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ORIGINAL

Evaluation of Accuracy for the Measurement of Octanol–Water Partition Coefficient by MEEKC

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Abstract Microemulsion electrokinetic chromatography (MEEKC) has been widely used as an indirect tool to measure octanol–water partition coefficients (logP_{ow}) of various kinds of compounds. In this paper, we present for the first time a mathematical model of the precision of logP_{ow} (ΔlogP_{ow}) as a function of the deviation of migration time (Δt_{m}) in MEEKC, and more importantly evaluated the accuracy of the MEEKC. Our model shows that for a given microemulsion system, there is an interval of migration times, where a high precision in the determination of logP_{ow} can be obtained. However, when the migration time approaches either the migration time of the electroosmotic flow or that of the microemulsion phase, the precision of logP_{ow} deteriorates rapidly. The model was experimentally verified by the microemulsion system with migration times of 6.50 and 32.00 min for the electroosmotic flow and microemulsion phase, respectively, and we found the useful logP_{ow} interval to be 0.50–5.50. The paper also demonstrates that the calibration constants between migration times t_{m} and predicted logP_{ow} values could be transferred with high accuracy from one MEEKC system to another as long as both systems are set up to use the same operational parameters.

Keywords Microemulsion electrokinetic chromatography · Octanol–water partition coefficients · Accuracy · Precision · Migration time

Introduction

The logarithm of octanol–water partition coefficient (logP_{ow}) is widely used as a general value for lipophilicity, which is an essential property of molecules, because it is highly related to solubility, membrane permeability, protein binding and so on [7]. A number of direct and indirect methods have been applied for logP_{ow} measurement [2]. The direct methods include conventional shake-flask method, stir flask, two-phase titration, etc., and the shake-flask method has historically been considered the standard assay. These direct methods have several limitations: they are time consuming, have low reproducibility, require relatively large amounts of pure sample and are difficult to automatize. The indirect methods include reversed-phase high performance liquid chromatography (RP-HPLC) [3, 4], reversed-phase thin-layer chromatography (RP-TLC) [31] and micelle electrokinetic chromatography (MEKC) [14, 17], which use instrumental techniques and are thus faster and easier to automate than direct methods. Nevertheless, these indirect methods still have some shortcomings. For example, the range of obtainable lipophilicity is limited and dependent upon the partition chromatographic system [12, 13]. Furthermore, in RP-HPLC and RP-TLC,

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the hydrogen bond effects must be considered in logP_{ow} determinations for compounds with hydrogen bond acceptor and donor, while in MEKC the electrostatic interactions between the polar solutes and the surface of the micelle must be considered.

In 1991, a branch of capillary electrophoresis, microemulsion electrokinetic chromatography (MEEKC), was developed [28], which almost possesses the required properties for estimating logP_{ow}, because of the particular compositions of buffer. The technique uses microemulsion to separate charged or uncharged solutes based on both their electrophoretic mobility and lipophilicity, and the latter directly determines the partitioning of analyte between the microemulsion pseudostationary phase and the aqueous phase. Since its invention, MEEKC has been widely used for measurement of logP_{ow} [1, 5, 6, 8–11, 15, 16, 18–26, 29]. However, thus far, the accuracy of logP_{ow} measurement by MEEKC has not been evaluated and there are several questions that need to be addressed. For example, what is the range of logP_{ow} measurement for a given microemulsion system? Is the measured value accurate in any range? How would the precision of logP_{ow} (ΔlogP_{ow}) be affected by the experimental uncertainty in measured migration time (Δt_m)? In this paper, a theoretical model for the correlation between ΔlogP_{ow} and Δt_m is presented and experimentally verified with some microemulsion systems. Using this model, it is demonstrated that acceptable precision and accuracy can be achieved for the measurement of logP_{ow} by MEEKC within a useful interval of a given microemulsion system.

Theoretic Calculations

The separation mechanism in MEEKC is based on the differential partitioning of analyte (uncharged ones) between the microemulsion pseudostationary phase and the aqueous phase, and the partitioning of analyte is related to its lipophilicity. Therefore, the migration time of an analyte is correlated to its lipophilicity. First, the capacity factor, k, for an uncharged analyte in MEEKC can be calculated as follows [8]:

$$k = \frac{t_m - t_o}{t_o(1 - t_m/t_{me})} \tag{1}$$

where t_o, t_{me} and t_m are the migration times of the electroosmotic flow (EOF), the microemulsion phase and the analyte, respectively.

Then the relationship between log k and logP_{ow} is known as the functional form [8]:

$$\log P_{ow} = a \log k + b \tag{2}$$

where a and b are constants that represent the slope and intercept of a linear correlation calibration. Once a and b are established using a set of compounds with known logP_{ow} values, Eq. 2 can be applied to determine logP_{ow} of other compounds.

Combining Eqs. 1 and 2, the following equation can be obtained:

$$\log P_{ow} = a \log \frac{t_m - t_o}{t_o(1 - t_m/t_{me})} + b \tag{3}$$

In order to find the correlation between the uncertainty, or precision of logP_{ow} (ΔlogP_{ow}) and the uncertainty of migration time measurement (Δt_m), logP_{ow} in Eq. 3 is differentiated with respect to t_m, leading to the following relationship:

$$d \log P_{ow} = 0.434a \frac{t_{me} - t_o}{(t_{me} - t_m)(t_m - t_o)} dt_m \tag{4}$$

or

$$\Delta \log P_{ow} = 0.434a \frac{t_{me} - t_o}{(t_{me} - t_m)(t_m - t_o)} \Delta t_m \tag{5}$$

Equation (5) shows that the extent of effects of Δt_m on ΔlogP_{ow} is given by the coefficient $0.434a \frac{t_{me} - t_o}{(t_{me} - t_m)(t_m - t_o)}$. For convenience, a function $f(t_m)$ that describes the importance of the analytes migration time upon the correlation is defined as:

$$f(t_m) = \frac{t_{me} - t_o}{(t_{me} - t_m)(t_m - t_o)} \quad (t_o < t_m < t_{me}). \tag{6}$$

Thus, ΔlogP_{ow} and Δt_m are simply correlated as:

$$\Delta \log P_{ow} = 0.434 \cdot a \cdot f(t_m) \cdot \Delta t_m \tag{7}$$

Equation (7) shows that as the value of $f(t_m)$ increases, ΔlogP_{ow} is more strongly affected by Δt_m.

Figure 1 shows the curve of $f(t_m)$ versus t_m for the microemulsion system (ME) used in our experiment, where t_o and t_{me} are 6.50 min and 32.00 min, respectively. It is obvious that within a relatively wide range of migration times (t_m), the value of $f(t_m)$ is small and almost constant, but as t_m approaches either t_o or t_{me}, the value of $f(t_m)$ increases rapidly and leads to unacceptable uncertainty in the prediction of logP_{ow} using Eq. 2.

To find the useful interval of analyte migration times, $f(t_m)$ in Eq. 6 is differentiated with respect to t_m and the requirement is implemented that d$f(t_m)$/dt_m must be numerically less than 1. Thus,

$$f'(t_m) = \frac{df(t_m)}{dt_m} = \frac{1}{(t_{me} - t_m)^2} - \frac{1}{(t_m - t_o)^2} \tag{8}$$

and the lower and upper limits of t_m (t_{m1}, t_{m2}) can be calculated by inserting either $f'(t_m) = -1$, or $f'(t_m) = +1$ into Eq. 8 and numerically solving the equation. For the microemulsion system with $t_o = 6.50$ min and $t_{me} = 32.00$ min, t_{m1} and t_{m2} are 7.66 and 30.84 min, respectively.

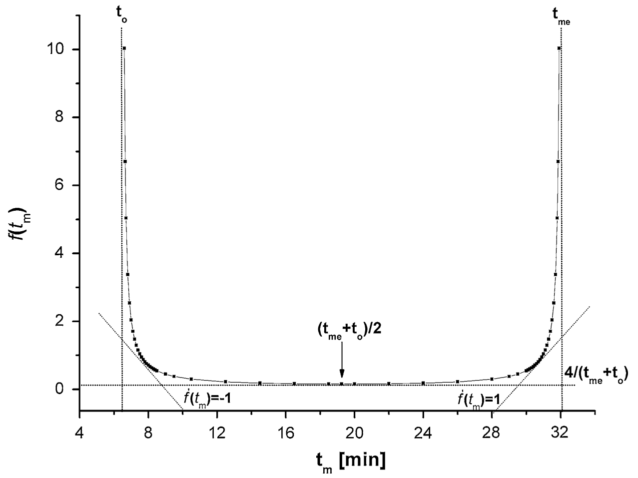

Fig. 1 The curve of $f(t_m)$ versus t_m for an MEEKC system with $t_o = 6.50$ min and $t_{me} = 32.00$ min

When $f'(t_m) = 0$, $f(t_m)$ is minimal. In this case, $t_m = \frac{t_{me}+t_o}{2}$, and $f(t_m)_{min} = \frac{4}{t_{me}+t_o}$. For our microemulasion system, $f(t_m)_{min}$ is calculated as 0.104 at $t_m = 19.25$ min, which is the center of the useful interval.

Experimental

Reagents

Fluorene (98%), pyrene (99%), benzanthracene (99%) and coronene (97%) were purchased from Aldrich Chemical Company, Inc. (USA). Biphenyl (AR) was made in the Department of Chemistry, University of Copenhagen (Denmark). 1-Heptane (AR), 1-butanol (99%), sodium dodecyl sulfate (SDS) and dimethyl sulfoxide (DMSO, AR) were purchased from Ferak (Germany), Sigma (USA) and E. MERCK (Germany), respectively. The water for solution preparation was deionized and purified through a Millipore (Water class 2) system.

Instruments

A Beckman P/ACE System 5000 (Beckman Instruments Inc., Fullerton, CA) equipped with P/ACE UV absorbance detector at 200 nm was employed for all MEEKC measurements. Data were collected at a rate of 5 Hz using System Gold (Beckman Instrments Inc. Fullerton, CA), and a presented chromatogram was redrawn using Microsoft Excel and Origin 8.0. An uncoated fused silica capillary (SGE, SGE Analytical Science Pty Ltd., Australia) of 75 µm i.d. and 56.5 cm length (50.3 cm to the detector), which was thermostated by a liquid coolant, was employed in the experiments. A PHM220 Lab pH Meter (MeterLab^{TM}, Radiometer, Villeurbanne, CEDEX-Lyon, France) was used in the measurement of pH for running media and sample solutions.

Preparation of Microemulsions and Sample Solutions

The microemulsion containing 45 mM SDS, 80 mM 1-heptane, 850 mM 1-butanol and 5 mM phosphate at pH 7.0 was prepared according to our previous work [30].

A tracer solution was prepared in the microemulsion system with 1/1,000 (*v*/*v*) of DMSO as the EOF tracer. Weighted amounts of the respective samples were dissolved in the microemulsion solution to give concentrations between 0.025 and 0.05 mg mL^{-1}.

Experiment of MEEKC

Before running of the MEEKC, the capillary was treated with 1 mol L^{-1} NaOH for 15 min, followed by a purge of 0.1 mol L^{-1} NaOH for 10 min, and then rinsed with water for 10 min and the microemulsion system for 10 min sequentially. Purges with 0.1 mol L^{-1} NaOH and water were performed periodically to remove contaminants from the capillary wall. Between the electrophoretic runs, the capillary was rinsed with microemulsion system for 5 min. All logP_{ow} determinations were based upon five successive electropherograms.

Results and Discussion

Determination of logP_{ow} Values Using MEEKC

In a previous paper [30], six compounds (sulfanilamide, aniline, *p*-toluidine, phenol, *β*-naphthol and naphthalene) with known logP_{ow} values from −1.05 to 3.33 were used to establish a calibration equation between logP_{ow} and measured migration times (t_m) as

$$\log P_{ow} = 2.42(\pm 0.25) \log k + 1.53(\pm 0.14);\ r = 0.9796 \tag{9}$$

This equation was used again in this paper to predict logP_{ow} values for a range of compounds with values of logP_{ow} known in the literature from −1.74 to 7.38. Although the original calibration equation was established using a MEEKC instrument different from that used here, the operating parameters for the two instruments were set up as identical as possible. Figure 2 shows the MEEKC electropherogram of five polyaromatic hydrocarbons (PAHs) with logP_{ow} values higher than those used previously to establish the calibration equation. The new results, together with those from our previous work [30], are displayed in Table 1. It is seen that the error between the logP_{ow} values measured by MEEKC and those of the literature is about or below 0.3 logarithm units in most cases, except for the compounds with logP_{ow} values greater than 5.00, indicating that the measurements were fairly accurate.

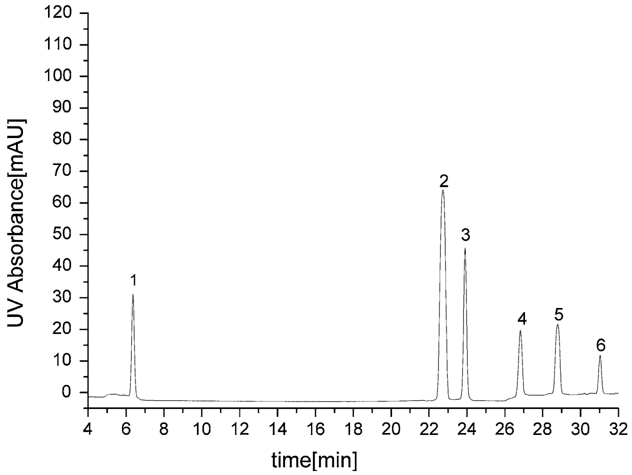

Fig. 2 MEEKC electropherograms for five PAHs. *Conditions* Microemulsion: 45 mM SDS, 80 mM 1-heptane, 850 mM 1-butanol and 5 mM phosphate, pH 7.0; separation voltage: 16.67 kV; injection: 34.5 mbar × 3 s; wavelength: 200 nm; peaks: *1* DMSO, *2* biphenyl, *3* fluorene, *4* pyrene, *5* benzanthracene, *6* coronene

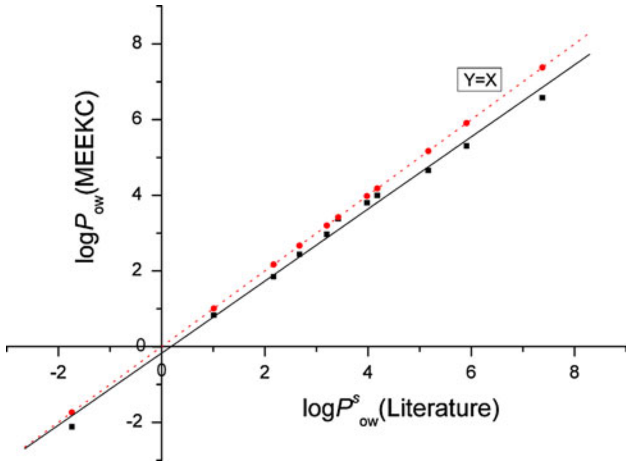

Fig. 3 Plot of experimentally obtained $\log P_{ow}$ values using MEEKC against literature $\log P_{ow}$ values, and the perfect fitting of $Y = X$

Figure 3 shows the $\log P_{ow}$ values determined by MEEKC and those from the literature correlated by the linear least-square fitting, as well as a perfect fit of $Y = X$. The slope and intercept by the linear least-square fitting are 0.952 (±0.026), −0.170 (±0.107), respectively, and the linear correlation coefficient r is 0.9963. This is a surprisingly good correlation between the MEEKC-determined values and those of the literature considering the fact that two different MEEKC instruments were used and the calibration equation obtained by one MEEKC instrument was transferred to the other. The observed deviation from the ideal correlation between measured $\log P_{ow}$ values and literature values seems to become larger at the extremes in agreement with the theoretical expectations found in "Theoretic Calculations". The measurement error includes both systematic error and experimental uncertainty. The systematic error is represented by the deviation of the linear least-square fitting from the perfect fit between the MEEKC-determined values and those of the literature. The experimental uncertainty of $\log P_{ow}$ can be evaluated by the residual between the measured values and the linear least-square fitting when the systematic errors are removed by the fit, which is called $\Delta\log P_{ow}$ (Experiment) here. This will be further discussed in detail in the next section.

Table 1 Comparison of $\log P_{ow}$ obtained by MEEKC versus literature values for 11 uncharged compounds

Compounds	t_m(min)	$\log P_{ow}$ (MEEKC)	$\log P^{s}_{ow}$ [References]	$\Delta\log P_{ow}$ (|MEEKC − literature|)	$\Delta\log P_{ow}$ (Experiment)
Acilovir	6.66[a]	−2.12	−1.74 [27]	0.38	0.293
Sulfafurazole	8.91[a]	0.83	1.01 [27]	0.18	0.038
Benzene	12.00[a]	1.85	2.17 [16]	0.32	0.045
Toluene	14.79[a]	2.44	2.69 [16]	0.25	0.068
Ethyl benzene	17.82[a]	2.97	3.20 [16]	0.23	0.094
Doxazosin	20.32[a]	3.38	3.42 [27]	0.04	0.294
Biphenyl	22.78	3.80	3.98[b]	0.18	0.181
Fluorene	23.84	3.99	4.18[b]	0.19	0.181
Pyrene	26.89	4.66	5.17[b]	0.51	0.092
Benzanthracene	28.96	5.31	5.91[b]	0.60	0.146
Coronene	31.01	6.58	7.38[b]	0.80	0.276

[a] Data measured in our previous work [30]

[b] Found in SciFinder Scholar (calculated using Advance Chemistry Development Software V9.04 for Solaris)

$\Delta\log P_{ow}$ (Experiment) = Residual (δ, experimental uncertainty) = |$\log P_{ow}$ obtained by MEEKC − $\log P_{ow}$ obtained by fitting equation from Fig. 3|

Table 2 Experimentally measured t_m values and estimation of $\Delta\log P_{ow}$ by our model for 11 uncharged compounds based upon Eq. 7

Compounds	t_m(min)	$\Delta\log P_{ow} = 0.434 \cdot a \cdot f(t_m) \cdot \Delta t_m$	Δt_m (95% confidence interval, $n = 5$)	$\Delta\log P_{ow}$ (Model)
Acilovir	6.66[a]	$\Delta(\log P_{ow}) = 6.606\Delta t_m$	0.062	0.409
Sulfafurazole	8.91[a]	$\Delta(\log P_{ow}) = 0.481\Delta t_m$	0.152	0.073
Benzene	12.00[a]	$\Delta(\log P_{ow}) = 0.243\Delta t_m$	0.232	0.056
Toluene	14.79[a]	$\Delta(\log P_{ow}) = 0.188\Delta t_m$	0.162	0.030
Ethyl benzene	17.82[a]	$\Delta(\log P_{ow}) = 0.167\Delta t_m$	0.133	0.022
Doxazosin	20.32[a]	$\Delta(\log P_{ow}) = 0.166\Delta t_m$	0.108	0.018
Biphenyl	22.78	$\Delta(\log P_{ow}) = 0.178\Delta t_m$	0.181	0.032
Fluorene	23.84	$\Delta(\log P_{ow}) = 0.189\Delta t_m$	0.179	0.034
Pyrene	26.89	$\Delta(\log P_{ow}) = 0.257\Delta t_m$	0.164	0.042
Benzanthracene	28.96	$\Delta(\log P_{ow}) = 0.392\Delta t_m$	0.198	0.077
Coronene	31.01	$\Delta(\log P_{ow}) = 1.104\Delta t_m$	0.193	0.213

[a] Data also obtained in our previous work [30]

Evaluation of the Accuracy of MEEKC Using the Deduced Theory

Equation (7) shows that the uncertainty in predicting log-P_{ow} ($\Delta\log P_{ow}$) is given by a constant multiplied by a function of the migration time $f(t_m)$ multiplied by the uncertainty in migration time (Δt_m). The importance of the function $f(t_m)$ in $\Delta\log P_{ow}$ has been discussed thoroughly in "Theoretic Calculations". However, in order to evaluate the full extent of uncertainty of our MEEKC system ($\Delta\log P_{ow}$), we need to know Δt_m as a function of t_m. To obtain that value, we recorded the electropherogram of all compounds five times and calculated the standard deviation of t_m for each compound. With the migration time for each compound given as the mean value of five determinations, we can estimate Δt_m as 1.24 times the standard deviation for a 95% confidence interval (CI), since:

$$\mathrm{CI} = \mathrm{mean} \pm \mathrm{CL} \tag{10}$$

where CL is confidence level, and for $n = 5$,

$$\mathrm{CL} = s \times 2.776/\sqrt{5} = s \times 1.24 \tag{11}$$

Therefore, the $\Delta\log P_{ow}$ values for each compound can be obtained using Eq. 7, which is called $\Delta\log P_{ow}$ (Model) here. All the data, including the experimentally measured Δt_m values, together with the calculated values of $f(t_m)$ and estimated $\Delta\log P_{ow}$ (Model) for all compounds are shown in Table 2.

To have a fair comparison for the model and experiment, the experimental uncertainty should be compared to CL,

$$\Delta\log P_{ow}(\mathrm{model}) = \mathrm{CL} \tag{12}$$

$$\Delta\log P_{ow}(\mathrm{experiment}) = \mathrm{Uncertainty} \tag{13}$$

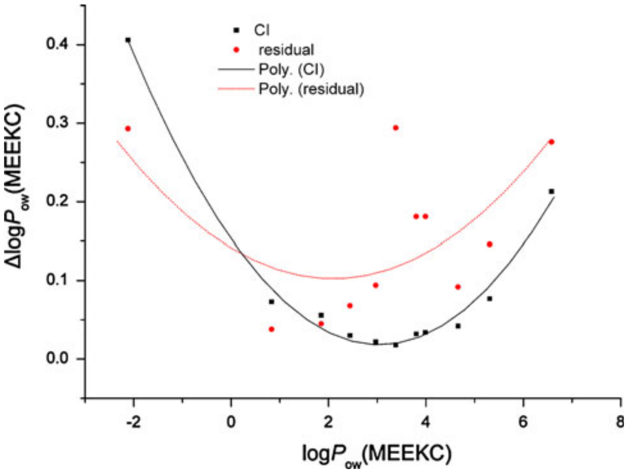

Fig. 4 The error of logP_{ow} ($\Delta\log P_{ow}$) versus logP_{ow}. The *solid line* (———) is polynormal of 95% confidence interval for random uncertainty(CI) versus logP_{ow}, which represents the $\Delta\log P_{ow}$ obtained from our model versus logP_{ow}, i.e., $\Delta\log P_{ow}$ (Model); see Table 2. The *dashed line* (•••••••••) is polynormal of residual versus logP_{ow}, which represents the errors between logP_{ow} values obtained experimentally by MEEKC and those from the linear least-square fitting, i.e., $\Delta\log P_{ow}$ (Experiment); see Table 1

Table 2 gives the experimentally measured Δt_m values, together with a calculated value of $f(t_m)$ and estimated $\Delta\log P_{ow}$ using Eq. 7 for all compounds. The curves of $\Delta\log P_{ow}$ including $\Delta\log P_{ow}$ (Model) and $\Delta\log P_{ow}$ (Experiment) as a function of logP_{ow} are shown in Fig. 4. These two curves show the same trend as the curve for $f(t_m)$ (Fig. 1), except that the rise at the extremes is slower, suggesting that the MEEKC system does not show an extremely abrupt transfer from a high precision to a low precision method, when the migration times approach either t_o or t_{me}. Instead, a somewhat smoother deterioration in the accuracy is observed. Nevertheless, there is still a wide range of $\log P_{ow}$ values that can be measured with fairly high precision. It is also noted in Fig. 4 that while following the same trend, most of the experimentally obtained $\Delta\log P_{ow}$ (Experiment) are somewhat greater than the pseudo-theoretical $\Delta\log P_{ow}$ (Model) versus $\log P_{ow}$. This thereby verifies the model for MEEKC accuracy. Based on the above observation, the high accuracy range of the system is estimated to be between a $\log P_{ow}$ value of 0.50 and 5.50, which is narrower than the range of 0–6.50 as estimated by the $f(t_m)$ curve alone. Outside the range of 0.50–5.50, the uncertainty increases rapidly.

Conclusions

A theoretical model for the dependence of the precision of $\log P_{ow}$ ($\Delta\log P_{ow}$) determinations upon deviations in migration time (Δt_m) in MEEKC was deduced. This model shows that in a given microemulsion system, there is a relatively wide range of $\log P_{ow}$ values that can be measured precisely and accurately. However, as the migration time of analyte approaches either the migration time of the EOF (t_o) or of the microemulsion phase (t_{me}), the precision of $\log P_{ow}$ measurement by MEEKC deteriorates relatively fast. For a system with t_o equal to 6.50 min and t_{me} equal to 32.00 min, respectively, the useful range of $\log P_{ow}$ for accurate measurement is from 0.50 to 5.50, which has been established by both theoretic calculation and experimental verification.

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