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Mathematical representation of analyte's capacity factor in binary solvent mobile phases using the Jouyban-Acree model

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Applicability of a solution model, namely the Jouyban-Acree model, for mathematical representation of capacity factors of phenobarbital, phenytoin and carbamazepine in mobile phases containing water and the organic modifiers: methanol, acetonitrile, acetone and tetrahydrofuran and also a number of data sets collected from the literature has been shown. The accuracy of the proposed model is compared with those of the linear model and the quadratic equation using average percentage deviation (APD) as an accuracy criterion. The obtained mean and standard deviation of APDs of the Jouyban-Acree, linear and quadratic models are 8.1 ± 8.4, 25.2 ± 18.0 and $14.5 \pm 16.2\%$, respectively. The results showed that the Jouyban-Acree model provided more accurate calculations than the previously published models and the mean differences were statistically significant ($p < 0.002$).

1. Introduction

Liquid chromatography, especially reversed-phase HPLC, has rapidly developed and is accepted as a reliable and versatile analytical tool for the separation and quantification of analytes in pharmaceutical analysis. However, in practical separations, optimization of mobile phase composition with respect to stationary phase, physicochemical properties and chemical structure of analytes and finding a good combination among them is usually the most difficult and time consuming step of work and is traditionally carried out by trial and error. The aim of this communication is to report capacity factors (k') of the analytes studied and to propose a mathematical model for calculating k' of analytes with respect to solvent composition of the mobile phase. The applicability of the model is shwon using k' of three anti-epileptic drugs along with a number of data sets (possessing more than seven experimental data points in each set) from the literature, and the accuracy of the model is compared with those of previous models.

2. Investigations, results and discussion

A solution model, namely the Jouyban-Acree model (Jouyban et al. 2004) showed good capability to calculate the solvent composition effects on different physico-chemical properties listed in a previous report (Jouyban et al. 2005). Its general form is:

$$\ln PCP_m = f_1 \ln PCP_1 + f_2 \ln PCP_2 + f_1 f_2 \sum_{i=0}^{q} K_i (f_1 - f_2)^i \quad (1)$$

Where PCP_m, PCP_1 and PCP_2 are the numerical values of the physico-chemical properties of the mixture and solvents 1 and 2, respectively, f_1 and f_2 are the volume (weight or mole) fractions of solvents 1 and 2 in the mixture and K_i represent the model constants. The adopted model for calculating k' of analytes could be written as:

$$\ln k'_m = f_1 \ln k'_1 + f_2 \ln k'_2 + f_1 f_2 \sum_{i=0}^{q} L_i (f_1 - f_2)^i \quad (2)$$

in which subscripts m, 1 and 2 refer to mixed solvent and neat solvents 1 and 2 of the mobile phase and L_i is the model constant. In some cases, the numerical values of k' in mono-solvent mobile phases, i.e. k'_1 and k'_2, could not be determined, therefore eq. (2) could be rearranged as:

$$\ln k'_m = J_1 f_1 + J_2 f_2 + f_1 f_2 \sum_{i=0}^{q} L_i (f_1 - f_2)^i \quad (3)$$

where J_1 and J_2 are two other model constants. These constant terms (i.e. J_1, J_2 and L_i) could be calculated by regressing $\ln k'_m$ against f_1, f_2, $f_1 f_2$, $f_1 f_2 (f_1 - f_2)$, $f_1 f_2 (f_1 - f_2)^2$ etc. Although one might find theoretical and/or semi-theoretical justifications for the model (Acree 1992), it would be best to view Eqs. (2) or (3) as a mathematical representation, rather than an equation derived from rigorous thermodynamic model. The previously published models for representation of k' with respect to solvent composition of mobile phase are the linear model (Kaliszan 1997) and the quadratic equation (Kaliszan 1997) expressed as Eqs. (4) and (5), respectively.

$$\ln k'_m = A f_1 + B \quad (4)$$

$$\ln k'_m = C f_1^2 + D f_1 + E \quad (5)$$

where A, B, C, D and E are the model constants.
The calculated k' is compared with experimental (observed) values and mean of the absolute percentage devia-

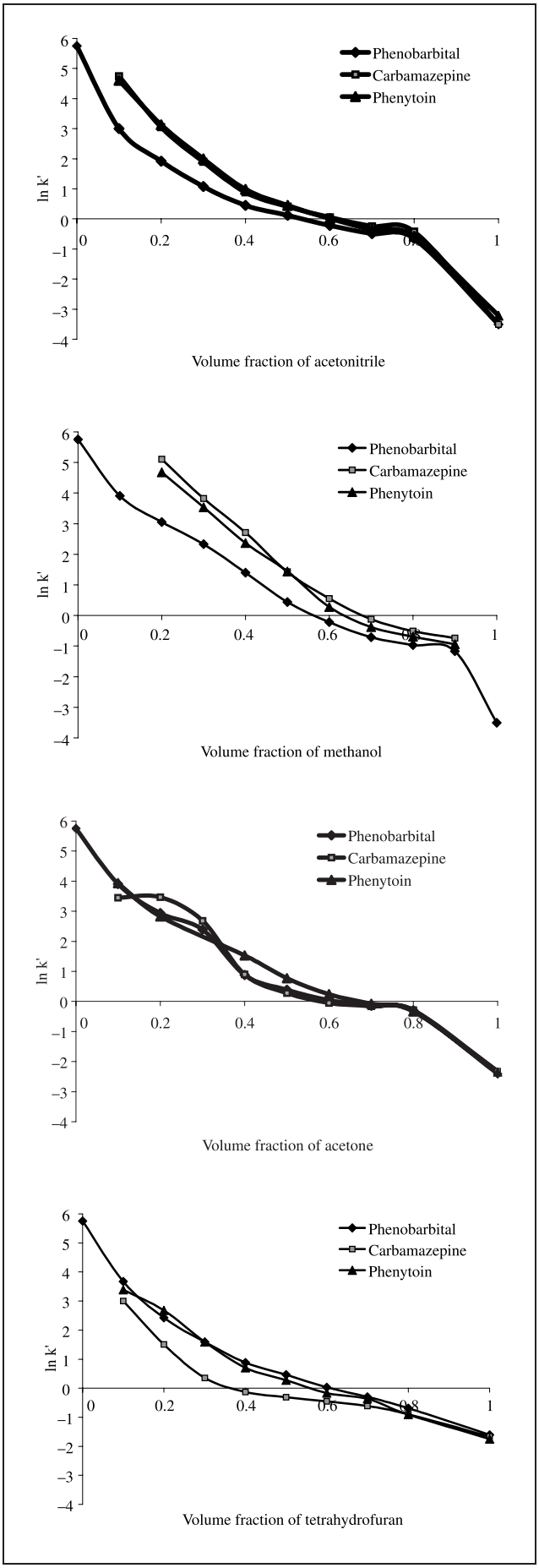

Fig.: Logarithm of capacity factors in different concentration of organic modifiers in the mobile phase

tion (APD) is used as an accuracy criterion. The APD is calculated using:

$$\mathrm{APD} = \frac{100}{\mathrm{N}} \sum \frac{|\mathrm{Calculated} - \mathrm{Observed}|}{\mathrm{Observed}} \qquad (6)$$

where N is the number of data points in each set.

The k′ of the analytes studied in different buffer and organic modifier volume fractions are shown in the Figure. We are interested to measure k′ of analytes in the entire solvent composition range from 0 to 1 with intervals of 0.1 volume fraction, however, for carbamazepine and phenytoin, very broad peaks are obtained at mono-solvent and a number of mixed solvent mobile phases, therefore, the data points are excluded from the calculations.

Logarithm of k′ of analytes collected in this work and also from the literature are fitted to Eqs. (3 with $q = 1$)–(5), and then the back-calculated k′ values are used to calculate APDs. The details of the data sets, the number of data points in each set, the references and also APDs for the models studied are listed in the Table. For the Jouyban-Acree model the minimum and maximum APDs are 1.0% (benzene in methanol + water) and 42.1% (carbamazepine in acetone + water). The linear model produced the highest and lowest APDs as 3.8 and 65.0% and the corresponding values for the quadratic equation are 1.4 and 67.6%, respectively. The overal APD for the Jouyban-Acree, linear and quadratic equations are 8.1 ± 8.4, 25.2 ± 18.0 and 14.5 ± 16.2%, respectively. The results of paired t-test between APDs of the proposed model and previous models show that the proposed model provides more accurate calculations ($p < 0.002$).

The accuracy of the Jouyban-Acree model could be improved using more curve-fitting parameters (i.e. q values in Eq. (3)). The APD (±SD) of Eq. (3) for $q = 1$, 2, 3 and 4 are 8.1 ± 8.4, 5.5 ± 5.2, 3.9 ± 3.3, 3.3 ± 2.9%, respectively. The statistical significance of the APDs is evaluated using paired t-test, where the differences between APDs of q with $(q + 1)$ are significant ($p < 0.02$). However, this improvement reaches the best value at $q = 4$ and a further increase in i value produces the same accuracy as $q = 4$.

In conclusion, the proposed model shows more accurate results to reproduce k′ values at different solvent composition of mobile phases and could be used to speed up the HPLC method development step where employing mixed solvent mobile phase is required.

3. Experimental

Methanol, acetonitrile, acetone and tetrahydrofuran, potassium hydrogen phosphate and sodium nitrite were purchased from Merck (Germany). Pure drugs were gifts from Sobhan, Daroupakhsh and Ruzdarou pharmaceutical companies. The liquid chromatographic system consisted of a Well-Chrom Maxi-Star K-1000 pump; a 4-channel K-5004 degasser, a Well-Chrom K-2500 UV detector and a Well-Chrom interface box all from Knauer Co. (Germany). The reversed-phase column was Nova-Pak C-18 with dimensions of 4.6×250 mm from Waters company (Massachusetts, USA). The ultrasonic water bath was used as degasser (Liarre Co., Bologna, Italy). A Millipore pump and 0.22 μm GVHP filters (Millipore, Ireland) were used for mobile phase filtration. Buffer solution was 4 mM phosphate buffer pH = 6, prepared by dissolving an appropriate amount of potassium hydrogen phosphate in double distilled water and pH adjusted by ortho-phosphoric acid. Mobile phases were prepared by mixing appropriate volumes of buffer and organic solvents followed by filtration. The filtered mobile phase was degassed for 15 min in an ultrasonic bath. The mobile phase was passed from column at 1 ml/min flow rate for conditioning the system (30 min). After conditioning, 20 μl of the analytes (100 ppm) were injected via injection loop. The k′ was evaluated from the retention time of the analyte, t_R, according to $k' = \frac{(t_R - t_0)}{t_0}$ in which t_0 is retention time of an unretained compound. A 50 ppm sodium nitrite solution was employed to measure t_0 values. All measurements were at least triplicates and the UV detector was set at 220 nm and used as detection system.

Table: Details of the data sets, number of data points in each set (N), references and average percentage deviations for Eqs. (3)–(5)

No.	Analyte	Organic modifier	N	eq. (3) with q = 1	eq. (4)	eq. (5)	Reference
1	Phenobarbital	Methanol	11	27.7	40.7	36.9	This work
2	Phenobarbital	Acetonitrile	10	14.5	65.0	67.6	This work
3	Phenobarbital	Acetone	9	17.9	44.2	31.5	This work
4	Phenobarbital	Tetrahydrofuran	10	12.5	42.6	20.2	This work
5	Carbamazepine	Methanol	9	7.3	64.0	17.0	This work
6	Carbamazepine	Acetonitrile	9	13.9	51.3	52.2	This work
7	Carbamazepine	Acetone	9	42.1	44.6	44.5	This work
8	Carbamazepine	Tetrahydrofuran	9	3.7	42.8	33.4	This work
9	Phenytoin	Methanol	9	9.0	64.0	23.4	This work
10	Phenytoin	Acetonitrile	9	12.6	40.6	39.9	This work
11	Phenytoin	Acetone	9	25.3	30.6	30.2	This work
12	Phenytoin	Tetrahydrofuran	10	13.8	40.7	17.9	This work
13	4-Aminophenol	Methanol	9	2.1	9.5	3.5	Oh et al. 1986
14	Phenol	Methanol	9	1.4	5.9	1.4	Oh et al. 1986
15	4-Nitrophenol	Methanol	9	2.7	5.1	2.9	Oh et al. 1986
16	4-Cresol	Methanol	9	3.2	4.4	3.7	Oh et al. 1986
17	4-Thiomethylphenol	Methanol	9	3.6	4.1	3.5	Oh et al. 1986
18	4-Chlorophenol	Methanol	9	2.9	3.8	3.1	Oh et al. 1986
19	Benzene	Methanol (C18 column)	9	7.1	9.9	9.2	Lee et al. 1989
20	Phenol	Methanol (C18 column)	9	5.5	9.9	6.3	Lee et al. 1989
21	Aniline	Methanol (C18 column)	9	5.4	9.2	5.5	Lee et al. 1989
22	Benzyl alcohol	Methanol (C18 column)	9	5.9	11.0	6.5	Lee et al. 1989
23	Phenol	Methanol (phenyl column)	9	5.6	16.9	6.2	Lee et al. 1989
24	Aniline	Methanol (phenyl column)	9	9.1	10.3	9.8	Lee et al. 1989
25	Benzyl alcohol	Methanol (phenyl column)	9	5.0	11.9	5.9	Lee et al. 1989
26	Acetophenone	Acetonitrile	10	5.7	22.6	6.0	Smith et al. 1987
27	Propiophenone	Acetonitrile	10	5.8	26.5	7.2	Smith et al. 1987
28	Butyrophenone	Acetonitrile	8	3.1	11.7	3.1	Smith et al. 1987
29	2-Phenylethanol	Acetonitrile	10	6.7	31.5	7.2	Smith et al. 1987
30	p-Cresol	Acetonitrile	10	6.5	27.5	6.5	Smith et al. 1987
31	Methyl benzoate	Acetonitrile	10	5.2	27.0	6.1	Smith et al. 1987
32	N-Methylaniline	Acetonitrile	10	4.4	13.8	4.9	Smith et al. 1987
33	Nitrobenzene	Acetonitrile	10	3.9	15.2	4.7	Smith et al. 1987
34	Toluene	Acetonitrile	8	2.1	8.7	3.2	Smith et al. 1987
35	Benzene	Methanol	11	1.0	21.2	3.0	LePree and Cancino 1998
36	Naphthalene	Methanol	10	1.1	20.7	5.1	LePree and Cancino 1998
37	Bromobenzene	Methanol	11	2.5	26.2	7.2	LePree and Cancino 1998
38	1-Iodonaphthalene	Methanol	12	1.7	20.2	3.9	LePree and Cancino 1998

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