Iranian Journal of Pharmaceutical Research (2004) 3: 23-27
Received: July 2003
Accepted: January 2004

Original Article

Application of the Phenomenological Model to Electrophoretic Mobility in Mixed Solvent Electrolyte Systems in Capillary Zone Electrophoresis

Abolghasem Jouyban[*a], Hak-Kim Chan[b], Maryam Khoubnasabjafari[c]

[a]*School of Pharmacy and Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.* [b]*Faculty of Pharmacy, The University of Sydney, Sydney, Australia.* [c]*Kimia Research Institute, Tabriz, Iran.*

Abstract

The phenomenological model of Khossravi and Connors (1992) has been adopted to calculate the electrophoretic mobility of drugs at different concentrations of solvents in a binary mixture. The accuracy and predictability of the model have been evaluated employing 14 experimental data sets by using average percentage mean deviation (APMD). The obtained APMD for correlative and predictive studies are within an acceptable error range and the results show that the model can be used in method development stage to speed up the optimisation process.

Key words: Mobility; Phenomenological model; Solvent effects; Capillary electrophoresis.

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 inorganic 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 (1-4).

Mixed solvent systems have been used in many CZE methods (5-9). The common method in optimising 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 behaviour of the analytes. This process continues until the solvent composition is optimised. It is obvious that the process is time-consuming, costly and in some cases, can be misleading. As an example, there is a reversed electromigration pattern for some analytes (10) and in order to identify the peaks appeared in the electropherogram, the analyst should inject the analytes from individual samples. This will further increase the number of experiments required in the process of method development. Mathematical modelling of solvent effects on the mobility of analytes in CZE could provide useful information for the analyst to employ a rational method for the optimisation of solvent composition in the running buffer.

Solution models such as the combined nearly ideal binary solvent/Redlich-Kister equation (CNIBS/R-K) (11) and the excess free energy (EFE) approach (12) have been successfully applied to calculate the

* corresponding author:
E-mail: ajouyban@hotmail.com

electrophoretic mobility of analytes in mixed solvent electrolyte systems. In a series of papers, Connors and co-workers have developed a phenomenological model for describing the solvent effects in mixed solvent systems. Based on this model, the observed solvent effects arise from the combination of three interactions: a) solvent-solvent interactions or medium effect, b) solute-solvent interactions or solvation effect and c) solute-solute interactions or intersolute effect. The model has been applied to solvent effects on the solubility of nonelectrolytes (13), surface tension (14), molecular complex formation (15), absorption spectra (16), instability rate constants (17-18) and capacity factor in RP-HPLC (19). The aim of this communication is to show the applicability of the phenomenological model to the electrophoretic mobility of the analytes in mixed solvent electrolyte systems employing experimental mobility data.

Theoretical background

In 1992, Khossravi and Connors developed a phenomenological model for describing the solvent effects on the equilibrium solubility of a solute in a binary solvent mixture. The total solvent effect ($\Delta G^0_{Solution}$) on chemical phenomenon is divided into three components namely, the general medium effect ($\Delta G^0_{General\ medium}$), the solvation effect ($\Delta G^0_{Solvation}$) and the intersolute effect ($\Delta G^0_{Intersolute}$) (13). Using the Leffler-Grunwald delta operator symbolism, the total solvent effect is defined as:

$$\delta_M \Delta G^0_{Solution} = \Delta G^0_{Total_{(x2)}} - \Delta G^0_{Total_{(0)}} \qquad (1)$$

where $\delta_M \Delta G^0_{Solution}$ is the transfer free energy, $\Delta G^0_{Total_{(x2)}}$ is the total solvent effect in mixed solvent and/or in pure cosolvent and $\Delta G^0_{Total_{(0)}}$ represents the total solvent effects in pure aqueous solution (x_2=0). Then the authors obtained Eq. 2 based on a two-step solvation process.

$$\delta_M \Delta G^0_{Solution} = \frac{(-kT\ln\beta_1 + gA\gamma')\beta_1 x_1 x_2 + (-kT\ln\beta_2 + 2gA\gamma')\beta_2 x_2^2}{x_1^2 + \beta_1 x_1 x_2 + \beta_2 x_2^2} \qquad (2)$$

where k is the Boltzmann's constant, T is the absolute temperature, β_1 and β_2 are equilibrium constants, gAγ' represents the general medium effect in which g is the curvature effect factor, A is the surface area of the cavity that must be created in the solvent to receive the solute molecule, γ' is given by $(\gamma_2-\gamma_1)/2$ in which γ_2 and γ_1 are the surface tensions of pure solvents 2 and 1, respectively, and x_1 and x_2 are the bulk mole fractions of solvents 1 and 2. To compute the model parameters, i.e. gA, β_1 and β_2, the experimental values of $\delta_M \Delta G^0_{Solution}$ are fitted into Eq. 2 using a nonlinear regression analysis (13).

In Eq. 2, the terms, k, T, gAγ', $\ln\beta_1$ and $\ln\beta_2$ possess constant values and it is the possible to rewrite Eq. 2 as (13):

$$\delta_M \Delta G^0_{Solution} = \frac{a\beta_1 x_1 x_2 + b\beta_2 x_2^2}{x_1^2 + \beta_1 x_1 x_2 + \beta_2 x_2^2} \qquad (3)$$

where a and b are unconstrained parameters.

Since ΔG^0_{Total} is equal to –kTlnXm (13) in which X_m is the mole fraction solubility of the solute, combination of Eqs. 1 and 3 yields:

$$-kT\ln X_m = kT\ln X_w + \frac{a\beta_1 x_1 x_2 + b\beta_2 x_2^2}{x_1^2 + \beta_1 x_1 x_2 + \beta_2 x_2^2} \qquad (4)$$

where X_w is the mole fraction solubility in aqueous solution (x_2=0).

As indicated in introduction, the phenomenological model has been applied to many phenomena other than the equilibrium solubility in mixed solvent systems. In electromigration in CZE, the general medium effect and solvation effect play important roles and it is suggested that an adopted form of the phenomenological model could be able to describe the electrophoretic mobility of an analyte in a mixed solvent buffer. The suggested form of the model is:

$$-kT\ln\mu_m = kT\ln\mu_w + \frac{a\beta_1 f_1 f_2 + b\beta_2 f_2^2}{f_1^2 + \beta_1 f_1 f_2 + \beta_2 f_2^2} \qquad (5)$$

where μ_m and μ_w are the electrophoretic mobility in mixed solvent and in aqueous

buffers (f_2=0), respectively, and f_1 and f_2 are the volume fractions of solvents 1 and 2 in the mixture. The model constants of Eq. 5 were computed by a non-linear least square analysis using Lavenberg-Marquardt algorithm and SPSS software.

To test the applicability of the model to real mobility data collected from the literature (10, 12, 20-21), the average percentage mean deviation (APMD) has been calculated using Eq. 6 as an accuracy criterion.

$$APMD = \frac{100}{N}\sum\left|\frac{(\mu_m)_{calculated} - (\mu_m)_{observed}}{(\mu_m)_{observed}}\right| \quad (6)$$

where N is the number of data points in each set. In addition, the individual percentage deviation (IPD) of calculated mobilities from observed values was computed by Eq. 7.

$$IPD = 100\left|\frac{(\mu_m)_{calculated} - (\mu_m)_{observed}}{(\mu_m)_{observed}}\right| \quad (7)$$

Results and Discussion

The experimental electrophoretic mobility data of the analytes in water-methanol based electrolyte systems were fitted to Eq. 5 using a nonlinear least square analysis. This analysis was called correlative method. The model constants and the calculated APMD values are shown in Table 1. As indicated in theoretical background, a and b are unconstrained parameters, therefore, they could have positive or negative values, depending on the experimental data. However, β_1 and β_2 are the equilibrium constants and should be greater than zero. This is the case for our data sets studied. The highest APMD value (1.40 %) was observed for atenolol and the lowest value (0.40%) was for monomethylamine. The overall APMD for 14 data sets studied is 0.95 ± 0.30 %. Figure 1 shows the calculated mobilities of labetalol against observed values and the coefficient of determination and also the best fit line. In addition to APMD, the relative frequency of IPD values at different error levels is shown in Figure 2. The proposed model produced IPD <1 in more than 60% of the cases. The corresponding value for IPD<4 is 99.4 %. These analyses show that the proposed model is an accurate model to correlate the mobility data in mixed solvent electrolyte systems. The correlative method could be employed to screen the experimental mobility data to find the possible outliers.

To investigate the prediction capability of the proposed model, each data set was divided into two subsets, i.e. training and test set. The training set includes the mobility data at f_2=1, 0.7, 0.3, 0.1 and 0. These five data points were used to train the model and calculate the model parameters. Data points other than training points were called the test set. The mobility of

Table 1. Details of data sets studied, their references, the model constants and average percentage mean deviation (APMD) for correlative and predictive equations

No.	Analyte	N[a]	Reference					Correlative	Predictive
				a ×10^{23}	b × 10^{23}	β_1	β_2	APMD	APMD[b]
1	Propranolol	13	20	415.9310	49.5546	1.6575	0.9665	1.11	3.35
2	Timolol	12	20	477.5110	82.3255	1.3518	1.1499	1.12	3.64
3	Atenolol	12	21	428.5600	90.0303	1.6824	0.9175	1.40	4.14
4	Alprenolol	13	21	396.0040	50.8492	1.6813	1.0201	1.03	2.74
5	Acebutalol	13	20	381.2300	46.7790	1.8561	0.8137	1.20	3.54
6	Labetalol	12	21	498.6440	148.8540	1.2567	1.2500	1.11	2.11
7	Metoprolol	13	21	410.7470	30.7956	1.6238	0.8819	1.15	3.17
8	Nadolol	11	12	383.0070	63.0397	2.0329	0.7950	0.71	1.91
9	Oxprenolol	11	12	363.4020	-6.6053	2.0155	0.8138	0.77	1.87
10	Pindolol	11	12	375.1890	51.4769	2.0486	0.8663	0.53	0.90
11	Monomethylamine	11	10	336.3590	112.8450	1.6108	0.6674	0.40	1.58
12	Dimethylamine	11	10	377.2910	80.7856	1.8331	0.9181	0.60	0.81
13	Diethylamine	11	10	334.5810	62.5104	9.0118	1.7774	1.03	1.61
14	Triethylamine	11	10	344.6800	1.8169	6.2869	1.7019	1.17	3.60
							Mean	0.95	2.50
							S.D.	± 0.30	± 1.10

[a] N is the number of data points in each set.
[b] The number of predicted data points is (N-5).

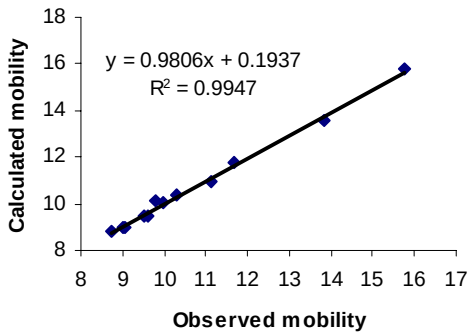

Figure 1. Plot of calculated mobilities (10^{-9} $m^2V^{-1}s^{-1}$) of labetalol versus observed values.

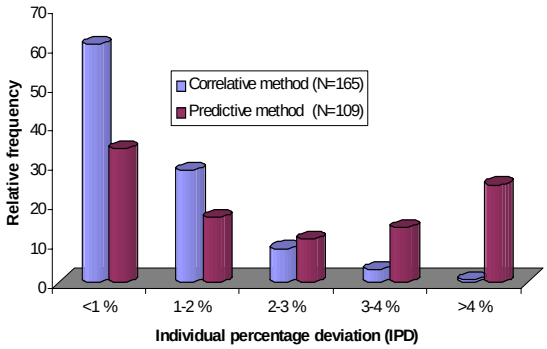

Figure 2. The relative frequency of individual percentage deviation (IPD) values at different error levels for correlative and predictive analyses.

analytes for the test set was predicted using trained model and then the predicted points were employed to compute APMD and IPD values. This analysis was called predictive method. The lowest APMD (0.81 %) was found for diemthylamine and the highest value (4.14 %) observed for atenolol. The overall APMD is 2.50 ± 1.10 %. The relative frequency of IPD is shown in Figure 2. As shown in the figure, the probability of predicting the electrophoretic mobility based on 5 data point training set with prediction error less than 4 % is 0.75. The results show that the proposed model is able to predict the mobility of analytes and the produced error could be considered in an acceptable range where the experimentally obtained relative standard deviation for repeated experiments is around 3.8 % (22).

To provide a more comprehensive equation, all data points for set numbers 1-7 from Table 1, collected from the same electrophoretic conditions, were fitted to Eq. 5 and the following equation was obtained:

$$-kT\ln\mu_m = kT\ln\mu_w + \frac{4.191\times10^{-21}\times1.631 f_1 f_2 + 7.198\times10^{-22}\times1.001 f_2^2}{f_1^2 + 1.631 f_1 f_2 + 1.001 f_2^2} \quad (8)$$

Equation 8 is able to reproduce the mobility data of 7 beta-blocker drugs in acetate buffer with APMD around 3.06 % (N=88). To test the prediction capability of this form, the mobility data of propranolol, timolol, atenolol and alprenolol was used as training set and the mobility of 3 other beta-blockers (set numbers 5-7 from Table 1) as a test set. The calculated APMD for predicted data points is 3.08 % (N=38). It should be noted that the mobility in pure aqueous buffer was the only required information for predicting the mobility of beta-blockers using the trained model. This type of computations is often required in pharmaceutical industry where a number of chemically related drugs are synthesized and/or extracted for assessment of their biological activity. In this process, an analytical method such as capillary electrophoresis method could be used to analyze the sample. Such an equation could help the analyst to speed up the method development process to save time and capital in the industry.

Conclusion

The phenomenological model was successfully employed to model the electrophoretic mobility of drugs in various binary solvent electrolyte systems. The average percentage mean deviation (APMD) between the experimental and calculated values was used as an accuracy criterion. The APMDs obtained for both correlative and predictive analyses varied between 0.40 % and 4.14 %. It is therefore concluded that the use of the proposed model is an efficient and effective tool for both mobility data modelling and prediction in CZE.

Acknowledgements

The authors would like to thank the Australian Department of Education, Training

and Youth Affairs and the University of Sydney for providing the IPRS and IPA scholarships.

References

(1) Miller JL, Shea D and Khaledi MG. Separation of acidic solutes by nonaqueous capillary electrophoresis in acetonitrile-based media combined effects of deprotonation and heteroconjugation. *J. Chromatogr. A* (2000) 888: 251-266

(2) Porras SP, Reikkola ML and Kenndler E. Electrophoretic mobilities of cationic analytes in non-aqueous methanol, acetonitrile, and their mixtures. Influence of ionic strenght and ion-pair formation. *J. Chromatogr. A* (2001) 924: 31-42

(3) Jalali-Heravi M and Garkani-Nejad Z. Prediction of electrophoretic mobilities of sulfonamides in capillary zone electrophoresis using artificial neural networks. *J. Chromatogr. A* (2001) 927: 211-218

(4) Timerbaev AR, Semenova OP and Petrukhin OM. Migration behavior of metal complexes in capillary zone electrophoresis. Interpretation in terms of quantitative structure-mobility relationships. *J. Chromatogr. A* (2002) 943: 263-274

(5) Pesek JJ and Matyska MT. Separation of tetracyclines by high-performance capillary electrophoresis and capillary electrochromatography. *J. Chromatogr. A* (1996) 736: 313-320

(6) Altria KD and Bryant SM. Highly selective and efficient separation of a wide range of acidic species in capillary electrophoresis employing non-aqueous media. *Chromatographia* (1997) 46: 122-130

(7) Hansen SH, Jensen ME and Bjornsdottir I. Assay of acetylsalicylic acid and three of its metabolites in human plasma and urine using non-aqueous capillary electrophoresis with reversed electoosmotic flow. *J. Pharm. Biomed. Anal.* (1998) 17: 1155-1160

(8) Castellanos Gil E, Van Schepdael A, Rots E and Hoogmartens J. Analysis of doxycycline by capillary electrophoresis method development and validation. *J. Chromatogr. A* (2000) 895: 43-49

(9) Cherkaoui S and Veuthey JL. Development and robustness testing of a nonaqeous capillary electrophoresis method for the analysis of nonsteroidal anti-inflammatory drugs. *J. Chromatogr. A* (2000) 874: 121-129

(10) Jouyban A, Batish A, Rumbelow SJ and Clark BJ. Calculation of electrophoretic mobility of amines in methanol-aqueous electrolyte systems. *Analyst* (2001) 126: 1958-1962

(11) Jouyban-Gh A, Khaledi MG and Clark BJ. Calculation of electrophoretic mobilities in water-organic modifier mixtures. *J. Chromatogr. A* (2000) 868: 277-284

(12) Jouyban A, Chan HK, Khoubnasabjafari M, Jouyban N and Clark BJ. Modelling the electrophoretic mobility of basic drugs in aqueous methanolic buffers in capillary electrophoresis. *Daru* (2001) 9: 1-5

(13) Khossravi D and Connors KA. Solvent effects on chemical processes: I. Solubility of aromatic and heterocyclic compounds in binary aqueous-organic solvents. *J. Pharm. Sci.* (1992) 81: 371-379

(14) Khossravi D and Connors KA. Solvent effects on chemical processes. 3. Surface tension of binary aqueous organic solvents. *J. Solution Chem.* (1993) 22: 321-330

(15) Connors KA and Khossravi D. Solvent effects on chemical processes. 4. Complex formation between naphthalene and theophyline in binary aqueous-organic solvents. *J. Solution Chem.* (1993) 22: 677-694

(16) Skwierczynski RD and Connors KA. Solvent effects on chemical processes. Part 7. Quantitative description of the composition dependence of the solvent polarity measure E_T (30) in binary aqueous-organic solvent mixtures. *J. Chem. Soc. Perkin Trans. 2* (1994) 467-472

(17) Skwierczynski RD and Connors KA. Solvent effect on chemical processes. 8. Demethylation kinetics of aspartame in binary aqueous-organic solvents. *J. Pharm. Sci.* (1994) 83: 1690-1696

(18) Lepree JM and Connors KA. Solvent effects on chemical processes. 11. Solvent effects on the kinetics of decarboxylative dechlorination of N-chloro amino acids in binary aqueous-organic solvents. *J. Pharm. Sci.* (1996) 85: 560-566

(19) Lepree JM and Cancino ME. Application of the phenomenological model to retention in reversed phase high-performance liquid chromatography. *J. Chromatogr. A* (1998) 829: 41-63

(20) Jouyban A, Chan HK, Clark BJ and Kenndler E. Mathematical representation of electrophoretic mobility in mixed aqueous-methanolic buffers in capillary zone electrophoresis. *J. Microcolumn Separation* (2001) 13: 346-350

(21) Jouyban A, Khoubnasabjafari M, Chan HK, Altria KD and Clark BJ. Predicting electrophoretic mobility of beta-blockers in water-methanol mixed electrolyte system. *Chromatographia* (2003) 57: 191-196

(22) Fu S and Lucy CA. Prediction of electrophoretic mobilities. 1. Monoamines. *Anal. Chem.* (1998) 70: 173-181