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Synthesis of lab-in-a-pipette-tip extraction using hydrophilic nano-sized dummy molecularly imprinted polymer for purification and analysis of prednisolone

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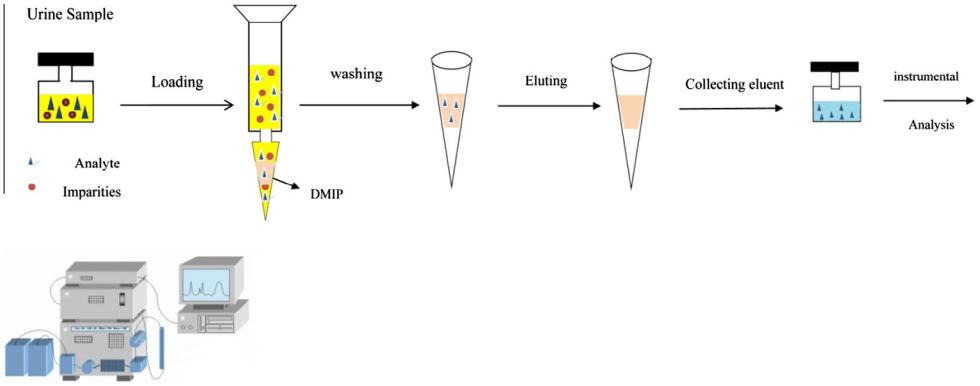
GRAPHICAL ABSTRACT

The PT-DMIP-HPLC-UV extraction procedure.



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ABSTRACT

A novel pipette-tip based on nano-sized dummy molecularly imprinted polymer (PT-DMIP) assisted by ultrasonication for the effective enrichment and analysis of prednisolone from urine samples was developed. The PT-DMIP cartridge was prepared by packing the dummy molecularly imprinted polymer at the tip of the micropipette. The polymerization used betamethasone (BM) as the dummy template, 3-aminopropyltrimethoxysilane (APTMS) as the functionalized monomer, tetraethyl orthosilicate (TEOS) as the cross-linker and aluminum ion (Al^{3+}) as a dopant to produce Lewis acid sites in the silica matrix for metal coordinative interactions with the analyte. Compared to conventional solid phase extraction (SPE), the PT-DMIP is cost-effective, fast, and easy to handle, while the system is very approachable and reduces the consumption of toxic organic solvent. HPLC-UV analysis revealed successful applicability of the sorbent for highly efficient extraction of perdnisolone from urine matrices. The extraction recovery was investigated and optimum conditions were obtained using central composite design. Good linearity for prednisolone in the range of 0.22–220 μg L^{-1} with regression coefficients of 0.99 reveals high applicability of the method for trace analysis. Under the optimized conditions, the recoveries are 89.0–96.1 with relative standard deviations (RSD) of less than 9.0%.

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1. Introduction

Prednisolone (11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl6,7,8,9,10,11,12,13,14,15,16,17-dodecahydrocyclopenta [a] phenanthren3-one) (Fig. 1a) is one of synthetic glucocorticoids with extensive usage in the treatment of acute rejection episodes, inflammatory conditions such as arthritis, colitis, asthma, certain skin rashes and bronchitis [1,2]. Moreover, prednisolone is also employed for organ transplants to decrease the risk of organ injection [3,4]. The metabolism of corticosteroids is highly dependent on individual situation [5–7]. The immunotherapy of acute injection is done by a fixed drug regimen intravenous on the first, third and fifth days of the treatment. This regime leads to a risk of subtherapeutic concentrations and toxic effects caused by overdosing [8]. These indicate the importance of measuring prednisolone in different matrices. Scientists have reported different methods for the pretreatment and determination of prednisolone based on liquid-liquid extraction combined with liquid chromatography [9], electrochemical technique [10], solid phase extraction combined liquid chromatography tandom mass spectrometry [11], micellar electrokinetic chromatography [12] and solid phase extraction combined liquid chromatography UV spectrometry [13]. Although these methods were simple and could just solve some certain matrix interferences problem, while they suffer from low acceptable selectivity and usage of high amount of organic solvent in pretreatment. Urine samples contain a very low level of prednisolone a useful technique should be employed for preconcentration of prednisolone. In this work, highly selective extraction of prednisolone was under taken by synthesis of a molecularly imprinted polymer (MIP) according to a sol-gel method. MIPs attain great attentions due to their favorable characteristics such as mechanical and chemical robustness, high selectivity with target molecule, high capacity and low cost of preparation [14]. Commonly, MIPs are synthesized by bulk polymerization in a mixture solution containing a template molecule, porogen reagents, functional monomer, cross-linker and initiator [15,16]. After the polymerization, ground and sieving, the template molecule was removed and functional binding sites were achieved [17]. Unfortunately, this method is time-consuming and the grinding and sieving are also labor intensive with consumption of large amount of polymers and incomplete template removal. Additionally, the irregular shape particles lead to reduction of extraction efficiency especially using MIPs as SPE sorbents [18]. Nano-structured MIP materials with extremely higher surface-to-volume ratio provide more complete removal of templates and better site accessibility [19–21]. This technique can produce homogeneous particles with the ideal porous structure decreasing consumption of toxic organic solvents, grinding and sieving. Moreover, inorganic silica-based polymer provides high mechanical stability, good solvent resistance and high efficiency [22–24]. Compared to acrylic-based MIP, sol–gel organically modified has been verified to supply more specific toward the target species and allow for faster diffusion of analytes at mild reaction temperature [25–28]. One of the MIPs disadvantages while using target molecules as templates to synthesize MIPs is leakage of residual template molecules after solvent extraction which lead to error in results which simply can be overcome using dummy template for the MIPs synthesis. As a pre-condition, the dummy molecule must resemble the target analyte in terms of shape, size and functionalities without interference in analytical determination [29,30].

Li and co-workers [31] reported the molecular imprinting using aluminum ion (Al^{3+}) to supply Lewis acid sites in the silica matrix. Metal coordinative interactions provide higher strength and selectivity compared to traditional interactions such as polar, hydrogen-bond and van der Waals forces [32].

This paper describes a novel and inexpensive strategy for synthesis of nano-sized dummy molecularly imprinted amine functionalized silica using a small amount of organic solvent. The prepared MIPs possessed good recognition ability toward prednisolone. Additionally, the leakages of residual templates were performed using betamethasone as the dummy template. Moreover, ultrasonic assisted extraction was employed for desorption of analyte. To the best of our knowledge, ultrasonic assisted extraction by PT-DMIP sorbent based on functionalized silica with metal doping has not been reported for prednisolone analysis. The attempt focused on development of simplified prednisolone enrichment method to enhance the selectivity of prednisolone analysis by HPLC-UV. The different parameters affecting the extraction efficiency have been optimized using experimental design methodology. Finally, the assay was fully validated and applied to the quantification of prednisolone in different urine samples.

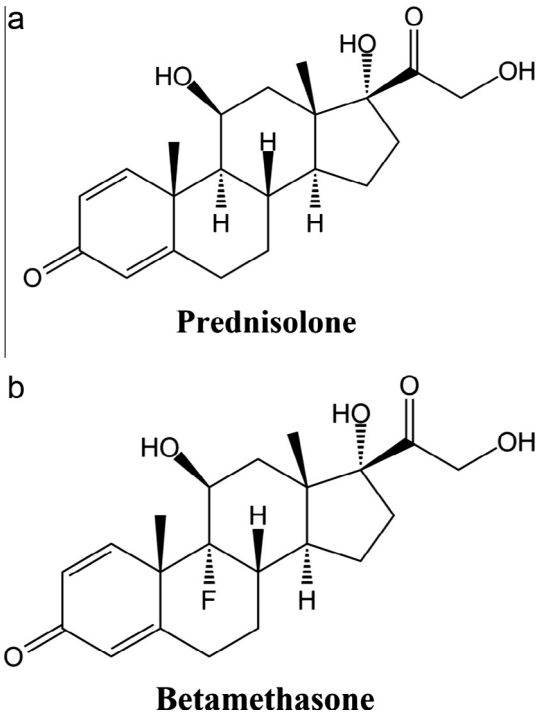

Fig. 1. The structures of (a) prednisolone and (b) betamethasone.

2. Experimental

2.1. Chemicals and reagents

Tetraethyl orthosilicate (TEOS), 3-aminopropyl trimethoxysilane (APTMS) and aluminum chloride hexaydrate ($AlCl_3{\cdot}6H_2O$) were obtained from Merck (Darmstadt, Germany). Prednisolone and betamethasone were obtained from Ministry of Health and Medical Education (Tehran, Iran), and their chemical structures are shown in Fig. 1. Other chemicals including ethylene glycol, methanol, ethanol, DMSO and acetic acid were purchased from Merck (Darmstadt, Germany). Urine samples were obtained from Healthy volunteers and stored at 4 °C until use.

2.2. Instrumentation and HPLC analysis

HPLC was performed with an Agilent 1100 liquid chromatography (USA), Quaternary Pump (model G1311A), Multiple Wavelength Detector (model G13658, setting at 254 nm for prednisolone), a sample injection valve with a 20 μL sample loop,