

Contichrom CUBE Instrument

Frequently Asked Questions (FAQ's)

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For what specific application is the Contichrom CUBE suited?

The Contichrom CUBE is a FPLC system capable of running the continuous capture process CaptureSMB. Furthermore, isocratic, step and linear gradient elution single-column “batch” processes are accessible.

For continuous polishing processes, the Contichrom CUBE Combined is required. This system adds linear gradient and inline dilution capabilities for continuous processes. These capabilities are required for continuous polishing processes.

Can I use my media (resin) and columns of choice on your system?

Yes. We can provide independent suggestions based on our experience with material from various vendors, if requested.

Will a Contichrom CUBE system meet my needs?

The Contichrom CUBE is the easiest way into continuous chromatography. Continuous capture chromatography improves both affinity resin utilization and buffer consumption, and offers a tremendously increased productivity.

At the same time, operating with only two affinity columns for capture with the CaptureSMB process, the Contichrom CUBE provides a comparable productivity and greater reliability than competitor systems with more columns. Furthermore, established twin-column CaptureSMB scale-up solutions for production in a GMP environment are available (Ecoprime Twin by YMC). Thus, if you want to make use of the advantages of continuous capture chromatography, the Contichrom CUBE will perfectly match your needs.

What benefits can I expect from the CaptureSMB process on the Contichrom CUBE?

Compared to single column affinity capture, the CaptureSMB process typically has the following benefits:

- The productivity is improved two- to three-fold
- The affinity resin capacity utilization is increased from 40%-60% to > 90%, reducing resin costs in the same proportion
- The buffer consumption is reduced by 40-60%
- The eluate pool concentration is increased by 40-60%

Compared to other multi-column affinity capture processes run on other chromatography systems, CaptureSMB has the following benefits:

- Reduced complexity in hardware and process design
- A software wizard for designing the continuous process based on a batch process

- Software-supported data evaluation, including intuitive process visualizations
- Proven virus safety with published virus clearance and carry-over studies
- Clear concept for process characterization and validation meeting regulatory requirements

What is the dynamic range of the Contichrom CUBE?

The Contichrom CUBE is available in two versions:

- Contichrom CUBE 30 with a flow rate range of 0.1-36 mL/min
- Contichrom CUBE 100 with a flow rate range of 0.1-100 mL/min.

Is there a scale-up system analog to the Contichrom CUBE?

Yes, YMC Process Technologies, which is like ChromaCon part of the YMC group of companies, offers the YMC Contichrom TWIN. It is based on the same technology as the Contichrom CUBE. The Contichrom TWIN provides seamless upscaling from the Contichrom CUBE.

Are the key components in the Contichrom CUBE easy to maintain or replace?

The Contichrom CUBE has been designed for maximum durability and reliability. For example, the UV detector uses durable LEDs as light source, as opposed to light bulbs with finite lifetimes. If still a component such as tubing, pump or valve head needs maintenance or replacement, it is easily accessible from outside of the system. Furthermore, our service partners and we provide excellent after-sales-services.

What sensors are included in the Contichrom CUBE?

- 2 UV detectors, each monitoring 280 and 300 nm simultaneously. One UV detector is located behind each of the two columns.
- 2 conductivity sensors, also located after each of the two columns.
- 1 pH detector behind the outlet valve.
- 2 pressure sensors, one at each pump.

What monitoring capabilities are additionally available for the Contichrom CUBE?

We offer variable wavelength UV detectors as optional accessories covering the range of 190-500 nm and multi-wavelength detectors covering UV/vis from 190-700 nm. It is possible to include other non-standard custom sensors, such as refractive index. Please contact sales@chromacon.com for further information.

Why does the Contichrom CUBE not have an air sensor?

Air sensors bring unnecessary dead volumes and the risk of false alarms. The latter is particularly disruptive for continuous chromatography operations. The Contichrom CUBE therefore instead relies on: 1) the buffer management module integrated in ChromIQ and 2) a pressure watch function. The buffer management system calculates current and required buffer volumes, issues warnings, and ultimately stops the pumps to preventing the system from running dry. The pressure watch function constantly monitors the pump pressures and instantly detects pressure drops caused by air.

What is in-line dilution?

In-line dilution is a term describing the dilution of a fluid stream with a second fluid stream. In chromatography, the eluent from one column can be diluted in line with a buffer of choice before entering the second column. Therefore, optimal chromatographic conditions are ensured on the second column, regardless of the elution conditions on the first column. An intermediary storage of the eluent in between steps is then not required.

The Contichrom CUBE is capable of performing inline dilution, however only if both the first and the second column are operated in isocratic or step elution mode. The Contichrom CUBE Combined can also perform in-line dilution in conjunction with gradient elution.

Is the system CE compliant?

Yes, the system has received a CE Mark. Further certifications include the NRTL Mark (Canada and USA conformity), CB Test Certificate from the IEC and the Korean Certification (KC) Mark.

Which operating software is used to control the Contichrom CUBE?

The Contichrom CUBE is operated through the ChromIQ software. Contichrom systems are always supplied with a laptop and a software license for the ChromIQ software. The software includes wizards to guide the user in the design of all processes that the system can run. For the Contichrom CUBE, wizards for the design of single column batch and CaptureSMB chromatography are included. Moreover, ChromIQ includes a data evaluation module.

Is the system designed to enable 21 CFR Part 11 compliance?

The ChromIQ software contains essential parts required for 21 CFR Part 11 compliance. However, it is not designed as a GMP production system. For these purposes, the YMC EcoPrime Twin has been designed, which is based on the same technology. The scale-up system is in full compliance to 21 CFR Part 11.

Is it possible to have a demonstration of the ChromIQ software?

Yes, this is possible. Please contact sales@chromacon.com to arrange a web-based demonstration.

Does the Contichrom CUBE have a reference history?

The Contichrom CUBE is being marketed and sold worldwide since 2015. Since then, numerous units have been installed in labs of pharmaceutical and biotech companies, as well as academic labs. Furthermore, processes have been scaled successfully from lab to GMP production.

What is the size of the system?

The dimensions are 37 cm x 51 cm x 45 cm (14.6" x 20.0" x 17.7"). It weighs 30 kg (67 lb) and thus fits nicely on any conventional lab bench. The optional fraction collector (R1) is 33 cm x 31 cm x 36 cm (13.0" x 12.2" x 14.1").

Are demo/rental systems available?

A limited number of demo / rental systems are available worldwide. Please contact sales@chromacon.com to check availability and arrange a rental.

Can the Contichrom CUBE run continuous polishing processes such as MCSGP or N-Rich?

No, the Contichrom CUBE only runs single column "batch" processes, connected (integrated) two-column "batch" processes, and continuous capture processes (CaptureSMB). To access continuous polishing processes, the extended Contichrom CUBE Combined is required. The additional CUBE+ module contains the pumps required for running continuous polishing with linear gradients and inline dilution.

How does CaptureSMB compare to periodic counter-current processes with more columns, such as 3C-PCC or 4C-PCC?

Several operating parameters, such as the feed titer, washing and cleaning protocols influence different multi-column processes differently. Therefore, a comprehensive answer can be quite complex. However, if restricted to realistic operating points (2.5-5 g/L titer, 15 min. cleaning in place), the CaptureSMB process is always competitive, and often even the most productive process. For details see *Biotech J.* **2016**, 11, 920-931. To discuss your specific conditions, please contact sales@chromacon.com.

What are the unique features of CaptureSMB compared to other 2-column capture processes that use a periodic counter-current principle?

The CaptureSMB process has the following unique features:

- Interconnected washing step: After a column is fully loaded and before it is eluted, it is washed. CaptureSMB ensures that no product is lost in this process step by passing the washing stream through both columns

- Modulated feed flow rate: The feed flow rate differs in the interconnected and the single column loading phases. This maximizes the overall productivity by ensuring that the processing times of both column are matched

What happens to the CaptureSMB process if the titer varies?

On the Contichrom CUBE and the YMC EcoPrime Twin, CaptureSMB is implemented with a dynamic process controller, AutomAb. AutomAb automatically detects variations in the feed titer and adjusts the process parameters automatically. AutomAb also offsets other external influences such as column aging, other feed variations or buffer inconsistencies.

What is the advantage a uniform feed flow rate?

Two arguments are frequently quoted as advantages for uniform feed flow rates in continuous chromatography:

1. For interconnecting a continuous perfusion upstream process with a continuous downstream process: In practice, for risk management reasons, a surge bag is used to collect the stream from the bioreactor, serving as balancing container and making a uniform feed flow rate into the downstream process obsolete. Likewise when used in conjunction with fed-batch fermentation, a uniform feed flow rate is not required either.
2. Reducing the feed flow rate during the single column loading phase reduces the productivity: Indeed, a multi-column process with a consistently higher flow rate would process more feed material in a given time. However, the additional columns and resin material nullifies the effect.

Thus, there are no advantages or tradeoffs associated with uniform or varying feed flow rates. In contrary, a uniform feed flow rate can limit operational flexibility with respect to titer variations and dynamic process control.

Which column dimensions are needed for CaptureSMB, compared to a conventional single column capture process?

As a guidance, the bed height of the column used in the reference single column capture process should be divided by two. If a 20 cm column is used in batch mode, CaptureSMB is most efficiently run with two 10 cm columns. This bed height is ideal for process development, because it can be scaled using standard column solutions.

Have virus clearance and virus carryover been investigated for the CaptureSMB process?

The virus clearance of the CaptureSMB process has been evaluated at an independent site. The virus clearance was found to be excellent. For further details, please contact sales@chromacon.com.

Is there a dynamic process control for CaptureSMB?

The CaptureSMB process can be controlled dynamically with AutomAb. AutomAb automatically adjusts the column load in response to changes of the feed titer and decreasing column capacity as a consequence of column aging, keeping the process at optimum capacity utilization, yield and productivity. Especially column aging cannot be avoided, making dynamic process control a “must have” process analytical tool (PAT).

How do you convert a conventional single-column capture process to a CaptureSMB process?

The ChromIQ software includes a CaptureSMB design wizard, which helps converting a single column batch capture process into a continuous process. In short, a single column breakthrough curve is recorded. Based on an analysis of its fractions, associated flow rate and definition of recovery and regeneration protocols, the software wizard converts the batch to a continuous CaptureSMB process and generates the corresponding method.

Is there acceptance for continuous manufacturing on the side of regulatory agencies?

Both the American FDA and the European EMA support initiatives towards continuous manufacturing. Through the use of continuous biomanufacturing, the agencies expect a more homogeneous quality and greater safety than with conventional batch processing. The FDA has Emerging Technology Programs to support companies considering to switch to continuous manufacturing. Does continuous downstream require continuous upstream?

Continuous downstream is compatible with continuous upstream and (fed-)batch upstream. In all cases continuous downstream processing provides the same advantages in terms of productivity, capacity utilization, buffer consumption and product concentration.