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Original Paper

Online preconcentration of arsenic compounds by dynamic pH junction-capillary electrophoresis

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An online preconcentration technique by dynamic pH junction was studied to improve the detection limit for anionic arsenic compounds by CE. The main target compound is roxarsone, or 3-nitro-4-hydroxyphenylarsonic acid, which is being used as an animal feed additive. The other inorganic and organoarsenic compounds studied are the possible biotransformation products of roxarsone. The arsenic species were separated by a dynamic pH junction in a fused-silica capillary using 15 mM phosphate buffer (pH 10.6) as the BGE and 15 mM acetic acid as the sample matrix. CE with UV detection was monitored at a wavelength of 192 nm. The influence of buffer pH and concentration on dynamic pH junction were investigated. The arsenic species focusing resulted in LOD improvement by a factor of 100–800. The combined use of C₁₈ and anion exchange SPE and dynamic pH junction to CE analysis of chicken litter and soils helps to increase the detection sensitivity. Recoveries of spiked samples ranged between 70 and 72%.

Keywords: Arsenic / Capillary electrophoresis / Dynamic pH junction / Roxarsone / Solid phase extraction

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1 Introduction

CE has been developed as a powerful separation and analysis technique for the speciation of arsenic compounds. The speciation of arsenic compounds is of interest due to the different toxicities of these compounds that might pose environmental and health problems. CE is an alternative technique to the more conventional HPLC technique for the determination of arsenic compounds due to the high efficiency, small sample requirement, and short analysis time. However, CE suffers from poor concentration sensitivity with UV detection, far inferior to the HPLC, because of the small injection volumes (typically <1% capillary length) and short optical path length. Most of the CE methods for the separation of arsenic deal with standard solutions [1–3]. Li and Li [4] reported an oncolumn preconcentration technique by large volume stacking and field amplified injection for the separation of selenium and arsenic compounds, with detection limits of below 25 ppb. For the analysis of real samples,

matrix interference will limit the CE separation to simple matrix systems [4, 5]. This represents a significant obstacle for the analysis of very low concentrations (ppb levels) of arsenic compounds in real samples by CE. Even though the use of an extended path-length cell has been reported to improve the detection limit to less than tenfold, most studies have been in the area of online preconcentration technique. Offline preconcentration by SPE can also be used to enrich the analytes, as well as a sample cleanup prior to CE analysis. An alternative way to improve the concentration sensitivity in CE is to perform an online preconcentration, which is a versatile method and more preferred since the preconcentration step is performed within the same capillary used for separation.

A variety of online preconcentration techniques have been developed in CE. Four of the most widely accepted online sample preconcentration techniques are field-enhanced sample stacking, transient ITP (t-ITP), sweeping, and dynamic pH junction [6]. Each method relies on a distinct focusing mechanism based on different electrolyte properties between sample and background solution (BGS), such as conductivity (ionic strength), electrolyte coion mobility, additive concentration (analyte-additive interactions), and buffer pH [7–9]. Accordingly, such methods are suitable for certain types of analytes based on their specific physicochemical properties in the buffer, such as charge, mobility, and pK_a.

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Abbreviation: BGS, background solution

Table 1. Structures and pK_a values of six arsenic compounds used in this study

Analyte	Molecular structure	pK _a	Analyte	Molecular structure	pK _a
Arsenite, As(III)		9.2 12.1	Dimethylarsinic acid, DMA		6.2
Arsenate, As(V)		2.3 6.7 11.6	3-Nitro-4-hydroxy-benzenearsonic acid (Roxarsone)		3.5
Monomethylarsonic acid, MMA		4.6 7.8	Phenylarsonic acid, PAA		3.6 8.8

Early reports by Sustacek *et al.* [10] used a dynamic pH gradient for the separation of purine and pyrimidine bases. Their approach was based on the controlled modification of the pH of the BGS in a suitable electrode chamber. Online preconcentration by dynamic pH junction represents an alternative technique that uses inexpensive buffer junction to generate a transient pH gradient within the BGS upon application of voltage [11]. The pH junction used in the capillary is dynamic in nature since the inlet is replaced by the BGS during the separation allowing migrating hydrogen, hydroxide, and buffer ions to gradually dissipate the pH difference. Thus, focusing of analytes with a dynamic pH junction is a selective process dependent upon specific analyte properties, such as the presence of acidic or basic functionalities.

In dynamic pH junction, the sample is dissolved in a different electrolyte type to optimize the pH junction range for the focusing of weakly acidic, basic, or zwitterionic analytes based on their pK_a. Selective focusing using dynamic pH junction has recently been applied to zwitterions, epinephrine, and other catecholamines and some weakly acidic compounds [12]. Concentration sensitivities and separation efficiencies better than 4.0×10^{-8} M and 1.0×10^6 theoretical plates have been reported for the velocity-difference induced focusing of nucleotides using dynamic pH junction in CE with UV detection [13]. Britz-McKibbin *et al.* [14] used a combination of dynamic pH junction and sweeping, referred to as dynamic pH junction-sweeping, for the analysis of picomolar levels of flavin metabolites in biological samples.

Roxarsone (3-nitro-4-hydroxy-phenylarsonic acid, 3-NHPAA) is being used in the poultry industry as a growth promoter to increase weight gain and improved feed efficiency. Studies have shown that very little roxarsone is retained in the chicken meat and most is excreted unchanged in the litter, and accumulates in the poultry bedding [15–17]. Generally the litter is used as fertilizer on agricultural fields and therefore resulting in a localized arsenic pollution that becomes subject of analytical interest. Although the toxicity of roxarsone is less than that of inorganic arsenic, roxarsone can degrade to produce more toxic inorganic forms of arsenic. Due to the presence of nitrate and natural organic matter (NOM), roxarsone can degrade and produce arsenite and arsenate.

Although dynamic pH junction has been widely used to optimize the separation of weakly acidic and basic analytes in CE [18, 19], none has been reported for the separation of arsenic compounds with a wide range of pK_a values, ranging from 2.3 to 9.2 (Table 1). The focusing of these compounds would present a challenge for the pH junction technique. In this report, the suitability of dynamic pH junction as an online preconcentration method was studied for the sensitivity enhancement of the arsenic compounds, to enable this technique to be applied for real poultry samples in routine CE separation. An enhancement in sensitivity is expected compared to conventional CZE injections. In order to obtain real samples, chicken were reared and fed with roxarsone drinks.

2 Experimental

2.1 Apparatus

All electrophoresis experiments were performed on an Agilent Technologies HP^{3D} CE instrument (Waldbronn, Germany) equipped with a diode array detector. Separations were performed using fused silica capillaries (Polymicro Technologies, Phoenix, AZ, USA), 50 μm id \times 360 μm od \times 66.5 cm effective length and detected on a normal detection cell. All the separations were carried out at 25°C. On-capillary UV diode-array detection was used, operated at a wavelength of 192 nm. Samples were injected hydrodynamically (50 mbar) and the separation voltage was +25 kV. Conductivities of samples and BGE solutions (BGSs) were measured using a YSI conductivity meter (Yellow Spring, Ohio, USA), and the pH values were measured and adjusted with the aid of a Hanna Instrument pH meter (Ann Arbor, MI, USA).

In the SPE procedure, a vacMaster-10 sample processing station (Supelco, PA, USA) with adjustable speed was used to extract the soil and litter samples with the C₁₈ and strong anion exchange (HAX) cartridges (International Sorbent Technology, Mid Glamorgan, UK).

2.2 Chemicals and reagents

Acetic acid, sodium acetate, and sodium hydroxide were obtained from Merck (Darmstadt, Germany). Thiourea was purchased from Fluka (St. Louis, MO, USA) while disodium hydrogen phosphate and trisodium phosphate were obtained from GCE Chemical (Australia). HPLC grade methanol was obtained from BDH Chemical (Victoria, Australia). The arsenic standards used were arsenious oxide (M & B, Denmark), dimethylarsinic acid (Aldrich Chemical, Milwaukee, WI, USA), monomethylarsonic acid (Chem Service, PA, USA), phenylarsonic acid (EP-grade, TCI, Tokyo, Japan), 3-nitro-4-hydroxyphenylarsonic acid (GR-grade, TCI), and sodium arsenate (Fluka, St. Louis, MI, USA). The commercial roxarsone solution was obtained from Alpharma Inc. (Pahang Pharmacy, Selangor, Malaysia). All the reagents were of analytical grade and used without further purification. All the solutions were prepared in deionized water purified with a Milli-Q system from Millipore (Bedford, MA, USA). BGS of 15 mM phosphate buffer at pH 10.6 was made by diluting the stock solutions of 100 mM Na₃PO₄ · 12H₂O and Na₂HPO₄ · 2H₂O in a ratio of 1:10 which was then degassed using vacuum sonication and filtered through a 0.45 μm syringe filter (Whatman, New Jersey, USA). The BGS was prepared fresh daily to ensure reproducible migration times.

2.3 Electrophoresis procedure

A new capillary was conditioned prior to use with 1 M NaOH (30 min), methanol (30 min), deionized water

(30 min), and finally the BGS (30 min). Between each injection, the capillary was flushed with 0.1 M NaOH (3 min), methanol (3 min), deionized water (3 min), and the BGS (5 min) to ensure reproducibility between runs. For the conventional CZE, samples were injected at 50 mbar for 5 s, while for the dynamic pH junction, injection was performed at 50 mbar for 150 s. The length of injected zones was calculated from the velocity of the liquid in the capillary at 50 mbar using a neutral marker, thiourea.

2.4 Real samples

Two-week-old chicks were fed with a solution of 3-nitro-100, a roxarsone solution which is a product of Alpharma Inc. Four liters of 40 ppm roxarsone was fed to the chicks for 2 days, and repeated again for days 6 and 7. After 6 wk, samples were taken which included chicken litter and soil bedding samples.

Chicken litter and soil samples were air-dried and ground to a powder. The samples were extracted using a water-soluble extraction [17]. A 2 g portion of the sample was weighed and for the spiked sample, 1 mL of a standard solution of roxarsone (4 ppm) was added. Then, water-soluble extraction was performed by adding 15 mL of deionized water into the sample, shaken for 1 h and sonicated for 30 min. The sample solution was then centrifuged at 5000 rpm for 45 min. An aliquot of 7 mL of the supernatant was pipetted to a clean centrifuge tube. HCl (300 μL , 2.6 M) was then added to flocculate the protein. A 5 mL of clear solution was pipetted into a new centrifuge tube and 230 μL of 6 M NaOH was added into the tube. The solution was passed through a C₁₈ cartridge to remove hydrophobic organic compounds. The C₁₈ cartridge had been preconditioned by methanol followed by preconditioning with deionized water. The supernatant was then passed through a strong anion exchange (HAX) cartridge. The HAX cartridge was preconditioned with 50% methanol/water v/v and deionized water. The retained roxarsone was eluted twice with 1 mL of 1 M acetic acid. Finally, the sample was filtered through a 0.45 μm Whatman Nylon membrane filter before injecting into the CE.

3 Results and discussion

3.1 Sample matrix pH

Arsenic compounds are rarely found in their uncharged states, and changes in local pH conditions could bring about large changes in their ionization. The focusing of these weakly ionic analytes by dynamic pH junction is influenced by the sample matrix pH and its ionic strength. The effect of sample matrix pH was examined

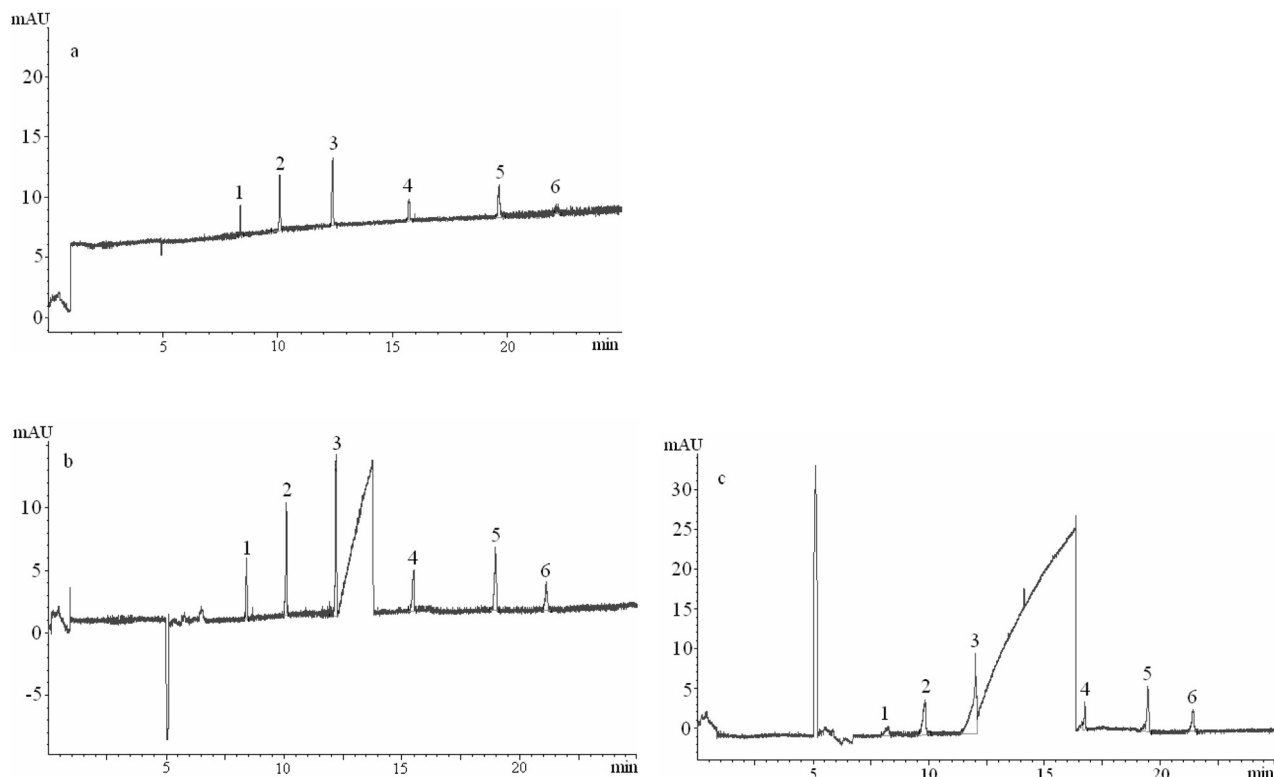


Figure 1. Effect of sample matrix pH on dynamic pH junction. Figure 1a shows a conventional CZE injection of 5 s using 15 mM phosphate buffer (pH 10.6). The dynamic pH junction was performed using a BGS, and 15 mM phosphate (pH 10.6); sample matrix was 15 mM acetic acid, at pH 3.5 (Fig. 1b) and pH 5.5 (Fig. 1c). Hydrodynamic injection of 50 mbar for 150 s, applied voltage +25 kV, capillary length 75 cm total (effective length 66.5 cm). Peak identification: 1, As(III); 2, DMA; 3, PAA; 4, MMA; 5, roxarsone; 6, As(V). A broad peak at about 14 min is due to acetic acid.

in the pH range of 3.5–6, in order to demonstrate selective focusing of these ionic analytes. The UV-visible detection of this mixture of inorganic and organoarsenic compounds posed a big problem. Inorganic As(III) and As(V) and the simple methylated MMA and DMA absorb in the low UV region. Based on our previous study, a wavelength of 192 nm was selected for the selective detection of the inorganic arsenic compounds but at the expense of the organoarsenic compounds. Acetic acid, 15 mM was selected as the buffer coion for the sample matrix based on its strong buffering capacity ($pK_a \sim 4.8$). The injection plug length was 33.2 cm (50 mbar, 150 s injection). The injection length in CE is usually limited to less than 1% of the capillary length, and this 150 s injection in dynamic pH junction is overloading the sample which will be focused to enhance the sensitivity. The pH of the sample matrix relative to the BGS plays an important role in analyte focusing when large sample injection plugs are used. In the pH range of 3.5–4.5, the effect of sample matrix pH could not be clearly observed. The migration behaviors of the arsenic compounds were consistent with their pK_a values. Arsenite, As(III) which is neutral at these pH values ($pK_a = 9.3$) migrated earliest followed by the other arsenic compounds, DMA ($pK_{a1} = 6.2$),

PAA ($pK_{a1} = 3.5$), MMA ($pK_{a1} = 3.6$), roxarsone ($pK_a = 3.5$), and As(V) ($pK_{a1} = 2.3$). Figure 1a shows a conventional injection CZE separation using 15 mM phosphate buffer at pH 10.6. A 5 s conventional injection was employed to evaluate the efficiency of the online preconcentration technique compared to the standard conventional injection. The effect of online preconcentration by dynamic pH junction is depicted in Fig. 1b for pH 3.5. The early eluting peaks are very sharp and focused while roxarsone, which is the last eluted peak, is reasonably well focused. A broad peak in the middle of the analysis time is due to acetic acid and this was confirmed by injection of a blank solution. The acetic acid peak assignment is also consistent with reports by Kim *et al.* [18] and Monton *et al.* [19]. The broad acetic acid peak could cause interference to nearby analyte peaks, especially to PAA and MMA. At higher pH of 5.5 (Fig. 1c) and 6.0, peaks of As(III), DMA, and PAA broaden and slightly longer migration times were observed. Peaks of roxarsone and As(V) could not be detected at the analysis time of below 25 min. The migration times are independent of the pH.

Figure 2 shows the variation of peak heights of the six arsenic compounds at the pH values tested. Good sensitivity in terms of peak height is observed at a pH value of

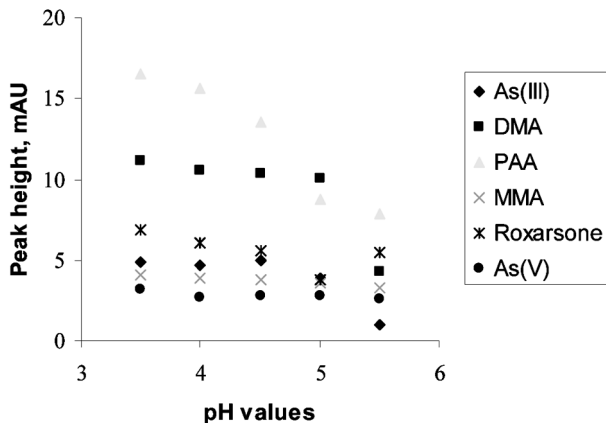


Figure 2. Variation in peak heights of the six arsenic compounds against the pH tested. Conditions are the same as in Fig. 1.

3.5. The separation and focusing were not successful at the higher pH of 5.5 due to small pH differences between BGS and sample matrix. Therefore, the optimized sample matrix pH for the selective focusing of arsenic compounds was at pH 3.5. Acetic acid buffer with pH lower than 3.5 is not possible to be tested as this is the lower limit of this buffer.

3.2 Effect of sample matrix concentration

The concentration of the sample matrix influences the separation efficiency of arsenic compounds since the dynamic pH junction involves titration of the sample zone. The effect of acetic acid concentration, at pH 3.5, was investigated in the concentration range of 5–25 mM. The migration time of the analytes did not shift much with increasing concentration of acetic acid. Figure 3 shows the effect of acetic acid concentration at pH 3.5 on the detection bandwidth at half height of six arsenic compounds. A detection bandwidth of less than 1 cm indicated that the analytes undergo band narrowing [18], and generally the bandwidth becomes broader as the analytes migrate across the capillary due to diffusion. The detector bandwidths of six arsenic compounds were narrowest using 15 mM acetic acid. At higher concentration of acetic acid, the bandwidths increased indicating that the arsenic peaks broadened gradually due to incomplete titration. The concentration of H⁺ was too high for the OH⁻ from the BGS; hence, the induced changes in ionization and mobility were less striking compared to previous lower H⁺ concentration. The optimum concentration at 15 mM acetic acid gave the best focusing.

3.3 Dynamic pH junction of arsenic compounds

A dynamic pH junction is usually used for the selective focusing of weak acids within the same pK_a range. How-

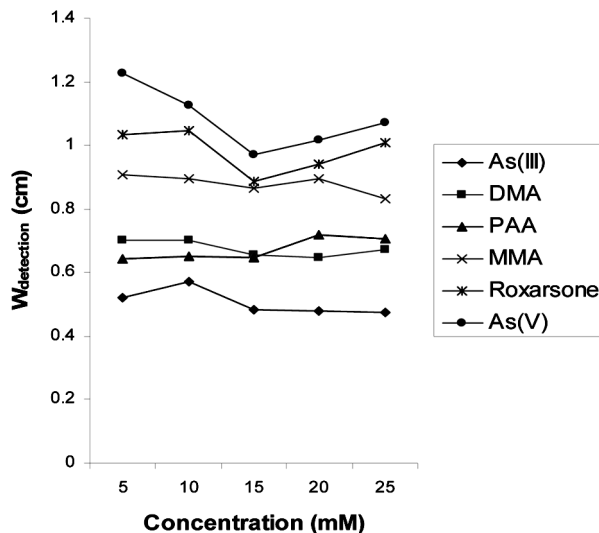


Figure 3. Effect of sample matrix concentration on detection bandwidth. Conditions: injection length 150 s and with concentration of the sample matrix varied from 5 to 25 mM acetic acid at pH 3.5.

ever, in this study, we use the dynamic pH junction to preconcentrate a variety of arsenic compounds with wide pK_a values. The arsenic compounds were dissolved in 15 mM acetate buffer (pH = 3.5) and the BGS was 15 mM phosphate buffer at a pH of 10.6. The LOD and sensitivity enhancement factor in terms of peak height (SEF_{height}) obtained for As(III), DMA, PAA, MMA, 3-NHPAA, and As(V) are summarized in Table 2. The sensitivity enhancement factor is calculated based on the ratio of the peak height obtained by dynamic pH junction to a normal CZE separation multiplied by the dilution factor of ten. A sensitivity enhancement of 33–51-fold was obtained with the dynamic pH junction. The LOD obtained for arsenic compounds with dynamic pH junction was in the range of 0.34–1.93 ppb while the LOD for the normal injection CZE was in the range of 193–292 ppb at an S/N of three in each case. Significant improvement in the LOD was obtained by dynamic pH junction, by a factor of 100–800. The difference between the SEF_{height} and the LOD is due to the low noise level when dynamic pH junction is employed. The low LOD obtained is comparable to CE technique employing element-sensitive detectors such as ICP-MS with reported LOD of 1.0–2.2 ppb for the inorganic and organic arsenic compounds [17] or MS which reported detection limits of 10–100 ppb for the organic arsenics and 65–250 ppm for the inorganic arsenics [20]. The online dynamic pH junction might provide an alternative CE technique with a UV detector for determining a low concentration of arsenic species in environmental samples without the need for expensive detectors.

Calibration graphs for all the arsenic compounds showed good linearity with squared correlation coeffi-

Table 2. Comparison of LODs and peak height between normal injection CZE and with dynamic pH junction CE and sensitivity enhancement factor (SEF_{height})

Arsenic compound	LOD (ppb)		Peak height (mAU)		SEF_{height}
	Normal injection ^{a)}	Dynamic pH junction ^{b)}	Normal injection	Dynamic pH junction	
As(III)	245	1.29	1.24	4.41	36
DMA	292	1.13	2.15	8.68	40
PAA	270	0.34	2.08	10.50	51
MMA	222	1.93	0.89	2.97	33
Roxarsone	193	0.44	1.06	4.92	46
As(V)	195	1.33	0.55	2.16	38

a) Normal sample injection using a low pressure of 1 s. BGS is 15 mM phosphate buffer, pH 10.6, detection wavelength 192 nm.

b) Dynamic pH junction injection using 150 s pressure injection.

Table 3. Reproducibility of migration time and peak height for arsenic compounds by dynamic pH junction CE

Compounds	RSD (% , $n = 3$)	
	Migration time	Peak height
As(III)	2.0	9.3
DMA	3.4	4.4
PAA	2.9	4.8
MMA	4.1	8.7
Roxarsone	4.7	14.2
As(V)	5.4	5.3

Conditions are the same as given in Fig. 1 at pH 3.5.

cient, r^2 greater than 0.99. A 2.0–5.4% RSD in migration times was achieved, which are acceptable values comparable with the conventional injection CZE-MS [19]. However, the RSD for the peak heights were slightly higher (4.4–14.2% RSD, Table 3), but the values are within the acceptable range for the online preconcentration technique [11, 19].

3.4 Application to real samples

Yalcin and Le [21] reported that the inorganic arsenics were completely retained on a silica-based strong anion exchange cartridge while they were almost completely unretained on the C_{18} cartridge. We used this combination of SPE cartridges to enhance the detection sensitivity of the dynamic pH junction for real samples. Test runs using standard arsenic solutions proved that the arsenic compounds were indeed retained by the anion exchange cartridge at the pH used in this study. The CE analysis with dynamic pH junction was monitored at a different wavelength of 254 nm, because we are monitoring the changes in the organoarsenic compound, *i.e.*, roxarsone which is less sensitive at 192 nm and less absorbed by interfering components of real samples.

Monitoring at a lower wavelength of 192 nm caused severe interference from the sample matrix which could not be removed by the SPE cartridges. Figure 4 shows the electropherogram for the soil sample after it had been extracted by the C_{18} and strong anion exchange cartridges. The C_{18} cartridge was used as a sample cleanup while the strong anion exchange cartridge served as an offline preconcentration step. A noisier background trace was observed compared to pure standards. A few unidentified peaks were seen in the figure and one peak in particular at ~ 7.8 min. A 5.7-times concentration factor based on the volume of solvents was used for the offline SPE and taking this factor into calculation, the combined use of SPE and dynamic pH junction CE gave a 71.9% recovery for the spiked soil samples.

The analysis of the spiked chicken litter sample is shown in Fig. 5. The electropherogram shows more matrix interference compared to the soil sample. A huge peak at 5.5 min is causing the roxarsone peak to be very small. An enlargement of the roxarsone peak is also shown in the inset of Fig. 4. Triplicate samples were tested and all the litter samples and spiked litter samples showed the same unknown peak at 5.5 min. Blank SPE cartridges elution did not show the peaks as in the litter sample. Difficulty in extracting the chicken litter samples was also reported by Rosal and coworkers [17]. A 70.3% recovery for the spiked litter sample was obtained after the clean-up with C_{18} and preconcentrating with the anion exchange cartridge.

4 Conclusions

A variety of arsenic compounds with a wide range of pK_a can be separated by dynamic pH junction-CE with direct UV detection. Online preconcentration with dynamic pH junction gave high sensitivity enhancement up to 100–800-fold without any pretreatment step. A higher concentration factor could be possible if the study focused

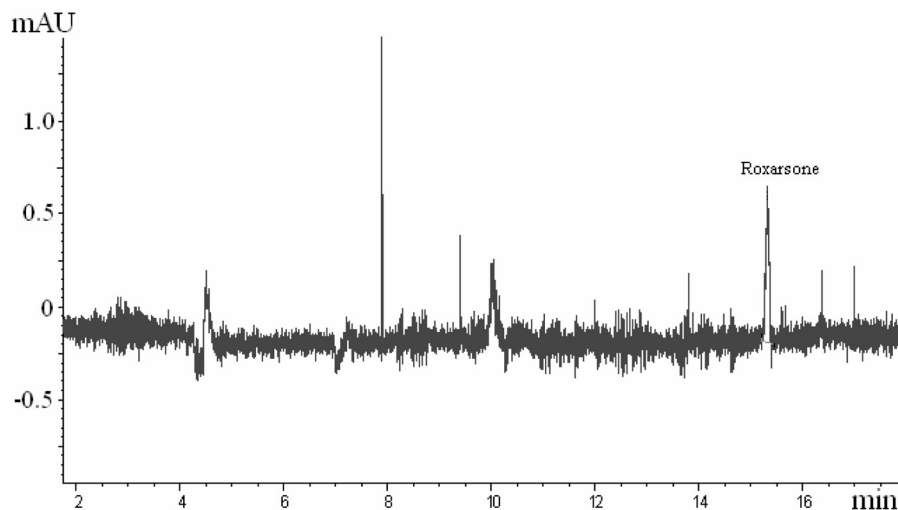


Figure 4. Electropherogram of soil sample spiked with roxarsone. Separation conditions: BGS, 15 mM phosphate (pH 10.6); sample matrix, 15 mM acetic acid, at pH 3.5. Hydrodynamic injection of 50 mbar for 150 s, applied voltage +25 kV, capillary length 75 cm total (effective length 66.5 cm). Detection wavelength was at 254 nm.

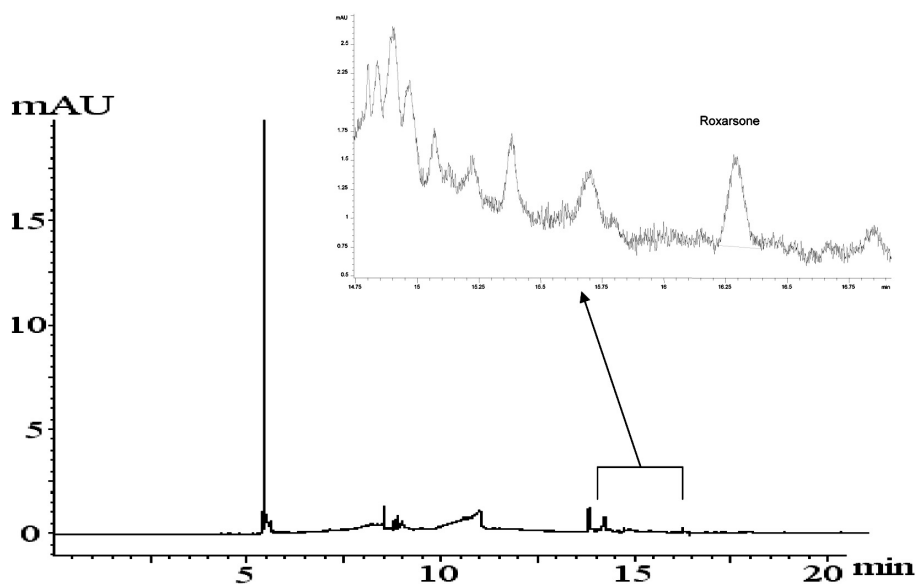


Figure 5. Electropherogram of spiked chicken litter sample. Separation conditions are the same as in Fig. 3. Also shown in the inset is the enlarged section showing the peak for roxarsone.

on a selected arsenic compounds with close pK_a range and the correct choice of wavelength for the inorganic or organoarsenic compounds. The low LOD of arsenic compounds in the range of 0.34–1.93 ppb has been successfully accomplished using this online preconcentration method. Significant improvement in detection limit can be attained if this pH junction is combined with a mass selective detector. However, when this technique was applied to real samples, the background signals were higher and difficulties were encountered during the extraction of the chicken litter. The use of C_{18} SPE cartridge did not alleviate the matrix interference effect. Spiked samples showed recoveries of 70–72%.

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