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The metal-organic framework MIL-101(Cr) as efficient adsorbent in a vortex-assisted dispersive solid-phase extraction of imatinib mesylate in rat plasma coupled with ultra-performance liquid chromatography/mass spectrometry: Application to a pharmacokinetic study☆

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ABSTRACT

Metal-organic framework MIL-101(Cr) was successfully used as an efficient sorbent in a vortex-assisted dispersive solid-phase extraction (VA-DSPE) and applied for the determination and the pharmacokinetic of imatinib mesylate in rat plasma by UPLC–MS/MS. In the enrichment of imatinib from rat plasma, the analyte was efficiently adsorbed on MIL-101(Cr) and simply recovered by using initial mobile phase (0.1% formic acid-methanol (6:4 *v*/*v*)) as elution solvent. Meanwhile, the protein in the plasma samples was excluded from the porous structure of MIL-101(Cr), leading to direct extraction of drug molecule from protein-rich biological samples without any other pretreatment procedure. After being removed, the supernatant was filtered and directly injected into the UPLC–MS/MS for the analysis of the target. The experimental parameters, including nature of MOFs, amount of MIL-101(Cr), pH value of aqueous solution, extraction time, type and volume of elution solvent, were systematically optimized. After VA-DSPE, chromatographic separation was performed on an ACQUITY UPLC® BEH C_{18} column (2.1 mm × 100 mm, 1.7 μm) with a 3 min gradient elution using 0.1% formic acid and methanol as mobile phase at a flow rate of 0.3 mL/min. The detection was accomplished on a tandem mass spectrometer via an electrospray ionization (ESI) source by multiple reaction monitoring (MRM) in the positive ionization mode. The lower limit of quantification of 1 ng/mL was achieved and the mean recovery of the analyte was higher than 81.2%. Moreover, computational simulation was primarily applied to predict the adsorption behavior and revealed the molecular interactions and free binding energies between MIL-101(Cr) and imatinib with the molecular modeling method, providing certain explanation of the adsorption mechanism. The originally established pretreatment and detection method has some merits, such as less solvent consumption, easy operation, higher sensitivity and lower matrix effect. And the MIL-101(Cr) exhibited a potential as an efficient sorbent in the enrichment of the analyte from complex biosamples.

1. Introduction

Imatinib mesylate (Gleevec) is the recommended first-line treatment for chronic myelogenous leukemia (CML). It is also used to treat other hematological malignancies that express a constitutively active form of the BCR-ABL [1] fusion protein as well as gastrointestinal stromal tumors due to its inhibitory effect on C-Kit receptor [2]. Therapeutic drug monitoring (TDM) is usually requested to provide the increasing evidence of the relationships between the plasma drug concentration and the therapeutic effects, between the effective concentration and the toxic concentration and between the drug–drug interactions or compliance [3]. In the clinical application, imatinib mesylate frequently causes large inter-individual while low intra-individual pharmacokinetic variability [4]. So it is essential to monitor the plasma concentration of the drug for each patient in order to obtain a good curative effect.

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Many methods for the quantification of imatinib in plasma have been described so far [5–9], but they have several shortcomings, such as low sensitivity, low extraction recovery, high matrix effect or time-consuming in the pretreatment process. For example, C. Arellano et al. [5] reported that the relatively higher limit of quantitation (LOQ) (10 ng/mL) and lower recovery (smaller than 50%) was obtained by using ethyl acetate liquid–liquid extraction for the sample preparation and even by UPLC–MS/MS for the determination. Titier et al. [6] applied UPLC–MS/MS for the quantification of imatinib in plasma samples. Although they obtained more satisfactory recovery, the quantitative limit was still 10 ng/mL. Roth et al. [7] employed perchlorate protein precipitation method for the pretreatment combined with HPLC-UV detection. It sounded simple and inexpensive, but lower sensitivity, i.e. higher LOQ (80 ng/mL) was acquired. The chromatogram also showed larger endogenous substance peaks. Therefore, developing efficient pretreatment method and sensitive detection is the object of great interest.

Recently, solid phase extraction (SPE) [8] has become a routine sample preparation technique and been well applied in the complex biological sample pretreatment as compared to protein precipitation [9] and liquid–liquid extraction (LLE) [10] due to its stronger purification ability, lower matrix effect and less consumption of organic solvents, and so on. Dispersive solid-phase extraction (DSPE), reported by Anastassiades et al. [11], is an expanded SPE procedure that involves a single extraction with solid sorbent and a rapid clean-up process. The improved method not only maintains the advantages of SPE, but also presents simpler operation, shorter extraction time and higher efficiency. So, DSPE is mainly used for the trace determination of parabens [12], benzoylurea insecticides [13], herbicides [14] from various complex medium. However, there is no report concerning the pretreatment of imatinib in complex plasma sample by DSPE method.

In the DSPE, sorbent plays a crucial role on the extraction efficiency. Metal-organic frameworks (MOFs) are a new class of hybrid inorganic-organic micro-porous crystalline materials through self-assembled straightforwardly between metal ions and organic linkers via coordination bonds [15]. In recent years, they have received special attention due to the unique structural architecture. The remarkable properties make MOFs promising in diverse applications, such as gas storage [16], separation [17], catalysis [18] and drug delivery [19]. A large number of reports have shown that the MOFs possess great potential in sorption-related fields [20–23]. However, only a few types of MOFs, such as ZIF-8 (ZIF, Zeolite Imidazolate Framework), MIL-100(Fe) and MIL-101(Cr) (MIL, Material Institute Lavoisier), are proved to be stable in aqueous solution. MIL-101(Cr) [24], being one of the most widely studied MOFs, has a cubic structure, a huge pore volume and pore sizes. It offers a unique high surface area, large pore windows and mesoporous pores, excellent chemical and solvent stability. Several typical examples were reported that MIL-101(Cr) was used as sorbent material in the pretreatment of benzophenones in toner [23], herbicides in peanuts [25] and in vegetable oil [26], providing an available possibility of sample pretreatment in biological samples. Yet, there is no previously literature published using MIL-101(Cr) as adsorption material for the extraction and the enrichment of small molecule drugs in plasma samples and its application to pharmacokinetics.

In this study, a novel vortex-assisted DSPE method for the extraction of imatinib mesylate in rat plasma was successfully developed using MIL-101(Cr) as sorbent for the first time. The DSPE conditions, such as nature of MOFs, amount of MIL-101(Cr), pH value of aqueous solution, extraction time, type and volume of elution solvent, were systematically optimized. The detection for the target analyte was performed by UPLC–MS/MS prior to a complete methodology validation. Then the established analytical method was applied to the pharmacokinetic study of imatinib mesylate in rat plasma. In addition, computational modeling technique was also adopted to discuss and explain the binding mechanism during the adsorption process of MIL-101(Cr) towards imatinib.

2. Experimental

2.1. Ethics statement

All procedures had the approval of the Animal Ethics Committee of the Shenyang Pharmaceutical University.

2.2. Reagents and materials

Imatinib mesylate (purity 99.7%, No. CPTA003) was purchased from Tianjin Chempharmatech Co., Ltd. (Tianjin, China). Sulfamethoxazole (SMZ) (internal standard, IS, purity 99.8%, No. 100025-200904) was obtained from National Institutes for Food and Drug Control. The MIL-101(Cr) and MIL-100(Fe) materials employed in the experiment have been previously synthesized and characterized through XRD, TGA, SEM and N_2 adsorption-desorption tests [27] in our laboratory. HPLC-grade acetonitrile, methanol and formic acid were acquired from Concord Technology (Tianjin, China). Ultrapure water was purified using a Milli-Q Reagent Water system (Millipore, Bedford, MA, USA). All of other reagents were analytical grade. The chemical structures of imatinib mesylate and IS are shown in 1s. 1 .

2.3. Instrumentation and analytical conditions

The UPLC–MS/MS system consisted of an ACQUITY Ultra Performance LC system (Waters, Milford, MA, USA) interfaced with a Waters Xevo TQ tandem quadrupole mass spectrometer (Waters, Milford, MA, USA). Chromatographic separation was achieved on an ACQUITY UPLC® BEH C_{18} column (2.1 mm × 100 mm, 1.7 μm). The mobile phase consisted of 0.1% (*v*/*v*) formic acid (A) and methanol (B) and the flow rate was set at 0.3 mL/min. The gradient program was set as follows: 0–1.5 min, 40–95% B; 1.5–2 min, 95% B; 2–2.1 min, 95–40% B; 2.1–3 min, 40% B. The total analysis time was 3 min. The column temperature was maintained at 30 °C and the auto-sampler was conditioned at 4 °C. The sample injection volume was 2 μL for analysis.

Electrospray ionization (ESI) in positive ion mode was utilized and the mass spectrometer was operated in the multiple-reaction monitoring (MRM) mode. The temperature of the ESI source during the operation was 150 °C and the desolvation temperature was 350 °C. The gas flow of the cone and the desolvation were set at 150 L/h and 650 L/h, respectively. The capillary voltage was set at 3000 V. The optimized precursor-to-product ion transitions monitored for imatinib $[M+H]^+$, SMZ $[M+H]^+$ were m/z 494.10 → 393.83 with cone 58 V and collision energy 24 V and m/z 253.93 → 155.41 with cone 35 V and CE 14 V, respectively.

2.4. Preparation of calibration standards and quality control samples

The stock solutions of imatinib were prepared in methanol and stored at −20 °C [28]. A standard solution of imatinib was prepared by weighing 10.06 mg of imatinib mesylate and dissolving in 100 mL of methanol. Standard solutions were then prepared by dilution in 40% methanol in water to obtain a series of mixed working solutions at appropriate concentrations of 10–20,000 ng/mL. The stock solution of the IS (1.0 mg/mL) was prepared by dissolving the reference standard in methanol. A working solution of IS (2.0 μg/mL) was prepared by diluting the stock solution of IS with 40% methanol in water. The calibration curve was prepared in blank rat plasma by adding appropriate amounts to 100 μL of