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Short communication

Selectivity coefficients of ion-selective magnesium electrodes used for simultaneous determination of magnesium and calcium ions

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ABSTRACT

Membrane ion-selective magnesium electrodes are commonly used to determine ionized magnesium concentration in blood serum and intracellular fluid by potentiometric clinical analyzers. The selectivity of these electrodes against calcium ion is typically insufficient to avoid calcium interference in blood serum analysis. For this reason the selectivity coefficient for calcium ion has to be studied to make possible any mathematical corrections for calcium ion influence. Existing methods relate to the thermodynamic concept of ISE response which suggest a single constant value of the selectivity coefficient and slope that are stable over the concentration ranges of calcium and magnesium ions in the samples. Unfortunately, this rarely happens, and we rather observe dependences on solution and membrane composition, readout time, matrices (anticoagulant, vial coats) that justify usage of apparent selectivities and slopes. To get the practical insight into the response of magnesium ion-selective electrodes a novel method for estimating the selectivity coefficients and the slope of the electrode characteristics is proposed. This method is an effective starting point for selecting electrodes and designing transient signal software in a potentiometric clinical analyzer. The method allows obtaining the ionized magnesium concentration in blood serum with minimal possible error by addressing the assessed targets, i.e. apparent selectivity and slope. The method is based on computer simulation and on the Nicolsky–Eisenman equation. Usually only a few iterations are needed to obtain stable congruent results. The method presented is particularly useful in conditions where is not possible to obtain calibration curve, which is typical for clinical analyzer where at most three point calibration is performed.

1. Introduction

The selectivity coefficients of ion-selective electrodes are determined in several ways [1–5]. The simplest and fastest method is based on measurements of the ion-selective electrode potential in separate solutions of 0.1 mol L^{-1} solutions of the main and the interfering ion (separate solutions method – SSM). Then the selectivity coefficient (K_{ij}^{Pot}) can be calculated from the Nikolsky–Eisenman semiempirical equation:

$$E = \text{const} + \frac{RT}{z_i F} \log(a_i + K_{ij}^{Pot} a_j^{zi/zj}) \quad (1)$$

where a_i and a_j denote activity of the main and interfering ions and z_i and z_j – their charge, respectively. R, F are gas and Faraday constant and T denotes absolute temperature.

A similar but fully empirical equation can be given as:

$$E = \text{const(app)} + S(\text{app}) \log(a_i + K_{ij}^{Pot}(\text{app}) a_j^{zi/zj}) \quad (2)$$

where index "app" means apparent.

Another method, called the mixed solution method (MSM), uses the measurements in solutions containing both the main and interfering ions. Usually, the concentration of the interfering ion is constant (fixed interference method FIM) and that of the main ion is changing, which leads to a calibration curve with a plateau caused by the interfering ion. Then K_{ij}^{Pot} is found using the SIMPLEX method (or other analogous) from the Nicolsky–Eisenman equation where "const", slope (RT/z_iF) and K_{ij}^{Pot} are the parameters. In the Gadzekpo and Christian method, the selectivity refers to the concentration of interfering ion, which changes by 10% the potentiometric response of the electrode for the main ion. A thorough discussion of these methods is given in the IUPAC recommendation [1]. Bakker [2] proposed measuring the selectivity of the electrodes with plastic ion-selective membranes not containing the main ion. The results obtained were more similar to the thermodynamic values expected from the stability constants of complexes

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Table 1
Composition of the calibration solutions (mmol L^{-1}).

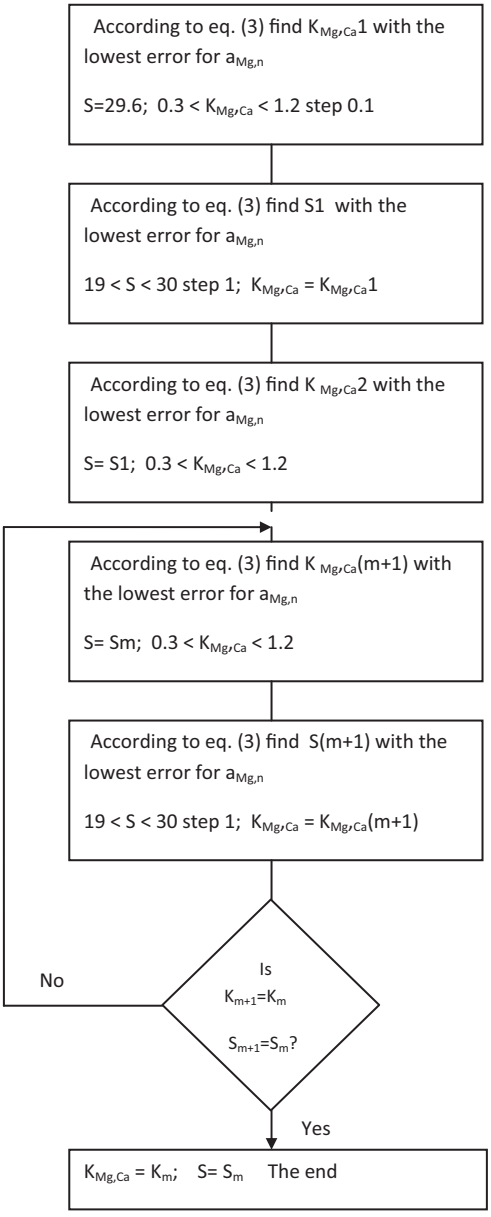
Component	STD 1	STD 2	STD 3
NaCl	140.0	120.0	150.0
KCl	4.5	6.0	3.0
$CaCl_2$	1.25	0.75	1.75
$MgCl_2$	0.75	0.50	1.50
TES	5 (pH 7.4)	5 (pH 7.0)	5 (pH 7.8)

of the ions with ionophores used in the membranes. Similar values were obtained when the sample solution with buffered main ion [3] or especially designed electrodes with lowered detection limit [4] were used to determine the selectivity coefficients with SSM. All these methods assumed idealized time-independent selectivity coefficient and slope. For this reason the experimental procedures were recently re-elaborated involving generalized ISE response theory [5].

Conventional methods, as introduced by IUPAC, are good enough for comparing various electrodes in the determination of the main ion. However, nowadays there are more and more analyses where the selectivity coefficient value is needed to calculate the activity of the main ion. A good example of such a situation is the determination of lithium and magnesium ions in blood serum. In the case of lithium ion, the influence of sodium could be quantitatively assessed due to a stable and matrix-independent $K_{Li,Na}$ selectivity coefficient value and independent measurement of sodium [6]. The influence of calcium on magnesium ion-selective electrode was found to be more complex [7]. It was observed that over short readout times the selectivity is time-dependant. More importantly, it was noticed that these time-dependent effects disappear after certain periods of read-out, although not necessarily the same selectivity coefficient and slopes were observed for these readouts over analytical concentration ranges of magnesium and calcium ions. The challenge in this case is to select the electrodes with acceptable apparent selectivities that are able to provide analytical sounded results for magnesium in blood (in the range 0.2–3.0 mmol L^{-1} and CV < 2%) irrespective of possible calcium ionized concentration changes in blood (in the range 0.5–2.5 mmol L^{-1}). This is a background of a method described here which is a way to estimate the apparent selectivity coefficients and the slopes of the electrode characteristics "on fly" in the environment of a real multiparameter clinical analyzer (see Scheme 1).

2. Experimental

The magnesium ion-selective membrane composition was as follows: 1% (w/w) ionophore ETH 5220 synthesized according to [6–8], 70 mol-% to ionophore potassium tetrakis-p-chloroborate (Sigma, Switzerland), 65% (w/w) plasticizer [electrode 1: o-nitrophenylphenyl ether (NPPE)/chloroparaffin (60% Cl) (ClP) = 1 + 1 (vol + vol); electrode 2: o-nitrophenyloctyl ether (NPOE)/ClP = 1 + 1 (vol + vol); electrode 3: NPOE; NPPE was from Kodak, USA; NPOE – from Sigma; ClP – from Scientific Polymer Products, USA], and 33% (w/w) poly(vinyl chloride) (PVC high molecular, Sigma). The membrane was placed in a flow-through electrode body manufactured by Kone Instruments, Finland. Potentiometric measurements were taken at 37 °C in a clinical analyzer



Scheme 1. Flow chart of computer simulation of S(app) and $K_{Mg,Ca}$(app).

Table 3
The selectivity coefficients and the slopes chosen from simulated curves (±SD), $K^{Pot}_{Mg,Ca}$ from SSM and MSM.

Electrode	$K^{Pot}_{Mg,Ca}$ (sim.) $n=24$	S (sim.) mV/dec $n=24$	$K^{Pot}_{Mg,Ca}$ SSM $n=3$	$K^{Pot}_{Mg,Ca}$ MSM $n=3$
1	0.74 ± 0.10	23.7 ± 2.5	0.66 ± 0.15	0.72 ± 0.20
2	0.89 ± 0.06	24.8 ± 2.3	0.84 ± 0.28	0.89 ± 0.25
3	1.85 ± 0.20	25.5 ± 1.5	0.94 ± 0.38	1.81 ± 0.35

Table 2
Composition of 24 aqueous solutions (mmol L^{-1}) containing cNaCl = 140.0 mmol L^{-1}, cTES = 5 mmol L^{-1}, pH 7.4, and varying concentration of $MgCl_2$ and $CaCl_2$.

$cCaCl_2$	$cMgCl_2$								
	0.50	0.60	0.75	0.90	1.00	1.10	1.25	1.50	
0.75	1	4	7	10	13	16	19	22	Number of solution
1.25	2	5	8	11	14	17	20	23	
1.75	3	6	9	12	15	18	21	24	

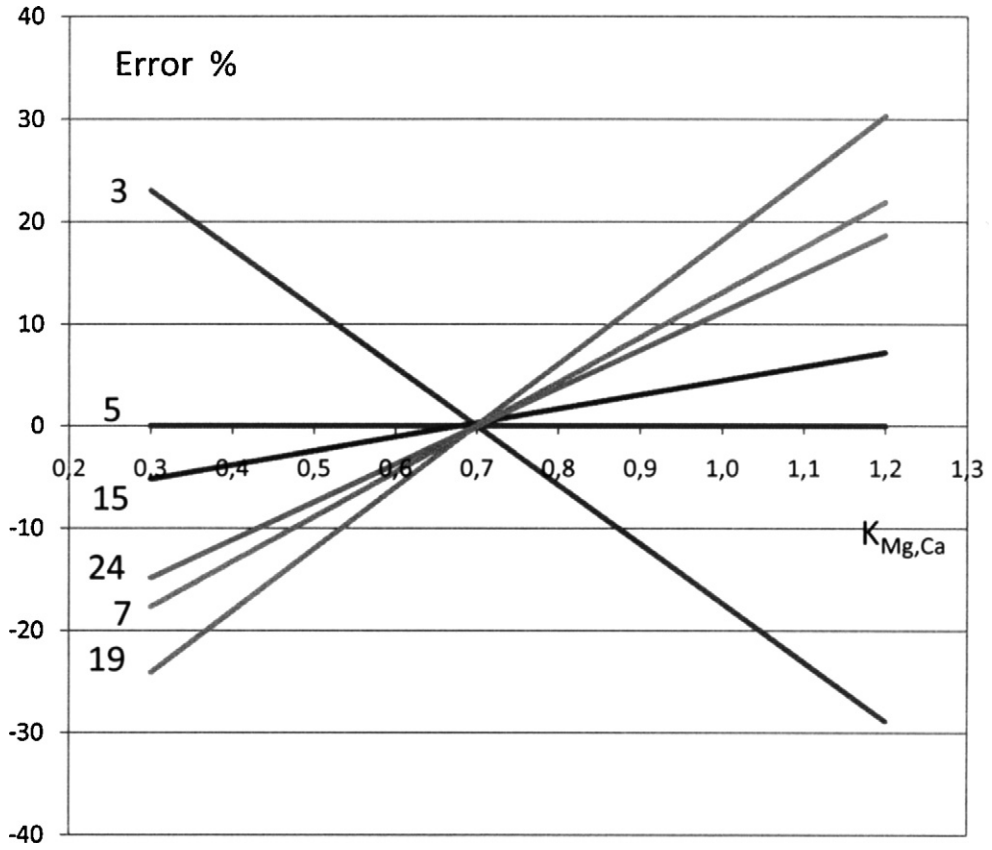


Fig. 1. Error in Mg activity due to improper selectivity coefficient taken for a model membrane with the calibration slope 29.59 mV/dec and the selectivity coefficient against Ca ion $K_{Mg,Ca} = 0.7$. Numbers refer to the solutions number in Table 2. Lines calculated according the Eq. (3).

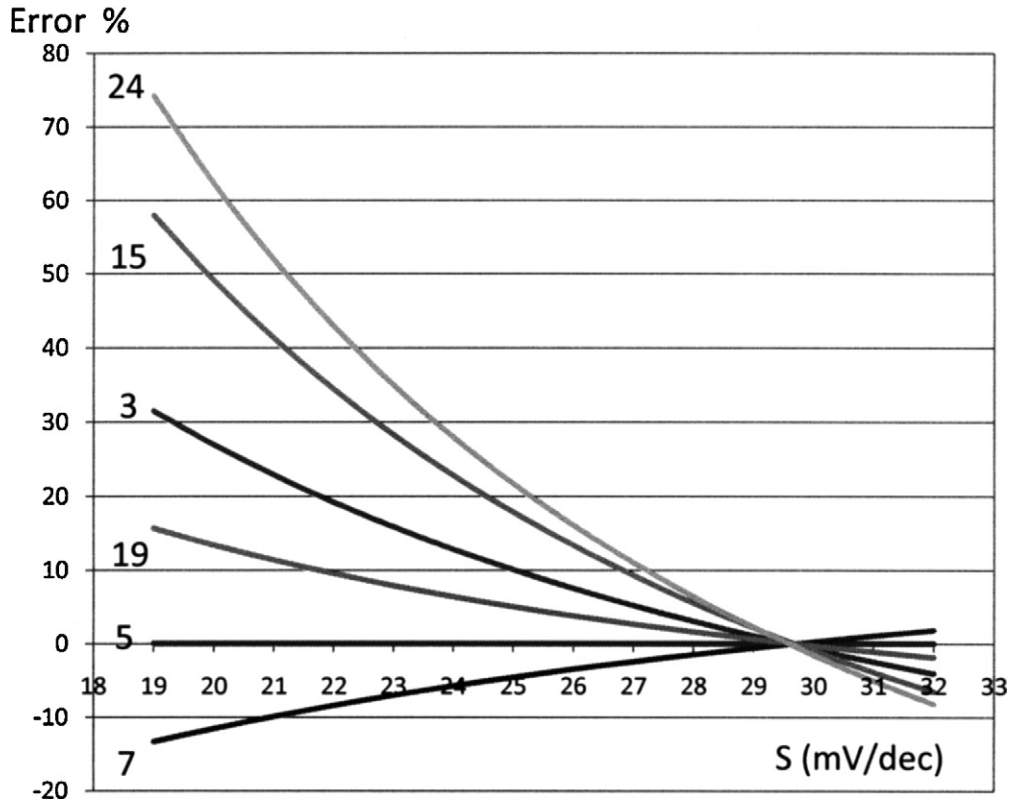


Fig. 2. Error in Mg activity due to improper slope of the calibration curve taken for a model membrane with the calibration slope 29.59 mV/dec and the selectivity coefficient against Ca ion $K_{Mg,Ca} = 0.7$. Numbers refer to the solutions number in Table 2. Line calculated according the Eq. (3).

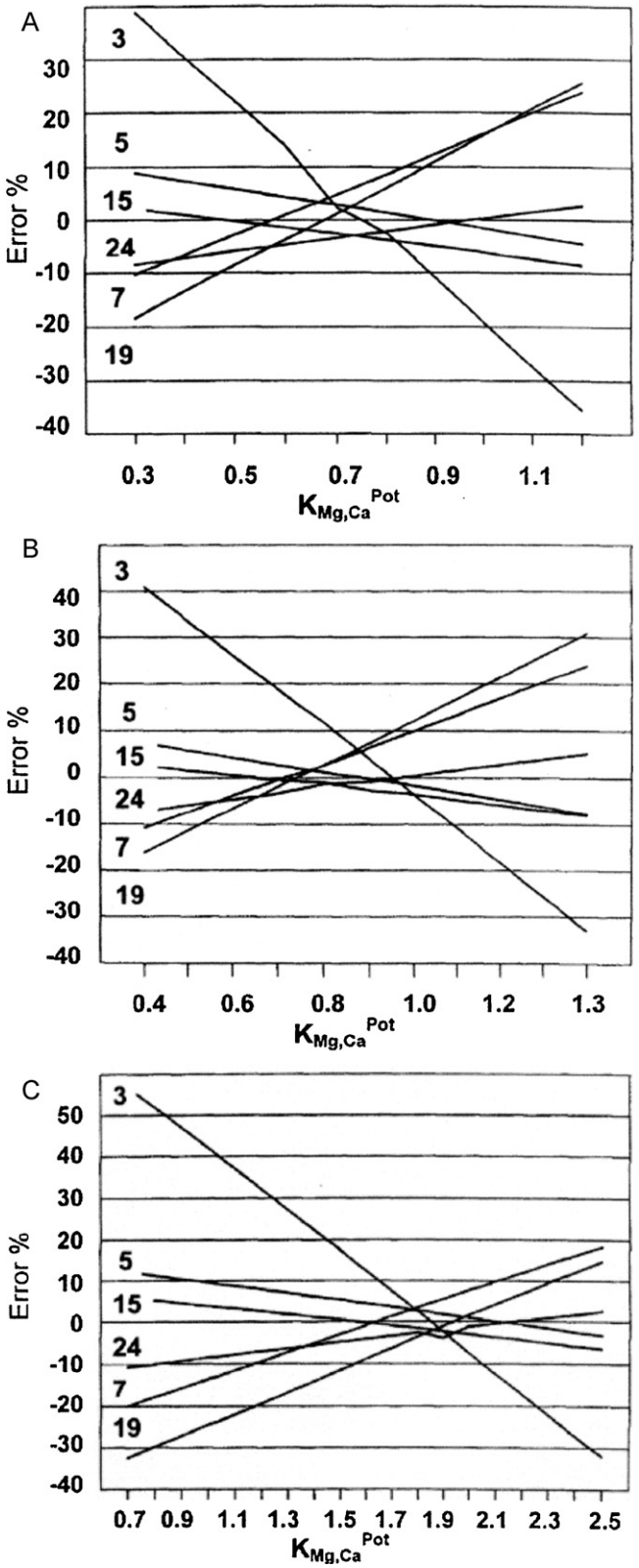


Fig. 3. The error of Mg^{2+} determination due to varying $K_{Mg,Ca}^{Pot}$, computer simulation, A – electrode 1, B – electrode 2, C – electrode 3. The numbers correspond to the solutions in Table 2.

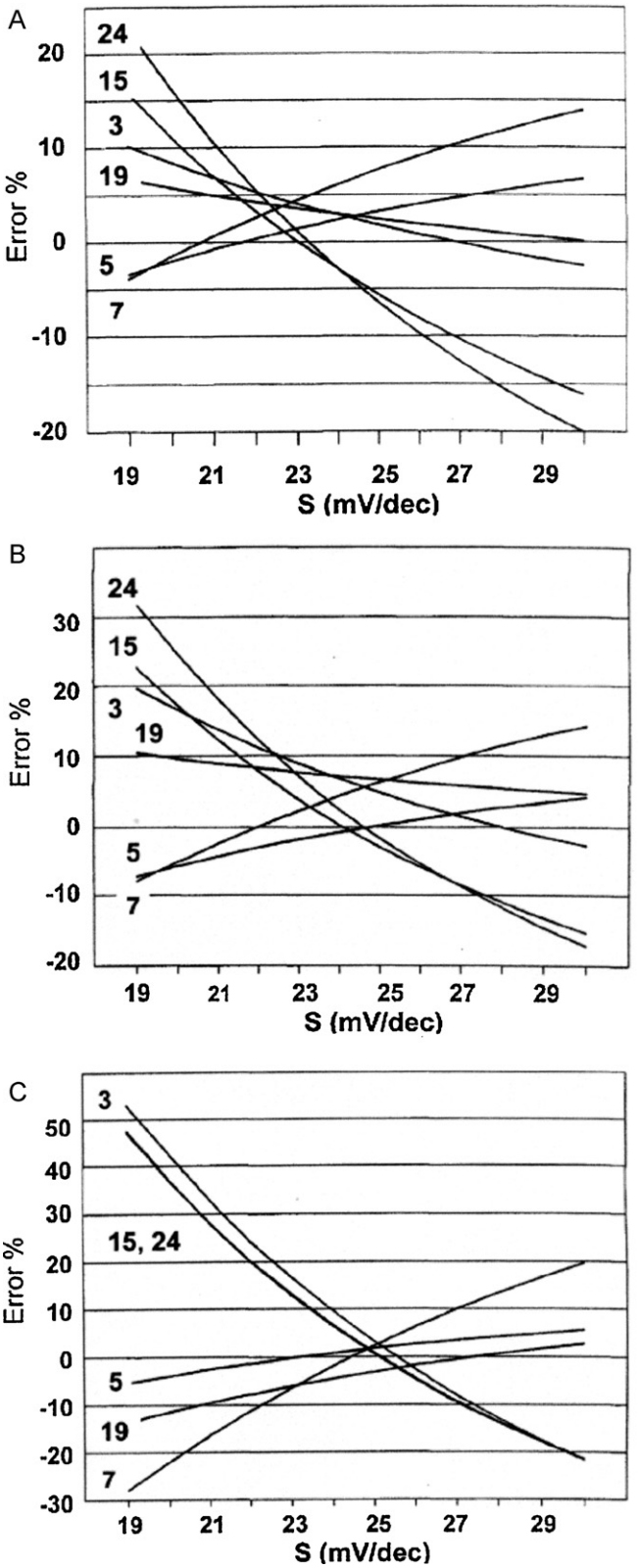


Fig. 4. The error of Mg^{2+} determination due to varying S, computer simulation, A – electrode 1, B – electrode 2, C – electrode 3. The numbers correspond to the solutions in Table 2.

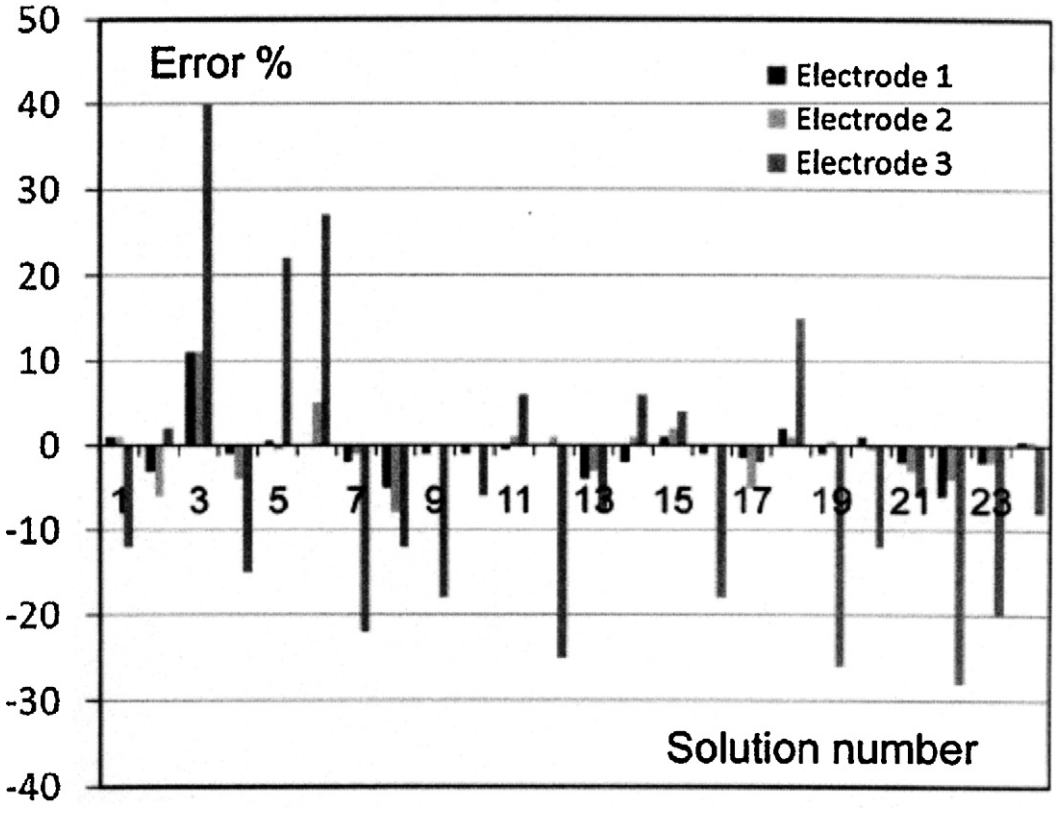


Fig. 5. The error of magnesium ion determination in aqueous solutions (Table 2) using the $K^{Pot}_{Mg,Ca}$ value obtained by the SSM.

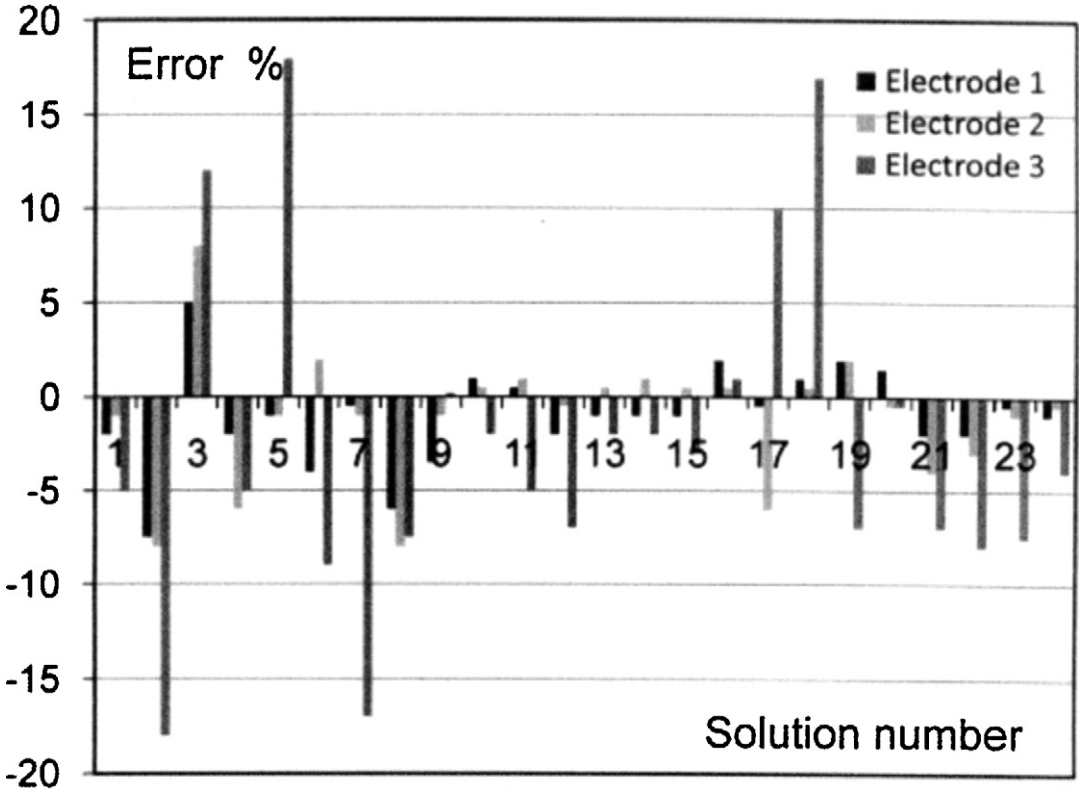


Fig. 6. The error of magnesium ion determination in aqueous solutions (Table 2) using the $K^{Pot}_{Mg,Ca}$ value obtained by the MSM.

Microlyte 6 (Kone Instruments) with three point calibration, 150 μl sample intake and accuracy of EMF measurements of ±0.01 mV. Other ion-selective electrodes used (Na^+, K^+, Cl^-, Ca^{2+}, pH and reference electrode) were commercial electrodes from Kone. Three calibration solutions were of the composition given in Table 1. All the salts and N-[(trishydroxymethyl)methyl]-2-aminoethanesulphonic acid (TES) were from Sigma. The magnesium electrode internal reference solution was STD 1 in Table 1, and the internal reference electrode was Ag/AgCl.

The selectivity coefficients were determined by the SSM [9] in 0.1 mol L^{-1} aqueous metal chloride solutions assuming the theoretical slope of electrode characteristics, by the MSM using measurements with three sets of solutions, with constant concentration of $CaCl_2$ each, as given in Table 2, and by calculating the selectivity coefficients using the Nicolsky–Eisenman equation. The third method based on computer simulation is explained below in detail. The activity coefficients were calculated according to Meier [10]. Experimental data were corrected for changes of the liquid junction potential using the Henderson approach [11]. The Microsoft Excel 2003 and 2007 were used for calculations.

3. Results and discussion

It was shown before that the membrane selective for magnesium ion shows a different dynamic response for changes of Mg^{2+} and Ca^{2+} activity in the solution [7,12]. This difference was attributed to the difference of solvated, Mg^{2+} and Ca^{2+} ions radiuses and resulting difference in ion mobilities, both in the membrane and bathing solution [13–15]. Transport process during equilibration influences the selectivity of the ion-selective membrane which is both time and Mg^{2+}/Ca^{2+} concentration ratio dependent [7,12–14]. These effects can be interpreted only via special mathematical algorithms [16].

Notwithstanding, also earlier it was theoretically proven and experimentally observed [7] that after sufficient readout time the electrical potential of magnesium selective membranes is time independent. That makes any practical implementation of magnesium ion selective electrode easier, even if thermodynamic prediction is still formidable. Existing methods relate to the thermodynamic concept of ISE response which suggest a single constant value of the selectivity coefficient and slope that remain unchanged over the concentration ranges of calcium and magnesium ions in the samples. Unfortunately, this happens rarely, and rather we observe dependences on solution and membrane composition, readout time, matrices (anticoagulant, vial coats) that justify usage of apparent selectivities and slopes. For this reason, it was especially interesting to compare the apparent time-independent selectivity coefficient against Ca^{2+} obtained by various methods and to evaluate its possible deviation with the aim of minimizing the error in the results obtained by the clinical analyzer.

In the clinical analyzer, the calibration curve covers a short range of concentration of ions typical for the clinical sample, e.g. blood serum (Table 1) [17]. Typically three point calibration curve is used to minimize the use of calibrators and at the same time to serve three important unknowns, i.e. apparent slope, selectivity coefficient and standard potential. The matrix of calibration solutions contains six ions that change their activity. One of the ions, namely calcium, interferes. The apparent slope of the calibration curve given by the Eq. (2) and obtained using calibrators of the clinical analyzer is not equal RT/z_iF as seen from the Eq. (1). This due to calcium interference and its bias on slope. No one of the methods estimating selectivity coefficients of ion selective electrodes matches the conditions found in the clinical analyzer. Therefore more advanced assessment on selectivity is of importance since it can be further employed in "on fly" corrections of selectivity-slope bias in the environment of a real clinical analyzer.

Figs. 1 and 2 show how the changes of selectivity coefficient and the changes of slope of the ion selective electrode characteristics influence the obtained result in magnesium activity. The lines are calculated based on the Nicolsky–Eisenman equation and for the model magnesium selective membrane assuming the slope $S = 29.59$ mV/dec and selectivity coefficient against calcium $K^{Pot}_{Mg,Ca} = 0.7$. To avoid the influence of "const" from the equation the difference of potentials for selected solutions from Table 2 and solution number 5 (Table 2) are taken. The solution number 5 is the closest to physiological one in the composition [17,18]. The used equation is as follows:

$$E_n - E_5 = S(\text{app}) \log \left[\frac{a_{in} + K^{Pot}_{ij}(\text{app}) \cdot a_{jn}}{0.6 + K^{pot}_{ij}(\text{app}) \cdot 1.25} \right] \quad (3)$$

where n indicates the number of solution in Table 2.

To obtain experimental results the potential value for each solution (Table 2) was measured in the clinical analyzer. The computer simulation was made taking the measured potential value for each solution and calculating the error changing $K^{Pot}_{Mg,Ca}$ at constant S and changing S at $K^{Pot}_{Mg,Ca}$ constant as shown on a flow-chart (Scheme 1). The starting value of S(app) was assumed to be theoretical. Such a simulation based on the Eq. (3) was carried out. Usually only a few iterations were needed to obtain stable constant results for $K^{Pot}_{Mg,Ca}$(app) and S(app), which are shown in Figs. 3 and 4. In both cases, all curves intersect in the vicinity of the region which corresponds to a point giving the lowest error. It is possible to evaluate the deviation of the intersection points to obtain results in the required range of error. The values of $K^{Pot}_{Mg,Ca}$(app) and S(app) with their deviation for the range of 10% error obtained by this method are shown in Table 3 and compared with the values of $K^{Pot}_{Mg,Ca}$ from SSM and MSM. From the simulated curves, it follows that both $K^{Pot}_{Mg,Ca}$(app) and S(app) values have a quite large useful range, which is very important for their application. The range includes the values of $K^{Pot}_{Mg,Ca}$ obtained by the MSM for all the three membranes and by the SSM for membranes 1 and 2. The selected solutions are presented in Figs. 3 and 4. However, the useful range of accepted error in magnesium ion determination, 10% in our case, eliminates electrode 3 that is clearly visible in Figs. 5 and 6. That means that the measurement in a whole matrix of various main and interfering ion concentrations is needed to accept or eliminate the electrode under consideration.

4. Conclusion

On the example magnesium ion-selective electrode that is poorly selective for interfering calcium ion we discuss the method of evaluation of apparent selectivity coefficient $K^{Pot}_{Mg,Ca}$(app) and slope S(app). It is shown that this method is very useful in visualizing possible errors due to their improper values for further practical applications. The method is particularly useful for determining selectivities and slopes in conditions where it is not possible to obtain a full calibration curve and where interfering effects have to be corrected "on fly", e.g. in specialized devices, such as the clinical ionized magnesium analyzers.

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