MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

GENERAL PHARMACOPOEIA MONOGRAPH

Ionometry **GPM**.1.2.1.0004.15

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The ionometry method is based on the determination of the activity (concentration) of the ions of interest by means of ion-selective (indicator) electrodes. An ion-selective electrode exhibits a selective sensitivity to certain ions; its potential depends on the content of these ions. This determination is based on the principle of potentiometric analysis, which involves measurement of the potential difference (electromotive force) of the indicator ion-selective electrode and the reference electrode that has a constant potential.

The relationship between the electromotive force of an electrode system and the activity of the potential-determining ion is described by the Nernst equation:

$$E = E_o + 2{,}303 \frac{R \cdot T}{z \cdot F} \lg a \qquad (1),$$

where: E is the potential difference between the measuring and the reference electrodes (electromotive force), mV;

E_0 is the standard electromotive force value at a=1, mV;
R is the universal gas constant, J/(mol·K);
T is the absolute temperature, K;
F is the Faraday constant, C/mol;
z is the charge of the ion being determined;
a is the activity or effective concentration of free ions in the solution related to the concentration by the following equation:

$$a = f \cdot C \qquad (2),$$

where:

C is the molar concentration, mol/L;
f is the activity coefficient.

For very diluted solutions, the activity coefficient almost equals one, and the activity of the ions is equal to their concentration.

If the activity coefficient is maintained at a constant level, the Nernst equation is as follows:

$$E = E_0 + \frac{k}{z} \cdot \lg (f \cdot C) \qquad (3), \quad \text{where}$$

$k = 2{,}303 \frac{R \cdot T}{F}$ – a coefficient showing the electromotive force change per lg a change unit, it can be calculated for any temperature according to the following equation:

$$k = [0{,}05916 + 0{,}000198 \cdot (t - 25^{\circ}\,C)] \qquad (4)$$

and is shown in Table 1.

Table 1

k values at different temperatures

Temperature, °C	k , V
15	0.0572
20	0.0582
25	0.0592
30	0.0602
35	0.0611

An activity coefficient (f) is considered constant if the same ion force is maintained across all measurements in the analyzed and calibration solutions. To create a constant ion force, a solution of an indifferent electrolyte (background solution) with a concentration exceeding 10 to 100 times the total concentration of other ions in the solution is added to the tested solution so that different quantities of the ion being analyzed can have no effect on the ion force of the solution and the activity coefficient of the ion being determined remains constant.

If $E = E_0 + \frac{k}{z} \cdot \lg f = E_o'$ and $S = \frac{k}{z}$,

where: S is the steepness of the electrode function, then

$$E = E_o' + S\,\lg C = E_o' - S \cdot pC \qquad (5),$$

where: $pC = -\lg C$.

Therefore, there is a linear relationship between the electromotive force of the electrode system and the concentration of the ion being determined at constant solution ion force and constant temperature.

ION ACTIVITY AND CONCENTRATION MEASUREMENT

Isometric measurements are carried out using an ionometer (a high ohmic potentiometer with an input resistance of at least 100 times the resistance of the electrodes used), which consists of an electrode system and a measuring transformer.

Potential ion-selective electrodes include electrodes with a liquid (plastified electrodes) or with a solid (monocrystalline, polycrystalline, or glass electrodes) membrane, electrodes with charged (positively or negatively) or uncharged mobile carriers, sensitized electrodes (electrodes with an enzymatic base, gas indicator electrodes). A chlorine – silver electrode or calomel electrode with appropriate indifferent connective liquids are predominantly employed as a reference electrode.

The instrument is graduated in millivolts or pX units. The ionomer is prepared for measurements and measurements are performed in accordance with the Instructions for Use of the device. Measurements are carried out at a constant temperature ± 0.5 °C and constant solution ion force. The electrodes are put into the tested solution, and the reading is recorded that is obtained upon slow and constant mixing.

If the measurements are frequent, the response is checked for stability and the calibration curve is checked for linearity over the concentration range of the tested solution. Otherwise, a check is performed prior to every set of measurements.

1. The graduation diagram method

The graduation diagram method involves the plotting of a diagram demonstrating the relationship between the electromotive force of the electrode system and the concentration of standard solutions with a known concentration, with subsequent calculation of the concentration of the tested solution based on the electrode system's electromotive force value measured in it. A graduation (calibration) diagram is plotted by the microprocessor of the measuring transformer automatically on the basis of input electromotive force values of the electrode system and respective pX values obtained by calibrating the ionomer in standard solutions (two or more). The choice of standard solution concentrations should correspond to the concentration range of the tested solutions: the extreme concentration values of the tested solutions should lie within the linear region of the calibration diagram. The pX value of the tested solution is obtained automatically on the calibration diagram, using the measured electromotive force value of the electrode system (E) – Figure 1.

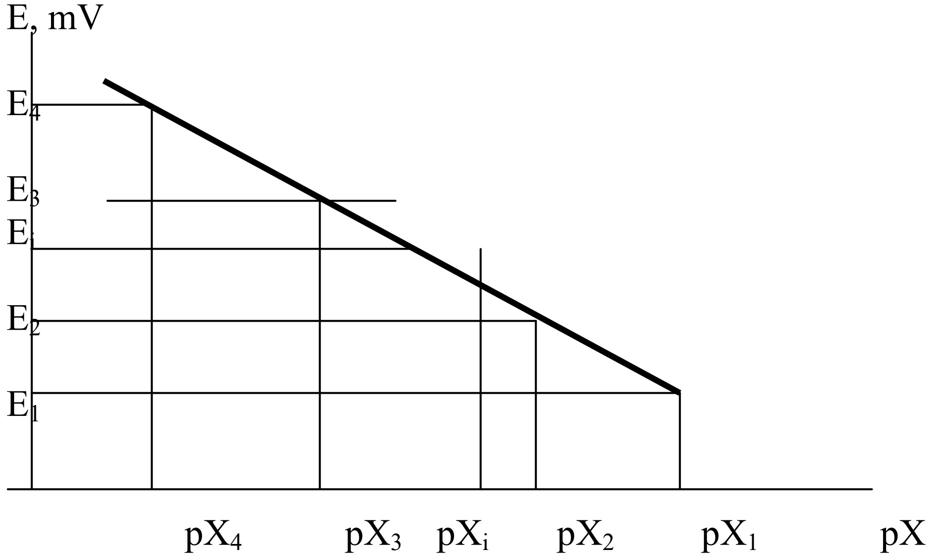

Figure 1. Graduation diagram demonstrating the relationship between the electromotive force of the electrode system and the concentration of the potential-determining ion.

Since pX = -lgC in diluted solutions, the molar concentration value (mol/L) is calculated according to the following equation:

$$C = 10^{-pX} \qquad (6),$$

The mass concentration of the ion (g/L) is calculated according to the following equation:

$$C = M \cdot 10^{-pX} \qquad (7),$$

where: M is the molar weight of the ion (g/mol).

In the presence of an effect of other components of the tested solution on the potential of the ion-selective electrode, the standard additions method should be used.

2. The standard additions method

This method is applicable for linear regions of the calibration curve.

2.1. The multiple additions method

A few (at least three) portions with volume V_0 ($V_0 \leq 0.01*V$) of a solution with a known concentration of the ion being determined are added to the tested solution with volume V prepared as specified in the Pharmacopoeia Monograph, observing that the ion force of the solution remains constant. The potential is measured before and after each addition, and the difference ΔE between the potential measured after the addition of the solution with the known concentration and the baseline potential of the tested solution is then calculated. The obtained value is related to the concentration of the ion being determined by the following equation:

$$\Delta E = S \cdot \lg\left(1 + \frac{C_0 \cdot V_0}{C \cdot V}\right), \qquad (8)$$

or

$$10^{\frac{\Delta E}{S}} = 1 + \frac{C_{0.} \cdot V_{0.}}{C \cdot V}, \qquad (9)$$

where: V is the volume of the tested solution, L;

C is the molar concentration of the ion being determined in the tested solution, mol/L;

$V_{0.}$ is the added volume of the standard solution, L;

$C_{0.}$ is the concentration of the ion being determined in the standard solution, mol/L;
S is the steepness of the electrode function determined experimentally at a constant temperature by measuring the potential difference of two standard solutions whose concentrations should differ 10-fold and correspond to the linear region of the calibration diagram, mV.

A diagram showing the relationship between $10^{\frac{\Delta E}{S}}$ and the addition volume $V_{0.}$ is plotted, and the obtained straight line is continued until it crosses the X axis. At the intersection, the concentration of the tested solution of the ion being determined is expressed by the following equation:

$$C = \frac{C_{0.} \cdot V_{0.}}{V} \qquad (10)$$

2.2 The single addition method

The volume $V_{0.}$ of the standard solution with the known concentration $C_{0.}$ is added to the volume V of the tested solution prepared as described in the Pharmacopoeia Monograph. The control solution is prepared under the same conditions. The potentials of the tested solution and the blank solution are measured before and after the addition of the standard solution. The concentration C of the ion being analyzed is determined using the following equation and making appropriate adjustments for the control solution:

$$C = \frac{C_{0.} \cdot V_{0.}}{10^{\frac{\Delta E}{S}} \cdot (V + V_{0.}) - V} \qquad (11)$$

where: V is the volume of the tested or the control solution, L;
C is the concentration of the ion being determined in the tested solution, mol/L;
V_0 is the added volume of the standard solution, L;
C_0 is the concentration of the ion being determined in the standard solution, mol/L;
ΔE is the difference of the potentials measured before and after the addition, mV;
S is the steepness of the electrode function determined experimentally at a constant temperature by measuring the potential difference of two

standard solutions whose concentrations differ 10-fold and correspond to the linear region of the calibration curve, mV.

3. pH value determination by potentiometry

The pH value (“power of hydrogen”), which characterizes the concentration of hydrogen ions in aqueous solutions, is the negative decimal logarithm of the activity of hydrogen ions

$$pH = - \lg a_{H^+} \qquad (12)$$

Potentiometric determination of the pH value is based on measurement of the electromotive force of an electrode system where an electrode (usually made of glass) sensitive to hydrogen ions is used as the ion-selective electrode and a standard electrode with a known potential (saturated calomel or chloride – silver electrode) is utilized as the reference electrode. In practice, the graduation diagram method is used to determine the pH value. The pH value of the tested solution is related to the pH value of the standard solution by the following equation:

$$pH = pH_S - \frac{E - E_S}{k}, \qquad (13)$$

where: E is the potential of the electrode in the tested solution, mV;

E_S is the potential of the same electrode in the solution with the known pH value (standard solution), mV;

k is a coefficient showing the electromotive force change per pH change unit, mV;

pHs is the pH value of the standard solution.

Apparatus. Ionometers or pH meters with a sensitivity of at least 0.05 pH units or 3 mV are used as the instrument for the potentiometric pH determination. The instrument should be calibrated by the standard buffer solutions described in the General Pharmacopoeia Monograph «Buffer solutions».

Procedure description. All measurements should be carried out at the same temperature, in the range from 20 °C to 25 °C, unless otherwise specified in the Pharmacopoeia Monograph. Table 2 shows the relationship between pH value and temperature for different standard buffer solutions used for instrument calibration. Standard titres may be used for the preparation of these solutions; industrial pH working reference standards may be used for the preparation of the buffer solutions.

Table 2

pH values of standard buffer solutions at different temperatures

Temperature, °C	0.05 M potassium tetra-oxalate solution	Potassium hydrogen tartrate solution saturated at 25 °C	0.05 M potassium dihydrogen nitrite solution	0.05 M potassium hydrogen phthalate solution	0.025 M potassium dihydrogen phosphate solution and 0.025 M sodium hydrogen phosphate solution	0.0087 M potassium dihydrogen phosphate solution and 0.0303 M sodium hydrogen phosphate solution	0.01 M sodium tetraborate solution	0.025 M sodium carbonate solution and 0.025 M sodium hydrogen carbonate solution	Calcium hydroxide solution saturated at 25 °C
15	1.67		3.80	4.00	6.90	7.45	9.28	10.12	12.81
20	1.68		3.79	4.00	6.88	7.43	9.23	10.06	12.63
25	1.68	3.56	3.78	4.01	6.87	7.41	9.18	10.01	12.45
30	1.68	3.55	3.77	4.02	6.85	7.40	9.14	9.97	12.29
35	1.69	3.55	3.76	4.02	6.84	7.39	9.10	9.93	12.29
$\frac{\Delta pH^{(1)}}{\Delta t}$	+0.001	-0.0014	-0.0022	+0.0012	-0.0028	-0.0028	-0.0082	-0.0096	-0.034

(1) – One degree Celsius change in pH.

If appropriate, temperature adjustments should be made in accordance with the instructions of the manufacturing enterprise. The instrument should be calibrated using a potassium hydrogen phthalate buffer solution (primary standard) and one of the buffer solutions with a different pH value (preferably one of the solutions specified in Table 2). The readings obtained on the device for the third buffer solution with an intermediate pH value should not differ from the pH value specified in the table for this solution by more than 0.05 pH units. The electrodes are immersed in the tested solution, and the pH value is measured under the same conditions as for the buffer solutions.

All tested solutions and standard buffer solutions should be prepared using carbon dioxide-free water; for this purpose, it should be boiled before use. The carbon dioxide-free water should have a pH value of 5.8 to 7.0.

Preparation of the standard buffer solutions

0.05 M potassium tetraoxalate solution. Dissolve 12.61 g of $KC_4H_3O_8 \cdot 2H_2O$ in the water, and bring the volume of the solution to 1000.0 mL with the same solvent.

Potassium hydrogen tartrate solution saturated at 25 °C. Shake an excess of $KC_4H_5O_5$ vigorously with the water at 25 °C. Filter or decant. Use this solution while it is fresh.

0.05 M potassium dihydrogen citrate solution. Dissolve 11.41 g of $KC_6H_7O_7$ in the water, and bring the volume of the solution to 1000.0 mL with the same solvent. Use this solution while it is fresh.

0.05 M potassium hydrogen phthalate solution. Take 10.13 g of $KC_8H_5O_4$ pre-dried at a temperature from 110 °C to 135 *°C* to a constant weight and dissolve this sample in the water, then bring the volume of the solution to 1000.0 mL with the same solvent.

0.025 M potassium dihydrogen phosphate solution and 0.025 M sodium hydrogen phosphate solution. Take 3.39 g of KH_2P0_4 and 3.53 g of Na_2HPO_4 pre-dried for two hours at a temperature from 110 °C to 130 °C to a constant weight and dissolve these samples in the water, then bring the volume of the solution to 1000.0 mL with the same solvent.

0.0087 M potassium dihydrogen phosphate solution and 0.0303 M sodium hydrogen phosphate solution. Take 1.18 g of KH_2PO_4 and 4.30 g of Na_2HPO_4 pre-dried at a temperature from 110 °C to 130 °C, dissolve these samples in the water, then bring the volume of the solution to 1000.0 mL with the same solvent.

0.01 M sodium tetraborate solution. Dissolve 3.80 g of $Na_2B_4O_7 \cdot 10H_2O$ in the water and bring the volume of the solution to 1000.0 mL with the same solvent. Store this solution protecting it from carbon dioxide.

0.025 M sodium carbonate solution and 0.025 M sodium hydrogen carbonate solution. Dissolve 2.64 g of Na_2CO_3 and 2.09 g of $NaHCO_3$ in the water, and bring the volume of the solution to 1000.0 mL with the same solvent.

When measuring the pH value in non-aqueous and mixed solvents, as well as in some colloidal systems, one should take into account that the obtained pH values are conditional.

Note. Buffer solutions stored in tightly closed neutral glass receptacles for 3 months. Buffer solutions should not be used in the presence of sedimentation or visible changes.