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# Preparation of magnetic ODS-PAN thin-films for microextraction of quetiapine and clozapine in plasma and urine samples followed by HPLC-UV detection

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ABSTRACT

In this study, conventional thin-film microextraction (TFME) was endowed with magnetic by introducing superparamagnetic $SiO_2$@$Fe_3O_4$ nanoparticles in thin-films. Novel magnetic octadecylsilane (ODS)-polyacrylonitrile (PAN) thin-films were prepared by spraying, and used for the microextraction of quetiapine and clozapine in plasma and urine samples, followed by the detection of HPLC-UV. The influencing factors on the extraction efficiency of magnetic ODS-PAN TFME, including pH, extraction time, desorption solvent, desorption time, and ion strength were investigated systematically. Under the optimal conditions, both analytes showed good linearity over ranges of 0.070–9.000 μg mL$^{-1}$ and 0.012–9.000 μg mL$^{-1}$ in plasma and urine samples, respectively, with correlation coefficients ($R^2$) above 0.9990. Limits of detection (LODs) for quetiapine in plasma and urine samples were 0.013 and 0.003 μg mL$^{-1}$, respectively. LODs for clozapine in plasma and urine samples were 0.015 and 0.003 μg mL$^{-1}$, respectively. The relative standard deviations (RSDs) for quetiapine and clozapine were less than 9.23%. After the validation, the protocol was successfully applied for the determination of quetiapine and clozapine in patients' plasma and urine samples with satisfactory recoveries between 99–110%. The proposed magnetic ODS-PAN TFME was very simple, fast and easy to handle. It showed high potential as a powerful pretreatment technology for routine therapeutic drug monitoring (TDM) in plasma and urine samples.

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## 1. Introduction

Quetiapine and clozapine, as the newer atypical antipsychotic drugs with distinct curative effect, are fairly prevailed in clinical practice on the therapy of schizophrenia [1]. But treatment in overdose might cause severe adverse effects including myocardial depression, ventricular arrhythmia, kidney or liver damage, even death [1,2]. Furthermore, fairly common polypharmacy treatment in clinic may increase the risk of adverse effects due to drug–drug interactions and obvious individual differences of patients. Hence, routine therapeutic drug monitoring of quetiapine and clozapine is strongly recommended in clinic, which can provide a chance to minimize the risk of toxicity, regulate dosage and maximize treatment especially for special patients like pregnant women, children and aged patients [3].

Several popular methods have been reported for the detection of quetiapine and clozapine in biological samples, involving liquid chromatography (LC) combined with UV [4–10], MS/MS [11–19] or coulometric [20], gas chromatography (GC) combined with MS [21], MS/MS [22] or nitrogen-phosphorus detection [23], and CE combined with UV [24] and electroanalysis [25,26]. Among those methods, reversed-phase (RP)-LC system is highly recommended for analysis of multiple trace drugs in complex biological samples due to its powerful capability of separating non-polar to medium-polar compounds, even for involatile and unstable substances [18,27]. Besides that, prior to instrumental analysis, an additional clean-up/enrichment procedure is quite essential to decrease the matrix interference and further improve the sensitivity of final detection [18,27]. To date, sample pretreatments of quetiapine and clozapine in biological samples have been reported frequently, including protein precipitation [16–18,25,26], liquid–liquid extraction (LLE) [11–15], dispersive liquid–liquid microextraction (DLLME) [9], solid-phase extraction (SPE) [4–8,10] and microextraction by packed sorbent (MEPS) [20,22].

Thin-film microextraction (TFME), as a novel format of solid phase microextraction (SPME) for enrichment/clean-up of analyte

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prior to instrumental analysis [28], has been attracted increasing attention in many fields, such as environment [29–31], food [32] and biology [33–36]. TFME is generally characterized by employing an extra support like stainless-steel rod, stainless-steel mesh or blade-shaped substrate to reinforce the polymeric membrane during sampling process [37,38]. Thanks to the features of large surface area-to-volume ratio and increased extraction phase volume, TFME is superior to the conventional SPME approaches in terms of high extraction rate and sensitivity without sacrificing the extraction time [28]. It is worth noting that the desired performances of TFME, such as extraction rate, sensitivity and reusability, primarily depend on the nature of membrane, thus exploring new membrane with outstanding properties is of great significance. In addition, to further explore the application of TFME in biological fluids, utilization of biocompatible membranes is supposed to be promising for reducing the irreversible adsorption of biological macromolecules, which can avoid the change of the kinetics of extraction during the process and thus extend the lifetime of TFME reuse. Polyacrylonitrile (PAN), normally as a membrane of dialysis and ultrafiltration, was chosen as a biocompatible binder in studies for preparation of thin-films due to its excellent physicochemical, mechanical stability and biocompatibility [36,39,40]. Some commercial adsorbents such as hydrophilic-lipophilic balanced (HLB) [31], strong anion exchange (SAX) [31], polystyrene-divinylbenzene (PS-DVB) [36], phenylboronic acid (PBA) [36] and silica-based-C18 [31,34,39,41] were dispersed into PAN glue to form membrane. Those membranes showed not only good adsorption capacity with analytes with the aids of dispersed adsorbents but also good biocompatible with biological matrix, providing a promising opportunity to widen potential application of TFME in a biological analysis field. Furthermore, the coating preparation method shows an obvious effect on the extraction via stability, surface area, recovery and reproducibility. Three traditional coating preparation methods including spraying, dipping and brush painting have ever been evaluated, and the spraying exhibited the best performance in Ref. [39].

In our previous work, two kinds of ODS-PAN and PEP (polar enhanced phase)-PAN thin-films were prepared by spraying, and had been successfully used for the analysis of three estrogens in aqueous tea extract and environmental water samples by HPLC-UV detection [42]. In the current study, the ODS-PAN thin-films were endowed with magnetic by adding home-made superparamagnetic $SiO_2$@$Fe_3O_4$ nanoparticles in ODS-PAN slurry before spraying. The obtained novel magnetic ODS-PAN thin-films can be easily collected against the wall of tubes by an external magnet, leading to a more convenient operating way of TFME. It was used for separation/preconcentration of quetiapine and clozapine in plasma and urine samples. The influencing factors on the extraction efficiency of magnetic thin-films for the analytes, such as pH, extraction time, desorption solvent, desorption time, and ion strength were investigated systematically. Under the optimal conditions, the proposed magnetic ODS-PAN TFME coupled with HPLC-UV was evaluated and applied for the determination of the analytes in clinical patients' plasma and urine samples.

## 2. Materials and methods

### 2.1. Chemicals and reagents

Quetiapine fumarate was kindly supplied by Hunan Dongting Pharmaceutical Co., Ltd. (Hunan, China) and its content was above 99%. Clozapine was purchased from the National Institute for the Control of Pharmaceutical and Biological Products, and its purity was 99.8%. Polyacrylonitrile (PAN) was purchased from Sigma-Aldrich. Silica-based-C18 particles (ODS, 50 μm) were spherical shape with 345 $m^2 g^{-1}$ surface area and 120 Å pore size, and purchased from H&E Co., Ltd (Beijing, China). Deionized water was thoroughly utilized in this study. Methanol, acetonitrile, isopropanol, acetone, cyclohexane, *N*,*N*′-dimethylformamide (DMF), ammonium acetate ($NH_4Ac$), triethoxysilane (TEOS), iron (II) chloride tetrahydrate ($FeCl_2{\cdot}4H_2O$), iron (III) chloride hexahydrate ($FeCl_3{\cdot}6H_2O$), ammonia ($NH_3{\cdot}H_2O$), sodium hydroxide (NaOH) and other normal reagents were supplied by Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). All above-mentioned reagents were of analytical grade except HPLC grade methanol, acetonitrile and isopropanol.

Two stock solutions (1.000 mg $mL^{-1}$) were prepared by individually dissolving appropriate amount of quetiapine (as standard compound of quetiapine fumarate) and clozapine in methanol, respectively. And then, a mixed standard solution (0.500 mg $mL^{-1}$) was prepared by mixing equal volume of the stock solutions of quetiapine and clozapine. All above solutions were stored in refrigerator at 4 °C. Working solutions were prepared daily by properly diluting the mixed standard solution with deionized water. The obtained aqueous standards were used for the optimization of the conditions of magnetic TFME.

### 2.2. Apparatus

The HPLC system (Hitachi, Hitachi High-Technological Corporation, Tokyo, Japan) consisted of a Model L-2130 pump, an auto-sampler with 20 μL sample loop, and an L-2400 UV detector. T-2000P software was used for the record of chromatogram and the calculation of peak area. Chromatographic separation was carried out on an Amethyst C18-P column (4.6 mm × 250 mm, i.d., 5.0 μm, Sepax Technologies Inc.). The mobile phase was the mixture of ammonium acetate (0.03 mol $L^{-1}$)-methanol (25:75, v/v) at a constant flow rate of 1.0 mL $min^{-1}$. The detection wavelength was set at 238 nm.

A Navo Nano SEM 450 scanning electron microscopy (FEI, Holland) was used for the characterization of the surface and section of thin-films. The magnetic property of the thin-films was studied using a PPMS-9T vibrating sample magnetometer (VSM) (Quantum Design, USA). The pH was adjusted through a Delta 320 pH meter (Mettler Toledo Instruments Co., Ltd., Shanghai, China) with a combined electrode. A HY-4 speed multi-function oscillator (Jintan Instruments Co., Ltd., Jiangsu, China) was applied to accelerate the equilibrium of extraction as well as desorption. Centrifugation was performed on a SC-06 low speed centrifuge (Anhui USTC Zonkia Scientific Instruments Co., Ltd., Anhui, China).

### 2.3. Preparation of silica-coated magnetic nanoparticles

The silica-coated magnetic nanoparticles ($SiO_2$@$Fe_3O_4$) have non-toxic coating and hydrophilic surface, showing better biocompatibility and stability in comparison with superparamagnetic $Fe_3O_4$ nanoparticles. So $SiO_2$@$Fe_3O_4$ nanoparticles were prepared in the study to endow the thin-films with magnetic. On the Basis of our previous works [10,43], $FeCl_3{\cdot}6H_2O$ (11.68 g) and $FeCl_2{\cdot}4H_2O$ (4.30 g) were dissolved in 200 mL deionized water with vigorous stirring under $N_2$ atmosphere protection at 80 °C. Then 22 mL of 28% $NH_3{\cdot}H_2O$ was added drop by drop, simultaneously producing deep-brown $Fe_3O_4$ microspheres. After 4 h of reaction, the $Fe_3O_4$ nanoparticles were collected by an external magnet, and washed four times with deionized water. The obtained $Fe_3O_4$ nanoparticles were dispersed in 40 mL of deionized water and 160 mL of methanol, followed by dropwise adding 4 mL of $NH_3{\cdot}H_2O$ and 3 mL of TEOS. The resulting mixture was stirred for 12 h at room temperature under $N_2$ atmosphere protection. The obtained $SiO_2$@$Fe_3O_4$ nanoparticles were sequentially washed with deionized water, methanol and deionized water again, each four times, last dried at 60 °C.

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