NEW MICRO-SOLID PHASE EXTRACTION TECHNIQUES BASED ON MESOPOROUS MATERIALS FOR SELECTED ANTIBIOTIC AND ANTIFUNGAL AGENTS

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'Praise to Allah who created the heavens and the earth, and made the darkness and light' (al-An'am 1)

Specially dedicated to my beloved families.

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ABSTRACT

New microextraction techniques have been developed for sample preparation of azole drugs and penicillins in water, milk and biological samples prior to their liquid chromatographic determination. A microextraction method based on solid phase membrane tip extraction (SPMTE) incorporated with mesoporous silica, MCM-41, was developed for the determination of azole antifungal drugs, namely voriconazole (VRZ), ketoconazole (KTZ) and itraconazole (ITZ) in human plasma. Under the optimized conditions, the method demonstrated good linearity ($r^2 \geq 0.9958$) over a concentration range of 60 - 8000 μg L^{-1} with low limits of detection in the range of 20 - 40 μg L^{-1}. MCM-41-SPMTE required only minute amounts of adsorbent (3 mg) and desorption solvent (100 μL) and proved a successful extraction technique with high relative recoveries in the range of 82.5 - 111.0% for the analytes. MCM-41 was also employed as adsorbent in dispersive micro-solid phase extraction (D-μ-SPE) of six azole antifungal drugs including VRZ, KTZ, miconazole (MCZ), clotrimazole (CTZ), fluconazole (FLZ) and econazole (ECZ). The optimized D-μ-SPE was successfully applied to the determination of azole drugs in urine and human plasma. The method showed good linearity ($r^2 \geq 0.9900$) over a concentration range of 0.1 - 10000 μg L^{-1}, excellent limits of detection in the range of 0.001 - 1.500 μg L^{-1} and good relative recoveries in the range of 80.9 - 116.8%. A D-μ-SPE method incorporating new mesoporous carbon COU-2 as adsorbent was developed for the determination of three penicillins in water and milk samples. Under the optimized conditions, COU-2-D-μ-SPE showed excellent limits of detection in the range of 0.06 - 3.3 μg L^{-1} for oxacillin, cloxacillin and dicloxacillin with good linearity ($r^2 \geq 0.9992$) in the concentration range of 0.1 - 5000 μg L^{-1} and good relative recoveries (80.3 - 113.6%). COU-2-D-μ-SPE is beneficial in terms of solvent saving, simplified analytical procedure and rapid extraction. The surface of COU-2 was further modified by functionalization with vinyl group to improve the extraction of target azole antifungal drugs by increasing the hydrophobicity of the adsorbent. Vinyl-COU-2 was used as adsorbent in D-μ-SPE (Vinyl-COU-2-D-μ-SPE) for the determination of azole antifungal drugs in water and biological samples. Excellent limits of detection (0.4 - 1.6 μg L^{-1}) were obtained for KTZ and ITZ, respectively, with good linearity ($r^2 \geq 0.9959$) in the concentration range of 1 - 400 μg L^{-1}. The method provided high enrichment factors up to 92 with excellent relative recoveries in the range of 89.8 - 113.9% for both analytes. The developed microextraction techniques combined with liquid chromatography have proved to be simple, rapid and efficient with performances that are superior to those of conventional methods and suitable for the determination of azole drugs and penicillins in water, milk and biological samples.

ABSTRAK

Teknik pengekstrakan mikro baharu telah dibangunkan untuk penyediaan sampel ubat azol dan penisilin di dalam sampel air, susu dan biologi sebelum penentuan kromatografi cecair. Kaedah pengekstrakan mikro berdasarkan pengekstrakan muncung membran fasa pepejal (SPMTE) bergabung dengan silika mesoliang, MCM-41, telah dibangunkan bagi penentuan ubat anti-kulat azol iaitu vorikonazol (VRZ), ketokonazol (KTZ) dan itrakonazol (ITZ) di dalam plasma manusia. Di bawah keadaan optimum, kaedah ini menunjukkan kelinearan yang baik ($r^2 \geq 0.9958$) bagi julat kepekatan 60 - 8000 µg L^{-1} dengan had pengesanan rendah dalam julat 20 - 40 µg L^{-1}. MCM-41-SPMTE hanya memerlukan sedikit amaun penjerap (3 mg) dan pelarut penyaherapan (100 µL) dan telah dibuktikan sebagai teknik pengekstrakan berjaya dengan pengembalian relatif yang tinggi dalam julat 82.5 - 111.0% bagi analit tersebut. MCM-41 juga telah digunakan sebagai penjerap dalam pengekstrakan mikro fasa pepejal serakan (D-µ-SPE) bagi enam ubat anti-kulat azol termasuk VRZ, KTZ, mikonazol (MCZ), klotrimazol (CTZ), flukonazol (FLZ) dan ekonazol (ECZ). Keadaan optimum D-µ-SPE telah berjaya digunakan bagi penentuan ubat anti-kulat azol di dalam urin dan plasma manusia. Kaedah ini menunjukkan kelinearan yang baik ($r^2 \geq 0.9900$) bagi julat kepekatan 0.1 - 10000 µg L^{-1}, had pengesanan cemerlang dalam julat 0.001 - 1.500 µg L^{-1} dan pengembalian relatif yang baik diperoleh di dalam julat 80.3 - 116.8%. Kaedah D-µ-SPE bergabung dengan karbon mesoliang baharu COU-2 sebagai penjerap telah dibangunkan bagi penentuan tiga penisilin di dalam sampel air dan susu. Di bawah keadaan optimum, COU-2-D-µ-SPE menunjukkan had pengesanan yang cemerlang dalam julat 0.06 - 3.3 µg L^{-1} bagi oksasilin, kloksasilin dan dikloksasilin dengan kelinearan yang baik ($r^2 \geq 0.9992$) dalam julat kepekatan 0.1 - 5000 µg L^{-1} dan pengembalian relatif yang baik (80.3 - 113.6%). COU-2-D-µ-SPE memberi kelebihan daripada segi penjimatan pelarut, prosedur analisis yang ringkas dan pengekstrakan pantas. Permukaan COU-2 telah diubahsuai dengan penambahan kumpulan berfungsi vinil untuk meningkatkan pengekstrakan ubat anti-kulat azol sasaran dengan meningkatkan sifat hidrofobik penjerap. Vinil-COU-2 digunakan sebagai penjerap dalam D-µ-SPE (Vinil-COU-2-D-µ-SPE) bagi penentuan ubat anti-kulat azol di dalam sampel air dan biologi. Had pengesanan yang cemerlang (0.4 - 1.6 µg L^{-1}) telah diperoleh bagi KTZ dan ITZ dengan kelinearan yang baik ($r^2 \geq 0.9959$) dalam julat kepekatan 1 - 400 µg L^{-1}. Kaedah ini menghasilkan faktor pemerkayaan yang tinggi sehingga 92 dengan pengembalian relatif yang cemerlang dalam julat 89.8 - 113.9% bagi kedua-dua analit. Teknik pengekstrakan mikro yang dibangunkan bergabung dengan kromatografi cecair terbukti sebagai mudah, cepat dan cekap dengan prestasi yang lebih baik berbanding kaedah konvensional dan sesuai digunakan bagi penentuan ubat azol dan penisilin di dalam sampel air, susu dan biologi.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

µ-SPE	-	Micro solid phase extraction
AIDS	-	Acquired immunodeficiency syndrome
AU	-	Arbitrary Unit
BET	-	Brunauer Emmet Teller
BJH	-	Barrett Joyner Halenda
CE	-	Capillary Electrophoresis
CLOX	-	Cloxacillin
CMC	-	Critical micelle concentration
CMK-1	-	Carbon molecular sieve
COU-2	-	Carbon Osaka University 2
CSM-LPME	-	Cone-shaped membrane protected liquid phase microextraction
CTABr	-	Cetyltrimethylammonium bromide
CTZ	-	Clotrimazole
D-µ-SPE	-	Dispersive micro-solid phase extraction
DAD	-	Diode array detector
DBP	-	Dibutyl phthalate
DICLOX	-	Dicloxacillin
DI-SDME	-	Direct immersion single drop microextraction
DLLME	-	Dispersive liquid-liquid microextraction
DSPE	-	Dispersive solid phase extraction
EIC	-	Extracted ions chromatogram
EU	-	European Union
FDA	-	Food and Drug Administration
FE-SEM	-	Field emission scanning electron microscope

FID	-	Flame ionization detector
FLZ	-	Fluconazole
FTIR	-	Fourier transform infrared
GC	-	Gas chromatography
HF-LPME	-	Hollow fiber liquid phase microextraction
HLB	-	Hydrophilic and lipophilic balance
HPLC	-	High performance liquid chromatography
HS-SDME	-	Head space single drop microextraction
I.D.	-	Internal diameter
ICP-OES	-	Inductively coupled plasma optical emission spectroscopy
ITZ	-	Itraconazole
IUPAC	-	International Union of Pure and Applied Chemistry
KH_2PO_4	-	Potassium dihydrogen phosphate
KTZ	-	Ketoconazole
LCT	-	Liquid crystal template
LLE	-	Liquid-liquid extraction
LLOQ	-	Lower limit of quantification
LOD	-	Limit of detection
LOQ	-	Limit of quantification
LPME	-	Liquid phase microextraction
MAE	-	Microwave-assisted extraction
MAX	-	Mixed mode anion exchanger
MCM-41	-	Mobil composition of matter no. 41
MCM-48	-	Mobil composition of matter no. 48
MCZ	-	Miconazole
MEPS	-	Microextraction in packed syringe
ME	-	Matrix effect
MIP	-	Molecularly imprinted polymer
MM-CPE	-	Mixed micelle-cloud point extraction
MRL	-	Maximum residue limit
MS	-	Mass spectrometry

MS/MS	-	Tandem mass spectrometry
NaCl	-	Sodium chloride
NH_4OH	-	Ammonium hydroxide
OXA	-	Oxacillin
PDMS	-	Polydimethylsiloxane
PEG	-	Polyethylene glycol
PP	-	Polypropylene
RSD	-	Relative standard deviation
SBA-15	-	Santa Barbara Amorphous No. 15
SBSE	-	Stir bar sorptive extraction
SDME	-	Single drop microextraction
SFE	-	Supercritical fluid extraction
SFODME	-	Solidification of floating organic dispersive liquid-liquid extraction
SPE	-	Solid phase extraction
SPME	-	Solid phase microextraction
SPMTE	-	Solid phase membrane tip extraction
TEOS	-	Tetraethyl orthosilicate
TIC	-	Total ions chromatogram
UESA-DLLME	-	Ultrasound-enhanced surfactant-assisted dispersive liquid-liquid microextraction
UV	-	Ultraviolet
Vinyl-COU-2	-	Vinyl functionalized carbon Osaka University-2
VRZ	-	Voriconazole

LIST OF SYMBOLS

%	-	Percent
°	-	Degree
°C	-	Degree celcius
µg kg^{-1}	-	Microgram per kilogram
µg L^{-1}	-	Microgram per liter
µg mL^{-1}	-	Microgram per milliliter
µL	-	Microliter
Å	-	Angstrom
cm^3g^{-1}	-	Centimeter cubed per gram
CO_2	-	Carbon dioxide
eV	-	Electronvolt
g	-	Gram
g/mol	-	Gram per mol
h	-	Hour
Log *P*	-	Partition coefficient
m/z	-	Mass to charge ratio
m^2g^{-1}	-	Meter square per gram
Mg	-	Milligram
Min	-	Minute
mL	-	Milliliter
Mm	-	Millimeter
MΩ	-	Megaohm
N	-	Number of replicate
N_2	-	Nitrogen
Ng	-	Nanogram

ng g^{-1}	-	Nanogram per gram
pg/g	-	Picogram per gram
pK_a	-	Acid dissociation constant
ppb	-	Part per billion
r^2	-	Coefficient of determination
rpm	-	Rotation per minute
s	-	Second
v/v	-	Volume per volume
w/v	-	Weight per volume

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

1.1 Research Background

Sample preparation is crucial to isolate the desired analytes from the sample matrix. This step also includes “clean up” procedures for very “dirty” and complex samples that instruments cannot handle directly. In addition, the sample preparation could concentrate analytes, improve sensitivity and reduces cost for instruments maintenance. Sample preparations are very commonly carried out using conventional extraction methods such as liquid-liquid extraction (LLE) and solid phase extraction (SPE) to isolate, extract and concentrate target analytes. However, LLE are time consuming, labour-intensive and multi-stage operations. SPE has significant improvement over LLE by minimizing the consumption of chemicals and disposal cost of organic wastes. Nevertheless, SPE suffers from a few drawbacks; it requires a large volume of elution solvent and the ease with which the adsorbent pores are blocked by matrix. In addition, time-consuming multi-step process in SPE may cause analyte loss especially for volatile compounds.

In order to solve the problems related to the conventional sample preparations methods, researches have been devoted to the development of miniaturized sample preparation which resulted in significant solvent and sample savings. Likewise, these approaches have improved the efficiency of sample enrichment, offer faster sample preparation and easier automation. These relatively new techniques include liquid phase microextraction (LPME) (Navarro *et al.*, 2013), dispersive liquid-liquid microextraction (DLLME) (Suh *et al.*, 2013) and adsorbent-based micro extractions

such as solid phase microextraction (SPME) (Cavaliere *et al.,* 2012), stir bar sorptive extraction (SBSE) (Maggi *et al.,* 2008) and dispersive solid phase extraction (DSPE) (Guan *et al.,* 2013). The main drawbacks of SPME are the preparation of fibers that requires very high-priced equipment, which contributes to the high price of commercially available SPME fibers. Furthermore, the fibers are fragile and must be handled with special care (Dalia *et al.,* 2005). As for SBSE, a few forms of SBSE coatings are commercially available including polydimethylsiloxane (PDMS) and PDMS-activated carbon (Montero *et al.,* 2004; Bicchi *et al.,* 2005) and more recently available, polar extracting phase, poly(ethylene glycol) (PEG) (Bratkowska *et al.,* 2012). The extraction interactions of most of these coatings are more suitable for non-polar and weak polar compounds, although polar compounds could be extracted by derivatization (Mao *et al.,* 2012).

The applications of mesoporous materials in sample preparation are rapidly increasing due to their interesting characteristics such as high surface area, large pore volume, tunable mesoporous channels, well-defined pore-size distribution, controllable wall composition and modifiable surface properties (Zhao *et al.,* 2012a).

This work focuses on the development of new microextraction techniques based on mesoporous materials and their applications to the analysis of water, milk and biological samples. New types of adsorbent are synthesized for use in solid phase membrane tip extraction (SPMTE) and dispersive micro-solid phase extraction (D-μ-SPE). The performances of the mesoporous materials were evaluated by determining selected model compounds of azole antifungals and penicillins in aqueous solution including complex matrices such as milk and biological samples.

1.2 Background of the Problem

Complex matrices such as biological samples usually contain proteins, salts, acids, bases and organic compounds with identical properties of the analytes. Besides, the analytes usually exist at low or trace level concentrations in the samples

(Kataoka, 2003). Because of this, sample preparations are necessary to improve the detection of the analytes by extraction and preconcentration techniques.

Regardless of the advances in separation and quantitation technologies, most of sample preparation procedures are based on conventional extraction methods such as liquid-liquid extraction (LLE), solid phase extraction (SPE), supercritical fluid extraction (SFE), microwave assisted extraction (MAE), etc. LLE faces several limitations such as large volume consumption of organic solvent, labor-intensive and high-cost operations. Although SPE has reduced many limitations in LLE, the main drawback for SPE is the multi-step procedures which can result in loss of analytes especially volatile compounds. Major problems related to SFE are the poor robustness of the system to maintain high-pressure delivery system and high purity of carbon dioxide. In addition, most of the organic solvents used in MAE may be dangerous to the operators and may result in environment pollution (Wang *et al.*, 2003).

1.3 Problem Statement

In order to overcome the above problems, many researchers have recently focused on the development of simple, rapid, efficient, economical and miniaturized sample preparation methods. Microextraction is defined as an extraction method where the volume of extracting phase is very small in relation to the volume of the sample and extraction of analytes is not exhaustive (Lord and Pawliszyn, 2000). Microextraction offers the unique advantages of high enrichment factor of analytes, sample and solvent savings, faster and efficient analysis per sample and the extraction is based on an equilibrium mechanism.

In-line with the environmental concerns and green chemistry, sample preparation methods that are environmentally friendly and economical are preferable for any analytical procedure. This study was set out to investigate new microextraction methods namely solid phase membrane tip extraction (SPMTE) and

dispersive micro-solid phase extraction (D-μ-SPE) incorporated with mesoporous materials for the determination of selected azole antifungal and penicillin drugs in water, milk and biological samples. SPMTE and D-μ-SPE require only minute amounts (microliter) of organic solvents for desorption which may contribute to green chemistry by producing less toxic wastes.

1.4 Research Objectives

The objectives of the study are as follows:

- To develop and apply mesoporous silica Mobil Composition Matter, MCM-41 solid phase membrane tip extraction (MCM-41-SPMTE) coupled with high performance liquid chromatography-ultra violet detector (HPLC-UV) for the analysis of selected azole antifungal drugs in human plasma sample.

- To develop and apply MCM-41 dispersive micro-solid phase extraction (MCM-41-D-μ-SPE) coupled with liquid chromatography-tandem mass spectrometry (LC-MS/MS) for the analysis of selected azole antifungal drugs in urine and human plasma samples.

- To develop and apply mesoporous carbon Carbon Osaka University, COU-2 dispersive micro-solid phase extraction (COU-2-D-μ-SPE) coupled with HPLC-UV for the analysis of selected penicillins in drinking water and commercial milk samples.

- To develop and apply vinyl-functionalized mesoporous carbon, vinyl-COU-2 dispersive micro-solid phase extraction (vinyl-COU-2-D-μ-SPE) coupled with HPLC-UV for the analysis of selected azole antifungal drugs in tap water, urine and plasma samples.

1.5 Scopes of the Study

Development and application of adsorbent based microextraction methods were investigated. Several important extraction parameters were optimized comprehensively and analytical performances of the developed method were evaluated in the study. MCM-41-SPMTE and MCM-41-D-μ-SPE methods were demonstrated to extract selected azole antifungal drugs in human plasma using HPLC-UV and LC-MS/MS. COU-2-D-μ-SPE was performed for the extraction of three penicillins namely OXA, CLOX and DICLOX in drinking water and milk samples. Several extraction parameters were explored and the newly synthesized adsorbent was compared with commercial activated carbons for CLOX analysis. The applicability of COU-2 to the analysis of weakly basic drugs and hydrophobic compounds were evaluated by functionalizing the surface with vinyl group, vinyl-COU-2-D-μ-SPE and the method was used in the extraction of azole antifungal drugs from aqueous sample. Several extraction parameters were optimized and the optimum conditions were applied to the analysis of water, milk and biological samples.

This study investigates the synthesis and applications of MCM-41 and COU-2 for the determination of selected azole antifungals and penicillins in aqueous samples. This work consists of seven chapters. Chapter 1 provides an overview of the study while Chapter 2 compiles the classification of azole antifungal and penicillin drugs with its analytical determination, introduction to conventional extraction and microextraction methods, potential microextraction methods of azole antifungal and penicillin drugs and last but not least the applications of mesoporous materials and organo-functionalized mesoporous materials in sample preparation.

Chapter 3 focuses on the application of MCM-41 incorporated with SPMTE coupled HPLC-UV for the determination of selected azole antifungal drugs in human plasma. Several important parameters namely, conditioning solvent, extraction time, desorption time, salt addition, sample pH, sample volume and desorption solvent were optimized. The separations and quantification of azole antifungal drugs namely

voriconazole (VRZ), ketoconazole (KTZ) and itraconazole (ITZ) were carried out on a Zorbax C_{18} column using HPLC-UV.

Chapter 4 describes the application of MCM-41 in the microextraction method termed D-μ-SPE coupled to LC-MS/MS for the determination of selected azole antifungal drugs in plasma and urine samples. Several important extraction parameters namely, desorption solvent, sample pH, salt addition, extraction time, desorption time and mass of adsorbent were optimized. The separations and quantification of six azole antifungal drugs (VRZ, KTZ, miconazole (MCZ), econazole (ECZ), clotrimazole (CTZ) and fluconazole (FLZ)) were carried out on a Zorbax C_{18} column using LC-MS/MS.

Chapter 5 reports the application COU-2 as an extraction adsorbent in D-μ-SPE coupled to HPLC-UV was investigated for the determination of β-lactam (penicillin) drugs in drinking water and milk samples. Several important extraction parameters namely, types of adsorbent, desorption solvent, sample pH, salt addition, desorption time and mass of adsorbent were optimized. The separation and quantification of three penicillins (oxacillin (OXA), cloxacillin (CLOX) and dicloxacillin (DICLOX)) was studied on a Zorbax C_{18} stationary phase in HPLC-UV.

Chapter 6 describes the application of vinyl-COU-2 as adsorbent in D-μ-SPE coupled to HPLC-UV for the determination of selected azole antifungal drugs in water and biological samples. Several important extraction parameters namely, types of adsorbent, desorption solvent, sample pH, salt addition, extraction time, desorption time and mass of adsorbent were optimized. The separations and quantification of two azole antifungal drugs (KTZ and ITZ) were carried out on a Zorbax C_{18} column using HPLC-UV.

Finally, Chapter 7 covers the overall conclusions and future directions for further studies. This chapter compiles the overall results obtained including the optimized conditions and the analytical performances of the developed methods. Future directions are presented and discussed for possible further study.

1.6 Significance of the Study

SPMTE has several important advantages in terms of fast extraction, minimum solvent consumption, low cost, simplicity, high sensitivity and precisions (See *et al.,* 2010). D-μ-SPE has been introduced to shorten the extraction time and simplify the SPE by expediting the analytes to interact equally with the adsorbent particles and thus achieving greater capacity per mass of adsorbent. Furthermore, D-μ-SPE avoids channelling or blocking that commonly occurs in conventional SPE cartridges or disk (Fu *et al.,* 2012). All these microextraction techniques reported here for the first time are incorporated with mesoporous materials, MCM-41 and COU-2 are rapid, simple, easy to use and perform, and inexpensive. Thus, they have great potential as alternative sample preparation methods to conventional sample preparation that also provide excellent and rapid sample clean-up for water, milk and biological samples.

MCM-41-D-μ-SPE method combined with LC-MS/MS detection provided high sensitivity with acceptable reproducibility and recoveries. The new idea of incorporating mesoporous materials with magnetite nanoparticles could simplify the conventional collection procedure in D-μ-SPE by eliminating centrifugation or filtration step in the extraction. This technique would be interesting alternative for rapid and fast analysis of target analytes. In addition, the current method should be applied to real-world biological samples or samples obtained from patients that have been administered with the selected drugs.

A new dispersive micro-solid phase extraction (D-μ-SPE) method incorporating mesoporous carbon, COU-2 was successfully developed for the extraction of selected penicillins in drinking water and milk samples. The COU-2-D-μ-SPE method was rapid, efficient and simple. A logical extension of the current work that would be the development of a fully automated D-μ-SPE in order to enhance the ease and simplicity of the method. Furthermore, other samples such as chicken muscle could be of interest for future directions.

Finally, this work has successfully developed a new extraction method termed vinyl functionalized COU-2 dispersive micro-solid phase extraction (vinyl-COU-2-D-μ-SPE) for the extraction of azole antifungal drugs in water and biological samples. The current method was developed with non-polar functionalization (vinyl) on the COU-2 surface to increase the hydrophobic characteristic of COU-2. In order to expand the horizon of microextraction methods, future work could investigate the possibility of functionalization of COU-2 with hydrophilic functional group to facilitate the rapid extraction of hydrophilic compounds. In such cases, the functional group chosen should be medium in polarity to avoid hydrophobic analytes from strongly retained on the carbon surface.

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