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Plastified poly(ethylene terephthalate) (PET)-toner microfluidic chip by direct-printing integrated with electrochemical detection for pharmaceutical analysis

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Abstract

Rapid separation and determination of acetaminophen and its hydrolysate with end-channel electrochemical (EC) detection integrated on a plastified poly(ethylene terephthalate) (PET)-toner microchip capillary electrophoresis (CE) system was investigated. In this separation and detection system, a Pt ultramicroelectrode integrated on a three-dimensional adjustor was used as working electrode. Factors influencing the separation and detection were investigated and optimized. Results show that acetaminophen and *p*-aminophenol can be well separated within 84 s with R.S.D. < 1% for migration time and R.S.D. < 3.6% for detection current for both analytes. Detection limits for both analytes are determined to be 5.0 μM (S/N = 3). This method has been successfully applied to the detection of trace *p*-aminophenol in paracetamol tablets. The results demonstrate that the PET-toner microchips can obtain better performance than PDMS microfluidic devices but at much lower cost.

Keywords: Poly(ethylene terephthalate) (PET)-toner; Microchip capillary electrophoresis; Electrochemical detection; Acetaminophen; *p*-Aminophenol

1. Introduction

During the past decade, considerable interest has been focused on micro-total analysis system (μTAS) or so called "lab-on-a-chip", and particular attention has been paid to capillary electrophoresis microchips due to its advantages over conventional analysis methods, such as rapid separation speed, high separation efficiency, low reagent consumption, reduced production of waste and use of energy, and its potential portability and disposability [1–8]. As yet, the μTAS has been developed, refined and applied to a variety of chemical and biological problem [2–4].

The microfluidic devices developed in the early years were mostly fabricated from silicon and glass using photolithography and etching technique [9,10]. However, these fabrication processes were costly, time-consuming, labor intensive, and clean-room conditions were required. The fabricated microfluidic devices are also fragile and mass production is not easy to be achieved. Recently, polymeric microchips are of increasing interest because they can offer attractive mechanical and chemical properties, low cost, ease of fabrication, biocompatibility, and higher flexibility and so on [11–13]. Polymeric materials, including poly(dimethylsiloxane) (PDMS) [14,15], poly(methyl methacrylate) (PMMA) [16], polycarbonate [8], polystyrene (PS) [17], and PET [18], have commonly been employed in the fabrication of microfluidic devices so far. Such polymeric chips have been fabricated using laser ablation, plasma etching [19], imprinting [20], hot embossing [16], injection molding [21], and compression molding [8] techniques. Recently, Lago et al. [22,23] described a very simple microfabrication process based on direct printing for mass production of microfluidic devices at very low cost. Compared

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to photolithography approaches, this process is an attractive alternative to other expensive, laborious, and time-consuming methods for microchannels fabrication. However, we found that such chips are not so durable during the operation procedures due to possible toner falling off the transparency in experiments. Therefore, we proposed an improved method for fabricating PET microchips with high stability and durability [24,25]. In our method, PET films with adhesive film were finally plastified on the microchips based on Lago's method.

Since Mathies et al. [26] developed a microchip-based CE–EC system for indirect electrochemical EC detection of DNA, EC detection has been offered great promise for designing self-contained and totally disposable μTAS. There are several advantages associated with EC detection such as extremely low cost, low-power requirement, high selectivity, remarkable sensitivity, inherent miniaturization, high compatibility advanced micromachining and microfabrication technologies [26–43]. EC detection has been proven to be a promising detection method and the most widely reported for microchip [44,45].

Acetaminophen, *N*-acetyl-*p*-aminophenol, or paracetamol, is a commonly used analgesic and antipyretic drug, formulated in a variety of dosage forms. *p*-Aminophenol, the primary hydrolytic degradation product of acetaminophen, can present in pharmaceutical preparations of acetaminophen as a synthetic intermediate or as a degradation product of acetaminophen [46]. Because *p*-aminophenol has significant nephrotoxicity and teratogenic effects, *p*-aminophenol is limited to the low level of 50 ppm (0.005, w/w) in the drug substance by the European, United States, and Chinese Pharmacopoeias. Therefore, establishment of a simple, economical, and accurate analytical method for the simultaneous determination of *p*-aminophenol and acetaminophen would be useful to medical manufacturers, etc., for investigation of the stability of acetaminophen, for pharmaceutical analysis, and for quality control. In our previous paper, we used PDMS chip for separation and electrochemical (EC) detection of the drug and its hydrolysis product. We noticed that the separation efficiency was not high enough, e.g., for separation and EC detection of trace amount of hydrolysis product in the acetaminophen contained buffer solution, realization of base line separation was quite tough due to the low electroosmosis of PDMS chip.

In the present paper, we report on an improved fabrication procedure for PET-toner microchips on the basis of the Lago's [22] method. This method is simple and the fabrication cost is very low. The separation and measurement of acetaminophen and its hydrolysate were investigated using such PET-toner microchip CE with end-channel EC detection. Fabricated microchips based on our method showed better mechanical stability and better durability [24]. Under optimum conditions, better results for separation and EC detection of acetaminophen and *p*-aminophenol were achieved.

2. Experiment

2.1. Materials and reagents

Transparency films (PET) (100 μm thick) were used for the base material (STD Printing Materials Limited Company, Suzhou, China). The plastification PET film, 80 μm thick with a 5 μm thick adhesive polyethylene adhesive on one side, was used for final plastification of the PET-toner microchips. All solvents and reagents were of analytical grade. Acetaminophen was obtained from Shanghai No. 3 Chemical Reagent Factory (Shanghai, China). *p*-Aminophenol was obtained from Shanghai Yiyuan Chemical Reagent Limited Company (Shanghai, China). Paracetamol tablets (500 mg acetaminophen per tablet) were purchased from local drug store. All aqueous solutions were prepared from deionized water (18 MΩ, PURELAB Classic, PALL, USA).

2.2. Preparation of the stock and standard solutions

Aqueous stock solution of 10 mM acetaminophen was used for further preparation of final solutions. *p*-Aminophenol was dissolved in a 0.05 M HCl aqueous solution to reach the final concentration of 10 mM, as it is stable in strong acidic medium. Both stock solutions of acetaminophen and *p*-aminophenol were kept at 4 °C. Sample solutions were prepared by diluting stock solutions with running buffer prior to use. The running buffer used as separation medium of CE was 10 mM acetate buffer (pH 5.0).

2.3. Tablet sample preparation

Five tablets (500 mg acetaminophen per tablet) were finely pulverized and dispersed in 40 mL of 0.5% acetic acid in 50 mL volumetric flask. The flask was shaken vigorously and then ultrasonically extracted for 10 min and diluted to required volume with 0.5% acetic acid. The mixture was centrifuged to obtain a clear solution. The supernatant was adjusted to the same pH value as that of the running buffer and then filtered through a 0.22 μm membrane for analysis. The sample was then spiked with appropriate amount of *p*-aminophenol for recovery experiments.

2.4. Microfabrication process

The layouts of the CE chips were designed using standard computer design software (Adobe Illustrator 9.0, Adobe). The fabricated PET CE microchip is schematically shown in Fig. 1A. The features in Fig. 1A were printed out on an EPL 5800 Laser Printer (Epson, Japan) with toner cartridge S050010 at 1200 dots per inch (dpi).

The detailed procedures used to create channels were described previously [22] except for the final plastification process that covers the final PET-toner microchip for ruggedness. The improved PET-toner microchip fabrication procedures can be briefly described as following [24,25]: the layout