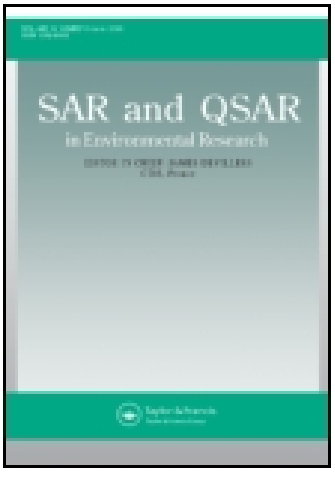


SAR and QSAR in Environmental Research

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsar20

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Published online: 04 Dec 2010.

To cite this article: X. R. Xia, R. E. Baynes, N. A. Monteiro-Riviere & J. E. Riviere (2007) A system coefficient approach for quantitative assessment of the solvent effects on membrane absorption from chemical mixtures, SAR and QSAR in Environmental Research, 18:5-6, 579-593, DOI: 10.1080/10629360701428540

To link to this article: http://dx.doi.org/10.1080/10629360701428540

*SAR and QSAR in Environmental Research*,
Vol. 18, Nos. 5–6, July–September 2007, 579–593

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# A system coefficient approach for quantitative assessment of the solvent effects on membrane absorption from chemical mixtures

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(*Received 27 August 2006; in final form 7 January 2007*)

A system coefficient approach is proposed for quantitative assessment of the solvent effects on membrane absorption from chemical mixtures. The complicated molecular interactions are dissected into basic molecular interaction forces via Abraham's linear solvation energy relationship (LSER). The molecular interaction strengths of a chemical are represented by a set of solute descriptors, while those of a membrane/chemical mixture system are represented by a set of system coefficients. The system coefficients can be determined by using a set of probe compounds with known solute descriptors. Polydimethylsiloxane (PDMS) membrane-coated fibres and 32 probe compounds were used to demonstrate the proposed approach. When a solvent was added into the chemical mixture, the system coefficients were altered and detected by the system coefficient approach. The system coefficients of the PDMS/water system were $(0.09, 0.49, -1.11, -2.36, -3.78, 3.50)$. When 25% ethanol was added into the PDMS/water system, the system coefficients were altered significantly $(0.38, 0.41, -1.18, -2.07, -3.40, 2.81)$; and the solvent effect was quantitatively described by the changes in the system coefficients $(0.29, -0.08, -0.07, 0.29, 0.38, -0.69)$. The LSER model adequately described the experimental data with a correlation coefficient ($r^2$) of 0.995 and $F$-value of 1056 with $p$-value less than 0.0001.

*Keywords:* Membrane absorption; Chemical mixtures; Solvent effects; System coefficient approach; Solute descriptors

## 1. Introduction

The absorption of drugs, cosmetics and toxic chemicals through biological membranes usually involves complex chemical mixtures. However, the data used in most prediction models are based on experimental data for individual chemicals because very limited experimental data are available for chemical mixtures [1–3]. The behaviour of the chemicals in the mixtures may differ considerably from that observed for individual

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*SAR and QSAR in Environmental Research*
ISSN 1062-936X print/ISSN 1029-046X online © 2007 Taylor & Francis
DOI: 10.1080/10629360701428540

chemicals [3]. While it is frequently difficult to assess the absorption of individual chemicals, it is challenging to quantitatively assess the absorption from chemical mixtures. This challenge has remained unmet without a clear framework nor a fundamental methodology [4]. Mechanistic combinations of the components in the chemical mixture were studied to identify possible mixture effects [5]. It seems formidable to study thousands of chemicals and millions of their mechanistic combinations [6, 7]. This problem is likely to become more serious with increasing number of chemicals required to be evaluated. Fundamental methodologies should be developed to study membrane absorption from mixtures.

Quantitative structure-activity relationships (QSARs) were developed to describe the membrane absorption of individual chemicals [8]. It is confirmed that lipophilicity and hydrogen bonding play important roles in controlling the permeability of the individual chemicals. Although the empirical models such as Potts and Guy's model for skin absorption are simple and applicable, the molecular descriptor based models can provide critical information on the molecular interactions of the absorption system [8, 9]. The linear solvation energy relationship (LSER) developed by Abraham has been used widely to describe the absorption of chemicals [10, 11]. The solvation property of a chemical was described by five solute descriptors. Each of the solute descriptors represents the relative strengths of a specific type of molecular interactions, while the corresponding regression coefficient represents the molecular interaction properties of the absorption system. When a change (e.g., solvent is added into the chemical mixture) occurs in the absorption system, its system coefficients will be altered. Therefore, the changes in the system coefficients can be used to study the effects of the chemical mixtures. Based on this principle, a system coefficient approach is proposed in this paper to quantitatively assess the mixture effects in membrane absorption from chemical mixtures.

Polydimethylsiloxane (PDMS) has been used widely as a barrier membrane for drug and chemical absorption or release studies [12–14]. We have developed a membrane-coated fibre (MCF) technique to study membrane absorption of chemicals [15, 16]. In the MCF technique, a polymer membrane coated onto a fibre is used as the absorption membrane to determine the membrane/solvent partition coefficients of chemicals. The MCF technique integrated the membrane absorption and quantitative analysis into one step and fully utilized the separation power of the automatic chromatographic instruments (GC or HPLC). It completely eliminates the emulsion problem and the other error sources associated with sample treatment and handling in water/solvent systems [17]. These features allow the MCF technique to have greater sensitivity, accuracy and high throughput in the quantitative assessment of the mixture effects. In this article, the principle and feasibility of the proposed approach were demonstrated by using 32 probe compounds and PDMS membrane-coated fibres. The system coefficient approach was used to study the solvent effects on the PDMS absorption of chemicals. The mixture effects modulated by different molecular interactions were discussed.

## 2. Model development

In the system coefficients approach, a chemical mixture is treated as a composition of a medium and other minor or trace chemicals. The medium is composed of the major components that dominate the physicochemical properties, while the minor or trace

components will not significantly alter the physicochemical properties of the chemical mixture. When a membrane is exposed to the chemical mixture, the membrane and the medium of the chemical mixture form an absorption system. The physical-chemical behaviour of a given chemical in the absorption system is governed by the relative molecular interactions of the chemical with the membrane and the medium.

The molecular interaction properties of a chemical are described by a set of effective solute descriptors [$R\ \pi\ \alpha\ \beta\ V$], while those of the absorption system (e.g. skin/chemical mixture) are described by a set of system coefficients [$r\ s\ a\ b\ v$]. A free energy related specific property ($SP$) can be correlated with the solute descriptors of the chemical and the system coefficients of the absorption system via the LSER equation [10]:

$$\log SP = c + rR + s\pi + a\alpha + b\beta + vV \quad (1)$$

where $\log SP$ is a specific free energy related property to be studied, such as permeability or partition coefficient; $R$ is an excess molar refraction representing the molecular force of lone-pair electrons; $\pi$ is the effective dipolarity and polarizability of the chemical; $\alpha$ is the effective H-bond acidity, a summation of the acidity from all H-bonds of the chemical; $\beta$ is the effective H-bond basicity, a summation of the basicity from all H-bonds of the chemical; and $V$ is the McGowan characteristic volume that mainly represents London dispersion. The solute descriptors, [$R\ \pi\ \alpha\ \beta\ V$], are characteristic parameters of the chemical. Their values will not change when the chemical is transferred from one medium system to another. Each of the solute descriptors represents the relative strength of a specific type of molecular forces of the chemical.

The system coefficients [$r\ s\ a\ b\ v$] are characteristic parameters of the absorption system. Their values will not change from one chemical to another. Each of the system coefficients represents the relative strength of a specific type of molecular forces of the absorption system: $c$ is a regression constant; can be treated as a system coefficient since it is related to the specific property of the system; $r$ represents the tendency of the system to interact with chemicals through $\pi^*$ and $n$-electron pairs; $s$ represents the tendency of the system to interact with dipolar/polarizable chemicals; $a$ is a measure of the H-bond basicity of the system, which describes the tendency of the system to interact with the H-bond acidity of the chemical; $b$ is a measure of the H-bond acidity of the system, which describes the tendency of the system to interact with the H-bond basicity of the chemical; $v$ is a combination of exothermic dispersion forces that make positive contributions; it mainly measures the hydrophobicity of the system.

### 2.1 *Determination of the system coefficients*

The system coefficients are properties of the absorption system; they will not change with minor or trace chemicals in composition or proportion. Therefore, the system coefficients can be detected by using a set of probe compounds with known solute descriptors. When a probe compound is added into the chemical mixture in trace concentration not affecting the system coefficients, a physicochemical parameter is measured experimentally, e.g. the partition coefficient of the probe compound ($\log K_{p/m}$) between the permeation membrane (p) and the chemical mixture (m). The $\log K_{p/m}$ value of the compound can be scaled into the solute descriptors of the

compound by the LSER equation ($\log SP = \log K_{p/m}$). A LSER equation matrix can be generated from all of the probe compounds (e.g., 32 probe compounds):

$$\log K^{n}_{p/m} = c + rR_n + s\pi_n + a\alpha_n + b\beta_n + vV_n \quad (n = 1, 2, 3, \ldots, 32) \tag{2}$$

where $n$ is the number of probe compounds. The system coefficients of the absorption system [$c$ $r$ $s$ $a$ $b$ $v$] can be obtained by multiple linear regression analysis of the LSER equation matrix (equation (2)).

### 2.2 *Changes in system coefficients*

When the major components change in composition or proportion, the system coefficients will be altered. Therefore, the changes in the system coefficients can be used to study the effects of the chemical mixture on membrane absorption from the chemical mixture. If the chemical mixture has a small change in the medium, this change will be reflected in the system coefficients, i.e. a small change will be introduced into the system coefficients [$\Delta c$ $\Delta r$ $\Delta s$ $\Delta a$ $\Delta b$ $\Delta v$]. The changes in the system coefficients can be obtained by subtraction of the system coefficients of the chemical mixture from those after the change:

$$\begin{aligned}[\Delta c\, \Delta r\, \Delta s\, \Delta a\, \Delta b\, \Delta v] &= [c\, r\, s\, a\, b\, v]_x - [c\, r\, s\, a\, b\, v]_o \\ &= [c_x - c_o\, r_x - r_o\, s_x - s_o\, a_x - a_o\, b_x - b_o\, v_x - v_o]\end{aligned} \tag{3}$$

where [$c$ $r$ $s$ $a$ $b$ $v$]$_o$ are the system coefficients of the original chemical mixture; [$c$ $r$ $s$ $a$ $b$ $v$]$_x$ are the system coefficients after the change of a major component in the chemical mixture and [$\Delta c$ $\Delta r$ $\Delta s$ $\Delta a$ $\Delta b$ $\Delta v$] are the changes of the system coefficients.

## 3. Materials and methods

### 3.1 *Chemicals and materials*

Acetone (GC grade) and ethanol (200 proof) were purchased from Sigma–Aldrich (St. Louis, MO). Deionised water was prepared from a Picotech Water System (Research Triangle Park, NC). A set of 32 probe compounds (table 1) having purity better than 98% were purchased from Sigma-Aldrich (St. Louis, MO). Solid-phase microextraction (SPME) devices and 100-μm PDMS membrane-coated fibre assemblies were purchased from Supelco (Bellfonte, PA).

Individual stock solutions with a concentration of 10.00 mg mL$^{-1}$ in acetone were prepared for each of the probe compounds. A standard mixture in acetone containing the 32 probe compounds with a concentration of 100 μg mL$^{-1}$ for each component was prepared from the individual stock solutions. A series of standard solutions in acetone were prepared from the standard mixture to be used as external calibration standards for GC/MS analysis. The probe compounds are volatile and some of them are toxic. All of the solution preparation processes were conducted in a fume hood with gloves and goggles.

The 32 probe compounds were classified into four groups (table 1) according to their PDMS absorption and GC/MS response characteristics. Group 1 was composed of 10 probe compounds having individual concentrations of 100 μg mL$^{-1}$; Group 2 was composed of 9 probe compounds having individual concentrations of 1000 μg mL$^{-1}$;

Table 1. Probe compounds with known solute descriptors and determined partition coefficients.

| # | *Probe compounds** | $R$ | $\pi$ | $\alpha$ | $\beta$ | $V$ | $log\ K_{p/w}$ | $log\ K_{P/E25}$ | $log\ K_{P/E35}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Chlorobenzene | 0.718 | 0.65 | 0.00 | 0.07 | 0.839 | 2.40 | 2.01 | 1.72 |
| 2 | Ethylbenzene | 0.613 | 0.51 | 0.00 | 0.15 | 0.998 | 2.71 | 2.32 | 1.98 |
| 3 | *p*-Xylene | 0.613 | 0.52 | 0.00 | 0.16 | 0.998 | 2.76 | 2.35 | 1.94 |
| 4 | Bromobenzene | 0.882 | 0.73 | 0.00 | 0.09 | 0.891 | 2.51 | 2.09 | 1.75 |
| 5 | Propylbenzene | 0.604 | 0.50 | 0.00 | 0.15 | 1.139 | 3.14 | 2.75 | 2.32 |
| 6 | 4-Chlorotoluene | 0.705 | 0.67 | 0.00 | 0.07 | 0.98 | 2.87 | 2.44 | 2.02 |
| 7 | Iodobenzene | 1.188 | 0.82 | 0.00 | 0.12 | 0.975 | 2.73 | 2.25 | 1.87 |
| 8 | Naphthalene | 1.360 | 0.92 | 0.00 | 0.20 | 1.085 | 2.83 | 2.28 | 1.82 |
| 9 | 1-Methyl naphthalene | 1.344 | 0.90 | 0.00 | 0.20 | 1.226 | 3.26 | 2.63 | 2.17 |
| 10 | Biphenyl | 1.360 | 0.99 | 0.00 | 0.22 | 1.324 | 3.37 | 2.75 | 2.23 |
| 11 | Toluene | 0.601 | 0.52 | 0.00 | 0.14 | 0.857 | 2.24 | 1.89 | 1.67 |
| 12 | Benzonitrile | 0.742 | 1.11 | 0.00 | 0.33 | 0.871 | 1.04 | 0.68 | 0.45 |
| 13 | Nitrobenzene | 0.871 | 1.11 | 0.00 | 0.28 | 0.891 | 1.21 | 0.91 | 0.70 |
| 14 | Methyl benzoate | 0.733 | 0.85 | 0.00 | 0.46 | 1.073 | 1.65 | 1.16 | 0.85 |
| 15 | 4-Chloroanisole | 0.838 | 0.86 | 0.00 | 0.24 | 1.038 | 2.37 | 1.88 | 1.46 |
| 16 | Ethylbenzoate | 0.689 | 0.85 | 0.00 | 0.46 | 1.214 | 2.12 | 1.56 | 1.16 |
| 17 | Methyl-2-methyl benzene | 0.772 | 0.87 | 0.00 | 0.43 | 1.214 | 2.15 | 1.56 | 1.26 |
| 18 | 4-Nitrotoluene | 0.870 | 1.11 | 0.00 | 0.28 | 1.032 | 1.77 | 1.34 | 1.02 |
| 19 | 4-Chloroacetophenone | 0.955 | 1.09 | 0.00 | 0.44 | 1.136 | 1.64 | 1.05 | 0.85 |
| 20 | Phenol | 0.805 | 0.89 | 0.60 | 0.30 | 0.775 | −0.18 | −0.34 | −0.50 |
| 21 | 4-Fluorophenol | 0.670 | 0.97 | 0.63 | 0.23 | 0.793 | −0.28 | −0.36 | −0.46 |
| 22 | Phenyl acetate | 0.661 | 1.13 | 0.00 | 0.54 | 1.073 | 0.86 | 0.70 | 0.23 |
| 23 | Acetophenone | 0.818 | 1.01 | 0.00 | 0.48 | 1.014 | 1.04 | 0.55 | 0.49 |
| 24 | *m*-Cresol | 0.822 | 0.88 | 0.57 | 0.34 | 0.916 | −0.03 | −0.25 | −0.22 |
| 25 | 4-Ethylphenol | 0.800 | 0.90 | 0.55 | 0.36 | 1.057 | 0.60 | 0.22 | 0.05 |
| 26 | 3,5-Dimethylphenol | 0.820 | 0.84 | 0.57 | 0.36 | 1.057 | 0.42 | 0.04 | 0.10 |
| 27 | 3-Chlorophenol | 0.909 | 1.06 | 0.69 | 0.15 | 0.898 | 0.31 | 0.17 | −0.11 |
| 28 | 4-Chloroaniline | 1.060 | 1.13 | 0.30 | 0.31 | 0.939 | 0.84 | 0.44 | 0.21 |
| 29 | 3-Bromophenol | 1.060 | 1.15 | 0.70 | 0.16 | 0.950 | 0.46 | 0.28 | −0.09 |
| 30 | Phenethyl alcohol | 0.784 | 0.83 | 0.30 | 0.66 | 1.057 | 0.12 | −0.05 | −0.30 |
| 31 | 3-Methyl benzyl alcohol | 0.815 | 0.90 | 0.33 | 0.59 | 1.057 | 0.17 | 0.07 | −0.22 |
| 32 | Benzyl alcohol | 0.803 | 0.87 | 0.33 | 0.56 | 0.916 | −0.35 | −0.87 | −0.42 |

*The probe compounds were classified into 4 groups according to their partition properties and GC/MS responses (Group 1: 1–10, Group 2: #11–19, Group 3: #20–29 and Group 4: #30–32). The values of the solute descriptors [$R\ \pi\ \alpha\ \beta\ V$] were recommended by Abraham [18]. The $\log K_{p/w}$ and $\log K_{P/E25}$ values were experimental partition coefficients between PDMS and water and 25% ethanol–water, respectively. The $\log K_{P/E35}$ values were predicted partition coefficient between PDMS and 35% ethanol-water with the system coefficients [0.52, 0.41, −1.25, −1.87, −2.98, 2.30].

Group 3 was composed of 10 probe compounds having individual concentrations of $1000\,\mu g\,mL^{-1}$ and Group 4 was composed of 3 probe compounds having individual concentrations of $2000\,\mu g\,mL^{-1}$. A working solution in water was prepared from the grouped mixture solutions to yield a composition of $10\,ng\,mL^{-1}$ of Group 1, $100\,ng\,mL^{-1}$ of Group 2, $1000\,ng\,mL^{-1}$ of Group 3 and $2000\,ng\,mL^{-1}$ of Group 4 compounds.

### 3.2 *Kinetic absorption*

The absorption experiments using the MCF technique were described in details elsewhere [15]. Here briefly, a glass vial was filled with 20 mL of the working solution, capped with Teflon lined silicone septa and equilibrated to 25°C. A preconditioned

PDMS fibre was inserted into the glass vial and immersed into the working solution to start the absorption experiment under constant stirring at 400 rpm and 25°C. At a given period of time, the fibre was removed from the vial and transferred into a GC injection port for quantitative analysis. The absorption amounts at a series of time points were measured to study the absorption kinetics.

### 3.3 *Equilibrium absorption*

The equilibrium amounts of the probe compounds were measured in the same procedures as the kinetic absorption experiments except that the absorption time was predetermined to ensure equilibrium was achieved for all of the probe compounds. The absorption equilibrium was achieved within 2 h for all of the probe compounds under constant stirring at 400 rpm and 25°C (referring to the result section). This experiment condition was used throughout the rest of the absorption experiments.

### 3.4 *Absorption in ethanol solutions*

The chemical mixtures of the probe compounds with different ethanol proportions were prepared from the grouped mixture solutions to obtain the working solutions with different ethanol proportions (0–50% v/v). The equilibrium absorption amounts of the probe compounds were determined by PDMS membrane-coated fibres in the each of the working solutions with three replications. The experimental procedures were same as those in the kinetic absorption experiments except the absorption time was 2 h under constant stirring at 400 rpm and 25°C.

### 3.5 *Quantitative analyses*

Quantitative and qualitative analyses were performed on an HP 5890 II gas chromatograph coupled with a HP 5970B mass selective detector. An HP 7673 automatic sampler was used to inject 0.5 μL of the calibration standard solution, while the membrane-coated fibres were injected manually. The injector was maintained at 280°C for sample vaporization and thermal desorption. A deactivated liner (2 mm in diameter) was used for liquid injection and fibre desorption in order to improve the chromatographic resolution. Separation was performed on a 30 m × 0.25 mm (i.d.) × 0.25 μm (df) Rtx-5MS capillary column (Restek Corp., Bellefonte, PA). The column oven was programmed as follows: held at the initial temperature 40°C for 2 min, ramped at 20°C min$^{-1}$ to 60°C, 3°C min$^{-1}$ to 97°C and held for 3.5 min, 20°C min$^{-1}$ to 200°C, and held for 5 min. An electronic pressure control was used to maintain a carrier gas flow of 1.00 mL min$^{-1}$ helium.

### 3.6 *Data analysis*

The partition coefficient of a probe compound in a given absorption system ($\log K_{p/m}$) was calculated from the equilibrium absorption amount ($n^o$) by the definition of the partition coefficient [15]:

$$K_{p/m} = \frac{C_{pe}}{C_{me}} = \frac{n^o V_m}{V_p(V_m C_o - n^o)} \quad (4)$$

where $C_o$ is the initial concentration of the compound in the working solution, $V_m$ is the volume of the working solution, $V_p$ is the volume of the PDMS membrane, $C_{pe}$ is the equilibrium concentration in the membrane ($C_{pe} = n^o/V_p$) and $C_{me}$ is the equilibrium concentration in the working solution ($C_{me} = C_o - n^o/V_m$).

The $\log K_{p/m}$ value of a probe compound was scaled to its solute descriptors via the LSER equation (equation (1)). A LSER equation matrix was generated from all of the probe compounds ($n = 32$). The LSER equation matrix of the PDMS/water system was given in table 1. The system coefficients were obtained by multiple linear regression analysis of the LSER equation matrix (equation (2)). The multiple linear regression analysis was performed by using SAS Analyst from SAS Institute Inc (Cary, NC).



## 4. Results

### 4.1 *Equilibrium absorption*

The absorption profiles of the probe compounds were obtained from their absorption amounts into the PDMS membranes at different time intervals. Figure 1 shows the absorption profiles of four compounds. Methyl benzoate reached equilibrium within 10 min; 4-chlorotoluene and acetophenone within 20 min, while biphenyl in 60 min. Biphenyl has the longest equilibration time of all 32 probe compounds in water solutions. When ethanol was added into the water solutions, the equilibration times of the probe compounds were reduced (results not shown). Therefore, absorption for 2 h under constant stirring at 400 rpm and 25°C could ensure the absorption equilibrium for all probe compounds.

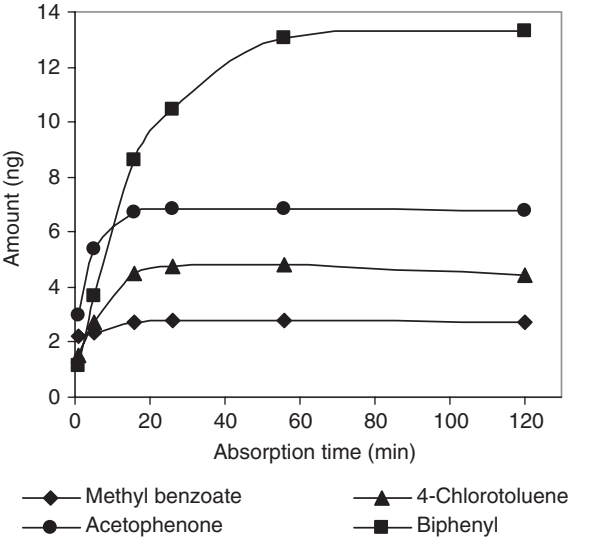


Figure 1. Absorption profiles of the probe compounds. The absorption amounts were measured by using 100 μm PDMS membrane-coated fibres in water solution of the probe compounds.

### 4.2 *Partition coefficients*

The equilibrium absorption amounts ($n^{\circ}$) were determined for each of the probe compound with PDMS fibres in aqueous solutions. The partition coefficient of a given probe compound was calculated from the initial concentration ($C_o$) and $n^{\circ}$ with equation (4), where the solution volume ($V_m$) was 20 mL and the membrane volume ($V$p) of the 100-μm PDMS membrane-coated fibres was 0.612 μL. The partition coefficients of the 32 probe compounds between PDMS membrane and water ($\log K_{p/w}$) were given in table 1.

### 4.3 *System coefficients*

The probe compounds with known solute descriptors were selected from those recommended by Abraham [18]. The solute descriptors of the 32 probe compounds [R $\pi$ $\alpha$ $\beta$ V] were given in table 1. The partition coefficient of a given probe compound ($\log K_{p/w}$) was determined in the water solution using PDMS membrane-coated fibres. The $\log K_{p/w}$ value of the compound was scaled to its solute descriptors via the LSER equation (equation (1)). A LSER equation matrix, [$\log K_{p/w}$; $R\ \pi\ \alpha\ \beta\ V$], was generated from all of the probe compounds ($n = 32$, equation (2)). In this regression, the experimentally determined $\log K_{p/w}$ values were the dependent variable, while the solute descriptors of the probe compounds [$R\ \pi\ \alpha\ \beta\ V$] were explanatory variables (table 1); the system coefficients $[c\ r\ s\ a\ b\ v]_{p/w}$ are the unknown quantities to be resolved from the regression analysis. The system coefficients of the PDMS/water system were obtained by multiple linear regression analysis of the LSER equation matrix:

$$\log K_{p/w} = 0.09 + 0.49R - 1.11\pi - 2.36\alpha - 3.78\beta + 3.50V, r^2 = 0.995 \quad (5)$$

The regression results suggested that the LSER equation explained 99.5% of the variation of the data. The $F$-value was 1056 with $p$-value $<0.0001$. The statistical results for individual explanatory variables are given in table 2. The solute descriptors $[\pi, \alpha, \beta, V]$ are significant factors in the LSER equation having $p$-values $<0.0001$ and $t$-values of $-9.36, -32.70, -27.75$, and 20.59, respectively. The $t$-value of the $R$ descriptor was 4.43 with a $p$-value of 0.0002.

### 4.4 *Partial regression plots*

Partial regression plots are diagnostic tool to evaluate the role of the individual variables within the multiple regression model. The partial regression plots of the

Table 2. Statistically estimated parameters for a PDMS/water system.

| *Variables* | *DF* | *Parameter estimate* | *Standard error* | *t-Value* | *p-Value* |
|---|---|---|---|---|---|
| Intercept | | 0.09 | 0.16 | 0.58 | 0.564 |
| $R$ | 1 | 0.49 | 0.11 | 4.43 | 0.0002 |
| $\Pi$ | 1 | −1.11 | 0.12 | −9.36 | <0.0001 |
| $\alpha$ | 1 | −2.36 | 0.07 | −32.70 | <0.0001 |
| $\beta$ | 1 | −3.78 | 0.14 | −27.75 | <0.0001 |
| $V$ | 1 | 3.50 | 0.17 | 20.59 | <0.0001 |

The parameters were obtained for the PDMS/water system using Analyst program in SAS software (SAS Institute Inc, Carry, NC).

PDMS/water system are shown in figure 2. The slopes of the partial regression plots were equal to the system coefficients, representing the contribution of the specific types of molecular interactions of the system to the partitioning process. It is noted that lone-pair electron interactions ($R$) was not a significant factor in the partitioning process.

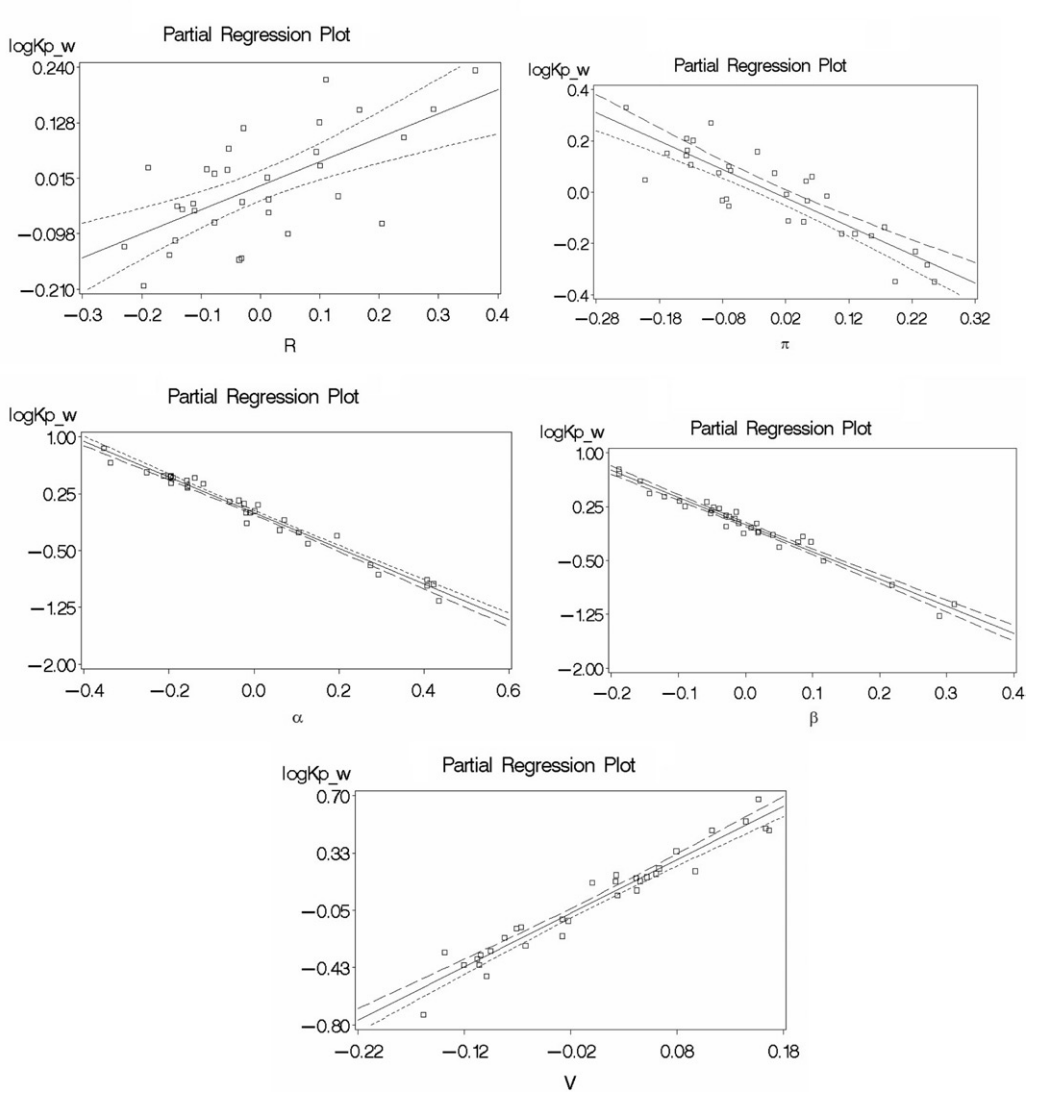


Figure 2. Contributions of the system coefficients to the partition coefficients. The partial regression plots were regression results of the LSER equation matrix generated from the experimental log $K_{p/w}$ values and the solute descriptors of the probe compounds. The regression line and the 95% confidence lines (dashed) are show in the partial regression plots. The slopes of the partial regression plots are the system coefficients representing the contributions of the specific types of molecular interactions to the partitioning processes.

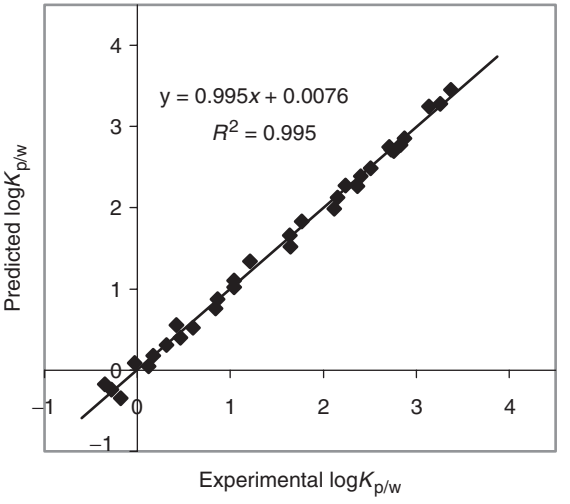


Figure 3. Correlation of the experimental log $K_{p/w}$ with the predicted ones.

The widely scattered points revealed loose correlation of the partition coefficient with the lone-pair electron interactions ($r^2 = 0.43$, with slope $r = 0.49$). Dipolarity-polarizability ($\pi$) was also a weak factor in the partitioning process with a slope of $-1.11$ ($s$) and $r^2$ of 0.77. The hydrogen-bond acidity ($\alpha$), hydrogen bond basicity ($\beta$) and hydrophobicity ($V$) were significant factors in the partition coefficients with slopes of $-2.36$ ($a$), $-3.78$ ($b$) and 3.50 ($v$) and with partial correlation coefficients ($r^2$) of 0.98, 0.97 and 0.94, respectively.

### 4.5 *Prediction accuracy*

The predicted log $K_{p/w}$ values were compared with the experimental determined ones to evaluate the prediction accuracy of the system coefficient approach (figure 3). The correlation coefficient between the predicted and experimental log $K_{p/w}$ values was 0.995, which suggested that high prediction accuracy could be obtained by the system coefficient approach.

### 4.6 *Solvent effects*

When ethanol was added into the aqueous solutions, the system coefficients were altered since the ethanol proportions were high enough to change the physiochemical properties of the medium. In order to study the solvent effects on the system coefficients, the system coefficients were determined at different ethanol proportions. The system coefficients of a PDMS/ethanol–water system were obtained in the same procedures as those for the PDMS/water system. For example, the partition coefficients of the PDMS/25% ethanol–water system (P/E25) were determined for all of the 32 probe compounds (table 1). A new LFER equation matrix was generated from the log $K_{P/E25}$ values of the probe compounds [log $K_{P/E25}$; $R, \pi, \alpha, \beta, V$]. The system coefficients of the P/E25 system obtained by multiple regression analysis of the equation matrix were $[0.38, 0.41, -1.18, -2.07, -3.40, 2.81]_{P/E25}$ with regression coefficient ($r^2$) of 0.991. The solvent effects of 25% ethanol on the system coefficients

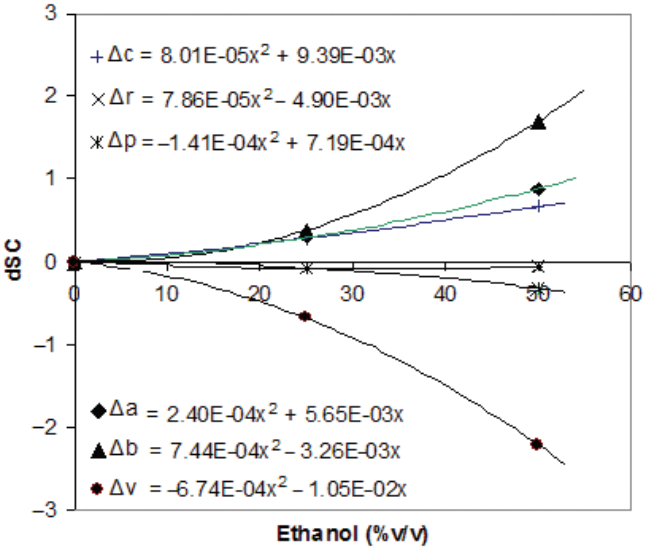


Figure 4. Ethanol effects on the system coefficients. dSC: changes in system coefficients ($\Delta c = c_x - c_o$, $\Delta r = r_x - r_o$, $\Delta s = s_x - s_o$, $\Delta a = a_x - a_o$, $\Delta b = b_x - b_o$, $\Delta v = v_x - v_o$), where $[c\ r\ s\ a\ b\ v]_o$ are the system coefficients of the original chemical mixture; $[c\ r\ s\ a\ b\ v]_x$ are the system coefficients after the change of a major component in the chemical mixture.

can be obtained by subtraction of the system coefficients of the PDMS/water system from those of the P/E25 system:

$$\begin{aligned}&[\Delta c, \Delta r, \Delta s, \Delta a, \Delta b, \Delta v]_{E25}\\ &= [0.38,\ 0.41,\ -1.18,\ -2.07,\ -3.40,\ 2.81]_{P/E25}\\ &\quad -[0.09,\ 0.49,\ -1.11,\ -2.36,\ -3.78,\ 3.50]_{p/w}\\ &= [0.29,\ -0.08,\ -0.07,\ 0.29,\ 0.38,\ -0.69]_{E25}\end{aligned} \tag{6}$$

The ethanol effects on the system coefficients of the PDMS/water system are shown in figure 4. The changes of the system coefficients $[\Delta c, \Delta r, \Delta s, \Delta a, \Delta b, \Delta v]$ were mapped over a range of ethanol concentration (0–50%). A set of system coefficients can be obtained for any ethanol concentration in this range. Therefore, the partition coefficient of a chemical of interest in a given ethanol concentration can be predicted from the system coefficients at the ethanol concentration and the solute descriptors of the chemical. For example, the partition coefficients of the 32 probe compounds predicted for 35% ethanol solution were given in table 1 where the system coefficients were [0.52, 0.41, −1.25, −1.87, −2.98, 2.30].

## 5. Discussion

### 5.1 *The MCF technique*

PDMS membrane is one of the most biological compatible synthetic materials. It has been widely used as model membrane for studying chemical absorption and

release [8, 12–14]. We have developed a membrane-coated fibre technique for determining the absorption kinetics of complicated chemical mixtures [15, 16]. Thus, PDMS membrane and a chemical mixture containing 32 probe compounds were selected in this paper to demonstrate the principle and feasibility of the system coefficient approach. PDMS membrane could be a reduced model for many practical applications, such as, the cell membrane absorption or dermal absorption from chemical mixtures.

### 5.2 *System coefficient approach*

When a PDMS membrane is exposed to a chemical mixture, the absorption process of a chemical is governed by the relative molecular interaction strengths of the chemical with the PDMS membrane and the chemical mixture. In the system coefficient approach, a set of probe compounds are used to detect the molecular interaction strengths and dissect the complicated molecular interaction strengths into five solute descriptors. Since the probe compounds are added in trace quantities, their addition would not change the system coefficients. If the molecular interaction characteristics (solute descriptors) of the probe compounds are known, the relative molecular interaction strengths of the absorption system can be resolved by the system coefficient approach. For example, the system coefficients of the PDMS/water system were $[0.09, 0.49, -1.11, -2.36, -3.78, +3.50]_{p/w}$ (equation (5)).

The contributions from different types of molecular interactions are represented by the system coefficients. Hydrogen bond acidity ($b = -3.78$) and hydrophobicity ($v = 3.50$) were two main types of molecular interactions in the PDMS/water system. The system coefficient $b$ represents the acidity of the absorption system since it describes the tendency of the absorption system to interact with the H-bond basicity ($\beta$) of the chemicals. Lone pair electrons ($r = 0.49$) and dipolarity/polarizability ($s = -1.11$) were weaker molecular interactions in the partitioning processes, while hydrogen bond basicity ($a = -2.36$) made moderate contribution to the partition coefficients. These results are supported by the partial regression plots of the system coefficients (figure 2).

### 5.3 *The LSER model*

The LSER model adequately described the experimental data with a correlation coefficient ($r^2$) of 0.995 (figure 3). From the partial regression plots (figure 2), it is known that descriptors [$\pi\ \alpha\ \beta\ V$] are four significant factors in the LSER model. This is also supported by the $t$-test that their probability values associated with the $t$-values are less than 0.0001 (table 2). The $R$ descriptor has a loose correlation in figure 2, it raise question whether it should be remained in the LSER model. The $t$-test result shows that when the $t$-value was 4.43, the $p$-value of the $R$ descriptor was 0.0002, which is less than 0.05 (a 95% significance criterion). Therefore, the $R$ descriptor should remain in the LSER model.

### 5.4 *Selection of the probe compounds*

The system coefficient approach uses a set of probe compounds to detect the molecular interaction strengths of the absorption system. The selection of the probe compounds is a critical step in the system coefficient approach. (i) The probe compounds should have reliable solute descriptors from reference handbooks or the literature. (ii) The probe

compounds should cover wide strength ranges of the molecular interactions, which will eventually determine the application range of the system coefficients. For a specific application, the ranges of the solute descriptors should cover the chemicals of interest. (iii) The probe compounds are added into the chemical mixture in trace concentrations not affecting the system coefficients. Analytical methods should be available for their quantitative analysis. (iv) The probe compounds should be chemically stable; metabolism and specific biological interactions are negligible during the absorption processes. (v) Passive diffusion is the main driving force in the absorption processes.

### 5.5 *Effective descriptors*

It is noted that a solute descriptor does not represent a simple 1 : 1 interaction; rather it represents the summation of a specific type of molecular interactions. For example, a compound may have several hydrogen-bond groups, while $\alpha$ represents the summation of the hydrogen-bond acidity from all hydrogen-bond groups of the compound. Similarly, a system coefficient represents the summation of a specific type of molecular interactions of the membrane/medium system. This assumption gives the system coefficient approach the advantages in quantitative assessment of the passive diffusion and non-specific molecular interactions, while it also place a limitation that structure dependent interactions such as drug-receptor interactions cannot be directly assessed.

### 5.6 *Solvent effects*

Solvents have been widely used to increase solubility of the active agents in industrial applications, medicine and pharmaceutical formulations. Solvent effects on the absorption of chemicals have been subjects of many studies [19]. However, quantitative assessment of the solvent effects on the absorption of chemical mixtures is difficult. Our group has previously reported a hybrid QSAR approach to quantitate mixture interactions on dermal absorption, although this approach does not allow for specific mechanistic interactions to be defined the present MCF approach does [20]. In the system coefficient approach, the solvent effects can be described by the changes in the system coefficients, which can be measured quantitatively. For example, the addition of ethanol to the water solution significantly changed the contributions of different types of molecular interactions (equation (6)). The hydrogen bond basicity and acidity became more important with 0.29 ($\Delta a$) and 0.38 ($\Delta b$) increases. The contribution of hydrophobicity to the partition coefficient was significantly reduced ($\Delta v = -0.69$).

The changes of the system coefficients with the ethanol concentration are further illustrated in figure 4. It shows that the hydrophobicity was modulated downward ($\Delta v$), i.e. the contribution of the hydrophobicity to the partition coefficient was reduced as the ethanol proportion increased. This is theoretically expected since the addition of ethanol into the water solution increases the hydrophobicity of the solution and consequently reduces the hydrophobicity difference between the PDMS and water solutions. If the hydrophobicity of the solution and the PDMS membrane are same, the hydrophobicity interactions of the compounds with the membrane and the solution will have no contribution to the partition coefficient. The contributions of hydrogen-bond basicity ($\Delta a$) and acidity ($\Delta b$) were both increased. These observations suggested that hydrogen-bonding interactions became more important as the ethanol proportion increased.

### 5.7 *Limitations of the system coefficient approach*

In the system coefficient approach, specific biological interactions are not considered. For example, drug-receptor interactions are structural dependent, which is not considered in the summation of a given type of molecular interactions. Therefore, the system coefficient approach can only provide predictions when passive diffusion is the primary transport mechanism. In fact, passive diffusion is the primary transport barrier in chemical absorption through lipophilic biological membranes [21, 22]. If the experimental observed values are significantly different from those predicted by the system coefficient approach, it indicates that biological specific interactions might occur during the absorption processes. Thus, the system coefficient approach can be used to detect possible specific interactions in complicated biological systems. Special methods should be used for measuring the contribution of the specific biological interactions. The basic values predicted by the system coefficient approach should be modified to account for the contributions of the specific biological interactions.

## 6. Conclusion

The system coefficients of an absorption system can be determined by using a set of probe compounds. The absorption property of a chemical can be predicted from the system coefficients and the solute descriptors of the chemical. The solvent effects of ethanol can be quantitatively assessed by using the system coefficient approach. These conclusions were supported by the experimental results of the PDMS absorption of 32 probe compounds.

## Acknowledgements

This work was supported by NIOSH, Grant R01-OH-07555 and US Air Force, Office of Scientific Research, Grants F49620-01-1-0080 and FA9550-04-1-0376.

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