MONITORING OF VANCOMYCIN IN HUMAN PLASMA VIA PORTABLE MICROCHIP ELECTROPHORESIS WITH CONTACTLESS CONDUCTIVITY DETECTOR AND MULTI-STACKING STRATEGY

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Specially dedicated to my beloved families for all support and encouragement in completing this study

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ABSTRACT

A new online multi-stacking preconcentration technique based on the hybrid integration of field-enhanced sample injection (FESI) and micelle-to-solvent stacking (MSS) was developed and implemented in a battery-operated aqueous-based microchip capillary electrophoresis (MCE) device with a commercially available double T-junction glass chip. Cationic analytes from two sample reservoirs were injected under FESI conditions and subsequently focused by MSS within the sample loading channel. The proposed multi-stacking strategy was verified under a fluorescence microscope using Rhodamine 6G as the model analyte, and a sensitivity enhancement factor (SEF) of up to 217-fold was achieved. The developed approach was subsequently implemented in the MCE, coupled with contactless conductivity detection (C^4D) in order to monitor the targeted antibiotic, namely vancomycin which was present in the human plasma samples. Moreover, the operation and parameters affecting the MSS, such as the BGE concentration, micelle concentration, focusing time, and methanol percentage in the sample solution were optimized and investigated. The multi-stacking and analysis time for vancomycin were 50 s and 250 s respectively, with the SEF of 83-fold as compared to the typical gated injection method. The detection limit of the method for the vancomycin spiked human plasma was 2.5 µg/mL, with intraday and interday repeatability (RSD) of 2.6% and 4.3%, respectively. The recoveries in the vancomycin spiked human plasma samples were 99.0 % –99.2 %.

ABSTRAK

Satu teknik baru prakepekatan pelbagai timbunan atas talian berdasarkan integrasi hibrid suntikan sampel peningkatan medan (FESI) dengan penimbunan misel kepada pelarut (MSS) telah dibangunkan dan dilaksanakan dalam peranti mikrocip elektroforesis kapilari (MCE) berasaskan fasa akueus yang beroperasi menggunakan bateri dengan dua cip kaca simpang-T yang tersedia secara komersial. Analit kationik daripada dua takungan sampel telah disuntik di bawah keadaan FESI dan kemudiannya difokuskan dengan MSS dalam saluran pemuatan sampel. Strategi pelbagai timbunan yang dicadangkan telah disahkan di bawah mikroskop pendarfluor menggunakan Rhodamine 6G sebagai model analit, dan faktor peningkatan kepekaan (SEF) sehingga 217 kali ganda telah tercapai. Pendekatan yang dibangunkan ini kemudiannya dilaksanakan dalam MCE, digandingkan dengan pengesanan kekonduksian tanpa sentuh (C^4D) untuk memantau antibiotik sasaran iaitu vankomisin yang hadir dalam sampel plasma manusia. Tambahan lagi, operasi dan parameter yang mempengaruhi MSS seperti kepekatan BGE, kepekatan misel, masa fokus dan peratus metanol di dalam larutan sampel telah dioptimumkan dan dikaji. Pelbagai timbunan dan masa analisis untuk vankomisin masing-masing adalah 50 s dan 250 s, dengan nilai SEF 83 kali ganda berbanding dengan suntikan melalui proses kawalan biasa. Had pengesanan bagi kaedah ini untuk suntikan vankomisin di dalam sampel plasma manusia adalah 2.5 µg/mL dengan keterulangan dalam hari dan antara hari (RSD) masing-masing adalah 2.0% dan 4.3%. Perolehan kembali bagi suntikan vankomisin di dalam sampel plasma manusia adalah 99.0 % - 99.2.

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LIST OF ABBREVIATIONS

BGE	-	Background electrolyte
CE	-	Capillary electrophoresis
CGE	-	Capillary gel electrophoresis
CIEF	-	Capillary isoelectric focusing
CITP	-	Capillary isotachophoresis
CMC	-	Critical micellar concentration
CTAB	-	Cetyltrimethylammonium bromide
CZE	-	Capillary zone electrophoresis
C^4D	-	Capacitively coupled contactless conductivity detection
DI	-	Ultrapure deionised
DPA	-	Differential pulsed amperometry
EC	-	Electrochemical
EOF	-	Electroosmotic flow
FASI	-	Field-amplified sample injection
FESI	-	Field-enhanced sample injection
FPIA	-	Fluorescence polarisation immunoassay
HPLC	-	High-performance liquid chromatography
ITP	-	Isotachophoresis
LE	-	Leading ion
LED	-	Light-emitting diode
LED-IF	-	Light-emitting diode-induced fluorescence
LIF	-	Laser induced fluorescence
LIFP	-	Laser-induced fluorescence polarisation
LLE	-	Liquid-liquid extraction
LOD	-	Limit of detection
LOQ	-	Limit of quantification

LVSS	-	Large-volume sample stacking
MEKC	-	Micellar electrokinetic capillary chromatography
MeOH	-	Methanol
MOPS	-	3-(n-morpholino)-propanesulfonic acid
MS	-	Mass spectrometry
MSS	-	Micelle-to-solvent stacking
MSSB	-	Micelle to solvent stacking boundary
NaOH	-	Sodium hydroxide
PDMS	-	Polydimethylsiloxane
PMMA	-	Polymethylmethacrylate
RIA	-	Radioimmunoassay
SCB	-	Solvent and the concentration boundaries
SDS	-	Sodium dodecyl sulphate
SDS-PAGE	-	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
SEF	-	Sensitivity enhancement factor
S/N	-	Signal-to-noise ratio
STS	-	Sodium tetradecylsulphate
TDM	-	Therapeutic drug monitoring
TE	-	Terminating ion
t-ITP	-	Transient isotachophoresis

LIST OF SYMBOLS

cm	-	Centimetre
h	-	Hour
I.D	-	Internal diametre
kHz	-	Kilohertz
kV	-	Kilovolts
mg/mL	-	Milligram per millilitre
min	-	Minute
mm	-	Millimetre
mM	-	Millimolar
ng/mL	-	Nanogram per millilitre
nm	-	Nanometre
s	-	Second
v/v%	-	Volume/volume percent
µg/mL	-	Microgram per millilitre
µL	-	Microlitre
µm	-	Micrometre

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CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Electrophoresis is the movement of electrically charged particles in a conductive medium (electrolyte) under the influence of an electric field. The separation of analytes is influenced by the principles of the charge-to-size ratio, as well as the phenomenon of the electroosmotic flow (EOF) of the background electrolyte within the fused silica capillary. Nowadays, the miniaturisation of analytical devices has become a popular trend in the analytical field for its simplicity and portability. In the early 1990s, the conventional capillary electrophoresis (CE) was successfully transformed and down-scaled into the microchip electrophoresis (MCE) platform by Manz and co-workers [1]. The ultimate goal of the MCE is to develop a miniaturised total analysis system, also known as lab-on-chip that integrates all the functions of the modern analytical laboratory in a single device. The principle and mechanisms of action for the MCE remain the same as the conventional CE. However, unlike the conventional CE that consists of only a single capillary, the microchip usually consists of single or multiple fluidic channels that can be wisely utilised. Moreover, the MCE offers the advantages of low cost, fast analysis time, small size, portability and low consumptions of solvent and solution.

Despite the advantages offered by MCE, one of the major drawbacks of the MCE system is currently the poor detection sensitivity due to the short optical path length and low sample detection volume. As a consequence, scientists have made considerable efforts to overcome this problem by developing high sensitive detection schemes as well as various online pre-concentration techniques and have subsequently incorporated them into the MCE platform. Although various detection systems, such as the laser induced fluorescence (LIF), mass spectrometry (MS), and electrochemical (EC) systems have significantly improved the detection sensitivity in the MCE, these systems normally require tedious derivative or sample labelling steps on the analysed samples and an unique interfacing devices in order to couple the MCE device with the detection system, which eventually increases the entire cost of the instrumentation. Hence, the development of new online pre-concentration techniques has become the main focus in order to increase the detectability of the MCE with the involvement of lower running costs. Several online pre-concentration techniques are successfully introduced in the MCE system, which includes field-amplified stacking [2-4], large-volume sample stacking (LVSS) [5], isotachophoresis (ITP) [6-8], sweeping [9], dynamic pH junction [10], and MSS [11].

The MSS was first introduced by Quirino in year 2009 [12]. Although the MSS is capable of increasing the detection sensitivity and pre-concentrates the analytes in conventional CE, it is not yet widely employed in the MCE platform due to the difficulty in generating and regulating the MSS stacking boundaries in short microchannels. Up to this moment, only one paper successfully demonstrated the application of MSS in MCE by using non-aqueous buffer media in order to monitor the anti-oestrogen drugs namely tamoxifen and its major metabolites present in the human plasma [11].

Vancomycin is an antibiotic which can induce ototoxicity and nephrotoxicity to humans and was therefore selected as a candidate for the purpose of therapeutic drug monitoring (TDM) in many countries around the world. TDM is a clinical practice whereby a clinician will determine/measure specific drugs at given intervals in order to maintain a constant concentration in a patient’s bloodstream, thus being

able to adjust the individual dosage [13]. According to the clinical practice guidelines that have been established by the Infectious Disease Society of America and the National Antibiotic Guideline of Malaysia [14], the monitoring of vancomycin by (assessing the concentration levels in adults and children) the blood serum level should range between 10 µg/mL and 20 µg/mL. Moreover, the frequency of monitoring the levels of vancomycin should be at least once per week for stable hemodynamic patients, while daily monitoring is required for hemodynamically unstable patients [15].

1.2 Problem Statement

Various analytical approaches have been introduced in order to determine the vancomycin content in biological fluids, which include spectrophotometric [16], immunologic [17], chromatographic [18, 19], and CE [20, 21] techniques in conjunction with a variety of detection systems. Although these reported methods were proven to be beneficial in monitoring the vancomycin content in biological and environmental samples, the lack of specificity, along with the bulky and expensive instrumentation and time-consuming and labour intensive instrumentation thereof still served as major drawbacks. Moreover, most of the established monitoring systems are not really portable, which restricts the access of TDM for patients living in rural and remote locations. Although the MCE system is capable of performing the rapid separation of the targeted analytes within a minute, the poor detection sensitivity due to the short optical path length or small detection volume often limits its practicability in various analytical approaches, especially in clinical studies. Hence, a new online pre-concentration technique, which is capable of being implemented in the portable MCE platform and enhancing the detection sensitivity of drug substances for clinical approaches, is necessary to be developed.

1.3 Objective of the Study

The objectives of this study are:

- To develop a portable battery-powered MCE system coupled with on-chip C^4D which is able to be used for the separation of charged analytes.

- To study the new multi-stacking strategy which involves the integration of FESI and MSS in the MCE and visualise the process involved using Rhodamine 6G as a model analyte and detected by a fluorescence microscope.

- To optimise the operation parameters and subsequently validate the established new multi-stacking strategy for monitoring the vancomycin present in the human plasma samples.

1.4 Scope of the Study

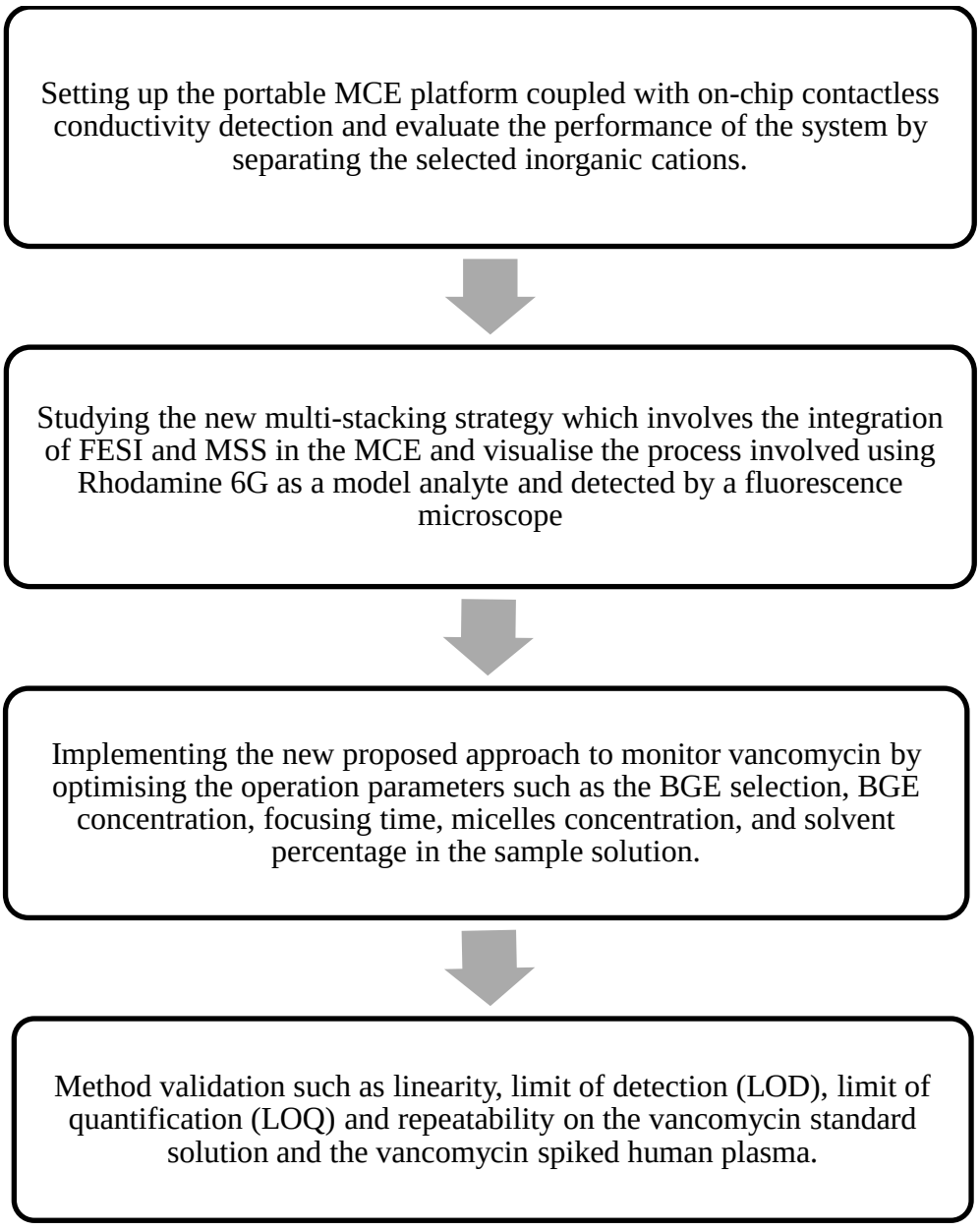
The present study demonstrates the development of a battery-powered portable MCE system. The functionality and performance of the MCE system is evaluated by conducting a simple inorganic cation separation using the floating and gated injection methods, respectively. An online pre-concentration technique that involves the multi-stacking strategy (FESI and MSS) is implemented on the established MCE system and the process is visualised using Rhodamine 6G as a model analyte and a fluorescence microscope as a detector. The developed approach is subsequently applied to the monitoring of vancomycin. The operational parameters involved in the multi-stacking strategy, such as the background electrolyte (BGE) concentration, focusing time, micelles concentration, and the organic solvent

percentage in the sample solution are comprehensively optimised using the established MCE system. The developed approach is then validated and subsequently applied in order to monitor the vancomycin drug present in the human plasma.

1.5 Significance of the Study

This study will significantly contribute to the understanding of the fundamental aspect of transferring the MSS technique from CE to the aqueous-based MCE platform. A monitoring assay for vancomycin is crucial for guiding treatment decisions, therapeutic monitoring, pharmacokinetic and bioavailability studies, as well as the quality control of the dosage forms. Hence, the portable MCE system allows the analysis to be performed on-site and this is especially important in improving the health quality in remote locations and rural areas. Moreover, the proposed portable miniaturised system is also capable of speeding up the analysis of vancomycin, which is significantly beneficial to the pharmacology laboratory in hospitals or clinical labs that need to process hundreds of patient samples daily. The proposed system has the potential to be transformed into a commercialisable point-of-care diagnostic device.

1.6 Flowchart/Scheme of the Whole Planned Work



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