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Electrophoretic behavior of alprenolol in mixed solvent electrolyte systems

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Abstract

The electrophoretic mobilities of alprenolol have been determined in a mixed solvent background electrolyte system containing sodium acetate (40 mM)+acetic acid (40 mM) as buffering agent and different volume fractions of water, methanol and ethanol using capillary electrophoresis. The mobility of alprenolol has been used to test the prediction capability of a model trained by previously reported mobility data of five beta-blocker drugs at the same electrophoretic conditions. The average percentage mean deviations (APMD) between experimental and predicted values were used as an accuracy criterion. The APMD (±SD) obtained for alprenolol data in binary/ternary solvent electrolyte system employing the mobility values in mono-solvent buffers was 4.37 (±3.50)% and the corresponding value for an ab initio prediction method was 7.65 (±4.30)%.

Keywords: Ab initio prediction; Electrophoretic mobility; Capillary electrophoresis; Alprenolol; Mixed solvent buffers

1. Introduction

Capillary zone electrophoresis (CZE) has become an important and efficient analytical technique in pharmaceutical/chemical analysis to separate a wide variety of ionic species ranging from small ions to macromolecules such as proteins. The most important parameter governing electrophoretic separations is mobility. A number of attempts have been made for mathematical representation of electrophoretic mobility data in CZE [1–5].

Mixed solvent systems have been used in many CZE methods [6–10]. The common method in optimizing the concentration of solvents in the mixture to achieve the best separation conditions is the trail and error approach. In practice the analyst adds a given concentration of the second solvent and then follows the separation behavior of the analytes. This process continues until the optimized solvent composition achieves. Mathematical modeling of solvent effects on the mobility of analytes in CZE could provide useful information for the analyst to employ a rational method for the optimization of solvent composition in the running buffer. In previous papers, the electrophoretic mobility of beta-blocker drugs have been measured and calculated using different numerical methods [11–13]. The main disadvantage of the proposed models is that the models require a minimum number of experimental data points for training the models and are not able to predict the electrophoretic mobility of the analytes using ab initio method. The aim of this work is to test such a capability to predict the electrophoretic mobility of alprenolol in binary/ternary mixed solvent electrolytes in CZE.

2. Experimental procedures

2.1. Instrumentation

All experiments were performed using a P/ACE system 5510 series instrument with Beckman P/ACE software (Beckman Instruments Europe, High Wy-

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combe, UK). The fused silica capillary used in this study was purchased from Composite Metal Services (Hallow, Worcester, UK) and was cut to a length of 37 cm (30 cm to the detector) × 75 μm i.d. The temperature of the capillary was kept at 25.0 °C using liquid coolant, however, there was no temperature control for the buffer vials. Samples were injected by pressure mode for 2 s and analytes were detected by direct UV detection at 214 nm. The applied voltage was 25 kV.

2.2. Chemicals

Alprenolol hydrochloride was purchased from Sigma Aldrich Company Ltd. (Poole, UK), acetic acid and sodium acetate were purchased from BDH Lab Supplies (Poole, UK), methanol (HPLC Grade) and ethanol were purchased from Riedel-de-Haen (Germany). Mesityl oxide was used as a neutral marker and purchased from Acros (New Jersey, USA) Milli-Q water from a Millipore Water Purification System (Watford, UK) was used throughout this project.

2.3. Method

A series of binary and ternary mixed aqueous/organic modifier buffers were prepared. Three stock acetate buffers were prepared in the three different solvents (100% water, 100% methanol, 100% ethanol) by adding 3.3 g (NaOAc, MW = 82.03 g) and 2.25 ml of glacial acetic acid into a 1 l volumetric flask. The pH of the pure aqueous buffer was 4.7. All the non-aqueous buffers contained the same amount of glacial acetic acid and sodium acetate. This ensured that the buffers show the maximum buffer capacity, since the concentration of weak acid and its conjugated base is the same. The samples were prepared at a concentration of 2 mM diluted with a 10% aqueous buffer solution. Mesityl oxide was added to the sample solution as a neutral marker.

2.4. Electrophoretic procedure

When a new capillary was used, it was washed with sodium hydroxide solution (1.0 M) for 1 h, deionized water (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 before each injection. A minimum of three repeats was made on each measurement.

2.5. Computational procedure

The (effective) electrophoretic mobility of analytes was calculated by:

$$\mu = \frac{L_t L_d}{V}\left(\frac{1}{t_m} - \frac{1}{t_0}\right) \quad (1)$$

where L_t and L_d are the total capillary length and length to the detector window in meters, V is the applied voltage, t_m and t_0 are migration times for the analytes and the electroosmotic flow, respectively. The mobilities are expressed as 10^9 m^2 V^{-1} s^{-1}.

In a previous paper, a mathematical model has been proposed to correlate the electrophoretic mobility of analytes with solvent composition of binary mixed solvent electrolyte systems [14]. The model was:

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

where μ is the electrophoretic mobility, subscripts m, 1 and 2 refer to mixed solvent, solvents 1 (water) and 2 (methanol), 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. The model could be extended based on Redlich–Kister method [15] and the extended form has provided more accurate results [13]. The extended form could be represented as:

$$\ln \mu_m = f_1 \ln \mu_1 + f_2 \ln \mu_2 + f_1 f_2[A_0 + A_1(f_1 - f_2) + A_2(f_1 - f_2)^2] \quad (3)$$

in which A_2 is a model constant. It is also possible to extend the model for calculating the mobilities in ternary solvent electrolyte systems as:

$$\begin{aligned}\ln \mu_m = {} & f_1 \ln \mu_1 + f_2 \ln \mu_2 + f_3 \ln \mu_3 \\ & + f_1 f_2[M_0 + M_1(f_1 - f_2) + M_2(f_1 - f_2)^2] \\ & + f_1 f_3[M'_0 + M'_1(f_1 - f_3) + M'_2(f_1 - f_3)^2] \\ & + f_2 f_3[M''_0 + M''_1(f_2 - f_3) + M''_2(f_2 - f_3)^2] \\ & + f_1 f_2 f_3[M'''_0 + M'''_1(f_1 - f_2 - f_3) \\ & + M'''_2(f_1 - f_2 - f_3)^2] \end{aligned} \quad (4)$$

in which subscript 3 refers to solvent 3 (i.e. ethanol), 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. (4) reduces to Eq. (3) when $f_3 = 0$ [13].

Eq. (4) has been trained employing the experimental mobility data of five beta-blockers in binary and ternary solvent mixtures reported in previous papers [11,13] then the electrophoretic mobility of alprenolol in mixed solvent electrolyte systems has been predicted using

the trained model. The deviations between the calculated and experimental mobilities have been computed using the average percentage mean deviation (APMD) by Eq. (5) as an accuracy criterion.

$$\mathrm{APMD} = \frac{100}{N} \sum \left| \frac{(\mu_m)_{\mathrm{calculated}} - (\mu_m)_{\mathrm{observed}}}{(\mu_m)_{\mathrm{observed}}} \right| \quad (5)$$

where N is the number of data points in each set. In addition the individual percentage deviation (IPD) of calculated mobilities from observed values were computed by Eq. (6).

$$\mathrm{IPD} = 100 \left\{ \frac{(\mu_m)_{\mathrm{calculated}} - (\mu_m)_{\mathrm{observed}}}{(\mu_m)_{\mathrm{observed}}} \right\} \quad (6)$$

Partial charge on the analytes and surface area of beta-blockers were calculated using HyperChem software [16].

3. Results and discussion

Table 1 shows the experimental electrophoretic mobility of alprenolol in binary and ternary solvent electrolyte systems and their standard deviations. All 60 data points from binary/ternary solvent mixtures has been fitted to Eq. (4) and the APMD obtained was 2.66 ± 2.16. The results for correlation studies of mobility data in binary/ternary solvent electrolyte systems are in a good agreement with previously reported APMDs for five beta-blocker drugs (see Table 2 in Ref. [13]).

The prediction capability of Eq. (3) has been examined using a minimum number of experimental mobility data points. The model produced reasonably accurate results and obtained prediction error was generally less than 2.6% [13]. However, the method needs a minimum number of five points. In another work, a possibility of calculating the mobility of structurally related analytes using Eq. (3) has been shown [12]. By considering these two aspects and in order to reduce in the number of experimental data required for mobility prediction in mixed solvent electrolyte systems, the experimental data points for previously studied beta-blockers (i.e. propranolol, practolol, timolol, labetaolol and atenolol) collected at the same analytical conditions using mixed solvent systems [11,13] were used to train Eq. (4). The experimental mobilities of five beta-blocker drugs 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 model. The mobility of alprenolol at binary/ternary solvent electrolyte systems was predicted, then APMD and IPD values were computed. In this numerical analysis, it is necessary to know the mobility of analyte in pure aqueous, methanolic and ethanolic buffers. The trained model is:

$$\begin{aligned} \ln \mu_m = & -17.68 f_1 - 18.15 f_2 - 20.00 f_3 \\ & + f_1 f_2 [-1.107 + 1.287(f_1 - f_2) + 1.196(f_1 - f_2)^2] \\ & + f_1 f_3 [-0.600 - 3.386(f_1 - f_3) - 0.083(f_1 - f_3)^2] \\ & + f_2 f_3 [1.098 + 2.093(f_2 - f_3) + 0.085(f_2 - f_3)^2] \\ & + f_1 f_2 f_3 [1.422 + 6.975(f_1 - f_2 - f_3) \\ & + 10.693(f_1 - f_2 - f_3)^2] \end{aligned} \quad (7)$$

Table 1 shows the predicted mobilities using a trained model (i.e. Eq. (7)) and the computed IPD values. The mobility of alprenolol at ($f_1 = 0.70$, $f_2 = 0.10$, $f_3 = 0.20$) is overestimated whereas the mobility at ($f_1 = 0.10$, $f_2 = 0.10$, $f_3 = 0.80$) is underestimated by the model. However, as shown in Fig. 1, most of the predicted mobilities are in good agreement with experimental values. The APMD $\pm$ SD was 4.37 ± 3.50. The relative frequency of IPDs sorted in ≤ 2, 2–5 and $> 5\%$ are 37, 35 and 28%, respectively.

To provide an ab initio prediction method, a reduced form of a quantitative structure property relationship [5] was employed to predict the mobility of alprenolol in pure aqueous, methanolic and ethanolic buffers. The previously published model is:

$$\ln \mu = K_0 + K_1 \mathrm{PQ} + K_2 V^{2/3} + K_3 \mathrm{TE} + K_4 \Delta H_f + K_5 \mathrm{MR} \quad (8)$$

where PQ is partial charge, $V^{2/3}$ denotes surface area, TE stands for total energy, ΔH_f represents heat of formation, MR is molecular refractivity and K_0–K_5 are the model constants which are calculated using a least squares analysis. The numerical values of independent variables (i.e. PQ, $V^{2/3}$, TE, ΔH_f and MR) of the analytes are calculated using HyperChem 7.0 software [16]. Eq. (8) needs at least six training data points since it possesses six model constants. It is possible to reduce Eq. (8) into a model with less model constants as:

$$\ln \mu = J_0 + J_1 \mathrm{PQ} + J_2 V^{2/3} \quad (9)$$

Eq. (9) was trained using five experimental data points of previously reported beta-blockers (details were listed in Table 2) and the obtained models for aqueous, methanolic and ethanolic buffers are as follow:

$$\ln \mu = -16.402 + 0.096 \mathrm{PQ} - 0.015 V^{2/3} \quad (10)$$

$$\ln \mu = -14.020 + 0.630 \mathrm{PQ} - 0.049 V^{2/3} \quad (11)$$

$$\ln \mu = -9.261 + 0.977 \mathrm{PQ} - 0.122 V^{2/3} \quad (12)$$

The predicted $\ln \mu_1$, $\ln \mu_2$ and $\ln \mu_3$ are -17.73, -18.26 and -20.07, respectively. These numerical values were used to predict the electrophoretic mobility of alprenolol in binary/ternary solvent electrolyte system using Eq. (13):

Table 1
The volume fraction of water (f_1), methanol (f_2) and ethanol (f_3), mean and standard deviation of electrophoretic mobility (μ, 10^9 m^2 V^{-1} s^{-1}) of alprenolol in mixed solvent electrolyte systems, the predicted mobilities (μ_p) using Eq. (7), individual percentage deviations (IPDs), average percentage mean deviation (APMD) and its standard deviation

No.	f_1	f_2	f_3	μ	SD_μ	μ_p	IPD
1	0.00	0.10	0.90	2.75	0.01	2.78	1.27
2	0.00	0.20	0.80	3.61	0.00	3.65	1.13
3	0.00	0.30	0.70	4.60	0.01	4.66	1.20
4	0.00	0.33	0.67	4.94	0.00	4.98	0.80
5	0.00	0.40	0.60	5.54	0.01	5.78	4.43
6	0.10	0.10	0.80	5.68	0.01	5.09	−10.35
7	0.20	0.00	0.80	6.33	0.01	6.28	−0.82
8	0.10	0.20	0.70	6.53	0.04	6.06	−7.17
9	0.00	0.50	0.50	6.90	0.02	7.02	1.68
10	0.30	0.00	0.70	7.11	0.02	7.71	8.56
11	0.20	0.10	0.70	7.19	0.04	6.98	−2.87
12	0.40	0.00	0.60	7.57	0.11	8.52	12.61
13	0.10	0.30	0.60	7.63	0.13	7.11	−6.83
14	0.30	0.10	0.60	7.90	0.03	8.16	3.23
15	0.20	0.20	0.60	8.19	0.04	7.73	−5.58
16	0.40	0.10	0.50	8.21	0.01	8.93	8.77
17	0.10	0.40	0.50	8.33	0.07	8.22	−1.27
18	0.00	0.60	0.40	8.33	0.14	8.32	−0.09
19	0.50	0.00	0.50	8.48	0.11	9.07	7.05
20	0.30	0.20	0.50	8.60	0.05	8.68	0.95
21	0.50	0.10	0.40	8.74	0.01	9.80	12.17
22	0.20	0.30	0.50	9.06	0.04	8.54	−5.71
23	0.10	0.50	0.40	9.13	0.10	9.38	2.76
24	0.00	0.66	0.34	9.34	0.08	9.12	−2.27
25	0.60	0.00	0.40	9.36	0.00	9.81	4.72
26	0.30	0.30	0.40	9.47	0.00	9.31	−1.69
27	0.00	0.70	0.30	9.51	0.05	9.66	1.59
28	0.50	0.20	0.30	9.61	0.00	10.54	9.79
29	0.40	0.20	0.40	9.64	0.02	9.45	−1.97
30	0.33	0.33	0.34	9.70	0.04	9.72	0.22
31	0.30	0.40	0.30	9.80	0.01	10.06	2.63
32	0.20	0.40	0.40	9.90	0.03	9.43	−4.80
33	0.60	0.10	0.30	10.05	0.00	11.16	11.05
34	0.50	0.30	0.20	10.38	0.01	11.29	8.71
35	0.40	0.40	0.20	10.43	0.01	10.83	3.83
36	0.40	0.30	0.30	10.47	0.04	10.08	−3.72
37	0.00	0.80	0.20	10.58	0.01	10.97	3.67
38	0.70	0.00	0.30	10.64	0.12	11.08	4.14
39	0.10	0.60	0.30	10.78	0.02	10.57	−2.00
40	0.20	0.50	0.30	10.85	0.06	10.39	−4.21
41	0.60	0.20	0.20	10.98	0.01	12.25	11.57
42	0.50	0.40	0.10	11.34	0.01	12.00	5.82
43	0.10	0.70	0.20	11.43	0.01	11.75	2.81
44	0.40	0.50	0.10	11.49	0.02	11.70	1.77
45	0.70	0.10	0.20	11.75	0.01	13.24	12.76
46	0.30	0.60	0.10	11.78	0.04	11.96	1.56
47	0.60	0.30	0.10	11.93	0.01	12.95	8.55
48	0.20	0.60	0.20	12.00	0.03	11.43	−4.76
49	0.00	0.90	0.10	12.03	0.01	12.17	1.23
50	0.80	0.00	0.20	12.89	0.04	13.24	2.75
51	0.60	0.40	0.00	13.06	0.01	13.15	0.68
52	0.10	0.80	0.10	13.10	0.06	12.89	−1.63
53	0.20	0.70	0.10	13.11	0.02	12.54	−4.33
54	0.67	0.33	0.00	13.71	0.01	13.89	1.27

Table 1 (*Continued*)

No.	f_1	f_2	f_3	μ	SD_μ	μ_p	IPD
55	0.70	0.30	0.00	14.29	0.02	14.31	0.11
56	0.70	0.20	0.10	15.16	0.07	14.44	−4.75
57	0.80	0.20	0.00	15.61	0.02	16.16	3.52
58	0.90	0.00	0.10	16.35	0.02	16.57	1.32
59	0.80	0.10	0.10	17.33	0.03	15.99	−7.73
60	0.90	0.10	0.00	17.72	0.07	18.56	4.73
							APMD = 4.37±3.50

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 40 mM sodium acetate and 40 mM acetic acid dissolved in binary/ternary solvent systems. The applied voltage was 25 kV. Temperature was 25 °C and the wavelength was 214 nm.

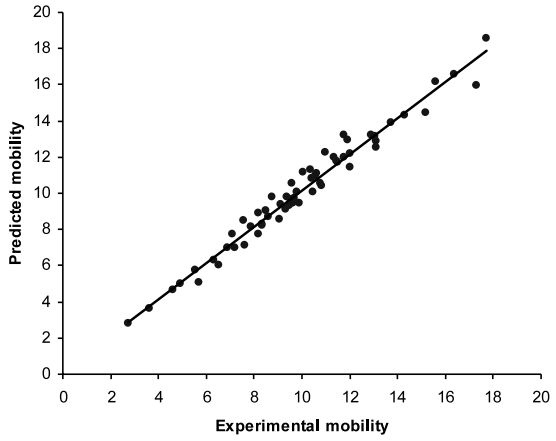

Fig. 1. The predicted electrophoretic mobility of alprenolol using Eq. (7) versus experimental values.

$$\begin{aligned}\ln \mu_m = &-17.73f_1 - 18.26f_2 - 20.07f_3 \\ &+ f_1f_2[-1.107 + 1.287(f_1 - f_2) + 1.196(f_1 - f_2)^2] \\ &+ f_1f_3[-0.600 - 3.386(f_1 - f_3) - 0.083(f_1 - f_3)^2] \\ &+ f_2f_3[1.098 + 2.093(f_2 - f_3) + 0.085(f_2 - f_3)^2] \\ &+ f_1f_2f_3[1.422 + 6.975(f_1 - f_2 - f_3) \\ &+ 10.693(f_1 - f_2 - f_3)^2] \end{aligned} \quad (13)$$

The AMPD±SD was 7.65±4.30. The prediction error is higher than that of Eq. (7), however there is no need to determine any mobility value for alprenolol.

In conclusion, it has been shown that the proposed model is capable of predicting electrophoretic mobility of alprenolol in binary/ternary solvent electrolyte systems with an acceptable prediction error using just three experimental data points from mono-solvent electrolyte systems and a minimum number of mobility data of other beta-blockers. This type of prediction could be used in industry to speed up the method development step of CZE methods in drug discovery process where a large number of experimental mobility data for structurally related drugs has been determined and stored. By using a quantitative structure property relationship model, it is possible to further reduce in the number of experimental data required in the prediction process and present an ab initio prediction method. This method produces slightly higher prediction error and further works are needed to develop such a pure predictive model.

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Table 2
Logarithm of mobility[a] of analytes in aqueous, methanolic and ethanolic buffers, surface area and partial charge of beta-blockers

	Analyte	ln μ_1	ln μ_2	ln μ_3	$V^{2/3}$	PQ
1	labetalol	−17.82	−18.60	−20.98	98.43	0.337
2	alprenolol	−17.68 [b]	−18.14 [b]	−20.01 [b]	90.00	0.272
3	atenolol	−17.72	−18.30	−20.11	91.85	0.302
4	practolol	−17.75	−18.32	−20.14	91.46	0.307
5	timolol	−17.76	−18.35	−20.50	96.30	0.558
6	propranolol	−17.68	−18.19	−20.04	89.67	0.263

[a] The mobilities were determined at the same electrophoretic conditions as explained in the footnote of Table 1.
[b] The mobility data of alprenolol was not included in the training process of Eq. (9).

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