University of Applied Sciences and Arts Northwestern Switzerland
School of Life Sciences

A current view on chiral separation

Hasler Patrick
Bachelor-Thesis, Molecular Life Sciences, Analytical Chemistry

Dr. Christian Mink and Stefan Ehmele, Syngenta Crop Protection AG
Dr. Markus Ehrat, EK Biosciences GmbH
Prof. Dr. Götz Schlotterbeck, University of Applied Sciences and Arts Northwestern Switzerland

ABSTRACT

Three analytical techniques have been used

- gas chromatography (GC)
- liquid chromatography (LC)
- supercritical fluid chromatography (SFC)

For the first time the four enantiomers of a unique cyclobutyl derivative were successfully separated by chiral GC analysis using a novel Chiraldex B-DM as stationary phase. Subsequently the developed method was validated and is already in use in research and development.

Further, methods for the active ingredients S-Metolachlor and Metalaxyl-M were developed and validated using a different but robust reversed phase LC technique. Also these methods will be used to determine content and enantiomeric excess simultaneously for the future for quality control in manufacturing. A cost-benefit analysis using the new method for Metalaxyl-M resulted in a cost saving of 43.1 %.

INTRODUCTION

Many pharmaceutical drugs and agrochemicals are chiral compounds. Chiral analysis is required due to

- different physiological properties (e.g. bioavailability, uptake)
- biological activity
- increased regulatory requirements
- analytical assistance for chiral synthesis and separation development

The aim of this thesis was to implement cost efficient analytical methods of chiral stationary phases to allow separation of enantiomeric enriched active ingredients.

Below the chemical structures of cyclodextrins (CDs, Figure 1) and the schematic separation mechanisms (Figure 2) of the corresponding GC columns are shown.

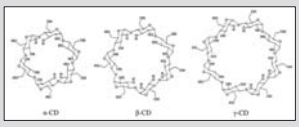

Fig. 1: chemical structures of α-CD, β-CD and γ-CD [2]

Fig. 2: schematic representation of an inclusion-complex (left) and surface interaction (right) of an analyte with CD [3]

RESULTS

All enantiomers of a cyclobutyl derivative were separated by chiral GC analysis using a Chiraldex B-DM as stationary phase (Figure 3).

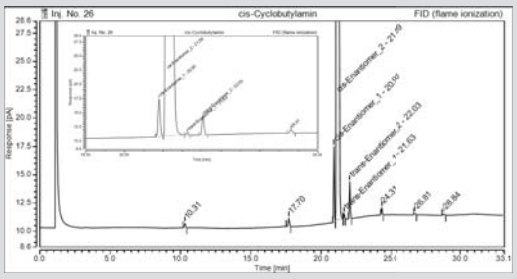

Fig. 3: GC-FID chromatogram, separation of the four enantiomers of the cyclobutyl derivative

The development of a new reversed-phase LC method for the fungicide Metalaxyl-M resulted in a cost saving of 43.1 %. In Figure 5 the chemical structures of Metalaxyl-M are shown. The optimized separation of the active ingredient Metalaxyl-M is shown in Figure 4.

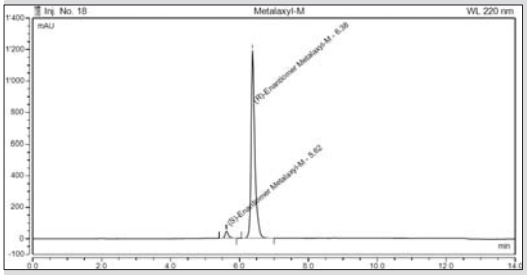

Fig. 4: HPLC UV chromatogram at 220 nm, S and R enantiomers of Metalaxyl-M

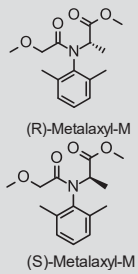

Fig. 5: Structures of the two Metalaxyl-M enantiomers

This method will be used in the future for quality control in manufacturing. This leads to the following advantages over the current set-up:

- simultaneous determination of AI content and enantiomeric excess
- use of one instrument
- one sample preparation
- shorter analysis time
- cost savings for used solvents
- and moreover environmental benefit due to less organic solvent usage

The cost-benefit analysis of IB_M15 is shown in Figure 6.

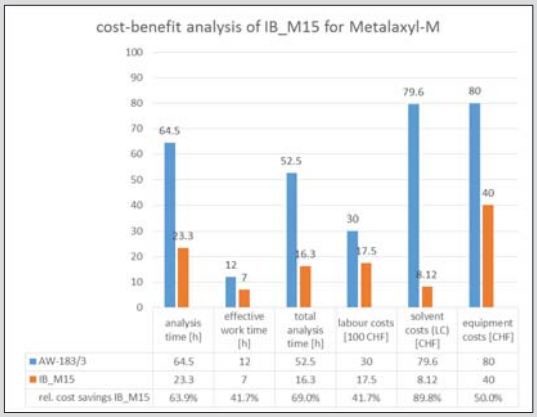

Fig. 6: cost-benefit analysis of the new developed reversed-phase LC method IB_M15 compared to the existing method

CONCLUSION AND OUTLOOK

Based on the results no predictions between molecular structure, stationary phase and successful chiral separation can be drawn. Like the cost-benefit analysis showed, reversed-phase LC methods are preferred over normal phase LC as it is more cost-efficient and environmentally beneficial.

Until now SFC is an expensive device and it is mostly used in R&D, only rarely used at manufacturing sites.

REFERENCES

[1] Cserháti, T.; Forgács, E. *Cyclodextrins in chromatography*; RSC chromotography monographs; Royal Society of Chemistry: Cambridge, 2003

[2] Biwer, A.; Antranikian, G.; Heinzle, E. *Appl. Microbiol. Biotechnol.* **2002**, *59* (6), 609–617

[3] https://www.sigmaaldrich.com/content/dam/sigma-aldrich/docs/Supelco/General_Information/1/T411101-oem-chiral.pdf (accessed Apr 30, 2017).