Acta Poloniae Pharmaceutica – Drug Research, Vol. 76 No. 4 pp. 635–643, 2019
DOI: 10.32383/appdr/105857

ISSN 0001-6837
Polish Pharmaceutical Society

APPROACH OF THE STATE PHARMACOPEIA OF UKRAINE TO ANALYTICAL PROCEDURES VALIDATION ON THE EXAMPLE OF CHLORIDE IONS ASSAY IN PERITONEAL DIALYSIS SOLUTIONS

NATALIIA HUDZ[1]*, DMYTRO LEONTIEV[2] and PIOTR P. WIECZOREK[3]

[1]Department of Drug technology and biopharmacy, Danylo Halytsky Lviv National Medical University, Pekarska street 69, Lviv, Ukraine
[2]Ukrainian Scientific Pharmacopoeial Center for Quality of Medicines, Astronomichna street 33, Kharkiv, Ukraine
[3]Department of Analytical and Ecological Chemistry, University of Opole, Pl. Kopernika 11, 45-040, Opole, Poland

Abstract: The objective of this study was to develop and validate an alternative analytical procedure for the total chloride assay in solutions for peritoneal dialysis (PD). The proposed analytical procedure was validated according to the requirements of the International Conference on Harmonization (ICH) Guideline: Topic ICH Q2(R1) and the approach of the State Pharmacopeia of Ukraine (SPU). The analytical procedure was specific. The linearity of the procedure was evaluated in the concentration range of 76 to 114 mmol/L of chloride ions (80-120% of the stated content (95 mmol/L)) with the regression equation y = 1.0029 · X -0.2269 and a correlation coefficient of 0.9989. The y-intercept of the regression line did not exceed the maximum permissible value of 2.6. The residual standard deviation (s_0/b = 0.65) of the calibration curve met the requirement for max s_0/b (0.84). The mean recovery was found as 100.07% ± 0.62%. The precision study also showed a low value of one-sided 95% confidence limit (Δ_Z = 1.15%) that did not exceed the critical value of 1.6%. The accuracy study also showed that the systematic error had not differed statistically from zero. The developed analytical procedure was also found to be robust and reproducible. The reproducibility studies were conducted with different samples of the same laboratory-made PD solutions in different days and laboratories. The performed studies indicated that the developed analytical procedure is simple, fast and cost-efficient, specific, linear, precise, accurate, and robust. The presented approach could be also applied to the validation of other assay analytical procedures.

Keywords: solutions for peritoneal dialysis, validation, argentometric method, chlorides assay, uncertainty

The quality issues in the pharmaceutical industry have become a very serious and domineering topic in the world (1-3). The apprehension and criticism of the quality and reliability of pharmaceutical products have increased substantially. Regulatory agencies and pharmaceutical manufacturers admit the necessity of systematic approaches for drug development, pharmaceutical products quality control and manufacturing processes (1, 3). As the analytical method development is a major contribution to the control strategy (4, 5), all analytical methods should be validated (6). However, there are few publications with justification or explanations of acceptance criteria computing methodology for method performance characteristics.

Peritoneal dialysis (PD) is an essential life-sustained treatment modality of renal replacement therapy, which is documented to cost less to health care systems in the world compared with hemodialysis (7, 8). To the best of our knowledge, scientific papers do not provide information on pharmaceutical development including analytical aspects of PD solutions of the first or second generations despite increasing the prevalence of PD patients in developed and developing countries.

The total chloride content is one of the critical quality attributes of PD solutions (7, 9). According to the British Pharmacopeia (9), an assay of chlorides is carried out using the two titrants: 0.1 M silver nitrate and 0.1 M ammonium thiocyanate for titration of silver nitrate excess. This procedure is time-consuming as it requires the preparation of many reagents (besides the two titrants, dilute nitric acid, dibutyl phthalate R, ferric ammonium sulfate).

* Corresponding author: e-mail: natali_gudz@ukr.net

Analytical quality by design (AQbD) is focused on systematic approaches, robust and cost-effective methods as well (1, 4, 5). Different authors propose various stages or elements of AQbD that mainly differ in stages names and very similar for essence (1, 2, 10, 11). A three-stage approach can be also employed to method validation (method design, method qualification, and continued method verification, respectively) (11). The stage of method design includes the definition of method requirements and conditions, design of an ATP for the method and definition of the intended purpose of the method (10-13). ATP means the combination of all method performance criteria (e.g. precision, accuracy, working range, linearity, sensitivity and the associated performance criterion) that direct the method development process or, in other words, ATP defines what to quantify, how to quantify and by what technique (1, 3, 12, 14-16).

The purpose of the elaboration of the tested analytical procedure was to support formulation development (to study an influence of hydrochloric acid on the total chloride content in solutions for PD), technological process (determine the chloride content on the stage of PD solutions preparation), to control a final product, to perform stability testing and the total chloride assay.

The State Pharmacopeia of Ukraine (SPU) developed requirements for analytical procedures validation independently on an analytical method with providing a quantified estimation of characteristics of analytical method performance and ATP for analytical procedures (17). According to the SPU, ATP for an analytical procedure is based on the requirement for uncertainty insignificance for analytical variation ($max\Delta_{As}$) with respect to the content limits of an active pharmaceutical ingredient. The SPU proposes the following formula for uncertainty for the content of an active pharmaceutical ingredient in the range of 95% to 105% of the stated amount:

$$max\Delta_{As} = 0.32 \cdot 5\% = 1.6\% \quad (17).$$

Also, in accordance with the approach of the SPU, any systematic component of uncertainty (bias, or δ) should be insignificant with respect to $max\Delta_{As}$:

$$max\ \delta = 0.32 \cdot max\Delta_{As} = 0.51\% \quad (17).$$

Therefore, the goal of the present study was to develop and validate a simple, rapid, and less time-consuming analytical procedure of an argentometric method for the assay of chlorides in PD solutions containing glucose and sodium lactate using the methodology of the SPU to analytical procedures validation.

MATERIALS AND METHODS

Equipment and chemicals

All the reagents used were of analytical or pharmacopeia grade. The reagents were purchased from the following companies: Malladi Specialties Limited (India), Macco organiques (Czech Republic), POCH (Poland), Chemical factory named by L. Karpov (Russian Federation), Chemical factory Kharkovreachim (Ukraine). Purified water was obtained by a Mili-Q-RO4 system (Millipore, Bedford, MA, USA).

In these studies, the following burettes were used: the capacity of 25 mL, graduation interval of 0.05 mL, and tolerance of ± 0.03 mL.

Preparation of stock and model solutions

Model solutions were prepared for the following formulation of the PD solutions: sodium 92 mmol/L, calcium 1.25 mmol/L, magnesium 0.25 mmol/L,

Table 1. Preparation of the stock solutions for the validation studies.

No.	Substance, grade	I	II	III	IV
1	NaCl, analytical grade	5.3805	-	0.5380 g	-
2	$CaCl_2 \cdot 6H_2O$, pharmaceutical grade	0.275	-	-	-
	$CaCl_2 \cdot 6H_2O$, pharmaceutical grade, 5.48% solution	-	-	0.5 mL	-
3	$MgCl_2 \cdot 6H_2O$, pharmaceutical grade	0.0512	-	-	-
	$MgCl_2 \cdot 6H_2O$, pharmaceutical grade, 1.02% solution	-	-	0.5 mL	-
4	Sodium lactate, 60% solution, pharmaceutical grade	7.4645	-	0.7467 g	0.7467g
5	Glucose monohydrate	-	42.5 g	4.25 g	4.25 g
6	1 M solution of hydrochloric acid	-	1.60 mL	160 µL	-
7	Aqua purificata	up 100 mL	up 1000 mL	up 100 mL	up 100 mL

Table 2. The composition of the tested laboratory-made PD solutions.

Sample number	Ions concentration, mmol/L					Glucose monohydrate concentration, g/L	Packaging
	Na^+	Ca^{2+}	Mg^{2+}	Cl^-	$CH_3CH(OH)COO^-$		
20413	132	1.25	0.25	95	40	42.5	glass
30513	132	1.25	0.25	95	40	15.0	-//-
40513	132	1.25	0.25	95	40	42.5	-//-
21116	132	1.25	0.25	95	40	42.5	polyvinylchloride (PVC)

lactate 40 mmol/L, chlorides 95 mmol/L, glucose monohydrate 42.5 g/L.

The compositions of the solutions for validation studies of the analytical procedure are presented in Table 1.

The first and second stock solutions were prepared by dissolving components indicated in Table 1 to obtain 100.0 mL and 1000.0 mL of the solutions, respectively. 9 model solutions were prepared by dilution of 8.0, 8.5, 9.0, 9.6, 10.0, 10.6, 11.0, 11.6 and 12.0 mL of stock solution I by stock solution II up to 100 mL.

The composition of the laboratory-made PD solutions for the validation studies of the tested analytical procedure is presented in Table 2.

Analytical procedure of direct argentometric method for the determination of chloride ions

10 mL of a model solution (or laboratory-made solutions for PD) were titrated with 0.1 M solution of silver nitrate (manufacturer "Argentum", Lviv, Ukraine) using 0.8 mL of 5% potassium chromate solution (manufacturer "Cherkasy factory of reagents", Cherkasy, Ukraine) as an indicator to an orange-yellow color, stirring constantly. The content of chloride ions should be from 95 to 105% of the stated amount. Each mL of 0.1 M silver nitrate is equivalent to 3.545 mg of Cl^-. The content of chloride ions (X_1), in mmol/L, in a solution, is calculated according to the following formula:

$X_1 = V_1 \cdot K \cdot 3.545 \cdot 1000 : 10 : 35.45 = V_1 \cdot K \cdot 10$,

where V_1 is a volume of 0.1 M solution of silver nitrate used in the titration of a tested solution, in ml, respectively; K is a correction coefficient to the molarity of 0.1 M solution of silver nitrate (7).

Titrations were performed in triplicate and the mean content was calculated.

pH-metric measure

The pH of some model solutions and PD solutions was measured in the temperature range of 20°C to 25°C. Before measurements, the pH meters were calibrated using buffer solutions with pH values of 4.01, 6.87 and 9.18.

Statistical analysis

The data analysis was performed using Microsoft Excel 2007 software.

RESULTS AND DISCUSSION

Validation was carried out according to the requirements of ICH Q2 (R1) guidelines and the SPU approach (17, 18). The characteristics studied were specificity, linearity and range, precision, accuracy, and robustness. The values of the selected critical characteristics should comply with the established ATP of the method. The linearity, accuracy, and precision were evaluated simultaneously for nine model solutions, in which the tested concentrations were evenly distributed within the specified range.

Specificity (selectivity)

Studies of establishing specificity were performed. With this purpose, 10 mL of solutions II and IV were titrated with 0.1 M solution of *silver nitrate* using 0.8 mL of 5% *potassium chromate solution* to an orange-yellow color, stirring constantly. The results of the specificity studies revealed that volume of 0.1 M solution of silver nitrate used for titration of solutions IV and II were 0.02 and 0.18 mL, respectively.

The consumed volume of 0.1 M solution of *silver nitrate* on the titration of solution IV is negligible compared with the volume consumed in the titration of a model solution of 80% of the stated content (0.02 mL : 8.37 mL · 100% = 0.24%; 0.24% ≤ 0.51%). Therefore, glucose and sodium lactate do not affect the chloride content and the elaborated analytical procedure can be regarded as specific. However, there is an influence of hydrochloric acid on the total chloride content that is obvious as silver nitrate determines all the chlorides

present in a solution: sodium chloride, calcium chloride, magnesium chloride, and hydrochloric acid. This influence is not negligible as 0.18 mL : 8.37 mL · 100% = 2.15%; 0.51% ≤ 2.15%. Therefore, this volume (0.18 mL) was subtracted from the volumes 0.1 M solution of *silver nitrate* consumed on the titration of the model solutions. Moreover, this procedure allows to measure chlorides content induced by hydrochloric acid in PD solutions (1.8 mmol/L).

Linearity and range of an analytical procedure

According to the recommendations of the ICH guidelines and the SPU, linearity is evaluated in the concentration range of 80-120% of the stated content (17, 18). Consequently, 9 model solutions of the different concentrations (80%, 85%, 90%, 96%, 100%, 106%, 110%, 116% and 120% of the stated content of chlorides (95 mmol/L) were prepared for linearity studies. The calibration curve was prepared in normalized coordinates. It was prepared by plotting the obtained content of the stated concentration (95 mmol/L) in percentages (Y-axis) against the concentration of the model solutions of the stated content in percentages (X-axis).

Requirements for a y-intercept (a) of a calibration curve

As stated by the SPU, the contribution of a *y-intercept* (a) of a calibration curve into uncertainty of a result should be insignificant in comparison with the maximally permitted uncertainty of the analysis ($\max\Delta_{As}$ = 1.6%) at limits of an active pharmaceutical ingredient of 95-105% of the stated amount in final pharmaceutical products (17):

$$|a| \le \frac{0.32 \cdot 1.6\%}{1 - (80:100)};\ |a| \le 2.6\%$$

Requirements for residual standard deviation (SD) of a calibration curve (s_0)

According to the approach of the SPU, in normalized coordinates the confidence interval of the dispersion of points around a *calibration* curve is equal to Student's distribution with degrees of freedom n-2 multiplied by s_0 and should not exceed the maximum permissible uncertainty of analysis (17):

$$\frac{s_0}{b} \cdot t(95\%, n-2) \le \max\Delta_{As}$$

Requirements for a correlation coefficient

Concentrations tested in the linearity study are characterized by SD ($s_{y,}\%$), which is expressed by commonly accepted equation as follows:

$$s_{y,}\% = \sqrt{\sum_{n-1}^{n} \frac{(X_i - \bar{X})^2}{n-1}}$$

where X_i – concentration of an i-solution (%); $\bar{X}$ – mean concentration of solutions; n – the number of points in a curve or, in other words, the number of model solutions.

According to the requirements of the SPU, analytical procedures of assay are validated in the range of 80-120% of the stated amount with a step of 5%. In such a case, computed s_y is equal to 13.69 (10). s_y was equal to 13.84 in this study for the used concentrations of model solutions of 80, 85, 90, 96, 100, 106, 110, 116 and 120% (17).

The following formulae were used to calculate a correlation coefficient for a calibration curve (17):

$$r \ge \sqrt{1 - \frac{s_0^2}{s_y^2}} \quad r \ge \sqrt{1 - \left(\frac{\Delta_{As}}{s_y \cdot t(95\%, n-2)}\right)^2}$$

Taking into account the requirements for s_0 and value of s_y, a correlation coefficient for the calibration curve of the tested procedure should be not less than:

$$r \ge \sqrt{1 - \frac{0.84^2}{13.84^2}} \ge 0.9982$$

Precision

The intra-assay precision (repeatability) was evaluated with SD of three titrations of each model solution. The intermediate (inter-assay) precision was verified by six titrations of one more model solution with the total chloride content of 100% of the stated content at other time but in the same laboratory. Moreover, this solution was prepared in a slightly different mode. To study the reproducibility of the tested procedure, titrations of the laboratory-made solutions were performed in different laboratories on different days (University of Opole (Poland) and Danylo Halytsky Lviv National Medical University (Ukraine)). Mean contents and RSD of assay results of replicates were calculated and compared.

Requirements for precision

The one-sided confidence interval of Δ_Z should not exceed the maximum permissible uncertainty of the analysis Δ_{As}: $\Delta_Z \le \max\Delta_{As}, \Delta_Z = s_Z(\%) \cdot t(95\%, n-1)$,

$$s_z(\%) = \sqrt{\sum_{i-1}^{n} \frac{(Z_i - \bar{Z})^2}{n-1}}$$

where s_z – SD calculated for the ratios «found/introduced» (Z_i) for all the model solutions used in the linearity study; t – one-sided Student's distribution for a 95% confidence interval with n-1 degrees of freedom.

Accuracy (trueness)

Requirements for accuracy

Accuracy is assessed by the two criteria: the criterion of statistical insignificance and the criteri-

on of practical insignificance if the first criterion does not meet the requirement.

Criterion of statistical insignificance

The systematic component of the uncertainty can be characterized by the difference of the mean value for the ratio "found/introduced" ($\bar{Z}$) from 100%. The systematic error statistically does not differ from zero if the deviation from 100% does not exceed its confidence interval:

$$\delta\% \le \frac{\Delta z}{\sqrt{n}} \qquad \delta\% = |\bar{Z} - 100|$$

where Δz is the confidence interval calculated by the formula: $\Delta_Z = s_Z(\%) \cdot t(95\%, n\text{-}1)$, where n – the number of points in the calibration curve.

Criterion of practical insignificance

If the above-mentioned ratio does not meet the established criterion of statistical insignificance, the criterion of practical insignificance (δ%) is used, which should be no more than $0.32 \cdot \max \Delta_{As}$:

$$\delta\% \le 0.32 \cdot \max \Delta_{As}$$

Robustness

This characteristic is related to the reliability of an analysis with respect to deliberate variations in method parameters. Among such variations can be the stability of analytical solutions, different equipment, different analysts, etc. (17-19). For its essence, robustness is connected with intermediate precision (inter-assay precision) (15, 17-19). For the robustness study of the analytical procedure, the two model solutions with the nominal content of chlorides of 100 % (model solution 5 and solution III) were compared. In fact, these studies were conducted in order to evaluate simultaneously the intermediate precision of the tested analytical procedure as well.

Table 3. Results of the linearity study.

No.	Concentration of a model solution (X), %	Real content (C), mmol/L	Content of the stated concentration, (C : 95 · 100), %	Mean content of the stated concentration, $\bar{Y}$ % ± SD	RSD, %	Z, % (Y : X · 100)
1	100	95	100	100	-	100
2 3 4	80	76.73 76.93 76.73	79.97 80.18 79.97	80.04 ± 0.121	0.151	100.05
5 6 7	85	82.45 81.95 81.95	85.93 85.41 85.41	85.58 ± 0.30	0.351	100.69
8 9 10	90	86.76 86.46 86.46	90.43 90.11 90.11	90.22 ± 0.185	0.205	100.24
11 12 13	96	90.67 90.47 90.97	94.87 94.66 94.66	94.73 ± 0.121	0.128	98.68
14 15 16	100	95.98 96.49 95.98	100.03 100.56 100.03	100.21 ± 0.306	0.305	100.21
17 18 19	106	102.31 102.01 102.51	106.62 106.32 106.84	106.59 ± 0.261	0.245	100.56
20 21 22	110	105.32 105.32 105.52	109.76 109.76 109.97	109.83 ± 0.121	0.110	99.85
23 24 25	116	111.53 111.03 110.53	116.23 115.71 115.19	115.71 ± 0.520	0.449	99.75
26 27 28	120	116.05 115.55 115.85	120.95 120.43 120.74	120.71 ± 0.262	0.217	100.59
29	Mean RSD	-	-	-	0.240	-
30	$\bar{Z} \pm S_z$	-	-	-	-	100.07 ± 0.62

Table 4. Results of the intermediate precision studies with elements of robustness.

Replicates of model solution 100%	Total chloride content		Corrected chloride content*	
	mmol/L	% of the stated content	mmol/L	% of the stated content
1	96.69	101.78	94.89	99.98
2	96.44	101.52	94.64	99.72
3	96.19	101.25	94.39	99.45
4	96.69	101.78	94.89	99.98
5	96.69	101.78	94.89	99.98
6	96.44	101.52	94.64	99.72
Mean	96.52	101.61	94.72	99.81
SD	0.2	0.22	0.20	0.22
RSD, %	0.21	0.21	0.21	0.22

* corrected chloride content = total chloride content - chloride content related with HCl

Table 5. Reproducibility studies performed on laboratory-made solutions.

Laboratory-made batch	Volume of 0.1 M solution of silver nitrate	Chloride content (mmol/L)	Mean of chloride content (mmol/L) ± SD	Chloride content (% of the stated content)	Mean of chloride content (% of the stated content) ± RSD	pH after sterilization
30513	9.65 9.65 9.65	96.5 96.5 96.5	96.5 ± 0	101.58 101.58 101.58	101.58 ± 0	5.44
	In 4 months					
	9.60 9.63 9.65	95.71 96.01 96.21	95.98 ± 0.25	100.75 101.07 101.28	101.03 ± 0.27	
					Δ = 0.55	
40513	9.50 9.35 9.45	95.0 93.5 94.5	94.33 ± 0.76	100.0 98.42 99.47	99.30 ± 0.80	5.25
	In 4 months					
	9.40 9.45 9.50	93.72 94.22 94.72	94.22 ± 0.50	98.65 99.18 99.70	99.18 ± 0.53	
					Δ = 0.12	
20413	9.50 9.50 9.45	95.0 95.0 94.5	94.83 ± 0.25	100 100 99.47	99.82	5.35
	In 4 months					
	9.43 9.40 9.45	94.02 93.72 94.22	93.99 ± 0.25	98.97 98.65 99.18	98.93 ± 0.27	
					Δ = 0.89	
21116	9.85 9.90 9.95	98.5 99.0 99.5	99.0 ± 0.50	103.68 104.21 104.74	104.21 ± 0.5	5.35
	In 4 months					
	10.30 10.25 10.28	102.69 102.19 102.49	102.39 ± 0.26	108.09 107.59 107.88	107.85 ± 0.26	
					Δ = 3.64	

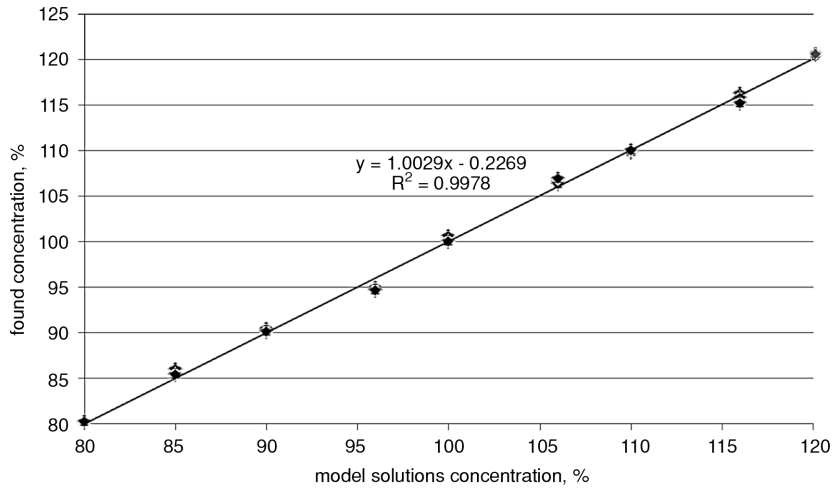

Figure 1. The calibration curve in normalized coordinates (dependence of obtained contents in percentage of the stated concentration (95 mmol/L) (Y-axis) on the concentration of the model solutions in percentage of the stated concentration (X-axis)

Table 6. Validation characteristics, their values and acceptance criteria of the tested analytical procedure.

Characteristics	Found value	Requirement 1	Requirement 2 (criterion of practical insignificance)	Conclusion
Slope (b)	1.0029	-	-	-
y-intercept (a)	0.2269	-	$\lvert a\rvert = \frac{0.32 \cdot \Delta As(\%)}{1 - (X_{min} : 100)} \le \lvert 2.6\% \rvert$ $\lvert a\rvert = \frac{0.32 \cdot 1.6\%}{1 - (80 : 100)} \le \lvert 2.6\% \rvert$	It meets the requirement
s_0	0.6495	-	-	-
s_0/b	0.65	$s_0/b \le \Delta_{As}$ (%) : t (95%, n-2) 1.6% : 1.8946 ≤ 0.84%	-	It meets requirement 1
Standard deviation, s_Y	13.84	-	-	-
Correlation coefficient, r	$r = \sqrt{0.9978} =$ $= 0.99890$	≥ 0.9982	-	It meets the requirement
Precision, Δ_Z	$\Delta_Z = s_Z$ (%) · t (95%, n-1), 0.62 · 1.8595 = 1.15%	$\Delta_Z \le \Delta_{As}$, z ≤ 1.6%, 1.15% ≤ 1.6%	-	It meets the requirement
Accuracy, $\lvert\bar{Z} - 100\rvert$	$\delta \le \lvert\bar{Z} - 100\%\rvert$ $\delta \le \lvert 100.07\% - 100\%\rvert = 0.07\%$	$\Delta_{max} \le \Delta_Z : \sqrt{n}$, 1.15% : 3 = 0.38%, 0.07% ≤ 0.38%	$\Delta \le \Delta_{As} \cdot 0.32\%$, $\delta \le 1.6 \cdot 0.32\% \le 0.51\%$	It meets requirement 1

The results of the linearity study of the analytical procedure are presented in Table 3.

The calibration curve was found to be linear in the concentration range of 76 to 114 mmol/L or of 80 to 120 % of the stated content of chloride ions (95 mmol/L) as shown in Figure 1.

The y-intercept (a = 0.2269) of the calibration curve (y = 1.0029 · X – 0.2269) was statistically insignificant as it did not exceed the maximum permissible value (max a = 2.6%). The residual SD of the calibration curve ($s_0/b = 0.6495$) met the requirement (max $s_0/b = 0.84$). The correlation coefficient (r = 0.9989) confirmed the linearity (min r = 0.9982). Therefore, the analytical procedure showed an acceptable level of linearity.

The mean recovery ($\bar{Z}$) was found to be 100.07% ± 0.62% with the low RSD values (0.128 – 0.449%) for the mean content of each model solution. The one-sided confidence interval for recovery (Δ_Z = 1.15%) was less than the critical value

(max Δ_Z = 1.6%). The bias (δ) of the analytical procedure estimated from the linearity studies was statistically insignificant (δ = 0.07%) as it was less than the value of $\Delta_Z/3$ = 0.38. Therefore, the found values of the mean recovery ($\bar{Z}$), the confidence interval for and bias met the predefined requirements of the ATP for the precision and accuracy of the developed analytical procedure.

pH of the model solutions and laboratory-made solutions was in the range of 5.01 to 5.10 and 5.25-5.44, respectively, that met the requirements of the British Pharmacopeia for pH of PD solutions (5.0-6.5) (9).

For the intermediate precision studies with elements of robustness, solution III was prepared in 4 months after linearity studies in a slightly modified mode compared with the preparation of nine model solutions. The results of the precision studies performed on solution III presented in Table 4.

For the analyzed solution III, the deviation "found/introduced" from 100% does not exceed max Δ_{As} (100% – 99.81% = 0.19%, 0.19% ≤ 1.6%), therefore the result is considered to be correct. ICH Topic Q2 (R1) and the SPU do not provide maximally permitted RSD for repeatability studies using three or six replicates (17, 18). However, some researchers put 2% as maximum RSD of assay results of six replicates for intra-assay precision evaluation (16, 19, 20). The RSD of the repeatability studies was 0.22%. Moreover, the values of RSD for this solution and model solution 5 (Table 3) did not differ (0.22% versus 0.305%) that it could indicate on the robustness of the developed procedure as there was no influence of the mode of model solutions preparation and time of performing analysis.
The results of the reproducibility studies performed on laboratory-made solutions in different laboratories are shown in Table 5.

It should be noted that these studies were conducted 4 months before the linearity studies in the first laboratory and at the time of the linearity studies in the second laboratory.

As can be seen from Table 6, reproducibility is characterized by the small difference of the mean contents (0.12-0.89%) of appropriate batches which is in the limits of the full uncertainty of the analysis Δ_{As} = 1.6%, with exception of the batch in PVC. Samples of this batch are held at room temperature without a secondary packaging which protects medicinal products from water evaporation through PVH walls. The increased chlorides content is explained by water evaporation during 4 months of storage. Some authors establish the criterion for robustness as < 10% contents difference (16).

The general information about the validation characteristics of the elaborated procedure is presented in Table 6.

CONCLUSION

A simple, rapid, specific, accurate, precise, reproducible, robust and inexpensive alternative analytical procedure of direct argentometric method was developed and validated for chlorides assay in PD solutions using the approach of the SPU to analytical procedures validation. The developed analytical procedure does involve one titrant and it thus has an economic and time advantage over the pharmacopeia procedure of the assay of chlorides in PD solutions with the usage of the two titrated solutions and some reagents. The studies had been performed for 8 months for establishing the robustness and reproducibility of the analytical procedure. Therefore, the developed alternative analytical procedure of direct argentometric method could be used with the purpose of the quality control of PD solutions for the determination of chloride ions either in the production process or in final products of PD solutions containing such active pharmaceutical ingredients as sodium chloride, magnesium chloride, calcium chloride, glucose, sodium lactate and excipient hydrochloric acid. The presented approach could be also applied to analytical procedures validation of chlorides assay in PD solutions which are slightly differed from the formulation stated in the paper and validation of other analytical procedures as well.

Acknowledgments

Co-author Nataliia Hudz is grateful to the International Visegrad Fund (contract No. 51700107) for providing the scholarship for the studies related to solutions for dialysis therapy.

REFERENCES

1. Jayagopal B., Shivashankar M.: Mech. Mater. Sci. Eng. Vol. 9, p.11 (2017).
2. Zhang L., Mao S.: Asian J. Pharm. Sci. 12, 1 (2017).
3. Schweitzer M., Pohl M., Hanna-Brown M., Nethercote P., Bormanare P. et al.: Pharm. Technol. 2, 52 (2010).
4. Musters J., Van Den Bos L., Kellenbach E.: Org. Proc. Res. Dev. 17, 87 (2013).
5. ICH Q8 (R2), Harmonised Tripartite Guideline, Pharmaceutical development, Current Step 4 version, in: Proceedings of the International

Conference on Harmonization, p. 24, Aug, 2009.
6. Shabir G.A.: J. Validation Technol. 10, 314 (2004).
7. Hudz N., Korytniuk R., Vyshnevska L., Wieczorek P.P.: Int. J. App. Pharm. 10, 59 (2018).
8. Hudz N., Korzeniowska K., Wieczorek P.P.: Acta Pol. Pharm. 75, 875 (2018).
9. British Pharmacopeia. British Pharmacopeia Commission, London 2009.
10. Peraman R., Bhadraya K., Padmanabha Reddy Y.: Int. J. Anal. Chem. Vol. 2015, 9 pages (2015).
11. Jadhav M.N., Tambe S.R.: Chromatogr. Res. Int. Article ID 676501 (2013).
12. Kochling J., Wu W., Hua Y., Guan Q., Castaneda-Merced J.: J. Pharm. Biomed. Anal. 125, 130 (2016).
13. Rozet E., Lebrun P., Debrus B., Boulanger B., Hubert P.: Trends Anal. Chem. 42, 157 (2013).
14. Mechmood Y., Tariq A., Jamshaid U., Jumshaid M.: Int. J. Pure Appl. Biosci. 3, 41 (2015).
15. Ferraz L.R.M., Santos F.L.A., Ferreira P.A., Maia-Junior R.T.L., Rosa T.A. et al.: Int. J. Pharm. Sci. Res. 5(11), 4666 (2014).
16. Malik D.S., Kaur G.: Indian J. Pharm. Sci. 80, 503 (2018).
17. The State Pharmacopeia of Ukraine. 2-nd edition. Kharkiv: State Enterprise "Ukrainian Scientific Pharmacopeial Center for the Quality of Medicinal Products", Vol. 1., p. 1128, 2015.
18. ICH Topic Q2 (R1), Harmonised Tripartite Guideline, Validation of analytical procedures: Text and methodology. Step 5. Note for guidance on validation of analytical procedures: Text and methodology (CPMP/ICH/381/95) in: Proceedings of European Medicines Agency, London, Nov, 1994.
19. Kumar M., Shukla A.K., Bishnoi R.S., Jain C. P.: Int. J. App. Pharm. 10, 92 (2018).
20. Gündogdu S.Ö., Şimşek F., Doganay A., Çapan Y.: Acta Pol. Pharm. 76, 49 (2019).

Received: 18.01.2019