

APPLICATION NOTE

Cannabinoid Purification and Scale-Up on Hipersep[®] Pilot

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Figure 1. Varicol® (advanced SMB) and Hipersep® with 99.99% solvent recycling for MTon Scale purification of natural extract for pharmaceutical application.

Introduction

For the outstanding efficiency and scalability, high performance liquid chromatography (HPLC) has been widely used for purification of high quality APIs and intermediates in 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® Pilot with Prochrom® LC150 (150mm i.d.) for manufacturing.

Acknowledgement

We thank Extract Labs™ for sharing the data and Nouryon for providing the bulk C18.



Purification of Cannabinoids

Cannabinoid oil extracted from cannabis plants contains various cannabinoids such as Δ^9 -tetrahydrocannabinol (Δ^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 few gram to Mton scale requires another level of expertise not only on the purification process but also the engineering requirement.

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 μ m, 100Å
Column size:	4.6 i.d. x 250mm
Mobile phase:	Mixture of Methanol and Water
Flow rate:	0.5 to 1mL/min
Temperature:	Room temperature to 25°C
Detection:	UV at 220 to 250nm

After the peak identification and optimization, the purification process was scaled up to Prochrom® LC150 using the same C18, which is available in bulk.

Process Scale-Up on Hipersep® Pilot

For predictable scale-up from the bench-top instrument to the production instrument, both the column diameter and length were increased to 150mm i.d. and 350mm 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 increase from 4.1mL to 6.2L.

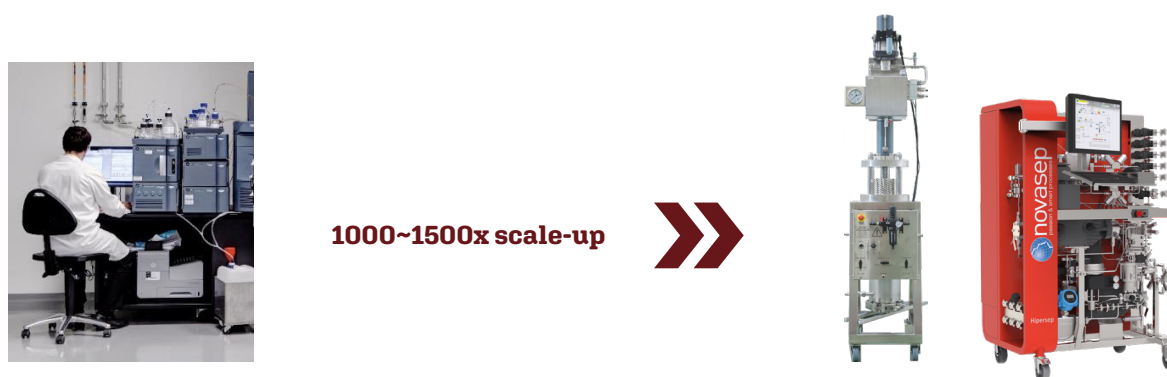
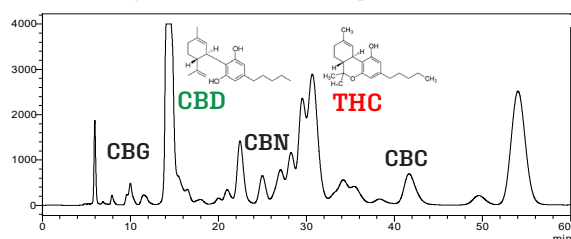
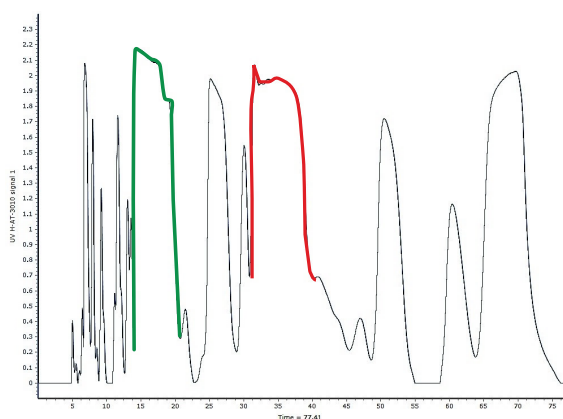


Figure 2. Approximately 1000~1500 times scale-up from analytical size column to Prochrom® LC150 with Hipersep® Pilot.

Diluted Injection on the bench-top HPLC



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® Pilot with Prochrom® LC150 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.



Overloaded injection on LC150 using Hipersep®

Figure 3. Comparison of the preparative chromatogram from Hipersep® Pilot and Prochrom® LC150 with diluted injection on the bench-top.

Conclusion

The purification process was successfully scaled-up from an analytical size column to Prochrom® LC150 using Hipersep® Pilot. Since the process is confirmed, it can be further linearly scaled up to larger size columns such as Prochrom® LC1000. It should be noted that Novasep has a patent pending for another CBD purification technique.

Prochrom Hipersep®

Skids and columns

	HIPERSEP®					
	Pilot	Process M	L	XL	XXL	Above
Productivity range [kg/day] in Batch mode	0,2-4	2-33	17-57	29-106	53-165	Customiza- tion
Productivity range [kg/day] in Cyclojet/Varicol®	8-12	14-99	114-171	212-318	330-495	
Typical Prochrom® column diameter [mm]	50/80/110/150	110/150/200 /300/450	450/590	590/800	800/1000	
Skid Flowrate [L/h]	6*-90	60-500 / 20-200 [Low Flow version]	300-1000	500-1600	1000-2500	
Gradient accuracy [%]	< 1					
Max pressure [bar]	100				70	
Explosion proof	Atex Zone II Class 1 Division 2					
Certifications / Equipment standards	CODAP/ASME for columns CE/UL for systems					
Configurable options	High pressure injection module, Eluent & feed filters, Heat exchanger, Backflush configuration valves, pH conductivity, Nitrogen flush for product recovery, Up to 10 collections, Solvent recycling, Cyclojet process					

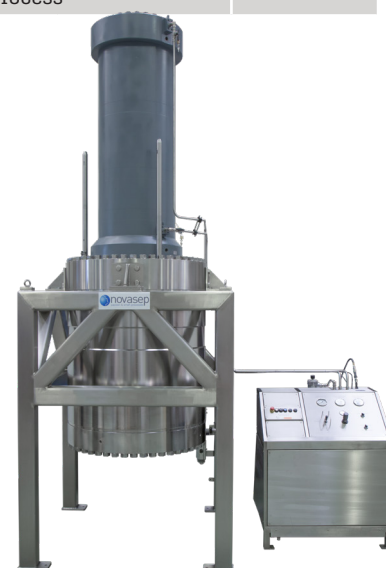
*Gradient accuracy <2% below 10L/h



Hipersep® Pilot



Hipersep® XXL

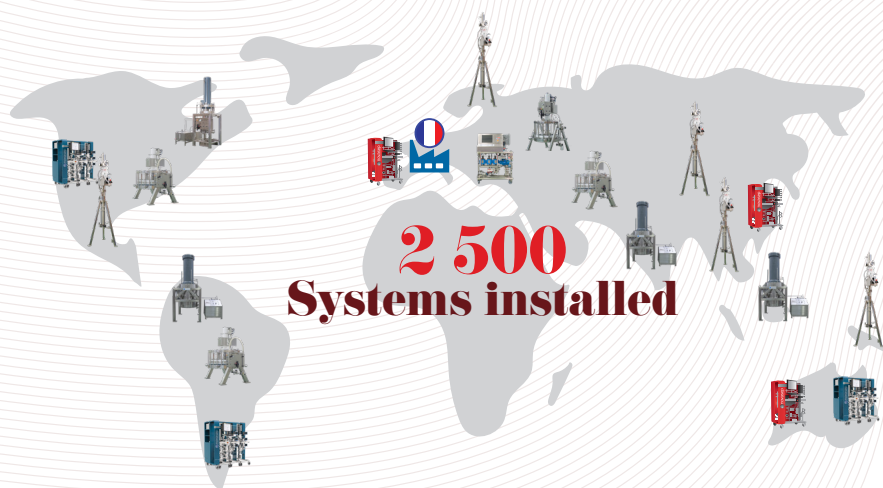


Prochrom® Hipersep® LC1000

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About Novasep

Novasep represents the combined expertise of specialists in purification processes and chemical synthesis. We strive to provide our customers with the best solutions to obtain pure active molecules. We aim to be a highly respected, top tier service provider in all our market segments through the passion of our people and excellence of our processes.



Services and technologies
for the life science industries

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