Prosudba kakvoće postupka za određivanje teških metala na reaktivnim nosačima

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Quality assessment of the procedure for determination of heavy metals on reactive carriers

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Quality control and validity check of the solid-phase spectrophotometric procedure (Me-SPS) for determination of heavy metals important in pharmaceutical practice: zinc (Zn-SPS), lead (Pb-SPS), and cobalt (Co-SPS) were performed using a very simple and informative prevalidation concept. Further, metrological characteristics of the Me-SPS procedure together with the diagnosis of particular prevalidation steps were evaluated. Favourable prevalidation characteristics, *i.e.*, ideal analytical function, homogeneity of data material, low limit of quantitation, and acceptable accuracy verified the quality of the Me-SPS procedure and pointed to the limitations of some investigated systems.

Keywords: analytical procedure quality control, prevalidation strategy, heavy metals, solid-phase spectrophotometry

Analytical procedures represent a special group of technical and scientific measurement systems. They are inseparable from their evaluation and optimization steps, as a logical connection between a real analytical problem and measurement. Modern analytical practice requires quality control and standardization of every analytical procedure, based on unbiased evaluation of the procedure's metrological characteristics. Evaluation of the optimum working conditions of the new procedures and their performance characteristics, ruggedness on small changes of working parameters, validation, and comparison with alternative methods, as well as investigation of the relationship between the acceptance criteria and the procedure data material are unavoidable links of a modern investigation of analytical procedures. Validation of the analytical procedure is undoubtedly an important part of the development of pharmacopoeial and other analytical procedures for quality control of medicines. However, validation is a long lasting and expensive process, which greatly depends on the purpose of the method, the chosen technique, and the procedure in question. Furthermore, there are no unique guidelines for how to perform a validation procedure. Available documents defining validation criteria that must be assessed during the development of an analytical procedure are not precise enough (1–7). They are usually restricted to general concepts and do not provide any experimental approach. In order to help pharmaceutical professionals to validate

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their analytical procedures, several guidelines are recommended (8–10). Further, an experimental design methodology (11–16) and robustness check (17–20) could be applied to demonstrate the set of conditions that are required to obtain a product or process with desirable and optimal characteristics. A comprehensive and informative prevalidation strategy, introduced by Grdinić and Vuković (21), comprises a new philosophy and approach to the evaluation and standardization of analytical procedures, offering new information about the method's figures of merit before starting the proper validation stage. Prevalidation is defined as the formal evidence that an analytical system does what it is supposed to do and is continuing to do so. This simple screening method has proven useful to prevalidate a new analytical method that has been developed or to verify that an analytical method adopted from some other source is applied properly. The aim of this work is to evaluate the metrological characteristics and diagnose the quality of the procedure for determination of heavy metals on reactive polymers (SPS-procedure).

EXPERIMENTAL

The experimental part comprises a description of the solid-phase spectrophotometric procedure used for determination of heavy metals (Me-SPS): zinc (Zn-SPS), lead (Pb--SPS), and cobalt (Co-SPS), as well as a methodological model for the prevalidation procedure.

Apparatus

A double beam UV-Visible spectrophotometer Cary 50 Bio (Varian, Inc., USA) with 1-mm quartz cells was used for all absorbance measurements.

Reagents

All chemicals of analytical-reagent grade as well as doubly distilled water were used throughout the work. Working standard solutions of metals of desired concentrations were prepared by appropriate dilution of the standard stock solution of each metal: Zn, Pb, and Co (Chameleon Reagent, Japan). 0.1% PAN, 1-(2-pyridilazo)-naphthol (Kemika, Croatia) was prepared daily in methyl alcohol. For preparation of 0.5 mol L^{-1} HEPES buffer solution (pH = 8.0), HEPES (Dotite, Japan) was dissolved in water and pH was adjusted with 1 mol L^{-1} NH_4OH.

PAN-resin. – Resin-reagent was prepared as follows. To about 100 mL of a solution containing 24 mL of 0.1% PAN in methyl alcohol, 30 g of cation-exchanger AG 50W-X2 in H^+-form (Bio-Rad Laboratories, USA, particle size of 150–300 μm) was added and the mixture was stirred. After stirring for 1 h, the resin-reagent was converted into the sodium form by addition of 1.0 L of 0.5 mol L^{-1} NaOH and the mixture was stirred for another 1 h. The resin was washed with water and dried in the air. Thus prepared resin was kept in a container at +4 °C.

General procedure

An appropriate volume of the standard stock solution containing 0.05 to 1.0 μmol L^{-1} of the metal was transferred into a 200-mL container. Twenty mL of HEPES buffer (pH = 8.0) was added and the volume was made up to 200 mL with water. PAN-resin (0.2 g) was added into the solution and the mixture was stirred for 30 min. The absorbance of sample (A_S) and the blank (A_B), at the absorption maximum of the reaction product Me-PAN in the resin phase (λ_1) and in the range where only the resin absorbs (λ_2), were measured (Table I). The net absorbance of the product species Me-PAN in the resin phase was calculated according to the equation:

$$A_{net} = A_S - A_B = (A_{S\lambda 1} - A_{B\lambda 1}) - (A_{S\lambda 2} - A_{B\lambda 2}).$$

The difference in absorbance at the absorption maximum and at the non-absorption wavelength was used.

Table I. Characteristic wavelengths of analytical systems

	Zn-SPS	Pb-SPS	Co-SPS
λ_1 (nm)	554	554	625
λ_2 (nm)	750	750	750

Prevalidation

Prevalidation strategy included a total of 24 measurements (n) divided into 6 analytical groups (j) of 4 experiments each (i) relating to the measured and blank values. Standards and blanks were measured in the standard working range of one power of ten (1.0 $x_U = x_1 = x_U$, upper level of analyte, 0.8 $x_U = x_2$, 0.6 $x_U = x_3$, 0.4 $x_U = x_4$, 0.2 $x_U = x_5$, and 0.1 $x_U = x_6 = x_L$, lower level of analyte), alternately in the following group sequence: 1, 6, 2, 5, 3, 4. Working standard solutions for the prevalidation procedure were prepared by appropriate dilution of the standard stock solution of the metal and measurements were performed according to the *General procedure*. Blank solutions were prepared and

Table II. Analytical parameters of Me-SPS systems

Analytical parameter	Zn-SPS	Pb-SPS	Co-SPS
Analyte	zinc	lead	cobalt
Analyte working range (μmol)	0.05–0.50	0.15–1.50	0.12–1.20
Reagent	PAN	PAN	PAN
Total volume (mL)	200	200	200
Matrix	–	–	–

absorbances were measured in the same manner, but with no analyte. Prevalidation strategy was explained in detail in a previous paper (21). Analytical parameters are presented in Table II.

RESULTS AND DISCUSSION

Complexes Zn-PAN and Pb-PAN sorbed on the resin phase showed maximum absorbance in the range from 554 to 560 nm (Fig. 1). In the same wavelengths range, the absorbance of the reagent blank was rather small. Product Zn-PAN possessed a second maximum around 520 nm. Absorption spectrum of Co-PAN significantly differed from the others and showed two maxima, at 584 and 625 nm. Further, the apparent molar absorptivities obtained for Zn (1.26×10^7 L mol^{-1} cm^{-1}), Pb (3.02×10^6 L mol^{-1} cm^{-1}), and Co (1.32×10^7 L mol^{-1} cm^{-1}) showed different spectrophotometric sensitivity of each metal. These differences in sensitivity and spectral characteristics of Me-PAN complexes were used to develop new methodological approach for simultaneous determination of heavy metals in a mixture without previous concentration or separation. Combination of the sensitive Me-SPS procedure and the chemometric algorithm of multicomponent analysis by multiple linear regression enables determination of a particular metal ion at the ng mL^{-1} level in a mixture of heavy metals. It was successfully applied to the determination of traces of heavy metals as impurities in pharmaceutical substances such as Cu in ascorbic acid, Pb in glucose, and Zn in insulin.

As part of the development of new methodology, validity and performance characteristics of the SPS procedure for determination of heavy metals on reactive carriers (Me-SPS) were evaluated using a comprehensive prevalidation strategy (21). The prevalidation system anatomy comprised a fixed general scheme of measurements to which a set of mathematical/statistical tests was applied that included various steps: characterization of analytical groups, checking the limiting groups, testing data homogeneity, estimation of the calibration and analytical evaluation function, outliers recognition, as well as estimation of the limiting values and the system's accuracy and precision.

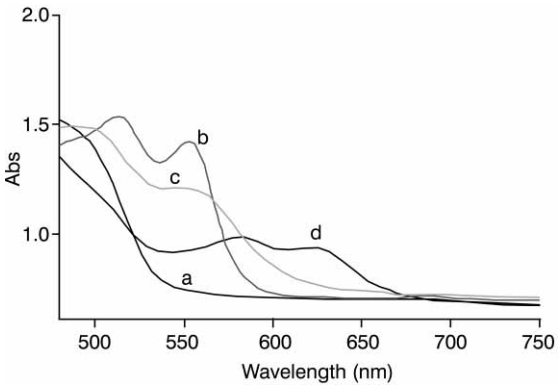

Fig. 1. Absorption spectra of products Me-PAN (0.20 g PAN-resin, V_{sample} 200 mL, optical cell length, 1 mm): a) blank, b) 0.8 μmol L^{-1} Zn, c) 0.9 μmol L^{-1} Pb, d) 0.5 μmol L^{-1} Co.

Characterization of groups 1 to 6

Arithmetic means as well as standard and relative standard deviations of the Me--SPS procedure have a predictive character and were used as a measure of precision. Standardized measurements and descriptive values of Me-SPS procedures are given in

Table III. Standard measurements for the Zn-SPS system

Group *(j)*	Sample No. *(i)*	x (μmol)[a]	B	$\bar{B}/s_B/s_{rB}$ (%)	y	$\bar{y}/s_y/s_{ry}$ (%)	S	$\bar{S}/s_s/s_{rS}$ (%)	A^b	$\bar{A}/s_A/s_{rA}$ (%)
1	I	0.50	0.062	0.060/ ± 0.002/ ± 3.9	0.870	0.871/ ± 0.006/ ± 0.7	0.808	0.811/ ± 0.006/ ± 0.7	1.616	1.622/ ± 0.011/ ± 0.7
	II		0.058		0.863		0.805		1.610	
	III		0.058		0.875		0.817		1.634	
	IV		0.062		0.876		0.814		1.628	
6	I	0.05	0.060	0.059/ ± 0.001/ ± 2.4	0.130	0.127/ ± 0.003/ ± 2.5	0.070	0.069/ ± 0.003/ ± 4.2	1.400	1.385/ ± 0.057/ ± 4.2
	II		0.057		0.130		0.073		1.460	
	III		0.057		0.124		0.067		1.340	
	IV		0.058		0.125		0.067		1.340	
2	I	0.40	0.058	0.059/ ± 0.001/ ± 1.7	0.691	0.697/ ± 0.008/ ± 1.2	0.633	0.638/ ± 0.009/ ± 1.4	1.583	1.595/ ± 0.023/ ± 1.4
	II		0.058		0.701		0.643		1.608	
	III		0.058		0.706		0.648		1.620	
	IV		0.060		0.688		0.628		1.570	
5	I	0.10	0.059	0.059/ ± 0.002/ ± 3.7	0.211	0.210/ ± 0.002/ ± 0.9	0.152	0.151/ ± 0.003/ ± 2.1	1.520	1.505/ ± 0.031/ ± 2.1
	II		0.060		0.211		0.151		1.520	
	III		0.056		0.209		0.153		1.530	
	IV		0.061		0.207		0.146		1.460	
3	I	0.30	0.060	0.059/ ± 0.002/ ± 3.7	0.543	0.545/ ± 0.010/ ± 1.8	0.483	0.486/ ± 0.008/ ± 1.7	1.610	1.620/ ± 0.027/ ± 1.7
	II		0.062		0.555		0.493		1.643	
	III		0.058		0.550		0.492		1.640	
	IV		0.057		0.533		0.476		1.587	
4	I	0.20	0.056	0.058/ ± 0.002/ ± 3.5	0.376	0.370/ ± 0.005/ ± 1.5	0.320	0.312/ ± 0.007/ ± 2.1	1.600	1.558/ ± 0.033/ ± 2.1
	II		0.058		0.371		0.131		1.565	
	III		0.061		0.369		0.308		1.540	
	IV		0.058		0.363		0.305		1.525	
$\bar{S}$ ($\bar{S}_r$, %)				± 0.002 (± 3.3)		± 0.006 (± 1.5)		± 0.006 (± 2.3)		± 0.033 (± 2.3)

[a] Amount of zinc.
[b] Measure of particular sensitivity, $A_n = S_n/x_n$.

Tables III–V. Acceptable precision was obtained for all types of absorbances in all investigated systems. A particularly high level of precision was obtained in the case of Zn--SPS, where all s_r values (S_{rB} from ± 1.7 to ± 3.9%, S_{ry} from ± 0.7 to ± 2.5%, S_{rS} from ± 0.7 to ± 4.2%) satisfied the strict prevalidation criteria ($s_r < \pm 5\%$). Higher fluctuations of s_r

Table IV. Standard measurements for the Pb-SPS system

Group *(j)*	Sample No. *(i)*	x (μmol)[a]	B	$\bar{B}/s_B/s_{rB}$ (%)	y	$\bar{y}/s_y/s_{ry}$ (%)	S	$\bar{S}/s_s/s_{rS}$ (%)	A^b	$\bar{A}/s_A/s_{rA}$ (%)
1	I	1.50	0.058	0.061/ ± 0.003/ ± 5.5	0.567	0.565/ ± 0.006/ ± 1.1	0.509	0.505/ ± 0.009/ ± 1.7	0.339	0.337/ ± 0.006/ ± 1.7
	II		0.065		0.557		0.492		0.328	
	III		0.061		0.571		0.510		0.340	
	IV		0.058		0.566		0.508		0.339	
6	I	0.15	0.061	0.058/ ± 0.002/ ± 3.3	0.113	0.120/ ± 0.006/ ± 4.9	0.052	0.062/ ± 0.008/ ± 12.1	0.347	0.413/ ± 0.050/ ± 12.1
	II		0.057		0.119		0.062		0.413	
	III		0.057		0.127		0.070		0.467	
	IV		0.058		0.122		0.064		0.427	
2	I	1.20	0.062	0.059/ ± 0.002/ ± 3.4	0.493	0.498/ ± 0.007/ ± 1.4	0.431	0.439/ ± 0.008/ ± 1.9	0.359	0.366/ ± 0.007/ ± 1.9
	II		0.058		0.500		0.442		0.368	
	III		0.058		0.507		0.449		0.374	
	IV		0.058		0.492		0.434		0.362	
5	I	0.30	0.057	0.058/ ± 0.002/ ± 3.2	0.171	0.172/ ± 0.003/ ± 1.6	0.114	0.114/ ± 0.004/ ± 3.4	0.380	0.381/ ± 0.013/ ± 3.4
	II		0.059		0.175		0.116		0.379	
	III		0.060		0.169		0.109		0.379	
	IV		0.056		0.174		0.118		0.384	
3	I	0.90	0.060	0.059/ ± 0.002/ ± 3.8	0.409	0.403/ ± 0.006/ ± 1.5	0.349	0.344/ ± 0.004/ ± 1.2	0.389	0.383/ ± 0.004/ ± 1.2
	II		0.056		0.397		0.341		0.379	
	III		0.058		0.399		0.341		0.379	
	IV		0.061		0.407		0.346		0.384	
4	I	0.60	0.058	0.060/ ± 0.002/ ± 3.2	0.300	0.296/ ± 0.006/ ± 1.9	0.242	0.237/ ± 0.006/ ± 2.6	0.403	0.395/ ± 0.010/ ± 2.6
	II		0.060		0.302		0.242		0.403	
	III		0.062		0.293		0.231		0.385	
	IV		0.058		0.290		0.232		0.387	
	$\bar{S}$ ($\bar{S}_r$ %)			± 0.002 (± 3.8)		± 0.006 (± 2.4)		± 0.007 (± 5.3)		± 0.022 (± 5.3)

[a] Amount of lead.
[b] Measure of particular sensitivity, $A_n = S_n/x_n$.

values (from ± 1.2 to ± 12.1%) were obtained for corrected absorbances (S) in the Pb-SPS system. Since corrected (net) absorbances were obtained by simple calculation using blanks and gross values, small deviations of these values could produce relatively high fluctuations of net absorbances.

Table V. Standard measurements for the Co-SPS system

Group *(j)*	Sample No. *(i)*	x (μmol)[a]	B	$\bar{B}/s_B/s_{rB}$ (%)	y	$\bar{y}/s_y/s_{ry}$ (%)	S	$\bar{S}/s_s/s_{rS}$ (%)	A^b	$\bar{A}/s_A/s_{rA}$ (%)
1	I	1.20	0.016	0.017/ ± 0.001/ ± 6.1	0.716	0.708/ ± 0.010/ ± 1.5	0.700	0.692/ ± 0.010/ ± 1.4	0.583	0.576/ ± 0.008/ ± 1.4
	II		0.016		0.705		0.689		0.574	
	III		0.018		0.717		0.699		0.583	
	IV		0.016		0.695		0.679		0.566	
6	I	0.12	0.016	0.016/ ± 0.001/ ± 8.0	0.078	0.077/ ± 0.004/ ± 5.0	0.062	0.061/ 0.004/± 7.0	0.517	0.508/ ± 0.035/ ± 7.0
	II		0.014		0.079		0.065		0.542	
	III		0.016		0.071		0.055		0.458	
	IV		0.017		0.079		0.062		0.517	
2	I	0.96	0.016	0.016/ ± 0.002/ ± 10.2	0.586	0.579/ ± 0.007/ ± 1.2	0.571	0.563/ 0.006/± 1.0	0.594	0.587/ ± 0.006/ 1.0
	II		0.016		0.576		0.560		0.583	
	III		0.014		0.571		0.557		0.580	
	IV		0.018		0.584		0.566		0.590	
5	I	0.24	0.016	0.016/ ± 0.001/ ± 7.7	0.140	0.141/ ± 0.004/ ± 2.5	0.124	0.125/ ± 0.002/ ± 1.8	0.517	0.520/ ± 0.009/ ± 1.8
	II		0.016		0.140		0.124		0.517	
	III		0.015		0.138		0.123		0.513	
	IV		0.018		0.146		0.128		0.533	
3	I	0.72	0.016	0.016/ ± 0.001/ ± 7.7	0.426	0.423/ ± 0.010/ ± 2.3	0.410	0.407/ ± 0.009/ ± 2.2	0.569	0.565/ ± 0.012/ ± 2.2
	II		0.016		0.410		0.394		0.547	
	III		0.018		0.433		0.415		0.576	
	IV		0.015		0.423		0.408		0.567	
4	I	0.48	0.015	0.016/ ± 0.001/ ± 8.3	0.290	0.290/ ± 0.004/ ± 1.5	0.275	0.274/ ± 0.005/ ± 1.9	0.573	0.571/ ± 0.011/ ± 1.9
	II		0.016		0.285		0.269		0.560	
	III		0.017		0.288		0.271		0.565	
	IV		0.014		0.295		0.281		0.585	
	$\bar{S}$ ($\bar{S}_r$ %)			± 0.001 (± 8.1)		± 0.007 (± 2.7)		± 0.007 (± 3.3)		± 0.017 (± 3.3)

[a] Amount of cobalt.
[b] Measure of particular sensitivity, $A_n = S_n/x_n$.

Checking of limiting groups 1 and 6

Results obtained in characterization of all analytical groups were used for further diagnosis in prognostic statistics, including a preliminary check of working range-limiting groups as the first step in mathematical/statistical evaluation of the system data. The emphasis of this checking was on quality control of measurements in the group with the smallest quantity of analyte, x_6. In all procedures, blank signals were significantly lower than the gross signals at the lower analyte level (0.059 < 0.127 in Zn-SPS system, 0.058 < 0.120 in Pb-SPS system, 0.016 < 0.077 in Co-SPS system) and the influence of blank values dispersion on the standard deviation of the procedure could be neglected (R1 and R2, Table VI). Furthermore, s_r values for both gross and corrected signals at lower and upper analyte levels were below ± 2.5% and ± 25%, respectively (R3, Table VI). The preliminary information obtained showed that determination limits (L_{DG}) in investigated systems were expected below the lower analyte level. Additional requirement of the possibility of distinguishing gross and blank signals at x_6 showed excellent (Zn-SPS system) and very good (Pb-SPS and Co-SPS systems) resolution of these signals (R4, Table VI). Predictive character of the preliminary linearity check showed that the linear calibration function is expected only in the Pb-SPS system (R5, Table VI). In addition to checking based on two limiting groups, systematic and deep evaluation of linearity involving all analytical groups is required.

Testing of data homogeneity

To make an objective decision about the homogeneity of blank signals in investigated systems, simple analysis of variance was applied to the six groups of blanks. Further, additional valuable information about homogeneity was obtained from the total standard deviation of blank signals (S_{rBN}) and the Barttlet test. Dispersion within individual groups statistically not different from dispersion between groups for the systems under study pointed to homogeneous blank values (R6, Table VII). Barttlet test was applied to s and s_r deviations for values of different origin (B, y, S, A, and values of the apparent amount of analyte $\hat{x}$). This valuable test pointed to high data homogeneity of standard and relative standard deviations for blank, gross, and corrected values for all systems (R9, Table VII). Inhomogeneity of s and s_r values was observed for A values in the Pb-SPS system. The rigorous requirement R7 (Table VII) showed that blanks were not small compared to the corresponding gross values obtained at x_1 and, therefore, influence of blanks cannot be completely neglected. Influence of inhomogeneity of blank values obtained in R7 could be considered less important since total s_r values for blank measurements in investigated systems were not above ± 50% (R8, Table VII). Since homogeneous blank values were obtained in all investigated systems, influence of blank values could be excluded and gross values were corrected with the grand blank mean ($\bar{B}_N$). Bartlett testing applied to the apparent amount of analyte, $\hat{x}$, pointed to strictly homogeneous values of $s_{\hat{x}}$ and $s_{r\hat{x}}$ for the Zn-SPS and Co-SPS systems, strictly homogeneous $s_{\hat{x}}$, and almost homogeneous $s_{r\hat{x}}$ values for the Pb-SPS system (Tables XI–XIII).

Table VI. Checking of limiting groups 1 and 6

Requirement No.	Zn-PAN		Pb-PAN		Co-PAN	
	Result	Diagnosis	Result	Diagnosis	Result	Diagnosis
R1	AC = 2.19	Blank signals were significantly lower than the signal on lower analyte level, x_6	AC = 2.06	Blank signals were significantly lower than the signal on lower analyte level, x_6	AC = 4.87	Blank signals were significantly lower than the signal on lower analyte level, x_6
R2	R = 11.9% s_{rB1} = ± 3.9% s_{rB6} = ± 2.4%	No significant influence of blank dispersions is expected	R = 10.6% s_{rB1} = ± 5.5% s_{rB6} = ± 3.3%	No significant influence of blank dispersions is expected	R = 38.7% s_{rB1} = ± 6.1% s_{rB6} = ± 8.0%	No significant influence of blank dispersions is expected
R3	s_{ry6} = ± 2.5% s_{rS6} = ± 4.2% s_{ry1} = ± 0.7% s_{rS1} = ± 0.7 % L_{DG} = 0.025 μmol $\bar{L}_{DG}$ = 0.005 μmol s_{rL}= ± 25.2%	Determination limit is expected below x_6	s_{ry6} = ± 4.9% s_{rS6} = ± 12.1% s_{ry1} = ± 1.1% s_{rS1} = ± 1.7% L_{DG} = 0.129 μmol $\bar{L}_{DG}$ = 0.026 μmol s_{rL}= ± 25.2%	Determination limit is expected below x_6	s_{ry6} = ± 5.0% s_{rS6} = ± 7.0% s_{ry1} = ± 1.5% s_{rS1} = ± 1.4 % L_{DG} = 0.072 μmol $\bar{L}_{DG}$ = 0.015 μmol s_{rL} = ± 25.2%	Determination limit is expected below x_6
R4	R = 15.00	Excellent resolution of signals	R = 8.00	Very good resolution of signals	R = 11.91	Very good resolution of signals
R5	R = 8.11	Linear calibration function is not expected	R = 3.06	Linear calibration function is expected	R = 3.75	Linear calibration function is not expected

Table VII. Homogeneity testing

Requirement No.	Zn-PAN		Pb-PAN		Co-PAN	
	Result	Diagnosis	Result	Diagnosis	Result	Diagnosis
R6	$s^2_{Bb} = 2.18 \times 10^{-6}$ $s^2_{Bw} = 3.69 \times 10^{-6}$ $R = 0.59$	Homogeneous blank values	$s^2_{Bw} = 3.30 \times 10^{-6}$ $s^2_{Bb} = 5.08 \times 10^{-6}$ $R = 0.65$	Homogeneous blank values	$s^2_{Bw} = 5.42 \times 10^{-7}$ $s^2_{Bb} = 1.68 \times 10^{-6}$ $R = 0.32$	Homogeneous blank values
R7	$\bar{B}_N < 0.004$ $\bar{B}_N = 0.059$	Influence of blank value is not negligible	$\bar{B}_N < 0.003$ $\bar{B}_N = 0.059$	Influence of blank value is not negligible	$\bar{B}_N < 0.004$ $\bar{B}_N = 0.016$	Influence of blank value is not negligible
R8	$s_{rBN} = \pm 3.1\%$ $s_{BN} = 1.83 \times 10^{-3}$		$s_{rBN} = \pm 3.7\%$ $s_{BN} = 2.17 \times 10^{-3}$		$s_{rBN} = 7.5\%$ $s_{BN} = 1.20 \times 10^{-3}$	
R9	$R(s_B) = 2.37$	s.h.	$R(s_B) = 1.59$	s.h.	$R(s_B) = 0.65$	s.h.
	$R(s_{rB}) = 2.27$	s.h.	$R(s_{rB}) = 1.41$	s.h.	$R(s_{rB}) = 0.73$	s.h.
	$R(s_y) = 7.46$	s.h.	$R(s_y) = 2.09$	s.h.	$R(s_y) = 5.82$	s.h.
	$R(s_{ry}) = 5.44$	s.h.	$R(s_{ry}) = 9.76$	s.h.	$R(s_{ry}) = 8.37$	s.h.
	$R(s_S) = 5.24$	s.h.	$R(s_S) = 2.94$	s.h.	$R(s_S) = 6.28$	s.h.
	$R(s_{rS}) = 8.39$	s.h.	$R(s_{rS}) = 21.92$	ih.	$R(s_{rS}) = 14.39$	h.
	$R(s_A) = 6.73$	s.h.	$R(s_A) = 24.35$	ih.	$R(s_A) = 12.45$	h.
	$R(s_{rA}) = 8.39$	s.h.	$R(s_{rA}) = 21.92$	ih.	$R(s_{rA}) = 14.39$	h.

sh – strongly homogeneous, h – homogeneous, ih – inhomogeneous

Relation between signal and concentration

Using the simple method of the least squares, significant correlations between the analyte amount and the signal in checked systems were established (R10–R12, Table VIII). It is important to emphasize that the lowest correlation was obtained for the Pb--SPS system. By systematic evaluation of the reality of constants in the complete analyte working range, ideal calibration and analytical evaluation functions were found in the Zn-SPS and Co-SPS systems (R13 and R14, Table VIII). The persistence of constant W in both analytical functions for the Pb-SPS system indicated curved analytical functions where the quadratic coefficient was statistically significant. Furthermore, data structure of the Pb-SPS system showed a lower quality level of data material. It could be presumed that narrowing the analyte working range between the lower and upper analyte level (prevalidation criteria) and changing the analyte content on the lower analyte level (21), x_L, could favourably influence the linearity of the analyte-signal relationship without outliers and produce more accurate and reliable data.

For all functions, the corresponding mean errors of the constants and the standard deviation of the analytical procedures (s_M) in the given working range were calculated

Table VIII. Quality of the analyte-signal relationship

Requirement No.	Zn-PAN		Pb-PAN		Co-PAN	
	Result	Diagnosis	Result	Diagnosis	Result	Diagnosis
R10	r = 0.9997 b = 1.6451 a = –0.0140 s_y = ± 0.0011 s_b = ± 0.0427 s_a = ± 0.0004 centroid = (0.26, 0.411)		r = 0.9950 b = 0.3369 a = 0.0224 s_y = ± 0.0063 s_b = ± 0.0340 s_a = ± 0.0025 centroid = (0.775, 0.284)		r = 0.9994 b = 0.5903 a = –0.0124 s_y = ± 0.0015 s_b = ± 0.0204 s_a = ± 0.0006 centroid = (0.62, 0.354)	
R11	R = 180.84	Significant correlation	R = 46.52	Significant correlation	R = 135.45	Significant correlation
R12	± C_b = 1.6451 ± 0.1203 ± C_a = –0.0140 ± 0.0012		± C_b = 0.3369 ± 0.0957 ± C_a = 0.0224 ± 0.0069		± C_b = 0.5903 ± 0.0576 ± C_a = –0.0124 ± 0.0016	
	t-testing for reality of calibration constants					
R13	$\boldsymbol{V}$ = 1.6060 R_V = 234.04 s_V = ± 0.0069 s_M = ± 0.0102 $\hat{S}$ = 1.606x	Ideal calibration function	$\boldsymbol{V}$ = 0.4348 R_V = 55.45 s_V = ± 0.0078 s_M = ± 0.0088 W = –0.0630 R_W = 10.14 s_W = ± 0.0062 $\hat{S}$ = 0.435x – 0.063x^2	Quadratic calibration function	$\boldsymbol{V}$ = 0.5758 R_V = 197.70 s_V = ± 0.0029 s_M = ± 0.0104 $\hat{S}$ = 0.576x	Ideal calibration function
	t-testing for reality of analytical evaluation constants					
R14	V = 0.62 R_V = 234.04 s_V = ± 0.0027 s_M = ± 0.0064 $\hat{x}$ = 0.62S	Ideal analytical evaluation function	V = 2.18 R_V = 24.43 s_V = 0.0891 s_M = 0.0324 W = 1.44 R_W = 7.02 s_W = ± 0.2058 $\hat{x}$ = 2.18S + 1.44S^2	Quadratic analytical evaluation function	V = 1.7357 R_V = 197.70 s_V = 0.0088 s_M = 0.0180 $\hat{x}$ = 1.74S	Ideal analytical evaluation function

(R13, Table VIII). Analytical functions were used for recognition of outliers and evaluation of analyte limiting values. The results of this systematic mathematical/statistical linearity testing were not in agreement with preliminary linearity testing (R5, Table VI). Since preliminary testing included only particular sensitivities of limiting groups 1 and 6, these results were not a reliable evidence of the signal-analyte relationship. The estab-

Table IX. Outliers testing

Requirement No.	Zn-PAN		Pb-PAN		Co-PAN	
	Result	Diagnosis	Result	Diagnosis	Result	Diagnosis
R15	$\|S^*\| < 2.069$	No outliers. Excellent data.	$2.807 > \|S^*_2\| > 2.069$	One outlier. No objection on the data.	$\|S^*\| < 2.069$	No outliers. Excellent data.
	$\|x^*\| < 2.069$	No outliers. Excellent data.	$2.807 > \|x^*_{2,7}\| > 2.069$	Two outliers. Unacceptable data.	$\|x^*\| < 2.069$	No outliers. Excellent data.

Table X. Estimation of limiting values

Requirement No.	Zn-PAN		Pb-PAN		Co-PAN	
	Result	Diagnosis	Result	Diagnosis	Result	Diagnosis
R16	Ideal calibration function $\hat{S} = 1.606x$ $S_D = 0.0619$ $L_D = 0.004$ μmol $L_Q = 0.011$ μmol	$S_D < S_6$ $L_D < x_6$ $L_Q < x_6$	$L_{DG} = 0.129$ μmol	$L_Q < x_6$	Ideal calibration function $\hat{S} = 0.5758x$ $S_D = 0.018$ $L_D = 0.007$ μmol $L_Q = 0.021$ μmol	$S_D < S_6$ $L_D < x_6$ $L_Q < x_6$

lished calibration and analytical evaluation functions were used for evaluation of apparent signal values ($\hat{S}$) and apparent quantities of analyte ($\hat{x}$), respectively. With the defined analytical evaluation function, it was possible to evaluate random and systematic deviations as a measure of accuracy of investigated analytical systems. Systems Zn-SPS and Co-SPS were characterized with systematic deviations ranging from –13.8 to +1.0% for the Zn-SPS system, and from –11.8 to +1.8% for the Co-SPS system. Random deviations obtained in Zn-SPS and Co-SPS systems varied from ± 0.7 to ± 4.2% and from ± 1.0 to ± 7.0%, respectively. The principal generator of random and systematic deviations was a small deviation of blank and gross values. As could be expected, the highest influence of fluctuations of blank and gross values on precision and accuracy was obtained in the group with the smallest quantity of analyte. Data structures for all investigated systems are presented in Tables XI–XIII.

Outlier recognition

The test proposed by Gottschalk was used for identification of regression outliers (22, 23). Outliers were checked in the set of signals (S) for the calibration function and in the set of analyte amount values (x) for the analytical evaluation function. Testing was done by comparison of $|S^*|$ and $|x^*|$ values with the t-values of confidence intervals for P

Table XI. Data structure for Zn-SPS system

j	*i*	*S*	$\hat{S}$	*ΔS*	*S**	*x*	$\hat{x}$	$\bar{\hat{x}}$	$S_{\hat{x}}$	$S_{r\hat{x}}$(%)	*Δx*	*Δx/x* ×100 (%)	$\Delta\bar{x}$	$\Delta\bar{x}/x$ ×100 (%)	*x**
1	I	0.811	0.803	0.005	0.490	0.50	0.503	0.505	± 0.003	± 0.7	+0.003	+0.6	+0.005	+1.0	0.457
	II	0.804		0.002	0.196		0.501				+0.001	+0.2			0.163
	III	0.816		0.014	1.373		0.509				+0.009	+1.7			1.339
	IV	0.817		0.011	1.079		0.507				+0.007	+1.3			1.045
6	I	0.071	0.080	0.010	1.010	0.05	0.044	0.043	± 0.002	± 4.2	–0.006	–12.9	–0.007	–13.8	1.013
	II	0.071		0.007	0.716		0.045				–0.005	–9.1			0.719
	III	0.165		0.013	1.304		0.042				–0.008	–16.6			1.307
	IV	0.066		0.013	1.304		0.042				–0.008	–16.6			1.307
2	I	0.632	0.642	0.009	0.921	0.40	0.394	0.397	± 0.006	± 1.4	–0.006	–1.5	–0.003	–0.7	0.948
	II	0.642		0.001	0.059		0.400				+0.000	+0.1			0.033
	III	0.647		0.006	0.549		0.403				+0.003	+0.8			0.523
	IV	0.629		0.014	1.411		0.391				–0.009	–2.3			1.438
5	I	0.152	0.161	0.009	0.843	0.10	0.095	0.094	± 0.002	± 2.1	–0.005	–5.4	–0.006	–6.3	0.849
	II	0.152		0.010	0.941		0.094				–0.006	–6.0			0.947
	III	0.150		0.008	0.745		0.095				–0.005	–4.8			0.751
	IV	0.148		0.015	1.431		0.091				–0.009	–9.1			1.438
3	I	0.484	0.482	0.001	0.118	0.30	0.301	0.302	± 0.005	± 1.7	+0.001	+0.2	+0.002	+0.8	0.098
	II	0.496		0.011	1.098		0.307				+0.007	+2.9			1.078
	III	0.491		0.010	1.000		0.306				+0.006	+2.8			0.980
	IV	0.474		0.006	0.568		0.296				–0.004	–1.3			0.588
4	I	0.317	0.321	0.001	0.116	0.20	0.199	0.194	± 0.004	± 2.1	–0.001	–0.4	–0.006	–3.1	0.131
	II	0.312		0.008	0.804		0.195				–0.005	–2.6			0.817
	III	0.310		0.013	1.294		0.191				–0.008	–4.2			1.307
	IV	0.304		0.016	1.588		0.190				–0.010	–5.1			1.601

Barttlet test for $\hat{x}$: $R(s) = 5.24$, sh – strongly homogeneous; $R(s_r) = 8.39$, sh – strongly homogeneous. Six groups mean of standard deviation for $\hat{x}$: $\bar{S}_{\hat{x}} = \pm 0.004$; $\bar{S}_{r\hat{x}} = \pm 2.3\%$.

= 95 and 99% confidence level (R15, Table IX). In the Zn-SPS and Co-SPS systems, no measurements differed unreasonably from the others in the set of results. On the other hand, inspection of the results in the Pb-SPS system indicated that one outlying value was obtained in the set of $|S^*|$ data, which is tolerable within the 24-data population. However, two outlying values were revealed in the set of $|x^*|$ data, which could raise objections to the homogeneity of the data material according to prevalidation acceptance criteria (Table IX). This could be excluded by narrowing the analyte working range.

Table XII. Data structure for Pb-SPS system

j	*i*	S	$\hat{S}$	ΔS	S^*	x	$\hat{x}$	$\bar{\hat{x}}$	$S_{\hat{x}}$	$S_{r\hat{x}}$(%)	Δx	$\Delta x/x$ ×100 (%)	$\Delta\bar{x}$	$\Delta\bar{x}/x$ ×100 (%)	x^*
1	I	0.508	0.511	+0.002	0.175	1.50	1.482	1.466	± 0.031	± 2.1	–0.018	–1.2	–0.034	–2.3	0.566
	II	0.498		–0.019	2.111		1.420				–0.080	–5.3			2.464
	III	0.512		–0.001	0.061		1.485				–0.015	–1.0			0.454
	IV	0.507		–0.003	0.289		1.478				–0.022	–1.5			0.679
6	I	0.054	0.064	+0.012	1.345	0.15	0.117	0.141	± 0.018	± 12.5	–0.033	–22.0	–0.009	–6.3	1.0160
	II	0.060		+0.002	0.206		0.140				–0.010	–6.4			0.295
	III	0.068		–0.006	0.705		0.159				+0.009	+6.3			0.289
	IV	0.063		+0.001	0.022		0.145				–0.005	–3.2			0.149
2	I	0.434	0.431	–0.003	0.012	1.20	1.206	0.124	± 0.028	± 2.3	+0.006	+0.5	+0.034	+2.8	0.186
	II	0.441		–0.011	1.241		1.244				+0.044	+3.7			1.351
	III	0.448		–0.018	2.038		1.268				+0.068	+5.7			2.098
	IV	0.433		–0.003	0.330		1.216				+0.016	+1.4			0.502
5	I	0.112	0.125	+0.011	1.228	0.30	0.267	0.267	± 0.010	± 3.6	–0.033	–11.1	–0.033	–10.9	1.024
	II	0.116		+0.009	1.000		0.272				–0.028	–9.4			0.869
	III	0.110		+0.016	1.797		0.254				–0.046	–15.2			1.408
	IV	0.115		+0.007	0.772		0.277				–0.023	–7.7			0.714
3	I	0.350	0.340	–0.009	0.987	0.90	0.935	0.920	± 0.013	± 1.4	+0.035	+3.9	+0.020	+2.2	1.086
	II	0.338		+0.001	0.076		0.910				+0.028	+1.1			0.304
	III	0.340		+0.001	0.076		0.910				+0.046	+1.1			0.304
	IV	0.348		–0.006	0.645		0.926				+0.023	+2.9			0.792
4	I	0.241	0.238	–0.004	0.430	0.60	0.611	0.596	± 0.017	± 2.9	+0.011	+1.9	–0.004	–0.7	0.342
	II	0.243		–0.004	0.430		0.611				+0.011	+1.9			0.342
	III	0.234		+0.007	0.823		0.580				–0.020	–3.4			0.627
	IV	0.231		+0.006	0.709		0.582				–0.018	–2.9			0.540

Barttlet test for $\hat{x}$: $R(s) = 4.97$, sh – strongly homogeneous; $R(s_r) = 19.16$, ah – almost homogeneous. Six groups mean of standard deviation for $\hat{x}$: $\bar{S}_{\hat{x}} = \pm 0.021$; $\bar{S}_{r\hat{x}} = \pm 5.6\%$.

Estimation of limiting values

For the systems where ideal calibration and analytical evaluation functions were obtained (Zn-SPS and Co-SPS), limits of detection and quantitation (3, 24, 25), as well as limiting signal values were significantly lower than the amount of analyte and net signal values at the lower analyte level (R16, Table X). Limit of quantitation in the Pb-SPS system characterized by the quadratic analytical evaluation function was evaluated accord-

Table XIII. Data structure for Co-SPS system

j	*i*	*S*	$\hat{S}$	ΔS	S^*	*x*	$\hat{x}$	$\bar{\hat{x}}$	$S_{\hat{x}}$	$S_{r\hat{x}}$(%)	Δx	$\Delta x/x$ ×100 (%)	$\Delta\bar{x}$	$\Delta\bar{x}/x$ ×100 (%)	x^*
1	I	0.700	0.691	–0.009	0.869	1.20	1.215	1.201	± 0.017	± 1.4	+0.015	+1.3	+0.001	+0.1	0.829
	II	0.689		+0.002	0.190		1.196				–0.004	–0.3			0.229
	III	0.701		–0.008	0.773		1.213				+0.013	+1.1			0.733
	IV	0.679		+0.012	1.152		1.179				–0.021	–1.8			1.191
6	I	0.062	0.069	+0.007	0.683	0.12	0.108	0.106	± 0.007	± 7.0	–0.012	–10.3	–0.014	–11.8	0.687
	II	0.063		+0.004	0.394		0.113				–0.007	–6.0			0.398
	III	0.055		+0.014	1.357		0.095				–0.025	–20.5			1.360
	IV	0.063		+0.007	0.683		0.108				–0.012	–10.3			0.687
2	I	0.570	0.553	–0.017	1.657	0.96	0.989	0.978	± 0.010	± 1.0	+0.029	+3.1	+0.018	+1.8	1.626
	II	0.560		–0.007	0.695		0.971				+0.012	+1.3			0.664
	III	0.555		–0.004	0.406		0.967				+0.007	+0.7			0.375
	IV	0.568		–0.013	1.272		0.982				+0.022	+2.3			1.241
5	I	0.124	0.138	+0.014	1.366	0.24	0.215	0.217	± 0.004	± 1.8	–0.025	–10.3	–0.023	–9.8	1.373
	II	0.124		+0.014	1.366		0.215				–0.025	–10.3			1.373
	III	0.122		+0.015	1.462		0.213				–0.027	–11.0			1.470
	IV	0.130		+0.010	0.981		0.222				–0.018	–7.4			0.989
3	I	0.410	0.415	+0.005	0.441	0.72	0.712	0.706	± 0.016	± 2.2	–0.008	–1.2	–0.014	–2.0	0.464
	II	0.394		+0.021	1.981		0.684				–0.036	–5.0			2.004
	III	0.417		–0.000	0.040		0.720				+0.000	+0.0			0.017
	IV	0.407		+0.007	0.634		0.708				–0.012	–1.7			0.657
4	I	0.274	0.276	+0.001	0.134	0.48	0.477	0.476	± 0.009	± 1.9	–0.003	–0.6	–0.004	–0.9	0.149
	II	0.269		+0.007	0.711		0.467				–0.013	–2.7			0.727
	III	0.272		+0.005	0.519		0.470				–0.010	–2.0			0.534
	IV	0.279		–0.005	0.444		0.488				+0.008	+1.6			0.428

Barttlet test for $\hat{x}$: $R(s) = 5.24$, sh – strongly homogeneous; $R(s_r) = 8.39$, sh – strongly homogeneous. Six groups mean of standard deviation for $\hat{x}$: $\bar{S}_{\hat{x}} = \pm 0.004$; $\bar{S}_{r\hat{x}} = \pm 2.3\%$.

ing to Gottschalk's heuristic requirement (22, 23) for the systems with more than one constant of analytical function (R16, Table X). All these calculated limiting values being below the respective x_6 level confirmed the quality of the measurements. The extensive prevalidation metrological characteristics critical for the selection of methodology for determination of heavy metals by the SPS procedure are summarized in Table XIV.

Table XIV. Prevalidation characteristics for the Me-SPS systems

Characteristic	Zn-SPS system	Pb-SPS system	Co-SPS system
Analyte working range (μmol)	0.05–0.50	0.15–1.50	0.12–1.20
Net signal range (absorbance)	0.069–0.811	0.062–0.505	0.061–0.692
Relationship analyte-signal	R = 0.9997	R = 0.9991	R = 0.9991
Calibration function	$\hat{S} = 1.606x$	$\hat{S} = 0.435x - 0.063x^2$	$\hat{S} = 0.576x$
Analytical evaluation function	$\hat{x} = 0.62S$	$\hat{x} = 2.18S + 1.44S^2$	$\hat{x} = 1.74S$
Standard deviation of procedure (μmol)	± 0.0064	± 0.0324	± 0.018
Limit of detection (μmol)	0.004	–	0.007
Limit of quantitation (μmol)	0.011	0.129	0.021

	Zn-SPS						Pb-SPS						Co-SPS					
Group data																		
Analyte amount (μmol)																		
Theoretical (μmol)	0.500	0.400	0.300	0.200	0.100	0.050	1.500	1.200	0.900	0.600	0.300	0.150	1.200	0.960	0.720	0.480	0.240	0.120
Found (μmol)	0.505	0.397	0.302	0.194	0.094	0.043	1.466	1.234	0.920	0.596	0.267	0.141	1.200	0.978	0.706	0.476	0.217	0.106
Random deviations																		
$S_{\hat{x}}$ (μmol)	± 0.003	± 0.006	± 0.005	± 0.004	± 0.002	± 0.002	± 0.031	± 0.028	± 0.013	± 0.017	± 0.009	± 0.018	± 0.017	± 0.010	± 0.016	± 0.009	± 0.004	± 0.007
$S_{r\hat{x}}$ (%)	± 0.7	± 1.4	± 1.7	± 2.1	± 2.1	± 4.2	± 2.1	± 2.3	± 1.4	± 2.9	± 3.6	± 12.5	± 1.4	± 1.0	± 2.2	± 1.9	± 1.8	± 7.0
Systematic deviations																		
$\Delta\bar{x}$ (μmol)	+0.005	–0.003	+0.002	–0.006	–0.006	–0.007	–0.034	+0.034	+0.020	–0.004	–0.033	–0.009	+0.001	+0.018	–0.014	–0.004	–0.023	–0.014
$\Delta\bar{x}$ (%)	+1.0	–0.7	+0.8	–3.1	–6.3	–13.8	–2.3	+2.8	+2.2	–0.7	–10.9	–6.3	+0.1	+1.8	–2.0	–0.9	–9.8	–11.8

CONCLUSIONS

Full prevalidation, as a part of prevalidation strategy, was used for a systematic and sophisticated validity evaluation of the procedure for determination of heavy metals (zinc, lead, cobalt) on reactive polymers. Analysis of variance, the Barttlet test, reality of linear analytical functions, agreement of actual (x) and appropriate ($\hat{x}$) values, as well as the elaborative system of prevalidation diagnostics for each prevalidation step confirmed the usefulness of investigated systems and pointed to the possible disadvantages and limitations of these systems. The investigated systems were characterized by a high level of precision, acceptable accuracy, high data homogeneity, and low limits of quantitation. Systems Zn-SPS and Co-SPS were characterized by both ideal calibration and analytical evaluation functions. Data structure of the Pb-SPS system showed a lower quality level of data material, which could be solved by changing the analyte working range.

Useful and informative prevalidation approach has proven valuable for evaluating the power of the SPS procedure for determination of heavy metals and can be recommended for solving problems arising in the application and evaluation of these analytical procedures. Furthermore, the prevalidation procedure pointed to an analytical procedure with good metrological characteristics that could be applied for determination of heavy metals in routine pharmaceutical analysis.

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Acronyms, codes and abbreviations. – a – intercept of a line, A – measure of particular sensitivity, $\overline{A}$ – particular sensitivity mean, AC – gross to blank signal ratio, b – slope of a line, B – blank signal, $\overline{B}$ – blank mean, $\overline{B}_N$ – grand blank mean, C_a – confidence limit for the intercept, C_b – confidence limit for the slope, Co-SPS – solid-phase spectrophotometric procedure for determination of cobalt, HEPES – 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid, L_D – limit of detection, L_{DG} – determination limit according to Gottschalk, L_Q – limit of quantitation, Me-PAN – complexes of metal ions with PAN reagent, Me-SPS – solid-phase spectrophotometric procedure for determination of heavy metals, PAN – 1-(2-pyridilazo)-naphtol, Pb-SPS – solid-phase spectrophotometric procedure

for determination of lead, r – determination coefficient, $R(s)$ – results of Barttlet testing of data homogeneity for standard deviations, $R(s_r)$ – results of Barttlet testing of data homogeneity for relative standard deviations, S – net signal, $\overline{s}$ – standard deviation mean, $\overline{S}$ – net signal mean, $\hat{S}$ – apparent signal value, S^*, x^* – outliers, s_a – standard deviation of intercept, s_A – standard deviation of particular sensitivities, s_b – standard deviation of slope, s_B – standard deviation of blanks, S_D – limiting value for net signal, s_{rA} – relative standard deviation of particular sensitivities, s_{rB} – relative standard deviation of blanks, s_{ry} – relative standard deviation of gross signals, s_{rS} – relative standard deviation of net signals, s_M – standard deviation of procedure, s_S – standard deviation of net signals, s_y – standard deviation of gross signals, s_y – random errors in y-direction, s_V, s_W – standard deviations of the function constants, s_{BN} – total standard deviation of blanks, s_{rBN} – total relative standard deviation of blanks, $\overline{s}_r$ – relative standard deviation mean, s^2_{Bb} – mean deviation between groups, s^2_{Bw} – mean deviation within groups, SPS-procedure – solid-phase spectrophotometric procedure, V, W – constants of analytical evaluation function, $\boldsymbol{V}$, $\boldsymbol{W}$ – constants of calibration function, x – amount of analyte, $\hat{x}$ – apparent quantities of analyte, y – gross signal, $\overline{y}$ – gross signal mean, Zn-SPS – solid-phase spectrophotometric procedure for determination of zinc.

S A Ž E T A K

Ocjena kakvoće postupka za određivanje teških metala na reaktivnim nosačima

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Koristeći jednostavnu i informativnu prevalidacijsku strategiju, provedena je kontrola kakvoće i provjera valjanosti postupka spektrofotometrije na krutoj fazi za određivanje teških metala (Me-SPS) važnih u farmaceutskoj praksi: cinka (Zn-SPS), olova (Pb-SPS) i kobalta (Co-SPS). Utvrđene su metrološke značajke Me-SPS postupka zajedno sa sustavom dijagnostike pojedinog prevalidacijskog koraka. Povoljne prevalidacijske značajke, kao što su idealna analitička funkcija, homogenost podataka, nizak prag određivanja i prihvatljiva točnost, potvrđuju kakvoću Me-SPS postupka i ukazuju na ograničenja nekih ispitivanih sustava.

Ključne riječi: kontrola kakvoće analitičkog postupka, prevalidacijska strategija, teški metali, spektrofotometrija na krutoj fazi

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