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Estimation of log P_{ow} values for neutral and basic compounds by microchip microemulsion electrokinetic chromatography with indirect fluorimetric detection (μMEEKC-IFD)

Jian Tu[a], H. Brian Halsall[a], Carl J. Seliskar[a], Patrick A. Limbach[a], Francisco Arias[b], Kenneth R. Wehmeyer[b,*], William R. Heineman[a]

[a] *Department of Chemistry, University of Cincinnati, OH 45221-0172, USA*
[b] *Procter and Gamble Pharmaceuticals, Analytical Sciences Department, 8700 Mason-Montgomery Road, Mason, OH 45040, USA*

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Abstract

Microchip microemulsion electrokinetic chromatography with indirect fluorimetric detection (μMEEKC-IFD) was used to obtain log *P* octanol/water (log P_{ow}) values for neutral and basic compounds. Six compounds, with log P_{ow} values between 0.38 and 5.03, were used to create a calibration curve relating the log of retention factors (log *k*) obtained from μMEEKC-IFD with the known log P_{ow} values. The log P_{ow} values for six additional compounds were determined using the log *k* values obtained by μMEEKC-IFD and the linear relationship between log P_{ow} and log *k* established for the standard compounds. The μMEEKC-IFD buffer was composed of 50 mM 3-[cyclohexylamino]-1-propane-sulfonic acid (CAPS) buffer (pH 10.4) containing 1.2% *n*-heptane (v/v), 2% sodium dodecylsulfate (w/v), 8% 1-butanol (v/v) and 4 μM 5-carboxytetramethyl-rhodamine (TAMRA) as the fluorophore probe for indirect detection. The μMEEKC-IFD provided an accurate method for estimating log P_{ow} values and also a means for analyzing compounds that are non-fluorescent.

Keywords: Multiplexed capillary electrophoresis; pK_a determination; High throughput

1. Introduction

Miniaturization of analysis has drawn tremendous attention and effort in recent years [1,2]. Microfluidic chips have been fabricated for, and applied to, various techniques including electrophoresis. Microchip capillary electrophoresis (CE) has been implemented for a range of applications such as determining endogenous extracellular signal-regulated protein kinase [3] and β-glucuronidase [4], the ultrafast analysis of oligosaccharides [5], high-speed chiral separation [6], separating and detecting of toxic metal ions [7,8], high-throughput screening [9], explosive compound analysis [10,11], and in other areas of molecular diagnostics [12,13], biomedical and pharmaceutical analysis [14]. These applications had faster analysis times and better separation efficiencies than traditional CE. Most microchip CE applications have been based on the use of fluorescence detection and to a lesser extent electrochemical and mass spectrometric detection [3,4,10,15–18]. However, fluorescence detection requires the analytes to possess an intrinsic fluorescence or to be derivatized with a fluorescent label. This requirement limits the application of the technology.

Indirect detection is a universal technique that can be used to analyze samples that have no inherent chromophore or fluorophore [19–22]. Indirect detection has been used in HPLC and CE for applications such as analyzing a pharmaceutical formulation [23], detecting inorganic and small organic ions and acids [24–26], determining the apparent stability constant of a complex [27], and analyzing beverages [28]. Indirect detection is achieved in microemulsion electrokinetic chromatography (MEEKC) by adding a fluorophore probe to

* Corresponding author. Tel.: +1 513 622 2149; fax: +1 513 622 0523.
E-mail address: wehmeyer.kr@pg.com (K.R. Wehmeyer).

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the running buffer, and is postulated to result from a change in the quantum efficiency of the fluorophore probe in the sample zone. The fluorescence efficiency of the fluorophore probe is higher inside the hydrophobic environment of the microemulsion particle and decreases as the fluorophore is displaced from the microemulsion particles by the analyte [11,29–31]. Indirect detection has been used in microchip systems for analyzing explosives using micellar electrokinetic chromatography (MEKC) [11]. Additionally, indirect fluorescence on microchips has been used to analyze phenols and amino acids using free zone electrophoresis [32,33]. In this mode of operation, the mechanism of the indirect detection is based on the displacement of the visualizing reagents from the sample zone to maintain local charge neutrality [33].

The hydrophobicity of compounds is one of the key parameters that affects the absorption and transportation of compounds into the body and target organs and plays one of the main roles in their biological and physiochemical behavior [34]. The logarithm of the partition coefficient between 1-octanol and water ($\log P_{ow}$) is generally used as a measure of a compound's lipophilicity. Log P_{ow} values have been shown to correlate with drug–receptor interactions, drug–biological membrane interactions, and have been widely used in developing quantitative structure–activity relationships [35].

Direct and indirect methods have been reported to obtain $\log P_{ow}$ values including the traditional shake-flask method [35–38], reversed-phase high performance liquid chromatography (RP-HPLC) [34,39,40], thin layer chromatography [41,42], MEKC [43–46], and MEEKC [47,48]. Only the shake-flask method measures $\log P_{ow}$ values directly. The other approaches are indirect measurements that are based on the construction of a correlation model between the logarithm of the thermodynamic retention factor ($\log k$), obtained using the separation technique, with known $\log P_{ow}$ values obtained by the shake-flask for a training set of compounds. The $\log P_{ow}$ values for test compounds are then determined based on their measured $\log k$ value using the mathematical relationship established for the training set.

Recently, we have demonstrated an application of MEEKC in a multiplexed (96 capillaries) format for the rapid determination of $\log P_{ow}$ values for neutral and basic small molecules [49]. Here we report the development of an approach for measuring $\log P_{ow}$ values using microchip MEEKC with indirect fluorescence detection (μMEEKC-IFD).

2. Experimental

2.1. Chemicals and reagents

Antipyrine, fluphenazine, imipramine, lidocaine, pyrimethamine, sodium tetraborate decahydrate (SigmaUltra), trifluoperazine, verapamil, sudan III, sudan IV, quinine, and 3-[cyclohexylamino]-1-propane-sulfonic acid (CAPS, SigmaUltra grade), were from Sigma (St. Louis, MO, USA). Acetanilide, dimethylsulfoxide (DMSO), indole, quinidine, 1-nitronapthalene, 1-phenyldodecane, 3-methyl-4-nitroanisole, 4-nitroaniline, rhodamine B, rhodamine B base, pyronin B, sulforhodamine B, rhodamine 6G, rhodamine 123 hydrate, orange T, 1-octanol (HPLC grade) and heptane (HPLC grade) were from Aldrich (Milwaukee, WI, USA). Sodium dodecyl sulfate (SDS, >99%), rhodamine 6G perchlorate and rhodamine B octadecyl ester perchlorate, were from Fluka (Milwaukee, WI, USA). *N*-hexylbenzene (98%) and *n*-octylbenzene (99%) were from Avocado Research Chemicals Ltd. (Heysham, Lancashire, UK). *N*-pentylbenzene (>98%) was from Lancaster Synthesis, Inc. (Pelhem, NH, USA). 5-Carboxytetramethyl-rhodamine (TAMRA) was from Molecular Probes Inc. (Eugene, OR, USA). Distilled-deionized water (dd-H_2O) was from a Milli-Q system (Millipore, Bedford, MA, USA). Reagent grade sodium hydroxide (0.1 and 1 M), hydrochloric acid (1 M) and HPLC-grade methanol were from J.T. Baker (Phillipsburg, NJ, USA).

A 50 mM CAPS buffer was prepared by dissolving CAPS in water and adjusting the pH to 10.4 with 1 M NaOH. The MEEKC buffer (50 mM CAPS/2% SDS (w/v)/8% 1-butanol (v/v)/1.2% heptane (v/v)) was prepared by wetting sodium dodecylsulfate with 1-butanol and *n*-heptane before adding 50 mM CAPS buffer. The solution was sonicated for 30 min and filtered through a 0.45 μm filter. It is stable at least for 2 months. TAMRA was dissolved in methanol as a stock solution and diluted to the desired concentrations with MEEKC buffer. TAMRA concentrations of 1, 4 and 8 μM were evaluated in the MEEKC running buffer.

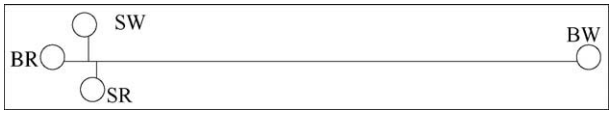

Fig. 1. Diagram of the Micralyne TT-100 chip. BR: buffer reservoir; BW: buffer waste; SR: sample reservoir; SW: sample waste.

2.2. Microchip separation equipment

All the microchip electrophoresis experiments were performed on Micralyne Microfluidic Tool Kit (μTK) instrument (Micralyne Inc., Edmonton, AB, Canada). The system consists of a high-voltage (HV) power supply and a laser-induced fluorescence (LIF) detection system made up a 532 nm frequency-doubled Nd-YAG laser (4 mW), dichroic beamsplitter, 550 nm long-pass filter, a 568.2 nm bandpass filter and a PMT detector. The μTK instrument was controlled by a LabView (National Instruments, Austin, TX, USA) executable file. The data were recorded and analyzed by TurboChrom 4.0 (Perkin Elmer Corp., Cupertino, CA, USA). All the microchip experiments were done on Micralyne TT-100 glass chips. A chip diagram is shown in Fig. 1. The detection distance was set at 8 mm from the intersection of the injection and separation channels.

2.3. Preparation of standards and test compound solutions

The standard and test compounds were prepared at 10 mg/ml in MEEKC buffer and then modified to contain 4% (v/v) DMSO and 1.2% (v/v) 1-phenyldodecane. In brief, approximately 5 mg of each compound were placed into individual glass vials and 0.5 ml of MEEKC buffer was added to the vials. The vials were capped and shaken by hand for 1 min and then 6 μl of 1-phenyldodecane were added to each vial. The vials were again capped and shaken by hand for 1 min. Finally, 20 μl of DMSO were added to each vial, the vials were capped and shaken by hand for 1 min. The prepared standards and samples were analyzed by μMEEKC-IFD within 30 min to limit potential degradation of the compounds at the elevated pH of the MEEKC buffer.

2.4. Microchip modification, preparation and storage

The glass microchips were modified at the four access holes by cutting the back ends of plastic micropipette tips (1–200 μl, VWR Scientific Products, West Chester, PA, USA) with a razor blade and gluing them around the access holes with two-part epoxy (Devcon Consumer Products, Des Plains, IL, USA) to create reservoirs. The microchip channels were conditioned by washing sequentially with 1 M HCl (5 min), 0.1 M NaOH (5 min), dd-H_2O (5 min) and MEEKC buffer with 4 μM TAMRA (1 min) at the beginning of the experiment. The washing procedures were done by applying vacuum to one reservoir and supplying the other three with the appropriate solution. After finishing the experiments, the channels were cleaned by washing with 1 M HCl (15 min), 0.1 M NaOH (4–8 h), and dd-H_2O (15 min). The channels were dried under vacuum and the microchip was stored dry.

2.5. μMEEKC-IFD separation conditions

Solutions were loaded manually in the access holes of the modified microchip using a micropipette. The sample solution (100 μl) was loaded into sample access reservoir (SR), and buffer solution (80–100 μl) was loaded into buffer access reservoir (BR), buffer waste reservoir (BW) and sample waste reservoir (SW). A 30 s electrophoretic conditioning step was done prior to the injections and then four consecutive on-chip injections were made by repeating the plug formation and separation steps shown in Table 1. The sample plug was formed at the intersection with EOF "pinching" by applying voltages at the SR and the BR and BW reservoirs while holding SW at ground. During the separation step, positive voltages were maintained at the SR and SW reservoirs to "pull-back" sample by pulling sample left at the injection channel back to the access holes therefore prevented sample leaking to the separation channel.

2.6. Calculation of log k and log P_{ow} values

The electropherograms generated by the μTK were analyzed by TurboChrom 4.0 to obtain the migration times of the peaks for DMSO, the neutral marker (t_{nm}), the compound (t_r) and 1-phenyldodecane, the microemulsion marker (t_{mm}). The k value was calculated using Eq. (1)

$$k = \frac{t_r - t_{nm}}{t_{nm}(1 - t_r/t_{nm})} \quad (1)$$

The log k value for the standards were used to construct a calibration curve by plotting the log k value for each standard versus its known log P_{ow} value. The log P_{ow} value for the test compounds were calculated based on the relationship established between log k and log P_{ow} for the standards.

3. Results and discussion

3.1. μMEEKC optimization

A representative electropherogram for imipramine obtained using μMEEKC-IFD with 4 μM TAMRA as the visualization agent is shown in Fig. 2. The first peak in the electropherogram is due to DMSO, the neutral marker, the second is a system peak, the third is imipramine and the last peak is 1-phenyldodecane, the microemulsion marker. The separation of the peaks was easily achievable, however the detection of the microemulsion marker and sometimes the test compounds could be difficult and careful optimization of the analysis conditions was required to obtain satisfactory results, as detailed below.

3.1.1. Influence of the laser focusing and alignment

The LIF detection system in the μTK uses an optical lens to focus the laser onto the separation channel in the microchip and to collect the fluorescence signal. The laser must be focused and aligned every time the microchip is loaded into the instrument. These adjustments are subjective and must be set carefully to obtain sufficient sensitivity from run to run. Less

Table 1
Injection protocol for μMEEKC-IFD

Step	Duration (s)	Sample, SR (kV)	Sample waste, SW (kV)	Buffer, BR (kV)	Buffer waste, BW (kV)
Conditioning	30	0.8	0.8	1	GND
Plug formation	60	0.7	GND	0.38	0.7
Separation	180	1.6	1.6	2	GND

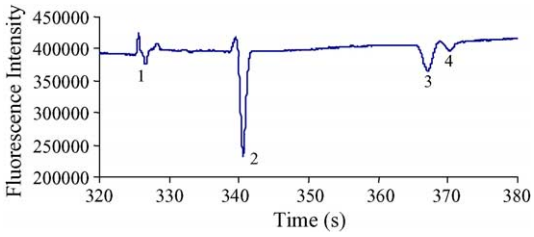

Fig. 2. Electropherogram for the separation of imipramine obtained by μMEEKC-IFD: (1) DMSO, (2) system peak, (3) imipramine and (4) 1-phenyldodecane. The CE conditions employed a 50 mM CAPS buffer (pH 10.4) containing 1.2% *n*-heptane (v/v), 2% sodium dodecylsulfate (w/v), 8% 1-butanol (v/v) and 4 μM 5-TAMRA and used the voltage program shown in Table 2.

than optimal focusing of the laser can result in difficulties in detecting some compounds and the microemulsion marker.

3.1.2. Choice of the fluorophore probe

Indirect detection in MEEKC is hypothesized to occur by a change in the quantum yield of the fluorophore probe as it is displaced from the hydrophobic microemulsion particle into the running buffer by the analyte [30]. A number of potential laser dyes with different charges and structures were evaluated to try to optimize the indirect response in the MEEKC buffer system. Therefore, in addition to TAMRA, eight laser dyes (rhodamine B, rhodamine B base, pyronin B, sulforhodamine B, rhodamine 6G, rhodamine 123 hydrate, rhodamine 6G perchlorate and rhodamine B octadecyl ester perchlorate) were tested as fluorophore probes to evaluate sensitivity and baseline stability. The concentration of each dye was adjusted between 1 and 10 μM so that a similar level of background signal was achieved with each dye. Although all dyes gave approximately the same detection sensitivity there were problems with some of the dyes. Using sulforhodamine B or rhodamine 6G in the MEEKC running buffer resulted in two major system peaks that complicated the assay and increased the probability that analytes would co-elute with the system peaks. Except for pyronin B, the other dyes gave only one system peak, but the system peak for them was very close to the migration time of the microemulsion marker and complicated the analysis. Although pyronin B could be used as a substitute for TAMRA, it offered no real advantages in terms of sensitivity and baseline stability; therefore, TAMRA was used for all these studies.

The concentration of the fluorophore probe is typically in the low μM range for optimal results in indirect fluorescence detection [11,31]. The TAMRA concentration in the MEEKC running buffer was evaluated at the 1, 4 and 8 μM level. Under our PMT settings concentrations greater than 10 μM saturated the LIF detector. The 1 and 8 μM TAMRA concentrations in the MEEKC running buffer gave a less stable baseline and more difficulty in obtaining reproducible results than did 4 μM TAMRA (data not shown), and so 4 μM TAMRA was used as the concentration of the fluorophore probe for all remaining studies.

3.1.3. Selection and optimization of the microemulsion marker

Being able to detect the microemulsion marker consistently is crucial for calculating the $\log k$. In addition to 1-phenyldodecane, several potential markers were evaluated including sudan III, sudan IV, quinine, orange T, *n*-pentylbenzene, *n*-hexylbenzene and *n*-octylbenzene. Several compounds were not detected (sudan III, sudan IV, quinine, orange T) presumably due to insufficient solubility in the MEEKC buffer. The *n*-pentylbenzene, *n*-hexylbenzene and *n*-octylbenzene gave similar detection as 1-phenyldodecane, however, *n*-octylbenzene gave split peaks (data not shown). The 1-phenyldodecane was chosen as the microemulsion marker since it is more hydrophobic than either the *n*-pentylbenzene or *n*-hexylbenzene. The best signal response was obtained at a volume ratio of 1.2% of 1-phenyldodecane in the MEEKC buffer. At lower concentrations the signal was smaller and higher concentrations often resulted in the collapse of the microemulsion system and separation of the layers. Therefore, a 1.2% concentration of 1-phenyldodecane was used for $\log P_{ow}$ experiments.

3.1.4. Conditioning and care of the glass microchip

The glass microchip surface is critical for reproducible performance. Upon applying voltage, a sample plug is formed at the intersection of the separation channel and injection channel. It has been demonstrated under the normal potential conditions used in our studies that an injection bias occurs for negatively charged species and less material is injected as the negative charge increases [50]. The microemulsion droplets carry a high negative charge due to the incorporation of the SDS and therefore the microemulsion droplets, the microemulsion marker, and the test species partitioned into the microemulsion particles experience a negative injection bias. The injection of the negatively charged microemulsion droplets was maximized by maintaining a strong EOF to "sweep" the negatively charged droplets from the injection plug into the separation channel. The EOF degraded under the conditions required for μMEEKC-IFD and it was necessary to clean the chips after several hours of continuous use in order to maintain a sufficient EOF. Therefore we routinely rotated multiple chips during a single day with some chips being cleaned while others were in use.

3.1.5. Influence of the voltage program

Electric field distribution often plays an important role in the improvement of the chip performance [50,51]. Therefore, the voltage program was optimized to increase the amount of the sample injected and to provide a stable background signal. The peak shapes and heights changed when the pinching voltages applied at the buffer and buffer waste varied during injection. The currents at the four access holes were monitored and used to guide the choice of the optimal voltages. During the plug formation step, positive currents around 5 μA were maintained at BR and BW to provide a "pinch" effect for the injection. Higher positive currents at BR and BW

resulted in sharper peaks but less sample was injected into the separation channel. During the separation step, negative currents of less than −10 μA were maintained at SR and SW to push the sample back into the injection channel. Lower separation voltages (1 kV versus 2 kV at the separation channel) improved the background stability, although increasing the electrophoretic run time. The microemulsion marker was more detectable with a 60 s-injection than a 30 s-injection (data not shown).

3.1.6. The effect of sample preparation

Sample preparation played an important role in the log P_{ow} determinations. The amount and order of addition of the neutral marker, DMSO, and the microemulsion marker, 1-phenyldodecane, were important. The amount of DMSO had to be optimized to provide a compromise between the detectability of the neutral marker and the stability of the microemulsion. DMSO at 1% (v/v) was not detectable, but at 10% (v/v) caused cloudiness in the sample indicating problems with the microemulsion. The best results were obtained by preparing the samples in the MEEKC buffer by dissolving, in order, the test compound, and the microemulsion marker, and then adding DMSO to 4% (v/v) as described in Section 2.

3.2. Calibration curve

A series of standard compounds including antipyrine: (log P_{ow} = 0.38[a]), 4-nitroaniline (log P_{ow} = 1.39[b]), lidocaine (log P_{ow} = 2.26[a]), pyrimethamine (log P_{ow} = 2.69[a]), imipramine (log P_{ow} = 4.80[a]) and trifluoperazine (log P_{ow} = 5.03[a]) were analyzed by μMEEKC-IFD to generate a calibration curve (log P_{ow} values from *a* [53] and *b* [46]). Each standard was injected four times and the average log *k* values obtained from the electropherograms were plotted versus their known literature log P_{ow} values to generate the universal calibration curve (Fig. 3). The plot was linear and the variability in the determination of the *k* value from the replicate injections of the standards were between 1.5 and 7.8% (Table 2).

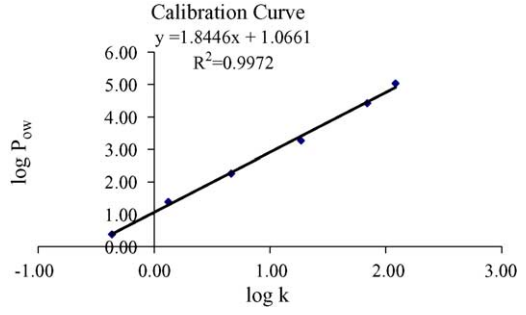

Fig. 3. Calibration curve generated by plotting log *k* obtained by μMEEKC-IFD for a series of standards (antipyrine, 4-nitroaniline, lidocaine, pyrimethamine, imipramine and trifluoperazine) vs. the published log P_{ow}. Published log P_{ow} obtained from references [46] and [53].

Table 2
Precision of *k* value determination for standards by μMEEKC-IFD[a]

Standard	*k*	%RSD
Antipyrine	0.42	7.8
4-Nitroaniline	1.30	1.9
Lidocaine	3.99	1.5
Pyrimethamine	18.53	2.6
Trifluoperazine	97.83	3.9

[a] $n = 3$.

3.3. μMEEKC-IFD determination of log P_{ow} for test compounds

A series of test compounds with known literature log P_{ow} values were analyzed by μMEEKC-IFD. The average log *k* value was calculated for each compound from its electropherogram, and the corresponding log P_{ow} value was calculated based on the standard curve (Table 3). The log P_{ow} values determined by the μMEEKC-IFD approach were within 0.20 log units for published log P_{ow} values less than 4 and within 0.45–0.55 log units for log P_{ow} values greater than 4. The higher variability for log $P_{ow} > 4$ is due to the fact that the compounds migrated close to the microemulsion marker making the determination of the *k* value more difficult. To increase the range of log P_{ow} values that can be examined the MEEKC buffer could be modified by increasing the concentration of the SDS. Finally, the variability in the determination of the log P_{ow} for one of the compounds, antipyrine, was examined over a three day period, and the between day %RSD for the compound was 5.4% (data not shown).

3.4. Reproducibility of μMEEKC-IFD

A number of factors can cause the migration times of the sample components to vary. For example, the use of multiple chips, room temperature fluctuations, buffer depletion in the chip reservoirs due to electrolysis, siphoning, viscosity changes caused by Joule heating and the surface tension of the meniscus in the buffer reservoirs can all affect the bulk flow on a microchip [52]. The large buffer volumes (150 μL) used in the modified chip reservoirs should have lessened the effects of buffer depletion, siphoning and meniscus sur-

Table 3
Comparison of log P_{ow} values from literature and μMEEKC-IFD[a]

Compound	log *k*	μMEEKC log *P*	Lit. log *P*[b]	Δlog *P*[c]
Acetanilide	−0.04	1.00	1.16[a]	−0.16
3-Methyl-4-nitroanisole	0.70	2.38	2.32[b]	0.06
Quinidine	1.27	3.46	3.44[a]	0.02
1-Nitronaphthalene	1.22	3.38	3.19[b]	0.19
Verapamil	1.68	4.24	3.79[a]	0.45
Fluphenazine	2.03	4.91	4.36[a]	0.55

[a] Lit. log *P* = literature value for log P_{ow} (*a* = literature log P_{ow} values obtained from Ref. [53] and *b* = literature log P_{ow} values obtained from Ref. [46]).
[b] μMEEKC log *P* = value of log P_{ow} calculated by μMEEKC-IFD.
[c] Δlog *P* = μMEEKC log P_{ow} − literature log P_{ow}.

Table 4
Precision of k value determination for test compounds by μMEEKC-IFD[a]

Compound	k	%RSD
Acetanilide	0.92	3.4
3-Methyl-4-nitroanisole	4.96	2.7
Quinidine	16.78	1.8
1-Nitronaphthalene	18.56	11.4
Fluphenazine	108.02	8.5

[a] $n = 3$.

face tension. Other variables such as chip-to-chip variability, Joule heating and temperature fluctuations were more difficult to control. Nevertheless, Eq. (1) predicts that variations in migration times should have a minimal or no effect on the k value determinations since the sample, the neutral marker and microemulsion marker migrations should all be affected similarly by changes in the EOF. The %RSD for replicate determinations of k values for the standards (Table 2) and samples (Table 4) were between 1.5 and 11.4, the great majority were less than 5%.

4. Conclusions

We have demonstrated that microchip capillary electrophoresis with indirect fluorimetric detection can be used to determine the $\log P_{ow}$ for neutral and basic compounds in a miniaturized format. The methodology is broadly applicable to any neutral or basic compound since the indirect detection provides a universal analysis mode. The current approach on glass microchips does not provide a speed enhancement versus conventional CE due to the need to empty and clean the sample reservoir for each new compound and the need to condition the chip after several hours of running with the MEEKC buffer. However, future efforts will involve the implementation of multilane glass and plastic chips. The use of a 12-lane chip in conjunction with simultaneous indirect LIF detection across the lanes would provide a significant increase in throughput. The use of cheap, disposable multilane plastic chips would provide a further speed enhancement since chips would not need to be cleaned or conditioned after use but rather could simply be discarded. In summary, the current work provides a proof-of-concept for employing microchip MEEKC in conjunction with indirect LIF detection to provide a means for obtaining $\log P_{ow}$ values for neutral and basic compounds.

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