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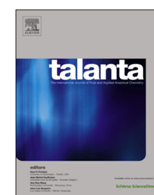

Sequential hollow-fiber liquid phase microextraction for the determination of rosiglitazone and metformin hydrochloride (anti-diabetic drugs) in biological fluids

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ABSTRACT

A new analytical method for the simultaneous determination of the antidiabetic drugs rosiglitazone (ROS) and metformin hydrochloride (MH) with marked differences in their affinity towards organic solvents (log *P* of 2.4 and −1.43, respectively) was developed. Prior to the HPLC separation, the drugs were subjected to a sequential hollow fiber liquid phase microextraction (HF-LPME) procedure. Two sequential HF-LPME approaches were considered, the preferred one involves the use of two vials containing solution mixtures for the extraction of ROS (vial 1) and MH (vial 2), respectively, but using the same fiber and acceptor phase. Important parameters that affect the extraction efficiency such as extracting solvent, donor phase conditions, HCl concentration, agitation, extraction time, addition of salt, etc. were studied. Under the optimum conditions, good enrichment factors (EF, 471 and 86.6 for ROS and MH, respectively) were achieved. Calibration curves were linear over the range 1–500 (r^2=0.998) and 5–2500 ng mL^{-1} (r^2=0.999) for ROS and MH, respectively. The relative standard deviation values (RSD%) for six replicates were below 8.4%. Detection and quantitation limits based on *S*/*N* ratio of 3 and 10 were 0.12, 1.0 and 0.36, 3.0 ng mL^{-1} for ROS and MH, respectively. The proposed method is simple, sensitive and opens up new opportunities for the microextraction of analytes with contrasting properties.

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1. Introduction

Treatment of diabetes mellitus using monotherapy with an oral anti-diabetic agent is insufficient to reach the target glycaemic goals in many patients, thus multi-drugs are necessary to achieve adequate control and satisfactory blood glucose levels. The combination of biguanides and thiazolidinedione derivatives is commonly used in clinical practice [1]. Metformin hydrochloride (MH) (biguanide class, Fig. 1), chemically [1,1-dimethylbiguanidehydrochloride], is an oral biguanide antihyperglycemic drug which is used to improve the insulin sensitivity, inhibits hepatic gluconeogenesis and reduces hepatic glucose production in patients that suffer from type 2 diabetes mellitus (T2DM) [2,3]. Rosiglitazone (ROS), (thiazolidinedione class, Fig. 1), chemically [[(±)-5-[4-[2-[*N*-methyl-*N* (2-pyridyl) amino] ethoxy] benzyl]-2,4-dione thiazolidine], is a drug for the treatment of T2DM which works by increasing the insulin sensitivity in the target tissues, as well as decreasing hepatic gluconeogenesis [4,5]. A combination of MH and ROS was found to be better in the treatment of T2DM compared to single-agent therapy alone due to its high effect on lowering blood glucose [6,7] and improving beta-cell function [8]. Furthermore, the combination tablet formulation is advantageous in terms of its convenience and patient compliance [9].

Several methods for the determination of ROS and MH either individually or simultaneously have been reported. High performance liquid chromatography with ultraviolet detection (HPLC–UV) [6–17] is the most commonly used method for the analysis of ROS and MH. However, high limit of quantitation (LOQ ≥ 20 ng mL^{-1}) was observed when UV detection was used [8,10,11,17]. Alternatively, HPLC with fluorescence detection (FL) [18,19] or tandem mass spectrometry (MS/MS) [2–4,20–27] was used. Although FL gives better sensitivity compared to UV detection, but the separation was rather long (≥15 min) [18,19]. LC–MS/MS is an efficient analysis tool providing low quantitation limits (≥1 ng mL^{-1}) [20–23], short run time, improved sensitivity and selectivity, but it is costly and the equipment is not always available in clinical laboratories. The use of gas chromatography

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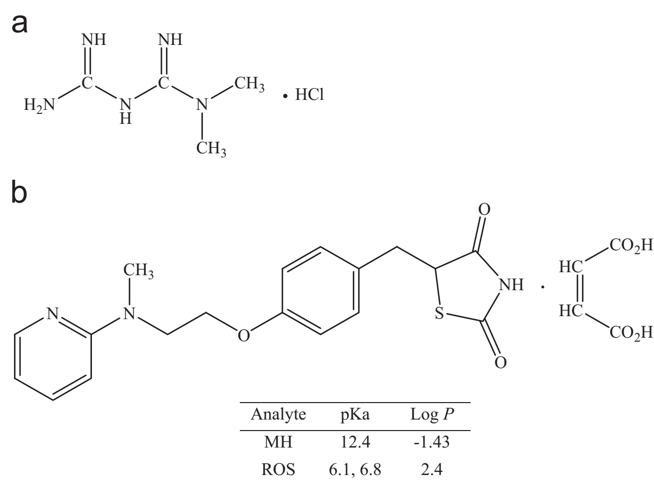

Analyte	pKa	Log P
MH	12.4	-1.43
ROS	6.1, 6.8	2.4

Fig. 1. Chemical structures, pKa and log P values of (a) metformin hydrochloride (MH) and (b) rosiglitazone (ROS).

coupled with nitrogen [28], flame ionization [29] or mass spectrometry (MS) detectors [30] for the analysis of MH was described. Capillary zone electrophoresis (CE) with UV detection [1,31–33] and MS [34] have also been reported.

Liquid–liquid extraction (LLE) [6,10,19,20,27], solid-phase extraction (SPE) [2,4,9,13,14,18,33] and protein precipitation [3,17,21,22,24–26,34] are the most widely used sample preparation technique for the analysis of ROS and MH in biological fluids. However, these techniques have many disadvantages as they usually require large volumes of high-purity solvents, multi-step and long extraction time which lead to analyte losses. To overcome these problems, microextraction techniques such as hollow fiber liquid phase microextraction (HF-LPME) has been used for the individual analysis of ROS [11,12] or MH [16] in biological fluids. The main advantages of the HF-LPME technique are fast, simple, inexpensive, low consumption of organic toxic solvents (only microliter volumes), no carry over due to the single use of the fiber and high enrichment factor. Also, the clean-up and pre-concentration of the analytes are done in a single step due to the small pore size of the hollow fiber membrane which act as a microfilter that eliminates interfering macromolecules and produce clean extracts that are suitable for direct instrumental analyses.

The simultaneous microextraction of ROS and MH is analytically challenging, if not impossible, due to the marked differences in their physical properties. Pertaining to extraction are the pKa and log P values of these drugs. MH is readily soluble in water, highly polar (log $P = -1.43$) and is strongly basic (pKa$=$12.4) while log P and pKa of ROS are 2.4 and 6.1, 6.8, respectively. Furthermore, MH is non-chromophoric. It is rationalized that in the absence of a simultaneous method for the microextraction, a sequential microextraction approach that extracts one drug, followed by the next one would also be worth considering. Since these two drugs had been individually extracted using the HF-LPME technique, the present studies is aimed at modifying and integrating these work for the sequential approach, that will eventually lead to the simultaneous HPLC determination.

2. Experimental

2.1. Chemicals and reagents

Metformin HCl (MH) and rosiglitazone maleate (ROS) reference standards were kindly donated by Hikma Pharmaceuticals (Amman, Jordan). Acetonitrile (HPLC-grade; 99.99%) was purchased from Fisher Scientific (Milwaukee, WI, USA). Methanol (HPLC-grade; $\geq$99.96%), hydrochloric acid (37%, w/w) were purchased from Merck (Darmstadt, Germany). *n*-Decane (99.0%) and *n*-tridecane (99.0%) were obtained from Acros Organics (Geel, Belgium). Pentafluorobenzoyl chloride (99.0%), Sodium hydroxide ($\geq$98.0%), dihexyl ether (97.0%), *n*-heptane (99.0%), *n*-hexadecane (99.0%) and nitrobenzene ($\geq$99.0) were purchased from Sigma-Aldrich (St. Louis, MO, USA). 1-Heptanol ($\geq$99.9%) and 1-octanol ($\geq$99.5%) were purchased from Fluka (Buchs, Switzerland). Phosphoric acid (85%) was purchased from Univar (Ingleburn, Australia). Ultrapure water (resistivity, 18.2 MΩ cm^{-1}) was produced by a Milli-Q system (Millipore, MA, USA). Blank plasma sample was kindly donated by Centre for Drug Research, Universiti Sains Malaysia, Penang. Human urine sample was obtained from a healthy student volunteer. Derivatizing solution was prepared by dilution 10 mg of Pentafluorobenzoyl chloride (PFBC) in 1 mL acetonitrile and stored at 4 °C until used.

2.2. Instrumentation

Chromatographic analyses were performed using a Hitachi LC-6200 intelligent pump (Tokyo, Japan) equipped with a Hewlett-Packard 1050 UV detector (Waldbronn, Germany). Sample injection was performed via a Rheodyne 7125 injection valve (Cotati, CA, USA) with a 5 μL loop. A PowerChrom data acquisition was obtained from eDAQ (Denistone East, Australia) and performed with PowerChrom software (version 2.7.2) to record and analyze the chromatographic data. The separation was obtained using a ODS Hypersil C18 column (250 × 4.6 mm, 5 μm). The mobile phase composition was a mixture of acetonitrile and 10 mM sodium phosphate buffer (pH 4.0) (60:40, v/v). The elution was performed under isocratic mode at a flow rate of 1.0 mL min^{-1}. The UV detection wavelength was set at 230 nm. Prior to the analysis, the mobile phase was filtered through nylon membrane filter (0.45 μm) from Agilent Technologies (Waldbronn, Germany) and degassed by ultrasonic bath for 15 min. For UV-scanning purpose, a Lambda 35 UV/vis system from Perkin Elmer (Waltham, MA, USA) was used. The extraction was performed using a 25 μL micro-syringe with a blunt needle tip (model 702SNR) and it was purchased from Hamilton (Reno, NV, USA). A multi-hotplate stirrer from DAIHAN scientific (Seoul, South Korea) was used for the stirring through the extraction process.

2.3. Preparation of stock standard solutions

ROS stock solution (1000 μg mL^{-1}) was prepared by dissolving the desired amount in acetonitrile, while MH stock solution (2000 μg mL^{-1}) was prepared in water. A mixture solution of ROS and MH (200 and 1000 μg mL^{-1}, respectively) was prepared by a proper dilution of the stock solutions in water and stored at 4 °C until use. Working standard solution was prepared daily by diluting the standard mixture in water as described in Section 2.5.

2.4. Minimizing the matrix effect of plasma and urine

In order to reduce the matrix effect of plasma sample, the following pretreatment steps have been conducted. 200 μL HCl (0.05 M) was added to the plasma sample (2 mL) spiked with standard mixture at the desired concentration. The sample mixture was vortex-mixed thoroughly for 30 s. The protein precipitation was accomplished by addition of acetonitrile (3 mL) and then the mixture was centrifuged at (1900 rpm) for 15 min. An aliquot of supernatant was collected and evaporated to dryness at 40 °C under gentle nitrogen stream. The dried residue was reconstituted with water as described in Section 2.5 for sequential HF-LPME analysis. In order to reduce the matrix effects (e.g., albumins,

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