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Monitoring of antifungal drugs in biological samples using ultrasonic-assisted supramolecular dispersive liquid–liquid microextraction based on solidification of a floating organic droplet

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ABSTRACT

A new method for the simultaneous determination of the three antifungal drugs using ultrasonic-assisted supramolecular dispersive liquid–liquid microextraction based on solidification of a floating organic droplet (UASMDLLME-SFO) was proposed. The supramolecular solvents produced from reversed micelles of 1-dodecanol (extraction solvent) in tetrahydrofuran (THF) were injected into the aqueous sample solution. Reverse micelle coacervates were produced in situ through self-assembly processes. The antifungal drugs were extracted from the aqueous sample into a supramolecular solvent. Sonication accelerated the mass transfer of the target analytes into the supramolecular solvent phase and enhanced the dispersion process. Some parameters affecting the extraction efficiency such as type and volume of the extraction solvent, pH, volume of the disperser solvent and ultrasound extraction time were investigated. Under optimum conditions, the limits of detections for ketoconazole, clotrimazole and miconazole ranged from 0.08 to 1.3 $\mu g L^{-1}$ and the relative standard deviations (RSDs, n = 5) < 6% were obtained. The method was successfully applied for preconcentration of the three drugs in biological and water samples.

1. Introduction

Antifungal medications are pharmaceutical fungicides used in different pharmaceutical dosage forms. Among the agents used, the imidazolic group drugs (azole antifungals) are considered to have a wide range of significant effects and suggested by the Food and Drug Administration (FDA) as therapeutic options for fungal infections [1]. Azole antifungal pharmaceuticals such as clotrimazole (CT), miconazole (MC), and ketoconazole (KC) are the compounds possessing five-membered ring structures containing two nitrogen atoms with a complex side chain attached to one of the nitrogen atoms. The structures and corresponding log P values (octanol–water partition coefficient) of these molecules are illustrated in Table 1 [2,3]. The first report of antifungal activity of an azole compound was already described in 1944 by Woolley [4]. Fungal growth has been inhibited by preventing the conversion of lanosterol to ergosterol as the main sterol of the fungal cell wall [5–7]. The occurrence of drug residues in the environmental impact is an important concern because little is known about their possible negative effects and they are continuously introduced into the environment [8]. It is found that many pharmaceutical compounds can be in the effluent of the environment at concentrations up to several micrograms per liter [9]. Therefore, due to the complexity of pharmaceutical matrix and because of the importance of determining the level of these agents in pharmaceutical preparations and biological fluids, an efficient, sensitive and selective analytical method is required. Several preconcentration methods such as liquid–liquid extraction [10], ultrasonic extraction [11], acid degradation [12], solid-phase extraction [13], supercritical fluid extraction [14] and hollow fiber based liquid phase microextraction (HF-LPME) [9] have been reported. However, there are some limitations in these methods, like time-consuming, high operational time, low transport rate, poor reproducibility, large volumes of solvents which are expensive, hazardous, and contaminant for the environment. Recently, an alternative to the organic solvents has been developed as the supramolecular assembly-based coacervates (SUPRAS). SUPRASs have been chosen as the most suitable systems for analytical applications to extract various compounds [15–23]. The SUPRASs are water-immiscible liquids made up of reverse micelles that aggregate at nanoscale dimensions dispersed in a continuous phase and provide different types of interactions with the organic compounds and hydrophobic metal complexes [24].

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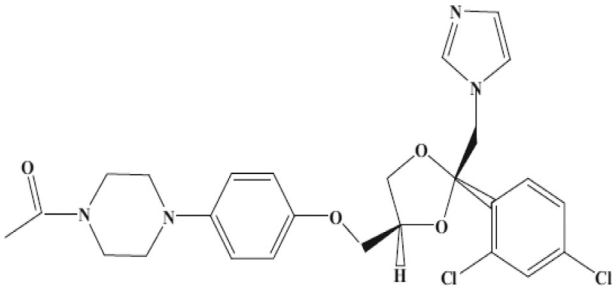
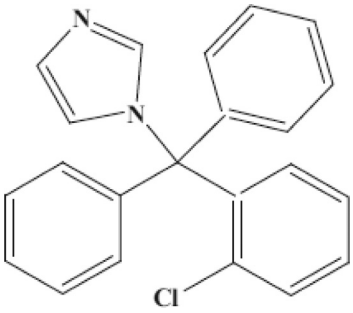
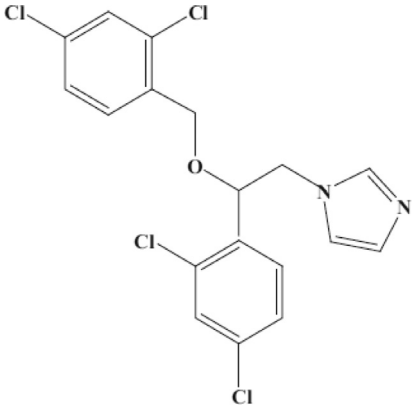
Table 1
Chemical structures and their corresponding log P values.

Analyte	Chemical structure	Log p
Ketoconazole		3.84
Clotrimazole		3.5
Miconazole		6.25

However, the method based on SUPRAS is a tedious, labor intensive and time consuming procedure. A combination of DLLME with the supramolecular solvent, the so-called supramolecular dispersive liquid–liquid microextraction (SM-DLLME) has been proposed [25]. Its main drawback is the use of handmade narrow neck centrifuge tube for removing the extracting phase[26]. Considering the characteristics of low-toxic organic solvents with a melting point near room temperature, a novel combination of SM-DLLME with the solidification of a floating organic drop microextraction technique, termed supramolecular dispersive liquid–liquid microextraction based on the solidification of floating organic drops (SM-DLLME-SFO), has been presented [26]. Ultrasound-assisted emulsification (USAEME) is an effective technique among the microextraction methods [27]. The ultrasound has the potential to increase the speed of homogenization, emulsification, and mass transfer between immiscible phases [28]. A combination of ultrasound and supramolecular based DLLME technique provides a strategy for enhancing sensitivity and a high preconcentration factor. The combination of ultrasound-assisted supramolecular solvent and dispersive liquid–liquid microextraction based on the solidification of floating organic drop (UASMDLLME-SFO) as a rapid method for the routine control of contaminations in different matrices has been introduced [24]. In this method, an appropriate amount of reverse micelles of 1-dodecanol in tetrahydrofuran was injected rapidly into the aqueous sample by a syringe and then the mixture was sonicated. The large contact surface between the extraction solvent and the sample speeds up the mass transference processes. Hence, extraction can be achieved within a few seconds. In the present study, the applicability of UASMDLLME–SFO was evaluated for the determination of some azole antifungals in some water and biological fluids.

2. Experimental

2.1. Reagents and materials

Standards of the three antifungal drugs were obtained by the Department of Pharmaceutics of Tehran University (Tehran, Iran) and used without further purification. HPLC-grade acetonitrile, sodium acetate, sodium chloride, 1-decanol, 1-undecanol, decanoic acid, 1-dodecanol and THF were purchased from Merck (Darmstadt, Germany). The stock standard solution of each compound (100 mg L^{-1}) was prepared in methanol. The prepared stock solutions were stored at 4 °C in the fridge. The working standard solutions were obtained by dilutions of the stock solution with deionized water immediately prior to the analysis. The biological