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Journal of Chromatography A, 807 (1998) 27–36

JOURNAL OF CHROMATOGRAPHY A

Review

Therapeutic drug monitoring by capillary electrophoresis

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Abstract

Because of the ease of analysis and the high resolution, drug analysis is becoming the best example for the application of capillary electrophoresis. Therapeutic drug monitoring is a specialized area of drug analysis performed in clinical laboratories for patient care. CE offers high resolution and speed with the low operating costs needed in patient care. However, CE has a few limitations, mainly poor detection limits and precision. Simple methods of stacking, which enhance drug detection to overcome the poor sensitivity of CE are stressed. Serum has a unique matrix with a high content of proteins and salts which can have adverse effects on separation by CE. For successful analysis, special maneuvers are employed to decrease these matrix effects. Studies that have addressed the improvement of the precision of CE are summarized. CE offers the possibility of bringing chiral separations into the routine arena. © 1998 Elsevier Science B.V.

Keywords: Reviews; Therapeutic drug monitoring; Sample stacking; Sample preparation; Drugs

Contents

0021-9673/98/$19.00
PII: S0021-9673(98)00073-9

1. Introduction

Drugs increasingly are analyzed by capillary electrophoresis (CE). Such analysis is performed for a variety of objectives: forensic toxicology, purity checks or metabolic studies, etc. Therapeutic Drug Monitoring (TDM) is a sub-specialty of drug analysis used for adjusting the patient drug dose to achieve optimum clinical response. In order to be suitable for TDM the analytical method has to be rapid, simple, precise and sensitive. CE has four major areas of strengths for TDM and three major areas of weakness. CE offers speed, ease, low cost of operation and high resolution to TDM, while it suffers from matrix effects, poor detection, and less than desirable precision. Here in this review the progress in TDM by CE is summarized. Those areas which hamper the widespread routine use of CE for TDM, are discussed with emphasis on simple stacking methods.

2. Sensitivity

Most of the drugs routinely analyzed for TDM are present in serum between 1–30 mg/l with the new ones in the μg/l range. In order to quantify such low levels in the presence of high concentrations of proteins (g/l), the drugs have to be concentrated either on or outside the capillary. Initial studies with commonly used drugs such as theophylline and phenobarbital have shown that such levels are detectable with simple stacking methods and with little sample preparation; however, some drugs require complex extraction and concentration steps. The real value of CE is not in analyzing those compounds, which have already established simple methods (e.g., immunoassays), but for those which do not have.

3. Matrix effects

Serum is the major fluid used for TDM. Occasionally, drugs are analyzed in urine. In CE, the resolution and plate number are affected greatly by the sample contents (matrix), especially the inorganic ions and the proteins. Unlike HPLC, matrix effects in CE can be a major problem preventing a successful analysis [1]. It is very easy to analyze pure standards in CE but running serum samples is much more difficult. Serum contains high concentration of proteins (60 000 mg/l) and salts (NaCl 140 mmol/l). The salts cause band spread, while the proteins bind to the capillary walls producing secondary interactions and affecting greatly the reproducibility. These effects become quite significant when the sample size is greatly increased [1].

4. Sample preparation for CE

Two general techniques are quite common for analysing TDM by CE: Capillary Zone Electrophoresis (CZE) and Micellar Electrokinetic Capillary chromatography (MEKC). The sample preparation for these two techniques is slightly different.

4.1. Direct serum injection

Provided the concentration of the analyte is high enough, small amounts of serum (or urine) can be injected directly or after simple dilution, on the capillary. To decrease the effects of the ions in the sample in CZE, the separation buffer has to be of high ionic strength [2,3]. However, proteins can not be tolerated easily in CZE. On the other hand, in MEKC a small amount of serum can be injected directly provided the drug migrates away from the serum proteins. The surfactants form micelles and solubilize the serum proteins. For example, Thormann et al. [4,5] have successfully applied this technique to the analysis of several drugs such as theophylline, caffeine and barbiturates by injecting serum directly. We have applied this technique in the analysis of the new antiepileptic drug felbamate [6]. The simplicity and the small sample volume used for the assay render this method suitable for monitoring the levels of these drugs in pediatric patients [4–6]. This technique is well suited for the analysis of neutral, non-polar and weakly ionized compounds.

4.2. Membrane filtration/dialysis

In this method the large molecules (mainly proteins) are removed; however, the salts which can

interfere in the separation remain in the sample and the filters are relatively expensive. An example is the analysis of serum nitrate by CE [7].

4.3. Acetonitrile deproteinization

Deproteinization with acetonitrile is used often in HPLC. However, in CZE, in addition to removing proteins the acetonitrile causes sample concentration on the capillary termed, 'stacking' as will be discussed in Section 5.2. The presence of acetonitrile and a high concentration of salts (~50 mmol/l of NaCl) in the final mixture allows sample injection of up to 50% of the capillary volume yielding a 5–30 fold concentration. This simple concentration method allows many drugs to be determined at concentrations of ~1 μg/ml (Figs. 1 and 2). The deproteinization decreases the need for washing the capillary between samples, thus speeding the analysis. This method is limited to CZE and is not suitable for MEKC [8].

4.4. Extraction

Solvent and solid-phase extraction followed by solvent evaporation, both traditionally used in HPLC and GC, can be used also in CE to remove the proteins and salts present in serum. Sample clean-up, concentration and matrix effects elimination are all achieved at the same time. Drugs present below 1 mg/l require extraction and concentration. Drug extraction from urine with minimal contamination remains a challenging problem. However, this technique is not very suitable for routine and emergency analysis. Lloyd [9] reviewed different strategies of sample pretreatment and methods for direct injection of bio-fluids for drug analysis by CE.

5. Concentration on the capillary: 'stacking'

Concentrating the sample on the capillary called 'stacking' is a simple technique that overcomes the

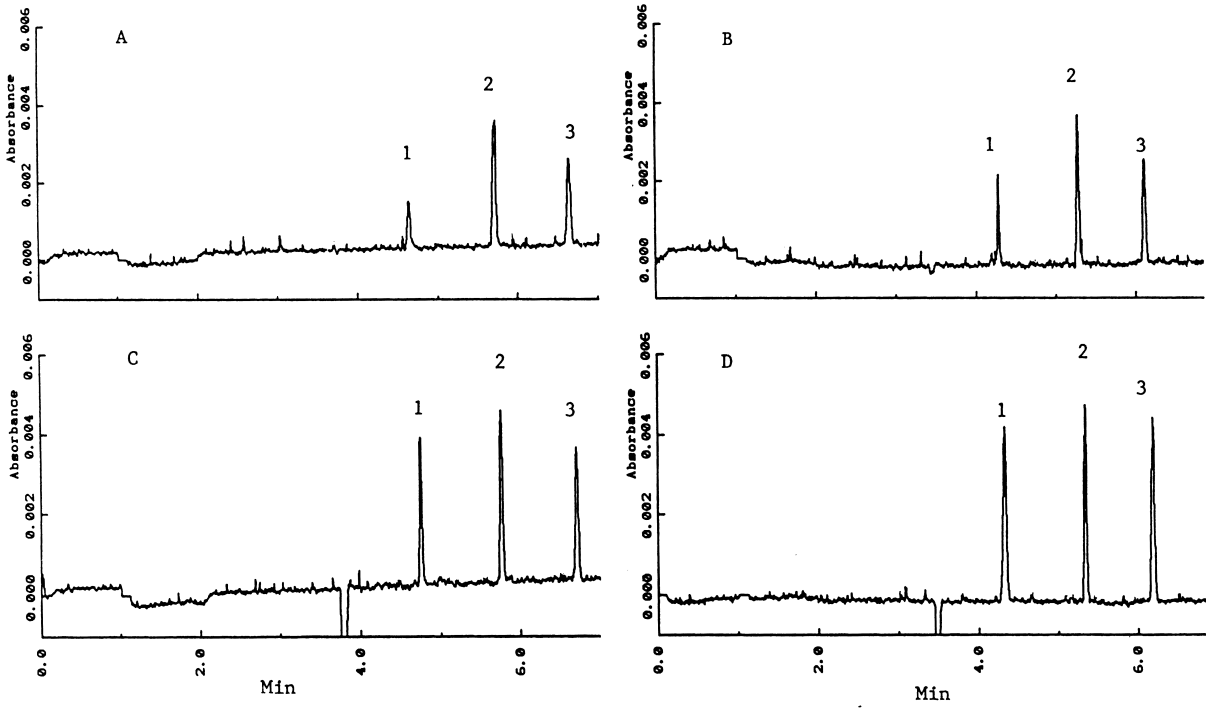

Fig. 1. Stacking by acetonitrile. Sample injection is 0.6% of the capillary volume. The compounds iohexol (1), theophylline (2) and phenobarbital (3) were dissolved in: (A) the separation buffer (borate 250 m*M*, pH 8.9); (B) the separation buffer at 25 m*M*; (C) acetonitrile–water (2:1, v:v); (D) acetonitrile–1% NaCl (2:1, v:v). With permission [9].

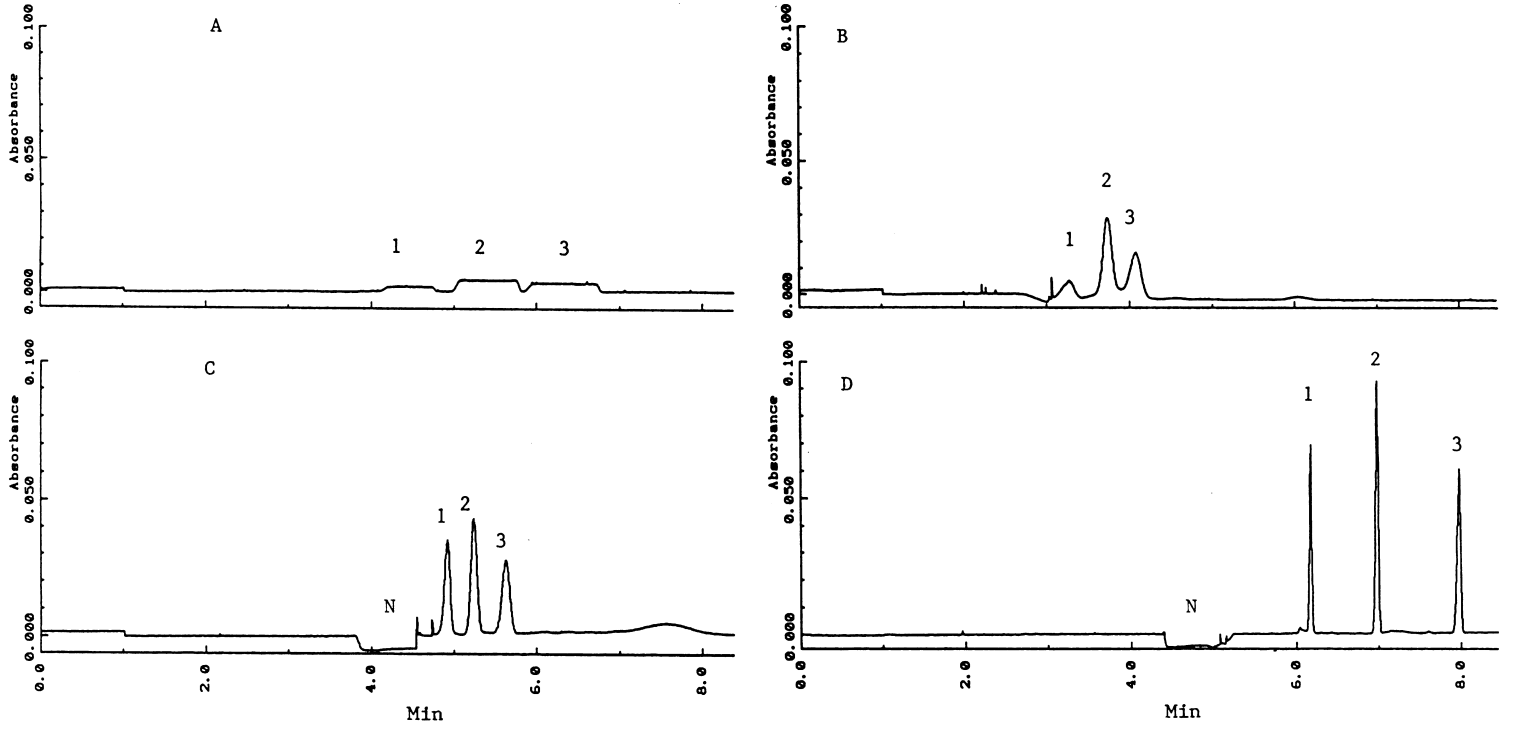

Fig. 2. Stacking by acetonitrile; as in Fig. 1 but the sample is 17% of the capillary volume (N=neutral compounds). Reproduced with permission from Ref. [9].

poor detection limits of capillary electrophoresis. Three general stacking methods are used in CE: (1) low ionic strength buffer in the sample (LISS), (2) stacking by inclusion of acetonitrile in the sample (AS), and (3) isotachophoresis (ITP).

5.1. Concentration on the capillary: 'stacking'

Several workers have used stacking in CZE by the use of dilute aqueous buffers in the sample [1,10]. This type of stacking is suited for analysis of compounds in a clean matrix devoid of a high concentration of proteins or salts. It is generally achieved by preparing the sample in the same separation buffer but at a lower (~10 time less) ionic strength (LISS) or by injecting a small plug of water before the sample [1,10]. A similar stacking can be obtained in the electrokinetic injection. Zhang et al. [11] used this technique to increase the sensitivity for amiodarone by several orders of magnitude [65]. However, the sample matrix has to be free from any salts.

5.2. Acetonitrile–salt mixtures

Acetonitrile is an effective and simple method to remove proteins from the sample. In (CZE) a unique type of stacking occurs when mixtures of acetonitrile and inorganic salts are present in the sample (not in the buffer) [12,13]. Acetonitrile stacking is used for samples with high concentrations of salts and/or proteins such as in the case of serum or food. This stacking is different from that occurring in LISS since it occurs in acetonitrile solutions and it is aided by the presence of high concentrations of inorganic ions in the sample. The overall effect is a better sensitivity and improved resolution. However, the stacking is modulated by many factors in the sample itself such as pH, ions, etc. [13] and enhanced by high ionic strength separating buffers [8]. However, not all drugs are stacked easily by acetonitrile. Stacking by acetonitrile is illustrated for iohexol, theophylline and phenobarbital (Figs. 1 and 2). In this graph the relative peak width to that of the neutral molecules indicates the degree of stacking achieved by this method. We have used this technique for the analysis of several drugs in serum as listed in Table 1.

5.3. Transient isotachophoresis

Isotachophoresis is a powerful method for concentration on the capillary. It is suited for samples with a high salt content. However, coupling it to CE is more difficult. A transient isotachophoretic step or self-stacking which occurs at the early part of the electrophoresis is more practical. Under these conditions a complementary suitable ion is added to the sample to act as leading/terminating ion [14–16] and a large volume is injected. The conditions for ITP can be fulfilled briefly before the separation is changed to CZE. The knowledge of migration rate of the different ions and a clever choice of the buffers are important in this technique; however, this can occur accidentally.

6. Drugs analyzed by CE

Table 1 lists many of the drugs, which have been analyzed in serum or urine by either CZE or MEKC with very few analyzed in pure solutions. Few of these methods used fluorescence or laser-induced fluorescence (LIF) detection. The majority have been validated for their linearity, detection limits, accuracy and precision. Few of these methods used sample extraction while the majority used direct injections or acetonitrile treatment. Some drugs such as the antifungal fluconazole have been analyzed after a variety of sample preparation methods [47]. The list of drugs analyzed by CE keeps on growing. On-line sample clean-up and concentration for drugs is an attractive idea which has been described by Strausbauch et al. [39] and Morita [50] and reviewed by Tomlinson et al. [51]. Nishi et al. [52] reviewed the different surfactants including the chiral ones which can be useful for drug separation. Several other reviews [53–56] in addition to a book [57] have dealt with analysis of drugs by CE reflecting the growing interest in this area.

7. Combination of CE and immunonssays

Many drugs such as tacrolimus and digoxin remain below the detection limits of CE or HPLC. Chen et al. [58] have described a method which has

Table 1. List of the drugs analyzed in serum or urine by CE

Class	Compound	Buffer/conditions	Reference
Antiepileptics			
Barbiturates diff.	MEKC	Phosphate 25 m*M*, pH 8.0, 50 m*M* SDS 210 nm	[17]
Barbiturates diff.	MEKC	Borate–phosphate, pH 7.8, SDS 50 m*M*, scanning	[5]
Felbamate	MEKC	Borate 100 m*M*, pH 8.4, SDS 55 m*M* 214 nm	[6]
Phenobarbital	MEKC	Borate 100 m*M*, pH 8.4, SDS 55 m*M* 214 nm	[6]
Penobarbital	CZE	Borate 300 m*M*, pH 8.5, 254 nm	[18]
Lamotrigine	CZE	Acetate buffer, 130 m*M*, pH 4.8, 214 nm	[20]
Gabapentin	CZE	Borate–phosphate, reaction with fluorescamine	[19]
Several	MEKC	Borate, pH 9.3 with extraction	[41]
Antiarrhythmic			
Amiodarone	CZE	Phosphate buffer, stacking	[11]
Desethylamiodarone	CZE	Phosphate buffer, stacking	[11]
Procainamide	CZE	Phosphate 50 m*M*, 200 nm	[22]
N-Acetylprocainamide	CZE	Phosphate 50 m*M*, 200 nm	[22]
Several	MEKC	Sample extraction	[21]
Cardiovascular			
Several	MEKC	Solid-phase extraction	[23]
Analgesics			
Acetaminophen	MEKC	Borate, pH 10 with SDS, 200 nm	[24]
Salicylic acid	MEKC	Borate, pH 10 with SDS, 200 nm	[24]
Salicylic acid	CZE	Borate, 175 m*M* pH 9.4	[28]
Ibuprofen	CZE	Borate 200 m*M*, 214 nm	[25]
Ketoprofen	CZE	Borate 250 m*M*, 254 nm	[26]
Antiasthmatics			
Theophylline	MEKC	Borate 6 m*M*, phosphate 10 m*M*, pH~9.0, 75 m*M* SDS, scanning	[4]
Theophylline	CZE	Borate 300 m*M*, pH 8.5, 254 nm	[3]
Theophylline	MEKC	Phosphate, 20 m*M*, pH 11, SDS	[44]
Theophylline	CZE/MEKC	Borate–phosphate pH 9, 280 nm detection	[49]
Caffeine	MEKC	Borate 6 m*M*, phosphate pH 10, pH~9.0, 75 m*M* SDS, scanning	[4]
Contrast agents/renal function			
Iohexol	CZE	Borate 220 m*M*, pH 8.8, 254 nm	[27]
Iopamidol	CZE	Borate 175 m*M* pH 9.4, 254 nm	[28]
Iothalamic acid	CZE	Borate 175 m*M*, pH 9.4, 254 nm	[28]
Immunosuppressant			
Cyclosporine	MEKC	Phosphate–borate, SDS, acetonitrile, 200 nm	[30]
Anti-tumor			
Suramin	CZE	Capso buffer, 63 m*M* pH 9.7, 25 nm	[31]
Suramin	CZE	Tris-borate, pH 8.6	[48]
Methotrexate	CZE	Tris-MES buffer, pH 6.7, extraction, LIF detection	[32]
Taxol	MEKC	Tris-borate, pH 8.5, 100 m*M* SDS, extraction, 230 nm	[33]
Cytosine-β-D-arabinoside	CZE	Citrate 40 m*M*, pH 2.5, extraction	[46]
Tomoxifin	CZE	Acetate, acetonitrile, methanol, extraction	[29]
Antibiotics			
Cefixime	CZE	Phosphate 50 m*M*, pH 6.8	[42]
Several	MEKC	Phosphate–borate with SDS	[43]
Amikacin	MEKC	Phosphate–borate, pH 7.0 derivatized, fluorescence	[41]
Miscellaneous drugs			
Nicotinic acid	CZE	Borate 10 m*M*, pH 9.3–phosphate, 10 m*M*, pH 2.3 254 nm	[34]
OH-Coumarin	CZE	Phosphate pH 7.5, extraction	[35]
Fosfomycin	CZE	Borate buffer, 254 nm	[36]
Heparinoid mimetics	MEKC	Phosphate buffer with SDS	[37]
β-Blockers, several	MEKC	SDS 50 m*M* in 100 m*M* borate buffer, pH 8.1	[38]
β-Blockers, several	CZE	Phosphate buffer, pH 3.1	[38]
β-Blockers, several	MEKC	Phosphate, pH 7.0 with *N*-acetyltrimethylammonium bromide	[45]
Glipizide	MEKC	Concentration on the capillary	[39]
Glyburide	MEKC	Concentration on the capillary	[39]
Fluorocytosine	MEKC	Phosphate–borate, pH 9.2, 210 nm	[40]
Different drugs	MEKC	Extraction	[21]
Fluconazole	MEKC	Direct injection or extraction, 190 nm	[47]

a potential for better sensitivity with simultaneous detection of several drugs based on a combination of immunoassay, laser-induced fluoresence and CE. In this system, prepared drug–fluorescent conjugates were mixed with the antibody and the unknown urine samples. After the competition reaction, the free-labeled drug was separated from the bound one by CE. Since this method requires many complicated synthetic steps for the preparation of the antibody and the tagged drugs, it is more suited for commercial companies. Cortisol, an endogenous substance and a drug, has been analyzed by a similar technique [59,60].

8. Comparison of CE to HPLC

Several studies have shown that CE when compared to HPLC for TDM is faster and easier [6,26,61–64] with better resolution [47,61] especially for the polar compounds [63]. CE has less operating costs [47]. Wynia et al. [64] determined the precision, linearity, ruggedness and detection limits for CE and HPLC using the antidepressant drug mirtazapine. The R.S.D. for CE was 0.6 while for HPLC was 0.2. The linearity for CE was 10–1400 μg/ml while for HPLC it was 4–800 μg/ml. Most workers agree that HPLC in general tends to give better precision and better sensitivity. The combination of special flow cells and stacking methods brings the sensitivity of CE more closely to that of HPLC [65].

9. Chiral separation

Although isomers have very close chemical structures, in many instances they have different biological effects or only one is metabolized. Chiral separations have generated great interest in CE because of the ease of analysis and the high resolution. Most of the chiral separations are performed on drugs in pure solutions (for purity checks). However, few studies have been performed on separations from biological fluids on drugs such cicletanine, warfarin and ibuprofen as listed on Table 2. Nishi [66] reviewed the enantiomers separation of drugs by electrokinetic chromatography using chiral micelles and proteins. Fanali [67] and Bojarski and Aboul-Enein [68] reviewed the identification of chiral drugs by CE including those present in biological fluids. D'Hulst and Verbeke [69] and Altria [70] et al. showed that limits of detection of <1% and 0.1%, respectively, are possible for minor enantiomer levels. CE offers very rapid, low cost and excellent separation for chiral separations but the reproducibility falls short that of HPLC [68,70,83].

Table 2
List of drugs which have been analyzed in serum or urine by chiral separation

Drug	CE Type	Fluid	Comments	Reference
Amphetamine	MEKC		Forensic glucopyranosyl isothiocyanate react, phosphate buffer pH 9.0 with SDS	[71]
Bupivacaine	MEKC	Serum	βCD, extraction	[82]
Ephedrine	MEKC	Urine	Deoxycarbonylvaline (phosphate, pH 8.8)	[72]
Cicletanine	MEKC	Plasma/Urine	γCD, borate 8.6 with SDS (plasma contained S+ while urine R-)	[73]
Mephenytoin	MEKC	Urine	Taurodeoxycholic acid (phosphate pH 7.2) the S only transformed into S-4-OHmeph	[74]
Mephenytoin	MEKC	Urine	βCD, phosphate–borate pH 9.1 with SDS	[75]
Ibuprofen	CZE	Serum	Maltrin M040 (TAPS/Tris 7.8) (order of migration dependent on the capillary coating)	[76]
Dimethindene	CZE	Urine	30 m*M* hydroxypropyl-β-CD, phosphate pH 3.3	[77]
Hexobarbital	MEKC	Plasma	βCD phosphate pH 7 with SDS	[78]
Warfarin	CZE	Serum	Glucidex tris phosphate pH 7	[79]
Warfarin	CZE	Plasma	Modified βCD phosphate, pH 8.3	[80]
Verapamil	CZE	Plasma	Trimethyl-βCD	[81]

10. Quantitation and reproducibility

A major obstacle for the widespread use of CE in routine analysis of drugs is the poor precision relative to that of HPLC. Precision is of utmost importance in routine work. Few studies have been devoted to understanding the sources of imprecision. For precision in CE, two parameters are important: peak area (or height) for quantification and migration time for drug identification. The precision for these two parameters in CE is less than that in HPLC. Fortunately, the migration time is more predictable in CE when compared to peak height (area) and can thus be corrected by employing references or internal standards [84]. Dose and Guichon [85] reported that a relative standard deviation (R.S.D.) of 1% for the migration time and peak area is possible by use of 2 internal standards. Siren et al. [86] have shown multiple standards of close migration bracketing the analyzed compound greatly improves the reproducibility to >1%. An R.S.D. of mobility of 0.01–0.03% can be obtained as well [87].

Imprecision in peak height (area) is related to a great extent to two factors: injection volume (or time) and capillary wall effects. The R.S.D. of peak height (area) is inversely related to sample concentration [80,88]. The precision improves with higher sample concentration especially when peak area instead of peak height is used [84,89]. Thus stacking methods indirectly improve the precision for peak area [13]. In general, but not always, peak area shows less variation than peak height with a wider range of linearity [84,89]. The precision of peak height vs. area depends on the software of the integrator and the sharpness of the peak. In the absence of the sample extraction, internal standards slightly improve the precision of peak height or area. Temperature control is also a critical factor in reproducibility in CE [90].

A thorough wash with NaOH (0.1–1 *M*) [91], phosphoric acid (100 m*M*) [1], acetonitrile or SDS (for MEKC) [92] decreases the wall effects and improve greatly the reproducibility of the migration time and peak height (area). Kelly et al. [93] presented data on electrolysis of the buffer and its effect on the precision. High ionic strength buffer at low current and zwitterionic buffers (which generates low current) improve the precision. Kelly et al. [93] described also several suggestions to decrease the effects of electrolysis of buffers.

11. Conclusions

Although CE has been shown to offer several advantages for TDM, it is not popular yet in the routine work compared to research analysis. The initial capital investment for the instrument is expensive. However, the cost of operation is much less than with HPLC. With stacking methods, CE has enough sensitivity and precision for the analysis of many of the drugs present in serum or urine. There is always a need for further sensitivity. Studies addressing new methods for stacking are welcomed. It is expected that coupling the stacking methods with specialized optical cells, such as the bubble or square cell, would increase further the CE sensitivity. It is expected that improvement for the precision would occur through buffer additives. Again the goal is to match or surpass that of the precision of HPLC. TDM by CE no doubt will keep on growing because of the continued introduction of new drugs.

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