APPLICATION NOTE

The Improved Chiral Resolution of Mecoprop Enantiomers on CHIRALPAK® IM

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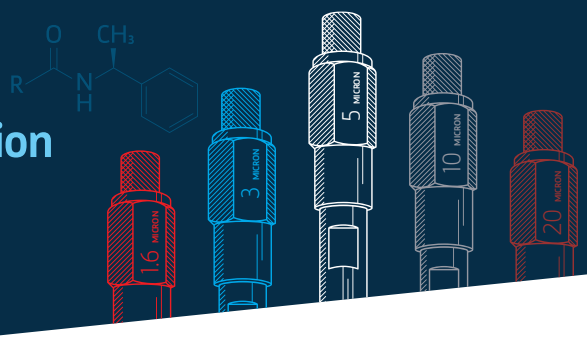

DAICEL Chiral Technologies

INTRODUCTION

Mecoprop (Figure 1) is a commonly used herbicide for controlling the growth of broadleaf weeds such as chickweed, dandelion, plantain, and thistle [1]. In 1980, it was determined that the R-mecoprop enantiomer has the herbicidal activity, although the compound is typically delivered as the racemic mixture [2]. The chiral separation was previously reported on CHIRALCEL® OZ-3, which is a coated tris (3-chloro-4-methylphenylcarbamate) cellulose-based chiral stationary phase (CSP). This separation utilized a traditional normal phase high performance liquid chromatography (NP-HPLC) mobile phase containing hexane (Hex) and ethanol (EtOH) [3]. Although baseline resolved, there is room to improve the resolution and selectivity to improve the limit-of-detection (LOD) or limit-of-quantification (LOQ).

Daicel's newest immobilized CSP, CHIRALPAK® IM, is the immobilized equivalent of CHIRALCEL® OZ-3, the only difference being the particle size (IM is 5 µm and OZ-3 is 3 µm). The added robustness coming from the immobilization process increases this selector's utility because of expanded solvent compatibility. For the separation of Mecoprop, this resulted in a significant improvement of the enantiomeric separation with the addition of dichloromethane (DCM), ethyl acetate (EtOAc), and methyl tert-butyl ether (MtBE) to the mobile phase.

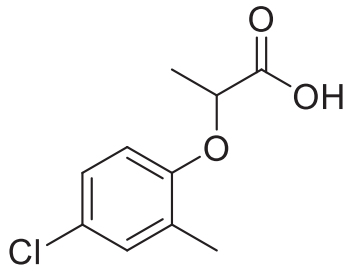

Figure 1: Mecoprop

EXPERIMENTAL

Chromatographic Conditions for the Separation of Mecoprop

Column	CHIRALCEL® OZ-H (150 mm x 4.6 mm i.d.) Part #: 42324	CHIRALPAK® IM (150 mm x 4.6 mm i.d.) Part #: 92324			
Mobile Phase	Hex-EtOH-TFA = 90-10-0.1 (v/v/v)	Hex-EtOH-TFA = 90-10-0.1 (v/v/v)	Hex-EtOAc-TFA = 90-10-0.1 (v/v/v)	Hex-MtBE-EtOH-TFA = 90-10-1-0.1 (v/v/v/v)	Hex-DCM-EtOH-TFA = 90-10-1-0.1 (v/v/v/v)
Flow Rate	1.0 ml/min				
Detection	UV 280 nm ref. 450 nm				
Temperature	25°C				
Sample	2.45 mg/ml in Mobile Phase				
Injection Volume	2 µl				

Mecoprop was purchased from Sigma Aldrich and used as-is. The solvents used were all purchased from Scientific Equipment Company (SECO), were HPLC-grade, and were used as-is. Specifically the hexanes (Hex) contained 95% n-hexane, and the EtOH was reagent alcohol (90% EtOH with 5% methanol and 5% isopropanol by volume). Screening and optimization were performed on an Agilent 1200 configured with high-pressure mixing quaternary mobile phase delivery system, vacuum degasser, autosampler, temperature controlled column compartment, and photodiode array UV detector. The instrument was controlled by an Agilent ChemStation Version RevB.04.03.

DISCUSSION

Mecoprop was prepared as a 2.45 mg/ml solution in Hex-EtOH = 90-10, and the separation from Daicel's application database (Hex-EtOH-TFA = 90-10-0.1 (v/v/v)) checked on both CHIRALCEL® OZ-H and CHIRALPAK® IM (Figure 2). This demonstrated less than baseline resolution on both columns – note the original separation in Daicel's database is on 3 µm and is just baseline

resolved [3]. The loss of separation on the larger particle size is not surprising or concerning, as an increased column broadening for the larger particle size is expected.

The separation on IM was optimized by replacing EtOH as a mobile phase component with EtOAc, DCM, or MtBE. Initially the separations with DCM and MtBE resulted in very broad or non-symmetrical peak shape. This was improved by the addition of 1% EtOH by volume back to the mobile phase. The EtOAc and optimized DCM and MtBE conditions all resulted in significant improvements in the chiral separation (Table 1). All methods resulted in an increased retention, which ultimately improved both the resolution and selectivity (Figures 3 and 4).

In particular, the DCM method yielded a significant separation that could be further optimized by the addition of more DCM to elute the enantiomers from the column faster. The additional DCM should also improve the compound solubility, which would indicate this method could be suitable for adaptation to a preparative separation.

Table 1: Chromatographic Performance of OZ-H and IM Separations

	RT_1	RT_2	K_1[a]	K_2[a]	α	R_s
OZ-H Hex-EtOH-TFA	2.29 mins	2.46 mins	0.33	0.42	1.30	1.30[b]
IM Hex- EtOH -TFA	2.33 mins	2.48 mins	0.35	0.44	1.25	0.94[c]
IM Hex-EtOAc-TFA	4.82 mins	5.85 mins	1.79	2.39	1.32	5.62[d]
IM Hex-DCM- EtOH-TFA	5.73 mins	8.81 mins	2.32	4.10	1.77	16.23[e]
IM Hex-MtBE- EtOH-TFA	3.77 mins	4.81 mins	1.18	1.79	1.51	8.71[f]

[a] Column void time (t0) was determined to be 1.727 mins using 1,3,5-Tri-tert-butylbenzene (TTBB) as a void marker

[b,c,d,e,f] Plate counts were determined to be 3446, 2414, 9915, 10998, and 11333 plates respectively

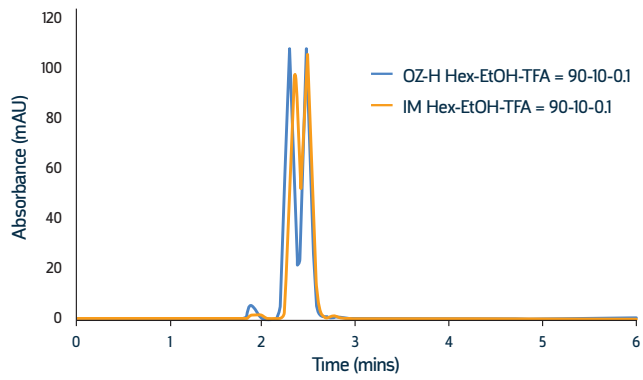

Figure 2: Separation of Mecoprop on CHIRALCEL® OZ-H and CHIRALPAK® IM with Hex-EtOH-TFA = 90-10-0.1 (v/v/v)

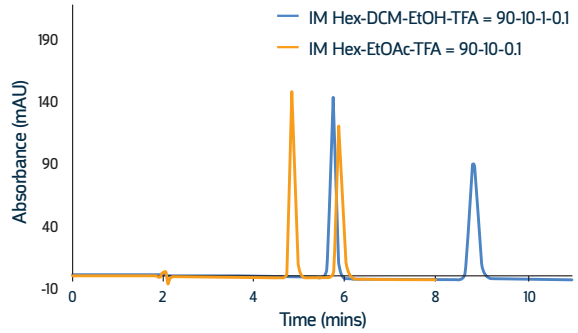

Figure 3: Separation of Mecoprop on CHIRALPAK® IM comparing Hex-DCM-EtOH-TFA and Hex-EtOAc-TFA Mobile Phases

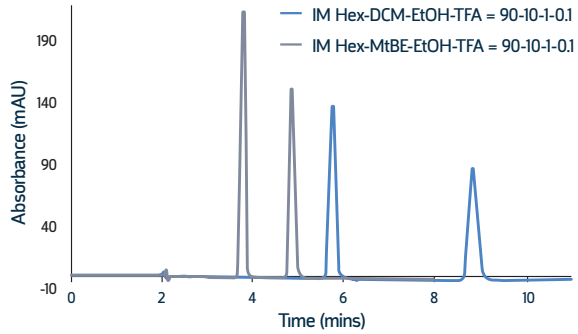

Figure 4: Separation of Mecoprop on CHIRALPAK® IM comparing Hex-DCM-TFA and Hex-MtBE-EtOH-TFA Mobile Phases

CONCLUSIONS

Changing solvent is often the quickest and most effective way to alter the selectivity of a chiral separation. Immobilization increases the range of solvent compatibility, allowing for previously inaccessible improvements to existing chiral separations, as demonstrated with the resolution of Mecoprop. Under traditional normal phase conditions with CHIRALCEL® OZ-H, the resolution was not baseline when the separation was checked on a 5 µm particle size. The access to EtOAc, DCM, and MtBE with CHIRALPAK® IM greatly influenced the analyte interactions with the CSP, and afforded significant improvements to the resolution and selectivity of Mecoprop enantiomers. The use of DCM in particular had a dramatic effect on the separation and afforded conditions that could be further adapted to a preparative scale application.

[1] https://en.wikipedia.org/wiki/Mecoprop

[2] Smith, G., Kennard, C.H.L., White, A.H., Hodgson, P.G. (±)-2-(4-Chloro-2-methylphenoxy)propionic acid (mecoprop). *Acta Crystallogr. B.* **1980**, *36(4)*, 992–994

[3] Daicel Application Database, https://search.daicelchiral.com/ja/cas/name/detail.html?application_id=490