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Analysis of Donnan-dialyzer irreproducibility and experimental study of a microfluidic parallel-plate membrane-separation module for total analysis systems

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ABSTRACT

We report irreproducibility analysis of miniaturized, batch, continuous stirred-tank Donnan dialyzers (CSDD) designed for a membrane-separation module of chemical analysis systems. Theoretical analysis indicates that a high exchange capacity of ion-exchange membrane (>1 mol L^{-1}) causes a significant irreproducibility of the CSDDs when the dialysate/sample volume is relatively small (<10 mL) and the ionic strength is low (<0.01 M). Numerical simulation based on Nernst–Planck flux equation and Donnan-equilibrium equation shows a significant deviation from the ideal Donnan-dialyzer response, and this irreproducibility is verified with experiments. In order to address the irreproducibility issue, we introduce a novel, microfluidic, parallel-plate Donnan-dialytic membrane-separation module (PDMM) with recirculation tube. The recirculation tube works as a dialysate/sample container as well as an effective mixer. The rationally designed PDMM has advantages over the CSDDs in that (1) the dialysis throughput is improved (6 folds), and (2) the dialysis irreproducibility is reduced (4 folds). Dialysis efficiency of our PDMM is also high (~91%), compared with that of flow-through parallel-plate dialyzers (usually ~1%).

1. Introduction

Since the advent of the first microfabricated gas chromatography on chip [1], the field of microanalytical systems, also referred as lab-on-a-chip or μTAS (micro-total-analysis-systems) has grown tremendously. The microanalytical systems promise to integrate time-consuming, labor-intensive, complicated analytical procedures into a single microinstrument and to revolutionize clinical, chemical, biological, and environmental analyses [2]. Despite some commercial success [3,4], many of novel, creative ideas for microanalytical-system research merely settled with scientific papers. Many believes, at least from the technical point of view, that difficulty of commercialization lies on the lack of effective sample-preparation methods seamlessly incorporated into the μTAS [5,6]. One has to solve "front-end problems": interfacing real-world sample with microfluidic systems, and preparing samples to render them suitable for downstream separation and detection [6].

Among sample-preparation techniques (e.g., separation, preconcentration, derivatization, biological sample treatment) [7,5], the separation is particularly challenging because raw sample matrix usually contains impurities of various sizes spanning nanoscale to microscales that may cause clogging in microfluidic channels and measurement interference [5]. For example, a microfluidic electrochemical nitrate sensor exhibited interference from various ionic species in groundwater [8], and tear proteins caused nonspecific surface fouling and background-signal increase in microfluidic Western blotting [9]. In order to isolate and clean up impurities, strategies implemented in microanalytical systems include solid-phase extraction [10], chelation [11], precipitation [12], differential diffusion between laminar flows [13] and membrane-based separation [14,15].

Dialysis is a well-established, attractive membrane-based separation technique. In general, dialysis is simple, reliable, high-throughput and modular [16]. Dialysis has been adopted for clinical applications [17] and environmental analysis [16,18]. Dialysis has been successfully employed for μTAS [15,19,20] as well. Passive dialysis employed for separation of neutral species has drawbacks: (1) poor dialysis efficiency of theoretically maximum 50% in equilibrium stopped-flow condition or commonly much less ($<1\%$) in a non-equilibrium continuous-flow mode [21], and (2) no permselectivity toward interferents of a similar size but different charges. Active or Donnan dialysis employs ion-exchange membrane for charge and size speciation.

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Donnan dialysis has advantages over electrodialysis as no external electric field is required. Analytes are not altered significantly electrochemically and less energy is consumed. Another excellent analytical aspect of Donnan dialysis is that it can enrich analytes (i.e., preconcentration) [22,23].

The conventional Donnan dialysis is far from being ideal for microanalytical systems. Firstly, dialysis efficiency is low in nonequilibrium continuous-flow mode [24]. Therefore, stopped-flow mode is often employed to improve the efficiency [22]. Solutions should be thoroughly agitated to improve mass transfer in the stopped-flow condition. Secondly, sample and dialysate consumption is large. A simple remedy could be to scale down solution containers to microscale. However, effective agitation in the microscale containers would be particularly challenging [25]. Thirdly, scaling down of physical dimensions of a dialyzer causes an unnotice but critical issue – irreproducibility. The analytes in sample solution are transferred to the dialysate through the membrane. Owing to a high concentration of fixed-ionic groups (i.e., >1 mol L^{-1}) and electroneutrality condition, the membrane acts as a "counterion storage". The stored counterions in high concentration cause the dialysis process to depend on the prior dialysis condition (i.e., irreproducible dialysis). The irreproducibility becomes significant when ionic strength is low and solution volume is small (typical for clinical and environmental samples and/or for microanalytical systems).

In the first part of this communication, the impact of the dialysis condition on the irreproducibility is for the first time, to the best of our knowledge, theoretically and experimentally analyzed. Equilibrium concentrations of ions in dialysate, sample and membrane phases of a Donnan dialyzer are modeled using the Nernst–Planck formulation and the Donnan equilibrium equation. The numerical model is used to predict the dialyzer output in a series of repeated dialysis steps, for three different cases of the dialyzer input (i.e., initial analyte concentrations in sample solution): (1) constant, (2) randomly changing, and (3) monotonically increasing. We also show how the irreproducibility is alleviated by increasing solution-to-membrane volume ratio, a critical dialyzer design parameter. The numerical model is verified by experiments using CSDDs fabricated in house.

There have been efforts to address the aforementioned issues of the conventional Donnan dialyzers for analytical systems. A long tubular ion-exchange membrane was used as a dialysate container and the tube was dipped into an agitated sample solution for analyte recovery under stopped-flow condition [26]. Cox et al. proposed a similar system with the difference being dialysate in flow condition for a high throughput [27], but the dialysis efficiency was low because of nonequilibrium condition. Instead of stirring, forcing solution through a dialyzer at a high flow rate yielded effective agitation and improved throughput [28,29]. A tubular membrane for dialysate solution was enclosed in a tube-like sample container and the sample solution was recirculated in a closed loop. Using the recirculation approach, the dialysis was completed at a reasonable speed [28]. On the other hand, Miliosavljevic et al. recirculated the dialysate solution through a parallel-plate Donnan dialyzer while the sample solution was stationary [30].

In the second part of the communication, we introduce for the first time, to the best of our knowledge, a parallel-plate Donnan-dialytic membrane-separation module (PDMM) with recirculation tubes for both dialysate and sample solutions *that does not require active agitation*. The PDMM is fully automated, and the dialyzer performance (e.g., throughput, reproducibility, dialysis efficiency) is improved over the CSDDs we tested. The novelty of the PDMM lies on a microfluidic parallel-plate dialyzer, recirculation of dialysate/sample solutions through small-bore tubes, and the use of equilibrium dialysis condition. A major difference from work by Velizarov et al. [29] is that (1) they use stirred tanks for agitation and (2) an enzyme bioreactor tank is connected to the recirculation loop for nitrate removal, which renders the system not amenable to a microfluidic/miniaturized format. By rational design, we achieve the following important results: (1) the dialyzer irreproducibility is significantly reduced by increasing the solution-to-membrane-volume ratio; (2) throughput is improved by forced convection in the both recirculation tubes; and (3) dialysis efficiency is much higher ($\sim$91%) than that of a flow-through dialyzer as the PDMM operates in an equilibrium condition. Additionally, the microchannel-based, simple dialyzer design is amenable to on-chip integration of the sample preparation module into microanalytical systems. Toward a total analysis system integrated with membrane sample preparation, dialysis experiments for nitrate, an important environmental analyte [31], are performed using the CSDDs and the PDMM, and the results are compared.

2. Experimental

2.1. Chemical reagents

In preparing reagents, 16 MΩ cm deionized (DI) water from Super-Q Plus High Purity Water System (Millipore, Billerica, MA, USA) was used. All chemicals were ACS reagent grade. Nitrate, chloride, and fluoride concentrations were measured using ion-selective electrodes (ISE) model 360-75, 364-75, and 365-75, respectively (SENTEK Limited, Essex, UK). Ion-strength adjuster (ISA) for the nitrate ISE was 5 mol L^{-1} ammonium sulfate solution, made with powder (Fluka, Buchs, Switzerland). ISA for the chloride ISE was 5 mol L^{-1} sodium nitrate solution made with powder (Aldrich Chemical Co., Milwaukee, WI, USA). No ISA was used for the Fluoride ISE. Chloride-ISE calibration standards were made by diluting a 1 mol L^{-1} NaCl stock solution, made with the powder (Fisher Scientific Co., Hampton, NH, USA). Nitrate-ISE calibration standards were prepared by sequential dilution of 0.1 mol L^{-1} $NaNO_3$ stock solution (Ionplus, Thermo Orion, Waltham, MA, USA), and this stock solution was also used for the measurement of membrane exchange capacity and selectivity. $NaNO_3$ sample solution (1 mmol L^{-1}) was made similarly. 1 mol L^{-1} of $NaNO_3$ was also prepared with the powder and this nitrate solution was used to exchange chloride ions in ion-exchange membranes with nitrate ions. NaF stock solution at 0.1 mol L^{-1}, purchased from Sigma (Fluka, Buchs, Switzerland), was diluted and used as dialysate, and used in membrane-selectivity measurement as well.

2.2. Measurement of membrane thickness and exchange capacity

Anion-exchange membranes (AEM) Neosepta AFN and ACS (Astom Corp., Tokyo, Japan) were used in this research. Both Neosepta membranes were saturated with chloride ions when received. After the membranes were thoroughly washed with DI water, a rectangular membrane piece ($\simeq 9.7$ cm^2) was stored in 100 mL of 0.1 mol L^{-1} $NaNO_3$ solution in an Erlenmeyer flask for 24 h. Chloride ions in the membrane phase were exchanged with nitrate in the solution phase. During the ion exchange, the flask was tightly sealed from ambient air, and shaken on an orbital mixer (Thermolyne Speed RotoMix M71735, Barnstead International, Dubuque, Iowa, USA). The mixture of nitrate and chloride in the flask was then drained, and stored in a polyethylene bottle. A 100 mL nitrate solution was added one more time, and the ion exchange was repeated. Then the ion exchange was repeated two more times with 50 mL nitrate solution. During this 96 h period, a total of 300 mL of solution was collected for later analysis. The membrane was quickly washed with DI water and blot-dried with filter paper. The thickness was quickly measured with a micrometer at 5 different points (i.e., four corners and center) and the average thickness was calculated.