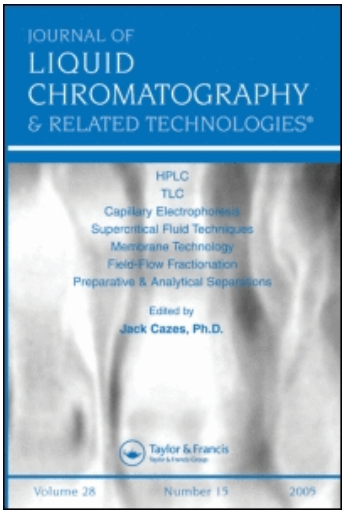

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Performance Characterization of Multi-Solvent Mobile Phase Systems in RP-HPLC by Multi-Criteria Decision Making Illustrated by the Comparison of Ternary and Quaternary Solvent systems

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PERFORMANCE CHARACTERIZATION OF MULTI-SOLVENT MOBILE PHASE SYSTEMS IN RP-HPLC BY MULTI-CRITERIA DECISION MAKING ILLUSTRATED BY THE COMPARISON OF TERNARY AND QUATERNARY SOLVENT SYSTEMS

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ABSTRACT

Combination of the Triangular Mixture Design Statistical Technique (TMDST) and Multi-Criteria Decision Making (MCDM) allows the evaluation of the performance of multi-solvent mobile phase systems for RP-HPLC with respect to two criteria simultaneously. If the minimal resolution of two adjacent peaks, Rsmin, and the retention time of the last peak of a chromatogram, kmax, are used as criteria for the optimization, then one can compare multi-solvent mobile phase systems by their MCDM plots. The solvent system that can give a chromatogram with an acceptable resolution in shortest possible analysis time for a given separation problem can be selected. Multi-solvent mobile phase systems that need a longer analysis time to obtain the same acceptable resolution for this separation, can be ruled out. This is demonstrated by the comparison of the performance of ternary and quaternary iso-eluotropic mobile phase systems in the separation of a mixture of benzene derivatives on a RP octyl column.

INTRODUCTION

In the optimization of HPLC separations methods for finding the eluent composition that provide a satisfactory separation have received much attention. Methods that model the capacity factors of the sample compounds as a function of the eluent composition have the advantage of finding the global maximum for the resolution in the investigated part of the factor space and provide the most unequivocal approach for the practitioner (1).

Several designs can be used to construct a model of the capacity factor. Factorial designs offer the possibility to use discrete variables, such as temperature, together with related variables, such as the solvent components of the mobile phase (2). The Prisma design approach can optimize both solvent selectivity and solvent strength (3). We will confine our attention to the triangular mixture design statistical technique (TMDST), as it is an extremely powerful method (2).

This method was introduced by Glajch et al. for optimising the solvent selectivity of iso-eluotropic quaternary mobile phase systems in RP-HPLC (4). Their approach was extended to normal phase separations on silica and normal bonded phases (5,6,7), to ion-pair RP-HPLC (8), and to gradient elution (9,10).

The TMDST was applied first by Belinky to ternary mobile phase systems in RP-HPLC for the optimization of the resolution (11). Weyland indicated the possibility offered by ternary systems for the simultaneous optimization of resolution and analysis time (12). This was realized qualitatively in ion-pair RP-HPLC (13). Then the technique was combined with the multi-criteria decision making (MCDM) method, which quantifies the pay-off between two criteria (14,15).

In this paper will be shown that the performance of multi-solvent mobile phase systems with respect to two criteria can be characterized and compared by MCDM-plots. As an example ternary and iso-eluotropic quaternary solvent systems are compared, because of experimental efficiency. Only one design is

needed to model the capacity factor as a function of the composition of three ternary and all iso-eluotropic quaternary solvent systems of a truncated pyramid (see Methods section).

First a short description of the TMDST will be presented, in which the differences in procedure for ternary and quaternary mixtures are stressed. Then a short explanation of the MCDM method will be given.

THEORY

Triangular Mixture Designs

In RP-HPLC a quaternary eluent usually consists of water and three organic modifiers, i.e. methanol (MeOH), acetonitrile (ACN), tetrahydrofuran (THF), selected according to the selectivity classification of Snyder (16), while a ternary eluent consists of water and only two modifiers. Three different ternary solvent systems can be made up from water and three modifiers.

D'Agostino (17) has pointed out that a quaternary mixture can be represented by a tetrahedron at the vertices of which the four pure solvents, water, MeOH, ACN, and THF, are located. If water is placed at the top of the tetrahedron and the three organic modifiers at the vertices of the ground surface, the three sides of the tetrahedron represent three ternary mixtures (Fig.1).

The initial step in the optimization of the composition of ternary as well of quaternary mobile phases is to constrain the factor space to the feasible region or optimization area; i.e. to choose a reasonable range of retention. For an iso-eluotropic quaternary system this constraint confines the factor space to a triangular cross-section of the tetrahedron. In this triangle the solvent strength is constant, and may be selected so that the capacity factor of the last eluted compound of the sample, kmax, is for example approximately equal to ten. This is

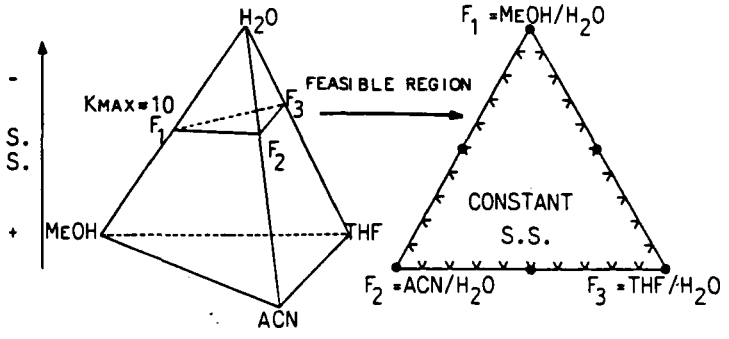

FIGURE 1.

Solvent tetrahedron and triangular mixture design for quaternary iso-eluotropic mobile phase optimization. The dots indicate individual mobile phase compositions at which retention data for all solutes are obtained. S.S. = solvent strength. F_1, F_2, F_3 are pseudo-components.

achieved by selecting the correct compositions for the three binary pseudocomponents at the vertices of the triangle (Fig.1).

For a ternary system the feasible region consists of a trapezoidal part of the solvent triangle. In this feasible region the solvent strength is not constant, but decreases from the lower towards the upper boundary. The upper boundary may be selected so that kmax is approximately equal to fifteen; for the lower boundary the capacity factor of the first peak, kmin, should be larger than about one (Fig.2). Ternary systems are not iso-eluotropic and in contrast to quaternary systems they offer the possibility for the simultaneous optimization of resolution and analysis time. Quaternary systems lack this possibility, but may offer greater selectivity.

The next steps in the optimization procedure are similar for both mobile phase systems: the capacity factors of the compounds of the sample are determined for at least six mobile phase compositions in the feasible region, if a quadratic model is used. Higher order models require more measurements. The capacity

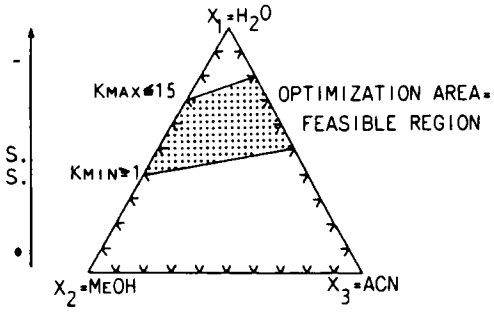

FIGURE 2.

Constrained triangular mixture design for ternary mobile phase optimization. S.S. = solvent strength, kmin = capacity factor of the first peak, kmax = capacity factor of the last peak.

factors are used to estimate the six model coefficients, A_1 to A_{23}, of the quadratic model:

$$\ln k = A_1F_1 + A_2F_2 + A_3F_3 + A_{12}F_1F_2 + A_{13}F_1F_3 + A_{23}F_2F_3 \qquad (1)$$

where in the quaternary case F_1, F_2 and F_3 are the fractions of the pseudocomponents, i.e. the binary iso-eluotropic mixtures of water and the respective modifiers. For a ternary mixture F_1, F_2, and F_3 are the fractions of the pure components, i.e. water and the two modifiers used.

Using the model the capacity factors of the sample compounds are predicted at all mobile phase compositions within the feasible region. In the optimization area a grid is constructed for which the (pseudo)components change by one per cent. At every mobile phase composition the resolution, Rs, is predicted for every pair of peaks from:

$$Rs = N^{0.5}(k_2 - k_1)/2(k_2 + k_1 + 2) \qquad (2)$$

where N is the plate number and k_2 and k_1 are the capacity factors of adjacent peaks. The minimal value, Rsmin, of the

resolutions obtained at every grid point, is plotted. The optimal solvent composition is found from the minimal resolution plot (see Figs. 4, 6).

Multi-Criteria Decision Making

In the previous section the resolution was used as a criterion for the separation, but the quality of a chromatogram can be characterized by additional criteria, of which the analysis time is one of the most important. Debets et al. (18) have shown that multicomponent criteria like the chromatographic optimization function (COF) (4), which combines resolution and analysis time in a single function, provide not always an unequivocal quantification of the quality of a chromatogram, and they will not be considered here.

In order to optimize simultaneously resolution and analysis time not only the minimal resolution, but also the capacity factor of the last eluted peak, kmax, is predicted at every solvent composition of the grid in the feasible region and serves as a measure for the analysis time.

Then the multi-criteria decision making (MCDM) method (14) is applied. To obtain a MCDM plot the values of Rsmin and kmax corresponding with one mobile phase composition are represented by one point in a diagram. This diagram has two perpendicular coordinate axes. On the horizontal axis, called the time axis, the values of kmax are plotted, while on the vertical axis the values of Rsmin are shown.

From the resulting scatterplot only the Pareto Optimal (PO) points are depicted in the diagram, because all other points represent inferior combinations of the two criteria. Only the PO points give the best possible combinations of both criteria. They show the pay-off between both criteria for a given mobile phase system, and characterize the performance of the eluent system by a single string of points (Figs. 5, 7). Therefore the performance of different mobile phase systems can be easily compared by means of their MCDM plots.

METHODS

Because we wanted to use the MCDM method for the comparison of ternary and quaternary iso-eluotropic mobile phases, we decided to investigate a constrained quaternary mixture design as shown in Fig.3. A ten term quadratic model was used to relate the logarithm of the capacity factor of a testcompound to the composition of the eluent mixture:

$$\ln k = A_1X_1 + A_2X_2 + A_3X_3 + A_4X_4 + A_{12}X_1X_2 + A_{13}X_1X_3 + A_{14}X_1X_4 + A_{23}X_2X_3 + A_{24}X_2X_4 + A_{34}X_3X_4 \quad (3)$$

With four component mixtures also a fourteen term special cubic model may be used (19), but a quadratic model was preferred

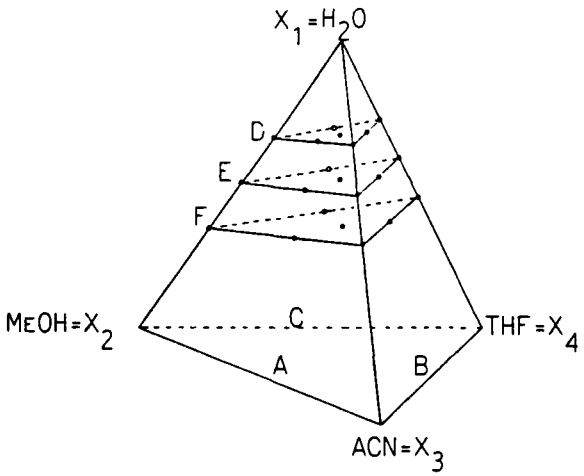

FIGURE 3.

Constrained quaternary mixture design. The sides of tetrahedron, A, B, C represent ternary systems; the cross-sections D, E, F represent iso-eluotropic quaternary systems.
The dots indicate individual mobile phase compositions at which retention data for all solutes are obtained.

because this more parsimonious model gave a slightly better fit. The factor space was constrained to the feasible region enclosed between the two triangular cross-sections D and F. In the iso-eluotropic triangle D the capacity factor of the last eluted compound, kmax, is smaller than about 20, while in the iso-eluotropic triangle F the capacity factor of the first eluted peak is greater than one. For the sake of clarity the feasible regions of the three ternary mobile phase systems A, B, and C will be compared with only three quaternary systems, D, E, and F (Fig. 3).

For the testsample we chose six benzene derivatives of varying polarity and functionality (Table 1) with the intention to have different selective interactions with the solvents. The capacity factors of these compounds were determined at the 21 eluent compositions shown in Fig. 3 and given in Table 2.
The sample compounds were injected individually to ensure positive peak identification. They were injected sequentially at the same mobile phase composition to avoid an undue number of column equilibrations. Therefore the experimental order was not randomised.

Experimental

The benzene derivatives were chemically pure ("zur synthese", Merck, Darmstadt, F.R.G.). Acetonitrile was of analytical grade (Merck, Darmstadt, F.R.G), methanol and tetrahydrofuran were of chromatographic quality (Baker Chemicals, and Merck respectively). Purified deionized water was used (Milli-Ro/Milli-Q, Millipore). The eluent mixtures were prepared volumetrically, filtered and degassed before use.

The HPLC apparatus was assembled from a Mini Pump and Pressure Monitor (LDC/Milton Roy), a Rheodyne 7125-047 injection valve, fitted with a 20 1 sample loop, a Model 220 dual channel fixed wavelength UV absorbance detector (254 nm) (Chromatronix) and a Model B40 recorder (Kipp Analytica).The column was a 20.0 *

TABLE 1

Compounds of the Testsample

1. Benzonitrile : C6H5-CN	4. 2-Phenylethanol : 2-C6H5-C2H4OH
2. Benzaldehyde : C6H5-CHO	5. Toluene : C6H5-CH3
3. Nitrobenzene : C6H5-NO2	6. p-Cresol : HO-C6H5-OCH3

TABLE 2

Eluent Compositions at the 21 Experimental Points of the Design of Fig. 3

Composition Number	Fractions MeOH	ACN	THF	Water
1	0.3000	0.0000	0.0000	0.7000
2	0.4500	0.0000	0.0000	0.5500
3	0.6000	0.0000	0.00000	.4000
4	0.0000	0.5150	0.00000	.4850
5	0.0000	0.3750	0.00000	.6250
6	0.0000	0.2350	0.00000	.7650
7	0.1500	0.1175	0.00000	.7325
8	0.2250	0.1875	0.00000	.5875
9	0.3000	0.2575	0.00000	.4425
10	0.0000	0.0000	0.48500	.5150
11	0.0000	0.0000	0.33750	.6625
12	0.0000	0.0000	0.19000	.8100
13	0.0000	0.2575	0.24250	.5000
14	0.0000	0.1875	0.16700	.6455
15	0.0000	0.1175	0.09500	.7875
16	0.1500	0.0000	0.09500	.7550
17	0.2250	0.0000	0.16880	.6062
18	0.3000	0.0000	0.24250	.4575
19	0.2000	0.1720	0.16200	.4660
20	0.1500	0.1250	0.11250	.6125
21	0.1000	0.0783	0.06330	.7584

4.0 mm I.D. stainless steel column packed with Nucleosil RP-8, particle size 5 μm, N = 3500. The flow rate was 1.07 ml/min. The dead time was measured as the first baseline distortion at every eluent composition.

Calculations were performed on the CDC 170/160 computer of the Groningen University Computing Centre, using programs written in Pascal, which are currently implemented for IBM PC as the Pareto Optimal Eluent Mixtures (POEM) package.

RESULTS AND DISCUSSION

The capacity factors of the six testcompounds measured at 21 mobile phase compositions are given in Table 3.
The capacity factors of Table 3 were used to estimate the regression coefficients of the quadratic model (eqn 3) for every compound. The mean coefficient of determination of the six models was equal to 0.98734, which means that the quadratic model explains approximately 97.5 per cent of the variability of the data and adequately describes the logarithm of the capacity factor as a function of the eluent composition. The minimal resolution, Rsmin, obtained for the separation of the six compounds, was predicted from the models for all mobile phase compositions of the feasible region using equation 2. This implies that the plate number remains constant for all solutes within the feasible region. This was not the case; the plate number varied with the solute used for its determination. Obviously this problem may be circumvented by using the separation factor instead of the resolution as a performance criterion. The value of the separation factor, however, is not a good criterion for the separation of a pair of peaks because its use takes no account of the effect of the capacity factor on the separation. Therefore it was decided to use a plate number of 3500, which is a very conservative estimate. Although this results in the prediction of minimal resolution values that are

TABLE 3

Capacity Factors of Benzene Derivatives at 21 Mobile Phase Compositions

Mobile Phase No.	Benzene Derivatives No. 1	2	3	4	5	6
1	6.08	6.51	7.35	4.08	15.22	4.70
2	2.23	1.99	3.04	1.72	5.78	1.85
3	1.03	0.97	1.44	0.82	2.41	0.86
4	1.69	1.45	2.03	0.96	3.03	1.20
5	2.77	2.19	3.64	1.40	6.16	1.92
6	9.23	7.15	12.45	5.25	23.15	12.25
7	5.57	4.28	7.63	3.02	14.26	4.37
8	2.55	2.15	3.51	1.66	6.32	2.05
9	1.24	1.11	1.66	0.88	2.63	0.98
10	1.19	1.04	1.54	0.77	2.50	1.33
11	2.74	2.06	4.34	1.64	8.12	3.80
12	7.16	4.86	14.54	4.34	--	12.47
13	1.13	1.01	1.45	0.77	2.41	--
14	2.51	2.03	3.81	1.57	6.97	2.82
15	5.46	3.93	8.89	3.23	20.47	6.61
16	5.97	4.75	11.12	4.54	24.89	10.22
17	2.54	2.03	4.69	1.92	8.74	3.62
18	1.08	0.98	2.01	0.96	3.17	1.26
19	0.99	0.86	1.42	0.83	2.46	1.03
20	--	1.83	3.49	1.50	6.67	2.59
21	--	5.85	9.67	3.89	15.51	7.30

Mobile Phase No.: see Table 2, Benzene derivative No.: see Table 1.

rather low, the comparison of the mobile phase systems remains valid because the plate number characterizes the column efficiency.

First the three ternary mobile phase systems, A, B and C (Fig.3) are considered. The response surfaces of Rsmin are shown in Figs. 4, a, b and c. For mixture A (water, ACN, MeOH) the solvent strength, expressed in kmax, ranges from 2.4 to 17.9, and the Rsmin varies from 0.0 to 1.5. The highest values of Rsmin are found at high solvent strength in the left upper corner of the response surface (Fig.4a). The range of kmax of

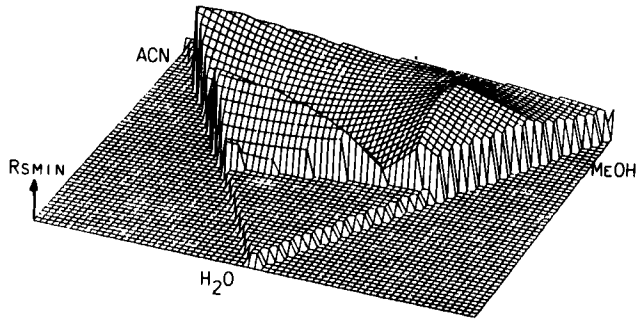

FIGURE 4A.

Plot of the minimal resolution, Rsmin, against eluent composition of the ternary mobile phase system A: water, acetonitrile, methanol.

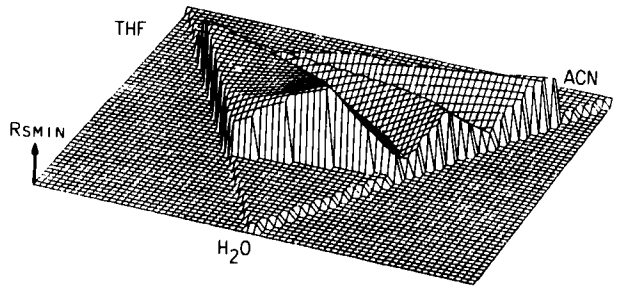

FIGURE 4B.

Plot of the minimal resolution, Rsmin, against eluent composition of the ternary mobile phase system B: water, tetrahydrofuran, acetonitrile.

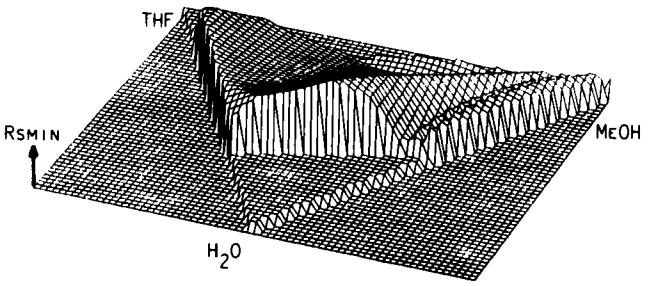

FIGURE 4C.

Plot of the minimal resolution, Rsmin, against eluent composition of the ternary mobile phase system C: water, tetrahydrofuran, methanol.

mixture B (water, THF, ACN) is from 2.4 to 25.5 and the Rsmin varies from 0.0 to 2.9, and the higher values of Rsmin are found on a ridge, that starts near the middle of the lower solvent strength boundary of the feasible region and descends leftwards to the higher solvent strength boundary (Fig.4b). In mixture C (water, THF, MeOH) the highest value of Rsmin, 2.0, lies on a similar ridge of the response surface, that descends from about the middle of the lower solvent strength boundary rightwards to the higher solvent strength boundary. Rsmin values ranging from 0.9 to 1.8 are found on a slope rising towards the THF-corner of the response surface (Fig.4c). The variation in the solvent strength is about the same as in the previous case and kmax ranges from 2.4 to 26.3. The three response surfaces of kmax of the ternary systems are not shown: they are smooth surfaces declining to the higher solvent strength boundary of the feasible region. These results demonstrate that the three ternary mobile phase systems span approximately the same range of solvent strengths. Their response surfaces of Rsmin differ considerably in shape and height of the maximum, as could be expected of mixtures consisting of different modifiers. Mixture A provides the lowest maximum of Rsmin, but a resolution of about 1.5 is attained in a short analysis time (kmax = 2.9). Mixtures B and C make higher resolutions possible, but at the cost of longer analysis times, because the higher values of Rsmin are attained at low solvent strength. The performances of the three ternary mobile phase systems with respect to resolution and analysis time are not easily evaluated by looking at the response surfaces of Rsmin and kmax, but can be compared easily by a glance at their MCDM plots (Fig.5). For any value of Rsmin up to 1.5 systems A, B and C provide the same resolution at the same analysis time. Up to Rsmin = 1.8, system B and C perform equally well, but resolutions higher than 1.8 can only be obtained by system B.

The response surfaces of Rsmin of the three quaternary iso-eluotropic mobile phase system, D, E and F (Fig.3), shown in Fig.6, a, b and c, are also quite different in shape and height.

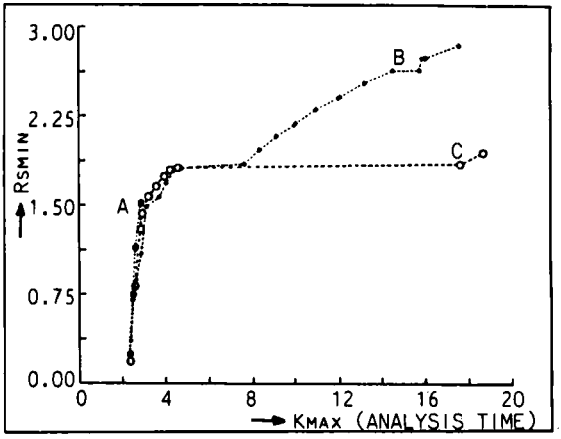

FIGURE 5.

Multi-Criteria Decision Making plots of the ternary mobile phase systems A, B and C. Analysis time (kmax) and eluent compositions for the maximal value of Rsmin are:
A: kmax = 2.9; water = 0.50, MeOH = 0.00, ACN = 0.50
B: kmax = 17.6; water = 0.78, ACN = 0.14, THF = 0.08
C: kmax = 18.6; water = 0.74, MeOH = 0.16, THF = 0.10

This great difference in shape was not expected, because the selectivity should remain constant if the ratio of the modifiers remains constant (9), which should lead to similarly shaped response surfaces. System D has the lowest solvent strength (kmax range: 15.3 - 25.5), and provides the highest values of Rsmin. Within this mixture triangle Rsmin varies from 0.0 to 2.9, and the highest values (1.0 - 2.9) are found on the obtuse ridge running upwards from the middle of the MeOH/H2O-THF/H2O side of the triangle to a point left of the middle of the ACN/H2O-THF/H2O side (Fig. 6a). The solvent strength of system E (Fig. 6b) is higher and also almost constant (range of kmax: 5.8 - 8.3). Values of Rsmin increase to about 1.3 on the ACN/H2O-MeOH/H2O side of the triangle, but the highest values of about 1.8 are found at a maximum located right of the middle very near the

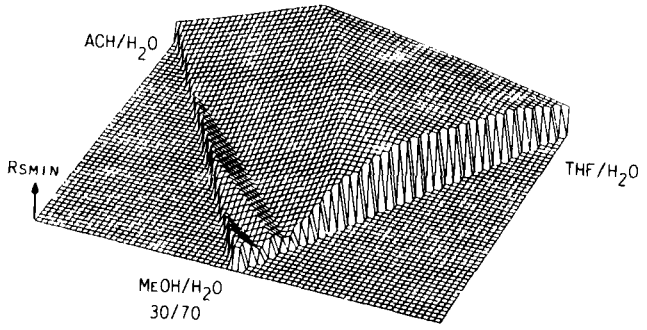

FIGURE 6A.

Plot of the minimal resolution, Rsmin, against eluent composition of the quaternary mobile phase system D with low solvent strength.

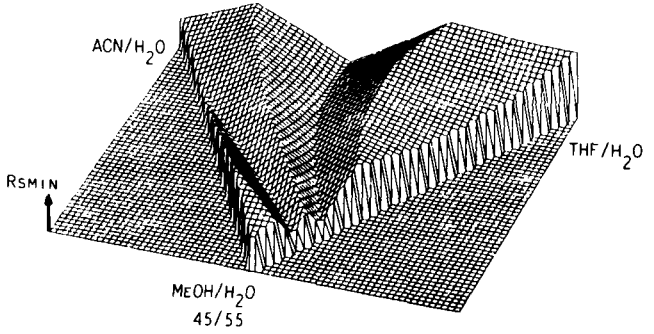

FIGURE 6B.

Plot of the minimal resolution, Rsmin, against eluent composition of the quaternary mobile phase system E with medium solvent strength.

ACN/H2O-THF/H2O side. System F (Fig. 6c) has the highest solvent strength (range of kmax: 2.4 -3.3) and the lowest maximal value of Rsmin, 1.5, which is found near the ACN/H2O vertex of the triangle. This value of Rsmin decreases gradually to 0.2 along a slope almost parallel to ACN/H2O-MeOH/H2O side of the triangle.

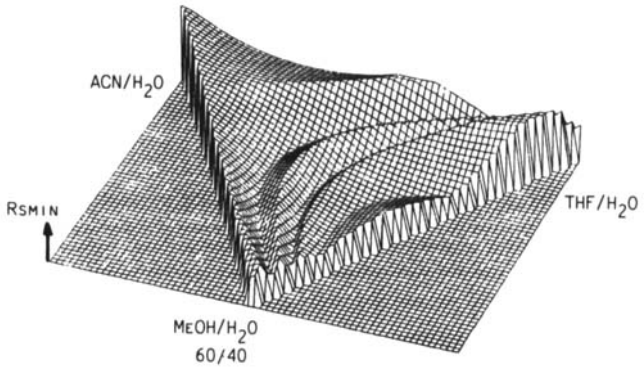

FIGURE 6C.

Plot of the minimal resolution, Rsmin, against eluent composition of the quaternary mobile phase system F with high solvent strength.

CONCLUSIONS

The shape of the MCDM plots of the quaternary iso-eluotropic (Fig. 7) and ternary (Fig.5) systems differs considerably. The chosen quaternary systems (D, E, F) have almost constant solvent strength, which causes the course of the MCDM plot to be almost parallel to Rsmin axis so that once an iso-eluotropic quaternary system has been chosen, an exchange between resolution and analysis time is not possible.

A Rsmin value up to 1.5 in the separation of this sample on the above mentioned column can be obtained by the three ternary mobile phase systems A, B and C and the quaternary mobile phase system F in the same analysis time, kmax = 2.9. For Rsmin values between 1.5 and 1.8 the ternary systems B and C give the best results. A Rsmin value of 1.8 can be obtained by both systems for kmax = 4.8; system E needs a longer analysis time of kmax = 6.9 for a maximal Rsmin value of 1.7, and system D needs a

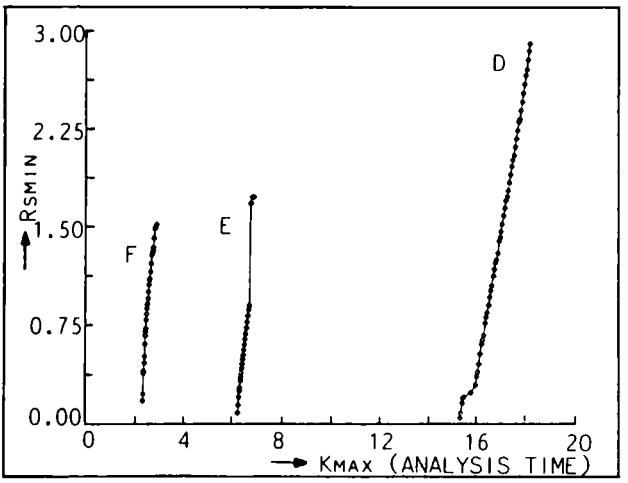

FIGURE 7.

Multi-Criteria Decision Making plots of the quaternary mobile phase systems D, E and F. Analysis time (kmax) and modifier concentrations for the maximal value of Rsmin are:
D: kmax = 18.3; MeOH = 0.00, ACN = 0.17, THF = 0.05
E: kmax = 6.9; MeOH = 0.02, ACN = 0.11, THF = 0.23
F: kmax = 2.9; MeOH = 0.00, ACN = 0.50, THF = 0.00

kmax value of 17.4 for a Rsmin value of 1.8. If higher values of Rsmin are desired, ternary system B or quaternary system D has to be used. For the separation of this sample with the ternary system B the gain in resolution can be quantitatively weighed against the loss of analysis time from the MCDM plot. Comparison of the MCDM plots of systems D, E and F suggests that the choice of the solvent strength also influences the maximal value of Rsmin that can be obtained.

If one wants to find the global maximum of the resolution in the shortest possible analysis time, a constrained quaternary design as shown in Fig. 3 should be used for which one MCDM plot could show the pay-off between resolution and analysis

time for the whole optimization area. Further research on this possibility is in progress.

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