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Correlation of retention factor of analytes in quaternary solvent mobile phases using the Jouyban-Acree model

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The Jouyban-Acree model has been used for the mathematical representation of retention factors of phenobarbital, phenytoin and carbamazepine in quaternary aqueous-organic solvent mobile phases. The accuracy of the proposed model is evaluated using average percentage deviation (APD) of experimental and calculated values as an accuracy criterion. The obtained mean and standard deviation of APDs of the model is $4.2 \pm 0.5\%$. The results showed that the Jouyban-Acree model provided accurate calculations and could be used in practice to speed up the method development process in which quaternary solvent mobile phases are required.

1. Introduction

Reversed phase high performance liquid chromatography has been accepted as a reliable and versatile analytical tool in pharmaceutical analysis. The common method in optimizing the solvent composition of the mobile phase is the trial and error approach when addition of an organic modifier is required to affect the analytical parameters. When binary solvent mixtures are not able to provide satisfactory results, ternary solvents and also quaternary solvent mixtures are used in practice and many validated chromatographic methods employ quaternary solvent mobile phases (as examples for analysis of anti-epileptic drugs see Ou and Rognerud 1984; Remmel et al. 1990). However, the number of possible solvent compositions of quaternary mixtures is very large and the trial and error approach is time consuming and also costly. The aim of this communication is to report the retention 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 experimental k values of phenobarbital, phenytoin and carbamazepine in mobile phases consisting of water-methanol-acetonitrile-tetrahydrofuran solvent mixtures.

2. Investigations, results and discussion

The Jouyban-Acree model showed a good capability to calculate the solvent composition effects on retention factor of analytes in binary solvent mixtures and presented as:

$$\ln k_m = A_1 f_1 + A_2 f_2 + f_1 f_2 \sum_{i=0}^{q} K_i (f_1 - f_2)^i \qquad (1)$$

where k_m is the retention factor of the analyte in the mixed solvent mobile phase, A_1, A_2 and K_i are the model constants, f_1 and f_2 are the volume (weight or mole) fractions of solvents 1–2 in the mixture (Jouyban et al. 2005a). The model has been extended for the mathematical representation of retention factors in mobile phases of ternary mixtures as:

$$\begin{aligned}\ln k_m = {} & J_1 f_1 + J_2 f_2 + J_3 f_3 + f_1 f_2 \sum_{i=0}^{q} L_i (f_1 - f_2)^i \\ & + f_1 f_3 \sum_{i=0}^{q} L_i' (f_1 - f_3)^i + f_2 f_3 \sum_{i=0}^{q} L_i'' (f_2 - f_3)^i \\ & + f_1 f_2 f_3 \sum_{i=0}^{q} L_i''' (f_1 - f_2 - f_3)^i \end{aligned} \qquad (2)$$

in which subscripts m, 1, 2 and 3 refer to mixed solvent and neat solvents 1–3 of the mobile phase, L_i terms are the model constants and $J_1 - J_3$ are the model constants. These constant terms (i.e. J_1, J_2, J_3 and L_i terms) could be calculated by regressing $\ln k_m$ against f_1, f_2, f_3, $f_1 f_2$, $f_1 f_2 (f_1 - f_2)$, $f_1 f_2 (f_1 - f_2)^2$ etc (Jouyban et al. 2005b). The model can be extended as Eq. (3) for representation of retention factor of analytes in quaternary solvent mixtures as:

$$\begin{aligned}\ln k_m = {} & J_1 f_1 + J_2 f_2 + J_3 f_3 + J_4 f_4 + f_1 f_2 \sum_{i=0}^{q} B_i (f_1 - f_2)^i \\ & + f_1 f_3 \sum_{i=0}^{q} B_i' (f_1 - f_3)^i + f_1 f_4 \sum_{i=0}^{q} B_i'' (f_1 - f_4)^i \\ & + f_2 f_3 \sum_{i=0}^{q} B_i''' (f_2 - f_3)^i + f_2 f_4 \sum_{i=0}^{q} B_i'''' (f_2 - f_4)^i \\ & + f_3 f_4 \sum_{i=0}^{q} B_i''''' (f_3 - f_4)^i + f_1 f_2 f_3 \sum_{i=0}^{q} T_i (f_1 - f_2 - f_3)^i \\ & + f_1 f_2 f_4 \sum_{i=0}^{q} T_i' (f_1 - f_2 - f_4)^i \\ & + f_2 f_3 f_4 \sum_{i=0}^{q} T_i'' (f_2 - f_3 - f_4)^i \\ & + f_1 f_2 f_3 f_4 \sum_{i=0}^{q} Q_i (f_1 - f_2 - f_3 - f_4)^i \end{aligned} \qquad (3)$$

Table 1: Retention factors of analytes in different compositions of quaternary solvent mobile phases

No.	Volume fraction				Retention factor		
	Water	Methanol	Acetonitrile	Tetrahydrofuran	Phenobarbital	Phenytoin	Carbamazepine
1	0.1	0.1	0.7	0.1	2.50	3.06	2.71
2	0.1	0.2	0.4	0.3	2.03	2.14	2.27
3	0.1	0.2	0.5	0.2	2.05	2.15	2.35
4	0.1	0.2	0.6	0.1	2.15	2.38	2.38
5	0.1	0.3	0.2	0.4	1.88	2.19	2.02
6	0.1	0.3	0.3	0.3	2.04	2.37	2.36
7	0.1	0.3	0.4	0.2	2.37	2.59	2.68
8	0.1	0.3	0.5	0.1	2.24	2.50	2.74
9	0.1	0.4	0.1	0.4	2.14	2.40	2.23
10	0.1	0.4	0.2	0.3	2.23	2.58	2.4
11	0.1	0.4	0.3	0.2	2.58	2.57	2.57
12	0.1	0.5	0.1	0.3	2.24	2.58	2.55
13	0.1	0.5	0.2	0.2	2.40	2.57	2.57
14	0.1	0.5	0.3	0.1	2.57	2.54	3.09
15	0.1	0.6	0.1	0.2	2.57	2.55	2.55
16	0.1	0.6	0.2	0.1	2.40	2.57	2.57
17	0.1	0.7	0.1	0.1	2.41	2.57	3.09
18	0.2	0.1	0.1	0.6	2.23	2.57	2.40
19	0.2	0.1	0.2	0.5	2.40	2.57	2.41
20	0.2	0.1	0.3	0.4	2.39	2.57	2.39
21	0.2	0.1	0.4	0.3	2.42	2.58	2.94
22	0.2	0.1	0.5	0.2	2.23	2.93	2.76
23	0.2	0.1	0.6	0.1	2.59	3.11	2.54
24	0.2	0.2	0.1	0.5	2.06	2.57	2.57
25	0.2	0.2	0.2	0.4	2.23	2.57	2.56
26	0.2	0.2	0.3	0.3	2.40	2.74	2.58
27	0.2	0.2	0.4	0.2	2.40	2.74	3.09
28	0.2	0.2	0.5	0.1	2.59	2.75	2.92
29	0.2	0.3	0.1	0.4	2.25	2.94	2.84
30	0.2	0.3	0.3	0.2	2.60	2.75	3.09
31	0.2	0.3	0.4	0.1	2.57	3.11	3.09
32	0.2	0.4	0.1	0.3	2.57	3.09	3.10
33	0.2	0.4	0.2	0.2	2.58	3.10	3.09
34	0.2	0.4	0.3	0.1	2.75	3.09	3.09
35	0.2	0.5	0.1	0.2	2.43	2.93	3.10
36	0.2	0.5	0.2	0.1	3.10	3.12	3.09
37	0.2	0.6	0.1	0.1	2.77	3.12	3.10
38	0.3	0.1	0.1	0.5	2.43	2.90	2.94
39	0.3	0.1	0.2	0.4	2.43	3.12	3.14
40	0.3	0.1	0.3	0.3	2.60	3.18	3.28
41	0.3	0.1	0.4	0.2	2.60	2.94	3.12
42	0.3	0.1	0.5	0.1	2.23	2.85	2.57
43	0.3	0.2	0.2	0.3	2.22	2.15	2.33
44	0.3	0.2	0.3	0.2	2.09	2.25	2.25
45	0.3	0.2	0.4	0.1	2.26	2.25	2.52
46	0.3	0.3	0.1	0.3	1.91	2.14	2.26
47	0.3	0.3	0.2	0.2	2.05	2.05	2.40
48	0.4	0.1	0.4	0.1	2.27	2.79	2.51
49	0.4	0.2	0.1	0.3	1.71	2.08	2.27
50	0.4	0.2	0.2	0.2	1.80	1.81	2.09
51	0.4	0.3	0.1	0.2	1.45	1.76	1.96
52	0.4	0.3	0.2	0.1	1.53	1.69	2.06
53	0.4	0.4	0.1	0.1	1.76	1.86	2.16
54	0.5	0.1	0.1	0.3	1.76	2.89	3.07
55	0.5	0.1	0.2	0.2	1.76	1.99	2.35
56	0.5	0.1	0.3	0.1	1.86	1.96	2.07
57	0.5	0.2	0.1	0.2	1.14	1.24	1.45
58	0.5	0.2	0.2	0.1	1.44	1.05	1.34
59	0.5	0.3	0.1	0.1	1.24	1.41	1.36
60	0.6	0.1	0.2	0.1	1.24	1.33	1.42
61	0.6	0.2	0.1	0.1	1.04	1.23	1.27
62	0.7	0.1	0.1	0.1	0.84	1.13	1.14

Table 2: List of analytes, average percentage deviation (APD), correlation coefficient (R) and F value of the proposed model (q = 1)

No.	Analyte	APD	R	F value[a]
1	Phenobarbital	3.7	0.998	523.9
2	Phenytoin	4.4	0.998	471.1
3	Carbamazepine	4.6	0.998	484.9

[a] All F values are statistically significant ($p < 0.0005$)

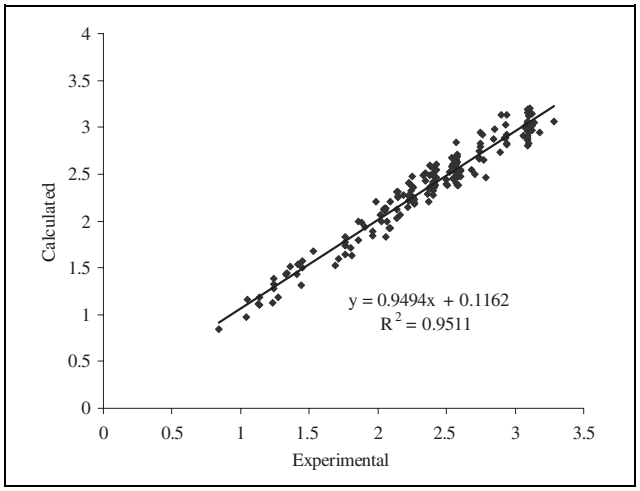

Fig.: Calculated retention factors of the studied analytes in quaternary solvent mobile phases vs. experimental values

in which B, T and Q are binary, ternary and quaternary interaction parameters (model constants) and subscript 4 is the fourth solvent.

Theoretical and/or semi-theoretical justifications for Eqs. (1)–(3) can be made as the retention factor is in fact a partition coefficient, the numerical value of which is determined by the difference in the chemical potentials of the solute in the mobile and stationary phases. Expressions for the chemical potential of a solute dissolved in mixed solvents have been derived previously (Acree 1992) from a two-body and three-body interactional mixing model. In the present case, it would be best to view the equations as mathematical representations, rather than equations derived from a rigorous thermodynamic model. This is particularly true of all mathematical representations that employ more than a few model constants. The model constants lose their physical significance as more and more constants are introduced into the mathematical expression.

The calculated k is compared with experimental (observed) values and mean of the absolute percentage deviation (APD) is used as an accuracy criterion. The APD is calculated using:

$$\mathrm{APD} = \frac{100}{\mathrm{N}} \sum \frac{|\mathrm{Calculated} - \mathrm{Observed}|}{\mathrm{Observed}} \qquad (4)$$

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

The k values of the analytes studied in different buffer and organic modifier volume fractions are listed in Table 1. As a general pattern, the more water (buffer) the mobile phase contains, the longer the retention (the higher the retention factor) of the analytes is.

Logarithms of k of analytes were fitted to Eq. (3 with $q = 1$), and then the back-calculated k values were used to determine APDs. The details of the data sets, the number of data points in each set, APDs for the proposed model, the correlation coefficients (R) and also the F values are shown in Table 2. The overall APD is $4.2 \pm 0.5\%$. The higher R and F values reveal that the model is capable of correlating the retention factor of analytes in quaternary solvent mobile phases. A plot of calculated retention factors of the analytes against the experimental values is shown in the Fig. 1 and good agreement is observed between calculated and experimental values.

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 chromatographic method development stage where employing quaternary solvent mobile phases is required.

3. Experimental

Methanol, acetonitrile, acetone, 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 (Massachusett USA). An 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 adjusting pH 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 an injection loop. The k value 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 at 220 nm was used as detection system.

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