

The Application of Multiplexed Microemulsion Electrokinetic Chromatography for the Rapid Determination of $\log P_{ow}$ Values for Neutral and Basic Compounds

COMMUNICATIONS

The authors used multiplexed microemulsion electrokinetic chromatography with ultraviolet absorbance detection to develop a rapid approach for obtaining $\log P_{ow}$ values of neutral and basic compounds. By using a series of compounds ($n = 42$) that covered a wide range of $\log P_{ow}$ values, they established a universal calibration curve relating the log of retention factors ($\log k$) obtained from multiplexed microemulsion electrokinetic chromatography to the known $\log P_{ow}$ values. The $\log P_{ow}$ values for additional compounds were obtained from their $\log k$ values by interpolating from the universal calibration curve. The multiplexed microemulsion electrokinetic chromatography performance for $\log P_{ow}$ determinations was reproducible for multiple days and provided a rapid and accurate approach for obtaining $\log P_{ow}$ values.



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Compounds' hydrophobicity plays a key role in their biological and physiochemical behavior (1–3). It is one of the key parameters that affects the absorption and transport of compounds into the body and target organs. The logarithm of the partition coefficient between 1-octanol and water ($\log P_{ow}$) generally is used as a measure of compound lipophilicity (1). The $\log P_{ow}$ coefficient for compounds has been shown to correlate with drug-receptor interactions and drug-biological membrane interactions, and it is used commonly to develop quantitative structure-activity relationships for compounds (1,2). Most marketed drugs have $\log P_{ow}$ values of 1–5 (1). The shake-flask method has been the most widely used technique for obtaining $\log P_{ow}$ values for diverse compounds; however, the shake-flask method is time-consuming and labor-intensive, and it requires significant amounts of compounds (1,4–6).

In today's modern drug discovery environment, combinatorial chemists generate large numbers of compounds in a relatively

short timeframe, and rapid approaches are needed to assess $\log P_{ow}$ values of these compounds (2,4,7). Several separation-based approaches for indirectly determining $\log P_{ow}$ values in a rapid fashion have been reported, including reversed-phase high performance liquid chromatography (HPLC) (2,3,8–11), thin-layer chromatography (12,13), micellar electrokinetic chromatography (MEKC) (7,14–16), and microemulsion electrokinetic chromatography (3,4, 17–19). All of these approaches are based upon the construction of a correlation model between the logarithm of the thermodynamic capacity factor ($\log k$), obtained using the separation technique, with known $\log P_{ow}$ values obtained by the shake-flask method for a training set of compounds. The $\log P_{ow}$ values for test compounds then are determined based upon their measured $\log k$ value using the mathematical relationship established for the training set.

Relative to the shake-flask method, reversed-phase HPLC offers several advantages for the determination of $\log P_{ow}$ values, including faster analysis times, improved

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reproducibility, wide dynamic range, and smaller amounts of sample necessary for testing (2,3). However, the reversed-phase HPLC approach generally has several shortcomings, including correlations that often are limited to compounds of a congeneric series and complications arising from undesirable secondary interactions between the compounds and the stationary phase (4,6,17). The limited correlation between $\log k$ and $\log P_{ow}$ obtained by reversed-phase HPLC is caused by several factors, including the lack of hydrogen-bond basicity of common reversed-phase sorbents and the contrasting dipolar characteristics of the sorbents relative to the octanol–water system (4–6,7,17,19). Chemists can obtain improved correlations by taking the hydrogen acceptor and donor effects into account (2,4,19). In addition, researchers have reported that using k_w (retention factor extrapolated to a 0% concentration of organic solvent) and adding *n*-octanol to the mobile phase improved partition coefficient–retention factor correlations for various drug-like compounds with a broad $\log P_{ow}$ range (10,11).

Researchers have used MEKC approaches for determining $\log P_{ow}$ values with several micelle types, including deoxycholic acid, sodium dodecyl sulfate (SDS), dodecyltrimethylammonium chloride, cetyltrimethylammonium chloride, and liposomes (17,20,21). Similar to those obtained by reversed-phase HPLC approaches, $\log P_{ow}$ values obtained by the MEKC method and the shake-flask method often exhibit limited correlation mainly because of hydrogen bonding and dipolar interaction differences between the systems (3,5,6,17). Microemulsion electrokinetic chromatography has provided improved correlations between $\log k$ and $\log P_{ow}$ values throughout a broad range of compounds (3,15).

In the early 1990s, the Mathies (22,23), Yeung (24,25), and Kambara (26) groups introduced parallel or multiplexed capillary electrophoresis. The use of multiplexed capillary arrays provide the potential of increasing the sample throughput without a tremendous increase in instrumentation complexity or cost. Initial efforts with multiplexed arrays focused on capillary gel electrophoresis for deoxyribonucleic acid (DNA) sequencing because of interest in the Human Genome Project (27–38). A few reports also addressed the development, characterization, and application of multiplexed CE for enzyme analysis, analysis of endogenous enzyme levels from *in vitro* cell systems, combinatorial screening of catalysis

reaction conditions, analysis of small organic molecules, metabolite analysis, and peptide mapping (39–45).

In this article, we report the application of multiplexed microemulsion electrokinetic chromatography with ultraviolet (UV) detection for the rapid determination of $\log P_{ow}$ values for neutral and basic small molecules. We used an array of 96 capillaries in conjunction with a microemulsion electrokinetic chromatography running buffer to establish the correlation between $\log k$ and $\log P_{ow}$ for a series of standard compounds. We determined the $\log P_{ow}$ values for a series of test compounds using the $\log k$ values obtained by multiplexed microemulsion electrokinetic chromatography analysis in conjunction with the correlation established between $\log k$ and $\log P_{ow}$ for the standard compounds.

Experimental

Chemicals: We obtained haloperidol from Research Biochemicals International (Natick, Massachusetts) and SDS (>99%) from Fluka (Milwaukee, Wisconsin). The sodium tetraborate decahydrate, 3-(cyclohexylamino)-1-propanesulfonic acid, 1-octanol (HPLC grade), and heptane (HPLC grade) were purchased from Sigma-Aldrich (Milwaukee, Wisconsin). All other reagents and test compounds were purchased from Sigma-Aldrich (Milwaukee, Wisconsin) and were of the highest available quality. We produced distilled, deionized water using a Milli-Q water-purification system (Millipore, Bedford, Massachusetts).

Reagents and solutions: We prepared a 20 mM borate buffer (pH 9.3) by adding 7.62 g of sodium tetraborate decahydrate to a 1-L volumetric flask and diluting it to volume with distilled, deionized water. We made a 68 mM 3-(cyclohexylamino)-1-propanesulfonic acid (pH 10.4) solution by adding 15.05 g of 3-(cyclohexylamino)-1-propanesulfonic acid and 800 mL of distilled, deionized water to a 1-L volumetric flask; stirring to dissolve the 3-(cyclohexylamino)-1-propanesulfonic acid; adjusting the pH to 10.4 with 1 N sodium hydroxide; and diluting the mixture to volume with distilled, deionized water.

We prepared a microemulsion electrokinetic chromatography buffer of 68 mM 3-(cyclohexylamino)-1-propanesulfonic acid–2.2% SDS (w/v)–8% 1-butanol (v/v)–1.2% heptane (v/v) by adding 22.05 g of SDS, 80 mL of 1-butanol, and 12 mL of *n*-heptane to a beaker and mixing them by swirling for 1 min. After the compounds were mixed, we added 800 mL of 68 mM

3-(cyclohexylamino)-1-propanesulfonic acid (pH 10.4) to the beaker and stirred the resulting mixture for several minutes or until all the SDS was dissolved. The solution then was sonicated for 30 min to produce a clear solution. After sonication, we transferred the solution to a 1-L volumetric flask and diluted it to volume with the 68 mM 3-(cyclohexylamino)-1-propanesulfonic acid (pH 10.4). We let the solution stand for 1 h and then filtered it through a 0.45- μ m filter. This solution was stable for at least two months at ambient temperature.

Preparation of standards and test compounds: We placed approximately 1 mg of each compound into individual glass vials and added 1 mL of the microemulsion electrokinetic chromatography buffer with 1% (v/v) dimethyl sulfoxide (DMSO) and 1 mg/mL of 1-phenyldodecane. We capped the vials, sonicated them for 10 min, and then placed a 0.20-mL aliquot of each sample into four consecutive wells of a 96-well plate. The prepared samples were analyzed by multiplexed microemulsion electrokinetic chromatography within 30 min to limit potential degradation of the compounds at the elevated pH of the microemulsion electrokinetic chromatography buffer.

Preparation of combined standards: We prepared a combined standard solution by adding approximately 1 mg each of antipyrine, phenylacetate, lidocaine, 9-fluorenone, fluphenazine, and pentachloronitrobenzene into a single glass vial and dissolving in 1 mL of the microemulsion electrokinetic chromatography buffer with 1% (v/v) DMSO and 1 mg/mL of 1-phenyldodecane. The combined standard solution was analyzed by multiplexed microemulsion electrokinetic chromatography on each day of analysis.

Multiplexed microemulsion electrokinetic chromatography separation conditions: The multiplexed microemulsion electrokinetic chromatography separations were performed using an MCE 2000 instrument from CombiSep (Ames, Iowa). The multiplexed CE instrument was equipped with a capillary array of 96 uncoated fused-silica capillaries (52 cm \times 75 μ m, 32 cm effective length). The capillary array was conditioned by washing sequentially with 0.1 N sodium hydroxide for 5 min; distilled, deionized water for 5 min; and 20 mM borate (pH 9.3) for 5 min at the beginning of the experiment. We introduced microemulsion electrokinetic chromatography buffer into the capillaries by vacuum filling or by electrophoresis at 4.5 kV. We injected test sam-

ples, standards, and combined standards by vacuum at -0.2 psi for 10 s. The separation was performed at 4.5 kV for 1.5 h. We used a detection wavelength of 214 nm for all analyses. Electropherograms were generated using the multiplexed CE system's software — MCE Manager (CombiSep). After analysis, the capillaries were washed sequentially with 0.1 N sodium hydroxide for 5 min and water for 5 min.

Calculation of log k and log P_{ow} values:

The electropherograms generated by the multiplexed CE software were processed using the Log P Calculator program (CombiSep), which automatically generated log k values from the electropherograms. We used the log k value for the standards or the combined standards to construct a calibration curve by plotting the log k value for each standard versus its literature log P_{ow} value. The log P_{ow} values for the test compounds were calculated automatically by the calculator program based upon the relationship established between log k and log P_{ow} for the standards.

Results

Multiplexed microemulsion electrokinetic chromatography separation: Figure 1 shows representative electropherograms obtained using multiplexed microemulsion electrokinetic chromatography for a series

of compounds. The first peak in each electropherogram is DMSO, the neutral marker (t_{nm}); the second peak is the compound (t_r); and the last peak is 1-phenyldodecane, the microemulsion marker (t_{mm}). We observed some variation in the migration time of the neutral marker and microemulsion marker across the capillaries. Others have reported variation in migration times across capillary arrays previously, and it is caused by differences in the surface properties of individual capillaries and the potential for slight temperature differences across the capillary array (34,42). The surface property differences and thermal gradients result in variation in the electroosmotic flow between the capillaries and hence differences in t_{nm} and t_{mm} between the capillaries of the array. However, the k value (equation 1) obtained for a compound analyzed on multiple capillaries should be unaffected because t_{nm} and t_{mm} are affected in a similar manner within a given capillary.

$$k = \frac{t_r - t_{nm}}{t_{nm} \left(1 - t_r/t_{mm}\right)} \quad [1]$$

Universal calibration curve: A series of standard compounds (see Table I) was analyzed by multiplexed microemulsion elec-

trokinetic chromatography to generate a universal calibration curve. Each standard was injected into four consecutive capillaries in the array, and Table I lists the average log k value obtained from the electropherograms and the relative standard deviation (RSD) for the averages. In general, the RSD values for the standards were in the 3–9% range, but a few compounds had larger deviations.

The accuracy and precision of the log k determinations also were examined for a subset of the standards during a three-day period (see Table II and Table III). As Table II shows, the log k values for the com-

Table I: Precision of log k values determined by multiplexed microemulsion electrokinetic chromatography*

Compound	log k	RSD (%)
Sulfaguanidine	-0.88	1.2
Sulfanilamide	-0.71	1.2
Nicotinamide	-0.97	0.0
2-Aminopyrimidine	-1.05	0.6
Caffeine	-0.73	0.0
Antipyrine	-0.42	1.2
Hydroquinone	-0.22	0.3
Benzamide	-0.34	1.5
Sulfamethoxazole	0.12	2.2
Aniline	-0.25	2.5
Chloramphenicol	0.09	8.4
Acetanilide	-0.11	9.1
Phenylacetate	0.13	1.4
Cortisone	0.38	5.2
Hydrocortisone	0.50	3.1
4-Chloroaniline	0.46	1.5
Nitrobenzene	0.27	4.8
<i>m</i> -Cresol	0.23	4.1
<i>p</i> -Cresol	0.33	5.9
Lidocaine	0.66	1.2
Ethylbenzoate	0.82	2.3
1-Naphthol	0.75	1.7
Toluene	0.77	1.0
2-Naphthol	0.72	2.3
Azulene	1.12	5.2
Haloperidol	1.26	2.5
Naphthalene	1.24	3.3
Chloropheniramine	1.23	4.2
Benzophenone	1.03	4.0
9-Fluorenone	1.22	2.6
Verapamil	1.38	4.2
Pentachlorophenol	1.31	0.9
Biphenyl	1.55	6.0
1-Methylnaphthalene	1.61	4.5
Fluphenazine	1.66	4.5
Imipramine	1.67	3.3
Bibenzyl	1.99	3.6
Desipramine	1.59	3.9
Pyrene	2.06	5.8
Trifluoperazine	1.65	1.3
Chlorpromazine	1.92	3.8
Pentachloronitrobenzene	2.03	4.5

* $n = 4$ for each compound.

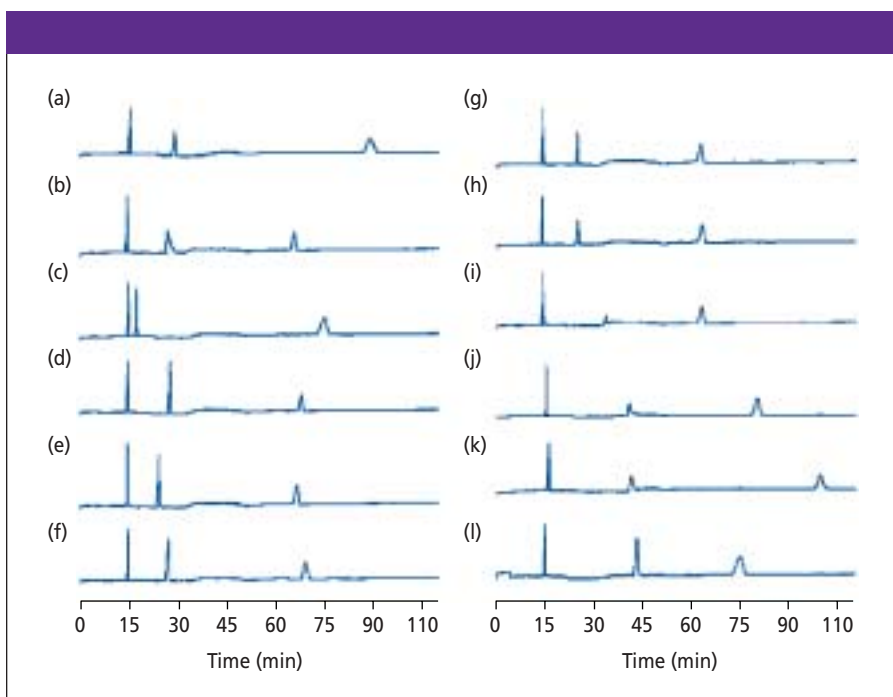


Figure 1: Electropherograms of a series of individual compounds obtained by multiplexed microemulsion electrokinetic chromatography using a 96-capillary array. The first and third peaks in each electropherogram are DMSO and 1-phenyldodecane, respectively, and the middle peak is the compound. The compounds were (a) oxytetracycline, (b) uracil, (c) sulfanilamide, (d) theophylline, (e) azathioprine, (f) sulfamethoxazole, (g) chloramphenicol, (h) phenylacetate, (i) hydrocortisone, (j) 4-chloroaniline, (k) *p*-cresol, and (l) lidocaine.

Table II: Between-day accuracy for log *k* determined by multiplexed microemulsion electrokinetic chromatography*

Compound	log <i>k</i>				
	Day 1	Day 2	Day 3	Average	RSD (%)
Sulfamethoxazole	0.11	0.17	0.13	0.14	21.74
Chloramphenicol	0.06	0.11	0.10	0.09	28.55
Phenylacetate	0.10	0.15	0.13	0.13	19.56
Hydrocortisone	0.46	0.51	0.48	0.48	5.32
4-Chloroaniline	0.48	0.48	0.46	0.47	2.19
<i>p</i> -Cresol	0.29	0.36	0.34	0.33	9.96
Lidocaine	0.68	0.69	0.60	0.66	7.39
Ethylbenzoate	0.79	0.83	0.83	0.82	2.99
1-Naphthol	0.71	0.76	0.77	0.75	4.37
2-Naphthol	0.69	0.73	0.74	0.72	3.94
Haloperidol	1.20	1.24	1.28	1.24	3.06
Chloropheniramine	1.21	1.24	1.26	1.24	1.93
9-Fluorenone	1.18	1.23	1.25	1.22	3.06
1-Methylnaphthalene	1.54	1.58	1.60	1.57	2.16
Fluphenazine	1.56	1.67	1.62	1.62	3.21
Pyrene	ND†	2.09	2.03	2.06	2.09
Chlorpromazine	1.85	1.94	1.96	1.92	3.09

**n* = 4 for each compound.
†ND = not determined.

pounds were reproducible between the three-day period with RSD values generally 2–7%. Compounds with log *k* values less than 0.2 demonstrated a higher variability, which indicated that polar, fast-migrating compounds apparently are more susceptible to small temperature and flow changes between days. As Table III shows, the reproducibility of the log *k* determinations between replicate capillaries within a day, as measured by the RSD, was generally 3–8%.

In Figure 2, the log *k* values for the standards were plotted versus their literature log *P*_{ow} values to generate the universal calibration curve. Table IV lists the log *P*_{ow} value calculated for each standard from the universal calibration curve (3,4,7,45–47). In general, log *P*_{ow} values obtained from the universal calibration curve were within 0.3–0.5 units of the corresponding literature log *P*_{ow} value (Table IV). We should note that the compounds should be in an uncharged state to obtain a relevant correlation with the literature log *P*_{ow} values (4,6). If a compound is charged, it can undergo electrostatic interactions with the charged microemulsion droplets and electrophoretic migration. The effects of either of these processes can cause the determined value of log *k* to deviate from the simple partition process. Although analysts can correct for these factors using a migration index concept (5), it is simpler to maintain all compounds in the neutral state. Therefore, the pH of the running buffer should be selected so that the basic compounds of interest will exist in their neutral form.

Combined standards calibration curve:

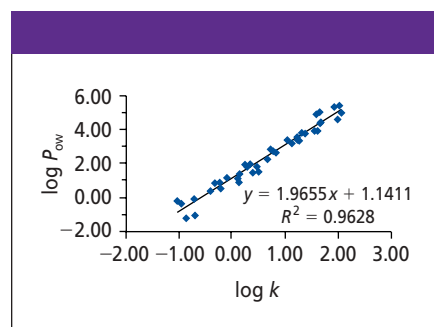
We chose a subset of the universal calibration standards and combined them in a single sample to allow the generation of a calibration curve for each plate of samples. We chose the subset of standards to provide a regression plot with a slope and intercept similar to the universal calibration curve and to span a wide range of log *P*_{ow} values. Figure 3a shows a representative electropherogram for the combined standard set. Figure 3b shows a representative calibration curve obtained for the combined standards. We examined the reproducibility of the combined calibration curve during a three-day period by monitoring the slope and intercept. As Table V shows, the combined calibration curve was highly reproducible between days, with RSD values for the slope and intercept of 0.30% and 3.5%, respectively.

Multiplexed microemulsion electrokinetic chromatography determination of log *P*_{ow} for test compounds: We analyzed a series of commercially available test compounds with known literature log *P*_{ow} values by multiplexed microemulsion electrokinetic chromatography using the combined calibration standard curve. We injected the test compounds into four consecutive capillaries, calculated the average log *k* value for each compound from their electropherograms, and calculated the corresponding log *P*_{ow} value for each test compound based upon the combined standard curve (see Table VI). As Table VI shows, the log *P*_{ow} values determined by the multi-

Table III: Between-day precision for log *k* determined by multiplexed microemulsion electrokinetic chromatography*

Compound	RSD for log <i>k</i> (%)		
	Day 1	Day 2	Day 3
Sulfamethoxazole	10.86	4.46	7.02
Chloramphenicol	14.88	2.11	8.44
Phenylacetate	14.14	8.54	16.05
Hydrocortisone	3.11	3.03	4.27
4-Chloroaniline	16.74	2.69	15.03
<i>p</i> -Cresol	1.97	5.92	19.02
Lidocaine	ND†	1.22	7.12
Ethylbenzoate	1.60	4.16	2.34
1-Naphthol	0.00	2.88	1.74
2-Naphthol	2.05	2.33	5.49
Haloperidol	2.50	2.47	4.41
Chloropheniramine	4.23	4.20	4.02
9-Fluorenone	3.63	2.56	3.83
1-Methylnaphthalene	7.82	4.51	3.55
Fluphenazine	7.00	4.54	3.09
Pyrene	ND†	4.46	5.76
Chlorpromazine	4.29	3.81	0.58

**n* = 4 for each compound.
†ND = not determined because *n* was fewer than four data points.

**Figure 2:** Universal calibration curve generated by plotting log *k* values obtained by multiplexed microemulsion electrokinetic chromatography for a series of individual standards versus their literature log *P*_{ow} values (Table I).

plexed microemulsion electrokinetic chromatography approach generally were within 0.5 units of the literature log *P*_{ow} value, with an average deviation of 0.23.

Reproducibility of the microemulsion electrokinetic chromatography buffer preparation: Four separate analysts prepared microemulsion electrokinetic chromatography buffer solutions on different days, and these solutions were used to determine the log *P*_{ow} values for a set of compounds. The RSD for the log *P*_{ow} values determined using the different buffer preparations ranged from 2.3% to 9.3% (see Table VII). These results indicate that careful microemulsion electrokinetic chromatography buffer preparation can yield

Table IV: Comparison between literature and multiplexed microemulsion electrokinetic chromatography log P_{ow} values

Compound	Literature log P_{ow} *	Multiplexed CE log P_{ow} †	Δ log P ‡
Sulfaguanidine	-1.22	-0.58	0.64
Sulfanilamide	-0.89	-0.25	0.80
Nicotinamide	-0.37	-0.77	-0.40
2-Aminopyrimidine	-0.22	-0.92	-0.70
Caffeine	-0.07	-0.29	-0.22
Antipyrine	0.38	0.32	-0.06
Hydroquinone	0.55	0.70	0.15
Benzamide	0.84	0.48	-0.36
Sulfamethoxazole	0.89	1.38	0.49
Aniline	0.90	0.66	-0.24
Chloramphenicol	1.14	1.32	0.18
Acetanilide	1.16	0.92	-0.24
Phenylacetate	1.41	1.39	-0.02
Cortisone	1.47	1.88	0.41
Hydrocortisone	1.53	2.11	0.58
4-Chloroaniline	1.83	2.05	0.22
Nitrobenzene	1.84	1.67	-0.17
<i>m</i> -Cresol	1.96	1.60	-0.36
<i>p</i> -Cresol	1.99	1.79	-0.20
Lidocaine	2.26	2.44	0.18
Ethylbenzoate	2.64	2.74	0.10
1-Naphthol	2.71	2.61	-0.10
Toluene	2.74	2.65	-0.09
2-Naphthol	2.84	2.56	-0.28
Azulene	3.20	3.34	0.14
Haloperidol	3.36	3.62	0.26
Naphthalene	3.37	3.58	0.21
Chlorpheniramine	3.39	3.55	0.16
Benzophenone	3.40	3.17	-0.23
9-Fluorenone	3.58	3.54	-0.04
Verapamil	3.79	3.85	0.06
Pentachlorophenol	3.81	3.71	-0.10
Biphenyl	3.95	4.19	0.24
1-Methylnaphthalene	3.95	4.30	0.35
Fluphenazine	4.36	4.40	0.04
Imipramine	4.42	4.42	0.00
Bibenzyl	4.60	5.04	0.44
Desipramine	4.90	4.27	-0.63
Pyrene	5.00	5.20	0.20
Trifluoperazine	5.03	4.37	-0.66
Chlorpromazine	5.35	4.91	-0.44
Pentachloronitrobenzene	5.40	5.12	-0.28

* Literature log P_{ow} is the literature value for log P_{ow} obtained from references 3, 4, 7, 45, 46, and 47.

† Multiplexed CE log P_{ow} is the value of log P_{ow} calculated by multiplexed microemulsion electrokinetic chromatography.

‡ Δ log P is the multiplexed microemulsion electrokinetic chromatography log P_{ow} value minus the literature log P_{ow} value.

reproducible results between analysts and between days.

Summary

Multiplexed microemulsion electrokinetic chromatography provides a rapid, accurate, and reproducible approach for determining the log P_{ow} values for neutral and basic compounds using small amounts of compound. It does not require the compounds to be highly pure because the impurities can be separated during electrophoresis, so they do not interfere with the log P_{ow} determination.

Additionally, this method offers the same advantages as similar single capillary CE methods (MEKC and microemulsion electrokinetic chromatography) but with a higher throughput because of the multiplexed capillary design. The results for between-day analyses demonstrated the approach was rugged and precise over time. The implementation of multiplexed microemulsion electrokinetic chromatography has the potential to allow the determination of log P_{ow} values for hundreds of compounds in a single day.

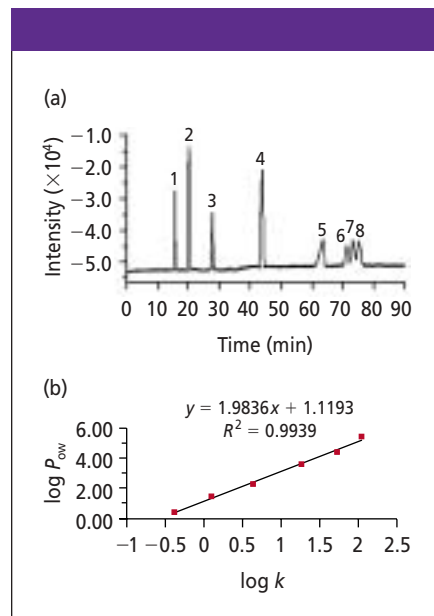


Figure 3: (a) Electropherogram of a combined standard obtained by multiplexed microemulsion electrokinetic chromatography. (b) Combined standard curve generated by plotting the log k values obtained for the combined standards shown in Figure 3a versus literature log P_{ow} values (Table I). Peaks in (a): 1 = DMSO, 2 = antipyrine, 3 = phenylacetate, 4 = lidocaine, 5 = 9-fluorenone, 6 = fluphenazine, 7 = pentachloronitrobenzene, 8 = 1-phenyldecane.

Table V: Between-day reproducibility of combined standard curve

Day	Slope	Intercept
1	1.9836	1.1193
2	1.9947	1.0438
3	1.9927	1.0833
Average	1.9903	1.0821
RSD (%)	0.30	3.49

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Table VI: Determination of log P_{ow} for test compounds by multiplexed microemulsion electrokinetic chromatography*

Compound	Multiplexed Microemulsion		
	Literature log P_{ow}	Electrokinetic Chromatography log P_{ow}	Δ log P_{ow}
Codeine	1.14	1.73	0.59
Nadolol	0.71	1.43	0.72
4-Nitroaniline	1.39	1.20	-0.19
Prednisone	1.46	1.80	0.34
Indole	1.66	1.97	0.31
Metoprolol	1.88	1.97	0.09
Quinoline	2.06	1.81	-0.25
3-Methyl-4-nitroanisole	2.32	2.50	0.28
Carbamazepine	2.45	2.46	0.01
Nabumetone	3.08	3.69	0.61
1-Nitronaphthalene	3.19	3.43	0.24
Primingethamine	3.27	3.27	0.00
Carbazole	3.29	3.66	0.37
Acridine	3.39	3.34	-0.05
p-Dichlorobenzene	3.39	3.71	0.32
Quinidine	3.44	2.93	-0.51
Azobenzene	3.82	4.54	0.72
Acenaphthene	3.92	4.33	0.41
Phenanthrene	4.46	4.81	0.35

*n = 4 for each compound.

Table VII: Between-analyst reproducibility of log P_{ow}

Analyst	Benzamide	p-Cresol	Imipramine	Chlorpromazine
A	0.84	1.75	4.36	4.57
B	0.88	1.79	ND*	5.11
C	0.72	1.72	4.36	4.57
D	0.81	1.80	4.82	5.52
Average	0.81	1.77	4.51	4.94
RSD (%)	7.94	2.31	5.92	9.31

*ND = not determined.

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