Enantioanalysis of pharmaceutical compounds

by

Tumelo Rameleko Mashile

Submitted in partial fulfillment of the requirements for the degree

MAGISTER SCIENTIAE

In the Faculty of Natural and Agricultural Sciences

University of Pretoria

Pretoria

November 2005

Enantioanalysis of pharmaceutical compounds

by

Tumelo Rameleko Mashile

Supervisor: Prof. Dr. Raluca-Ioana Stefan-van Staden

Department of Chemistry

University of Pretoria

Degree: Magister Scientiae

SYNOPSIS

Due to the differences in pharmacokinetics and pharmacodynamics of the enantiomers of the same chiral pharmaceutical substance, there is a high need of reliable analytical methods for enantiopurity tests of them in the raw material as well as in its pharmaceutical formulations. If some of the chiral pharmaceutical compounds can be delivered as racemates, there are many others for which the enantiopurity is essential. Enantioanalysis using enantioselective, potentiometric membrane electrodes became a good alternative of the chromatographic methods due to its high reliability.

To have reliable analytical information it is necessary to use reliable analytical methods and electrodes. The most reliable design for the enantioselective, potentiometric membrane electrodes proved to be the one based on carbon paste. This electrodes are made by mixing graphite powder with paraffin oil to give carbon paste, which is modified by the addition of a chiral selector (e.g., cylodextrins, maltodextrins, macrocyclic antibiotics and fullerenes).

The high sensitivity, selectivity, enantioselectivity, accuracy and precision made the enantioselective, potentiometric membrane electrodes suitable to be used for the enantioanalysis of different pharmaceutical compounds such as S- and R-deprenyl and S-ibuprofen as raw materials and in their pharmaceutical formulations.

Acknowledgements

I would like to send my heartfelt gratitude to the following people for their sterling support that they gave to me throughout the whole project.

To my supervisor Prof Raluca I. Stefan, I am very much grateful and appreciative of the unwavering support and experienced guidance that you have given me throughout the entire time of this project.

To my colleagues, Dr B. Lal, L. Holo and R. Bokretsion, your contribution in this project did not go unnoticed, it has been a wonderful and fulfilling experience working with you lovely people.

Last, but not least in importance, I am as always grateful to my very humble family for the concrete support and the strong confidence that they showered me with during the time of this project.

Much appreciation to the NRF sponsor for the financial support which they put towards the execution of this project.

Introduction

Chirality is a very important issue for different compounds of pharmaceutical and biological importance. In the modern pharmaceutical industry chirality has become a major concern. This is attributed largely to a heightened awarness that enantiomers of a racemic drug may have different pharmacological activities, as well as different pharmacokinetics and pharmacodynamic effects. The importance of chiral drugs, specifically single isomer drugs in the pharmaceutical market has grown at an exponential rate each year, due to recent developments in the area of chiral drug technologies. The gains in potency, efficacy and selectivity obtained by treatment with single isomer drugs are undeniable. Therefore, enantiopurity is now imperative in the production of most pharmaceutical products with a chiral moiety.

The challenges imposed on the pharmaceutical companies by the problems emanating from the side effects that could be caused by the presence of an undesirable component in racemic drugs, or problems arising from the different pharmacokinetics and pharmacodynamic effects that may be triggered by each of the enantiomer, has further stimulated the imperativeness to find an analytical method that can discriminate between the two enantiomers. These methods will be very helpful and should exhibit reliable analytical information, fast analysis, and could be employed for the enantiopurity tests of pharmaceutical compounds.

In molecular recognition of enantiomers, electrochemical sensors are a very good alternative for chromatographic and structural analysis techniques. Electrochemical sensors have superceded and out classed the other techniques with respect to many analytical aspects, including the high reliability that is given by high precision, high reproducibility, rapidity, and due to the fact that electrochemical sensors can be used directly for measurement of compounds in solution, without any prior separation of the substances that has to be analysed.

The primary aim of this dissertation is to construct reliable enantioselective, potentiometric membrane electrodes to be applied in enantiomeric analysis of pharmaceutical compounds: deprenyl and ibuprofen. Carbon paste are proposed as matrix for the sensors ' design, since it has proved to be the most reliable design, and due to the economic convenience of using carbon which can be easily obtained from the abundantly available and affordable graphite powder. For the selection of the best chiral selector, chiral recognition that is based on selective binding is considered.

Direct potentiometry was employed for the assay of enantiomers in pharmaceutical tablets and raw materials. The selection of the type of electrode and matrix of its membrane was done in accordance with the complexity of the structure of the enantiomer to be determined.

DECLARATIONS

I declare that the dissertation, which I hereby submit for the degree MSc at the University of Pretoria, is my own work and has not previously been submitted by me for a degree at this or any other tertiary institution.

Tumelo R. Mashile

Pretoria 7 February 2006

Table of contents

List of publications

1. Determination of S-(+)-ibuprofen using enantioselective, potentiometric membrane electrodes based on macrocyclic antibiotics

   R.I. Stefan-van Staden, T.R. Mashile, B. Lal, K.C. Mathabate, J.F. van Staden

   J.Pharm.Biomed.Anal., Submitted.

2. Enantioselective assay of S-(+)-ibuprofen using enantioselective, potentiometric membrane electrodes based on maltodextrins

   R.I. Stefan-van Staden, T.R. Mashile

   Sens.Actuators B, In Press (SNB 9191).

3. Determination of R-deprenyl using a maltodextrin based enantioselective, potentiometric membrane electrode

   R.I. Stefan-van Staden, T.R. Mashile

   Instrum.Sci.Technol., Submitted

4. Enantioselective, potentiometric membrane electrodes based on α-, β- and γ-cyclodextrins as chiral selectors for the assay of S-deprenyl.

RI Stefan-van Staden, T.R. Mashile, J.F. van Staden, H.Y. Aboul-Enein

Anal.Chim.Acta, Submitted.

5. Enantioselective, potentiometric membrane electrodes based on C_{60} fullerene derivatives for the assay of deprenyl

   R.I. Stefan-van Staden, T.R. Mashile, B. Lal

   Anal.Chem., Submitted.