Process economy effects of modernizations in vaccine purification

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Process economy effects of modernizations in vaccine purification

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Introduction

The vaccine industry is currently considering modernization of old, legacy processes. Old purification steps are being made obsolete by introducing modern purification techniques, aiming for increased quality and production efficiency, while reducing cost. One approach to increase safety and productivity is to use closed single-use (SU) processing systems, preferably in combination with modern separation principles.

Size exclusion chromatography (SEC) is a technique traditionally used for reduction of impurities in vaccine processes, and separation is based on size of the molecules. A built-in disadvantage is that relatively large columns are required in production scale as the load is volume-based.

A different technique, separating biomolecules on size, called core bead chromatography has been developed. The core bead technology allows for dual functionality, combining size separation with bind-elute chromatography. Viruses and other large entities pass outside the beads, while impurities (< M_r 700 000) penetrate the inert outer shell and bind to the ligands in the inner core (Fig 1).

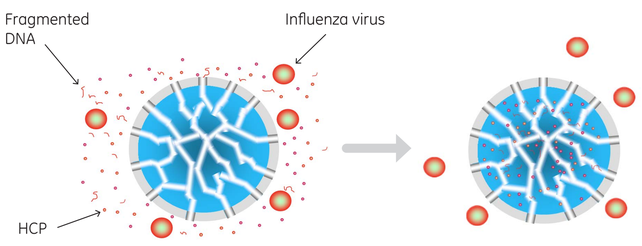

Fig 1. Purification principle of Capto™ Core 700 chromatography resin: fragmented DNA and host cell protein (HCP) bind to the core, while viruse particles remain in the void.

Small-scale experiments

Small-scale experiments were performed to compare SEC and core bead chromatography.

Influenza virus (A/Solomon Island/3/2006 H1N1), cultivated in MDCK cells, clarified by normal flow filtration 2 + 0.6 µm, and thereafter concentrated 20-fold and diafiltrated on an M_r 500 000 hollow-fiber membrane to 20 mM Tris, 150 mM NaCl, pH 7.5, was used as model system. Concentrated feed was treated with Benzonase™ (Merck KGaA). Experiments were run in triplicate. Hemagglutinin (HA) yield and HCP removal were comparable between the two techniques (Fig 3). For SEC, 4.7 mL feed was processed in 2.5 h and for core bead chromatography 10 mL feed in 1.5 h.

(A)

Column:	Tricorn™ 10/600
Resin:	Sepharose 4 Fast Flow
Column volume (CV):	47 mL
Sample load:	0.1 CV
Flowrate:	30 cm/h
HA yield:	86%
HCP removal:	31%
Cleaning in place:	1 M NaOH
Process time:	2.5 h

(B)

Column:	Tricorn 5/50
Resin:	Capto Core 700
Column volume (CV):	1 mL
Sample load:	10 CV
Flowrate:	100 cm/h
HA yield:	85%
HCP removal:	32%
Cleaning in place:	30% 2-propanol in 1 M NaOH
Process time:	1.5 h

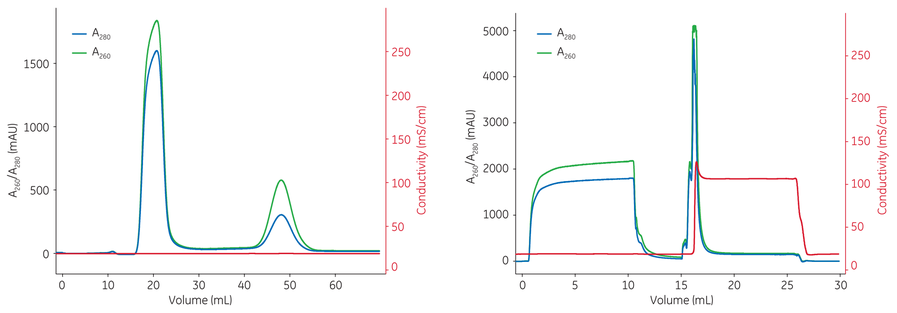

Fig 3. Chromatograms for (A) SEC and (B) for core bead chromatography. Experiments run on ÄKTA™ chromatography system using 20 mM Tris, 150 mM NaCl, pH 7.5 buffer as mobile phase.

Operational cost

Core bead chromatography presented 56% to 59% lower operational cost at 200 L scale and 66% to 70% lower operational cost at 2000 L scale compared with SEC (Fig 4). The SU approach for core bead chromatography gave 7% and 12% lower cost for 200 L and 2000 L scales, respectively. To scale up from 200 L to 2000 L, the operational cost increased 12% to 16% for core bead chromatography and 36% for SEC.

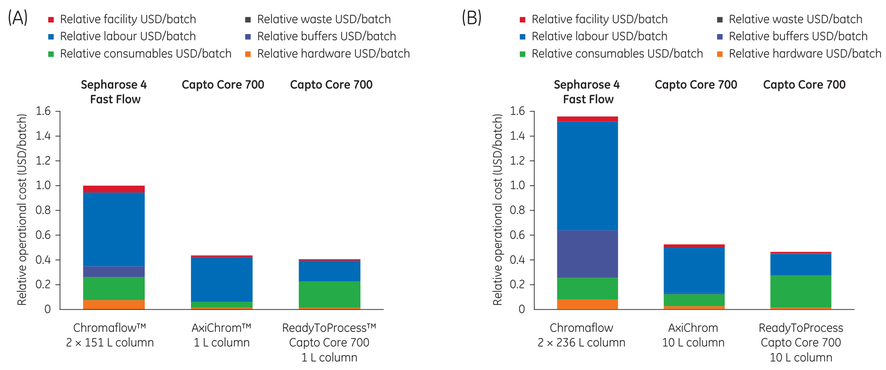

Fig 4. Operational cost for core bead chromatography and SEC in (A) 200 L and (B) 2000 L scales. The operational cost are relative to Sepharose 4 Fast Flow in Chromaflow 2 × 151 L column at 200 L scale.

Productivity

The productivity for SEC does not increase when scaling up due to limitations in the size of the column, which must be cycled at a certain point, resulting in longer process times. Here, the productivity for SEC is 300–400 mg HA/h at both scales (Fig 5). Core bead chromatography has linear scalability, giving constant process time when scaling up. Therefore, the productivity increases with scale.

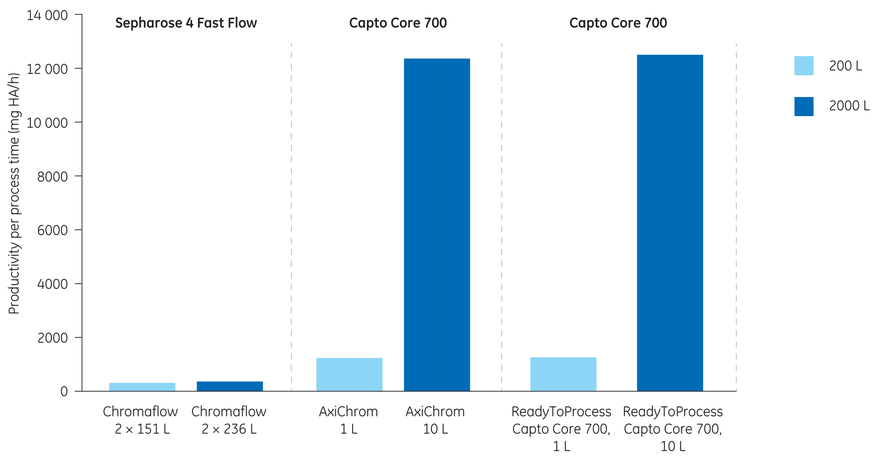

Fig 5. Productivity for core bead chromatography and SEC at 200 L and 2000 L scales.

Operational cost calculation model

Assumptions for the calculation model that compares core bead chromatography and SEC (Fig 2).

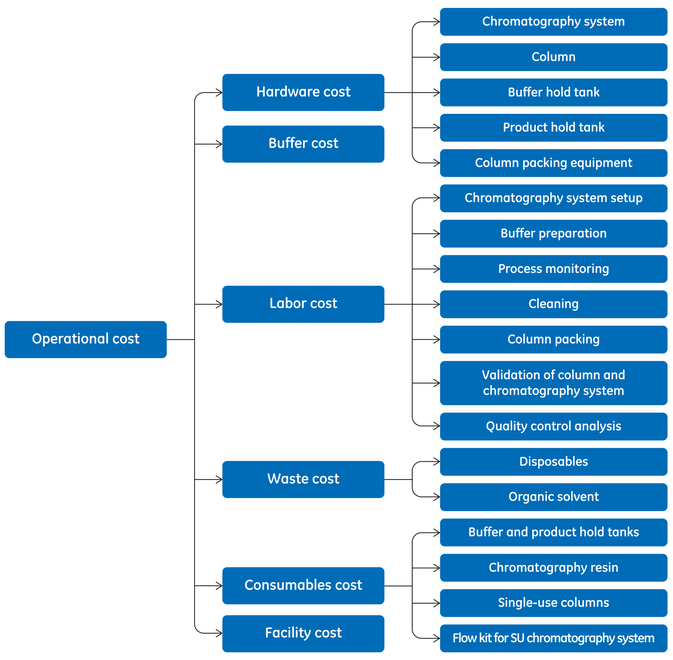

Fig 2. The different components included in the operational cost calculation model.

General assumptions:

- 40 batches/year
- 100 USD/h for labor and overhead count
- Buffer cost 1 USD/L
- 20 cycles life time for Capto Core 700 resin
- 100 cycles life time for Sepharose™ 4 Fast Flow resin
- SEC column scale-up based on constant bed height
- Core bead column scale-up based on column volume and residence time
- SU equipment for buffer and product hold
- Facility cost/m^2 from Biosolve™ (BioPharm Services)
- 10 years hardware depreciation time, 10% interest rate
- 20 years facility depreciation time, 3% interest rate

Summary

A process economic assessment is important when shifting to a different purification technique and can be applied to all vaccines and expression systems.

Here, small-scale experiments showed that performance in terms of HA yield (%) and HCP removal (%) were comparable for SEC and core bead chromatography, using influenza virus produced in MDCK cells as model system.

The productivity is significantly higher for core bead chromatography compared with SEC, especially at 2000 L scale, as core bead chromatography allows linear scalability, while the SEC column must be cycled.

Core bead chromatography presented lower operational cost than SEC as a result of:

- lower hardware cost
- smaller footprint
- faster processing
- reduced buffer cost and water for injection (WFI consumption

The most favorable option, both in terms of operational cost and productivity, for investigated scales were core bead chromatography with an SU approach.

At the scales investigated in this study, the column sizes required for SEC are not compatible with a closed SU system approach.

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