

Use of capillary electrophoresis coupled to UV detection for a simple and rapid analysis of pharmaceutical formulations in a quality control laboratory in a hospital pharmacy

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ABSTRACT

Study objectives: To develop and validate generic methods for the determination of 15 basic compounds by capillary electrophoresis in 21 different hospital formulations, including solutions for ophthalmic, oral, topical and intravenous use.

Methods: Three methods were used. The first one was based on an aqueous background electrolyte (BGE), a short-end injection technique, and was used for most of the tested pharmaceutical compounds (60%). The second method was based on a hydro-organic BGE and was applied to the analysis of unstable compounds in aqueous solutions and/or to reduce solute adsorption on the capillary walls (catecholamine compounds and tropane alkaloids). A short-end injection technique was also used. The third method allowed the analysis of the only pharmaceutical formulation containing two active drugs: phenylephrine and homatropine. To obtain a sufficient resolution between the two substances and to reduce the homatropine adsorption to the capillary wall, a conventional injection ("long-end injection") and a non-aqueous BGE were used. This method was also used for the analysis of homatropine ophthalmic solution.

Results: All methods were validated according to SFSTP (*Société Française des Sciences et Techniques Pharmaceutiques*) recommendations [1]. Good quantitative performances were obtained for all validated pharmaceutical formulations. Trueness (closeness of agreement between the average value of the determined concentrations and the known concentration) values between 95.8% and 102.5% were obtained with repeatability and intermediate precision values of 0.4% to 4.1% and 0.5% to 4.7%, respectively.

Conclusion: The three methods were successfully applied to routine analysis in the quality control laboratory of the Pharmacy Department of the University Hospitals of Geneva. For economic, ecological and time-consuming reasons, capillary electrophoresis has shown a great potential for the rapid and simple quality control of pharmaceutical formulations in hospital pharmacy.

KEYWORDS

Basic drugs, capillary electrophoresis (CE), generic methods, pharmaceutical analysis, quality control

INTRODUCTION

Quality control of pharmaceutical formulations is mainly performed by liquid chromatography (LC) coupled to UV detection. An example of the supremacy of LC-UV in the pharmaceutical field can be observed in the international pharmacopoeias, such as the

European Pharmacopeia [2], which consider it as one of the analytical techniques of choice together with gas chromatography and thin-layer chromatography. Nonetheless, in recent years, capillary electrophoresis (CE) has raised great interest for the analyses of pharmaceutical compounds [3-5]. Its success is mainly because of its low cost, high efficiency, reduction in solvent consumption and great versatility. Moreover, method development in CE is often faster than LC development methods. However, CE is well-known for its lack of sensitivity caused by the low amount of sample injected in the capillary and the short detection pathway of the light. This limitation undoubtedly represents a real problem for the quantification of samples with a low concentration of analytes, such as biological or trace analyses, but it is not the case for the analysis of pharmaceutical formulations that possess, generally, active drug(s) concentration(s) in the order of mg/mL.

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Until recently, in our quality control laboratory, the quantification of active drugs in pharmaceutical formulations produced by the hospital pharmacy was mainly performed by LC-UV or by simple UV, i.e. spectrophotometry, after a sample purification step. Six different analytical columns with more than six different mobile phase compositions and internal standards were required to perform the LC quantification of 12 active drugs contained in 18 pharmaceutical formulations. These LC-UV methods

involved not only a large amount of solvent but were also time-consuming (mean analysis time of 10 minutes). Two ophthalmic solutions (active drugs: cocaine and oxybuprocaine) and a codeine syrup, which belong to the oldest formulations produced in the department, were analysed by three different simple UV methods. All these 15 compounds are small basic drugs with chromophore groups (see Table 1) and are therefore particularly adapted to CE-UV analysis. In order to reduce the cost and analysis time, and to homogenise the analytical procedures, three generic CE-UV methods for the quantitative determination of 15 basic active drugs present in 21 different pharmaceutical formulations were developed, validated and applied for the routine analysis in our quality control laboratory.

MATERIALS AND METHODS

Chemicals

Adrenaline-d-hydrogentartrate (batch number: 1082648), atropine sulphate (batch number: 442755/1), ephedrine hydrochloride (batch number: 1167365), isoprenaline hydrochloride (batch number: 1098560), procaine hydrochloride (batch number: 456651/1), ammonium acetate (batch number: 1171125), concentrated phosphoric acid (batch number: 63330) and tris(hydroxymethyl)-aminomethane (tris) (batch number: 1153482) were obtained from Fluka (Buchs, Switzerland). Cocaine hydrochloride (batch number: 2006.05.0422), morphine hydrochloride (batch number: 2006.06.0833) and tetracaine hydrochloride (batch number: 2006.06.0249) were obtained from Hanseler AG (Herisau, Switzerland). Homatropine hydrobromide (batch number: A0219470) was obtained from Acros (Geel, Belgium). Ketamine hydrochloride (batch number: 0505A432), lidocaine hydrochloride (batch number: 06B09-N02), oxybuprocaine hydrochloride (batch number: 0504A677), phenylephrine hydrochloride (batch number: 06A04-N08) and scopolamine hydrobromide (batch number: 06H28-N03) were purchased from Fagron GmbH (Barsbuttel, Germany). Concentrated acetic acid (batch number: K32207563), sodium hydroxide (batch number: B870898), acetonitrile (batch number: I380030) and

Table 1: Compounds and pharmaceutical formulations

Compound	Pharmaceutical preparation	Formulation
Adrenaline-d-hydrogen tartrate 0.1 mg/mL	Intravenous solution	H ₂ O, NaCl, sodium metabisulphite
Adrenaline-d-hydrogen tartrate 1.0 mg/mL	Intravenous solution	H ₂ O, NaCl, sodium metabisulphite
Atropine sulphate 0.1 mg/mL	Intravenous solution	H ₂ O, NaCl
Atropine sulphate 5.0 mg/mL	Ophthalmic solution	H ₂ O, NaH ₂ PO ₄ , Na ₂ HPO ₄
Cocaine HCl 50 mg/mL	Ophthalmic solution	H ₂ O, HCl/NaOH
Codeine phosphate 2.5 mg/mL	Syrup	H ₂ O, sucrose, methylparaben
Ephedrine HCl 10 mg/mL	Intravenous solution	H ₂ O, NaCl
Homatropine HBr 20 mg/mL	Ophthalmic solution	H ₂ O, NaCl
Weak ophthalmic injection: homatropine HBr 4.0 mg/mL and phenylephrine HCl 0.5 mg/mL	Ophthalmic solution	H ₂ O, NaCl, K ⁺ , Mg ²⁺ , Ca ²⁺ , acetate, citrate (artificial aqueous humor)
Isoprenaline HCl 0.1 mg/mL	Intravenous solution	H ₂ O, NaCl, sodium metabisulphite, lactic acid, sodium lactate, HCl
Ketamine HCl 1.0 mg/mL	Intravenous solution	H ₂ O, NaCl
Lidocaine HCl 40 mg/mL	Oral solution	H ₂ O, NaCl, methylparaben, propylparaben, cyclamate sodium, saccharin, methylene blue, orange aroma
Morphine HCl 20 mg/mL	Oral solution	H ₂ O, EDTA, sodium metabisulphite, potassium sorbate, magenta I
Morphine HCl 0.5, 1.0, 5.0 and 10 mg/mL	Oral solution	H ₂ O, parabens EtOH, sucrose, orange aroma, citric acid
Oxybuprocaine HCl 10 mg/mL	Ophthalmic solution	H ₂ O, NaCl, HCl 0.1 N/ NaOH 0.1 N
Phenylephrine HCl 0.1 mg/mL	Intravenous solution	H ₂ O, NaCl
Scopolamine HBr 2.5 mg/mL	Ophthalmic solution	H ₂ O, NaCl
Tetracaine HCl 50 mg/mL	Local solution	H ₂ O, methylene blue

Produced by Pharmacy Department, University Hospitals of Geneva

methanol (batch number: I397318) were provided by Merck (Darmstadt, Germany). Codeine phosphate (batch number: 04-00995) was purchased from Macfarlan Smith Ltd (Edinburgh, Scotland). Ultra-pure water, used for standard and sample preparation, and water for injection used in the preparation of pharmaceutical formulations were supplied by a Milli-Q Plus unit from Millipore (Bedford, MA, USA) and Bichsel Laboratories (Interlaken, Switzerland), respectively.

The pharmaceutical formulations were produced in-house by the production unit of the hospital pharmacy. They include ophthalmic, oral and intravenous solutions containing mainly sodium chloride 0.9% and additional appropriate adjuvants required by the specific administration route, e.g. preservatives, flavouring, saccharine (see Table 1).

Preparation of background electrolytes

A different background electrolyte (BGE) was used for each CE method. For the first method, an aqueous BGE constituted from a 50 mM tris-phosphate buffer set at pH 2.5 was prepared. For this purpose, a solution of phosphoric acid 50 mM was prepared by dilution of the concentrated acid solution and a solution of tris at 1 M was added to adjust the solution to pH 2.5. For the second method, a hydro-organic buffer corresponding to a mixture of the aqueous BGE aforementioned (50 mM tris-phosphate buffer set at pH 2.5) and acetonitrile (80:20, v/v) was used. The third BGE was a non-aqueous buffer constituted from a mixture of acetonitrile:methanol (90:10, v/v) containing 25 mM ammonium acetate and 1 M acetic acid. All BGEs were degassed in an ultrasonic bath for 10 minutes before use.

Instrumentation and electrophoretic procedures

Electrophoresis was performed using a HP^{3D}CE system (Agilent Technologies, Waldbronn, Germany) equipped with a diode-array detector, an autosampler and a power supply able to deliver up to 30 kV. A CE Chemstation (Agilent Technologies) was used for CE control, data acquisition and data handling. For all methods, analyses were achieved in bare fused-silica capillaries from BGB Analytik (Böckten, Switzerland) whose dimensions were 50 and 375 µm for internal and external diameters, respectively, with total lengths of 64.5 cm (effective lengths either 56.5 or 8.5 cm). Before its first use, each capillary was sequentially washed with methanol, sodium hydroxide 0.1 M, water, methanol, hydrochloric acid 0.1 M, water and BGE for five minutes each. The thermostat of the capillary was set at 25°C and detection was performed at 200 nm with a band width of 10 nm. In all

the tests, a voltage of 30 kV was applied. Samples were injected in hydrodynamic mode to fill approximately 1% of the effective capillary length. Each sample was injected in duplicate. The other electrophoretic procedures were different according to the method used.

Method 1 (aqueous method)

The aqueous method used a 50 mM tris-phosphate buffer set at pH 2.5 and the short-end injection technique with an effective capillary length of 8.5 cm. Before injection, the capillary was rinsed using pressure (940 mbar) for three minutes with fresh, running buffer. The sample was injected by applying -20 mbar for five seconds, followed by a post-plug of buffer (four seconds at -15 mbar). The detector response time was 0.1 second.

Method 2 (hydro-organic method)

As for the first method, method 2 also used the short-end injection technique, and the injection and detection parameters were the same. The running buffer was a mixture of the aqueous BGE used for method 1 and acetonitrile (80:20, v/v). Before injection, the capillary was rinsed for three minutes with BGE. When tropane alkaloids were analysed, the capillary was rinsed for two minutes with sodium hydroxide 0.1 M, followed by two minutes with water and three minutes with the running buffer.

Method 3 (non-aqueous method)

The non-aqueous method required 25 mM ammonium acetate and 1 M acetic acid in acetonitrile-methanol (90:10, v/v) as running buffer. Before injection, the capillary was flushed for three minutes with the running buffer. Injection was performed in conventional mode ("long-end injection") by applying a pressure of 40 mbar for 10 seconds. A voltage of 30 kV with an initial ramping of 500 V/sec was applied. The effective length was 56 cm and the response time was 0.2 second. Before its first use, the capillary was sequentially washed with sodium hydroxide 0.1 M, water and BGE for five minutes each.

Method validation

Validation of the developed methods was based on the validation guide proposed in 2003 by the SFSTP commission [1]. Each pharmaceutical formulation was validated over three days. In order to validate a response function, to estimate precision (repeatability and intermediate precision) and trueness, two kinds of samples were used: calibration samples and validation samples. Two independent series of calibration samples at three concentration levels (80%, 100% and 120% of the target concentration) were prepared in water (in methanol, for method 3) to determine a response function on each validation day.

The concentration of active drug in standard samples of 100% was in the order of 0.1 mg/mL. Four validation samples were prepared each day, at three concentration levels 80%, 100% and 120%. The normalised area of target compound (area/migration time) was divided by the normalised area of internal standard for calculation.

An ANOVA analysis (analysis of variance) was run to obtain precision, repeatability (intra-day precision) and intermediate precision (inter-day precision) of the developed methods.

Sample preparation

Preparation of calibration samples and validation samples

For the calibration samples, all standard stock solutions were prepared by dissolving each compound in water (containing 0.1% sodium disulphite for adrenaline and isoprenaline) in a concentration similar to the pharmaceutical formulations. The internal standard stock solution was prepared by dissolving either lidocaine or procaine in water at a concentration of 10 mg/mL. Three calibration samples at 80%, 100% and 120% were prepared by diluting the appropriate volume of standard and internal standard stock solutions in water, or in methanol, whenever the non-aqueous method was used.

For the validation samples, the stock quality control solutions at the same concentrations as the pharmaceutical solutions were prepared by dissolving each compound in the appropriate adjuvant solution in order to mimic the actual pharmaceutical formulations (see Table 1). The validation samples at 80%, 100% and 120% were prepared the same way as the standard samples.

Sample preparation from the pharmaceutical formulations

For routine analysis, the pharmaceutical formulations were diluted by the same factor as the 100% validation samples.

RESULTS AND DISCUSSION

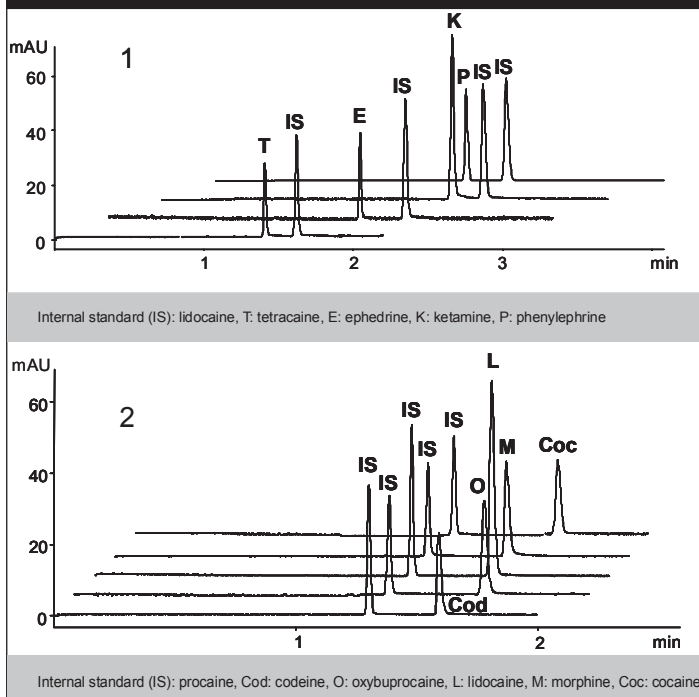
Development of the capillary electrophoresis method

The primary goal was to set up a generic method to analyse all the active drugs of interest in our laboratory (see Table 1). Because all these drugs are basic and possess a chromophore group, CE-UV appears particularly adapted into performing their analysis. Our first approach was based on the development of a conventional capillary zone electrophoresis (CZE) method with a conventional BGE, i.e. a 50 mM tris-phosphate buffer with a pH adjusted to 2.5. A capillary with a total length of 64.5 cm, an effective length of 56.5 cm and

an internal diameter of 50 μm was used. A voltage of 30 kV was applied and a generated current of 30 μA was recorded. Under these conditions, analysis times between eight and 10 minutes were obtained (data not shown). However, as the pharmaceutical formulations of interest contained mainly a single, active drug, a large migration window is not necessary and the analysis time can be reduced. For this purpose, several CE strategies can be applied, such as the use of a high electric field (HEF), a dynamic coating and the short-end injection technique [6, 7]. To avoid increased Joule heating often obtained with HEF, and to reduce the analysis cost because commercialised solutions of coating polymers are generally expensive, the short-end injection technique was chosen. The latter was carried out by reducing the effective capillary length (L_e) by performing the injection on the detector side ($L_e = 8.5$ cm), instead of the conventional injection on its opposite side ($L_e = 56$ cm), with the same 64.5 cm capillary. The generated current was maintained and no additive material was required. The injection was slightly modified: -20 mbar for five seconds (corresponding to 1% of L_e) was applied instead of 40 mbar for 10 seconds. With the short-end injection technique, the running time was less than 2.5 minutes (see Figure 1). Lower efficiencies (factor 4) than those obtained with the conventional injection technique were observed but they remained acceptable (c.a. 50,000, data not shown). Although the injected amount was reduced, good sensitivity was maintained because of a decrease in longitudinal diffusion [6, 7]. Short-end injection with the aqueous buffer (method 1) can be applied for nine out of 15 active drugs (corresponding to 11 different pharmaceutical formulations). Depending on the migration time of the active drug under study, either procaine or lidocaine was used as internal standard. For drugs with migration times (t_m) less than 1.5 minutes (ephedrine, ketamine, phenylephrine and tetracaine) the internal standard was lidocaine ($t_m = 1.7$ minutes) (see Figure 1.1), for drugs with migration times greater than 1.5 minutes (cocaine, codeine, oxybuprocaine, lidocaine and morphine), the internal standard was procaine ($t_m = 1.3$ minutes) (see Figure 1.2).

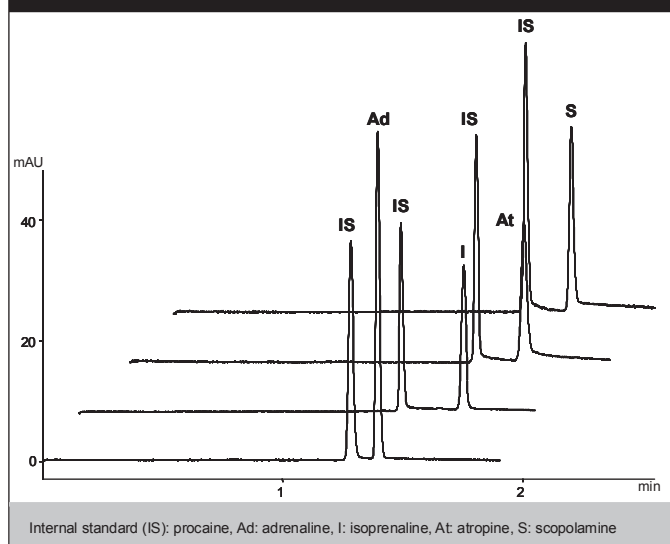
Method 1 was not the method of choice to analyse adrenaline, isoprenaline and tropane alkaloids (atropine and scopolamine). Indeed, adrenaline and isoprenaline are unstable in aqueous media [8] and capillary wall adsorption of tropane alkaloids was observed with aqueous buffer [9, 10]. To overcome these limitations, an organic solvent had to be added to the running buffer. A tris-phosphate 50 mM pH 2.5 – acetonitrile (80:20, v/v) running buffer was found to give appropriate separation. Working with

Figure 1: Electropherograms obtained by method 1 for the analysis of nine formulations



a hydro-organic buffer was not sufficient to avoid solute adsorption on to the capillary wall and a further capillary wash with sodium hydroxide 0.1 M and water, for two minutes each, was recommended [9]. All other analytical parameters were maintained as in method 1. Analysis times were less than two minutes and procaine was chosen as

Figure 2: Electropherograms obtained by method 2 for the analysis of four formulations



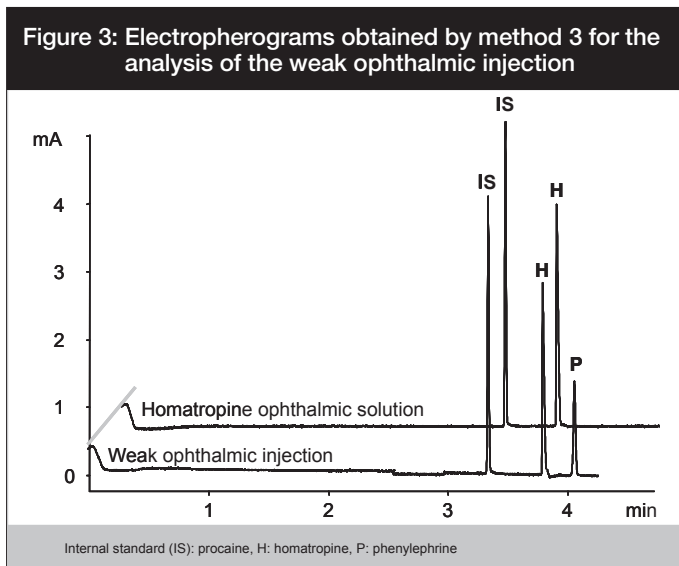
the internal standard. The generated current was 28 μ A. Electropherograms obtained for the analyses of adrenaline, isoprenaline and tropane alkaloids are shown in Figure 2.

With these two short-end injection techniques, it was not possible to get a separation of phenylephrine from homatropine, the two active drugs contained in the ophthalmic formulation called weak ophthalmic injection. In order to enlarge the migration window while keeping the solute adsorption on the capillary wall to a minimum, a conventional injection technique ($L_e = 56$ cm) was used together with the hydro-organic buffer used for method 2. Under these conditions, a good resolution between the two drugs was obtained with an analysis time of 10 minutes (data not shown). To decrease analysis time and maintain good performances such as a sufficient resolution and an absence of solute adsorption on to the capillary wall, an organic buffer was tested [11, 12]. Ammonium acetate 25 mM, acetic acid 1 M in methanol-acetonitrile (10:90, v/v) was found appropriate to obtain high efficiencies ($n = 300,000$), an excellent resolution between phenylephrine and homatropine ($R_s = 10$) and a short analysis time (4.5 minutes) (method 3). No homatropine adsorption was observed (no peak tailing was present). Injection was achieved by applying a pressure of 40 mbar for 10 seconds. A current of 12 μ A was recorded. Procaine was also chosen as an internal standard. A typical electropherogram obtained from analysis of weak ophthalmic injection is illustrated in Figure 3. Given that the pharmaceutical formulation containing only phenylephrine (see Table 1) had already been analysed by method 1, and to avoid having three different CZE methods to quantify two compounds, homatropine ophthalmic solution was also determined with method 3. For method 3, about 140 mL of organic solvents were used for the analysis of one formulation (20 mL for the BGE and 120 mL for the preparation of samples).

Our laboratory had three CZE methods for quantifying 15 basic active drugs present in 21 different pharmaceutical formulations. Before their routine application, validation of the developed methods had to be achieved.

Validation results

The optimised method was validated for each pharmaceutical formulation according to the SFSTP recommendations [1]. In particular, the V2-proposed protocol was applied. For this protocol, in one series, calibration was realised without a matrix (in water) and could contain three concentration levels for a simple regression model; a minimum of three validation samples in matrix at three concentration levels was determined.



All validations were performed for three series. For all analysed compounds, the determined response functions were linear and the coefficients of determination were greater than 0.995 (data not shown). Four independent series of validation samples at the same concentration levels were also analysed on each validation day. After fitting the calibration curves for each pharmaceutical

compound on each day, concentrations of the validation samples were computed from the analytical response. Trueness was expressed as the mean concentration found for all validation samples at each concentration level. Variances of repeatability and intermediate precision were computed from the estimated concentrations. Trueness and precision results are summarised in Tables 2, 3 and 4 according to the CZE methods.

For method 1, trueness values between 96.8% and 102.4% were obtained with repeatability and intermediate precision values between 0.4% and 2.8% and between 0.5% and 2.8%, respectively (see Table 2). Similar results were obtained with method 2 (see Table 3). All trueness values were between 97.4% and 102.5%, and repeatability and intermediate precisions values between 0.6% and 4.1% and between 0.5% and 4.7%, respectively. Low precisions were obtained for atropine validation with repeatability and intermediate precision values higher than 4%. The low photochemical stability of atropine in solution could explain this lack of precision. Good validation results were also obtained with method 3 (see Table 4). Indeed, trueness values were between 95.8% and 101.8%, with repeatability and intermediate precision values between 0.9% and 2.6% and between 0.8% and 3.0%, respectively.

Table 2: Validation results for compounds analysed by method 1

Compound	Cocaine	Codeine	Oxybuprocaine	Lidocaine	Morphine			Ephedrine	Ketamine	Phenylephrine	Tetracaine
Concentration (mg/mL)	50	2.5	10	40	0.5	10	20	10	1.0	0.1	50
VS 80%											
Trueness (%)	100.6	98.8	100.4	101.8	100.1	100	100.3	102.4	99.9	100.0	99.7
Repeatability (%)	2.4	2.8	1.4	1.0	1.5	0.8	1.1	1.7	1.7	1.4	0.8
Intermediate precision (%)	2.5	2.8	1.5	1.3	1.4	1.0	1.2	2.8	2.0	1.9	1.0
VS 100%											
Trueness (%)	99.9	97.8	100.2	101.3	99.5	99.7	99.3	99.4	100.8	97.6	100.5
Repeatability (%)	1.9	1.5	1.0	0.9	1.1	0.9	1.1	0.9	2.7	1.8	0.6
Intermediate precision (%)	2.2	1.5	1.2	1.1	1.2	1.3	1.5	1.7	2.3	2.0	0.6
VS 120%											
Trueness (%)	99.8	98.9	100.7	101.2	99.2	100.3	99.6	99.5	99.5	96.8	99.7
Repeatability (%)	1.5	1.8	0.8	1.2	1.1	1.0	1.0	1.4	1.4	2.5	0.4
Intermediate precision (%)	2.7	3.2	1.0	1.1	1.1	1.4	1.6	2.6	2.4	2.5	0.5

Method 1: Short-end injection and aqueous buffer; VS: validation sample

Table 3: Validation results for compounds analysed by method 2

Compound	Adrenaline		Atropine*		Isoprenaline	Scopolamine
Concentration (mg/mL)	0.1	1.0	0.1	5.0	0.1	2.5
VS 80%						
Trueness (%)	102.5	100.5	102.5	101.3	101.8	102.3
Repeatability (%)	0.6	1.2	2.6	2.5	1.1	2.2
Intermediate precision (%)	0.5	1.3	4.0	2.7	1.0	2.1
VS 100%						
Trueness (%)	101.8	99.5	99.5	100.6	102.3	101.2
Repeatability (%)	1.1	0.8	0.8	3.8	0.9	1.2
Intermediate precision (%)	1.2	1.4	1.6	4.2	1.1	1.9
VS 120%						
Trueness (%)	100.2	98.4	97.4	98.5	101.6	101.4
Repeatability (%)	1.1	1.2	2.4	4.1	1.5	1.5
Intermediate precision (%)	1.3	2.3	3.1	4.7	1.9	1.8
Method 2: Short-end injection and hydro-organic buffer; VS: validation sample *VS concentration levels: 75%, 100%, 125%						

Application to routine analysis of pharmaceutical formulations

The validated CZE methods were successfully applied to pharmaceutical formulations produced by the production unit of the hospital pharmacy. According to the validations, three calibration samples in water (in methanol when method 3 was applied) at 80%, 100% and 120% were prepared to determine the response function, and three samples of the formulation of interest were prepared for each dosage. An entire cycle of formulation quantification, including sample preparation, CZE analysis and data handling, was achieved in two hours instead of four to five hours in comparison with conventional LC methods (i.e. a time gain factor of 2). In our laboratory, three fused-silica capillaries preconditioned and dedicated for each CZE method are ready for use to perform these formulation analyses instead of six different LC columns used previously. The three CZE buffers are always kept at 4°C and prepared every month.

Table 4: Validation results for weak ophthalmic injection and atropine ophthalmic solution analysed by method 3

Compound	Weak ophthalmic injection		
	Homatropine	Homatropine	Phenylephrine
Concentration (mg/mL)	20	4.0	0.5
VS 80%			
Trueness (%)	99.5	101.8	98.1
Repeatability (%)	0.9	1.0	0.9
Intermediate precision (%)	0.8	2.6	1.5
VS 100%			
Trueness (%)	100.4	99.7	96.0
Repeatability (%)	1.1	2.6	2.3
Intermediate precision (%)	1.2	3.0	2.1
VS 120%			
Trueness (%)	100.6	99.6	95.8
Repeatability (%)	1.2	1.3	1.4
Intermediate precision (%)	1.4	2.3	2.3
Method 3: Conventional injection and non-aqueous buffer; VS: validation sample			

To date, more than 100 batches of pharmaceutical formulations have been analysed by these three generic methods. Table 5 shows examples of results obtained for the analysis of five pharmaceutical formulations with the developed CZE methods and with "old" analytical methods for the same formulation. A good concordance was observed between the percentages of the active drug in the formulations

Table 5: Analysis of five formulations by CZE methods and "old" analytical methods

Pharmaceutical formulations	CZE methods (% of active drug)	Old analytical method (% of active drug)
Cocaine ophthalmic solution	103% (method 1)	101% (single UV)
Phenylephrine	87% (method 1)	88% (LC)
Ephedrine	107% (method 1)	104% (LC)
Isoprenaline	103% (method 2)	105% (LC)
Homatropine	103% (method 3)	106% (LC)
UV: ultraviolet; LC: liquid chromatography		

measured by the two different methods. The developed CZE methods were found suitable to perform the routine analysis of active drugs contained in the formulations produced by the production unit of the hospital pharmacy.

CONCLUSION

Three reliable and rapid CZE methods were developed and validated for the routine analysis of 15 active drugs contained in 21 hospital formulations. The developed methods exhibited good quantitative performance in terms of trueness and repeatability, and a total analysis time between two and four minutes. Therefore, with these CZE methods, the analysis time was reduced by

a factor of two to three in comparison with conventional methods applied in our laboratory. Moreover, the developed CZE methods represent a significant improvement not only for economic reasons (expensive LC columns are substituted with cheaper fused-silica capillaries) but also for ecological reasons (low consumption of organic solvents). In this context, CE is a particularly interesting and complementary technique (compared with LC) for a control quality laboratory in a hospital pharmacy. Moreover, simple CE methods can also be developed for the quantification of acidic compounds (using BGE at basic pH) and neutral compounds (adding surfactants to BGE).

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