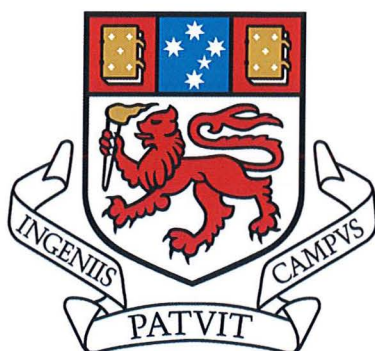


**Consideration of Capillary Electrophoresis as an  
Analysis Technique for the Intended Application of  
Therapeutic Drug Monitoring of Antipsychotics.**



**UNIVERSITY  
OF TASMANIA**

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Submitted in fulfilment of the requirements for the Degree of

Doctor of Philosophy

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## **Declaration of Originality**

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by another person except where due acknowledgment is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

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Kara Johns

September, 2013

## Statement of Co-Authorship

The following people contributed to the publication of the work undertaken within Chapter 2.

Candidate (80%) and Dr Michael Breadmore (10%) contributed to the idea, its formalisation and development. Dr Bruno Raimondo (5%) and Professor Paul Haddad (5%) assisted with refinements and presentation.

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## **Ethical Conduct**

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety committee of the University.

Kara Johns

September, 2013.

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The work presented within this thesis was completed with passion for what the developed methods may actually provide to people dealing with schizophrenia within our communities. As we break the negative stigma and improve the treatment options, there is hope that people directly and indirectly affected by mental illness may be able to fulfil their lives in the way they had always wished.

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## Abstract

The use of therapeutic drug monitoring (TDM) when prescribing antipsychotics is not yet considered a routine care procedure, despite evidence and opinion regarding its benefit. Amongst the arguments against the inclusion of TDM, are the many logistical deficiencies that prevent the TDM service from being as optimal as warranted. It has been identified that improvements within the service being offered for TDM may result in improvements with the overall TDM practice; which may result in an increase usage. It was recognised that altering the analysis technique to a faster, more versatile process, may be impacting on the overall service that could be offered and thus improve the holistic practice of TDM of antipsychotics. Capillary electrophoresis (CE) was chosen for consideration as an alternate analysis technique, primarily due to the known ability of this technique to achieve fast separations of structurally similar compounds and its ability to be readily implemented in small potentially portable lab-on-a-chip devices. It was therefore the aim of this thesis to develop and consider CE methods for the analysis of antipsychotics for the intended application of TDM.

The development of CE methods was performed in a step-wise manner, through an understanding of the applications use. The first method developed was aimed at a secondary application of TDM of compliance monitoring and achieved through an extensive examination of a multivariate optimisation of separation parameters using the modelling software known as Peakmaster. Through this work a set of parameters was identified that allowed for the separation of 17 antipsychotics within 5 minutes. The optimal method was subsequently validated for evaluation and found to be analytical suitable for consideration within a compliance monitoring setting. In addition, the developed separation was successfully adapted for compatibility with a mass spectrometer detector

(CE-MS), however this was not considered appropriate for clinical application at this stage due to instrumental weakness observed during this work.

The second stage of focus was to progress the method development specifically towards TDM appropriate applications. This was achieved by developing the first separation for aripiprazole and both main metabolites. Here a separation was achieved for three structurally similar compounds within nine minutes and found to be ideal for the intended application of TDM. Having successfully developed a CE method suitable for TDM, the final method was developed with the aim of incorporating the two positive elements of the prior two methods: many compounds within one method and achieve separation of structurally similar compounds. Consequently a method was developed incorporating five popularly prescribed antipsychotics and metabolites, resulting in a separation of 13 compounds within eight minutes.

The methods developed and presented within this thesis were considered suitable for the intended application of TDM. Due to the speed and resolution achieved within the separations, it was foreseeable that the implementation of these methods would have the potential of improving the versatility of the TDM service and therefore potentially improve the usage of TDM for antipsychotics. It was clearly acknowledged that further assessment would be necessary (such as tandem testing) before suggesting these methods be implemented. However the work here supports the idea of changing the analytical technique employed for the process of TDM of antipsychotics to CE, as a modification that would allow for improvements to the overall service delivered.

## Publications and Presentations

### Publications

K. F. Johns, et al., 2009 *Evaluation of Peakmaster for computer aided multivariate optimisation of a CE separation of 17 antipsychotic drugs using minimal experimental data*. *Electrophoresis*. **30**(5): p. 839-847.

### Presentations

IATDMCT 10<sup>th</sup> International congress

Nice, France, September 2007

Poster entitled: Monitoring of Anti-Psychotics: improving the analytical methodology for compliance and therapeutic drug monitoring with capillary electrophoresis-mass spectrometry.

19<sup>th</sup> International Symposium on Pharmaceutical and Biomedical Analysis (PBA)

Gdansk, Poland, June 2008

Poster entitled: Computer aided multivariate optimization of a capillary electrophoresis separation of 17 anti-psychotics for compliance monitoring.