CHIRAL SEPARATION OF KETOCONAZOLE AND ITRACONAZOLE ANTI-FUNGAL DRUGS USING EXPERIMENTAL AND COMPUTATIONAL APPROACHES

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DEDICATION

In the loving memory of my late father, Arsad Dolah, my strength and my biggest influence in my life. My mother Rafeah Deraman, and my husband Ibrahim Bidin who is always supportive and patiently waiting for me to complete this thesis. I dedicate this thesis to all of you.

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ABSTRACT

Drugs with multiple chiral centers were observed as very effective for treating various diseases. However, the enantiomeric resolution of multiple chiral center racemates is not much developed compared to racemates having a single asymmetric center. This work aimed to develop a chiral separation method for antifungal drugs using electrokinetic chromatography (EKC) and to elucidate mechanism of enantioseparation using a computer-aided molecular modelling study. Two azole antifungal drugs were selected namely ketoconazole and itraconazole, which consists of two and three chiral centers, respectively. The separation for ketoconazole was achieved using heptakis (2,3,6-tri-*O*-methyl)-β-cyclodextrin (TM-β-CD), a commonly used chiral selector, as it is relatively inexpensive and has a low UV absorbance in addition to an anionic surfactant, sodium dodecyl sulfate. The optimum conditions for chiral separation of ketoconazole was achieved using 10 mM phosphate buffer at pH 2.50 containing 20 mM TM-β-CD, 5 mM SDS, and 1.0% (v/v) methanol with an applied voltage of 25 kV at 25°C with a 5-s hydrodynamic injection time at 50 mbar. The four ketoconazole stereoisomers were successfully resolved within 17 min (total analysis time was 28 min including capillary conditioning). The migration time precision of this method was examined to give a repeatability and reproducibility with RSDs $\leq$ 5.80% (n = 3) and RSDs $\leq$ 8.88% (n = 9), respectively. A computational study, using quantum mechanics calculations with AutoDock and semi-empirical PM3 calculations, were used to predict the enantiodiscrimination of ketoconazole enantiomers. A Density Functional Theory (DFT) single-point calculation at the level of B3LYP/6-311G (d,p) was performed for the PM3-optimized complexes to obtain more accurate binding energy and also electronic structures of the complexes. Molecular docking and DFT were simulated to predict the enantioresolution of itraconazole with two types of cyclodextrins (CDs), TM-β-CD and (2-hydroxylpropyl)-γ-cyclodextrin (HP-γ-CD). The difference in energies of the inclusion complexes between the enantiomers and CD is a measure of chiral discrimination, which results in the separation of the enantiomers in the experimental studies. The dual-CD and triple-CD methods were developed for chiral separation of itraconazole using EKC. Highly sulfated β-cyclodextrin (S-β-CD), (2-hydroxylpropyl)-β-cyclodextrin (HP-β-CD), TM-β-CD and HP-γ-CD were screened as possible chiral selectors for enantioseparation of itraconazole. The enantioseparation of itraconazole was achieved using 10 mM phosphate buffer solution at pH 3.62 containing a mixture of 10 mM of each HP-β-CD, TM-β-CD and HP-γ-CD and an applied voltage of 25 kV at 25°C. Both computational and experimental investigations complement each other prior to chiral recognition mechanism. Combination of molecular modelling and capillary electrophoresis appears as a new emerging method for chiral analysis of pharmaceutical drugs.

ABSTRAK

Dadah dengan beberapa pusat kiral telah diamati sangat berkesan untuk merawat pelbagai penyakit. Walau bagaimanapun, resolusi enantiomer rasemat dengan pusat kiral berganda tidak banyak dibangunkan berbanding dengan rasemat yang mempunyai pusat asimetri tunggal. Kajian ini bertujuan untuk membangunkan kaedah pemisahan kiral bagi dadah antikulat menggunakan kromatografi elektrokinetik (EKC) dan menentukan mekanisme enantiopemisahan menggunakan kajian pemodelan molekul berbantukan komputer. Dua dadah antikulat azol telah dipilih iaitu ketokonazol dan itrakonazol, masing-masing mempunyai dua dan tiga pusat kiral. Pemisahan ketokonazol berjaya diperoleh menggunakan (2,3,6-tri-*O*-metil)-β-siklodekstrin (TM-β-CD), satu pemisah kiral yang biasa digunakan kerana ia relatif tidak mahal dan mempunyai keserapan UV yang rendah sebagai tambahan kepada surfaktan anion, natrium dodesil sulfat (SDS). Keadaan optimum bagi pemisahan kiral ketokonazol telah diperoleh menggunakan larutan penimbal fosfat 10 mM pada pH 2.50 yang mengandungi 20 mM TM-β-CD, 5 mM SDS, dan 1.0% (v/v) metanol pada voltan gunaan 25 kV pada 25°C dengan masa suntikan hidrodinamik 5-s pada 50 mbar. Empat stereoisomer ketokonazol berkenaan telah berjaya dipisahkan sepenuhnya dalam masa 17 min (jumlah masa analisis ialah 28 min termasuk pengkondisian kapilari). Kepresisan masa migrasi kaedah ini telah dikaji untuk memberi keterulangan dan kebolehulangan dengan masing-masing RSDs $\leq$ 5.80% (n = 3) dan RSDs $\leq$ 8.88% (n = 9). Satu kajian komputeran menggunakan pengiraan mekanik kuantum dengan AutoDock dan pengiraan semi-empirik PM3 telah digunakan untuk meramalkan enantiodiskriminasi ketokonazol. Pengiraan titik tunggal Teori Fungsi Ketumpatan (DFT) pada tahap B3LYP/6-311G (d,p) telah dilakukan daripada kompleks PM3 yang dioptimumkan untuk mendapatkan tenaga ikatan dan struktur elektronik kompleks tersebut yang lebih tepat. Dok molekul dan DFT telah disimulasikan untuk meramalkan enantioresolusi itrakonazol dengan menggunakan dua jenis siklodekstrin (CD), TM-β-CD dan (2-hidroksilpropil)-γ-siklodekstrin (HP-γ-CD). Perbezaan tenaga kompleks rangkuman antara enantiomer dan CD adalah ukuran diskriminasi kiral, yang menghasilkan pemisahan enantiomer dalam kajian eksperimen. Kaedah dwi-CD dan tri-CD telah dibangunkan untuk pemisahan kiral itrakonazol menggunakan EKC. β-siklodekstrin yang sangat tersulfat (S-β-CD), (2-hidroksilpropil)-β-siklodekstrin (HP-β-CD), TM-β-CD dan HP-γ-CD telah disaringkan sebagai pemilih kiral yang mungkin untuk pemisahan enantiomer itrakonazol. Pemisahan enantiomer itraconazol telah dicapai menggunakan larutan penimbal fosfat 10 mM pada pH 3.62 mengandungi campuran HP-β-CD, TM-β-CD dan HP-γ-CD, setiap satu 10 mM dan voltan gunaan 25 kV pada 25°C. Kedua-dua penyiasatan komputeran dan eksperimen saling melengkapkan antara satu sama lain sebelum mekanisme pengecaman kiral. Gabungan pemodelan molekul dan elektroforesis kapilari muncul sebagai kaedah baharu bagi analisis kiral dadah farmaseutikal.

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LIST OF ABBREVIATIONS

BGE	-	Background electrolyte
CD	-	Cyclodextrin
TM-β-CD	-	Heptakis-(2,3,6-tri-*O*-methyl)-β-cyclodextrin
HP-β-CD	-	Hydroxylpropyl-β-cyclodextrin
HP-γ-CD	-	Hydroxylpropyl-γ-cyclodextrin
CD-EKC	-	Cyclodextrin-modified electrokinetic chromatography
CE	-	Capillary electrophoresis
CMC	-	Critical micelle concentration
CZE	-	Capillary zone electrophoresis
DAD	-	Diode-array detection
DFT	-	Density functional theory
EKC	-	Electrokinetic chromatography
EOF	-	Electroosmotic flow
GC	-	Gas chromatography
HPLC	-	High-performance liquid chromatography
MEKC	-	Micellar electrokinetic chromatography
PM3	-	Parameterized model number 3
SDS	-	Sodium dodecyl sulphate
SFC	-	Supercritical fluid chromatography
SPE	-	Solid-phase extraction
UV	-	Ultraviolet

LIST OF SYMBOLS

Å	-	Armstrong
α	-	Alpha
β	-	Beta
°C	-	Degree Celsius
Δ	-	Delta
γ	-	Gamma
µA	-	Micro ampere
µL	-	Micro litre
g	-	Gram
g/mol	-	Gram per mole
i.d.	-	Inner diameter
kV	-	Kilovolts
mg	-	Milligram
min	-	Minutes
µg/mL	-	Microgram per millilitre
mL/min	-	Millilitre per minute
mmol	-	Millimole
pKa	-	Acid dissociation constant
ppm	-	Part per million
R_s	-	Peak resolution
r^2	-	Coefficient of determination
rpm	-	Rotation per minute
s	-	Second
t_m	-	Migration time
v/v	-	Volume per volume

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CHAPTER 1

INTRODUCTION

1.1 Research Background

Over the last 50 years drug stereochemistry has become a significant issue for both the pharmaceutical industry and the regulatory authorities since the problems associated with drug stereochemistry are complex. Many pharmaceutical drugs are known to be a racemic mixture. Such mixtures are regarded by some as ‘compounds containing 50% impurity’ which sometimes can cause toxic effects to the patients (Hutt and O’Grady, 1996). Since then, most of the top selling drug companies around the world are administered as single enantiomers that is worth of the desired physiological activity. Thus the development of methods for the production of enantiomerically pure compounds and the assessment of their enantiomeric purity have become more and more important specially in life science applications, such as biochemical, toxicological, forensic and pharmaceutical research. The development of single-enantiomer drugs is preferred because of the reduced risk of side effects.

In the last two decades, the incidence of serious fungal infections has grown dramatically due to the increase of risk groups: the advent of human immunodeficiency virus (HIV) or undergoing anticancer chemotherapy or the increased use of immunosuppressive therapies in organ transplantation (Thienpont *et al*., 1999; Crego *et al*., 2001; Castro-Puyana *et al*., 2005). Amphotericin B (Fungizone) is a conventional topical antifungal drug was used to treat fungal infections. However, this drug is associated with significant toxicity, including infusion-related events, such as chills, fever, headache, nausea and vomiting (Saag and Dismukes, 1988). The availability of the azole antifungal agents represents a major advancement in the management of systemic fungal infections as they present low toxicity. Ketoconazole and itraconazole antifungal drugs have become frequently used as alternatives to Amphotericin B since they have versatility of

administration and a broad spectrum (Rotstein *et al*., 1992; Ahmed *et al*., 1998; Dilmaghanian *et al*., 2004). However, since these two azoles are chiral compounds, they also are not free from adverse side effects due to different properties of stereoisomers. Therefore, it is important to promote the chiral separation for chiral ketoconazole and itraconazole antifungal drugs in order to eliminate the unwanted isomer. The structures of these two azoles used in the study use are shown in Figure 1.1. Ketoconazole and itraconazole consists of multiple chiral centers with two and three chiral centers, respectively.

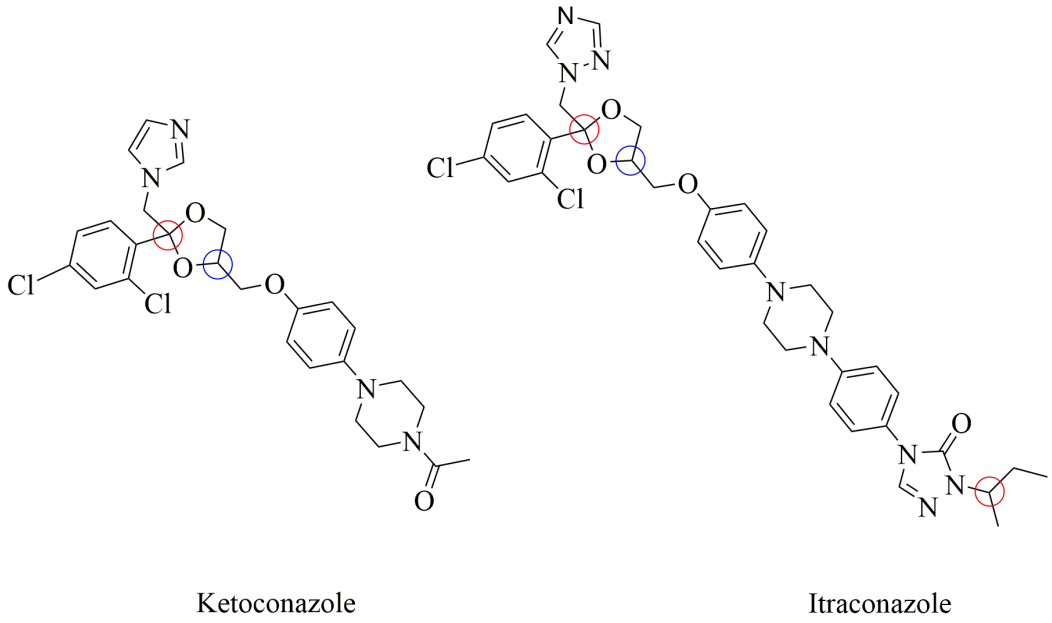

Figure 1.1 Structures of antifungal azole compounds, ketoconazole and itraconazole

Enantiomeric resolution becomes more challenging when dealing with multichiral center racemates since it is very difficult to find the identical properties of the enantiomers (Ali *et al*., 2016). However, this challenge may be tackled by a versatile capillary electrophoresis (CE) technique which has rapidly attracted attention as a promising technique for enantioseparation due to its high separation efficiency and flexibility (Terabe and Otsuka 1994; Nishi and Terabe 1995). One of the most attractive advantages of CE for the separation of enantiomers is easy changes of separation media in the method development, that is, one can easily alter

the separation solution to find the optimum separation media and one can also use an expensive chiral selector because of the small amounts of media required (Nishi, 1996). Chiral separation using CE also do not require a chiral stationary phase (CSP) like in HPLC since the chiral selectors can be directly added into the background electrolyte (BGE) to provide a chiral environment and form enantiomer-chiral selector complexes with analytes (Li *et al*., 2015a).

Mechanistic aspect of enantioseparation becomes interesting since it may provide valuable information such as prediction of elution order, appropriate chromatographic conditions and types of analytes separable with a given selector (Maier *et al.*, 2001). Additionally, it is desirable to obtain the structural models that explain the binding forces in chiral recognition to understand qualitatively the mechanism of enantioseparation. Computational investigations concerning chiral recognition of ketoconazole and itraconazole with cyclodextrins (CDs) have been performed to get further insight into the mechanism involved.

Molecular modelling might be used as a supportive tool to enhance our understanding of chiral recognition. Molecular docking approaches proved to be very useful for the evaluation of chiral recognition systems. Molecular docking is aimed at explaining possible chiral recognition mechanism between the selected antifungal drugs and CDs as chiral selector. Furthermore, the computational tools employed in molecular modelling such as quantum mechanics and molecular mechanics have reached high level of sophistication allowing prediction of intermolecular binding scenarios between molecules (Maier *et al.*, 2001).

1.2 Problem Statement

Currently, the separation of the enantiomers of a chiral compound with a single center of chirality is no more the issue since tremendous researches have shown an excellent separation in separating compounds with a single chiral center. However, the separation of enantiomers with multiple chiral centers becomes more challenging since it is very difficult to choose suitable chiral selectors that have the ability to differentiate several chiral centers simultaneously.

A variety of chiral selectors are available for chiral separation such as crown ethers, CDs, macrocyclic antibiotic and chiral surfactant. Among these chiral selectors, CDs offer great advantages in chiral separation as they can differ in selectivity of the enantiomers. Besides, CDs are commercially available at a cheaper price compared to macrocyclic antibiotic such as vancomycin. The application of CDs as chiral selector in CE has made CE a feasible technique for the separation of a large number of chiral compounds including azole antifungal drugs.

Previously, studies on ketoconazole (Castro-Puyana *et al*., 2005) and itraconazole (Castro-Puyana *et al*., 2006) antifungal drugs with multiple chiral centers were performed with single CDs using CE. However, only half of the stereoisomers were successfully resolved. Therefore, in order to improved and enhanced the resolution of stereoisomers of ketoconazole and itraconazole drugs, modifications in BGE solution was performed such as addition of surfactant and the use of dual and triple CDs.

Even though CE can offers a great advantage that is easy to choose a number of chiral selectors for chiral separation, however, the screening of suitable chiral selectors is a time consuming (Jimidar *et al*., 2004). Furthermore, the lack of fundamental understanding of the chiral recognition mechanisms draw researchers' attention to employ computational techniques in chiral separation. Currently, tremendous articles were published on computational studies concerning chiral recognition mechanism. However, only one article was published on computational study of chiral recognition mechanism of ketoconazole with β-cyclodextrin (β-CD)

as chiral selector (Redenti *et al*., 1999), and the study of chiral recognition mechanism of itraconazole has not been reported so far. Hence, it is our interest to perform computational studies on these two antifungal drugs so that we can get further insight into the chiral interactions and mechanism in the enantioseparation process.

1.3 Aims and Objectives

The aim of the study is to develop computational and experimental studies for chiral separation of ketoconazole and itraconazole antifungal drugs using molecular modelling and electrokinetic chromatography (EKC), respectively. The interaction and possible chiral recognition mechanism of ketoconazole and itraconazole antifungal drugs with the CDs chiral selector will be elucidated using computational approach via molecular docking studies. The objectives of this study are to:

1. optimize separation of chiral ketoconazole and itraconazole antifungal drugs using CDs as chiral selector in EKC.

2. elucidate mechanism of ketoconazole antifungal drug enantioseparation using computer-aided molecular modelling study.

3. screen and predict potentials of dual and triple CD system for enantioseparation of itraconazole antifungal drug using molecular modelling technique, then testing the results using experimental approach.

1.4 Scope of the Research

The focus of the research is to separate two azole chiral drugs, ketoconazole and itraconazole using EKC due to its high efficiency, short analysis time and wide application range. EKC is known as a suitable and simple method for separation of either acidic or basic drugs. The mechanism of enantioseparation was elucidated using a computer-aided molecular modelling study. The interaction of enantiomers with CD as chiral selector and their binding energies were studied for the chiral recognition mechanism. Separation of four and eight stereoisomers of ketoconazole and itraconazole, respectively still has not been achieved by far using EKC technique. Therefore, studies on these two antifungal drugs should be interesting for the purpose of enantioseparation mechanism.

However, it is very important to note that the results derived from molecular modelling generally do not account for the presence of modifiers, ions, effects of differential solvation of the diastereomeric complexes and the underlying support (Maier *et al.*, 2001). Therefore, there is still limited knowledge on chiral discrimination processes and phenomena when comparing experimental enantioselectivity data with the results of molecular modelling.

1.5 Significance of Research

Chirality is a major concern in the modern pharmaceutical industry and still a scientific challenge especially to predict successful baseline separations of chiral compounds. Hence there is a great need to develop suitable method for analysis and separation of chiral compounds especially for compounds with multiple chiral centers. In this study, multiple chiral centers ketoconazole and itraconazole antifungal drugs were successfully separated and developed using EKC method with multiple CDs. For the first time we have succeeded in the enantioseparation of four stereoisomers of ketoconazole using EKC with addition of small amount of anionic surfactant, sodium dodecyl sulphate (SDS) and addition of three different type of

CDs simultaneously in the CE BGE. In addition, the use of dual and triple CDs shows significant results in obtaining a complete separation of itraconazole stereoisomers.

This study also contributed to the combination of experimental and computational studies using molecular modelling approaches to obtain further insight into formation of complexes of chiral compounds with CDs as chiral selectors. Molecular docking was successfully performed using Autodock 4.2 software which minimized the cost as the usage of certain software are quite expensive. To the best of our knowledge, the use of dual CDs in modelling the host-guest system was also the first to be performed using Autodock software.

1.6 Outline of the Thesis

This thesis consists of seven chapters. Chapter 1 describes the research background, problem statement, objectives, scope as well as significance of the study.

Chapter 2 reports the literature search related to stereoisomers of chiral compounds, the importance of chiral separation, introduction to azole antifungal drug, review on previous enantioseparation of ketoconazole and itraconazole drugs, capillary electrophoresis as a chiral separation technique, cyclodextrin as a chiral selector and last but not least the trends in molecular modelling studies related to chiral analysis.

Chapter 3 explores the enantioseparation of ketoconazole using CD-EKC. This chapter reports on the optimization of several parameters of CD-EKC system including concentration of heptakis (2,3,6-tri-*O*-methyl)-β-cyclodextrin (TM-β-CD) used, concentration of sodium dodecyl sulphate (SDS), pH effect, buffer phosphate concentration, effect of separation temperature, effect applied voltage, and effect of addition organic modifiers. Method validation is also reported in this chapter which

discussed on linearity, precision and limit of detection (LOD) of the method developed. Furthermore, the method developed was applied to real sample analysis in urine and cream formulation using solid phase extraction (SPE) as a sample pre-treatment.

Chapter 4 describes the computational investigations on chiral recognition of ketoconazole and TM-β-CD. Molecular docking was performed to investigate the mechanism of chiral recognition of ketoconazole and TM-β-CD using MS Modelling software and Autodock software. In this chapter, four stereoisomers of ketoconazole was placed into CD cavity manually to study the inclusion mechanism and obtain the binding energy of the complexes using MS Modelling software. The binding energy of the complexes was calculated using PM3 with Gaussian 09 software. Next, molecular docking of ketoconazole with TM-β-CD was performed using Autodock software. Further calculations of binding energies from molecular docking with Autodock were performed with Gaussian 09 software using PM3 and DFT method. Results from molecular docking showed that the magnitude of binding energy difference which indicates the enantiodiscrimination of the separation. The interactions involved in the formation of complexes are also discussed in this chapter.

Chapter 5 explores the molecular docking of itraconazole drugs with two types of CDs. TM-β-CD and HP-γ-CD were selected as hosts to differentiate the ability of different size cavity in the formation of complexes. Difference of functional groups were also taken into accounts as the factors in the complexes formation. In this chapter, the formation of the complexes was explored using single macromolecule and dual macromolecules as host/s. The binding energy was calculated with Gaussian 09 using DFT method. The binding energy differences of complexes obtain from TM-β-CD and HP-γ-CD was also compared. Furthermore, the chapter discussed on chiral separation of itraconazole using CD-EKC. The discussion involved the screening process to find the suitable chiral selector using dual and triple CDs system. Native CDs namely TM-β-CD, hydroxylpropyl-γ-cyclodextrin (HP-γ-CD), and hydroxylpropyl-β-cyclodextrin (HP-β-CD) were used for screening. Charged CDs namely highly sulphated β-CD was also used for

screening purposes. This chapter also reports the optimization of several parameters of CD-EKC system including concentration of CDs used, pH effect, buffer phosphate concentration, effect of separation temperature, effect applied voltage, and effect of addition organic modifiers. The optimum separation achieved in experimental studies was compared with the results obtained in computational study.

Lastly, chapter 6 presents the overall conclusions and suggestion for further studies. This chapter summarizes the result obtained throughout the study such as the optimum conditions of the enantioseparation of ketoconazole and itraconazole. In addition, the chiral discrimination for both ketoconazole and itraconazole obtained from molecular docking are also summarized in this chapter. Suggestions for further studies are presented.

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