APPLICATION NOTE

Separation of Mirtazapine on CHIRALPAK® IK-3

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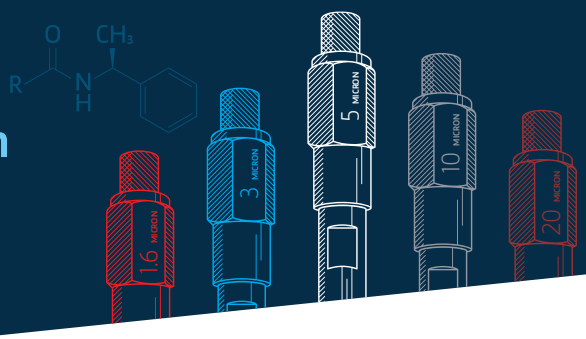

DAICEL Chiral Technologies

INTRODUCTION

Mirtazapine is an approved antidepressant, with other studies exploring its use to treat sleep apnea, substance abuse withdrawal symptoms, and as an antihistamine. The (S) enantiomer, Esmirtazapine, was under investigation as a treatment for insomnia and vasomotor symptoms associated with menopause. In support of such investigations, it would be helpful to establish an effective chiral analysis allowing for rapid and accurate quantification.

While there are already several methods published in the literature for the separation of mirtazapine, they all present some less-than-ideal characteristics, whether it be a large particle size, unnecessarily long analysis time, or poor resolution.

Daicel's newest immobilized chiral stationary phase (CSP), CHIRALPAK® IK-3, has been found to provide a better alternative to these published methods. CHIRALPAK® IK-3 is an immobilized cellulose-based CSP functionalized with tris (3-chloro-5-methylphenyl) carbamate selectors, and offers unique separations characteristics not available in any other commercially available chiral phase. The added robustness coming from the immobilization process increases its utility as a result of expanded solvent compatibility.

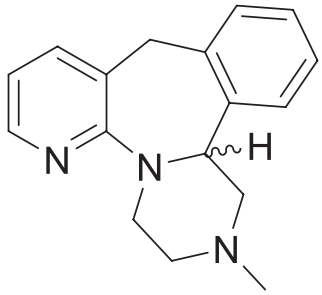

Figure 1: Mirtazapine

EXPERIMENTAL

Chromatographic Conditions for the Separation of Mirtazapine		
Column	CHIRALPAK® IK-3 (150 mm x 4.6 mm i.d.) Part #: 91524	
Mobile Phase	Hex-IPA-DEA = 90-10-0.1 (v/v/v)	Hex-EtOH-DEA = 90-10-0.1 (v/v/v)
Flow Rate	1.0 ml/min	
Detection	UV 230 nm ref. 450 nm	
Temperature	25°C	
Sample	2.0 mg/ml in EtOH	
Injection Volume	2 µl	

Mirtazapine and Diethylamine (DEA) were purchased from Sigma Aldrich and used as-is. The solvents used were all purchased from Pharmco, were HPLC-grade or higher, and were used as-is. Specifically the hexanes (Hex) contained 95% n-hexane. The ethanol (EtOH) was reagent alcohol, which contains 90% EtOH, 5% methanol, and 5% isopropanol (v/v/v). Initial screening and optimization were performed on an Agilent 1200 equipped with a quaternary mixing pump and utilized a DAD.

DISCUSSION

Mirtazapine was prepared as a 2.0 mg/ml solution in EtOH, and screened on Daicel's library of 3 µm immobilized CSPs with Hex-EtOH-DEA = 80-20-0.1 (v/v/v) and Hex-IPA-DEA = 70-30-0.1 (v/v/v). This produced several partial or near-baseline separations. Of those separations, CHIRALPAK® IK-3 exhibited more favorable characteristics of a chiral separation, that being good peak shape and selectivity with reasonable retention times. Other columns showed longer retention and/or a greater degree of tailing. The separations on IK-3 were optimized by increasing the retention by decreasing the percentage of alcohol. For Hex-IPA, it was found that 10% IPA yielded a baseline separation of the enantiomers, with an analysis time of less than 6 mins (Figure 2).

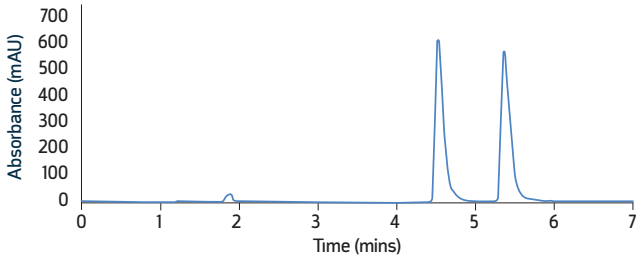

Figure 2: : Separation of Mirtazapine on CHIRALPAK® IK-3 with Hex-IPA

For Hex-EtOH, 10% alcohol also produced a baseline separation in under 4.5 mins, with good peak shape and selectivity. Typically, a smaller percentage of EtOH is required to produce a similar separation to IPA, as it is a stronger eluting solvent. However in this case, EtOH helps improve the peak shape (less tailing), and thus 10% can be used to further reduce the analysis time (Figure 3).

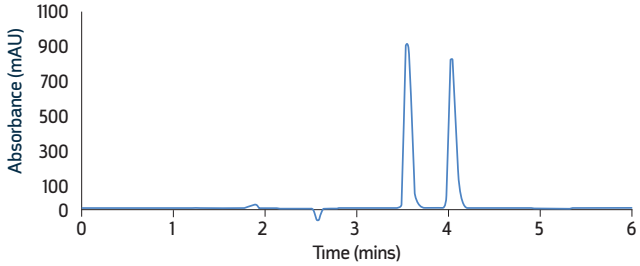

Figure 3: Separation of Mirtazapine on CHIRALPAK® IK-3 with Hex-EtOH

CONCLUSIONS

The unique separation characteristics of CHIRALPAK® IK-3 yielded new baseline separations for mirtazapine not previously reported in the literature. These should serve as important methods for the analysis of mirtazapine and esmirtazapine going forward. It also shows that continued development of new chiral stationary phases is important. The best way to affect selectivity and separation performance is by changing the phase system (solvents or CSP). With mobile phase combinations well established, the greatest potential for finding new separations is with the release of new chiral selectors.