CYCLODEXTRIN-MODIFIED MICELLAR ELECTROKINETIC CHROMATOGRAPHY FOR THE ENANTIOSEPARATION OF IMIDAZOLE AND VINPOCETINE DRUGS

SITI MUNIRAH BINTI ABD WAHIB

UNIVERSITI TEKNOLOGI MALAYSIA

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"……Act! Allah will behold your actions, and (so will) His messenger and the believers, and ye will be brought back to the Knower of the Invisible and the Visible, and He will tell you what ye used to do" (A Taubah: verse 105)

This Thesis is dedicated to my beloved family.

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ABSTRACT

In the present work, cyclodextrin-modified micellar electrokinetic chromatography (CD-MEKC) method was developed and applied for enantioseparation of three imidazole drugs and vinpocetine. The three imidazole drugs namely tioconazole, isoconazole and fenticonazole were simultaneously separated for the first time by MEKC technique using dual cyclodextrin (CD) approach. A combination of two neutral CDs; 2-hydroxypropyl-γ-CD (HP-γ-CD) and heptakis (2,6-di-*O*-methyl)-β-CD (DM-β-CD) (35 mM: 10 mM) in background electrolyte (BGE) containing 35 mM phosphate buffer (pH 7.0), 50 mM sodium dodecyl sulfate (SDS) and 15% (v/v) acetonitrile at 27 kV and 30^{o}C gave the best separation of six stereoisomers of imidazole drugs with resolutions, R_s 1.90-27.22 and peak efficiencies, N > 180 000 in less than 15 min. The samples were injected electrokinetically at 3 kV for 3 s and detection was carried out at 200 nm. The method was linear over the concentration range of 25-200 mg/L ($r^2 > 0.998$) and the detection limits (S/N = 3) of the three imidazole drugs were found to be 2.7-7.7 mg/L. The CD-MEKC method was successfully applied to the determination of the three imidazole drugs in spiked human urine to give mean recoveries ranging from 72.3 to 107.5% (RSD < 6%, n = 3). The method was also applied to the analysis of commercial cream formulation of tioconazole and isoconazole. Good mean recoveries were obtained, ranging from 93.6-100% (RSD < 7%, n = 3). The best chiral separation of vinpocetine that gave four resolved peaks was achieved using 40 mM HP-β-CD in 50 mM phosphate buffer (pH 7.0) consisting of 40 mM SDS and 10% v/v acetonitrile at a separation temperature of 25^{o}C and separation voltage 25 kV. Samples were injected electrokinetically at 5 kV for 7 s. Vinpocetine detection was accomplished using diode array detector at 200 nm. The complete vinpocetine separation was achieved in less than 15 min with peak resolution, R_s 1.40-5.80.

ABSTRAK

Dalam kajian ini, kaedah kromatografi elektrokinetik misel terubahsuai siklodekstrin (CD-MEKC) telah dibina dan diaplikasikan untuk pemisahan enantiomer tiga dadah imidazol dan vinposetin. Tiga dadah imidazol iaitu tiokonazol, isokonazol dan fentikonazol telah dipisahkan secara serentak untuk pertama kalinya menggunakan teknik MEKC dengan dua siklodektrin (CD). Kombinasi dua CD neutral; 2-hidroksipropil-γ-CD (HP-γ-CD) dan heptakis(2,6-di-*O*-metil)-β-CD (DM-β-CD) (35 mM: 10 mM) dalam latarbelakang elektrolit yang mengandungi 35 mM larutan penimbal fosfat (pH 7.0), 50 mM natrium dodesil sulfat (SDS) dan 15% v/v asetonitril pada 27 kV dan 30°C telah memberikan pemisahan terbaik bagi enam stereoisomer dadah imidazol dengan resolusi, R_s 1.90-27.22 dan kecekapan puncak, N > 180 000 dalam masa kurang daripada 15 min. Sampel disuntik secara elektrokinetik pada 3 kV selama 3 s pada pengesanan panjang gelombang 200 nm. Kaedah ini adalah linear dalam julat kepekatan 25-200 mg/L (r^2 > 0.998) dan had pengesanan (S/N = 3) tiga dadah imidazol yang diperoleh ialah 2.7-7.7 mg/L. Kaedah CD-MEKC ini telah diaplikasikan dengan jayanya bagi penentuan tiga dadah imidazol dalam sampel air kencing dengan purata perolehan semula dalam julat 72.3 hingga 107.5% (RSD < 6%, n = 3). Kaedah ini juga telah diaplikasikan kepada analisis krim formula komersial tiokonazol dan isokonazol. Purata perolehan semula yang baik telah diperoleh dalam julat 93.6-100% (RSD < 7%, n = 3). Pemisahan kiral terbaik vinposetin yang memberikan empat puncak diperoleh menggunakan 40 mM HP-β-CD dalam 50 mM larutan penimbal fosfat (pH 7.0) yang mengandungi 40 mM natrium dodesil sulfat (SDS) dan 10% v/v asetonitril pada suhu pemisahan 25°C dan voltan pemisahan 25 kV. Sampel disuntik secara elektrokinetik pada 5 kV selama 7 s. Vinposetin dikesan menggunakan pengesan susun atur diod pada panjang gelombang 200 nm. Pemisahan lengkap vinposetin telah diperoleh dalam masa kurang daripada 15 minit dengan resolusi puncak yang baik, R_s 1.40-5.80.

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LIST OF ABBREVIATIONS

ACN	-	Acetonitrile
BGE	-	Background electrolyte
CD	-	Cyclodextrin
CD-EKC	-	Cyclodextrin-modified electrokinetic chromatography
CD-MEKC	-	Cyclodextrin-modified micellar electrokinetic chromatography
CE	-	Capillary electrophoresis
CM-β -CD	-	Carboxymethyl-beta-cyclodextrin
CS	-	Chiral selector
CZE	-	Capillary zone electrophoresis
DM-β-CD	-	Heptakis (2,6-di-*O*-methyl)-beta-cyclodextrin
EKC	-	Electrokinetic chromatography
EKI	-	Electrokinetic injection
EOF	-	Electroosmotic flow
GC	-	Gas chromatography
GC-MS	-	Gas chromatography-mass spectroscopy
HPLC	-	High Performance Liquid Chromatography
HP-α-CD	-	Hydroxypropyl-alpha-cyclodextrin
HP-β-CD	-	2-hydroxypropyl-beta-cyclodextrin
HP-γ-CD	-	2-hydroxypropyl-gamma-cyclodextrin
LC	-	Liquid chromatography
MEKC	-	Micellar electrokinetic chromatography
MeOH	-	Methanol
RP-TLC	-	Reverse phase-Thin layer chromatography
S-β-CD	-	Sulfated-beta-cyclodextrin
SDS	-	Sodium dodecyl sulfate
SPE-RP	-	Solid Phase Extraction-Reverse phase
TM-β-CD	-	Heptakis (2,3, 6-tri-*O*-methyl)-beta-cyclodextrin

LIST OF SYMBOLS

cm	-	Centimeter
i.d.	-	Inner diameter
kV	-	Kilo volt
N	-	Peak Efficiency
R_s	-	Resolution
T	-	Temperature (˚C)
µg	-	Micro gram
µL	-	Micro liter
µm	-	Micro meter

CHAPTER 1

INTRODUCTION

1.1 Background of Study

A great number of pharmaceuticals and drugs especially originated from natural products are chiral. It is well known that a chiral compound consists of one or more stereogenic center in which one chiral center provides two stereoisomers. Even though the stereoisomers are enantiomer pair, they usually display different biological activity, potency and mode of action. For this reason, chirality emerges as part of the important objectives in pharmaceutical, biomedical and analytical area.

Chromatography methods are one of the major analytical techniques for chiral separation. To achieve successful enantioseparation of the target analytes, chiral stationary phases or chiral mobile phases additives are used (Wang *et al*., 2008). However, the use of chiral stationary phase as well as the large amounts of consuming reagents of chiral mobile phases additives involve high cost. Capillary electrophoresis (CE) has shown to be a powerful and versatile technique for a wide variety of chiral drug separations (Zhou *et al*., 2002; Servais *et al*., 2005; Kitagawa *et al*., 2006; Liu *et al*., 2009). By means of CE, the use one or more chiral selectors that is introduced in the running buffer can be performed without the need of expensive chiral stationary phases. Other advantages of CE are high efficiencies, rapid, simple and since only consume small amount of chemical, the use of expensive chiral selector is affordable compared to chiral mobile phase additives of HPLC (Rizzi, 2001; Matthijs *et al*., 2004).

In general, enantiomer separation is based upon the formation of diastereomeric complex between the stereoisomers and a chiral selector and separation can be obtained only if these complexes have different equilibrium constants. By using CE, chiral selector is introduced to the background electrolyte (BGE). However, it does not guarantee the successful enantioseparation of all target analytes. The most important rule for enantiomer separation is that the chiral selector must be compatible in size and structure to the racemate. The chiral selectors have the ability to interact with the enantiomers stereospecifically. The interactions can be stabilized by interactives forces such as hydrogen bonding, Van der Waals, steric effects, electrostatic forces or π-π interaction (Bressolle *et al*., 1996; Ali *et al*., 2006). Cyclodextrin (CD) is by far the most popular chiral selectors used in CE (Cserhati, 2008; Scriba, 2008). CD discriminates between enantiomers via inclusion into their hydrophobic cavity (Chankvetadze, 1997; Wang *et al*., 1998; Wan Ibrahim *et al*., 2009a).

Micellar electrokinetic chromatography (MEKC) is one of the CE modes that is widely applied for hydrophobic compounds to increase selectivity (Wan Ibrahim *et al*., 2007; Bao *et al*., 2008; Felhofer *et al*., 2009; Hui *et al*., 2009; Pérez-Fernández *et al*., 2010). Sodium dodecyl sulfate (SDS) is a well-known anionic surfactant in MEKC applications. Normally, it is added in the running buffer above its critical micellar concentration (CMC) ~8 mM to act as a pseudostationary phase. Enantiomer separations by cyclodextrin-modified micellar electrokinetic chromatography (CD-MEKC) have become a viable technique in CE (Kodama *et al*., 2002; Eder *et al*., 2006; Li *et al*., 2006; Kodama *et al*., 2007; Wan Ibrahim *et al*., 2007; Wan Ibrahim *et al*., 2009a; Wan Ibrahim *et al*., 2009b; Hermawan *et al*., 2010; Wan Ibrahim *et al*., 2010). By using this approach, the chiral recognition does not only rely on the partition of aqueous and micellar phase, but also on the entrapment of solute into the cavity of the CD. CD-MEKC technique is favourable due to its applicability for neutral and charge analytes. For neutral solute, it is partitioned between the micellar and the aqueous CD phases (Kodama *et al*., 2002; Deeb *et al*., 2011). For charged analyte, it will involve combination of distribution of solute in micellar and aqueous phases and also

differences in electrophoretic mobility to achieve separation (Van Zomeren *et al*., 2000).

1.2 Problem Statement

Chirality is a main issue whether in development or marketing of pharmaceutical products, therefore, chiral separations have gained a great attention in pharmaceutical and biomedical studies. Imidazole drugs has been widely used as antifungal in clinical studies and most of the drugs exist in chiral form. To date, several studies on enantioseparation of imidazole drugs have been carried out using CE (Penn and Goodall, 1993; Chankvetadze *et al*., 1995; Ferguson *et al*., 1996; Dong *et al*., 1998; Van Eeckhaut *et al*., 2000; Quaglia *et al*., 2002; Lin *et al*., 2003; Castro-Puyana *et al*., 2005; Castro-Puyana *et al*., 2007; Hermawan *et al*., 2010; Rousseau *et al*., 2011). However, no simultaneous separation of tioconazole, isoconazole and fenticonazole enantiomers were reported using CE.

Vinpocetine is well-known for various cerebrovascular diseases and the interesting point is, it is a chiral drug with two chiral centers. HPLC chiral α_1–acid glycoprotein column (chiral-AGP) has been used to separate vinpocetine enantiomers. However, it is reported that the gradient elution method was not suitable for chiral separation of the drug and the analysis time is long (~40 min) (Herényi and Görög, 1992). There was only one report concerning enantioseparation of vinpocetine using CE (Sohajda *et al.*, 2010), but the study focused on the determination of stability constants of vinpocetine and two others vinca alkaloids with several cyclodextrins (CDs). Furthermore, only resolution of two vinpocetine peaks were described. As CD-MEKC technique is feasible for chiral separation of hydrophobic compounds and this approach is claimed to have better selectivity owing to the partition of a hydrophobic compound can take place between the bulk aqueous, micellar and also entraption with CD, thus, it is our interest to develop CD-MEKC technique for enantioseparation of vinpocetine and the three selected

imidazole drugs using easily available and cheap CDs with good resolution for all separation peaks within the shortest possible time.

1.3 Aim and Objectives of Research

The aim of the research is to enantiomerically separate three selected imidazole drugs and enantiomers of vinpocetine using CD-MEKC technique. The objectives of the study are to ;

1. screen general and inexpensive CDs as the most suitable chiral selector (CS) to separate the three selected imidazole drugs and the enantiomers of vinpocetine, respectively by using MEKC technique.

2. investigate and optimize the influence of different chiral selector concentrations, buffer concentrations, sodium dodecyl sulfate (SDS) concentrations, pH, addition of different organic modifiers, voltage and temperature on the enantioresolution of selected imidazole drugs and vinpocetine respectively.

3. apply the developed method to the analysis of selected imidazole drugs in pharmaceutical and biological samples.

1.4 Scope of Study

In the present work, the application of CD-MEKC technique was employed for two different types of drugs. The first application was conducted for simultaneous enantioseparation of three imidazole drugs namely tioconazole, isoconazole and fenticonazole. Single CD and dual CD systems were investigated using neutral CDs in an attempt to discriminate three pairs of selected imidazole drugs enantiomers.

Neutral CDs are used as they are cheaper and easily available. The influence of separation parameters such as chiral selector concentrations, buffer concentrations, buffer pH, and organic modifier concentrations on the enantioresolution of selected imidazole drugs were also explored. The optimized CD-MEKC method was validated and applied to human urine and cream samples. For sample pretreatment, solid phase extraction (SPE) procedure was carried out to isolate the drugs from the both samples.

The second application involves the separation of four stereoisomers of vinpocetine since it has not been achieved before. The scope of the work on vinpocetine is limited to finding optimum condition for the enantioseparation of four stereoisomers. For enantiomeric separation of vinpocetine, the evaluation of CD-EKC technique with several neutral and charged cyclodextrins as preliminary study was performed followed by CD-MEKC technique. Several neutral cyclodextrins were investigated in an attempt to discriminate the two pairs of vinpocetine enantiomers. The influence of other separation parameters were also investigated using the selected cyclodextrin as chiral selector.

1.5 Significance of Study

CD-MEKC technique is a good attempt to enantioseparate the three imidazole drugs and vinpocetine since it offers higher selectivity for hydrophobic compounds. Inexpensive neutral cyclodextrin (CD) is employed in the present work, therefore it involves low-cost separation. The elucidation of simultaneous enantioseparation of selected imidazole drugs can provide an effective and less time-consuming separation because the three imidazole drugs can be separated at the same time under the same separation conditions. The proposed method can also be potentially applied to the other drugs of similar group. Proper selection of CD as selector and easy variation of separation conditions in CD-MEKC method is expected to contribute to the best separation of four vinpocetine peaks within the shortest analysis time.

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