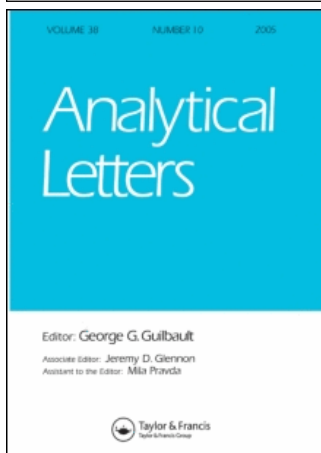


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## ELECTROPHORESIS

# Comparison of On-Line Concentration Methods in Capillary Zone Electrophoresis for Analysis of Water-Soluble Vitamins

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**Abstract:** The separation of water-soluble vitamins by capillary zone electrophoresis was developed, in which on-line concentration methods, namely field-enhanced sample stacking and dynamic pH junction, were utilized to improve the detection sensitivity. The effects of some critical parameters, including pH and concentration of background electrolyte, sample matrix pH and concentration, and injection volume were examined. The effects of field-enhanced sample stacking and dynamic pH junction on the separation resolution and concentration efficiency were compared. The limits of detection of the vitamins were from 6 to 119 ng ml<sup>-1</sup> ( $2.7 \times 10^{-8}$  to  $53.4 \times 10^{-8}$  M) based on the signal-to-noise ratio of 3 and the relative standard deviations of migration time and peak area for each vitamin (1 µg ml<sup>-1</sup>) were less than 3.5% using the field-enhanced sample stacking as an on-line concentration method. The developed method was applied to the analysis of water-soluble vitamins in corns.

**Keywords:** Capillary zone electrophoresis, field-enhanced sample stacking, dynamic pH junction, water-soluble vitamins, corn

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## INTRODUCTION

Capillary electrophoresis (CE) has become one of the most powerful separation and analysis techniques because of its advantages, including high separation efficiency, short analysis time, and low sample consumption. However, the detection sensitivity in CE is poor especially when using UV detection, resulting from the narrow optical path length and the small sample volumes (normally less than 10 nl). On-line sample concentration technique represents an effective and versatile way to enhance the detection sensitivity in CE. A very attractive feature of on-line sample concentration techniques is that they do not require any modification in commercial CE instruments since the concentration step is performed within the same capillary used for separation. Currently, several on-line sample concentration techniques in CE have been reported, in which the most popular techniques were field-enhanced sample stacking (Chien and Burgi 1992; Quirino and Terabe 1998; Zhang and Thormann 1998; He and Lee 1999; Shihabi, 2000; Quirino and Terabe 2000; Chen et al. 2004; Jia et al. 2005), sweeping (Quirino and Terabe 1998; Palmer et al. 1999; Kim et al. 2001; Quirino et al. 2002; Markuazewski et al. 2003; Jia et al. 2004), transient isotachopheresis (Foret et al. 1992; Beckers 1993; Krivankova et al. 1997; Hirokawa et al. 2001), and dynamic pH junction (Britz-McKibbin et al. 1998; Britz-McKibbin and Chen 2000; Wang et al. 2002; Kim et al. 2003; Jia et al. 2004; Monton et al. 2005).

Field-enhanced sample stacking is one of the most efficient concentration techniques in CE (Chien and Burgi 1992; Quirino and Terabe 1998; Zhang and Thormann 1998; He and Lee 1999; Quirino and Terabe 2000; Shihabi, 2000; Chen et al. 2004; Jia et al. 2005). In general, the samples are dissolved in a low electric conductivity matrix (e.g., water) while the background electrolyte (BGE) is in a high electric conductivity (Chien and Burgi 1992). When the sample and BGE are simultaneously present inside a capillary, after application of voltage, the sample region will experience a higher electric field compared to the background region (Quirino and Terabe 2000). Since the electrophoretic velocity is proportional to the field strength, sample ions migrate at a much faster velocity in the sample region than that in the background region and stack at the boundary between the sample and background regions.

Dynamic pH junction is an efficient on-line concentration technique for the weakly ionic analytes if the difference in pH between the sample matrix and BGE can cause significant changes in their mobilities (Britz-McKibbin et al. 1998; Britz-McKibbin and Chen 2000; Wang et al. 2002; Kim et al. 2003; Jia et al. 2004; Monton et al. 2005). It was first reported by Britz-McKibbin et al. (1998). Focusing is hypothesized to be caused by the formation of a transient pH titration within the sample zone, which results in rapid focusing of analytes that undergo velocity changes in the selected pH range. This technique has already been applied to the analysis of zwitterionic epinephrine (Britz-McKibbin et al. 1998), catecholamines and weakly

acidic compounds (Britz-McKibbin and Chen 2000), nucleotides (Jia et al. 2004), trace proteins (Wang et al. 2002), cationic analytes (Kim et al. 2003), peptides (Monton et al. 2005), aromatic acids, flavins, folate derivatives, bases, and ribonucleosides (Jia et al. 2004).

It is well known that vitamins are indispensable for the normal growth and function of human and animal bodies. Lack of vitamins can cause serious diseases even though only small concentrations are required to maintain good health. Food is the main resource of vitamins for humans and animals. According to their solubilities, vitamins are divided into two groups, water-soluble vitamins and fat-soluble vitamins. Many methods have been developed for the determination of water-soluble vitamins, including HPLC (Amin and Reusch 1987; Moreno and Salvado 2000; Heudi et al. 2005), capillary zone electrophoresis (CZE) (Chiari et al. 1993; Jegle 1993; Huopalahti and Sunell 1993; Boonkerd 1994; Schiewe et al. 1995; Fotsing et al. 1997), and micellar electrokinetic chromatography (MEKC) (Boonkerd 1994; Gomis et al. 1999; Hu et al. 2001). To the best of our knowledge, no on-line concentration methods in CZE were used to improve the detection sensitivities of water-soluble vitamins.

In this study, on-line concentration methods (including field-enhanced sample stacking and dynamic pH junction) in CZE were investigated to improve the detection sensitivities of water-soluble vitamins. The effects of some critical parameters including pH and concentration of BGE, sample matrix pH and concentration, and injection volume, were examined. The developed CZE method combining with field-enhanced sample stacking was applied to the analysis of water-soluble vitamins in corns.

## EXPERIMENTAL SECTION

### Chemicals and Reagents

Sodium hydroxide, sodium borate, boric acid, sodium dihydrogenphosphate, and disodium hydrogenphosphate were purchased from Guangzhou Chemical Reagent Factory (Guangzhou, China). Phosphoric acid was obtained from Guangzhou jinhuada Chemical Reagent Co., Ltd (Guangzhou, China). These reagents were of analytical-reagent grade. Methanol (HPLC grade) was purchased from SK Chemicals (Ulsan, South Korea).

Vitamin standards, which included thiamine hydrochloride, riboflavin, nicotinic acid, nicotinamide, calcium pantothenate, pyridoxine hydrochloride, pyridoxal hydrochloride, pyridoxamine dihydrochloride, folic acid, D-biotin, cyanocobalamin, and ascorbic acid, were purchased from Chem Service (West Chester, USA). Stock solutions of standards were prepared as 2 mg ml<sup>-1</sup> in deionized water and stored at 4°C in brown bottles.

Water used for BGE and sample preparations was obtained from an Elga water purification system (ELGA, UK). All solutions were sonicated and filtered through 0.45  $\mu\text{m}$  cellulose acetate filters (Sartorius, Gottingen, Germany) prior to use.

### Apparatus and Procedure

All electrophoresis experiments were performed on a Beckman P/ACE MDQ capillary electrophoresis system (Beckman Coulter) equipped with a photodiode array detection UV detector. Separations and focusing were carried out in a fused-silica capillary, 60.2 cm total length (50 cm effective length)  $\times$  75  $\mu\text{m}$  i.d. (Beckman Coulter). The detection wavelength was 210 nm and the capillary temperature was thermostated at 25°C. The separation voltage was set at 20 kV. Data were collected using Beckman P/ACE workstation version 32 Karat software.

New capillaries were first rinsed with 1.0 M NaOH (30 min), followed by methanol (30 min), deionized water (60 min), and finally with the BGE (60 min). Each separation was preceded by a 2 min rinse with 0.1 M NaOH, followed by 3 min rinse with the BGE to ensure run-to-run reproducibility. The sample was introduced using a low-pressure (0.5 psi) ranging from 3 to 60 s.

### Sample Preparation

The sample preparation procedure was similar to the method described previously with some modification (Jia et al. 2004). Briefly, weigh 120 mg corn sample accurately (Sartorius CP224S analytical balance, Goettingen, Germany) and put it into a 15 ml plastic tube. Cold methanol ( $-20^\circ\text{C}$ , 4 ml) was added to the tube containing the corn sample. The methanol solution was mixed thoroughly for about 30 s and then placed at  $-20^\circ\text{C}$  for 30 min. The solution was centrifuged at  $4^\circ\text{C}$  and 5000 rpm for 30 min. The upper layer was withdrawn and centrifugally filtered through a Millipore 5-kDa-cutoff filter to remove proteins and other debris. The filtrate was evaporated using a micro centrifugal vacuum concentrator Christ RVC 2-18 (Osterode am Harz, Germany) at  $30^\circ\text{C}$ . Prior to analysis, the dried sample was reconstituted in 1 ml of deionized water.

## RESULTS AND DISCUSSION

### Optimization of the Separation Conditions

In the optimization experiments, the samples were dissolved in deionized water. At first, the effect of the concentration of BGE in the range from 50

to 200 mM on the separation of the water-soluble vitamins was investigated while keeping the pH of borate at 8.5. The experimental results showed that the twelve water-soluble vitamins obtained optimum separation with the concentration of borate at 160 mM.

Next, the effect of the pH of the BGE ranging from 7.5 to 9.2 on the separation was studied while keeping the concentration of borate at 160 mM. In the pH range from 7.5 to 9.2, three vitamins (nicotinamide, cyanocobalamin, and pyridoxamine dihydrochloride) migrated with the electroosmotic flow (EOF) as they are neutral in the pH range. Other nine vitamins (thiamine hydrochloride, riboflavin, pyridoxal hydrochloride, pyridoxine hydrochloride, D-biotin, ascorbic acid, calcium pantothenate, nicotinic acid, and folic acid) obtained baseline separation at pH 8.5, at which, thiamine hydrochloride migrated faster than the EOF, while the other eight vitamins migrated slower than the EOF.

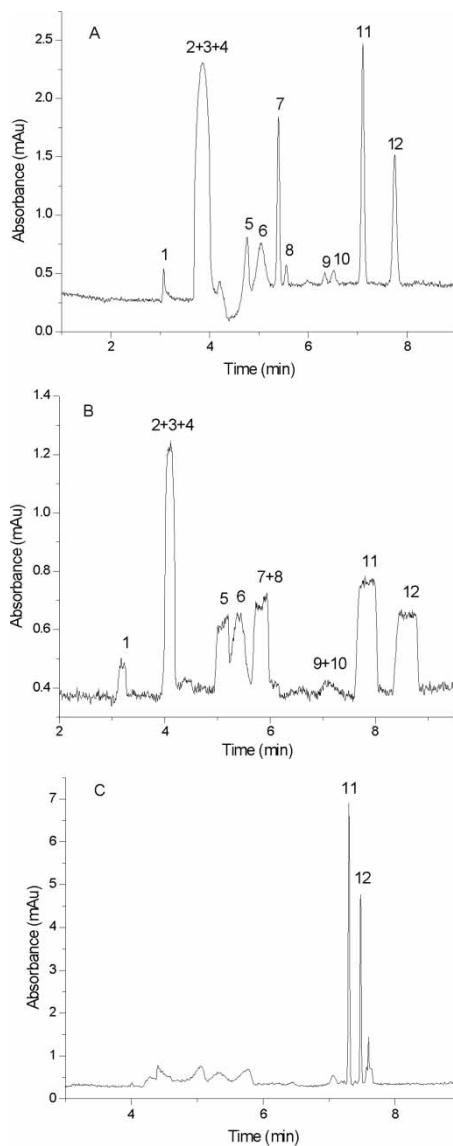
Based on the above results, the BGE containing 160 mM borate (pH 8.5) was used to investigate the on-line sample concentration.

### **On-line Sample Concentration Field-enhanced Sample Stacking**

At first, field-enhanced sample stacking was used as an on-line sample concentration method to improve the detection sensitivities of the nine water-soluble vitamins. The effect of the injection time in the range from 3 to 60 s on the concentration efficiency and the resolution of the vitamins were investigated while keeping water as sample matrix. The peak heights of the vitamins increased with the increase of the injection time. However, the resolution of the vitamins deteriorated gradually with the increase of the injection time. With the injection time at 20 s, the nine vitamins can be separated baseline, as shown in Fig. 1A. When the injection time exceeded 20 s, several vitamins co-migrated due to the peaks broadening. Comparing with the separation result using water as sample matrix, the peaks of vitamins broadened much more seriously using BGE as sample matrix with the injection time at 20 s, as depicted in Fig. 1B, since no field-enhanced sample stacking existed. Considering the separation resolution and concentration efficiency, the injection time 20 s using water as sample matrix was utilized to improve the detection sensitivities of the vitamins. The sensitivity enhancement of the vitamins in terms of the peak height ( $SEF_{\text{height}}$ ) was in the range from 3- to 8-fold comparing with the injection time 3 s using BGE as sample matrix.

### **Dynamic pH Junction**

Next, dynamic pH junction was used to improve the detection sensitivities of the vitamins. In dynamic pH junction, the composition of sample matrix



**Figure 1.** Electropherograms of vitamins in different sample matrix (A) water, (B) BGE, and (C) 75 mM phosphate buffer (pH 6.0). Experimental conditions: fused-silica capillary 60.2 cm (effective length 50 cm)  $\times$  75  $\mu$ m i.d.; BGE, 160 mM borate (pH 8.5); injection, 0.5 psi  $\times$  20 s; applied voltage, 20 kV; capillary temperature, 20°C; detection wavelength, 210 nm. The concentration of each vitamin is 1  $\mu$ g ml<sup>-1</sup>. Peak identification, 1, thiamine hydrochloride; 2, nicotinamide, 3, cyanocobalamin, 4, pyridoxamine dihydrochloride; 5, riboflavin; 6, pyridoxal hydrochloride; 7, pyridoxine hydrochloride; 8, D-biotin; 9, ascorbic acid; 10, calcium pantothenate; 11, nicotinic acid; 12, folic acid.

relative to the BGE plays a key role to achieve the highest concentration effect. Optimization of the sample matrix composition consisted of selection of optimum pH, ionic strength, and injection length. The effect of the sample matrix pH on the concentration efficiency was first investigated while keeping the injection time at 20 s and the concentration of phosphate at 75 mM. When the sample matrix pH was in the range from 3.0 to 7.0, only nicotinic acid and folic acid can be focused and separated, while the peaks of other vitamins broadened seriously. With the pH of sample matrix at 6.0, nicotinic acid and folic acid obtained the highest concentration effect, as shown in Fig. 1C. Then the concentration of phosphate buffer (pH 6.0) as sample matrix was optimized with the injection time at 20 s. The experimental results showed that nicotinic acid and folic acid achieved the highest concentration effect with the concentration of phosphate buffer at 75 mM, as shown in Fig. 1C. The effect of the injection volume on the concentration efficiency was also studied. The peak heights of nicotinic acid and folic acid increased with the increase of the injection time. Other vitamins can not be focused. With the injection time at 20 s, nicotinic acid and folic acid were focused and separated. When the injection time exceeded 20 s, nicotinic acid and folic acid co-migrated. The  $SEF_{\text{height}}$  of nicotinic acid and folic acid using dynamic pH junction with the injection time at 20 s were 19 and 17, respectively, comparing with the injection time 3 s using BGE as sample matrix.

### Comparison of Field-enhanced Sample Stacking and Dynamic pH Junction

When field-enhanced sample stacking was used as an on-line sample concentration method, nine water-soluble vitamins can be focused and separated baseline. While using dynamic pH junction as an on-line concentration method, only nicotinic acid and folic acid were focused and separated. The experimental results showed that field-enhanced sample stacking was more suitable for the concentration of most water-soluble vitamins than dynamic pH junction. Considering the separation resolution and the concentration efficiency, field-enhanced sample stacking was utilized as an on-line sample concentration method to further investigate the quantitation of the nine vitamins.

### Quantitation

The quantitation experiments were performed using 160 mM borate (pH 8.5) as the BGE, water as the sample matrix and with the injection time at 20 s (0.5 psi). A series of vitamins with the concentration ranging from 1 to 10  $\mu\text{g ml}^{-1}$  were used to determine the calibration parameters for the nine vitamins. The sample with the concentration of each vitamin at 1  $\mu\text{g ml}^{-1}$  was utilized for the determination of the reproducibility with three consecutive runs.



The limits of detection (LOD) for the vitamins were calculated at signal to noise ratio equal to 3 ( $S/N = 3$ ). The reproducibility data obtained for the migration time and peak area, the calibration function (peak area versus concentration in  $\mu\text{g ml}^{-1}$ ), linearity of the calibration function, and detection sensitivity (LOD) for the determination of the vitamins are shown in Table 1. The LODs of the nine vitamins were in the range from 6 to  $119 \text{ ng ml}^{-1}$  or  $2.7 \times 10^{-8}$  to  $53.4 \times 10^{-8} \text{ M}$ . The relative standard deviations (RSDs) for the migration time and peak area of each vitamin were less than 3.5%. The linearity of the calibration functions for the nine vitamins were satisfactory with the correlation coefficients above 0.9969.

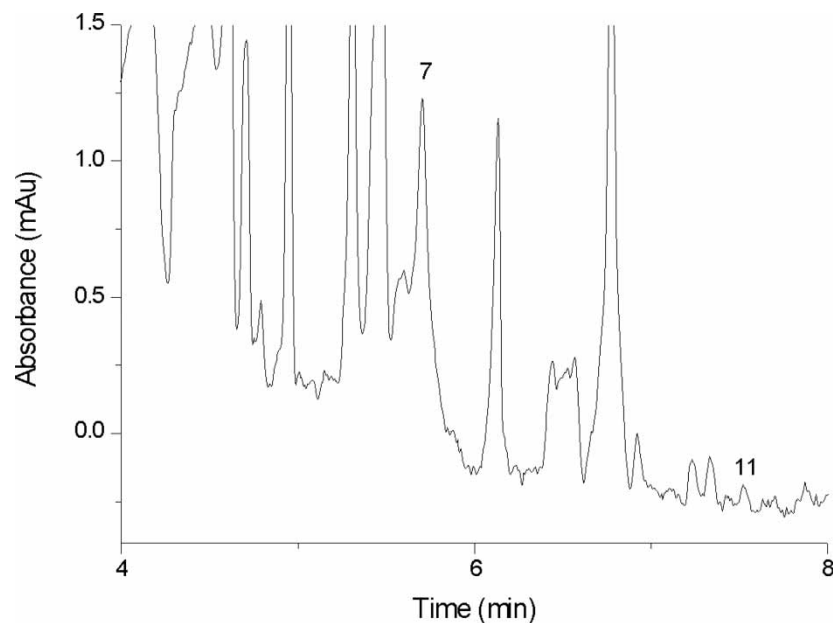
### Analysis of Corn Samples

The developed method was applied to the analysis of water-soluble vitamins in corns. Figure 2 shows the electropherogram of the corn sample. The water-soluble vitamins in the sample were identified by three methods: (1) comparing their migration times with those of standards; (2) spiking the standards to the sample; (3) comparing the peak spectrum with that of the standard with same migration time since a photodiode array UV detector was used in the CE system. Two vitamins (pyridoxine hydrochloride and nicotinic

**Table 1.** Reproducibility, linearity, and sensitivity for the vitamins using the field-enhanced sample stacking CZE method.

Analyte	Calibration function	$r^2$	LOD ( $S/N = 3$ )		RSD (% , $n = 3$ ) (each vitamin $1 \mu\text{g ml}^{-1}$ )	
			$\text{ng ml}^{-1}$	$10^{-8} \text{ M}$	Migration time	Peak area
Thiamine hydrochloride	$y = 0.8176 x + 0.0954$	0.9995	32	9.5	0.09	1.0
Riboflavin	$y = 3.2961 x - 0.9015$	0.9992	25	6.6	0.05	3.1
Pyridoxal hydrochloride	$y = 3.5810 x + 0.3234$	0.9998	35	17.2	0.10	1.1
Pyridoxine hydrochloride	$y = 4.6026 x - 0.0631$	0.9999	9	4.4	0.08	0.1
D-biotin	$y = 0.5729 x + 0.0852$	0.9999	71	29.1	0.11	1.4
Ascorbic acid	$y = 0.3839 x + 0.0599$	0.9975	94	53.4	0.10	3.5
Calcium pantothenate	$y = 0.5093 x + 0.0349$	0.9969	119	24.9	0.07	0.7
Nicotinic acid	$y = 7.5976 x + 0.1858$	0.9999	6	4.9	0.12	0.5
Folic acid	$y = 6.1389 x - 0.9641$	0.9995	12	2.7	0.11	1.4

$y$ : peak area;  $x$ : analyte concentration ( $\mu\text{g ml}^{-1}$ );  $r$ : correlation coefficient.



**Figure 2.** Electropherogram of the corn sample. Experimental conditions are the same as in Fig. 1A. Analyte peak numbering is the same as in Fig. 1A.

acid) were detected in the corn sample. The contents of pyridoxine hydrochloride and nicotinic acid were evaluated to be  $6.67 \pm 0.17$  and  $0.25 \pm 0.01 \mu\text{g g}^{-1}$ , respectively, by triplicate analysis of the corn sample. The recovery experiments were carried out based on a certain concentration of each vitamin added to the sample. The recoveries for the two vitamins were determined to be 106% (pyridoxine hydrochloride) and 100% (nicotinic acid), respectively, by triplicate analysis, with the RSD lower than 3.8%.

## CONCLUSIONS

Two on-line concentration methods, namely field-enhanced sample stacking and dynamic pH junction, were studied to improve the detection sensitivities of the water-soluble vitamins in CZE. When field-enhanced sample stacking was used as an on-line sample concentration method, nine water-soluble vitamins can be focused and separated baseline. While using dynamic pH junction as an on-line concentration method, only nicotinic acid and folic acid were focused and separated. The field-enhanced sample stacking was more suitable for the concentration of most water-soluble vitamins than dynamic pH junction. The field-enhanced sample stacking CZE method was quantified and applied to evaluate two water-soluble vitamins contents (pyridoxine hydrochloride and nicotinic acid) in corns.

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