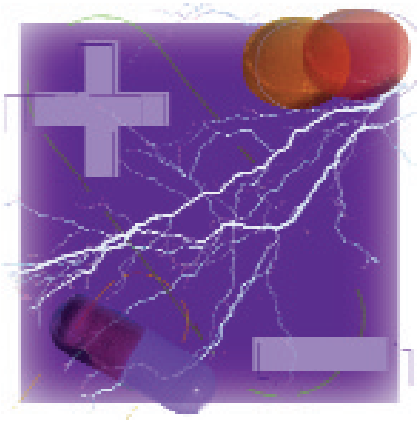

Validating CE Methods for Pharmaceutical Analysis

H. Fabre, University of Montpellier, Montpellier, France,
and K.D. Altria, GlaxoSmithKline, Ware, Hertfordshire, UK.

Capillary electrophoresis has become one of the most advanced separation techniques for pharmaceutical analysis. It is a useful and reliable alternative or complementary technique to liquid chromatography in many areas, including main component assay, impurity determination, enantiomeric separations, identity confirmation and stoichiometry determination. Other areas of interest within the pharmaceutical industry are trace residues determination in cleaning validation and tablet dissolution testing. Numerous validated methods have appeared in the literature, and methods have been included in regulatory submissions by drug companies.

A major advance for capillary electrophoresis (CE) was its recognition by the regulatory authorities. A general monograph on CE is now included in the *USP* (1), which has also been published in the European (2) and Japanese Pharmacopoeias (3). CE methods have emerged in the *European Pharmacopoeia* for levocabastine hydrochloride impurities, and a draft monograph for erythropoietin concentrated solution has been presented in *Pharmeuropa* (4).

In this column we will consider the key features for method validation of small molecules using CE in the context of the pharmaceutical industry. A useful guide for method validation in analytical chemistry is the Eurachem guide (5), which discusses when, why and how methods should be validated. However, for the pharmaceutical industry, the main reference source is the *International Conference on Harmonization (ICH) Guidelines* (6), which provides recommendations on the various characteristics to be tested for the most common types of analytical procedures developed in a pharmaceutical laboratory:

- identification tests
- quantitative tests for the control of chiral and achiral impurities
- assay of a major component in a drug substance, a drug product or in a sample solution taken from a dissolution bath.

This article examines the different characteristics to be tested (specificity, linearity, accuracy, precision, solution stability, limits of detection and quantification, and robustness), and outlines the specific aspects that should be considered for a CE method. As method validation is not only a process of evaluating characteristics but also of judging suitability for intended use, examples will also be given that demonstrate the performance capabilities of CE methods. Both the similarities and differences between CE and liquid chromatography (LC) will be emphasized. Table 1 presents some examples of validated CE methods.

Specificity (Selectivity)

This is described as the ability of a method to discriminate the analyte from all potential interfering substances. It confirms that the signal measured is caused solely by the analyte.

For an identification method, specificity is usually investigated by comparing the response of reference samples containing only the analyte with the response of samples in which potential interferences have been added. It is also possible to compare the results with those of other independent methods/techniques, preferably based on different separation principles.

For an assay method, specificity is assessed by injecting a test solution spiked with degradation products, synthesis intermediates, excipients from the formulation (degraded and non-degraded) at their expected level; internal standard solution and extraction solvents are also injected. It may also be appropriate to inject sample solutions degraded under stress conditions of temperature, pH, humidity, light and oxidation and examine the degradation profiles. An automated co-injection of the impurity (7), which is an easy way to confirm the identity of the impurity, is feasible on most commercial instruments.

Another way to validate the specificity is to assess peak homogeneity or peak purity (7, 21). This can be achieved using a diode array detector, which is often incorporated in CE instruments. The techniques that can be used for peak purity assessment are similar to those used in high performance liquid chromatography (HPLC) (spectral suppression, absorbance ratio etc). It is also possible to collect and analyse the peak of interest by an orthogonal technique, such as HPLC (22).

It is important in CE to assess the repeatability of selectivity by repeatedly injecting and analysing standard and test solutions with the same set of separation vials. This is necessary as electrolysis of the buffer occurs (23) under the applied voltage, which yields a change in the electrolyte pH and may alter the electroosmotic flow velocity and the compound ionization. The selectivity will be particularly altered if the buffer pH is close to the pK_a of the analytes. It is, therefore, essential in CE to determine at the optimization stage of the method how many injections can be made with the same set of separation vials. This will depend largely on the buffer capacity of the electrolyte, electrolyte reservoir volume, operating current and run time.

It is also necessary when using substituted

cyclodextrins (CDs) for enantiomeric separations to confirm that CDs from different batches or different suppliers give similar selectivity, as different degrees of substitution, polydispersity or purity of the CDs, even using identical nominal reagents, may alter the selectivity (24).

Linearity of the Calibration Line/Range

The linearity of the response as a function of analyte concentration (or amount) should be assessed in the range of interest.

For an active ingredient assay in a formulation, the linearity is assessed in the range 50–150% or 80–120% or 60–140% of the target concentration (25). For an impurity, the linearity should be tested in the presence of the main component around the maximum tolerated level of impurity (e.g., from the limit of quantification to 200% of the maximum tolerated level). For dissolution testing, the range should cover ±20% over the range specified for batch release (14). The linearity, residuals and *y*-intercept should be evaluated by ANOVA (14). A plot of residuals may also be performed to assess any curvature or bias in the data.

Typically, linearity is assessed in CE by injecting the same volume of a standard solution but at different concentrations (typically five concentrations). The calibration line–response as a function of the injected amount (or concentration) can also be constructed using different injection volumes of a single standard solution. However, the regression line for different injection volumes does not go through the origin (7) because of spontaneous injection. The linear range of the ultraviolet (UV) detectors in CE is more restricted than in HPLC because of the circular geometry of the capillary used for detection, which increases scattered light. However, the linear range is sufficiently extended for most applications, even when assay and purity determinations are performed in a single injection. For indirect UV detection, which is a common detection mode for small inorganic anions and cations, the linear range is more restricted (about two decades) (26) than with direct UV detection as it depends on the concentration of the UV absorber added to the electrolyte. If the sample to be analysed contains ions at very different concentrations, it is difficult to perform quantification of them all in a single injection; a dilution of the sample may be needed to analyse ions at a high concentration. Another alternative is to use conductivity detectors, which give a higher linear range for small ion analysis.

Peak areas (PAs) are generally used as responses in CE as they give a wider linearity range than peak heights, which are affected by peak distortion at high concentrations. In addition, areas can be corrected by dividing by their respective migration times (MTs) to take into account any possible drift of MTs. Many applications (7–20) show acceptable linear data and intercepts close to the origin in the range of interest for CE methods.

Accuracy and Recovery Studies

The accuracy expresses the closeness of agreement between the value found and the value that is accepted as a reference value. Accuracy measurement measures systematic errors but also random errors in the whole analytical process. However, accuracy will depend on the number of determinations.

It is very common when analysing a formulation to evaluate accuracy by performing recovery experiments. This is achieved by placebos spiked with known amounts of analyte in the range of interest. Accuracy is useful for measuring losses caused by solute binding with excipients and solubility effects at varying concentrations. The results found are compared with the concentration added, and recoveries are calculated. The spiking range could be, for example, 80–120% (or 50–150% or 60–140%) of the target concentration for a main peak assay (25) and from the limit of quantification to 150 or 200% of the tolerated level for impurities. Three independent determinations at several levels are recommended (25, 27).

Accuracy may also be assessed by comparing the results of the same test samples analysed by the method undergoing validation and a method considered as a reference method. Where possible, a method based on different separation principles (orthogonal) should be used. Cross-correlation between HPLC and CE has often been used. Table 2 presents the comparison of the results obtained in HPLC and in micellar electrokinetic capillary chromatography (MECC) for the related impurities of cefotaxime. Figure 1 presents a typical electropherogram corresponding to the MECC separation.

For comparison of impurity levels quoted as % area/area, normalized peak areas (areas divided by the respective MTs, often stated as corrected peak areas (CPAs)), must be used in CE to compensate for the different residence times of the species in the detector. In HPLC, all analytes travel through the detector at the same speed (that of the mobile phase) and hence have the same residence time in the detector cell. However in CE, the residence time of the species depends on their mobility. Within a run, species that have a higher apparent mobility (a shorter MT) will give a lower response than species with a lower mobility, for species with the same absorptivity and concentration. Normalization allows the areas to be corrected for differences in MTs (7). It may also be necessary, when comparing CE results with thin-layer chromatography (TLC) or HPLC results, to consider a possible change in response factors for

Table 1: *Examples of Validated CE Methods.*

Application	Validation Aspects*									Solute(s)
	1	2	3	4	5	6	7	8	9	
Impurities	✓	✓	✓	✓	✓	✓		✓	✓	Cefotaxime (7)
	✓	✓	✓	✓	✓	✓		✓	✓	Ibuprofen and codeine (8)
	✓	✓	✓	✓	✓	✓	✓	✓	✓	Ranitidine (9)
Assay	✓	✓	✓	✓	✓	✓	✓	✓	✓	Protein (10)
	✓	✓	✓	✓	✓	✓	✓	✓		Acidic drugs (11)
	✓	✓	✓	✓	✓	✓		✓		Hydrochlorothiazide and chlorothiazide (12)
	✓	✓	✓	✓	✓	✓	✓	✓		Basic drugs (13)
	✓	✓	✓	✓	✓	✓	✓	✓		Acamprosate (14, 15)
Chiral	✓	✓	✓	✓	✓	✓	✓	✓		Ropivacaine (16)
	✓	✓	✓	✓	✓	✓		✓		BMS-180431-90 (17)
Drug counter-ions	✓	✓	✓	✓	✓	✓		✓	✓	Calcium (18)
	✓	✓	✓	✓	✓	✓		✓		Acetate (19)
Contamination studies	✓	✓	✓	✓	✓	✓	✓	✓	✓	Various (20)

* 1 = specificity (selectivity); 2 = linearity; 3 = accuracy/recovery; 4 = injection repeatability; 5 = method repeatability; 6 = solution stability; 7 = method robustness; 8 = cross-validation; 9 = limits of detection and quantification.

impurities from one method to another one, because of changes in absorptivity under the different method conditions.

Precision

Precision expresses the degree of scatter between a series of measurements under prescribed conditions. Precision may be considered at three levels:

Repeatability: refers to the variability when the method is performed by the same analyst on the same piece of equipment over a short timescale.

First, the repeatability of the CE system (MTs, PAs) should be assessed at one or several concentration levels, depending on the use of the method. Important factors to consider for repeatability at the optimization stage of the method are well established (28); the most important one being the use of an internal standard (IS). The relative standard deviations (RSD) for MTs or relative MTs (analyte/IS) are better than 1% if the electrolyte composition and the rinse steps between injections have been suitably optimized. For identification with the highest confidence level, the use of mobilities, which can be automatically calculated by the software, is recommended as they give the lowest RSD (29). The repeatability of PAs in CE is generally lower than in HPLC because of the small injected volumes (between 2 and 20 nL), but is significantly improved by the use of an IS (Table 3). The RSD of successive injections (typically 10 injections) for a main compound is generally lowered from 2% (without IS) to less than 1% using relative PAs or relative CPAs (analyte/IS).

The repeatability of the entire analytical procedure should be demonstrated by performing independent determinations (typically 10) on real samples, at least at the target concentration or at several levels depending on the use of the method (14).

Intermediate precision: relates to precision when one or several factors are changed in the method within a single laboratory.

The factors to be changed may include

- the capillary: the separation should be repeated on capillaries from different batches and different suppliers on the same day
- the day of operation: freshly prepared electrolyte, sample and test solutions should be tested on each of the operating days
- the operator: different analysts should independently prepare sample and standard solutions, their own capillaries and electrolytes
- the sources of reagents or electrolytes. It can also be important to assess whether the method can be transferred (31) to another type of instrument. Slight modifications in the method are necessary to achieve similar separations, as instruments have different injection procedures, use capillaries of different lengths and have detection windows at a variable distance from the injection point. To facilitate method transfer the injected volume, applied electric field, effective capillary length and size of the detector window for the CE method should be indicated.

The factors to be changed can be analysed simultaneously, (e.g., recovery studies can be performed on three different days by three analysts, each one independently preparing solutions (14)). Inter-day and capillary supplier variations can be tested together. ANOVA can be used to determine whether the capillary brand or the inter-day repeatability significantly influence the assay (25).

Reproducibility: (the largest measure of precision normally encountered) refers to inter-laboratory precision, when the same sample is analysed by several laboratories for comparative purposes. Reproducibility is not part of the Marketing Authorization dossier, but is recommended for official methods.

The acceptable results of an inter-laboratory trial that involved seven pharmaceutical companies performing three different CE methods (an MECC method for the assay of a main component in tablets, a chiral separation method using β-CD, and a drug stoichiometry determination) (32–34) show that CE methods can be transferred in different

Table 2: *Comparison of MECC and HPLC Results for Related Impurities (%, area/area) of Cefotaxime (from reference 7).*

	Batch A		Batch B		Batch C		Batch D		Batch E		Batch F	
	MECC	HPLC	MECC	HPLC	MECC	HPLC	MECC	HPLC	MECC	HPLC	MECC	HPLC
DA	0.56	0.53	0.53	0.60	0.48	0.66	0.49	0.58	0.49	0.49	0.49	0.44
DO	0.43	0.43	0.41	0.42	0.38	0.44	0.30	0.32	0.40	0.43	0.40	0.41
DIM	0.29	0.14	0.31	0.14	0.29	0.15	0.35	0.21	0.39	0.17	0.35	0.16
F	0.04	0.04	0.07	0.05	0.04	0.04	0.09	0.08	0.05	0.05	0.06	0.04
TH	0.02	ND*	ND*	ND*	0.02	ND*	0.02	ND*	0.06	ND*	0.09	ND*
AN	0.05	0.05	0.02	ND*	0.04	0.09	ND*	ND*	0.04	0.13	0.08	0.12
L	0.20	0.17	0.19	0.18	0.18	0.15	0.26	0.22	0.20	0.23	0.20	0.21
Unk.	0.11	0.38	0.21	0.38	0.37	0.39	0.21	0.64	0.32	0.40	0.28	0.33
Total	1.72	1.74	1.76	1.77	1.79	1.92	1.71	2.11	1.96	1.90	1.95	1.71

ND* = none detected

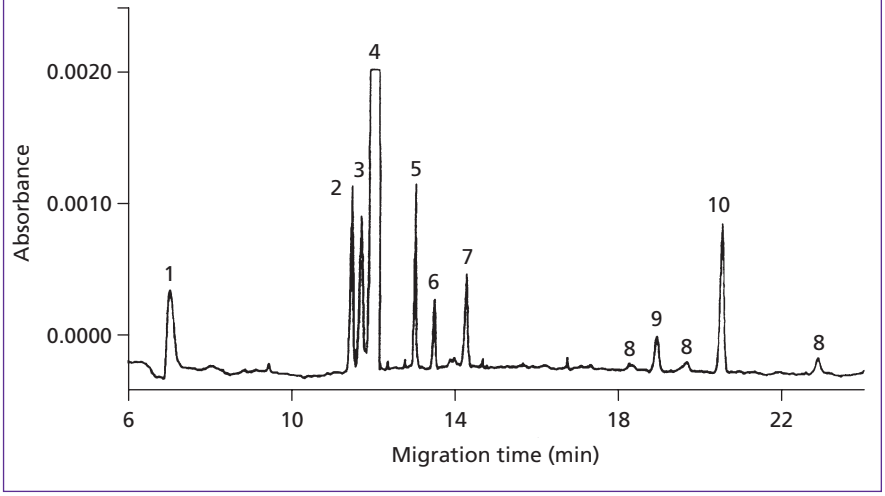

Figure 1: *Typical electropherogram of a cefotaxime sample (2.5 g/L) spiked with 0.2% (w:w) of each impurity. Peaks: 1 = electroosmotic flow, 2 = deacetylcefotaxime, 3 = deacetoxycefotaxime, 4 = cefotaxime sodium, 5 = cefotaxime dimer, 6 = N-formyl cefotaxime, 7 = thiazoximic acid, 8 = unknown, 9 = cefotaxime anti-isomer, 10 = deacetylcefotaxime lactone.*

laboratories using different instruments, if they are properly developed and described.

Stability of Solutions

This criterion is not listed separately in the *ICH Guidelines* as it is included in robustness testing (and studied in the development stage of the method). It is important to notify in a protocol the shelf-life of the solutions.

As in HPLC, stability of test and standard solutions should be assessed at least over a period of time covering preparation and analysis, and also a possible instrumental delay. It is also of major interest in CE to test the stability of the electrolyte solution. In contrast to HPLC in which the mobile phase is prepared daily because of the important volume that is required, in CE there is a low consumption volume (typically 10–20 mL per day) of electrolyte solution, which can be prepared for several days, weeks or months. The shelf-life of an electrolyte solution is very variable. A phosphate borate electrolyte can be stored at room temperature in a plastic container for at least three months (11); an electrolyte containing chromate and tetradecyltrimethylammonium bromide for small anion analysis should be prepared daily (35). Additives such as cyclodextrins promote growth of bacteria.

Robustness

Robustness relates to the capacity of the method to remain unaffected by small but deliberate variations introduced into the method parameters. It is an intra-laboratory study that allows information to be obtained on effects of minor changes in a quick and systematic manner. Robustness is not listed in the *ICH Guidelines* as a criterion to be part of method validation. However, it is mentioned that it should be tested at an appropriate stage of method development to demonstrate reliability/durability of the method. Robustness testing in CE is intended to detect method factors that may influence the assay, sensitivity or selectivity.

The most relevant factors to investigate are the electrolyte composition, injected volume, detection wavelength, separation temperature and rinse times etc. These factors are varied around the value set in the method to reflect changes likely to arise in different test environments. Experimental designs have been used for robustness testing in CE as they allow the testing of several factors with a minimal number of experiments. Fractional factorial designs (Plackett and Burman or other fractional designs) can be used as screening designs (15) to identify the critical factors in the method. If some factors are found to be slightly critical but if the responses (e.g., resolution) are found to be within acceptable criteria in each experiment, screening designs may be sufficient to conclude that the method is sufficiently robust for its intended use. If some factors are found to be very significant a response surface design can be used to gain more insight into the method and predict the variation of the response (e.g., resolution) inside or slightly outside the area investigated in the screening design. Central composite designs are well suited to robustness testing. The factors that were found to produce relatively large effects in the screening design are typically varied at five levels and a central point (method at the nominal level) is repeated throughout the design (15). The response surface plot gives a visual approach to the variations that can be expected in the area investigated.

Robustness testing can be easily performed in CE by comparison with HPLC because of the short equilibration time when changing the composition of electrolyte and the fact that instrumentation is automated. In addition, separations are generally rapid, which means that robustness testing may be performed within a short time. A central composite design (four factors, five levels) with 30 experiments (60 injections) allows testing of separation robustness between two compounds (2 min run time, 4 min of analysis) in only 5 h (15).

Table 3: *Improvement of Measurements Using an Internal Standard (from reference 30).*

	No Internal Standard	With Internal Standard
Repeatability of PAs (RSD, %; n=6 injections)	2.53 (capillary 1) 5.77 (capillary 2)	0.35 (capillary 1) 0.87 (capillary 2)
Recovery (relative error, %; n=2 injections)	1.21 (capillary 1, day 1) −6.48 (capillary 2, day 2)	0.50 (capillary 1, day 1) −0.01 (capillary 2, day 2)
Linearity (r^2, determination coefficient)	0.9863_3 (day 1) 0.9968_4 (day 2)	0.9999_7 (day 1) 0.9997_3 (day 2)

Limits of Detection and Quantification (LOD and LOQ)

The LOD corresponds to the lowest concentration or amount of analyte that can be confidently detected by the method. The LOQ corresponds to the lowest concentration or amount of analyte that can be determined with suitable precision and accuracy. These two parameters are determined for impurities and/or degradation products and for trace level determinations, such as contamination studies (20).

There are several approaches to evaluate the LOD and LOQ. The most widely used is based on the signal-to-noise ratio (*S/N*) obtained from samples spiked with the analyte. An *S/N* ratio of 3 is generally considered as statistically acceptable for the LOD. The LOQ can be evaluated in a first approach by testing the repeatability of successive injections of standard solution at low concentration levels (a concentration that gives an *S/N* ratio of 10 may also be used). Based on the RSD obtained, the LOQ is subsequently validated by replicate analysis (≥ 6) of samples prepared around this concentration. A relative error of ±10% and a repeatability of about 10% are acceptable for impurities at the LOQ.

The LODs and LOQs in CE are generally higher (in concentration) than in HPLC because of the small optical path (50–100 µm) used for UV detection and small injected volumes (2–20 nL) compared with HPLC (10 mm optical path and 10–200 µL). However, several factors should be optimized (36) at the stage of method development to improve limits of detection and quantification:

- the sample solvent: the use of a solvent of low conductivity with respect to the electrolyte yields a stacking effect and increases the analyte signal
- the optical path: a bubble cell or a high-sensitivity cell increases the optical path
- the capillary diameter: increasing the capillary diameter results in an increase of the optical path and the injected volume; the limit is the increase of current and subsequent Joule effect, which causes band broadening
- the injection volume: increasing the injected volume results in an increase of the signal if the sample is in a suitable solvent but may have a detrimental effect on resolution
- the detection wavelength: detection at low wavelength (200 nm or lower), which is very common in CE because of the transparency of the separation electrolyte, may often be used for a better LOD.

LOD and LOQ in CE are typically lower than 0.05 and 0.1%, respectively, for impurities. Limits of quantification (0.01%, m/m) and detection (0.005%, m/m) were reported for homotaurine when determined as an impurity in calcium acamprosate drug substance (27).

System Suitability

The criteria set for a method depend on the usage of the method. For example, if the method is a limit test then a simple measurement of LOD may be sufficient. However, for an impurity determination method, all validation aspects discussed in this article would need to be addressed and the system suitability test would have particular emphasis on resolution and sensitivity (signal/concentration) or detection limit. Peak symmetry is often included in HPLC methods as it gives an indication of column performance; however, it is not normally specified in CE as high sample concentrations often produce asymmetric peaks. Maximum tolerance values for injection precision are also routinely quoted in assay methods.

Conclusion

We have shown in this issue of "CE Currents" that the methodology of method validation in CE is similar to that of HPLC, but that there are particular aspects to consider, which are summarized below:

- the treatment of a new capillary
- capillary variations (lot, suppliers)
- reagent source variations (preprepared electrolyte, purity of chemicals)
- instrument transfer
- operator training (cutting of the capillary, alignment of the detector window)
- robustness testing (fully assessed for indirect UV detection).

It may also be important to be reminded of some key points that should be described in a CE method:

- total length and effective length of the capillary
- electric field V/cm and the current developed
- injected volumes, which should be calculated
- rinse procedure between injections
- maximum number of injections that can be made with the same set of separation vials
- detailed preparation of the electrolyte
- rinse procedure after use and storage
- treatment of the capillary before reuse.

In routine applications, dedication of one capillary to each application (particularly if surfactants are present in the electrolyte) is recommended, as is performing system suitability tests comparable with those used in HPLC to assess selectivity, resolution and system precision.

In our laboratories, reliable and reproducible results are routinely obtained in CE if the methods are correctly optimized, described, validated and applied by operators using good working practices. A great deal of literature references present acceptable data for method validation in CE, confirming the reliability of the technique for routine quality control of drugs. CE can be used without restrictions as an alternative or complementary technique to HPLC in many fields of applications within the pharmaceutical industry. It can even supersede liquid chromatography in particular areas such as enantiomeric separations or analysis of small ionic compounds with no chromophores.

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Huguette Fabre is a Professor of Analytical Chemistry in the Faculty of Pharmacy, University of Montpellier, Avenue Charles Flahault, 34 060 Montpellier Cédex 2, France, fax +33 4 67 52 89 15; e-mail hfabre@pharma.univ-montp1.fr. She organizes training courses in Montpellier for the pharmaceutical industry in CE (a French and English course will be given by Dr K.D. Altria in May 2001) and on method validation. Further information can be obtained from http://www.ceandcec.com/quality_control.htm

"CE Currents" editor Kevin D. Altria is senior principal scientist in the analytical sciences department at Glaxo SmithKline R&D, Ware, Hertfordshire, UK, and is a member of the Editorial Advisory Board of LC•GC Europe. *Direct correspondence about this column to "CE Currents," K.D. Altria, Analytical Sciences, GlaxoSmithKline, Park Road, Ware, Hertfordshire SG12 0DP, UK, fax +44 1920 882 295, e-mail: kda8029@GlaxoWellcome.co.uk, website: http://www.ceandcec.com/*

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