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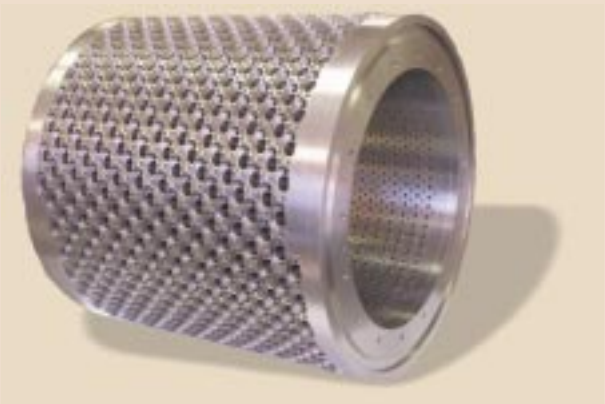
Partitron 25

The first industrial centrifugal partition chromatograph

We specialize in purification of Actives Pharmaceutical Ingredients (APIs), and have built the first production scale centrifugal liquid-liquid chromatograph (25 liters). Models up to 40 liters are now available on the market. We offer either the complete process engineering or contract manufacturing of small natural or synthetic APIs and proteins/antibodies.

Applications

Alkaloids
Antibodies
Antibiotics
Carotenoids
Enzymes
Dyes
Hormones
Lipids
Peptides
Polyphenols
Saponins
Stilbenes…



Centrifugal Partition Chromatography (CPC) is a liquid-liquid partition purification technology which differs from HPLC by the use of a centrifugal field for the immobilization of the liquid stationary phase instead of silicagel.

During the past two decades the structural complexity of the Active Pharmaceutical Ingredients (APIs) has dramatically increased and process engineers are more and more frequently confronted with difficult chromatographic separations. Problems encountered with poor sample solubilities and unwanted interactions with the silica support can be avoided using centrifugal liquid-liquid partition. Both techniques: Counter-Current Chromatography (CCC) and Centrifugal Partition Chromatography (CPC) are used successfully on a laboratory scale, but have never been scaled-up to the industrial production level.

Bench top (0.25 L) and pilot-scale (5 L) CPC units are available from EverSeiko (Sanki)(Japan) and Kromaton (France). These models have all a build in rotor made from staked engraved disks which is limited to an operating pressure of about 60 bars. The Partitron chromatograph with a rotor capacity of 25 liters (Patent pending) has been designed to meet the most rigorous industrial criteria. All wetted parts are made of titanium and perfluoropolymer seals. The rotor, cast in one piece, has been tested at 250 bars and can be operated up to 150 bars (2,100 psi) and even 200 bars (2,900 psi) for future models.

In CPC the absence of a solid support has not only production costs benefits, i.e. following different ratios of stationary to mobile phase inside the rotor and inside an HPLC column, CPC uses on average 10 times less solvent than HPLC, but avoids unwanted interactions with silicagel: irreversible adsorption , rearrangement, epimerization,… In addition, unlimited solvent mixtures can be used, at any pH, with or without additives like anti-oxidants or buffers. The biocompatible titanium authorizes purification of proteins in aqueous two phase systems (ATPS), and the pressure limit of 150 bars allows supercritical CO2 extraction and/or chromatography.

Advantages of CPC in comparison to filled columns

- *Production costs reduced on average 2.5 to 3 times.*
- *Solvent consumption reduced on average 10 times.*
- *High selectivities obtained by a skilled solvent mixture design allow final purities > 99, 5 % for most APIs.*
- *No losses of toxic compounds by irreversible adsorption on silicagel.*
- *Highly reproducible process and linear scale-up from lab- to pilot- and production-scale*
- *Can be used for any purpose: from metallic cation separations to proteins purifications.*
- *Easy sanitization.*
- *Easy automation (only liquids).*

Typically throughputs of several hundred kilograms per year need high flow-rates and therefore high centrifugal fields to avoid bleeding of the stationary phase, that is to say high rotational speeds and consequently high back-pressures.

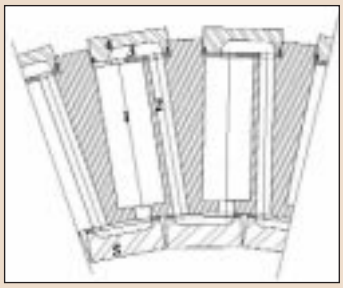
The pressure limit of about 60 bars of the lab scale and pilot models from the market is imposed by the stacked disk assembly which needs Teflon® sheet gaskets between the individual disks. The assembly is held in place by bolting and a limiting pressure is applicable to the mechanical assembly by bolts to prevent excessive creep of the Teflon®. Larger disks would exacerbate the problem and add another limitation: the deleterious effect of the Coriolis force

To circumvent these problems we decided to overcome this disadvantage by designing a robust rotor in order to push back well this pressure limitation beyond the hundred bars. This purpose was achieved by drilling cylindrical partition cells radially through the wall of a cylindrical one-piece metallic cylinder. Titanium was chosen for its lightness, chemical inertness and biocompatibility.

Specifications

Partitron 25

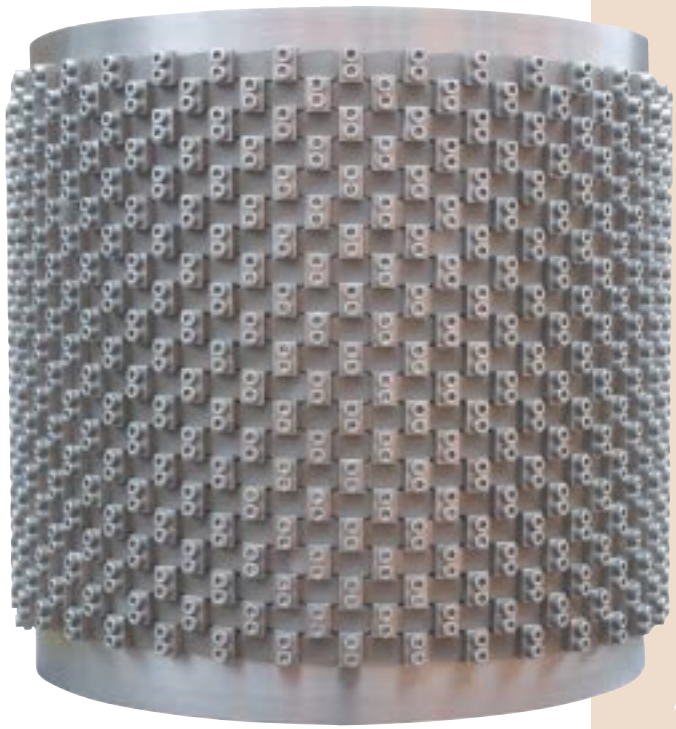
Dimensions: 150 x 100 x 185 cm (L x D x H) + remote (6 m) control panel
Weight: 1,200 kg (2,640 lbs)
Power: 7.5 HP, 380 V, 3 Ø
Tubing: 1/4"



1 - Partition cell
2 - Duct
3 - Connnecting channel
4 - 5 closings

Rotor

titanium + fluoro-elastomer seals
Dimensions: 60 x 67 cm (Ø x h)
Weight: 450 kg (990 lbs)
Number of cylindrical (22 x 70 mm) partition cells: 766
Total volume: 25 liters (nominal); 22,4 liters with knitted titanium wire Multiknit® packings
Rotary seals 1/4" Deublin (tungsten carbide)
Selection valves: Two 4-Ports for ascending - descending mode and injection - elution selection
Rotation speed: 150 to 1500 rpm
Pressure limit: 150 bars
Patent WO 2004/079363
US 2004-0173534-A1



Test experiments

■ ***Naphtalene : Heptanes - Acetonitrile 1:1 (v/v) system***

Descending mode - Stationary phase retention: 84%
The theoretical plate number is higher than the cell number: 920 versus 766 and one physical cell generates 1.2 Theoretical Plates instead of 0.38 for the cells of the Sanki LLI-7.

Flow-rate (ml/min)	*500*	*500*
Speed (rpm)	*900*	*1.300*
Theoretical Plates N	*610*	*920*
Back-pressure (bars)	*93*	*127*

■ ***Myoglobin : PEG 1,000 - K_2HPO_4 : 12.5:12.5 (w/w) system***

Descending mode - Stationary phase retention : 62.8%
Injection of 500 mg myoglobin gives a peak eluting after 45 min with an efficiency of 579 Theoretical Plates, 5 time more than published for the CPC Sanki LLB-M.

200 ml/min	*300 ml/min*
70 bars	**84 bars**

The Partitron 25 apparatus is able to retain high volumes of stationary phase including the difficult-to-retain aqueous two phase systems. It makes it an apparatus of exceptional value for the large scale purification of proteins. Of particular interest are the monoclonal antibodies directed toward tumors, which are currently worldwide under development.

The absence of dead zones and the ease of sanitization make it particularly suitable for the isolation of antibodies from plants (farming) or cell cultures.

From a speculative point of view, the high operating presure could allow for the use of supercritical carbon dioxide, which is known as an efficient diluent for ionic liquids, making the combination of these neoteric solvents attractive for the near future of "green chromatography". In these conditions, the new Partitron 25 could well be used as a reactor-separator.

The actual 150 bar pressure limit will be increased in the forthcoming series of machines to 200 bars by preparing larger rotor diameters up to 100-110 cm and, subsequently, reducing the maximum rotational speed from 1,500 to 500 rpm. These changes will permit use of rotary seals working up to 200 bars with L/min flow rates. This extension of the working presure will correlatively allow a greater number of separation cells, i.e., 1,000 to 1,500 in order to pass the 2,000 theoretical plate count in efficiency. The apparatus volume could also be extended as high as 30 to 50 liters.