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# Cannabinoid Purification and Scale-Up on Hipersep® Flowdrive Pilot

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## Abstract

High performance liquid chromatography (HPLC) offers outstanding efficiency and scalability for the purification of high-quality APIs and intermediates in the pharmaceutical industry.

The application has been broadened to purification of natural extracts, which are often very complex mixtures.

This application note presents the preparative HPLC purification of cannabinoids. The process was developed using a bench-top HPLC instrument and then directly scaled-up to Hipersep® Flowdrive Pilot with Hipersep® Prochrom 150 (150 mm i. d.) for manufacturing.

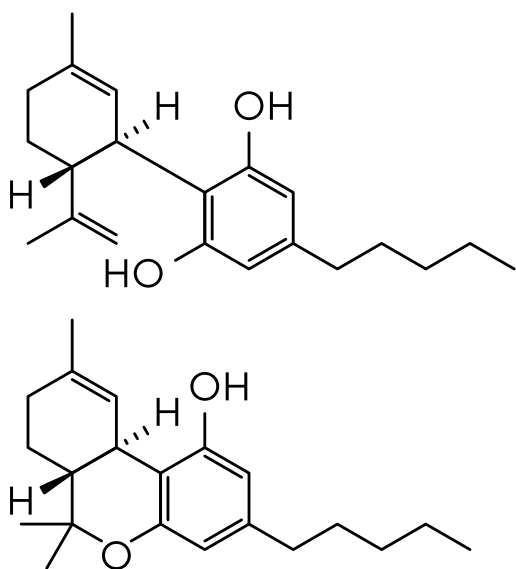
### Acknowledgments

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# Introduction

Cannabinoid oil extracted from cannabis plants contains various cannabinoids such as  $\Delta^9$ -tetrahydro-cannabinol ( $\Delta^9$ -THC), which is a well-known psychoactive compound, and cannabidiol (CBD). Although one of the main objectives is to remove THC and pesticides, the demand of purifying rare cannabinoids such as cannabigerol (CBG) cannabinol (CBN) and cannabichromene (CBC) has been considerably increased.

Since the cannabinoids have very similar structures and similar chemical and physical properties, purifying them with high purity and yield is certainly a challenging task. In addition, robust scale-up of the purification process from a few grams to Mton scale requires another level of expertise not only on the purification process but also the engineering requirement.



**Figure 1:** 2D Structures of Cannabidiol (CBD, above) and Tetrahydrocannabinol (THC, below)

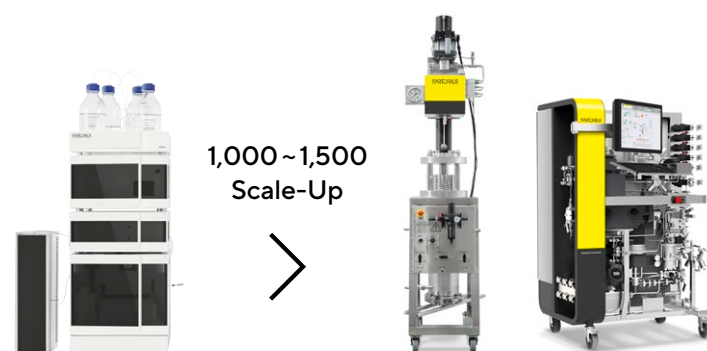
# Materials and Methods

In order to achieve the target products with a high purity at a preparative scale, cannabinoid oil was first obtained from the plant by extraction followed by several unit operations. Then, the purification condition was developed and optimized at bench scale using an analytical size column packed with C18 stationary phase. The purification condition is described below.

**Stationary phase:** Kromasil C18, 13  $\mu\text{m}$ , 100 $\text{\AA}$   
**Column size:** 4.6 i. d.  $\times$  250 mm  
**Mobile phase:** Mixture of Methanol and Water  
**Flow rate:** 0.5 to 1 mL/min  
**Temperature:** Room temperature to 25  $^{\circ}\text{C}$   
**Detection:** UV at 220 to 250 nm

After the peak identification and optimization, the purification process was scaled up to Hipersep<sup>®</sup> Prochrom 150 using the same C18, which is available in bulk.

For predictable scale-up from the bench-top instrument to the production instrument, both the column diameter and length were increased to 150 mm i. d. and 350 mm length in order to maximize the production rate. Then, the flow rate was adjusted to maintain the run time per injection considering the changes on the column diameter and length. Overall, the column volume was increased from 4.1 mL to 6.2 L.



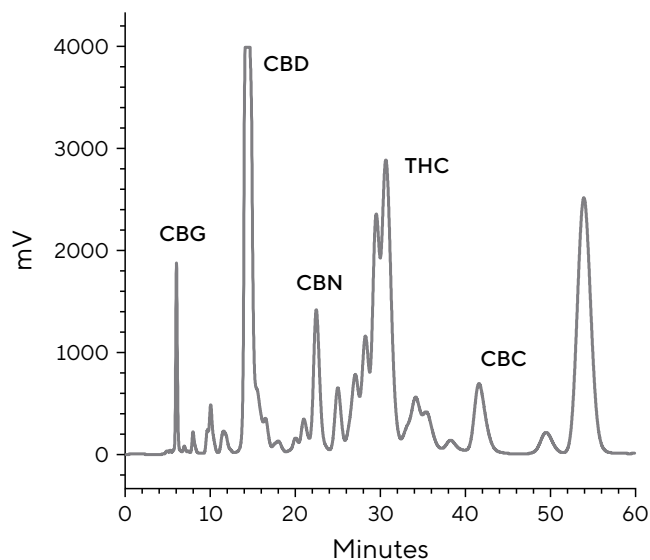
**Figure 2:** Approximately 1000~1500 Times Scale-Up From Analytical Size Column to Hipersep<sup>®</sup> Prochrom 150 With Hipersep<sup>®</sup> Flowdrive Pilot.

# Results

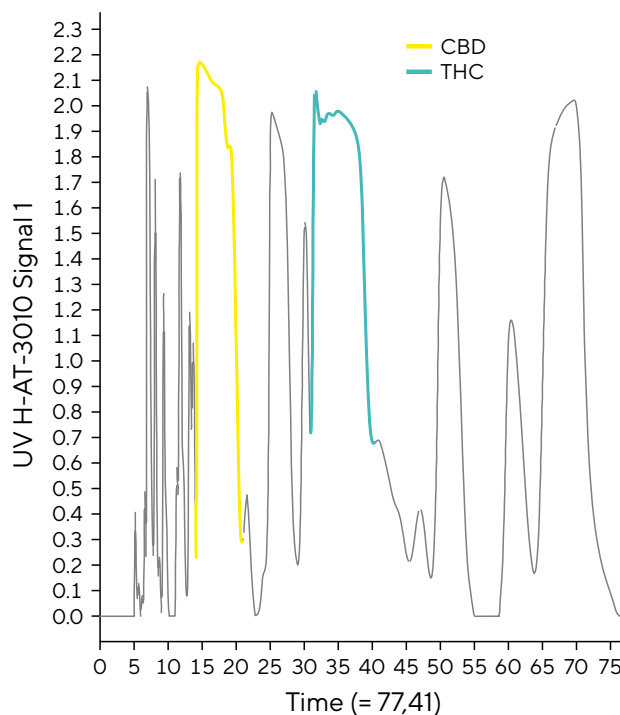
As shown in Figure 3, the purification was linearly scalable so the elution of each cannabinoid could be easily identified on the preparative chromatograms from Hipersep® Flowdrive Pilot with Hipersep® Prochrom 150 compared to the analytical chromatogram from the bench-top HPLC using the 4.6 mm i.d. column.

In addition to CBD and THC, the process allows one to purify several rare cannabinoids with a high purity as well.

**Diluted Injection on the Bench-Top HPLC**



**Overloaded Injection on Hipersep® Prochrom 150 Using Hipersep® Flowdrive Pilot**



**Figure 3:** Comparison of the Preparative Chromatogram From Hipersep® Flowdrive Pilot and Hipersep® Prochrom 150 With Diluted Injection on the Bench-Top

# Conclusion

The purification process was successfully scaled-up from an analytical size column to Hipersep® Prochrom 150 using Hipersep® Flowdrive Pilot. Since the process is confirmed, it can be further linearly scaled up to larger size columns such as Hipersep® Prochrom 1000.

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