RAPID SFC SEPARATION OF **ANALOGS OF THALIDOMIDE ON DAICEL CHIRALPAK® IA-U**

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APPLICATION NOTE

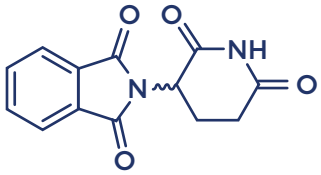
INTRODUCTION

1957 saw the launch of Thalidomide (Figure 1) as an over-the-counter treatment for anxiety, sleeplessness, and morning sickness. Just 4 years later, after a concerning number of birth defects were reported by mother's taking the medication during pregnancy, the drug was pulled from the market. Further investigation lead to the discovery of the importance of enantiomeric separations, as only one of the enantiomers of Thalidomide was actually responsible for these birth defects, while the other was responsible for the positive attributes.

In the years since this initial launch, several analogs of Thalidomide have been prepared and launched as their own separate treatments for different indications. Lenalidomide (Revlimid®) and Pomalidomide (Pomalyst®) are two such examples (Figure 2), both used as chemotherapeutic agents for the treatment of multiple myeloma. Similar to Thalidomide, they exist as a pair of enantiomers, and therefore might require a chiral separation to access their respective levels in a pure drug product.

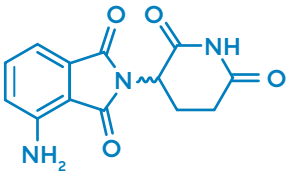
The launch of Daicel polysaccharide chiral stationary phases in a sub-2 µm particle size has afforded the analytical chemist the ability to perform chiral method development screening quickly with increased resolution. Because of the already low viscosity of SFC mobile phases, it is well suited to provide ultra-fast separations that were once not achievable. This application highlights the separations of Lenalidomide and Pomalidomide individually, as well as in a mixture with Thalidomide, for a six (6) peak separation.

FIGURE 1:

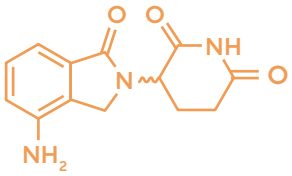


THALIDOMIDE

FIGURE 2:



POMALIDOMIDE



LENALIDOMIDE

EXPERIMENTAL

CHROMATOGRAPHIC CONDITIONS FOR THE SEPARATION OF LENALIDOMIDE, POMALIDOMIDE, AND THALIDOMIDE

CHIRALPAK® IA-U - (50 mm X 3.0 mm I.D.)	
PART #:	80U82
MOBILE PHASE	50-50 = CO_2-MeOH
FLOW RATE	1.5 ml/min
DETECTION	UV, 220 nm, ref. 360 nm
TEMPERATURE	35°C
SAMPLE	1 mg/ml in MeOH (Lenalidomide and Thalidomide) or 2 mg/ml in MeOH (Pomalidomide)
INJECT. VOL.	5.0 µl

FIGURE 3:

SUB MINUTE SFC SEPARATION ON CHIRALPAK® IA-U

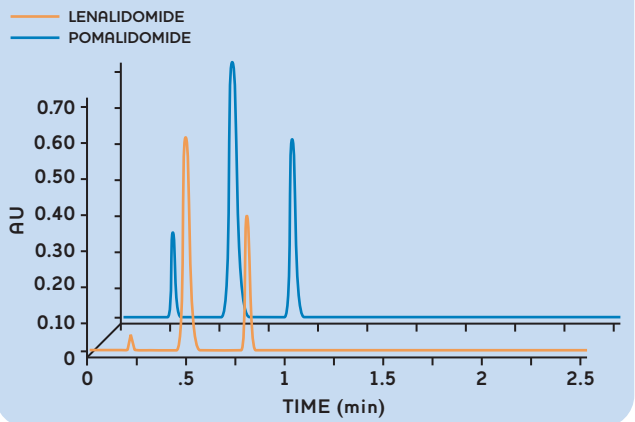


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FIGURE 4:

OPTIMIZED SFC SEPARATION CHIRALPAK® IA-U

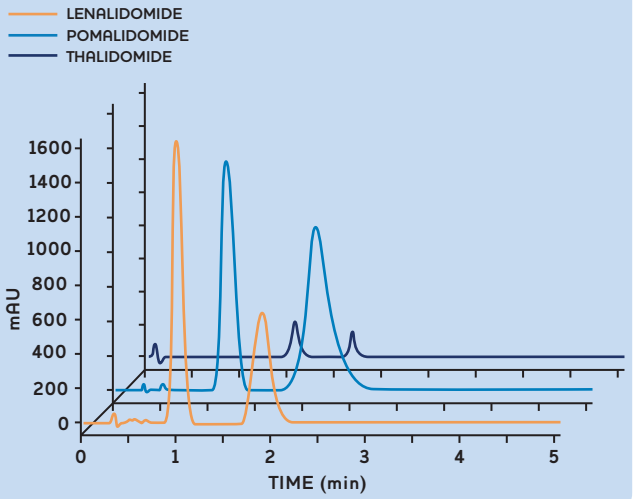
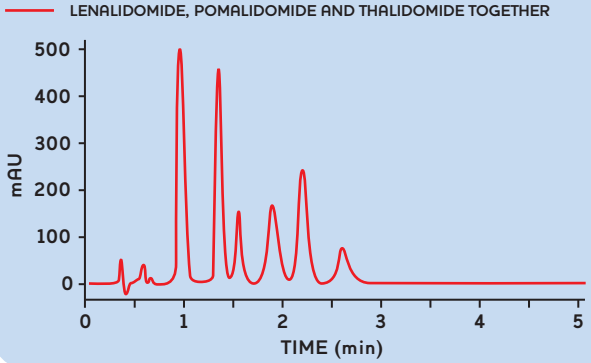


FIGURE 5:

OPTIMIZED SFC SEPARATION ON CHIRALPAK® IA-U



DISCUSSION

The SFC separation of Lenalidomide can be accomplished on CHIRALPAK® IA-U in less than 40 seconds using 50% MeOH as a modifier, and a flow rate of 3 ml/min (Figure 3). Although Lenalidomide is a basic molecule, it was found that no additive was required, further simplifying the separation.

A similar separation of Pomalidomide is observed under identical conditions with CHIRALPAK® IA-U, also in less than a minute (Figure 3).

In order to achieve baseline resolution when mixed together, the separation of Lenalidomide and Pomalidomide was slowed to 1.5 ml/min (Figure 4). When Thalidomide is added to the mixture, a separation of all 6 peaks can be clearly observed (Figure 5). While this sort of an analysis would not typically be routine for the testing of these compounds, it demonstrates the capabilities of Daicel's sub-2 µm polysaccharide CSPs to perform this sort of complicated analysis were it required.

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