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Mathematical representation of electrophoretic mobility of basic drugs in ternary solvent buffers in capillary zone electrophoresis

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Abstract

The electrophoretic mobilities of two β-blocker drugs, i.e., labetalol and atenolol, have been determined in a mixed solvent background electrolyte system containing sodium acetate+acetic acid as buffering agent and different volume fractions of water, methanol and ethanol using capillary electrophoresis. The produced data and three other sets collected from a recent work are employed to study the accuracy and prediction capability of a mathematical model to calculate the electrophoretic mobility with respect to the volume fractions of the solvents in the mixture. The results show that the proposed model is able to correlate/predict the mobility within an acceptable error range and it is possible to use the model in industry to achieve the optimum solvent composition for the buffer where using a ternary solvent system is required. The average percentage deviations (APDs) obtained for correlated and predicted data points are 0.71–2.48 and 1.72–4.39%, respectively. The accuracy of the proposed model is compared with that of a mixture response surface method and the results show that the proposed model is superior from both correlation and prediction points of view. The possibility of calculation of the mobility of chemically related drugs in water–methanol–ethanol mixtures using the proposed model is also shown and the produced prediction APD is ~8%.

Keywords: Mathematical modelling; Background electrolyte composition; Electrophoretic mobility prediction; Beta-blockers

1. Introduction

Capillary electrophoresis (CE) is a technique that has become a well established method in the separation of a variety of compounds of pharmaceutical interest. Most of the work with CE has involved aqueous running buffer, however organic solvents have been used in conventional electrophoresis and isotachophoresis for many years. The area of mixed solvent background electrolytes (BGEs) has a lot of potential in CE. This area exploits the vastly different physicochemical properties of organic solvents to control the electroosmotic flow (EOF) and analyte migration [1–3]. It is not a novel technique for binary, ternary and even quarternary mobile phases that have been used in high-performance liquid chromatography (HPLC) for many years, but it is only recently that binary and ternary BGEs have been explored in CE. One example of the use of a

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binary BGE is the separation of paraquat and diquat herbicides in water and acetonitrile mixtures [4]. Binary BGEs are also employed in other validated CE methods [5–11]. Less work has been performed on ternary solvents in the BGE. A simple CE separation of four structurally related prostaglandins in a running buffer containing acetonitrile, methanol and water (total organic solvents=80%) has been reported [12]. The authors explained that the binary mixtures of methanol and acetonitrile are not able to resolve all the prostaglandins studied and this could be achieved by addition of 20% water to methanol–acetonitrile (75:25, v/v). Under optimised conditions, the method was then validated to international conference on harmonization (ICH) guidelines. In addition, ternary solvent BGEs are used in reported CE methods [13,14].

It is generally difficult to predict the effects of organic solvents on the electrophoretic mobility of analytes and electroosmotic flow without using experimental mobility data. Increasing the number of organic solvent components in the BGE leads to an increase in the number of experiments for optimisation, which is generally performed by trial and error. Thus, the use of a mathematical equation to reduce the time spent on optimisation is of utmost importance and interest, especially to the pharmaceutical industry who are forever searching for reductions in method development times.

This work is an extension of previous work [15,16] which have highlighted the possibility of minimising the number of experiments to predict the mobility of drugs in mixed solvent systems by the use of the mathematical models. To show the applicability of the proposed model on real data the electrophoretic mobility of two β-blocker drugs, i.e., labetalol and atenolol, have been determined in a ternary solvent BGE. In addition, three other mobility data sets for practolol, timolol and propranolol [17] have been employed as further experimental data sets. The accuracy of the proposed model is compared with that of a previous mixture response surface model [17] using average percentage deviation (APD) and also distribution of individual percentage deviations as comparison criteria. The prediction capability of the model is evaluated by using a minimum number of data points for model training and predicting the other data points. Also, the proposed model is employed to predict the mobility of labetalol and atenolol in ternary solvent acetate buffer using experimental points of three other β-blocker drugs in the same mixed solvent buffer which provide a pure predictive equation.

2. Theoretical treatment

In our earlier work [15], a solution model has been proposed to compute the electrophoretic mobility of analytes in binary solvent electrolyte systems. The model is:

$$\ln \mu_m = f_1 \ln \mu_1 + f_2 \ln \mu_2 + f_1 f_2 [A_0 + A_1(f_1 - f_2)] \quad (1)$$

where μ is the electrophoretic mobility, subscripts m, 1 and 2 refer to mixed solvent, solvents 1 and 2, respectively, f is the volume fraction of the solvent in the mixed solvent system and $A_0 - A_1$ are the model constants calculated by a least-squares analysis. It has been shown that the numerical values of A terms are nearly constant for the mobility of structurally related drugs in a given binary solvent BGE [16]. Therefore, it is possible to predict the mobility of similar drugs in a given BGE by a trained model using experimental data of other chemically related drugs.

To provide more accurate predictions, one could employ more curve-fitting parameters such as:

$$\ln \mu_m = f_1 \ln \mu_1 + f_2 \ln \mu_2 + f_1 f_2 [A_0 + A_1(f_1 - f_2) + A_2(f_1 - f_2)^2] \quad (2)$$

where $A_0 - A_2$ are the model constants. An extended form of the model is applicable for ternary solvent mixtures:

$$\begin{aligned} \ln \mu_m = {} & f_1 \ln \mu_1 + f_2 \ln \mu_2 + f_3 \ln \mu_3 \\ & + f_1 f_2 [M_0 + M_1(f_1 - f_2) + M_2(f_1 - f_2)^2] \\ & + f_1 f_3 [M'_0 + M'_1(f_1 - f_3) + M'_2(f_1 - f_3)^2] \\ & + f_2 f_3 [M''_0 + M''_1(f_2 - f_3) + M''_2(f_2 - f_3)^2] \\ & + f_1 f_2 f_3 [M'_0{}'' + M'_1{}''(f_1 - f_2 - f_3) \\ & + M'_2{}''(f_1 - f_2 - f_3)^2] \end{aligned} \quad (3)$$

in which subscript 3 refers to solvent 3, M_0–M_2, M'_0–M'_2, M''_0–M''_2 and $M'{}''_0$–$M'{}''_2$ are the model

constants calculated by fitting ($\ln \mu_m - f_1 \times \ln \mu_1 - f_2 \times \ln \mu_2 - f_3 \times \ln \mu_3$) against $f_1 f_2$, $f_1 f_2(f_1 - f_2)$, $f_1 f_2(f_1 - f_2)^2$, $f_1 f_3$, $f_1 f_3(f_1 - f_3)$, $f_1 f_3(f_1 - f_3)^2$, $f_2 f_3$, $f_2 f_3(f_2 - f_3)$, $f_2 f_3(f_2 - f_3)^2$, $f_1 f_2 f_3$, $f_1 f_2 f_3(f_1 - f_2 - f_3)$ and $f_1 f_2 f_3(f_1 - f_2 - f_3)^2$ using a no intercept least-squares analysis. It is obvious that Eq. (3) reduces to Eq. (2) when $f_3 = 0$.

The correlation ability and prediction capability of the proposed equation (Eq. (3)) for calculating mobility data in mixed solvent electrolytes have been compared with those of a mixture response surface method from a previous work [17]:

$$\ln \mu = B_1 f_1' + B_2 f_2' + B_3 f_3' + \frac{B_4}{f_1'} + \frac{B_5}{f_2'} + \frac{B_6}{f_3'} + B_7 f_1' f_2' + B_8 f_1' f_3' + B_9 f_2' f_3' + B_{10} f_1' f_2' f_3' \quad (4)$$

where B_1–B_{10} are the model constants and f_1'–f_3' is the modified volume fraction of solvents 1–3 in the mixture. The modified volume fractions are computed by $f' = 0.96f + 0.02$ [17].

3. Experimental

3.1. Instrumentation

All experiments were performed using a P/ACE system 5510 series instrument with Beckman P/ACE software (Beckman Instruments Europe, High Wycombe, UK). The fused-silica capillary was purchased from Composite Metal Services (Hallow, UK) and was 37 cm (30 cm to the detector) × 75 μm I.D. The temperature of the capillary was kept at 25.0 °C using a liquid coolant. Samples were injected by low pressure (0.5 p.s.i.) for 2 s and analytes were detected at 214 nm (1 p.s.i. = 6894.76 Pa). The applied voltage was 25 kV.

3.2. Materials

The analytes labetalol hydrochloride and atenolol hydrochloride were purchased from Sigma–Aldrich (Poole, UK). Acetic acid and sodium acetate were purchased from BDH (Poole, UK). Methanol (HPLC grade) and ethanol were purchased from Riedel-de Haen (Seezle, Germany). Mesityl oxide was used as a neutral marker and purchased from Acros (NJ, USA). Milli-Q water from a Millipore water-purification system (Watford, UK) was used.

3.3. Methods

A series of binary and ternary mixed aqueous–organic modifier buffers was prepared by mixing three stock acetate buffers prepared in the three pure solvents (water, methanol and ethanol) by dissolving 3.3 g sodium acetate and 2.25 ml of glacial acetic acid in a 1-l volumetric flask in the appropriate solvent. The molar concentration of acetate and acetic acid in the buffers were 40 and 40 m*M* and the ionic strength is 40 m*M*. The expected pH for aqueous buffer was 4.7 based on the Henderson–Hasselbalch equation. However, we did not measure pH for the buffers prepared through this work. All non-aqueous buffers contained the same molar amount of acetic acid and sodium acetate. The samples were prepared at a concentration of 2 m*M* diluted with a 10% aqueous buffer solution. Mesityl oxide was added to each sample solution as a neutral marker.

3.4. Electrophoretic procedure

When a new capillary was used, it was washed with sodium hydroxide solution (1.0 *M*) for 1 h, deionized water for 30 min, sodium hydroxide solution (0.1 *M*) for 30 min and running buffer for 30 min. The daily wash cycle before starting experiments was sodium hydroxide solution (0.1 *M*) for 15 min, water for 10 min, followed by running buffer for 10 min. A shorter wash procedure of 1 min sodium hydroxide solution (0.1 *M*) and 2 min running buffer was employed prior to injection. A minimum of three repeats was made on each measurement.

3.5. Computational procedure

The measured effective electrophoretic mobility data from ternary and binary mixtures have been fitted to the equations studied to assess their correlation abilities. The model constants for the equations were computed by using a least squares analysis. The calculated mobilities have then been compared with

experimental values and the APD was used as the correlation/prediction accuracy criterion. APD was calculated by:

$$\mathrm{APD} = \frac{100}{N} \cdot \sum_{1}^{N} \frac{|\mu_{\mathrm{calc}} - \mu_{\mathrm{exp}}|}{\mu_{\mathrm{exp}}} \quad (5)$$

where N is the number of data points. The individual percentage deviation (IPD) was also computed using:

$$\mathrm{IPD} = 100 \cdot \left(\frac{|\mu_{\mathrm{calc}} - \mu_{\mathrm{exp}}|}{\mu_{\mathrm{exp}}} \right) \quad (6)$$

In another numerical analysis, the prediction capabilities of the equations have been studied by dividing the experimental data points into training and prediction sets. The APD and IPD of predicted mobilities are also computed. All calculations were carried out by the statistical package for social sciences (SPSS version 10.0) for Windows.

4. Results and discussion

Table 1 shows the experimental effective mobility (±SD) of labetalol and atenolol in ternary solvents. As a general pattern, the higher the water volume fractions in the mixtures, the higher the mobility as the maximum mobility has been observed in pure aqueous buffer. With higher ethanol volume fractions in the mixtures the lower the mobility has been observed and the pure ethanolic buffer moves the analytes with the least speed. These observations could be confirmed considering the lower dielectric constant of ethanol and its higher viscosity where both of the parameters reduce the migration of the ions. Figs. 1–3 show the electrophoretic mobility of the analytes in binary solvent electrolyte systems. In all binary mixtures, atenolol ($M_r = 266.34$, $pK_a = 9.6$) migrates faster than labetalol ($M_r = 329.4$, $pK_a = 8.7$) which could be justified considering higher charge-to-mass ratio of atenolol.

To compare the correlation ability of the models for correlating the mobility data in binary and ternary solvent electrolyte systems with respect to the solvent composition, the experimental data has been fitted to Eqs. (3) and (4) and the back-calculated mobilities have been employed to compute APD values. This numerical analysis has been called correlative analysis. Table 2 represents APD values from correlative analysis for the drugs studied in this work and three other β-blocker drugs which have been reported in an earlier work [17] using Eqs. (3) and (4). The mean APD values for water–methanol, water–ethanol, methanol–ethanol and water–metha-

Table 1
Electrophoretic mobility (10^{-9} m^2 s^{-1} V^{-1}) of labetalol and atenolol at different volume fractions (f) of water (solvent 1), methanol (solvent 2) and ethanol (solvent 3) in the solvent mixtures

No.	f_1	f_2	f_3	Labetalol		Atenolol	
				Mean	SD	Mean	SD
1	0.10	0.20	0.70	4.02	0.04	5.62	0.15
2	0.10	0.30	0.60	4.69	0.09	6.43	0.07
3	0.10	0.40	0.50	5.30	0.11	6.92	0.07
4	0.10	0.50	0.40	5.77	0.08	7.58	0.01
5	0.10	0.60	0.30	6.92	0.07	8.98	0.04
6	0.10	0.70	0.20	7.56	0.03	9.70	0.00
7	0.10	0.80	0.10	8.58	0.04	10.86	0.28
8	0.20	0.10	0.70	4.63	0.02	6.04	0.05
9	0.20	0.20	0.60	5.38	0.03	6.82	0.00
10	0.20	0.30	0.50	6.16	0.18	7.62	0.04
11	0.20	0.40	0.40	6.84	0.06	8.40	0.02
12	0.20	0.50	0.30	7.19	0.02	9.26	0.03
13	0.20	0.60	0.20	8.38	0.01	10.24	0.03
14	0.20	0.70	0.10	9.36	0.03	11.19	0.07
15	0.30	0.10	0.60	5.45	0.14	6.72	0.01
16	0.30	0.20	0.50	6.08	0.04	7.50	0.16
17	0.30	0.30	0.40	6.71	0.14	8.12	0.01
18	0.30	0.40	0.30	7.01	0.01	8.36	0.01
19	0.30	0.60	0.10	8.52	0.05	10.43	0.01
20	0.33	0.33	0.34	6.75	0.03	8.47	0.00
21	0.40	0.10	0.50	6.02	0.03	7.38	0.01
22	0.40	0.20	0.40	6.93	0.01	8.62	0.04
23	0.40	0.30	0.30	7.11	0.01	9.33	0.01
24	0.40	0.40	0.20	7.76	0.01	9.82	0.01
25	0.40	0.50	0.10	8.58	0.04	10.26	0.01
26	0.50	0.10	0.40	6.52	0.02	7.98	0.00
27	0.50	0.20	0.30	7.26	0.01	8.74	0.03
28	0.50	0.30	0.20	7.90	0.02	9.45	0.03
29	0.50	0.40	0.10	8.62	0.02	10.33	0.00
30	0.60	0.10	0.30	7.79	0.04	9.20	0.03
31	0.60	0.20	0.20	8.55	0.03	9.99	0.02
32	0.60	0.30	0.10	9.32	0.01	10.82	0.00
33	0.70	0.10	0.20	9.34	0.05	10.87	0.03
34	0.70	0.20	0.10	12.47	0.04	14.15	0.04
35	0.80	0.10	0.10	14.63	0.05	16.33	0.02

The experiments were carried out at least in triplicate. The electrolyte was 80 m*M* acetate buffer containing different concentrations of solvents 1–3. The applied voltage was 25 kV. Temperature was 25 °C.

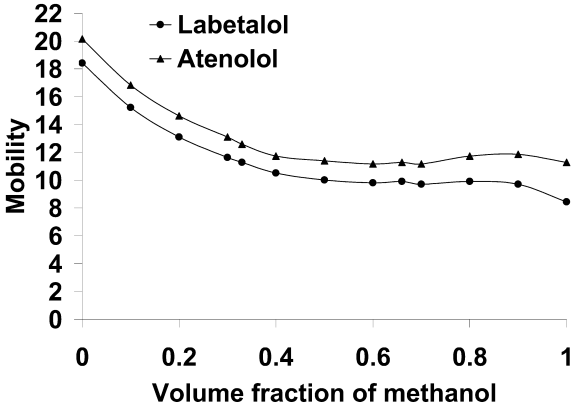

Fig. 1. Electrophoretic mobility of β-blockers in water–methanol. The experiments were carried out at least in triplicate with a 37 cm (30 cm effective length)×75 μm I.D. fused-silica capillary. The electrolyte was 80 m*M* acetate buffer containing different concentrations of the solvents. The applied voltage was 25 kV. Temperature was 25 °C and the wavelength was 214 nm.

nol–ethanol and binary+ternary mixtures using Eq. (3) are 0.71, 1.86, 0.94, 2.24 and 2.48%, respectively. The corresponding values for Eq. (4) are 1.29, 1.40, 1.09, 2.59 and 6.14%. The mean differences between the APDs of Eqs. (3) and (4) for binary mixtures of water–methanol, ternary mixtures of water–methanol–ethanol and total binary+ternary mixtures are statistically significant (paired *t*-test, $P<0.048$). The corresponding statistical parameters of Eq. (3) for the analytes studied are shown in Table 3. The high *R* and *F* values indicate that the model fits well the experimental data and the trained

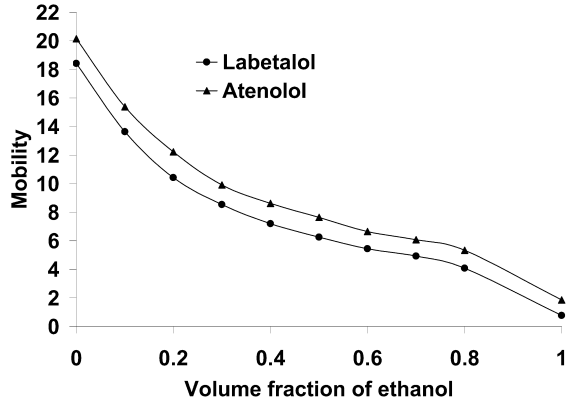

Fig. 2. Electrophoretic mobility of β-blockers in water–ethanol. Experimental conditions as in Fig. 1.

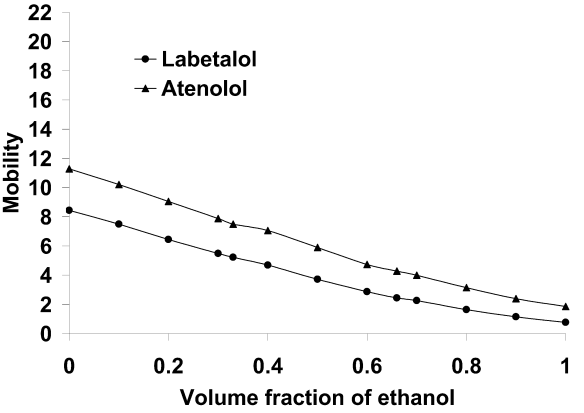

Fig. 3. Electrophoretic mobility of β-blockers in methanol–ethanol. Experimental conditions as in Fig. 1.

models are statistically significant ($P<0.0005$) for all five correlations.

The applicability of the proposed model has also been evaluated by employing the electrophoretic mobility data of two other basic drugs, i.e., salmeterol and phenylpropanolamine, in water–methanol–acetonitrile based acetate buffers taken from a previous work [18]. The mobilities have been measured up to 70% (v/v) acetonitrile. This ternary solvent system is more applicable system in practice and is able to provide wider solvent property range, however, we did not use in this work as a model system (because of acetate solubility limitation at higher acetonitrile concentrations). As indicated in a previous paper [15], in the case of unknown mobility value in a single solvent buffer system, the proposed equation could be rearranged as:

$$\begin{aligned}\ln \mu_m = {} & f_1 \ln \mu_1 + f_2 \ln \mu_2 + K f_3 \\ & + f_1 f_2 [M_0 + M_1(f_1 - f_2) + M_2(f_1 - f_2)^2] \\ & + f_1 f_3 [M_0' + M_1'(f_1 - f_3) + M_2'(f_1 - f_3)^2] \\ & + f_2 f_3 [M_0'' + M_1''(f_2 - f_3) + M_2''(f_2 - f_3)^2] \\ & + f_1 f_2 f_3 [M_0''' + M_1'''(f_1 - f_2 - f_3) \\ & + M_2'''(f_1 - f_2 - f_3)^2] \end{aligned} \quad (7)$$

where *K* is a model constant. All data points for salmeterol and phenylpropanolamine in water–methanol–acetonitrile buffers have been fitted to Eq.

Table 2
Average percentage deviations (APDs) for mobility of β-blockers in ternary and binary solvent electrolyte systems using correlative analysis

No.	Analyte	Water–methanol ($N^a=13$)		Water–ethanol ($N^a=10$)		Methanol–ethanol ($N^a=13$)		Water–methanol–ethanol ($N^a=35$)		Binary + ternary solvents ($N^a=68$)	
		Eq. (3)	Eq. (4)	Eq. (3)	Eq. (4)	Eq. (3)	Eq. (4)	Eq. (3)	Eq. (4)	Eq. (3)	Eq. (4)
1	Labetalol	0.69	1.08	2.65	1.49	0.69	0.89	2.19	2.38	2.61	7.24
2	Atenolol	0.70	0.81	1.77	1.01	1.08	1.12	2.49	2.60	2.41	5.20
3[b]	Practolol	0.42	0.84	1.60	1.35	0.82	0.80	2.13	2.67	2.28	5.32
4[b]	Timolol	1.13	2.46	1.83	1.61	1.03	1.41	2.45	2.65	2.70	6.87
5[b]	Propranolol	0.59	1.25	1.44	1.53	1.09	1.21	1.94	2.66	2.41	6.05
Mean		0.71[c]	1.29[c]	1.86[d]	1.40[d]	0.94[d]	1.09[d]	2.24[e]	2.59[e]	2.48[f]	6.14[f]
SD		0.26	0.68	0.47	0.24	0.18	0.25	0.23	0.12	0.17	0.91

[a] N is the number of correlated data points in each set.
[b] The experimental data has been collected at the same conditions described in the Experimental section and taken from a recent paper [17].
[c] The mean difference is statistically significant (paired t-test, $P<0.048$).
[d] The mean differences are not statistically significant (paired t-test, $P>0.1$).
[e] The mean difference is statistically significant (paired t-test, $P<0.041$).
[f] The mean difference is statistically significant (paired t-test, $P<0.0005$).

(7) and the APDs obtained are 1.68 and 1.14% ($N=29$), respectively.

To test the prediction capability of the equations, the data sets have been evaluated by dividing the whole data points in each set into training and prediction sets. The experimental mobilities in pure solvents 1–3, at binary mixtures with volume fractions of 0.3, 0.5 and 0.7 and in ternary mixtures with solvent compositions ($f_1=0.2$, $f_2=0.4$, $f_3=0.4$), ($f_1=0.4$, $f_2=0.2$, $f_3=0.4$) and ($f_1=0.4$, $f_2=0.4$, $f_3=0.2$) have been used to train the models. The total number of training data points in each set was 15. The trained models have been employed to predict the mobilities at other solvent compositions in binary and/or ternary solvent mixtures. This numerical method has been called predictive analysis. Table 4 represents APD values for predictive analysis using Eqs. (3) and (4). For Eq. (3), methanol–ethanol mixtures produced the least mean APD (1.72) value and water–methanol–ethanol mixtures showed the largest mean APD of 4.39% whereas the minimum and maximum APDs for Eq. (4) are 6.70 (water–ethanol mixtures) and 9.63% (water–methanol–ethanol mixtures), respectively. The mean differences for APDs of Eqs. (3) and (4) are statistically significant for all mixed solvent systems (paired t-test, $P<0.005$). These results shows that Eq. (3) possess higher prediction capability than Eq. (4). Fig. 4 shows a plot of predicted mobilities by trained Eq. (3) using 15 experimental data points versus the observed values for total predicted points (mobility in ternary and binary solvent buffers).

In order to compare the models from individual percentage deviations point of view, the IPDs for correlative and predictive analyses using Eqs. (3) and (4) have been studied. For correlative analysis

Table 3
The correlation coefficient, F value and curve-fitting parameters calculated by fitting total binary + ternary solvent mobility data into Eq. (3) for data sets studied

No.	R	F	M_1	M_2	M_3	M'_1	M'_2	M'_3	M''_1	M''_2	M''_3	M'''_1	M'''_2	M'''_3
1	0.996	633	−0.938	1.932	1.476	−0.827	−4.753	−0.527	1.239	4.139	0.203	0.881	3.023	15.086
2	0.990	224	−1.189	0.738	0.934	−0.531	−3.004	−0.236	1.035	2.787	0.095	1.772	1.900	8.628
3	0.990	240	−1.199	0.676	0.957	−0.573	−3.102	−0.103	0.879	2.894	0.132	1.769	2.345	9.723
4	0.995	445	−1.029	1.517	1.325	−0.694	−4.130	−0.008	0.788	3.867	0.393	1.444	2.368	11.385
5	0.992	296	−1.150	0.770	1.079	−0.576	−3.556	−0.076	1.122	3.478	0.165	1.547	3.131	11.009

Table 4
Average percentage deviations (APDs) for mobility of β-blockers in ternary and binary solvent electrolyte systems using predictive analysis

No.	Analyte	Water–methanol ($N^a=8$)		Water–ethanol ($N^a=5$)		Methanol–ethanol ($N^a=8$)		Water–methanol–ethanol ($N^a=32$)		Binary + ternary solvents ($N^a=53$)	
		Eq. (3)	Eq. (4)	Eq. (3)	Eq. (4)	Eq. (3)	Eq. (4)	Eq. (3)	Eq. (4)	Eq. (3)	Eq. (4)
1	Labetalol	1.88	12.75	4.57	8.15	1.77	9.78	4.57	12.04	3.74	11.44
2	Atenolol	1.91	5.52	3.19	5.91	1.88	7.00	4.76	7.76	3.75	7.13
3[b]	Practolol	1.08	6.71	3.78	5.98	1.11	6.95	4.54	8.00	3.43	7.46
4[b]	Timolol	2.90	12.91	2.86	7.52	1.91	8.25	4.34	10.68	3.62	10.35
5[b]	Propranolol	2.88	10.07	3.73	5.93	1.95	9.26	3.74	9.65	3.34	9.30
Mean		2.13[c]	9.59[c]	3.63[c]	6.70[c]	1.72[c]	8.25[c]	4.39[c]	9.63[c]	3.58[c]	9.14[c]
SD		0.77	3.40	0.65	1.06	0.35	1.29	0.39	1.81	0.18	1.85

[a] N is the number of predicted data points in each set.
[b] The experimental data has been collected at the same conditions described in the Experimental section and taken from a recent paper [17].
[c] The mean differences are statistically significant (paired t-test, $P<0.005$).

using Eq. (3), in more than 80% of the cases, the IPD is <4% where the acceptable error range for electrophoretic mobility data is around 4% [19]. In less than 3% of the cases, the produced IPD is >8%. For predictive analysis using Eq. (3), the probability of IPDs <4, 4–8 and >8% are 0.65, 0.26 and 0.09, respectively. This means that the model is capable of predicting unmeasured mobilities in binary/ternary solvent electrolytes by using just 15 experimental data points for each analyte. The probability of correlating mobilities using Eq. (4) with IPD>8% is 0.32 and with IPD<4% is 0.43. The corresponding probabilities for predictive purposes are 0.43 and 0.35. As a result, Eq. (3) is superior to Eq. (4) from both correlation and prediction points of view. It should be noted that Eq. (3) employs the electrophoretic mobilities in pure solvent BGEs and also three more curve-fitting parameters in comparison with Eq. (4).

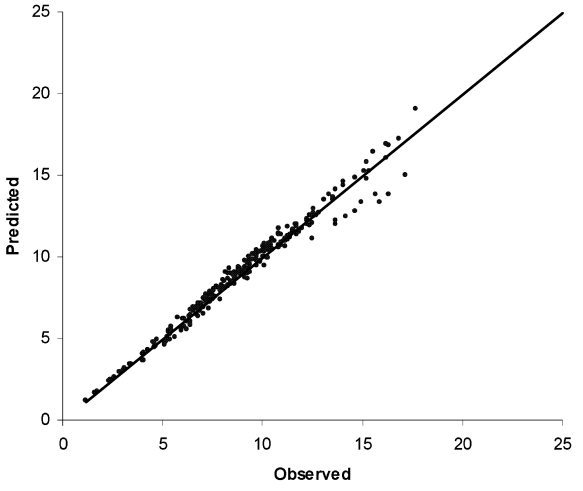

Fig. 4. Plot of the predicted mobilities (10^{-9} m^2 s^{-1} V^{-1}) by trained Eq. (3) using 15 experimental data points versus observed values ($N=265$).

As noted in Section 2, the prediction capability of Eq. (1) to predict the electrophoretic mobility of β-blockers in a binary solvent electrolyte system has been shown [16]. The model has been trained employing the experimental mobility of atenolol, alprenolol, labetalol and metoprolol in water–methanol based buffer, and then the mobility of propranolol, timolol and acebutalol have been predicted using trained model and mobility values in pure solvent buffers (i.e., μ_1 and μ_2). The obtained APD value for 32 predicted mobilities is 1.23%. For this prediction method only two experimental data for each analyte is required. To show the applicability of this numerical analysis to the mobility data in ternary solvent BGEs using Eq. (3), the mobility of practolol, timolol and propranolol in water–methanol–ethanol mixtures are used as training set ($N=45$) and the mobilities of labetalol and atenolol are predicted using μ_1, μ_2 and μ_3 values and the obtained APD is 8.00% ($N=133$). The obtained APD for Eq. (4) employing the same training and prediction sets is 21.65% and this could be considered as another advantage of the proposed equation. The 8% is a

relatively high error in comparison with the corresponding value for binary mixtures, however, it provides useful information for faster optimization process of analytical conditions for structurally related drugs in industry where a large number of such compounds have been synthesized/extracted for further assessments and researchers need a feasible analytical technique like CE. In conclusion, the proposed model is able to compute the mobility in mixed solvent BGEs and one can use it to predict the possibility of successful resolution between the analytes of interest in all solvent compositions of binary and ternary solvents by collecting just 15 experimental data for each analyte and the expected APD is 3.58% which could be considered to be an acceptable error range when it is compared to experimental relative standard deviation for repeated experiments. To provide more accurate predictions, it is possible to employ more curve-fitting parameters, however, the model will need more data points for training.

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