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Electrokinetic Chromatography: An Historical Review of Developments in Theory and Practice

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Abstract

During three decades since the introduction of electrokinetic chromatography (EKC), a large number of research and development efforts have defined the technique and demonstrated numerous applications. Theory has been developed and the fundamental factors affecting performance have been characterized, allowing rational method development and optimization. Numerous materials have been introduced for use as pseudostatonary phases, and their separation performance and selectivity characterized. EKC has been applied to numerous analytical problems, and also to characterize both analytes and pseudostationary phase materials. Although it was originally thought to be an insurmountable challenge, EKC has been combined with mass spectrometry to provide selective, qualitative and sensitive detection. EKC has also been demonstrated to be effective for online analyte focusing using various approaches, thus helping to overcome the low concentration sensitivity of the technique. This review provides introduction to EKC for the novice, and highlights important fundamental, theoretical and practical developments in the field.

Keywords: Electrokinetic Chromatography, Pseudostationary phase, Mass Spectrometric Detection, Analyte Focusing, Selectivity, Band Broadening.

1. Introduction

It has been 31 years since the introduction of micellar electrokinetic chromatography (MEKC) with the seminal paper by Shigeru Terabe et al.[1] That paper has been cited nearly 1,400 times. SCOPUS returns a total of more than 4,500 articles, including about 150 articles per year over the last several years, with the term electrokinetic chromatography in the title, abstract or key words. Clearly the approach has generated significant interest in the community. Yet, the technique and its advantages and limitations remain unfamiliar to many. The purpose of this review is to provide students of chromatography and other interested readers with an overview of the development of the technique, focusing on the theory and fundamentals that can be used to apply the technique to analytical problems. As such, emphasis is placed on early reports in which theory and fundamental developments were introduced and described, with significantly less emphasis on recent specific applications.

The original paper by Terabe et al.[1] presented some very nice separations of phenolic compounds (Figure 1), and the authors stated that "Electrokinetic separations with micellar solutions in open-tubular capillaries have been proved to be a high-resolution chromatographic method." But the paper was also prescient regarding what the technique might be useful for, stating that "the use of a surfactant solution in an aqueous organic solvent will expand the applicability of this method to water-insoluble compounds," and "electrokinetic separations with micellar solutions would be useful for studying chemistry of micelles as well as for analytical purposes."

Published work since then does span a broad range of applications, and includes fundamental work regarding analytical performance, the introduction of novel materials as pseudostationary phases, development of methods to preconcentrate analytes before analysis, and the use of electrokinetic chromatography (EKC) to characterize micelles and other materials. Given the breadth of work and the number of publications, it is clearly not possible to produce a comprehensive review of the topic. Rather, this review will highlight specific developments in an effort to provide the reader with an overview and understanding of the method and its unique qualities and capabilities. Readers are referred to a recent text[2] and reviews[3,4] on electrokinetic chromatography wherein the topics presented here are discussed in greater detail.

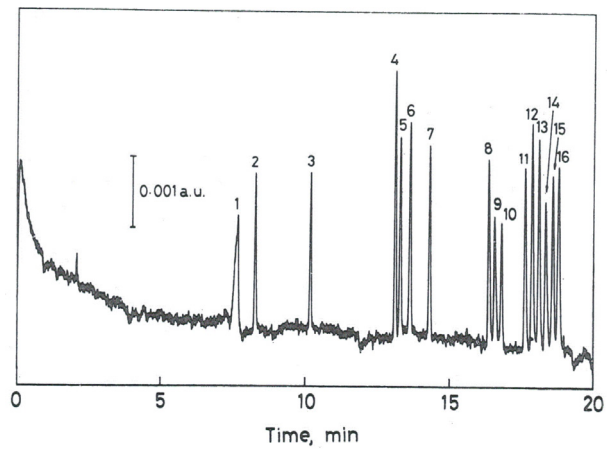

Figure 1. MEKC separation of phenols reported in 1984 by Terabe et al. 1. water, 2. acetylacetone, 3. phenol, 4. o-cresol, 5. m-cresol, 6. p-cresol, 7. o-chlorophenol, 8. m-chlorophenol, 9. p-chlorophenol, 10. 2,6-xylenol, 11. 2,3-xylenol, 12. 2,5-xylenol, 13. 3,4-xylenol, 14. 3,5 xylenol, 15. 2,4 xylenol, 16. p-ethylphenol. 50 mM SDS in pH 7.0 borate-phosphate buffer, detection at 270 nm. Reprinted with permission from ref. 1. Copyright 1984, American Chemical Society.

2. The Basics

EKC is a modification of capillary electrophoresis (CE) in which a material, the so-called pseudostationary phase (PSP), is added to the background electrolyte (BGE) to effect the separation of nonionic compounds and/or to alter the separation selectivity for ionic compounds. The instrumentation and fused silica capillaries typically used are the same as those used in CE. Like CE, the capillary is filled with a buffered electrolyte solution and the separation is conducted under the influence of a strong applied electric field.

In fused silica capillaries, the negative surface charge on the internal capillary walls, combined with the

applied electric field, results in a robust electroosmotic flow (EOF) toward the cathode. This EOF represents a non-selective transport mechanism that affects all dissolved components with the same velocity. The EOF velocity v_{eo} is proportional to the electric field strength, E,

$$v_{eo} = E\mu_{eo} \quad (1)$$

where μ_{eo} is the electroosmotic mobility. μ_{eo} is proportional to the zeta potential at the capillary wall and inversely proportional to the viscosity of the BGE.

In the standard configuration, the PSP is an amphiphilic anionic material that is dissolved or dispersed in the BGE at a uniform concentration. Terabe et al. used micelles of sodium dodecyl sulfate (SDS) when they introduced the approach, and SDS continues to be used extensively today. The electrophoretic mobility of the anionic PSP ($\mu_{ep,psp}$), combined with the strong applied field, results in a velocity relative to the BGE and against the electroosmotic flow that is also proportional to the electric field strength:

$$v_{rel} = E\mu_{ep,psp} \quad (2)$$

The net velocity of the PSP is the sum of the electroosmotic and relative velocities:

$$v_{psp} = v_{eo} + v_{rel} \quad (3)$$

Since the relative velocity is typically lower in magnitude and in the opposite direction of the EOF, the PSP migrates in the same direction as the electroosmotic flow but with a lower velocity. This configuration establishes a condition in which two uniformly-distributed phases, the BGE and the PSP, migrate from the anode toward the cathode with different velocities. The net velocity of the PSP is a significant departure from conventional chromatography, in which the stationary phase is fixed in place, that results in significant differences in the theory and applicability of EKC.

Nonionic analytes migrate in this system at a velocity (v_{mig}) that depends on the fraction of analyte associated with the PSP (f_{psp}) vs the BGE (f_{BGE}):

$$v_{mig} = f_{psp}v_{psp} + f_{BGE}v_{eo} \quad (4)$$

These fractions ($f_{BGE} + f_{PSP} = 1$) are directly related to the chemical affinity of the analyte for the PSP relative to the BGE, and thus different analytes with unique affinities migrate at unique velocities. An analyte with no affinity for the PSP ($f_{BGE} = 1$) will migrate at v_{eo}, while one with very high affinity for the PSP ($f_{psp} = 1$) will migrate at v_{psp}. Analytes with intermediate affinities migrate at intermediate velocities.

Separations are carried out over a capillary length, *l*, from the inlet of the capillary to the detector. The migration times of nonionic analytes with no affinity for the PSP (t_0), with very high affinity for the PSP (t_{psp}), and with intermediate affinity (t_{mig}) are given by

$$t_0 = \frac{l}{v_{eo}} \quad (5)$$

$$t_{psp} = \frac{l}{v_{psp}} \quad (6)$$

$$t_{mig} = \frac{l}{v_{mig}} \quad (7)$$

respectively. It is important to recognize that all neutral analytes elute from the capillary in the time window between t_0 and t_{psp} ($t_0 \leq t_{mig} \leq t_{psp}$), which is termed the migration range. This limited migration range is a significant departure of EKC from conventional chromatography and is a direct result of the net mobility of the PSP.

The retention factor, *k*, is defined in the same way in EKC as in other forms of chromatography as the amount of analyte in the PSP divided by the amount of analyte in the mobile phase. f_{psp} and f_{BGE} are each clearly a function of *k*, and rearrangement of these relationships and Equations 4 through 7 above yields Equation 8,[1]

$$k = \frac{t_{mig} - t_0}{t_0(1 - \frac{t_{mig}}{t_{psp}})} \quad (8)$$

which is now a well-recognized equation in EKC. As in conventional chromatography, $k \rightarrow 0$ as $t_{mig} \rightarrow t_0$. However, unlike conventional chromatographic techniques in which $k \rightarrow \infty$ as the retention time $t_r \rightarrow \infty$, in EKC $k \rightarrow \infty$ as $t_{mig} \rightarrow t_{psp}$. This is another statement of the limited migration range: k varies from its limits of zero (where $f_{BGE} = 1$) to infinity (where $f_{psp} = 1$) as t_{mig} varies from its limits of t_0 to t_{psp}.

The separation presented in Figure 2 demonstrates the migration range. In this separation, t_0 is marked by the migration of acetone, which has very low affinity for the SDS PSP, whereas t_{psp} has been estimated by a method first described by Bushey and Jorgenson.[5] The analytes are a homologous series of nonionic alkyl phenyl ketones of increasing hydrophobicity and increasing retention factor. All of the homologs elute between t_0 and t_{psp}, and the t_{mig} of the later-eluting homologs with high retention factors approach but do not exceed t_{psp}.

3. Resolution

A measure of success in any analytical separation is the resolution between adjacent analyte peaks, defined in EKC as in other modes of chromatography as

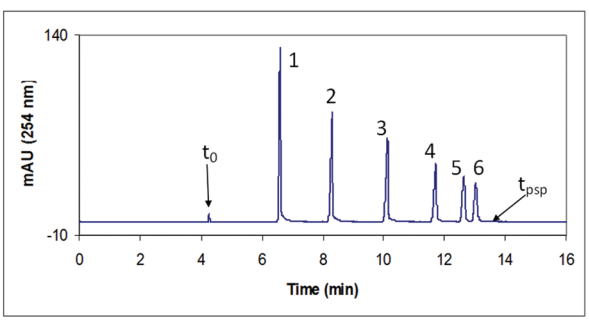

Figure 2. Representative MEKC separation. t_0 is acetone, 1.acetophenone (k=1.1), 2. propiophenone (k=2.4), 3.butyrophenone (k = 5.4), 4. valerophenone (k = 12), 5. hexanophenone (k = 30), 6. heptanophenone (k = 72). 50 mM SDS in 20 mM TRIS buffer at pH 7.0.

$$R_s = \frac{t_{mig2} - t_{mig1}}{0.5(w_1 + w_2)} \quad (9)$$

where the subscripts indicate two analytes to be separated and where w refers to the widths at the base of the peak. Substitution and rearrangement of this equation with equations for the theoretical plate count (N), retention factor, and selectivity ($\alpha = k_2/k_1$) terms yields the master resolution equation. In EKC, the master resolution equation is[6]

$$R_s = \left(\frac{\sqrt{N}}{4}\right)\left(\frac{\alpha - 1}{\alpha}\right)\left(\frac{\bar{k}}{\bar{k} + 1}\right)\left(\frac{1 - t_0/t_{psp}}{1 + kt_0/t_{psp}}\right) \quad (10)$$

The first three parenthetical terms in this equation are the same as those found in the master resolution equation for conventional chromatography. The fourth parenthetical term accounts for the effect of the limited migration range, and is unique to EKC. Each of the factors affecting resolution can be considered separately.

3.1. Theoretical Plate Counts

Equation 10 indicates that resolution is improved with higher plate counts, increasing with the square root of N. As a general rule, theoretical plate counts in EKC are much higher, by an order of magnitude or more, than those observed in conventional liquid chromatography. This represents a significant advantage of EKC.

Given the flat flow profile of the EOF and the lack of multiple path or eddy diffusion effects, the dominant band broadening mechanism in EKC (as in CE) is expected to be longitudinal diffusion, with the variance of an analyte zone increasing with migration time as $\sigma^2 = 2Dt_{mig}$. If mass transfer kinetics were slow this could also have a significant effect on band broadening in EKC. If longitudinal diffusion were the only broadening mechanism, plate counts would increase with applied voltage (reduced t_{mig}) and would be higher for compounds with smaller diffusion coefficients. The effective diffusion coefficient must be weighted to take into account the fraction of analyte in the BGE vs the PSP

and the different diffusion coefficients when dissolved in the two media:[7]

$$D = f_{BGE}D_{BGE} + f_{PSP}D_{PSP} = \frac{D_{BGE}}{k+1} + \frac{kD_{psp}}{k+1} \quad (11)$$

Given that the analytes are generally low molecular weight compounds and PSPs are generally larger structures, D_{BGE} is greater than D_{PSP}, and the effective diffusion coefficients for analytes with higher retention factors are less than those with lower retention factors. This, in turn, should lead to higher plate counts for more highly retained compounds.

In a series of papers, Joe Davis and his group investigated and presented the theoretical and observed MEKC plate counts for analytes with a range of retention factors at different SDS concentrations,[7-9] and Davis presented a review of these and other efforts to characterize band broadening in MEKC shortly thereafter.[10] These authors found that, with the inclusion of instrumental band broadening due to injection and detection, broadening due solely to longitudinal diffusion was sufficient to describe the dispersion of weakly to intermediately retained neutral analytes over a wide range of SDS concentrations and field strengths. However, they observed significantly lower plate counts than predicted by theory for highly retained compounds and high SDS concentrations. They concluded that variation in SDS micellar mobility due to Joule heating effects, resulting from high current at high SDS concentrations and field strengths, was the primary source of the additional dispersion observed. They observed little or no evidence of mass transfer kinetics (non-equilibrium) affecting plate counts.

Peak asymmetry, either tailing or fronting, is also observed in some cases at high analyte concentrations and/or low PSP concentrations. This has deleterious effects on peak widths, N, and R_s. Smith and Davis performed careful studies into the cause of peak tailing in MEKC with SDS micelles. They found that Langmuir-type non-linear isotherm models could accurately predict the shape of tailing peaks, although possible effects of changes in buffer conductivity or micellar mobility at high analyte concentrations could not be ruled out entirely.[11] Williamson and Davis observed that anti-Langmuir isotherm models could explain observed peak fronting.[12,13] In a follow-on study, Liu and Davis[14] observed no systematic differences in isotherms measured by MEKC vs head-space gas chromatography, lending credence to the observation that non-linear isotherms are the primary cause of peak asymmetry.

3.2. Selectivity

Separation selectivity, α, is based on differences in the affinity of the analytes for the PSP vs the BGE, and can thus be altered by changing the chemistry of either or both phases. Separation selectivity for weak acids or bases can be affected by the pH of the BGE, and the addition of organic modifiers to the BGE can also affect the separation selectivity for many analytes. A large number of PSPs with varied selectivity has been introduced and characterized, including various anionic[15-19] and cationic[20-24] surfactants, mixed micellar phases,[25-30] microemulsions,[31-33] polymers,[34-39] and nanoparticles.[36,40-46] The effect of changes in PSP selectivity on *Rs* and migration order can be seen in Figure 3. Recent reports allow organization of the various PSPs by the chemical interactions and separation selectivity that they offer.[47-49] The ease with which the PSP can be replaced and the separation selectivity altered is an advantage of EKC over conventional chromatography. The chemistry and characterization of PSPs is discussed in greater detail in Section 4 of this review.

3.3. Retention Factor

The final two parenthetical terms in Equation 10 describe the effect of retention factor on resolution. Like conventional chromatography, the resolution increases rapidly with increases in the retention factor in the range of zero to about one or two. However, unlike conventional chromatography, and as a direct consequence of the limited migration range, resolution is diminished as the retention factor is increased further.[6,50] This can be

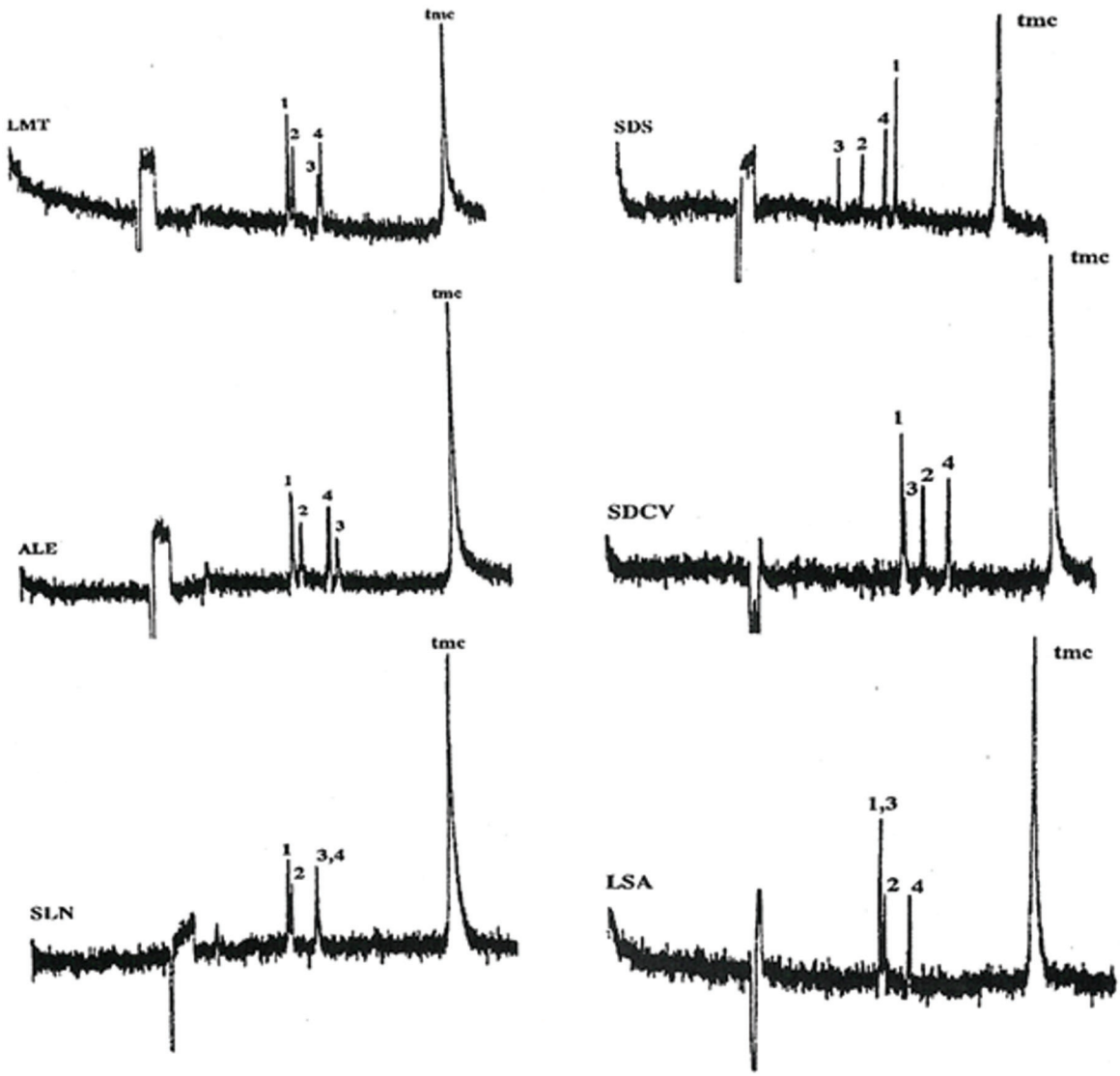

Figure 3. EKC separations of 1. chlorobenzene, 2. p-chlorophenol, 3. p-chloroacetophenone, 4. bromobenzene using anionic surfactants with different head group chemistry. LMT = *N*-lauroyl-*N*-methyltaurate, ALE = *N*-lauroyl-*N*-methyl-β-alaninate, SDCV = (*S*)-*N*-dodecoxycarbonyl valine, SLN = *N*-lauroylsarcosinate, LSA = laurylsufoacetate. Reproduced with permission from ref. 18.

seen by inspection of the separation in Figure 2. The plate number remains nearly constant throughout the separation, and the α between adjacent pairs of peaks in the homologous series also remains nearly constant. The resolution, however, is diminished for the later-eluting peaks with high retention factors relative to those with retention factors in the range of one to two.

The decrease in resolution at higher values of the retention factor is described by the final parenthetical term in Equation 10, and further analysis of this term indicates that the rate of decrease is related to the magnitude of the ratio t_0 / t_{psp}.[6,50] Given constant values for N and α, the maximum resolution is obtained at an optimal *k* value:[50]

$$k_{opt} = \sqrt{t_{psp} / t_0} \qquad (12)$$

The optimal values of the retention factor for maximum resolution as a function of time lie in the range of 1.2 to 2.[50]

The consequences of the relationship between retention factor and resolution are significant and extensive. First, it shows that it is important to be able to adjust the separation conditions such that k values lie in an optimal range. Second, it demonstrates that EKC is most effectively applied to the separation of analytes with a limited range of affinities for the PSP; separation of a mixture of analytes having both very low and very high k values under a single set of conditions is especially challenging. Third, it is clear that the separation of a mixture of analytes with high affinity for the PSP is difficult; very hydrophobic compounds, for example, show very high affinity for SDS and it is difficult to achieve their separation by MEKC. Finally, it demonstrates the importance of the ratio t_0/t_{psp}; separation performance and the applicability of EKC are both improved under conditions that reduce this ratio.

Fortunately, there are a variety of means to adjust the retention factor to optimize EKC separations. The simplest approach is to adjust the concentration of the PSP, which affects the volumetric phase ratio.[6,50] The relationship between PSP concentration and retention factor in MEKC is[6]

$$k = K\bar{v}(C_{surf} - CMC) \qquad (13)$$

where K is the equilibrium distribution coefficient for the analyte between the PSP and the BGE, $\bar{v}$ is the partial specific volume of the surfactant, C_{surf} is the surfactant concentration and CMC is the critical micelle concentration of the surfactant. When non-micellar PSPs are employed the CMC is effectively 0. The range of operative PSP concentrations is fairly broad, but is limited. At overly low PSP concentrations, peak asymmetry, migration reproducibility and analyte solubility problems can become problematic, whereas at excessively high PSP concentrations plate counts can be diminished due to Joule heating effects (see Section 3.1).

Equation 13 also suggests a second means to adjust k, which is to alter the distribution coefficient K. This is most commonly achieved through the addition of organic modifiers such as methanol, acetonitrile or urea to the BGE, which reduce the magnitude of K. The fraction of organic modifier that can be added to micellar systems is limited, however, by instability of the micelles at modifier concentrations above ~20-30%.[51,52] Cyclodextrins were introduced early in the development of EKC as additives to provide competitive solvation of hydrophobic analytes[53] and they have been used extensively primarily as chiral additives. The K for weak acids or bases can be changed significantly by suppression of ionization through changes in BGE pH, leading to weaker affinity for oppositely charged PSPs and stronger affinity for like charged PSPs. It is also possible to select a different PSP for which the analytes have weaker affinity. For example, bile salt micelles were demonstrated early on to be more stable in the presence of organic modifiers and to have a more polar interior, allowing separation of hydrophobic compounds difficult to analyze with SDS MEKC.[54] Polymeric PSPs were likewise demonstrated to be stable in the presence of organic modifiers and to be more polar, allowing separations of polynuclear aromatic hydrocarbons.[37,39]

The range of suitable k values and overall resolution performance can be improved by reduction of the ratio t_0/t_{psp}, which can be accomplished by reducing the EOF or increasing the mobility of the PSP.[55] The addition of methanol to the BGE is commonly used as a means to reduce EOF in fused silica capillaries. This results in an enhancement of the migration range and can improve resolution, but also increases the analysis time. The use of microemulsion PSPs has also been proven to allow a wide and effective migration range.[32,33,56]

4. Pseudostationary Phases

The PSP lies at the heart of EKC separations, playing the role of the stationary phase in conventional chromatography and providing the separation selectivity. It is not surprising, therefore, that a variety of PSPs have been developed and studied, just as a variety of stationary phases have been developed for liquid and gas chromatography. The fact that the PSP is dissolved

in the BGE and can be easily and inexpensively altered or replaced is a significant advantage of EKC over conventional chromatography, which requires exchange of expensive columns to alter the stationary phase chemistry.

When developing new PSPs, it is important to consider several important characteristics that affect their performance. The PSP must be soluble or form stable suspensions in the BGE and must be ionic at the pH of the BGE. The PSP must have sufficient electrophoretic mobility to provide a broad migration range. As the primary limitation to high plate counts is Joule heating, the PSP should not increase the conductivity of the BGE too greatly. It is important to consider that slow mass transfer or PSP polydispersity could contribute to band broadening, although this has not typically been observed. Because the PSP migrates through the detector, it should not interfere with detector performance. The PSP should be available in pure form. If the PSP is a self-assembly such as a micelle, vesicle, or micro-emulsion, then the conditions under which the assembly forms and remains stable must be considered. Surfactants with high CMC are not suitable, since the high concentrations required to generate and maintain micelles result in high current and excessive Joule heating. The assemblies must form and be stable at temperatures close to room temperature that are accessible with commercial instrumentation.

The original work, and by far the most published work since that time, utilized SDS micelles as the PSP. It is interesting to note that, even after 30 years of development, SDS remains one of the most suitable and effective PSPs. It has a low CMC of 3 to 5 mM in most BGE, is commercially available in very high purity, has a reasonable electrophoretic mobility that provides a typical t_{psp}/t_0 value of about three, has strongly acidic ionic head groups and is soluble in nearly all BGEs, has a Krafft temperature well below room temperature, generates monodisperse micelles, and allows for very high plate counts of a few hundred thousand. A significant limitation of SDS is that it is not compatible with electrospray ionization mass spectrometric (MS) detection, showing high background, significant ionization suppression, and fouling of the ESI interface.[57-61] Another limitation with SDS and other micellar systems is that the process of self-assembly into micelles is altered or disrupted in the presence of organic solvents at concentrations above 20 or 30% by volume,[51,52] making it difficult to optimize the retention factors for highly hydrophobic compounds. Finally, SDS offers only one PSP with a given separation selectivity, and this selectivity may not be ideal for all separations. These limitations have served as the primary motivations for the development and characterization of additional PSPs.

Retention and selectivity characteristics are important to the applicability of different PSPs. For this reason, there has been significant effort expended to characterize different PSPs using the linear solvation energy relationships (LSER) model.[62-65] This model allows the estimation of the energy of various chemical interactions relative to the BGE, including dispersion, dipole-dipole and hydrogen bonding, and has thus provided information about the retention and selectivity characteristics of various PSPs.

4.1. Micellar PSPs

The primary interest in different surfactant micellar PSPs is in the different selectivity that they may offer relative to SDS micelles. These materials do not necessarily offer higher stability or improved compatibility with MS detection, and often have inferior aggregation behavior relative to SDS.

A variety of anionic[15-19] surfactant micelles have been introduced as PSPs. Trone and Khaledi[17] observed some differences in selectivity among sodium sarcosinate surfactants with different alkyl chain lengths, but observed similar selectivity with between sodium tetradecyl sulfate and sodium dodecyl sulfate. The range of effective alkyl chain lengths is limited by high CMCs for shorter chains and high Krafft temperatures for longer chains. The same authors also studied a series of surfactants with different ionic head groups, and found much more significant differences

in selectivity among these materials.[18] The differences in selectivity are demonstrated in Figure 3. Nishi et al. also reported significant differences in separation selectivity among anionic surfactants with different head group chemistries.[15] Introduction of a chiral head group on surfactants was demonstrated to provide chiral selectivity.[66-68] Although differences in separation selectivity are observed as the chemistry of the ionic head group is changed, recent classification systems based on LSER parameters have put various anionic hydrocarbon surfactants in a single group of PSPs along with SDS,[48,49] indicating that this approach has limited promise to offer substantial variations in selectivity.

Bile salt surfactants, which have chiral centers and form micelles with greater stability in organic solvent modified BGEs, were also introduced for the separation of pharmaceuticals,[16] hydrophobic compounds[54] and enantiomers.[69] In an early example, bile salt micelles were shown to offer selective separations of compounds that were not resolved with SDS micelles.[16] Studies of retention and selectivity by LSER indicated minor differences between different bile salts, but that the bile salts as a group were significantly different from SDS micelles.[70,71] When classified by LSER parameters, bile salts fall into a different group from SDS micelles.[48,49]

Lithium perfuorooctane sulfonic acid (LiPFOS) has also been shown to offer unique selectivity relative to SDS micelles,[70] and is grouped in terms of LSER characteristics with other perfluorinated surfactants.[48,49] LiPFOS and another perfluorinated surfactant, perfluorooctanoic acid, have been shown to be compatible with electrospray ionization and MS detection.[72,73]

The separation selectivity can also be altered and adjusted using mixed micellar phases.[25-30] When using mixtures of ionic and nonionic surfactants, the electrophoretic mobility of the PSP and the migration range are diminished as the proportion of nonionic surfactant is increased.[25]

The cationic surfactant cetyltrimethylammonium bromide has been used extensively as a PSP. In the case of cationic surfactants, the surfactant adsorbs to the capillary walls to form admicelles or a bilayer. This reverses the polarity of the zeta potential at the surface, and results in a reversal of the EOF direction to be in the direction of the anode. The cationic surfactants have electrophoretic mobility in the direction opposite to the EOF, toward the cathode, and thus a similar condition is established as when anionic surfactants are utilized. CTAB micelles have been characterized by LSER,[20,74] and classification of the surfactant by LSER parameters places it in the same group as the bile salt sodium cholate.[48,49] A series of cationic surfactant micelles with different head group structures,[20-23] including an ionic liquid structure[20] and a phosphonium head group,[23] have also been characterized by LSER and shown to provide different selectivity and in some cases a broader migration range.

4.2. Microemulsions

Oil in water microemulsions consist of a surfactant like SDS, an oil (often octane or heptane), and a cosurfactant such as 1-butanol in the BGE. As PSPs, these materials offer enhanced solubilization capacity, a broad and adjustable migration window (up to 55 min)[32,56] and a fluid interior that may enhance mass transfer rates. The presence of the organic cosurfactant in the BGE may also reduce k for hydrophobic compounds. It is possible, through variation in the composition of the microemulsion, to significantly alter the separation selectivity.[32] This approach, which has the acronym MEEKC, has become prominent in recent years with about one in four applications of EKC using microemulsion PSPs. The approach has been described in extensive reviews.[31,33]

4.3. Cyclodextrins

Cyclodextrins are nonionic cyclic oligosaccharides that are soluble in aqueous BGEs and offer a hydrophobic interior as well as multiple chiral centers. The first separations using anionic cyclodextrin derivatives as

the PSP were reported very early in the development of EKC.[75] Neutral cyclodextrins were introduced several years later in combination with ionic micelles to effect the separation of hydrophobic compounds[53,76-78] and to offer chiral selectivity.[77,79-81] Nonionic cyclodextrins were also introduced for chiral separations of ionizable analytes.[82-84] Vigh and various coworkers introduced and commercialized a series of sulfate-modified ionic cyclodextrins for use in chiral separations.[85-88] A recent review article discusses the theory of migration when multiple selectors such as cyclodextrins are utilized.[89]

4.4. Vesicles and Liposomes

Vesicles are composed of one (unilamellar) or more (multilamellar) concentric spherical bilayers of surfactants surrounding an internal cavity of solvent. Multilamellar vesicles are not suitable for use as PSPs with UV detection because of excessive light scattering by these relatively large structures. Vesicles are often formed from double chain surfactants or a combination of anionic and cationic surfactants, while liposomes are vesicles composed of phospholipids.

Hong et al.[90] introduced vesicles formed from sodium dodecyl sulfate and n-dodecyltrimethylammonium bromide and reported a broader migration range and stronger hydrophobic interactions than observed with SDS micelles alone. Pascoe and Foley[91] studied additional mixed surfactant vesicles and characterized their retention and selectivity characteristics using LSER and also reported an extended migration range and greater lipophilicity than SDS micelles. The migration range for mixed surfactant systems is a function of the ratio of anionic to cationic surfactant in the vesicle, and the broader migration range is primarily a result of reduced electroosmotic flow rather than high electrophoretic mobility of the vesicles. Vesicles of the double chain surfactant bis(2-ethylhexyl)sodium sulfosuccinate (AOT) were introduced for the separation of antioxidants[92] and were also characterized in terms of selectivity and performance.[91] These structures also offer a broad migration range, with electrophoretic mobility similar to SDS micelles.

An early comprehensive study on the use of liposomes was published by Wiedmer et al.,[93] who compared the separation performance and selectivity of three liposome systems. A single liposome structure was also characterized by LSER in a later study.[91] The migration range and selectivity of liposomes is a function of their composition, and optimized compositions offer performance similar to SDS micelles. Because of their similarity to biological membranes, liposomes the use of liposomes as PSPs has evolved to be primarily for measurement and characterization of the interactions between solutes and phospholipid bilayers.[94-99]

4.5. Polymers

Polymeric PSPs were introduced in the early 1990s[37,38] and Palmer has published a series of reviews on the topic.[34-36,100,101] The initial motivation for polymeric PSPs was to utilize a highly stable structure that would remain effective with high concentrations of organic solvent modifiers, thus allowing the separation of hydrophobic compounds.[37,39] As more polymeric materials were developed and characterized, it became apparent that they can also offer significantly different separation selectivity as well as compatibility with MS detection.[102,103] For example, a series of siloxane polymers[104-108] was shown to offer unique and adjustable selectivity, and recent studies have classified these materials in a unique group based on LSER parameters.[48,49] Statistical copolymers of an anionic acrylamide and lipophilic acrylamides and amides also offer different selectivity depending on structure,[109-111] and are classified in terms of retention and selectivity together with bile salts, cationic surfactants and microemulsions. Polymerized micelles with amino acid ionic head groups were demonstrated to offer chiral selectivity[112] and are compatible with MS detection.[103] A representative chiral separation of β-blockers using a chiral polymerized micelle and UV and MS detection can be seen in Figure 4.[113] The applicability and performance

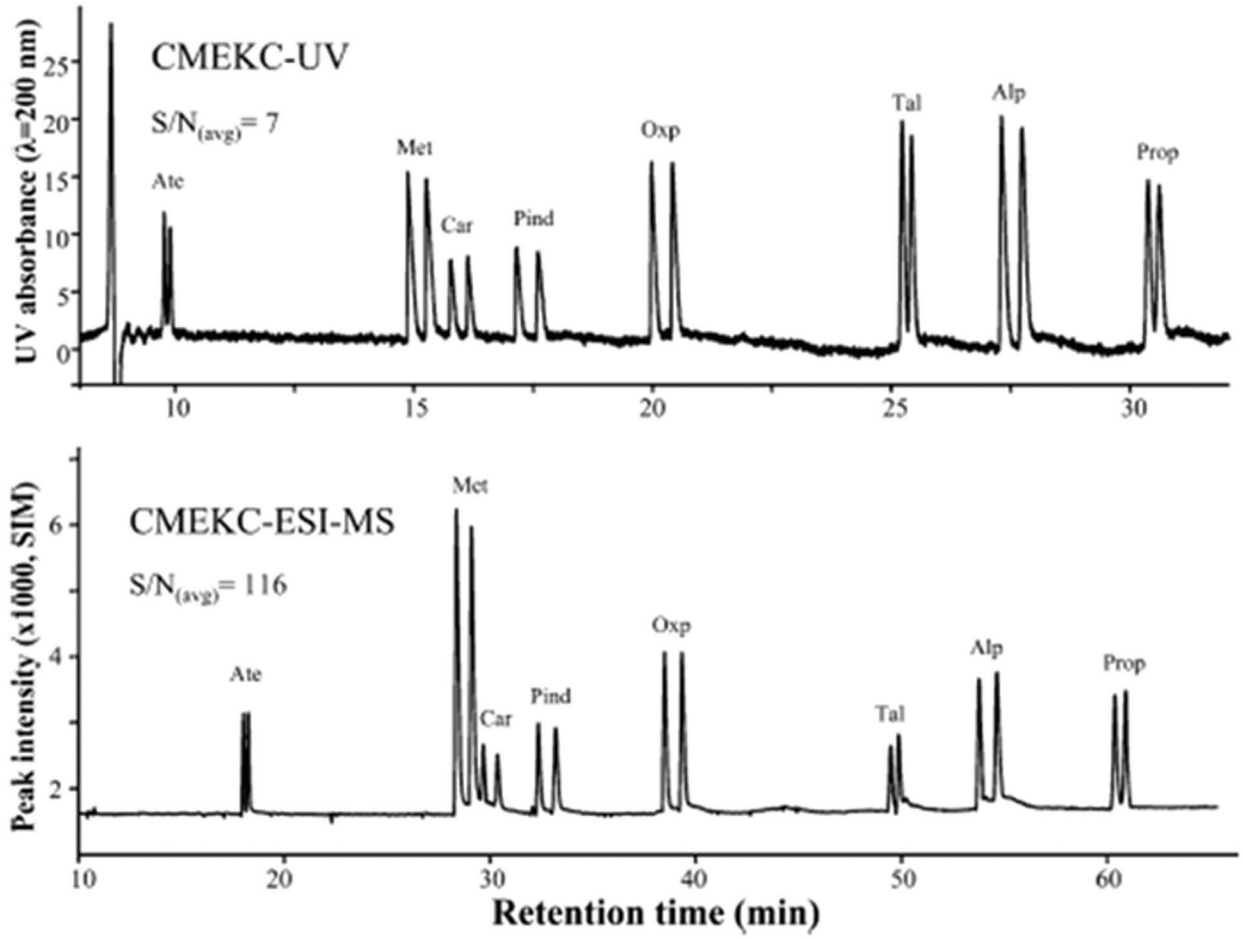

Figure 4. Simultaneous chiral separation of β-blockers with a chiral polymeric surfactant as PSP using UV and ESI-MS detection. Ate = atenolol, Met = metoprolol, Car = carteolol, Pind = pindolol, Oxp = oxprenolol, Tal = talinolol, Alp = alprenolol, Prop = propranolol. Reproduced with permission from ref. 113. Copyright 2005, American Chemical Society.

of these various polymeric materials are excellent, but general adoption and application have been hampered by lack of commercial availability.

More recently, nanoparticle materials composed of polymers have received significant attention.[43-46,114-116] These PSPs also offer compatibility with MS detection[43,44,46,115] and the capability to introduce unique selectivity or alter the selectivity through changes in structure and chemical composition.[114,116] Separations utilizing a latex nanoparticle with mass spectrometric detection are presented in Figure 5. A unique feature of some nanoparticle PSPs is that they do not significantly increase the conductivity of the BGE,[44] which allows very fast separations at high field strength without significant losses in plate counts due to Joule heating.

5. Characterization of Analytes and PSPs

Although EKC has been applied primarily for analytical separations and analysis, the approach has also proven to be useful for the characterization of analyte partitioning and of various PSP properties. The materials and structures commonly used as PSPs have additional applications in e.g. catalysis and drug delivery, making their characterization of significant interest.

The primary application for characterization of analytes is to measure their affinity for the PSP as

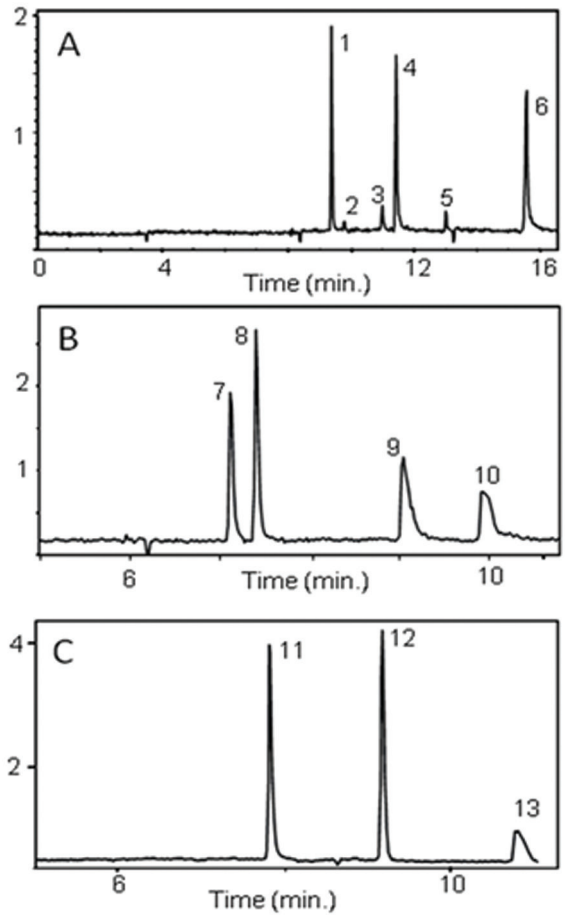

Figure 5. EKC separations with MS detection using 0.2% latex nanoparticle as the PSP in 20 mM ammonium carbonate at pH 10. A. Alkylphenyl ketones and phthalates in 20% acetonitrile, 1. diethylphthalate, 2. butyrophenone, 3. valerophenone, 4. dipropylphthalate, 5. hexanophenone, 6. dibutylphthalate: B. β-blockers in 10% acetonitrile, 7. atenolol, 8. metoprolol, 9. alprenolol, 10. propranolol; C. Pharmaceuticals in 20% acetonitrile, 11. diphenhydramine, 12. salbutamol, 13. nortriptyline. Generated with permission from ref. 44. Copyright 2010, American Chemical Society.

a proxy for affinity for biological lipid bilayers or for octanol-water partition coefficients ($P_{o/w}$). Lipid bilayer affinity and $P_{o/w}$ values are used extensively in pharmacology and environmental chemistry. It has already been noted in Section 4.4 that measurement of solute portioning has become a primary application of EKC with liposome PSPs.[94-99] Liposome EKC has also been used to estimate skin permeability,[117,118] blood-brain barrier transport,[119] ecotoxicity,[120] and screening of drug-induced phospholipidosis risk.[121] Octanol water partition coefficients have most often been correlated with retention factors in MEEKC,[122-133] although vesicles have also been investigated for this purpose.[134] Tu et al.[131] made the MEEKC measurements in a microchip system, and Xia et al.[132,133] reported methods to obtain improved correlation of MEEKC results with $P_{o/w}$ values. MEEKC has also been investigated as a means to determine brain tissue partitioning of central nervous system drugs.[135]

A few approaches have been reported to utilize EKC to measure the CMC of micelle-forming surfactants. Terabe et al.,[6] in one of the original reports on EKC, utilized the relationship between k and surfactant concentration in Equation 13 to estimate the CMC of SDS. Lin et al.[136] modeled analyte mobility as function of SDS concentration to observe and report CMC values, concentrations at which premicellar aggregation begins, and the minimum concentration where micelles are stable aggegrates.

It has already been noted in earlier sections that LSER studies have been used extensively to characterize the solvent properties of PSPs. The results until 2008 were summarized by Poole et al.[137] and recent work has developed classification schemes for PSPs based on LSER results.[48,49]

EKC has also been utilized to measure PSP diffusion coefficients. Davis reported a method based on Equation 11 and his model of diffusional and instrumental dispersion in EKC to determine self-diffusion coefficients for SDS micelles.[8,138] Muijselaar et al.[139] also utilized Equation 11 along with a stopped-flow method to measure self-diffusion coefficients for SDS micelles.

6. Mass Spectrometric Detection

No analytical separation technique can be truly competitive without being interfaced with MS detection. MS provides for sensitive and selective detection, as well as qualitative information about the analytes. The most commonly utilized method for ionization and interfacing to MS detection in CE is electrospray ionization (ESI).

However, this has been a significant challenge and limitation for EKC, because the BGE and PSP are both introduced into the ESI interface. With non-volatile surfactants like SDS at relatively high concentrations (~2% wt/vol), this can lead to fouling of the interface,[60] suppression of ionization[57-59] and signal interference in the mass spectrum[58] (signals for SDS are observed at +266, +289, +311, +599 and -265 m/q). In spite of these concerns, there are several reports of successful coupling of EKC with ESI-MS using SDS[60,140,141] or CTAB[142] surfactants.

A variety of approaches have been introduced to allow EKC-ESI-MS detection while minimizing or eliminating the negative consequences of the PSP entering the interface. The use of volatile surfactants has been demonstrated to minimize ion suppression and fouling of the interface.[72,73] Alternatively, partial-filling EKC under conditions where the PSP does not enter the detector can be used[143,144] as can conditions under which the PSP migrates in the opposite direction of the detector.[145] Both approaches are somewhat more difficult to optimize, and partial filling can lead to a significant loss in plate counts due to defocussing of analytes at the PSP boundary.[144]

Perhaps the most successful and most frequently applied approach to EKC-ESI-MS is to utilize high molecular weight polymeric materials as the PSP. These materials typically have lower surface activity and thus do not suppress ionization as effectively as surfactants. Further, the high molecular weight of the materials means that they do not produce interfering signals in the mass range of interest. Ozaki et al. first demonstrated this approach using an acrylate copolymer.[58,102,146] Polymerized chiral surfactants of various forms and chemistries were also demonstrated to allow EKC-ESI-MS of enantiomers.[103,113,147,148] This approach is illustrated in Figure 4 and has been applied in numerous analyses since.[e.g. 149] Nanoparticle PSPs have also been shown to be compatible with ESI-MS detection by several authors,[43,44,46] as illustrated in Figure 5.

Another approach to coupling with MS detection is to use an alternative interface. EKC with SDS micelles can be conducted with little or no interference using a photoionization interface.[150] Ionization of less photoinactive compounds can be enhanced in this system through use of a photoactive dopant.[151]

7. Analyte Focusing

A significant limitation of CE and EKC methods is the relatively low concentration sensitivity of on-capillary UV detection, which is fundamentally limited by the short optical path length. It is not surprising, then, that methods to focus or preconcentrate analytes online have received and continue to receive significant attention. Quirino and Terabe initiated these efforts late in the 1990s, and developed and introduced several highly-successful approaches that continue to be used today.[152-155] The ability to effectively preconcentrate and focus analytes prior to separation and detection is one of the most significant strengths of EKC.

Initial efforts by Quirino and Terabe demonstrated that analytes dissolved in low conductivity matrices containing the PSP could be focused at the interface with higher conductivity BGE due to enhancement of the electric field in the sample zone.[156,157] These methods led to up to 10 fold increases in the analyte concentration, which could be further enhanced to over 100 fold by injection of a plug of water in front of the sample zone.[158,159] In the same period, Quirino and Terabe introduced a fundamentally new approach, termed sweeping, in which the sample is injected in a matrix devoid of PSP and analytes are dissolved, transported and focused by the PSP as it migrates through the sample zone.[160-163] Analytes are focused solely by sweeping when the sample zone has the same conductivity as the BGE, and by a combination of sweeping and sample stacking when the sample zone has lower conductivity than the BGE. Palmer et al. described similar approaches shortly thereafter.[164,165] Sweeping is more effective for analytes with high affinity for the PSP, and was shown to allow up to several thousand fold enhancement in

analyte concentration. Using a combination of field enhanced sample injection and sweeping, Quirino and Terabe were able to show concentration enhancements of nearly a million fold.[166]

A method similar to sweeping, termed transient trapping, was introduced by Sueyoshi.[167] In this approach, the separation channel is only partially filled with micellar solution. The theory and mechanism of the approach have been investigated and described recently.[168]

Quirino has also developed additional methods for analyte preconcentration. Analyte transported by micelles to a zone boundary where dilution of the surfactant leads to collapse of the micelles is focused at that boundary.[169-171] The method, termed analyte focusing by micellar collapse (AFMC), is able to provide two orders of magnitude enhancement in analyte concentration. In a separate report, Quirino demonstrated conditions under which the migration direction of cationic solutes is reversed at a boundary between a micellar sample zone and a BGE containing organic solvent,[172-174] and this approach has been extended and combined with field enhanced stacking for focusing of anions.[175]

8. Applications

EKC methods and approaches continue to be developed and applied to a variety of analytical problems, with most of the 150 or more publications appearing each year describing specific applications. Early in the development of EKC a review might cover applications of EKC to a wide variety of analyses. One such comprehensive review, for example, discussed applications of MEKC to the analysis of vitamins, amino acids, and pharmaceuticals.[176] A review from nearly ten years ago discussed a variety of applications of MEEKC.[177] More recently, however, EKC methods are more likely to be discussed along with other methods as part of a review of a particular type of analysis. This is perhaps evidence of widespread acceptance and utilization of the technique. As examples, EKC applications have been included in reviews concerning the analysis of peptides,[178] natural products,[179] pharmaceutical impurities,[180] phthalates in environmental samples,[181] and analytical applications in toxicology.[182]

A very few quite recent representative papers have been chosen to be highlighted here because they demonstrate recent applications of the methods and procedures presented in earlier sections. Xu et al. utilized a polymeric PSP for the analysis of corticosteroids in cosmetics.[183] Wang et al. developed an EKC-MS/MS method for separation of enantiomers of warfarin and metabolites utilizing a chiral polymeric surfactant, and applied it to monitor metabolism of warfarin in clinical studies.[149] D'Orazio et al. reported a method utilizing dispersive liquid-liquid microextraction and EKC-MS with volatile perfluorooctanoic acid as the PSP for the analysis of estrogenic compounds in yogurt and milk.[184] Wu et al. utilized a combination of field amplified stacking and reversed field stacking for preconcentration and EKC separation of antibiotics, and Hsiao et al. utilized AFMC for preconcentration of UV absorbing compounds in suncreens.[185] And, in an interesting report out of Brazil, Bastos et al. utilized multivariate methods to optimize the EKC separation and analysis of the HIV drug nelfinavir mesylate and synthetic impurities.[186]

9. Concluding Remarks

Over thirty plus years of development of theory, materials, methods and applications, EKC has progressed from a novel high performance whim to an accepted method in the separation science toolbox. The approach continues to be investigated and applied frequently, and the development of new approaches to allow online preconcentration and MS detection of analytes continues to expand its applicability. Given a sustained level of interest and effort, combined with full understanding and application of underlying principles, strengths and limitations, the technique has a bright and promising future.

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