxiliary substances and fillers (Fig. 1).

In parallel with the development of the technology of tablet production, quantitative analyses were developed. Here, we describe the results.

## EXPERIMENTAL

**Reagents.** Acetonitrile (for gradient chromatography, Sigma) and ultrapure water (prepared on a Direct Q Millipore setup; resistivity, 18.2 MΩ/cm) were used to prepare eluents and to dissolve standards and test samples. Standards for the test drugs were pharmaceuticals verified by quality control for compliance to their certificates. The other chemicals used were of at least pure for analysis grade.

**Instruments.** Chromatography was carried out on a Waters Alliance 2695 chromatograph equipped with a Waters 2996 diode-matrix detector. The certified holdup of the chromatograph was 0.650 mL. A column $150 \times 4.6$ mm and a protective precolumn $12.5 \times 4.6$ mm were used, both packed with Zorbax SB C8 reversed-phase stationary phase with the particle size 3.5 μm (Agilent Technologies). Thermostating was at 40°C. The eluent pH was monitored with a pH-673M pH-meter/millivoltmeter equipped with a glass indicator electrode and a silver chloride reference electrode.

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**Solution preparation.** For analysis, carefully ground tablets (exact weight, 0.160 g) were placed into a volumetric flask 100 mL in capacity, $CH_3CN$–$H_2O$ (1 : 4 vol/vol, 40 mL) was added, stirred for 3 min, brought to the volume with the same solvent mixture, and again stirred. To prepare solutions of standards (hereafter, reference solutions), Paracetamol (about 0.040 g) and Ibuprofen (about 0.080 g), both exact weights, were placed into a volumetric flask 100 mL in capacity, the same $CH_3CN$–$H_2O$ mixture (1 : 4) (40 mL) was added and stirred until dissolution; then, solution A (5.0 mL) was added, the same mixed solvent was added to brought the mixture to the required volume, and stirred. Solution A was prepared as follows. Caffeine (about 0.200 g), Drotaverine hydrochloride (about 0.160 g), and Phenobarbital (about 0.040 g), all exact weights, were placed to a volumetric flask 100 mL in capacity, 40 mL of the mixture was added, again stirred until dissolution, brought to the volume with the same solvent mixture, and again stirred. Model solutions for checking the adequacy of the results were prepared in the same manner as reference solutions, but with the proper amount of placebo (a mixture of all components except for the analyte substances). The number of active components in model solutions was varied, covering a range of ±20% of the claimed values.

All solutions were filtered through a hydrophilic membrane filter with 0.45 μm pores (fluoroplastic filters are preferred for their stability in water–acetonitrile solutions).

**Analytical procedure and data processing.** Test and reference solutions were chromatographed. The eluent composition was varied according to the program displayed in Table 1.

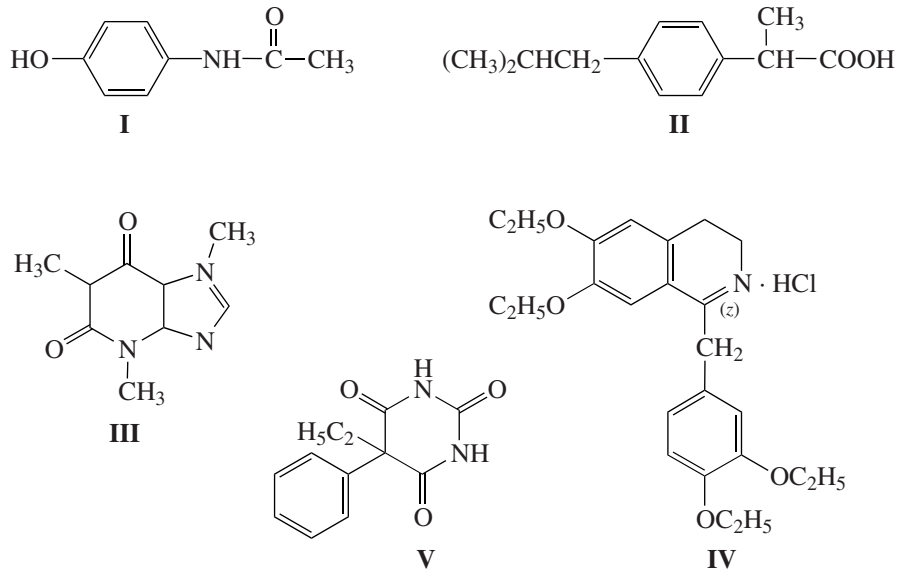


**Fig. 1.** Components of Pentamax tablets.

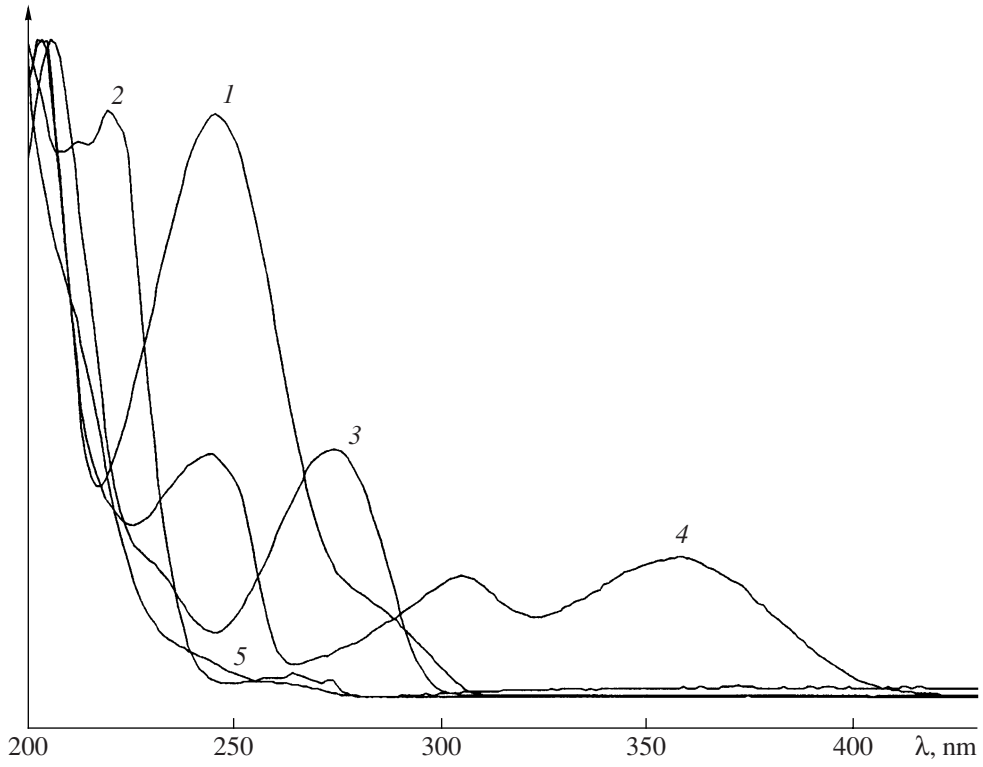


**Fig. 2.** Normalized absorption spectra of (*1*) Paracetamol, (*2*) Ibuprofen, (*3*) Caffeine, (*4*) Drotaverine, and (*5*) Phenobarbital.

The eluent flow rate was 1.0 mL/min; the injected volume was 20.0 μL; the detection wavelength was 210 nm. The peak areas for the analyzed components were determined, and the content of each component was found from

$$X = (S_{test} m_{st} m_{av})/(S_{st} m_{gr}),$$

where $S_{test}$ and $S_{st}$ are mean the peak areas for the analyzed component in the chromatograms of the test solution and reference solution, respectively; $m_{st}$, $m_{av}$, and

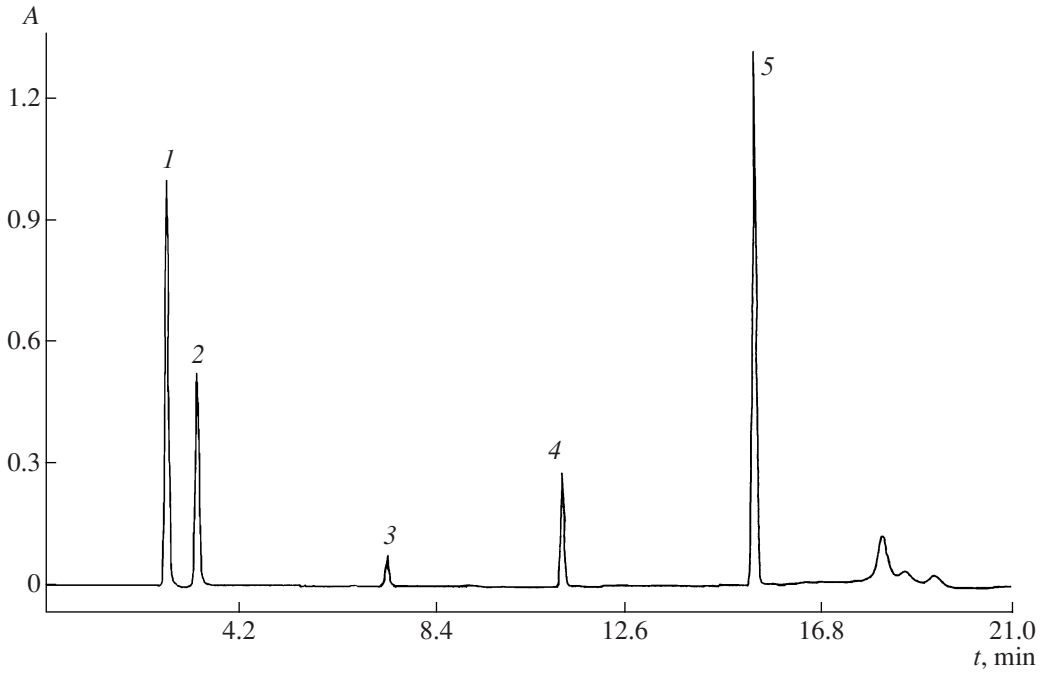


**Fig. 3.** Chromatogram of the test solution for analysis of Pentamax tablets: (*1*) Paracetamol, (*2*) Caffeine, (*3*) Phenobarbital, (*4*) Drotaverine, and (*5*) Ibuprofen.

$m_{test}$ are, respectively, the weight of the standard in the reference solution, the average tablet weight, and the weight of ground tablets taken for preparing the test solution (g).

## RESULTS AND DISCUSSION

**Optimum analytical parameters.** Figure 2 shows the absorption spectra for the analyzed components recorded on-line with a diode-matrix detector. The detection wavelength of 210 was determined with reference to the properties of Phenobarbital, whose absorption is sufficient for reliable determination only in the short-wavelength spectral range.

The eluent acidity was determined proceeding from the properties of Ibuprofen, a major component. To provide the optimum retention of Ibuprofen and the symmetry of its peak, Ibuprofen acid was converted to a molecular form via decreasing the eluent pH to 2.5. To provide the required resolution of the "critical peak

**Table 1.** Gradient program for the eluent composition

| Time, min | Eluent composition, vol % | |
|---|---|---|
| | $CH_3CN$ : 0.025 M $KH_2PO_4$ = 7 : 3 | $CH_3CN$ : 0.025 M $KH_2PO_4$ = 1 : 4 |
| 0 | 20 | 80 |
| 4 | 30 | 70 |
| 16 | 100 | 0 |
| 17 | 100 | 0 |
| 18 | 20 | 80 |
| 21 | 20 | 80 |

Note: pH ($K_2PO_4$) 2.5.

**Table 2.** Metrological characteristics of analysis of Pentamax tablets

| Component | Metrological characteristics | | | | | |
|---|---|---|---|---|---|---|
| | $S_{max}$, g | $S^2_{max}$ | $\varepsilon_{max}$, % | $e_{r(av)}$, % | $\Delta e_r$, % | $e_{r\,max}$, % |
| Paracetamol | 0.00024 | $5.98 \times 10^{-8}$ | 2.39 | –0.051 | 0.169 | –1.33 |
| Caffeine | 0.00006 | $8.16 \times 10^{-8}$ | 2.99 | –0.038 | 0.134 | –1.33 |
| Ibuprofen | 0.00029 | $7.17 \times 10^{-8}$ | 1.92 | –0.043 | 0.126 | –1.43 |
| Phenobarbital | 0.00001 | $1.59 \times 10^{-10}$ | 3.40 | –0.089 | 0.108 | 1.06 |
| Drotaverine hydrochloride | 0.00007 | $4.34 \times 10^{-9}$ | 3.55 | 0.024 | 0.162 | 1.34 |

**Table 3.** Analysis of three samples of tablets Pentamax

| Component | In one tablet, g ($n$ = 9; $P$ = 0.95) | | | | | |
|---|---|---|---|---|---|---|
| | Technical norm | $x_{av}$ | $s$ | $s_{x_{av}}$ | $\Delta x_{av}$ | $\varepsilon$, % |
| Paracetamol | 0.285–0.315 | 0.298 | 0.002 | 0.00067 | 0.00158 | 0.53 |
| | | 0.306 | 0.005 | 0.00167 | 0.00395 | 1.29 |
| | | 0.294 | 0.004 | 0.00133 | 0.00316 | 1.07 |
| Caffeine | 0.04625–0.05375 | 0.0492 | 0.0009 | 0.00030 | 0.00071 | 1.45 |
| | | 0.0501 | 0.0007 | 0.00023 | 0.00055 | 1.10 |
| | | 0.0498 | 0.0006 | 0.00020 | 0.00047 | 0.95 |
| Ibuprofen | 0.380–0.420 | 0.389 | 0.004 | 0.00133 | 0.00316 | 0.81 |
| | | 0.404 | 0.005 | 0.00167 | 0.00395 | 0.98 |
| | | 0.395 | 0.003 | 0.00100 | 0.00237 | 0.60 |
| Phenobarbital | 0.009–0.011 | 0.0099 | 0.0004 | 0.00013 | 0.00032 | 3.19 |
| | | 0.0105 | 0.0005 | 0.00017 | 0.00040 | 3.76 |
| | | 0.0097 | 0.0003 | 0.00010 | 0.00024 | 2.44 |
| Drotaverine hydrochloride | 0.0370–0.0430 | 0.0401 | 0.0007 | 0.00023 | 0.00055 | 1.38 |
| | | 0.0388 | 0.0007 | 0.00023 | 0.00055 | 1.43 |
| | | 0.0397 | 0.0008 | 0.00027 | 0.00063 | 1.59 |

pair"[2] (Paracetamol and Caffeine peaks) and the optimum retention time of the last (Ibuprofen) peak, two stages were introduced to the proposed gradient program at which the concentrations of the organic modifier in the eluent were varied at different rates. The first stage (before the Caffeine elution peak) is slower; the second (before the Ibuprofen elution peak) is more rapid. This schedule ensures the optimum separation of the analyte mixture (Fig. 3); the use of other columns can require corrections.

[2] See Schoeunmakers, P.J., *The Optimization of Chromatographic Selectivity: A Guide to Method Development*, Amsterdam: Elsevier, 1986. Translated under the title *Optimizatsiya selektivnosti v khromatografii*, Moscow, 1989.

**Analysis of model mixtures.** Seventeen solutions were prepared in which the content of the analyzed compounds was ±20% of the values specified by the formulation. The solutions were analyzed as described in the section *Analytical procedure and data processing*, and the results were processed as introduced/found using Excel worksheets. Table 2 displays the results. Comparing the mean relative precisions of component determinations ($e_{r(\mathrm{av})}$) with the corresponding confidence ranges $\Delta e_r$, we find no systematic error ($e_{r(\mathrm{av})} < e_r$). The peak areas for the analyzed compounds are linear functions of their concentrations in the specified range (the correlation coefficient, $K_{\mathrm{corr}} > 0.99$).

**Analysis of tablet samples.** Preproduction tablet samples were analyzed by the procedure developed. The results of these analyses (Table 3) were in accord with the normative documentation and technological parameters.