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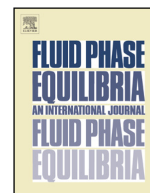

Surfactant/ionic liquid aqueous two-phase system extraction coupled with spectrofluorimetry for the determination of dutasteride in pharmaceutical formulation and biological samples

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ABSTRACT

A novel separation/analysis method was developed for the determination of dutasteride in a pharmaceutical formulation and biological samples, which based on surfactant dodecyl sodium sulfate (SDS)/ionic liquid 1-hexyl-3-methylimidazolium bromide (IL, $[C_6min]Br$) aqueous two-phase system (ATPS) extraction coupled with spectrofluorimetry. The ATPS was formed owing to new ordered molecular assembly SDS/IL, which not only extracted dutasteride but also sensitized its fluorescence intensity due to synergistic sensitizing effect. Under optimum conditions, a linear calibration curve was obtained in the range of 0.016–0.64 $\mu g\ mL^{-1}$ with $r = 0.9991$ ($n = 8$). The detection limit was 2.2 $ng\ mL^{-1}$. The preconcentration factor was 7.5. The proposed green analytical procedure was satisfactorily applied to the analysis of dutasteride in dutasteride soft gelatin capsule and human serum with the recovery of 96.7–108.0%. The obtained results of this work were in good agreement with the results of HPLC. The extraction mechanism ATPS-based was also discussed.

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1. Introduction

Extraction of active chemical compounds from natural products is one of the most important research areas for pharmaceutical and chemical industries [1]. Aqueous two-phase systems (ATPS) have been used for recovering biological products from different sources, owing to several advantages: (1) providing environments gentle enough to preserve the functionality of biomolecules; (2) scaling up the operation is easy; (3) mass transfer is fast and (4) equilibrium can be reached in a matter of seconds [2]. Aqueous two-phase systems usually establish in polymer/salt [2], polymer/polymer [3], cationic/anionic surfactants [4], ionic liquids/salt [5] and surfactant/ionic liquid [6–8] solutions. Ionic liquids (ILs) have proven to be safe and sustainable alternatives to organic solvents for many applications in industry and chemical manufacturing [9]. The IL-salt ATPS has many advantages, such as low viscosity, little emulsion formation, no need of using volatile organic solvent, quick phase separation, high extraction efficiency, and gentle biocompatible environment [8], and has been used to extract proteins [10], amino acids [11], drugs [12] and so on. Refs. [6–8] reported the properties of ATPS of surfactant/ionic liquids, and thought this new ATPS has such advantages as easy preparation, low viscosity characteristics and recyclable utilization [8] and is expected to become a new highly efficient separation system [6]. But to the best of our knowledge, until now ATPS of surfactant/ionic liquids has been seldom applied for the separation and analysis of drugs.

Dutasteride is the first dual type 1 and type 2 5-alpha reductases inhibitor. It inhibits the 5AR isoenzymes (type 1 and type 2) that mediate the synthesis of androgen dihydrotestosterone and cure benign prostatic hyperplasia [13]. The common side effects of the drug include sexual problems and dizziness [14]. Dutasteride reaches peak serum concentrations (C_{max}) approximately 2–3 h after oral administration, and single doses of dutasteride of 0.1–40 mg result in C_{max} values of 0.6–166 $ng\ mL^{-1}$. The terminal elimination half life is 3–5 weeks, and the drug remains detectable in serum for 4–6 months after treatment is discontinued [15]. For medication safety, it is necessary to monitor the concentration of dutasteride in serum and in pharmaceutical formulations. Furthermore, the concentration of dutasteride in biological samples is usually low and matrix is complex. Therefore, an efficient preconcentration/separation technique is frequently required.

Literature survey reveals that LC–MS–MS [16,17] has been reported for analysis of dutasteride in plasma, HPLC [15,18] and

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Table 1
The sources and mass fraction purity of the materials used in this paper.

Chemical name	Source	Purification methods	Final purity (mass fraction) (%)	Analysis method
Dutasteride standard	Jiangsu Lianhuan Pharmaceutical Co., Ltd, Jiangsu, China	None	99.7	HPLC[a]
Anhydrous ethanol	Sinopharm Chemical Reagent Co., Ltd, Shanghai, China		99.6	GC[b]
Methanol			99.8	
NH_4Ac			99.0	Titration[c]
KCl			99.7	AAS[d]
K_2HPO_4			99.2	
SDS	Sangon Biotech (Shanghai) Co., Ltd, Shanghai, China		99.2	UV–vis[e]
$[C_6min]Br$	Prepared in our lab	Extraction with ethyl acetate, rotary evaporation followed by vacuum drying	98.5	

[a] HPLC, high performance liquid chromatography.
[b] GC, gas chromatography.
[c] Titration, acid–base titration after distillation.
[d] AAS, atomic absorption spectrophotometer.
[e] UV–vis, ultraviolet–visible absorption spectrum.

HPTLC [19] for analysis of dutasteride in pharmaceutical formulations. However, although with relative low limit of detection ($100\,pg\,mL^{-1}$) [16] LC–MS–MS method involves a complex procedure and expensive instrumental set up which an ordinary laboratory cannot afford. HPLC had relatively high limit of detection $-0.05\,\mu g\,mL^{-1}$ [15] or $0.5\,\mu g\,mL^{-1}$ [18]. Hence a simple and sensitive analysis method is imperative to develop for the determination of dutasteride in biological samples and pharmaceutical formulations.

Nowadays spectrofluorimetry attracts more and more interest with its high sensitivity and selectivity and simplicity, and has been used extensively in the analysis of drugs [20,21]. Moreover, the spectrofluorimetry sensitivity can be further improved by (1) sensitizers such as fluorescence probe [22], surfactant [23], ionic liquid [24]; (2) sample pretreatment/enrichment technique [24]. The goal of this study was to develop and validate a simple and sensitive spectrofluorimetry method for the determination of dutasteride in human serum and pharmaceutical formulations.

In examination, it was found that dodecyl sodium sulfate (SDS) and 1-hexyl-3-methylimidazolium bromide ($[C_6min]Br$) ATPS was spontaneously generated due to the formation of new ordered molecular assembly, and dutasteride could be extracted by this ATPS. Moreover, the fluorescence intensity of dutasteride was greatly enhanced owing to synergistic sensitization of the new ordered molecular assembly. Based on the above discussion, a spectrofluorimetric method coupled with APTS extraction was developed for the determination of dutasteride in its pharmaceutical dosage form and in human serum. The obtained results were in good agreement with that of HPLC. The mechanism of ATPS extraction was also formulated.

2. Experimental

2.1. Apparatus and reagents

A F-4500 spectrofluorimeter (Hitachi, Japan) was used for all the fluorescence measurement, with excitation slit at 10.0 nm and emission slit at 5.0 nm, $\lambda ex = 249$ nm and 1-cm quartz cell. All absorption spectral recordings and absorbance measurements were performed on a UV 2501 spectrophotometer (Shimadzu, Japan). The pH measurements were done by a pH S-25 pH meter (Shanghai, China) with a precision of ± 0.01 pH. The conductivity determination was carried out on a DDS-11A digital conductivity instrument with a measurement range of $0–2 \times 10^5\,\mu s\,cm^{-1}$ (Shanghai, China). Prior to measurements the conductivity cell was calibrated with a $10\,mmol\,L^{-1}$ KCl solution. The LC-10A liquid chromatograph (Shimadzu, Japan) equipped with UV spectrometer was used for chromatography analysis. A DK-S22 thermostatic water-bath with temperature fluctuation of $\pm 0.5\,^{\circ}C$ (Shanghai Jinghong Laboratory Instrument Co., Ltd., China) was used to control temperature. A centrifuge Model 80-2 (Shanghai Pudong Physical Optics Instrument Factory, China) was used to accelerate the phase-separation process. More detailed information about the materials use in this paper is given in Table 1. Among these reagents, IL was synthesized according to the method proposed by Wei and coworkers [25]. Doubly deionized water (DDW) was used for preparation of solutions.

A dutasteride stock solution of $4.0\,mg\,mL^{-1}$ was prepared by dissolving 0.20 g of dutasteride in 50 mL of anhydrous ethanol and kept in coolness and darkness. The stock solution was further diluted with anhydrous ethanol to obtain a standard working solution of $0.10\,mg\,mL^{-1}$ before using.

$0.050\,g\,mL^{-1}$ SDS solution, $0.10\,g\,mL^{-1}$ IL solution, series of HAc–NaAc buffer solution (pH 5.0–6.5), NH_4Ac buffer solution (pH 7.0), NH_3–NH_4Cl buffer solution (pH 7.5–9.5) and $0.10\,g\,mL^{-1}$ K_2HPO_4 were prepared.

2.2. Analytical method

2.2.1. SDS/$[C_6min]Br$ ATPS extraction procedure

To a 35.0 mL centrifuge tube, 2.4 mL $0.050\,g\,mL^{-1}$ of SDS solution, 3.0 mL $0.10\,g\,mL^{-1}$ of $[C_6min]Br$ solution, 4.5 mL of NH_4Ac buffer solution (pH = 7.0) and adequate dutasteride standard or sample solution were added. After that the solution was diluted to 30.0 mL with distilled water. Then the solution was manually shaken and a cloudy mixture was formed. Finally the cloudy solution was centrifuged for 5 min at 3000 rpm. Accordingly, after centrifugation two well-defined phases were formed, extracting dutasteride into the bottom phase.

2.2.2. Fluorescence measurements

After carefully removing the upper phase with microsyringe, 0.3 mL of anhydrous ethanol and 0.2 mL of NH_4Ac buffer solution (pH = 7.0) were added into bottom phase, then the bottom phase

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