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Correlation of Countercurrent Extraction with Countercurrent Chromatography in Aqueous Matrixes. An Improved Model

Tiing Yu,* Chia Shan Liang, and Sheng-Kang Luo

Department of Applied Chemistry, National Chiao Tung University, Hsinchu, Taiwan, Republic of China

A mathematical model was employed to simulate supercritical fluid extraction (SFE) efficiency in aqueous matrixes with supercritical fluid chromatography (SFC) data in a previous study. The SFE extraction vessel, i.e., the column for the SFC, was mathematically divided into limited layers. The analyte mass was uniformly distributed in the vessel before extraction. However, it changed when the fluid flowed through the aqueous sample and reached the column outlet. The mass redistribution as a function of the layer was computed using a countercurrent distribution approach. Afterward, each layer was considered to undergo a chromatographic process simultaneously. Each layer's chromatographic capacity factor and peak width were calculated using the true SFC experimental data, and the sum of all these peak distributions as a function of time gave the extraction efficiency. In this work, the mass redistribution was calculated through a chromatographic approach, which predicted the extraction recovery better than the previous approach. Both the previous SFE and the newly acquired liquid/liquid extraction data using a countercurrent chromatographic apparatus were examined to demonstrate the upgrading of the model using this new chromatographic approach. Significant improvements were observed, especially for analytes with small capacity factors. The simulation deviations came mainly from the fact that analyte molecules in the individual layers would shift away from Gaussian shapes that were assumed in the model.

Supercritical fluid extraction (SFE) has drawn a great deal of attention in solid sample preparation in recent years.[1−4] It also shows promise for extracting trace organic contaminants from water.[5−7] Proteins[8,9] and metal ions[10,11] were extracted by supercritical fluid CO_2 (SF CO_2) from aqueous solutions by using adequate surfactants and chelating agents. SFE techniques were also used to extract substances from pharmaceutical and food products.[12,13] SF CO_2 separates from extracted substances at the collection conditions and thus saves the labor of concentration procedures. In addition, since varying the temperature and pressure may change the solvent strength of SF CO_2, SFE furnishes more versatility with using conventional liquid extraction.

Since SFE and supercritical fluid chromatography (SFC) processes share some similarities, research has been performed to relate SFE with SFC in solid matrixes,[14,15] even though the SFE process was recognized as being much more complicated.[16,17] We proposed a model[18] recently to correlate SFE with SFC in aqueous matrixes. It enables the prediction of analyte extraction efficiency as a function of extraction time using the analyte capacity factor and peak standard deviation obtained by SFC. Since SFC operations are more straightforward than SFE operations, SFE optimizations may be more easily accomplished using the model. A countercurrent distribution (CCD) approach was employed in the previously proposed model to calculate analyte mass distribution in the extraction vessel as part of the simulation procedures. The CCD approach departed from reality because it assumed a thermodynamic equilibrium, which was not truly followed by the extraction process in this study. Even so, the simulated data agreed with the experimental data very well for analytes of large capacity factors while the deviation increased as the capacity factors became smaller. In this study, the analyte mass distribution was solved using a chromatographic approach, which mirrored the extraction process better than the CCD approach. The SFC

* Corresponding author: (tel) (886)-3-573-1673; (fax) (886)-3−572−3764; (e-mail) tyu@cc.nctu.edu.tw.

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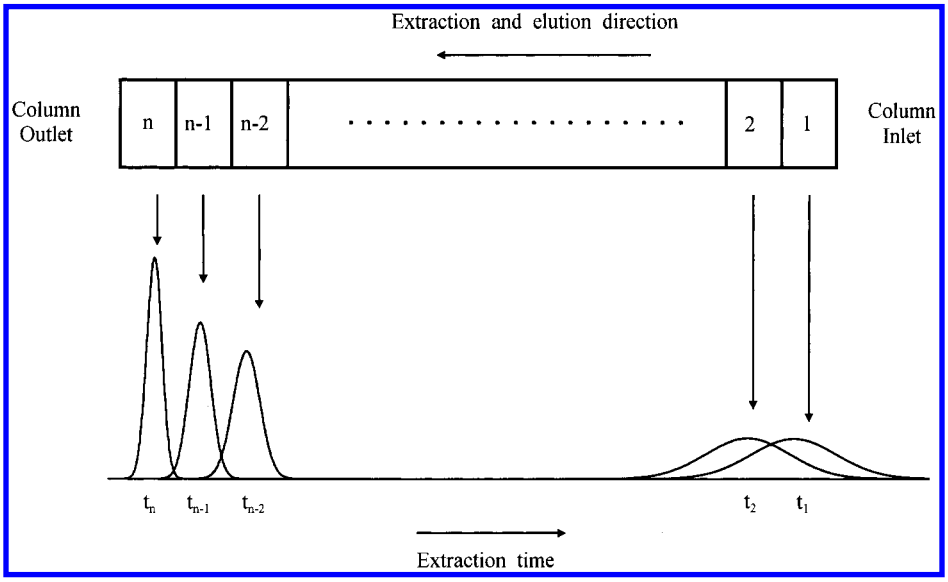

Figure 1. Theoretical model for the correlation of extraction with chromatography. The extraction vessel (column) was divided into *n* layers, and the analyte was uniformly distributed. During extraction, analyte molecules in all layers were assumed to undergo chromatography and form Gaussian peaks all the way to the outlet. Accordingly, layers close to the column outlet, traveling shorter distances during extraction, gave relatively sharp peaks while those close to the column inlet gave relatively broad peaks.

data obtained previously[18] were recalculated with this new model and compared with the SFE experimental data. In addition, some liquid/liquid extraction data were obtained with the same countercurrent apparatus and simulated by using this new model. The results demonstrated that this modified approach improved the simulation considerably.

THEORY

A model was developed previously[18] to predict SFE extraction recovery curves using chromatographic data. Basically, the simulation involved two steps: mass redistribution calculation using a CCD approach and correlation of extraction with chromatography. The second step, i.e., the correlation of extraction with chromatography, remains unchanged while the first step, i.e., the mass redistribution calculation using the CCD approach, is replaced by a chromatographic (CH) approach in this study. The correlation of extraction with chromatography and the mass redistribution using the CH approach will be thoroughly elucidated to furnish the complete simulation in this work while the CCD approach will be briefly described for comparison.

Correlation of Extraction with Chromatography. The extraction process in liquid matrixes involving partitioning of analyte molecules between the extractant and the matrix is analogous to the chromatographic process in liquid stationary phase. One of the differences comes from the fact that a sample plug is introduced to the column inlet for a chromatographic process while the analyte molecules are evenly distributed in the vessel for an extraction process. Assume the extraction vessel (i.e., the chromatographic column) is equally divided into *n* layers, as shown in Figure 1. During extraction, analyte molecules in each layer are considered experiencing individual chromatographic elution simultaneously. The elution time for analyte molecules located at the inlet side of the vessel is relatively longer than that at the outlet side, which therefore results in relatively broader "peaks" coming from the vessel. Prediction of extraction efficiency can be accomplished if all these peak shapes and retention times can be derived using the true chromatographic data. A Gaussian distribution of the experimental chromatographic peak can be expressed as

$$y(t) = h_c e^{-((t-t_{R_c})^2/2\sigma_c^2)} \quad (1)$$

where $y(t)$ is the population under the Gaussian peak as a function of t, h_c, the peak height, t_{R_c}, the peak retention time, and σ_c, the standard deviation. Assuming Gaussian shapes of all the "imaginary" peaks due to the individual layers, the peak distributions can be expressed as

$$y_i(t) = h_i e^{-((t-t_{R_i})^2/2\sigma_i^2)} \qquad i = 1, ..., n \quad (2)$$

where $y_i(t)$ represents the analyte mass under the peaks as a function of time t, h_i, the peak height, t_{R_i}, the peak retention time, and σ_i, the standard deviation. The column efficiency, H, is defined as

$$H = \sigma_c^2/L \quad (3)$$

where L is the column length, i.e., the elution distance for the true chromatographic solute plug. If H is constant from column inlet to outlet, σ_i for each layer should be related to σ_c by the following equation:

$$\sigma_i^2 = (L_i/L)\sigma_c^2 \qquad i = 1, ..., n \quad (4)$$

where L_i, the elution distance for analyte molecules in layer i, i.e., the distance from the column outlet to the head of layer i, is given by

$$L_i = L(1 - (i - 1)/n) \qquad i = 1, ..., n \qquad (5)$$

Apparently L_1 equals L, the column length, because its corresponding layer locates right at the column inlet that mimics the sample plug injection in a chromatographic process well. Combining eqs 4 and 5 yields

$$\sigma_i^2 = \sigma_c^2(1 - (i - 1)/n) \qquad i = 1, ..., n \qquad (6)$$

Retention time for each "imaginary" peak is linearly related to the elution distance from the layer head to the vessel outlet:

$$t_{R_i} = t_{R_c}(1 - (i - 1)/n) \qquad i = 1, ..., n \qquad (7)$$

The standard deviation, σ_i, for the individual peak can be expressed as

$$\sigma_i = A_i/h_i\sqrt{2\pi} \qquad i = 1, ..., n \qquad (8)$$

where A_i are the individual peak areas and h_i, the peak heights. If analyte molecules are distributed uniformly in the column, the area A_i under individual peaks should be equal, and can be expressed as

$$A_c = A_1 = A_2 = ... = A_n \qquad (9)$$

where A_c stands for the peak area of the true chromatography. Since A_c, h_c, and t_{R_c} can be acquired through the real chromatographic experiment, the standard deviation, σ_c, can be calculated using eq 8, only by changing the index i's into c's in the equation. Parameters including standard deviation, retention time, and peak height for each layer can then be computed using eqs 6−9. All these values are then substituted into eq 2 to calculate $y_i(t)$ for the individual layers. Extraction recovery can thus be calculated by taking the quotient of the summation of $y_i(t)$ divided by the total area as a function of time:

$$r(t) = \sum_i y_i(t) / \sum_i A_i \qquad i = 1, ..., n \qquad (10)$$

Recall that the simulation is made possible by assuming analyte molecules in each layer are undergoing chromatography at the same time. It may not come this way unless the mobile phase also uniformly distributes in the column in the meantime. In other words, eq 10 becomes effective only when the solvent front reaches the column outlet. However, once the solvent front moves from the column inlet to outlet, the mass (or concentration) in each layer no longer stays uniform as assumed before. Accordingly, a mass redistribution calculation must be executed before the above simulation can be carried out.

Mass Redistribution by Countercurrent Distribution Approach. The mass (or concentration) gradient formed when the solvent moved from the column inlet to the outlet was estimated by a CCD approach in our previous study. Initially, the CCD operation was used to fabricate chromatographic process by adopting the concept of stepwise stage extraction,[19,20] such as occurs in a series of separation funnels. Two presuppositions are made for the CCD approach: true equilibrium is reached in each discrete stage, and longitudinal diffusion of analyte is prevented. While a complete derivation can be found in our previous study,[18] the analyte quantity was calculated according to the following equation:

$$Q_i' = Q_i \frac{k'}{1 + k'} + Q_{i-1}\frac{1}{1 + k'} \qquad (11)$$

where Q_i' is the total analyte quantity remaining in both mobile and stationary phases of the ith layer after each CCD step, Q_i is the total analyte quantity in the ith layer before each CCD step, and Q_{i-1} is the total analyte quantity in the $(i - 1)$th layer before each CCD step. Iterative calculations of eq 11 using a computer program gave the analyte mass distribution when the solvent reached the outlet. Once the analyte mass redistribution was obtained, an adjustment was made by multiplying the term $y_i(t)$ in eq 10 by the analyte mass fraction to calculate the extraction recovery curve.

Mass Redistribution by Chromatographic Approach. The CCD approach, although providing a reasonable calculation for extraction efficiency, did not really reflect the nature of the chromatographic process proposed in this mathematical model. We then realized that the same concept described in the Correlation of Extraction with Chromatography section can be adopted to estimate the analyte mass distribution as the solvent front reached the column outlet. The extraction vessel is again divided into limited, n layers, shown in Figure 2. Analytes in each layer start the chromatography process as described above. Only the starting times are different for individual layers, depending on the location of the layer. Layers at the column inlet side undergo chromatography relatively earlier and the elution times are relatively longer, resulting in broader peaks. However, as the layer locates gradually closer to the column outlet, the elution time gets shorter during the interval when the solvent front flows from the column inlet to the outlet. The peak width, as shown in Figure 2, becomes smaller and smaller near the outlet. As long as the peak locations and their corresponding widths can be determined, the integration of the area under the peaks gives the mass distribution as a function of the layer number.

Notice that we will use j as the index instead of i for all the arrays in this section in order to distinguish from the equations derived in the above sections. Whenever the solvent front reaches the head of a layer, the chromatography begins for the analyte molecules in this particular layer. The elution time, t_{E_j}, for each layer is defined as the time span when the solvent front migrates from the head of the individual layers to the column outlet. t_{E_j} for each layer is related to t_s, the time for the solvent sweeping the whole extraction column, in the following equation:

$$t_{E_j} = t_s(1 - (j - 1)/n) \qquad j = 1, ..., n \qquad (12)$$

t_s can be determined experimentally by the solvent front marker.

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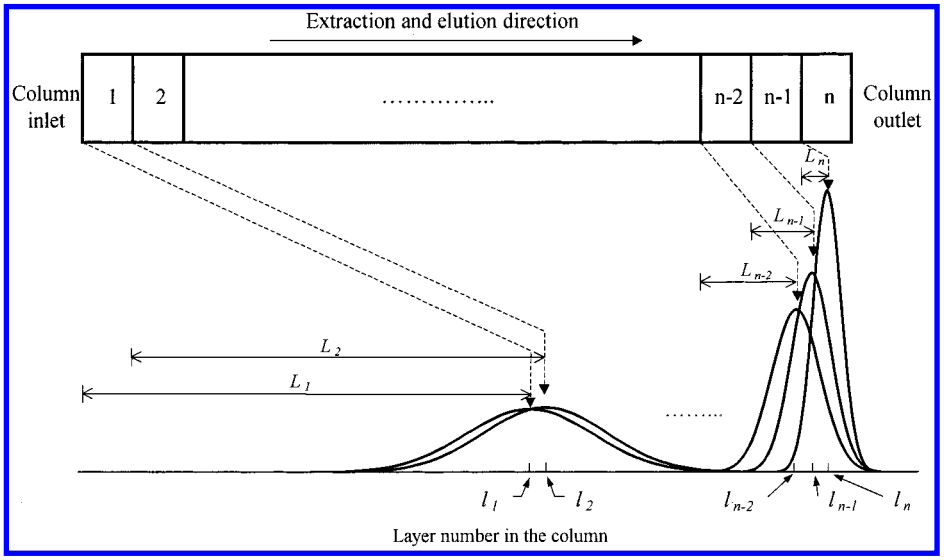

Figure 2. Chromatographic approach to calculate the mass redistribution in the vessel after the extraction solvent reaching the vessel outlet. During extraction, each layer was considered undergoing chromatographic process. The elution distance, L_j, for individual layer was dependent on where it was located. Analyte molecules at the vessel inlet side, traveling longer distances, produced broader Gaussian peaks; while those at the outlet side produced sharper peaks. The peak standard deviations, σ_j, and locations, l_j, could be derived from the chromatographic data; therefore the mass distribution in the column could be calculated by adding up the masses under all the peaks at each layer.

The average linear rate of analyte migration, $\bar{v}$, is obtained by

$$\bar{v} = n/t_{R_c} \tag{13}$$

The peak location, l_j, in terms of layer number when the solvent reaches the column outlet can then be calculated by the following equation:

$$l_j = (j - 1) + \bar{v}t_{E_j} \qquad j = 1, ..., n \tag{14}$$

The elution distance, L_j, i.e., the distance from the head of the layer to the peak in the unit of layer number can be expressed in the following equation:

$$L_j = \bar{v}t_{E_j} \qquad j = 1, ..., n \tag{15}$$

Since L_j in eq 15 is in the unit of layer number, the column length L in eq 4 should be substituted by n, the total layer number in the column, to calculate the standard deviation, σ_j:

$$\sigma_j^2 = \frac{L_j}{L}\sigma_c^2 = \frac{\bar{v}t_{E_j}}{n}\sigma_c^2 \qquad j = 1, ..., n \tag{16}$$

Combining eqs 12, 13, and 16 yields

$$\sigma_j^2 = \frac{n - j + 1}{n}\frac{t_s}{t_{R_c}}\sigma_c^2 \qquad j = 1, ..., n \tag{17}$$

Assuming Gaussian peaks formed from all the layers in the column, the mass population as a function of time can be expressed

$$y_j(t) = h_j e^{-((t-t_{E_j})^2/2\sigma_j^2)} \qquad j = 1, ..., n \tag{18}$$

Since we want to calculate the mass redistribution as a function of layer number instead of as a function of time, we need first to explore the relation between the layer number and extraction time in order to modify eq 18. The Gaussian distributions as a function of layer, $y_j(l)$, can be related to those as a function of time, $y_j(t)$, in the following:

$$y_j(l)\,dl = y_j(t)\,dt \qquad j = 1, ..., n \tag{19}$$

$y_j(t)$ obtained from eq 19 is substituted into eq 18 to yield

$$y_j(l) = h_j e^{-((t-t_{E_j})^2/2\sigma_j^2)}\,dt/dl \qquad j = 1, ..., n \tag{20}$$

The extraction time t can be related to the peak position l as

$$t = l/\bar{v} \tag{21}$$

Take the derivative of both sides of the equation to obtain

$$dt/dl = 1/\bar{v} \tag{22}$$

Substituting t, dt/dl, and t_{E_j} from eqs 21, 22, and 12, respectively, into eq 20 to yield

$$y_j(l) = (h_j/\bar{v})e^{-((l-l_j)/2(\bar{v}\sigma_j^2)} \qquad j = 1, ..., n \tag{23}$$

All the parameters h_j, $\bar{v}$, l_j, and σ_j in the above equation can be calculated from the peak retention time, peak height, and the standard deviation of the true experimental chromatographic run using eqs 8, 13, 14, and 17. Accordingly, the analyte mass as a function of layer number, $y_j(l)$, for individual layers using the CH approach, can be calculated using eq 23. Integration of areas under all the Gaussian peaks at each layer renders the mass redistribution of the analyte as a function of layer number in the column

when the solvent migrates from the column inlet to the outlet. Once the analyte mass redistribution is obtained, again an adjustment is made by multiplying the term $y_j(t)$ in eq 10 by the analyte mass fraction to calculate the extraction recovery curve.

EXPERIMENTAL SECTION

Ethyl acetate, methanol, and *n*-hexane were all HPLC-grade, purchased from Mallinckrodt (Paris, KY). Naphthalene (+99%) was obtained from Sigma (St. Louis, MO), benzaldehyde (+99%) from Aldrich (Milwaukee, WI), 2-naphthol (+99%) from Riedel-de Haen (Seelze, Germany), and phenol (99.5%) from Merck (Darmstadt, Germany). The preparation for the solvent systems was done by mixing liquids in a separatory funnel in a conventional manner for countercurrent chromatography (CCC). Once the two phases were separated, the extraction sample solutions were prepared by doping the analyte compound in the stationary phase. The concentration of all the solutions for extraction was 10 ppm, while the sample concentration for chromatography was 1000 ppm. Naphthalene was added to the sample solutions to work as the solvent front marker.

The apparatus used for extraction and chromatography was a slow-speed rotating countercurrent chromatograph.[21] This laboratory-made assembly is described in more detail elsewhere.[22,23] Refer to our previous study for setup details. Minor modifications were made to adapt this liquid/liquid extraction and chromatography system. A 36-mL sample solution aliquot was first injected to the column. The mobile phase was then pumped in to undergo an extraction process. When the extraction was finished, a sample solution (100 μL) was injected to start the chromatography. The flow rates for extraction and chromatography were all kept at 0.8 mL/min.

RESULTS AND DISCUSSION

Both the supercritical fluid/liquid chromatography and extraction (SF/liquid) system and the liquid/liquid chromatography and extraction (liquid/liquid) system were studied in this work to investigate the correlation between chromatography and extraction. These two systems will be examined separately, and then a comparison between them will be given.

Liquid/Liquid System. All computations were performed using 900 layers, the same as in the previous study.[18] Experimental data for benzaldehyde and phenol were used to calculate mass distribution curves by CCD and CH methods. The results are illustrated in Figure 3. Before the solvent front just made contact with the sample solution, the analyte mass was evenly dispersed, shown as curve 1 in the figure. After the extractant solvent flowed through the sample solution, the analyte mass distribution was changed. The CCD approach assumed that thermodynamic equilibrium was reached at each layer while the solvent flowed through. This would not happen in a true extraction or chromatographic process. Curve 3 (CH approach) with a less steep slope than curve 2 (CCD approach) at the rising part reflects the dynamic property of chromatography. Notice that curve 3 in Figure 3 drops out of the bound of 900 layers. In reality, the solute molecules of course cannot move faster than the solvent front.

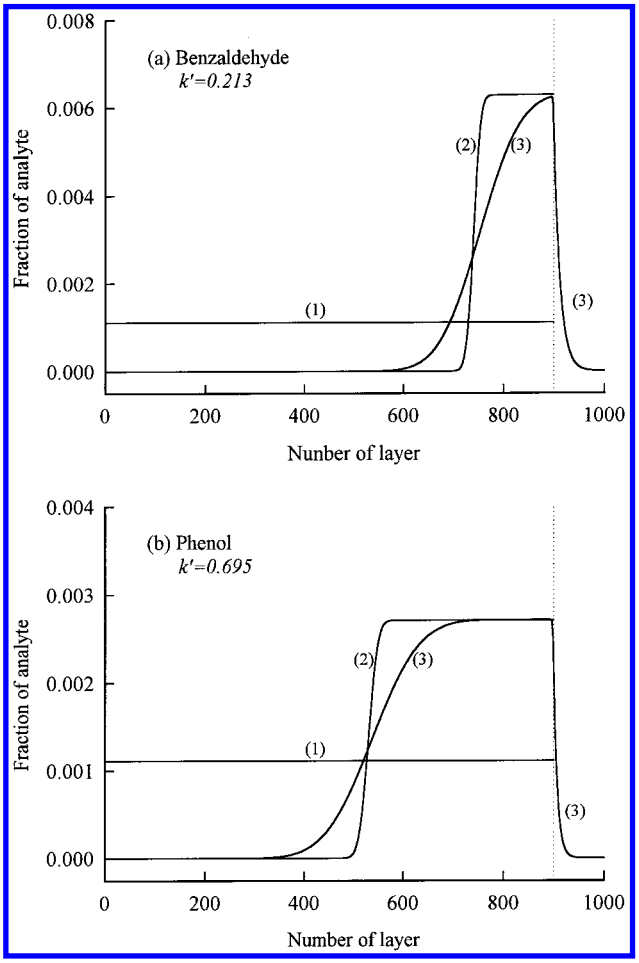

Figure 3. Simulated mass redistribution curves, using CCD and CH approaches, for samples benzaldehyde (k' = 0.213) (a) and phenol (k' =0.695) (b) of the liquid/liquid system. Curve 1, analyte mass distribution before the solvent entering the column; curve 2, analyte mass distribution after the solvent front reached the column outlet using the CCD approach; curve 3, analyte mass distribution after the solvent front reached the column outlet using the CH approach.

This happened because finite layers were assumed and the layer thickness was essentially ignored. Accordingly the tailing of several simulated Gaussian peaks near the column outlet may appear beyond the column outlet. Fortunately, this small portion did not influence the results to any significance.

Four experiments were performed mainly for acquiring cases with different capacity factors. The deviation between the predicted and the experimental recoveries is plotted as a function of the experimental recovery using both approaches, shown in Figure 4. It clearly demonstrates that a substantial improvement is observed for analyte with a small capacity factor. For example, ~35% improvement was observed when the experimental recovery was at 0.6 for benzaldehyde (k' = 0.213). The improvement gradually decreases as k' value becomes greater.

SF/Liquid System. Our previous work on the correlation between extraction and chromatography involved using SF CO_2 in aqueous matrixes. Refer to our previous study for experimental detail. The predicted data were then all obtained using the CCD approach. In fact, the discrepancies observed previously incited us to improve the simulation by introducing the CH approach. Accordingly, the deviations were examined for the previous

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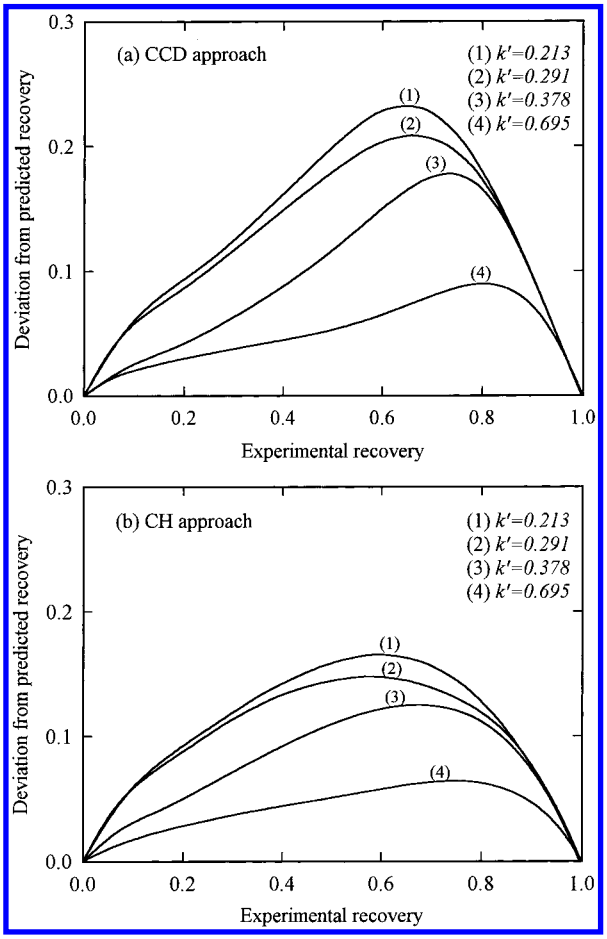

Figure 4. Deviation between the simulated and the experimental recovery curves as a function of the experimental recovery for the liquid/liquid system using the CCD approach (a) and the CH approach (b). Experimental conditions: (for $k' = 0.213$) benzaldehyde, mobile phase is the upper phase of hexane/ethyl acetate/methanol/water (7:3:5:5); (for $k' = 0.291$) 2-naphthol, mobile phase is the upper phase of hexane/ethyl acetate/methanol/water (7:3:5:5); (for $k' = 0.378$) 2-naphthol, mobile phase is the upper phase of hexane/ethyl acetate/methanol/water (8:2:5:5); (for $k' = 0.695$) phenol, mobile phase is the upper phase of hexane/ethyl acetate/methanol/water (7:3:5:5).

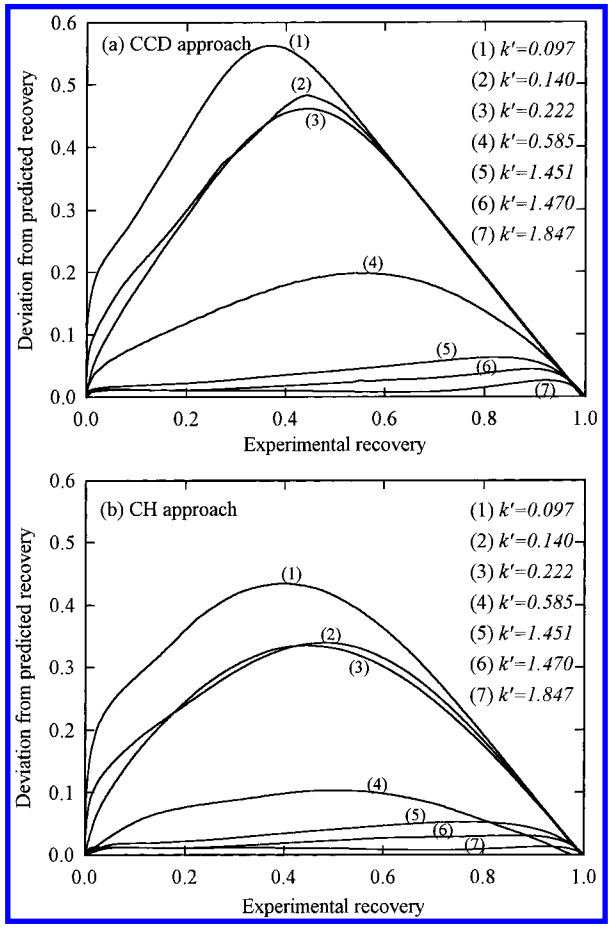

Figure 5. Deviation between the simulated and the experimental recovery curves as a function of the experimental recovery for the SF/liquid system using the CCD approach (a) and the CH approach (b). Experimental conditions: (for $k' = 0.097$) acetophenone, 130 bar, 50 °C; (for $k' = 0.140$) benzaldehyde, 90 bar, 43 °C; (for $k' = 0.222$) benzaldehyde, 100 bar, 50 °C; (for $k' = 0.585$) benzaldehyde, 100 bar, 55 °C; (for $k' = 1.451$) 2-naphthol, 130 bar, 50 °C; (for $k' = 1.470$) *m*-cresol, 130 bar, 50 °C; (for $k' = 1.847$) 2-naphthol, 100 bar, 40 °C.

system using both CCD and CH approaches, shown in Figure 5. Apparent improvements were also perceived. Again, the results using the CH approach prevailed over those using the CCD approach.

Liquid/Liquid System versus SF/Liquid System. Although experiments with the same k' values for both systems were not performed, one can still easily recognize that the deviations for the liquid/liquid system are smaller than those for the SF/liquid system no matter which approach was used. When a small sample plug is injected from the column inlet in a normal chromatographic run, the analyte molecules undergo thousands of transfers between the mobile and stationary phases during the elution. The random residence time of molecules in the two phases eventually creates a distribution similar to a Gaussian curve if the column is not overloaded. The band breadth increases as it moves down in the column because more time is allowed for spreading due to this transfer process and longitudinal diffusion in which analyte molecules diffuse from the concentrated center to the more dilute regions ahead of and behind the band center. Recall our basic presupposition: the extraction vessel was evenly divided into finite layers and each layer underwent chromatography simultaneously. Look more closely at how solute molecules in an independent layer actually respond during extraction. Imagine a solute plug migrates down in the vessel. Its mass (or concentration) would seem to form a Gaussian distribution gradually, according to the two basic processes just described. However, this sample plug was not alone when moving down the vessel during extraction. Instead, molecules in the plug were actually surrounded by other solute molecules of neighboring layers. Considering the high-stationary and mobile-phase volume in the CCC column sample overloading should not occur; therefore, the mass-transfer process would stay the same to result in Gaussian shapes for molecules in the individual layers. On the other hand, the longitudinal diffusion should no longer follow the general behavior of a chromatographic process in which diffusion occurs parallel and antiparallel to the flow direction with equal magnitudes. The actual direction and the magnitude of analyte molecules should depend on the concentration gradient that they came upon locally. For example, the simulated curve in Figure 3 revealed a concentration plateau at the column outlet portion. The solute longitudinal diffusion in this region might be highly reduced over predicted.

This apparently deviated from what would have happened for the chromatographic process. Furthermore, a large back-diffusion toward the inlet was expected because of the mass accumulation at the outlet. The more the longitudinal diffusion deviated from the chromatographic process, the worse the prediction would be. Since the solute diffusion in SF CO_2 is usually 1−2 orders faster than in liquids, indeed more pronounced deviations have been observed in the SF/liquid system. In either the liquid/liquid or SF/liquid system, higher prediction errors are noticed for cases with smaller capacity factors. As can be seen in Figure 3, the concentration accumulated very quickly at the outlet portion for analyte with a small k' (0.213) value compared with a large k' (0.695) value. Due to the large concentration gradient, the longitudinal diffusion with a large magnitude toward the vessel inlet direction would strongly spoil the proposed Gaussian shapes for individual layers, therefore resulting in greater error.

CONCLUSIONS

Correlation between chromatography and extraction in aqueous matrixes using the CCC apparatus has been studied. The extraction vessel was evenly divided into finite layers. The extraction process was considered as simultaneous chromatographic processes for individual layers. The analyte molecules in individual layers were assumed to be maintaining Gaussian distributions all the way through the extraction. The peak widths and capacity factors of all the Gaussian peaks were calculated using the real chromatographic data. The accumulation of the peak distributions as a function of time furnished the recovery curve for the extraction. The simulation course also involved calculation for analyte mass redistribution while the solvent front flowed through the aqueous solution. The CH approach used in this study has been proved superior to the previously proposed CCD approach for both liquid/liquid and SF/liquid systems. The predicted curves matched the experimental data very well for analytes with larger capacity factors while the deviation became gradually greater with the decreasing capacity factor. The deviation occurred mainly due to the situation that the chromatographic peaks for the individual layers departed from perfect Gaussian shapes as proposed. Any experimental conditions that enhanced this departure would expand the deviation.

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