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ARTICLES

Kinetic–Chromatographic Determination of 4-Methylaminoantipyrine in Pentalgin N and Pentalgin FS Tablets

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Abstract—4-Methylaminoantipyrine (4-MAAP) is the main product of analgin decomposition in aqueous–organic solutions used in the analysis of Pentalgin N and Pentalgin FS tablets. The determination of 4-MAAP in tablets is complicated by the fast decomposition of analgin in the course of sample dissolution. The use of nonaqueous solvents in subsequent HPLC analysis is unreasonable, because the shapes of analyte peaks are deteriorated and the decomposition of analgin is not prevented. A procedure for the kinetic–chromatographic determination of both 4-MAAP in tablets and its amount at the moment of sample dissolution is proposed.

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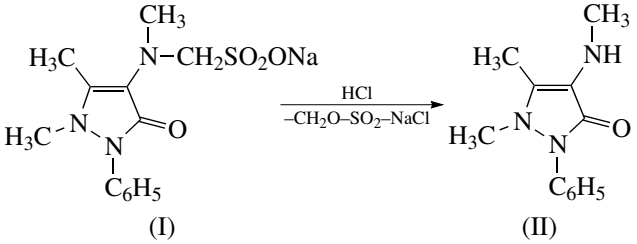
Pentalgin N and Pentalgin FS Tablets are commercially produced five-component pharmaceuticals with analgetic and antipyretic effects. A rather unstable analgin becomes yellow upon storage. The color of similar multicomponent preparations containing no analgin remains unchanged. It is known that analgin (I) is unstable in aqueous and aqueous–organic solutions [1–5] and that 4-methylaminoantipyrine (II) is the main product of its decomposition [6]:



(I) (II)

The decomposition of analgin in tablets can occur in the presence of moisture upon storage. In addition, the further decomposition of 4-MAAP with the formation of a colored product is possible.

According to prevailing regulations, the "colored impurities" index is used to characterize this process. This index is estimated by the absorbance of a test solution at 420 nm, at which only the yellow decomposition product absorbs light whereas the other tablet components are optically inert. This procedure is characterized by low sensitivity and poor reproducibility of the results. The Pharmacopeial Committee ordered the producer of the above pharmaceuticals to introduce a procedure for determining 4-MAAP, the decomposition product of analgin, into the regulations.

The goal of this work was to develop a procedure for the quantitative determination of 4-MAAP in Pentalgin N and Pentalgin FS tablets in routine analysis.

EXPERIMENTAL

Reagents. To prepare mobile phases (MPs) and dissolve the reference and test samples of the studied pharmaceuticals, we used acetonitrile for gradient chromatography, methanol for chromatography (Merck, Germany), and ultrapure water with a specific resistance of 18.2 MΩ/cm obtained on a Direct Q instrument (Millipore). To record IR spectra, we used KBr for spectroscopy (Fluka, US). Pharmaceutical analgin, checked by the quality control department of the plant and complying with all requirements of the regulations, was used. The remaining reagents were of analytical or better grade.

Instruments. A Waters Alliance 2695 chromatograph with a Waters 2996 diode-array detector was used at room temperature. The dead volume of the chromatograph declared in the data sheet was less than 0.650 mL. A column 3.9 × 150 mm with a precolumn 3.9 × 20 mm filled with the reversed-phase Nova-PAK C18 adsorbent with a particle size of 4.0 μm (Waters) were used. The IR spectra of analgin, the product of its decomposition, and 4-methylaminoantipyrine prepared as tablets with KBr in the ratio 1 : 300 were recorded on

an Avatar 360 IR-Fourier spectrometer (Nicolet, United States).

Preparation of solutions. Analgin solution. Analgin (about 0.0600 g) was dissolved in 20 mL of water in a 100.0-mL volumetric flask; the solution was diluted to the mark with water and stirred.

4-MAAP solution. Analgin (~0.0600 g) was placed in a 100.0-mL volumetric flask, 20 mL of a 1 M HCl solution was added, and the solution was diluted with water to the mark and heated for 2 h on a water bath at 60°C. The concentration of 4-MAAP was calculated by the assumed reaction equation and confirmed by HPLC.

Test solution. About 0.1460 g of triturated Pentalgin N (0.1600 g of Pentalgin FS) tablets and 0.5 g of Na_2SO_3 were placed in a 100.0-mL volumetric flask, 10 mL of water was added, and the solution was stirred for 1 min. A 30-mL portion of acetonitrile was added and shaken for 3 min. The solution obtained was diluted with water to the mark, stirred, and filtered through a hydrophilic membrane filter with a pore size of 0.45 μm. Fluoroplastic filters stable in water–acetonitrile solutions are preferable.

Reference solution. A 0.5-g portion of Na_2SO_3 was placed in a 100.0-mL volumetric flask, 20 mL of water was added, the solution was stirred until the salt was dissolved, and 5 mL of acetonitrile and 2.0 mL of the test solution were added. The solution obtained was diluted with water to the mark, stirred, and filtered through a hydrophilic membrane filter with a pore size of 0.45 μm.

Mobile phases. As mobile phases (MPs), we used solutions containing acetonitrile, a 0.025 M KH_2PO_4 solution, and water in the volume ratio 10 : 25 : 65 for MP A and 60 : 25 : 15 for MP B.

Extraction of 4-MAAP from solutions of analgin and tablets. To decompose analgin to the greatest extent, we used its solutions stored for three days after preparation. The tablets to be analyzed were carefully triturated and heated for 3 h at 110°C. 4-Methylaminoantipyrine was extracted with three 20-mL portions of chloroform from 100 mL of the solution and with a single 20-mL portion of chloroform from 0.140 g of triturated tablets. The extracts were evaporated, the residue was dissolved in 20 mL of an acetonitrile–water mixture (1 : 1 v/v), transferred to a 100.0-mL volumetric flask, diluted with water to the mark, and filtered through a 0.45-μm fluoroplastic membrane filter. The solutions obtained were chromatoghraphed under the conditions given below.

Determination of the coefficient of analgin response with respect to 4-MAAP. The knowledge of the response coefficient simplifies the procedure of routine analysis by eliminating the use of a 4-MAAP solution as a reference and replacing it with a dilute test solution, the reference solution. The response coefficient of analgin with respect to 4-MAAP was determined from the results of the chromatographic analysis of solutions containing 0.0120 mg/mL analgin and 0.0108 mg/mL 4-MAAP (2% of the concentration of analgin in the test solution is the MPC for 4-MAAP).

Table 1. Calculation of the response coefficient (K_{resp}) of analgin with respect to 4-MAAP

Analgin		4-MAAP	
Concentration, mg/mL	S, mV s	Concentration, mg/mL	S, mV s
0.012	320128	0.0108	433026
	318617		432066
	317328		434158
	317498		429476
	316148		433860
	315079		428489
	317345		434190
	316224		434262
	315038		434816
	317045		432705
S_{aver}, mV s (average)	317045		432705
K_{resp}	0.657 ± 0.003 ($P = 0.95$, $n = 10$)		

The response coefficient K_{resp} was determined by the equation

$$K_{resp} = (S_{an}c_{4\text{-MAAP}})/(S_{4\text{-MAAP}}c_{an}), \quad (1)$$

where S_{an} and c_{an} are the peak area and concentration of analgin and $S_{4\text{-MAAP}}$ and $c_{4\text{-MAAP}}$ are the peak area and concentration of 4-MAAP, respectively. The calculations of the response coefficient are presented in Table 1.

Determination procedure and calculation of results. Aqueous solutions of analgin, 4-MAAP, extracts, and Pentalgin N tablets were analyzed in the gradient elution mode at a flow rate of MP of 1.0 mL/min and detected at 244 nm using the following program:

Time, min	0	10	11	12	152
MP A, vol. %	100	0	0	100	100
MP B, vol. %	0	100	100	0	0

Pentalgin FS tablets were analyzed in a similar gradient elution mode; it differed from the previous analysis in the maximum concentration of MP B (80 vol %) required for the better resolution of paracetamol and analgin peaks.

Each of the aliquot portions (20 μL) of the test and reference solutions was chromatographed at least twice. The peak area of 4-MAAP in the test solution and that of analgin in the reference solution were calculated, and the concentration of 4-MAAP in the ana-

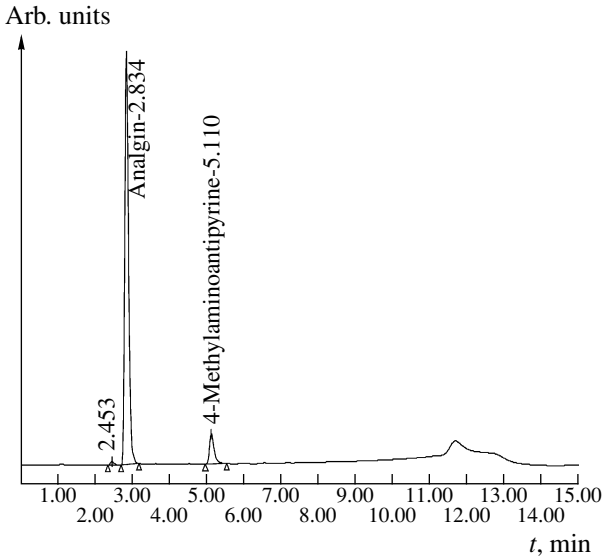


Fig. 1. Chromatogram of an aqueous solution of analgin (0.6 mg/mL) 20 min after its dissolution.

lyzed tablets c_{imp} was found in percentage of the analgin concentration using the equation

$$c_{imp} = (c_{an}K_{resp}S_0)/S_{an}, \quad (2)$$

where S_0 is the peak area of 4-MAAP at the initial moment of time; S_{an} is the peak area of analgin in the chromatogram of the reference solution; c_{an} is the concentration of analgin in the reference solution as a percentage of the initial concentration (2.0 vol %); and $K_{resp} = 0.657$ is the coefficient of analgin response with respect to 4-MAAP.

The peak area of 4-MAAP at the initial moment of time S_0 was calculated by the equation

$$S_0 = S_{last} - (S_{last} - S_1)t/\Delta t, \quad (3)$$

where S_{last} is the peak area of 4-MAAP in the last chromatogram; S_1 is the peak area of 4-MAAP in the first chromatogram; t is the time from the moment of sample dissolution to the emergence of the 4-MAAP peak in the last chromatogram, min; and Δt is the time between the moments of the elution of 4-MAAP peaks in the first and last chromatograms, min.

RESULTS AND DISCUSSION

Two main techniques were considered while developing the procedure for determining the decomposition product of analgin (4-MAAP) in tablets.

The first is the preliminary isolation of 4-MAAP from tablets together with its simultaneous preconcentration and the following determination of 4-MAAP by HPLC. In this case, two variants can also be feasible: (1) the dissolution of a dry residue after evaporating the extractant in a water–organic solvent and the determination of 4-MAAP by reversed-phase HPLC; and (2) the use of a chloroform extract to determine the 4-MAAP impurity by normal-phase HPLC.

The second technique is the dissolution of a sample in a polar organic solvent or an aqueous–organic mixture and the subsequent determination of 4-MAAP under the conditions of chromatographic separation previously found for the quantitative analysis of Pentalgin N tablets [7].

Analysis of extracts from aqueous solutions of analgin and tablets. After evaporating the chloroform extracts of the aqueous solutions of analgin, an oily yellow substance was obtained from the neutral solution and a colorless crystalline substance was obtained from a 0.2 M HCl solution. The chromatograms of both products exhibited a peak with $t_{retention}$ ~ 5.1 min. The peak of analgin ($t_{retention}$ ~2.6 min) was present only in the chromatogram obtained for the extract from the aqueous solution. The peak of 4-aminoantipyrine was absent.

A peak with $t_{retention}$ ~5.1 min was also present in the chromatogram of the chloroform extract of tablets, along with the peaks of all active substances present in tablets. Thus, chloroform is not a selective extractant for 4-MAAP and preliminary extraction is unreasonable.

Analysis of aqueous solutions of analgin. The aqueous solutions of analgin (in 0.2 M HCl, pH 8.0) used in this work were analyzed under the specified conditions. The chromatogram of the solution with pH 8.0 (Fig. 1) and that of the test solution of tablets (Fig. 2) contained a peak with $t_{retention}$ ~ 5.1 min, and its area grew after subsequent injections. Because these solutions also contained analgin, this peak was assigned to the product of analgin decomposition. The analgin peak was virtually absent from the chromatogram of the hydrochloric acid solution of analgin (its area was smaller than 0.2% of the initial value), whereas the area of a rather large peak at $t_{retention}$ ~ 5.1 min remained unchanged in the repeated analysis. The absence of 4-aminoantipyrine from both solutions was confirmed by the analysis of these solutions to which 4-aminoantipyrine ($t_{retention}$ ~ 4.9 min) was added. Thus, analgin decomposed in all solutions to form a single (main) product. According to [6], this occurred in acidic solutions. The acidic solution remained colorless, and, according to our data, the concentration of the decomposition product remained unchanged for at least 7 days.

Analysis of IR spectra of analgin, the product of its decomposition, and 4-aminoantipiryne was carried out to additionally confirm the nature of the forming impurity.

A broad band in the wave number region of 1230–1150 cm^{-1} and some weak bands corresponding to the absorption of the detaching –O–SO_2–O– group in the range from 1440 to 1350 cm^{-1} disappeared in going from the spectrum of analgin to the spectra of its

decomposition product and 4-aminoantipiryne [8]. In the spectrum of 4-aminoantipiryne, two intense bands at 3430 and 3322 cm^{-1}, typical of primary amines, were present; and, in the spectrum of the decomposition product of analgin, a band at 3334 cm^{-1} referred to secondary amines was observed [8].

Hence, 4-aminoantipiryne is not the decomposition product of analgin in aqueous solutions. The results obtained and the published data point to the fact that 4-MAAP is the decomposition product of analgin.

Stability of analgin in methanolic solutions. It has been found earlier that, as the concentration of acetonitrile was increased, the stability of analgin in the solution is enhanced [1]. Therefore, it was assumed that an anhydrous solvent should be used to determine 4-MAAP in tablets to avoid the overestimation of the results because of the decomposition of analgin in the solution. One of a few solvents dissolving analgin is methanol. However, it was found that analgin also decomposed in methanol containing less than 0.1% water to give 4-MAAP (Table 2).

Determination of 4-MAAP in Pentalgin N and Pentalgin FS tablets. Thus, it is difficult to find a solvent for analgin in which it does not decompose to form 4-MAAP. It is not easier to find a selective extractant for the impurity to be determined. Therefore, we proposed another solution for this problem based on the kinetic approach. The area of the 4-MAAP peak at a certain moment in time corresponds to its total amount formed in tablets upon storage and in the solution during the dissolution of a sample. To minimize the second component, we proposed that the kinetic regularity be used for the reaction of the first (pseudo-first) order

$$c_A = c_A^{eq}(1 - e^{-kt}), \quad (4)$$

where c_A and c_A^{eq} are the concentrations of the reaction product at a moment of time t (min) and at the moment the equilibrium is attained (M), respectively, and k is reaction rate constant, min^{-1}.

Because the sample was dissolved under the conditions of the maximum stabilization of analgin [1], it may be assumed that the time of observation (the period of the three first injections) was the initial period of the

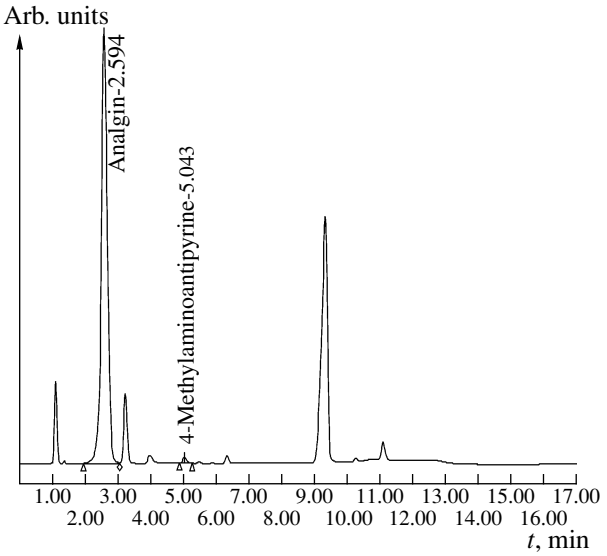


Fig. 2. Chromatogram of a test solution for determining 4-MAAP in Pentalgin N tablets (the not unindicated peaks: sulfite ($t_{retention}$ ~ 1.1 min); caffeine (3.2 min); codeine (4.0 min); phenobarbital (6.4 min); and naproxen (9.3 min).

decomposition of analgin in the sample, that is, the reaction time t was rather short. In this case, we can assume that all terms of the Maclaurin-series expansion of the summand e^{-kt}, except for the first and second terms, can be neglected:

$$c_A = c_A^{eq}\left[\left(1 - \left(1 + \frac{-kt}{1!} + \frac{(-kt)^2}{2!} + \ldots + \frac{(-kt)^n}{n!} + \ldots\right)\right] \approx c_A^p kt. \quad (5)$$

The total concentration of the decomposition product, in this case, will be as follows:

$$c_A^{total} = c_A^0 + c_A^p kt, \quad (6)$$

where c_A^{total} is the concentration of the decomposition product in tablets, and the second factor corresponds to

Table 2. Determination of 4-MAAP in Pentalgin FS tablets using different solvents (P = 0.95; n = 3; K_{resp} = 0.657)

Solvent	t, min	S_{an}, mV s	Series 2012002			Series 3012002			Series 4012002		
			S, mV s	c, %	c_0, %	S, mV s	c, %	c_0, %	S, mV s	c, %	c_0, %
30 vol % CH_3CN	10	311764	38990	0.165		40222	0.170		45241	0.192	
5.0 mg/mL	26	309833	51189	0.217		54439	0.231		58393	0.247	
Na_2SO_3, H_2O	42	308531	62033	0.263	0.136	68521	0.290	0.133	72496	0.307	0.155
CH_3OH	10	327772	49271	0.198		52294	0.210		59909	0.241	
	26	327034	56477	0.227		60714	0.244		70968	0.285	
	42	325381	64055	0.258	0.179	69311	0.279	0.189	81082	0.326	0.215

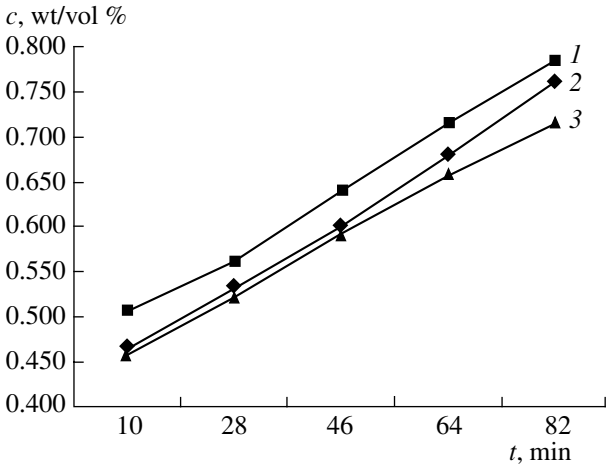


Fig. 3. Concentration of 4-MAAP in test solutions of Pentalgin N tablets as wt/vol % of analgin amount in tablets as a function of time from the moment of sample dissolution (*1*, series 35102005; *2*, series 22072005; and *3*, series 471105).

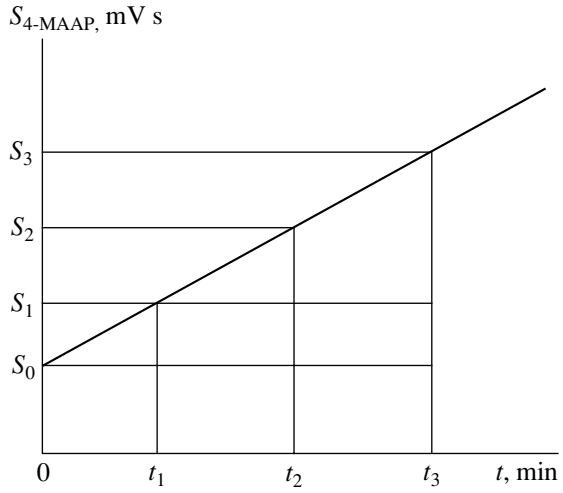


Fig. 4. Calculation of the 4-MAAP peak area at the moment of sample dissolution.

the amount of the decomposition product formed in the solution.

It follows from equation (6) that the concentration of the decomposition product in the initial period of the reaction should increase linearly and the interception of the linear dependence $c_A^{total} = f(t)$ with the ordinate axis will correspond to the concentration of A at the initial moment of time.

The experimental data obtained confirmed the assumptions of the first (pseudo-first) order of the reaction and of the linear character of the $c_A^{total} = f(t)$ dependence within the period of reaction observation (Fig. 3). Thus, the correlation coefficient of the linear dependence of the 4-MAAP peak area on time from the moment of sample dissolution was higher than 0.99 for six test samples of Pentalgin N tablets (Table 3).

Thus, at least two chromatograms of a test solution are required to determine the initial concentration of 4-MAAP. Its concentration in tablets can be calculated by Eq. (2) from the areas of the 4-MAAP peaks. Figure 4 elucidates the calculation of the 4-MAAP peak area at the initial moment of time (S_0). Six samples of Pentalgin N tablets and three samples of Pentalgin FS tablets were analyzed. The concentration of 4-MAAP in Pentalgin N tablets was calculated in two ways: by dividing the impurity peak area by the peak area of analgin in the reference solution (formula 2) and by dividing the impurity peak area by the peak area of analgin in the test solution. The results obtained were identical (Table 3), which points to the proportionality of the analgin peak area to its concentration in the range test solution–reference solution.

Pentalgin FS tablets were analyzed using different solvents: a water–acetonitrile mixture in the presence of Na_2SO_3 and methanol (Table 2). The higher concentration of 4-MAAP was obtained using methanol. This can be explained by the decomposition of 4-MAAP in the presence of Na_2SO_3 (pH ~ 8.5). This assumption was confirmed by the analysis of three solutions of 4-MAAP in the first solvent. For each solution, three successive chromatograms were obtained. The areas of the 4-MAAP peaks in them were as follows:

Number of solutions	1	2	3
$S_{4\text{-MAAP}}$, mV s	453893	455202	443783
	446554	450670	438407
	439612	441687	432851

The first solvent is more suitable for work and is less dangerous from the viewpoint of accident prevention.

The performance characteristics of the proposed kinetic–chromatographic procedure for determining 4-MAAP were estimated by the added–found method in the analysis of model solutions containing all active and auxiliary substances of tablets. The samples of commercially produced triturated tablets to which a solution of 4-MAAP prepared by the above-mentioned procedure was added were used as a placebo, a sample containing all components of the test sample except for analyte. The following results were obtained: $s_{max} = 0.078\%$; $s_{max}^2 = 0.006$, $\varepsilon_{cp} = 9.2\%$, $\varepsilon_{max} = 17.3\%$, $e_{raver} = 0.044\%$, $e_{rmax} = 3.64\%$, and $\Delta e_r = 0.673\%$. It follows from these data that the systematic error of analysis is absent, because the average value of the relative error e_{raver} is lower than its confidence level Δe_r. The procedure is recommended for inclusion in the regulations for the routine control of pharmaceutical products.

Table 3. Determination of 4-MAAP in Pentalgin N tablets

Experiment 8-1103					
t, min	10	26	42	58	74
K_{resp}	0.657				
S_{an}, mV s	14178039	14130544	14922563	14884209	14916333
S_{anr}, mV s	276876	271105	266680	273029	267758
S_{imp}, mV s	104537	117521	132871	147835	163576
$c_{imp\ an}$, %	0.484	0.546	0.585	0.653	0.720
$c_{imp\ anr}$, %	0.496	0.570	0.655	0.711	0.803
$c_{imp\ an\ 0}$, % (K_{corr}) ($P = 0.95$, $n = 5$)	0.446 ± 0.008 (0.996)				
$c_{imp\ anr\ 0}$, % (K_{corr}) ($P = 0.95$, $n = 5$)	0.449 ± 0.007 (0.998)				
$c_{imp\ an\ form\ 0}$, % ($P = 0.95$, $n = 3$)	0.452 ± 0.009				
Experiment 9-1203					
S_{an}, mV s	14736771	14633284	14635571	14523160	14579480
S_{anr}, mV s	297893	285011	281888	286298	285393
S_{imp}, mV s	106239	120039	135575	148466	163574
$c_{imp\ an}$, %	0.474	0.539	0.609	0.672	0.737
$c_{imp\ anr}$, %	0.469	0.553	0.632	0.681	0.753
$c_{imp\ an\ 0}$, % (K_{corr}) ($P = 0.95$, $n = 5$)	0.433 ± 0.001 (0.999)				
$c_{imp\ anr\ 0}$, % (K_{corr}) ($P = 0.95$, $n = 5$)	0.435 ± 0.009 (0.996)				
$c_{imp\ an\ form\ 0}$, % ($P = 0.95$, $n = 3$)	0.429 ± 0.012				
Experiment 10-1203					
S_{an}, mV s	15185632	15130436	15132783	15191173	15169451
S_{anr}, mV s	274999	270255	269818	273876	272113
S_{imp}, mV s	108955	121933	137514	149956	165705
$c_{imp\ an}$, %	0.471	0.529	0.597	0.649	0.718
$c_{imp\ anr}$, %	0.521	0.593	0.670	0.719	0.800
$c_{imp\ an\ 0}$, % (K_{corr}) ($P = 0.95$, $n = 5$)	0.432 ± 0.004 (0.999)				
$c_{imp\ anr\ 0}$, % (K_{corr}) ($P = 0.95$, $n = 5$)	0.480 ± 0.007 (0.998)				
$c_{imp\ an\ form\ 0}$, % ($P = 0.95$, $n = 3$)	0.478 ± 0.009				
Series 35102005					
t, min	10	28	46	64	82
S_{an}, mV s	15968782	15933235	15914377	15881760	15914359
S_{imp}, mV s	123081	135576	154853	172974	189951
$c_{imp\ an}$, %	0.506	0.559	0.639	0.716	0.784
$c_{imp\ anr\ 0}$, % (K_{corr}) ($P = 0.95$, $n = 5$)	0.459 ± 0.007 (0.998)				
Series 471105					
S_{an}, mV s	16067073	15988669	16027684	15839998	15794131
S_{imp}, mV s	112197	126807	144354	158498	172105
$c_{imp\ an}$, %	0.459	0.521	0.592	0.657	0.716
$c_{imp\ anr\ 0}$, % (K_{corr}) ($P = 0.95$, $n = 5$)	0.423 ± 0.003 (0.999)				

Note: S_{an} is the area of the analgin peak in a test solution; S_{anr} is the area of the analgin peak in the reference solution; S_{imp} is the area of the 4-MAAP peak; $c_{imp\ an}$ and $c_{imp\ an\ 0}$ are the concentration of 4-MAAP calculated from the analgin peak in the test solution and the corresponding initial concentration, respectively; $c_{imp\ anr}$ and $c_{imp\ anr\ 0}$ are the concentration of 4-MAAP calculated from the analgin peak in the reference solution and the corresponding initial concentration, respectively; $c_{imp\ an\ form\ 0}$ is the concentration of 4-MAAP calculated by formula (1); and K_{corr} is the correlation coefficient of the linear dependence of 4-MAAP concentration on time from the moment of dissolving a sample.

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