Multimilligram Stack Injection Chiral Separation of MDMA

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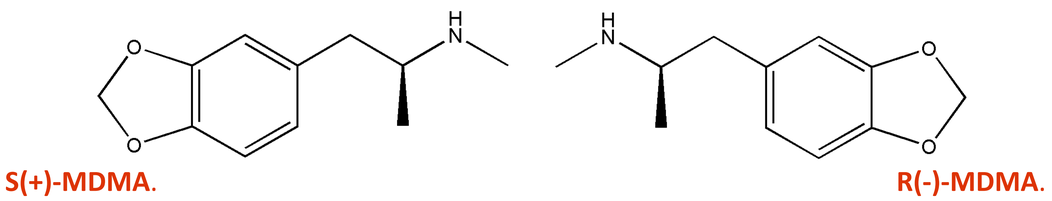
Introduction

MDMA (3, 4-methylenedioxy-methamphetamine), widely known as Ecstasy, is a drug of abuse used as a racemate. Studies have shown that (S)-(+)-MDMA is more active than the (R)-(−)-MDMA on the central nervous system and contributes more to the serotonergic degeneration associated with MDMA consumption. Furthermore, while (R)-(−)-MDMA has shown to be responsible for oxidative damage in rat liver, the (S)-(+)-MDMA seems to preserve it. These differences justify the need for isolating MDMA as pure enantiomers [1,2].



S(+)-MDMA. R(-)-MDMA.

Figure 1. MDMA enantiomers

As reported, the enantiomers of MDMA have been isolated so far by two different LC approaches using cyclodextrin as the chiral selector in reversed phase mode, in diluted conditions[1,2]. For achieving high productivity in multimilligram separations, high resolution and sample overload are recommended. To circumvent this problem, this work reports a multimilligram separation of MDMA enantiomers by batch chromatography under mass overload with stack injection on a CHIRALPAK ID column.

Experimental

Chromatographic Conditions

• MDMA was resolved with a CHIRALPAK ID column (150 x 10 mm, 20 µm). The mobile phase consisted of an mixture of acetonitrile and DEA 0.1% at a flow rate of 5.0 mL/min, λ=270nm, and injection volume of 0,5mL were used with a total of 27 injections in two cycles.

• MDMA was dissolved with mobile phase at a concentration of 10 mg/mL.

Results and Discussion

• CHIRALPAK ID under polar organic conditions showed good enantioresolution for MDMA enantiomers (Rs > 3.0).

• In order to optimize MDMA enantiomeric purification, the preparative separation was carried out with stack injection under mass overload condition.

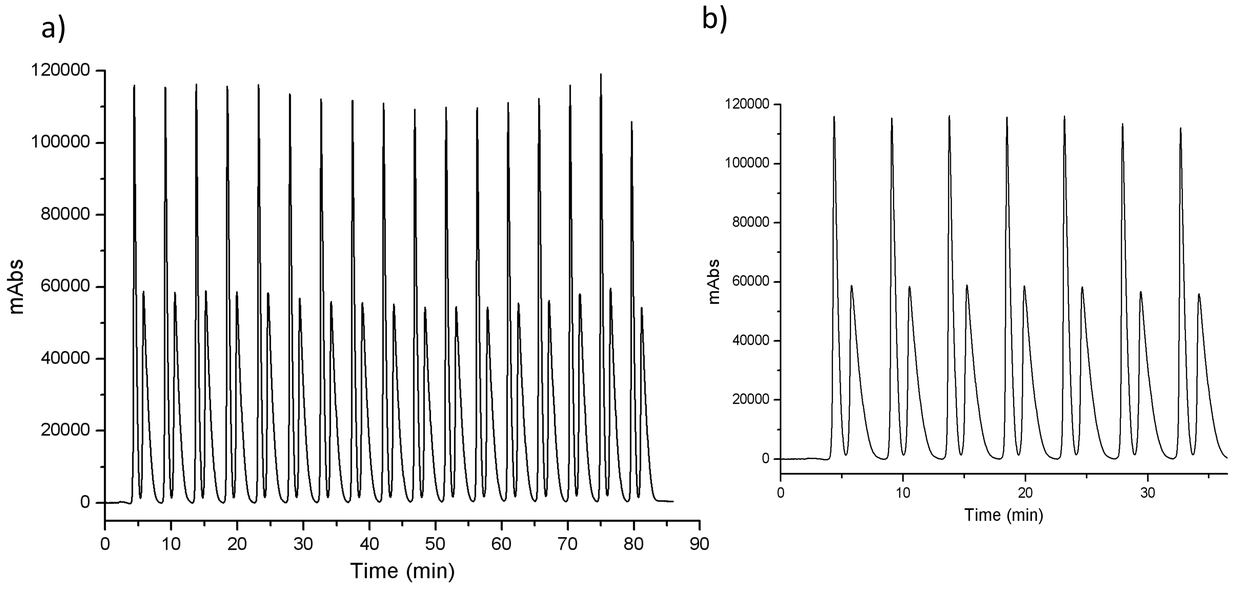


Figure 2. Chromatographic separation of MDMA with stack injection, a) first cycle, b) enlarged.

Table 1. Process parameters for the enantiomeric purification of MDMA

Preparative Separation Parameters	Values
(S)-(+)-MDMA e.r. (%)	>99.9
(S)-(+)-MDMA mass collected (mg)	63.1
(S)-(+)-MDMA rate of production (mg/day)	574.4
(S)-(+)-MDMA Recovery (%)	93.5
(R)-(-)-MDMA e.r. (%)	>99.9
(R)-(-)-MDMA mass collected (mg)	64.0
(R)-(-)-MDMA rate of production (mg/day)	582.6
(R)-(-)-MDMA Recovery (%)	94.8
Time Comsuption (min)	158.2
Mobile Phase Comsuption (mL)	790.0

• Elution order of the isolated enantiomers was determined by optical rotation of the solutions (10mg/mL) of the isolated enantiomers in either ethanol or water. The second eluted enantiomer was identified as (R)-(-)-MDMA. It is important to mention that the optical rotation of the enantiomers was inverted in the chromatographic mobile phase used for the isolation.

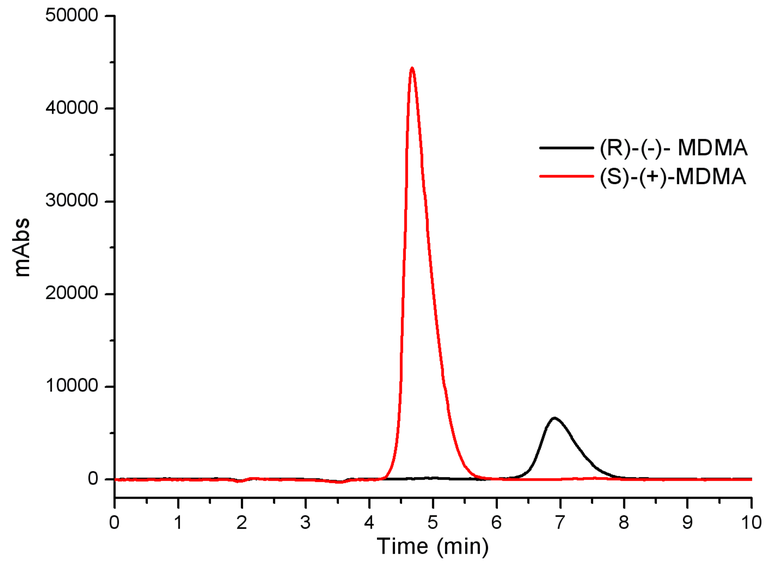


Figure 3. MDMA enantiomers

• The use of stack injection provides, approximately, 30% of economy in time and mobile phase consumption, comparing with conventional batch chromatography under the same chromatographic conditions.

Conclusions

MDMA enantiomers were obtained in the rate of 577 milligrams/day with high enantiomeric purity by preparative batch chromatography with stack injections under mass overload conditions. The isolated enantiomers will be used in a ^{1}H HR/MAS NMR study for the determination of the chiral recognition process of CHIRALPAK ID and MDMA.

Acknowledgements

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2. M.R. Meyer, F.T. Peters, H.H. Maurer, Drug Metab. Dispos. 36 (2008) 2345–2354