



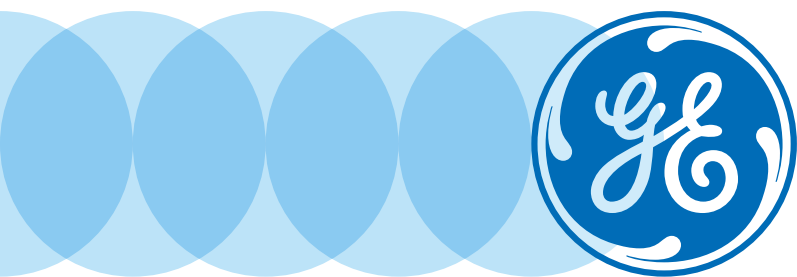
Purification of monoclonal antibodies using modern chromatography media and membranes

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Purification of monoclonal antibodies using modern chromatography media and membranes



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The use of monoclonal antibodies (MAbs) and MAb conjugates as biopharmaceuticals have increased over the last decade. As a result, more cost-effective, efficient, and flexible process purification solutions are of high priority for MAb manufacturers. Increasing product titers upstream can introduce challenges in downstream purification processes. With increased MAb titers, the cell culture supernatant might contain an elevated number of impurities (e.g., aggregates) that need to be separated from the target molecule.

This white paper is a guide to the development of MAb purification platforms and provides an overview of GE Healthcare's offering of process chromatography media (resins) and membranes for MAb purification processes. An introduction to high-throughput process development (HTPD) is also given, together with specific case studies on the development purification steps.

Introduction

Representing about 36% of the total biopharmaceutical market, with an annual sales growth rate of approximately 10%, MAbs are the single largest class of biological drugs today (1). The rapidly growing demand for MAbs has triggered a need for an elevated manufacturing capacity. As a consequence, the antibody titers in upstream cell culture processes have dramatically increased. Improved productivity upstream has put greater demand on downstream processing to address the high titers of MAbs in harvested cell culture fluids.

As a class of molecules, MAbs exhibit many shared properties that make them well-suited for a platform approach to downstream processing. Technology platforms (i.e., standard sets of unit operations, conditions, and methods applied to a given class of molecules) allow for efficient processing from research and development, through clinical phase trials, to the manufacturing of the final product. Downstream MAb purification platforms commonly include a protein A-based capture step followed by one or two polishing steps to remove remaining impurities (Fig 1). The use of platforms for MAb production is well-established. However, continuous improvements of these platforms are desirable as technologies are evolving. New chromatography media are introduced with enhanced features, such as higher binding capacity or better selectivity.

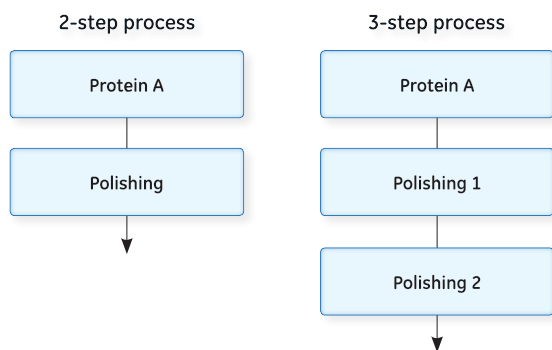


Fig 1. Platform process options for the purification of MAbs.

MAb purification toolbox

GE Healthcare chromatography media for MAb purification are all based on high-flow agarose base matrices. The capture step of the purification process is most commonly performed using protein A media such as MabSelect SuRe™ or MabSelect SuRe LX media. For the polishing steps, ion exchangers such as Capto™ S ImpAct and Capto Q media or multimodal chromatography media such as Capto adhere, Capto adhere ImpRes, or Capto MMC ImpRes

are used. Charged chromatography membranes, such as ReadyToProcess™ Adsorber Q can be used as an alternative to Capto Q in certain applications. An overview of GE Healthcare's MAb purification toolbox is given in Table 1. To facilitate effective process development, our selection of chromatography media and membranes is available in bulk, as prepacked columns or membrane cartridges, as well as in a broad range of scalable HTPD formats.

Table 1. Overview of MAb purification toolbox of chromatography products

Product	Particle size (µm)	Ligand
MabSelect SuRe	85	Alkali-stabilized protein A-derived (<i>E.coli</i>)
MabSelect SuRe LX	85	Alkali-stabilized protein A-derived (<i>E.coli</i>)
Capto S ImpAct (bind-elute mode)	50	Negatively charged sulfonate group and a neutral pyrrolidone
Capto Q (flow-through mode)	90	Quaternary amine
Capto adhere ImpRes (flow-through or bind-elute mode)	40	N-benzyl-N-methyl ethanol amine
Capto adhere (flow-through mode)	75	N-benzyl-N-methyl ethanol amine
Capto MMC ImpRes (bind-elute mode)	40	N-benzoyl homocysteine
ReadyToProcess Adsorber Q		Quaternary amine

Efficient capture of MABs

The high yields and the selectivity that result in an excellent purity (often 99% or more) make protein A-based affinity chromatography a suitable choice for the MAb capture step. MabSelect SuRe media consists of an alkali- and protease-stabilized, recombinant protein A ligand coupled to a rigid, high-flow agarose matrix. The stability of the protein A ligand minimizes ligand leakage and allows for the use of rigorous and cost-effective cleaning procedures based on NaOH. The highly cross-linked agarose matrix of MabSelect SuRe media enables the use of high flow velocities at production scale.

To meet the needs associated with high-titer upstream processes, MabSelect SuRe LX medium was introduced (2). Compared with MabSelect SuRe medium, MabSelect SuRe LX offers an increased dynamic binding capacity (DBC) at a slightly longer residence time. Between 20% and 46% higher binding capacity for various MABs has been demonstrated (3).

Compared with a conventional protein A medium, process economy can be significantly improved by using MabSelect SuRe media in purification of MABs (4). When purifying MABs from high-titer cell culture supernatants, economy was demonstrated to be even further improved by the use of MabSelect SuRe LX medium in the capture step of the downstream purification process (Fig 2).

Product amount: 500 kg
 Bioreactor size: 10 000 L (1 g/L)
 5000 (3, 5 g/L)
 Column size: 20 cm bed height
 Column lifetime: 120 cycles (Sephacrose™ Fast Flow)
 200 cycles (MabSelect SuRe and MabSelect SuRe LX)
 Process time: 10–15 h

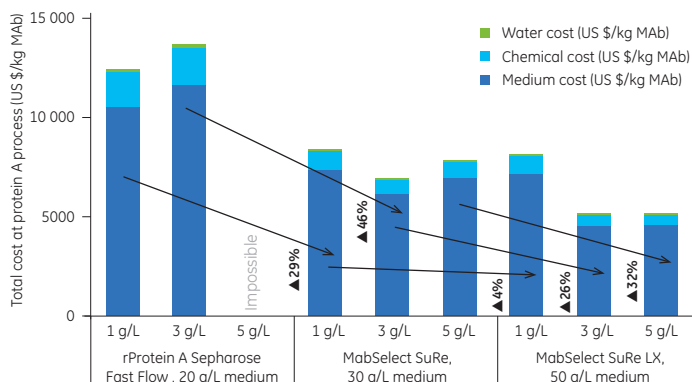


Fig 2. Cost performance comparison of protein A chromatography media. The use of MabSelect SuRe media can significantly improve process economy. For purification of MABs from high-titer productions, MabSelect SuRe LX medium can improve process economy even further. Image adapted from Kobayashi and Ueda. *BioPharm Intl*, 12, 28–31 (2013) (4).

Variable loading concept for increased productivity

The productivity of a chromatography step can be improved by applying the concept of variable loading. Variable loading means that the loading step is divided into two or more parts. In a three-step loading procedure for MabSelect SuRe LX, for example, the material is initially loaded at a high flow rate (i.e., short residence time). When 80% of the capacity at 10% breakthrough is reached, the flow rate is decreased, resulting in an intermediate residence time. Again, when 80% of the breakthrough capacity is reached at this particular flow rate, the flow rate is once more decreased to allow a long residence time (Fig 3).

Variable loading is a known concept (5), but with modern protein A media, the benefits are significantly improved. With MabSelect SuRe LX, a productivity gain of close to 50% has been demonstrated with maintained capacity and purification performance (Fig 4). Variable loading has also been shown to improve the binding capacity of MabSelect SuRe LX medium (6).

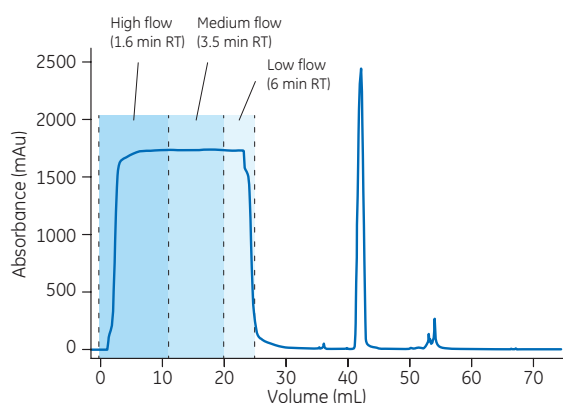


Fig 3. Variable loading on MabSelect SuRe LX medium. In a three-step loading procedure, sample was loaded at stepwise decreasing flow rate, corresponding to residence times of 1.6, 3.5, and 6 min. A sample load of 80% of DBC at 10% breakthrough was applied for each step. The results, in terms of recovery and purity, were comparable with loading at a constant flow rate corresponding to a residence time of 6 min.

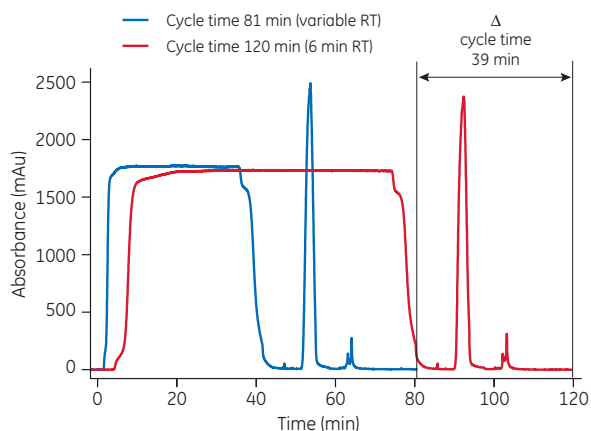


Fig 4. Loading on MabSelect SuRe LX medium using a fixed flow rate corresponding to a residence time (RT) of 6 min (red) or stepwise increasing flow rates corresponding to residence times of 1.6, 3.5, and 6 min (blue). Applying a variable loading concept, productivity could be increased by close to 50% by a 30% reduction in cycle time, with maintained capacity and purification performance.

High-resolution polishing

The polishing steps following the capture step can be performed in either bind-elute (binding) or flow-through (nonbinding) mode.

Two-step process with polishing in flow-through mode

Capto adhere and Capto adhere ImpRes media can both be used for polishing in a two-step process (Fig 5). Both media are based on the same multimodal anion exchange ligands and exhibit similar ligand densities. Hence, both media display high selectivity compared with traditional ion exchangers and are highly efficient in removing remaining impurities like aggregates, host cell protein (HCP), DNA, and viruses.

The difference between the two media is the particle size. Capto adhere ImpRes medium has a smaller particle size (40 μm) than Capto adhere medium (75 μm). The smaller particle size enables higher resolution, whereas the larger particle size of Capto adhere gives the medium excellent pressure/flow properties. Hence, the choice between Capto adhere and Capto adhere ImpRes needs to be made on a case-by-case basis.

Three-step process with traditional ion exchangers

A three-step purification process, with two polishing steps based on one cation exchanger and one anion exchanger, is a classical way of purifying MABs.

Cation exchangers are used for the removal of HCP, protein A, aggregates, and fragments. The cation exchange step is commonly followed by an anion exchange step (run in flow-through mode) for removal of remaining impurities such as DNA.

Chromatography media and membranes suitable for polishing in a three-step purification process are Capto S ImpAct, Capto Q, and ReadyToProcess Adosorber Q (Fig 5). Typical results from a traditional three-step process are shown in Table 2.

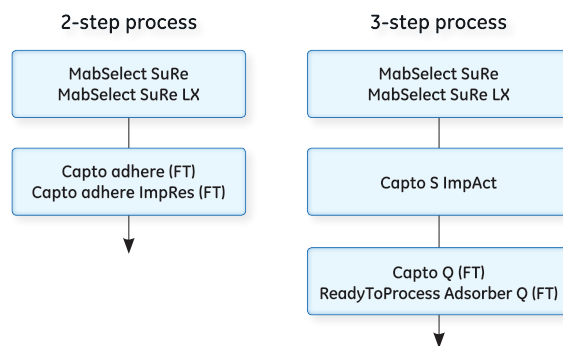


Fig 5. Platform process alternatives suitable for use in majority of MAB purifications. FT = flow-through mode.

Table 2. Results reflecting a typical outcome of a traditional tree-step process

Process step	MAb yield (%)	Aggregates (%)	HCP (ppm)	Leached ligand (ppm)
MabSelect SuRe LX	95	2 to 3	300 to 2000	4 to 15
Capto S ImpAct	90	< 1	< 100	< 1
Capto Q	99	< 1	< 5	< 1
Total process yield	~ 86			

Chromatography media versus membranes

ReadyToProcess Adsorber is a range of chromatography membranes for purification of MAbs and other large biomolecules. The membranes have their ligand covalently attached as a flexible hydrogel to a stabilized, reinforced cellulose sheet, rather than to a bead as for media. The ionic charged or hydrophobic membrane surface and macroporous structure of the membranes allow capture and polishing of target biomolecules at high flow rates.

ReadyToProcess Adsorber membranes are delivered ready for use, resulting in short preparation times without the need for column packing and testing. With a single-use design, the membranes contribute to reduced cleaning and validation time as well as associated costs. Furthermore, chromatography membranes consume less buffer than traditional packed bed chromatography, reducing floor space requirements and costs even further compared with auxiliary systems and operations. After use, the membranes are easily disposed.

MAB polishing is one of the primary applications for the ReadyToProcess Adsorber Q membrane. A process economy analysis indicates that ReadyToProcess Adsorber Q can be a cost-efficient alternative to Capto Q medium in small- to mid-scale and low-frequency manufacturing. Conventional packed bed chromatography, on the other hand, displays significant economic advantages in large-scale and repetitive manufacturing. For more challenging purifications, packed bed chromatography is more versatile and, by that, more beneficial. More information on this comparison can be found from the data file for ReadyToProcess Adsorber Q, S, and Phen membranes (29148491 AA). The choice between the two different formats requires careful analysis and will always be case-dependent.

More challenging purifications

For increased resolution when removing challenging impurities, Capto adhere ImpRes can be run in bind-elute mode in a two-step process (7). As Capto adhere ImpRes has a smaller particle size, this medium enables higher resolution when purifying in bind-elute mode. The higher resolution can be beneficial, for example, for removal of challenging fragments or aggregates. A smaller particle size also means higher binding capacity and improved robustness towards residence time (Fig 6).

For more challenging aggregates, Capto adhere or Capto adhere ImpRes can be used as alternatives to Capto Q in the last step of a tree-step process (Fig 7).

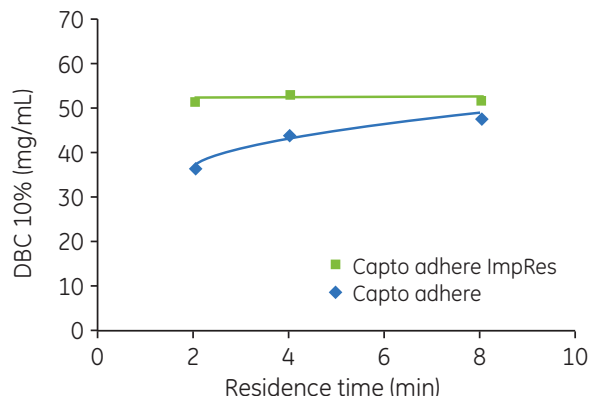


Fig 6. Dynamic binding capacity at 10% breakthrough as a function of residence time. Comparison of Capto adhere ImpRes with Capto adhere media.

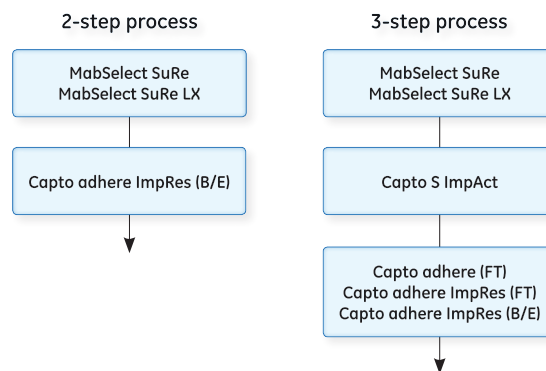


Fig 7. Platform process alternatives for use in challenging MAb purifications. FT = flow-through mode, B/E = bind-elute mode.

High-throughput process development (HTPD)

High throughput in process development is highly beneficial in research efforts for developing optimized and robust protocols for purification of MAbs.

By the introduction of HTPD tools, significant gains in efficiency could be achieved. HTPD solutions can reduce both the required amount of sample and the time needed for development of various chromatography steps.

GE Healthcare's PreDicator™ 96-well filter plates or PreDicator RoboColumn™ units, prefilled with BioProcess™ chromatography media, are suitable for efficient high-throughput screening of both different chromatography media and different chromatographic conditions during process development. Defined conditions can be verified and further optimized using small-scale columns (Fig 8). PreDicator filter plates are also available with ReadyToProcess Adsorber membranes.

More information on HTPD can be found in the handbook 28940358 (8).

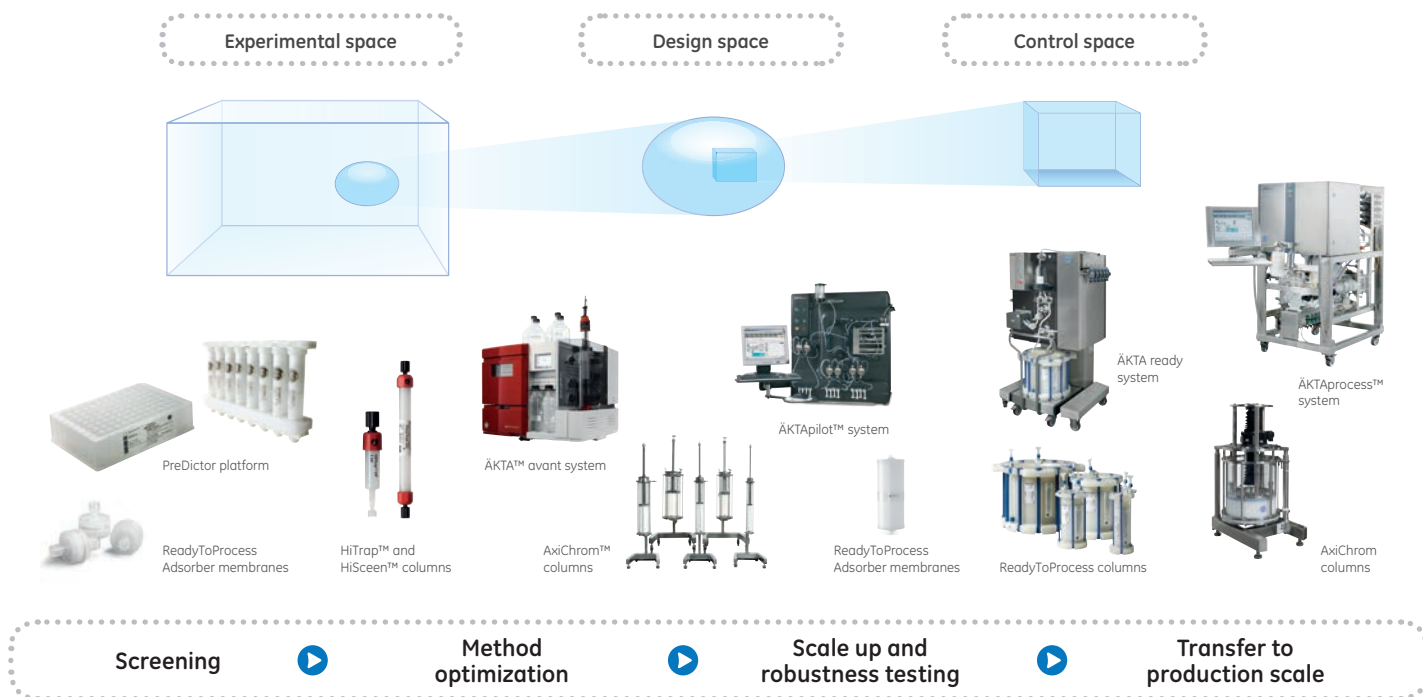


Fig 8. HTPD workflow including initial screening, verification, and further optimization of chromatography conditions in the purification of a target protein.

Case studies

The objective of these case studies was to evaluate different strategies for polishing of MABs. Both two- and three-step processes were evaluated. Different MABs were used in these studies. The purification targets were set to > 90% yield over each process step and < 1% aggregates and < 20 ppm HCP in the final product.

Development of the polishing step (flow-through mode) of a two-step process

Screening of flow-through conditions for MAB1 using Capto adhere ImpRes was initially conducted in PreDictor 96-well filter plates. Further optimization was performed in small-scale columns using a design-of-experiments (DoE) approach.

Conditions screened were pH 4.7 to 5.7, 0.032 to 0.42 M ionic strength (IS), and 60 to 100 g/L sample load. Responses monitored were aggregates, HCP, and product yield. Data were evaluated with MODDE™ software.

The results are illustrated in Figure 9. The contour plots display low aggregate content at high pH and high IS (Fig 9A), low HCP content at high pH and low IS (Fig 9B), and highest yield at low pH and low IS (Fig 9C).

As the optima do not coincide, a sweet spot analysis was performed with the target values given above. The green area of the sweet spot plot shown in Figure 10 represents the conditions where all three criteria are met. Run conditions further verified in small-scale columns were pH 5.7, 0.23 M IS, and 80 g/L sample load. The predicted run conditions where all three target criteria were met correspond well with the verification experiment (Table 3).

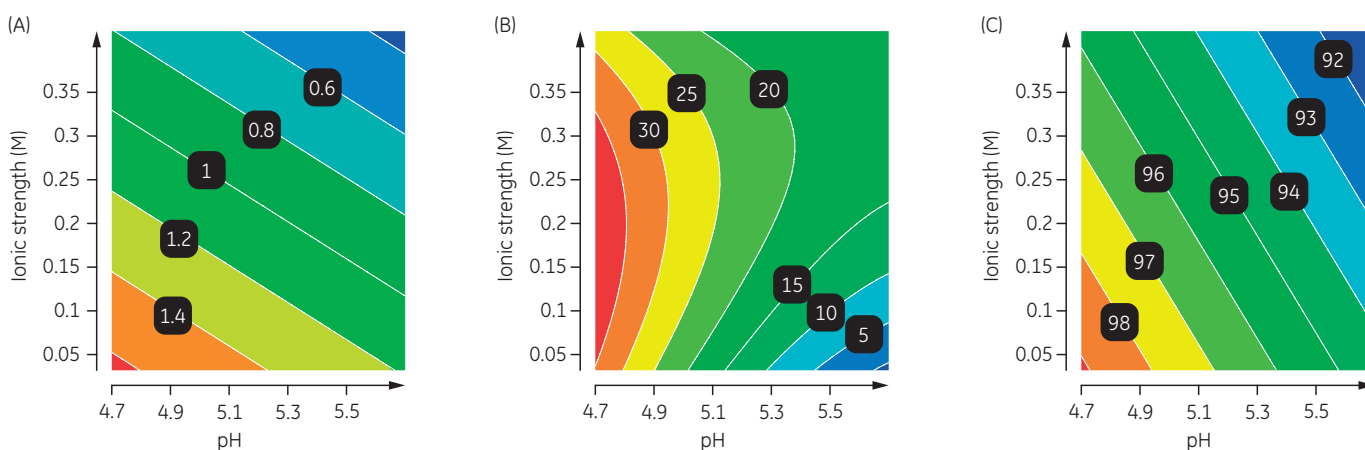


Fig 9. Contour plots showing the results from screening of flow-through conditions for the polishing step of the purification of MAB1. Responses (black squares) were (A) aggregates (%), (B) HCP (ppm), and (C) yield (%).

Examples where Capto adhere medium, based on the larger particle size, have been used in polishing steps can be viewed in Application notes 28950960 and 28907889 (9, 10).

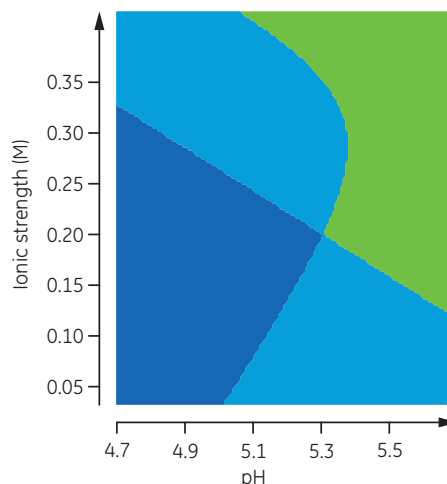


Fig 10. Sweet spot analysis with aggregates < 1%, HCP < 20 ppm, and yield > 90% as target criteria for the purification of MAB1.

Table 3. Predicted and verified Capto adhere ImpRes run conditions (flow-through mode) for purification of MAB1 (verified run conditions were pH 5.7, 0.23 M IS, and 80 g/L sample load)

	Yield (%)	Aggregates (%)	HCP (ppm)
Start		2.0	280
Prediction	93	0.8	15
Verification	92	0.6	15

Note! Protein A levels were below detection limit after the Capto adhere ImpRes step.

Development of a three-step process for a MAb with low monomer stability

For the more challenging MAb2, prone to aggregation at pH above 6, a multimodal anion exchange medium was used as an alternative in the final polishing step in a three-step process.

The initial protein A capture step was followed by a polishing step using Capto S ImpAct cation exchange medium. Over this step, the aggregate concentration was reduced from 3% to 1.2% at a MAb monomer yield of 91%. The MAb concentration in the pool was determined to 11.3 g/L. The host cell protein (HCP) and protein A concentrations were reduced from 298 to 151 ppm and from 3.6 to < 1 ppm, respectively. The good selectivity of Capto S ImpAct between MAb monomer, aggregates, and HCP can be seen from the chromatogram in Figure 11.

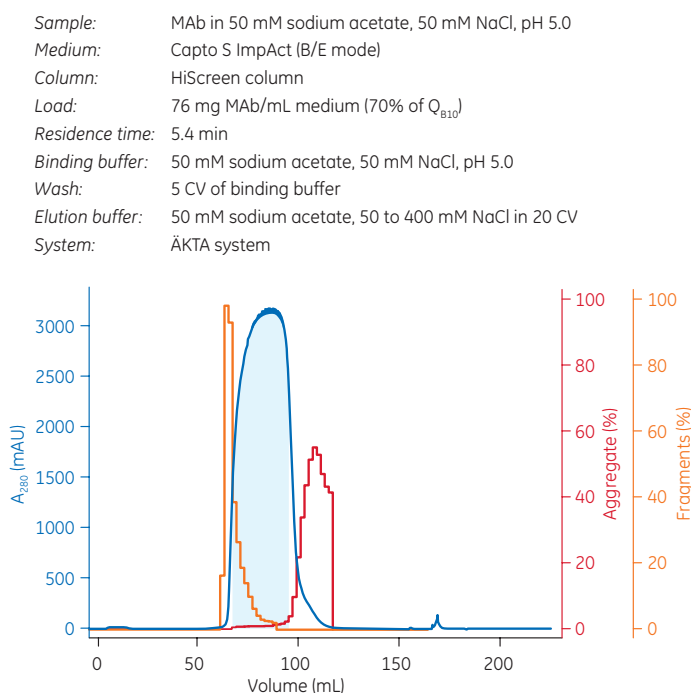


Fig 11. Initial MAb polishing. The fragments (orange histogram) elutes at the front of the elution peak (blue UV trace), whereas the aggregates (red histogram) elutes in the tail of the elution peak. The light blue area under the curve corresponds to pooled product fractions.

For the final polishing step, Capto Q using standard conditions with loading at a pH of 7.5 was initially evaluated for this MAb. However, due to a low monomer stability of the MAb at a neutral pH, aggregates tended to generate over the Capto Q step (data not shown). Hence, Capto adhere ImpRes was evaluated as an alternative to Capto Q for the final polishing step. In addition to efficient removal of HCP, leached protein A, and MAb aggregates, Capto adhere ImpRes has a broader window of operation and can be operated at a lower pH than Capto Q. A chromatogram for the Capto adhere ImpRes step is shown in Figure 12. The overall results from the described three-step MAb purification process shown in Table 4 are comparable with typical results from a traditional three-step process (Table 2).

More details about the development of this three-step MAb purification process can be found in Application note 29132569 (11).

Sample: MAb in 25 mM sodium phosphate, 150 mM NaCl, pH 6.3
Medium: Capto adhere ImpRes (FT mode)
Column: Tricorn™ 5/50
Equilibration buffer: 25 mM phosphate, 150 mM NaCl, pH 6.3
Load: 150 mg MAb/mL medium at a flow rate of 0.5 mL/min
Residence time: 5.4 min
System: ÄKTA system

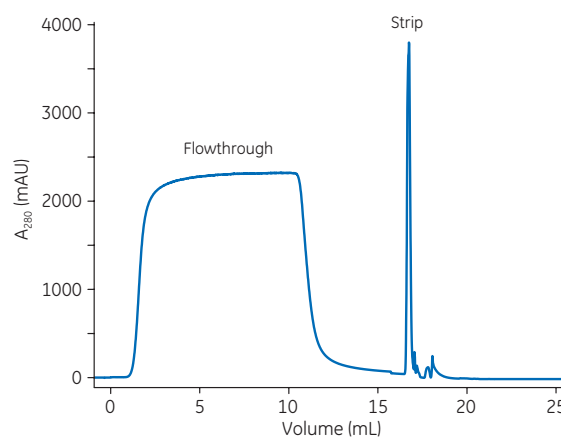


Fig 12. Final MAb polishing using Capto adhere ImpRes. The first UV peak represents the loading phase (product pool), where the MAb flows through the column, whereas impurities such as MAb aggregates, HCP, protein A, DNA, and viruses bind to the medium. The second peak contains mainly impurities that are stripped of the column with 100 mM acetic acid.

Table 4. Results from the three-step purification process for MAb3

Process step	MAb yield (%)	MAb concentration (mg/mL)	Aggregates (%)	HCP (ppm)	Leached ligand (ppm)
MabSelect Sure LX	99	37	2.9	298	3.6
Capto S ImpAct + buffer change	91	8.3	1.4	154	< 1
Capto adhere ImpRes	94	5.7	0.9	11	< 1
Total process yield	85				

Capto adhere ImpRes in bind-elute mode

Because of poor resolution between the monomer and aggregates, MAb3 could not be purified in flow-through mode on Capto adhere ImpRes. Hence, bind-elute mode was evaluated. Screening of binding conditions for Capto adhere ImpRes was performed in PreDictor 96-well filter plates. Conditions screened were pH 4 to 8 and 0 to 300 mM NaCl. The highest SBC was obtained at high pH and low salt concentration (Fig 13).

Studies of different elution strategies were done in small-scale columns, with a pH gradient from pH 7.8 to 4, with or without addition of salt. In this case, the results showed that addition of 100 mM NaCl in the elution buffer resulted in improved aggregate removal. As shown in Figure 14, aggregates eluted in the tail of the peak. At 90% yield, the aggregate content was reduced from 1.2% to 0.3% when run in bind-elute mode.

Based on the results from gradient elution, a step elution protocol was developed. Binding was performed at pH 7.8 and elution by addition of 45 mM NaCl and reducing pH to 5.4 (Fig 15). Strip was performed at pH 3.5. Analyses of the elution pool showed 0.5% aggregates at 90% yield, low HCP content, and a protein A level below detection limit. Results are summarized in Table 5.

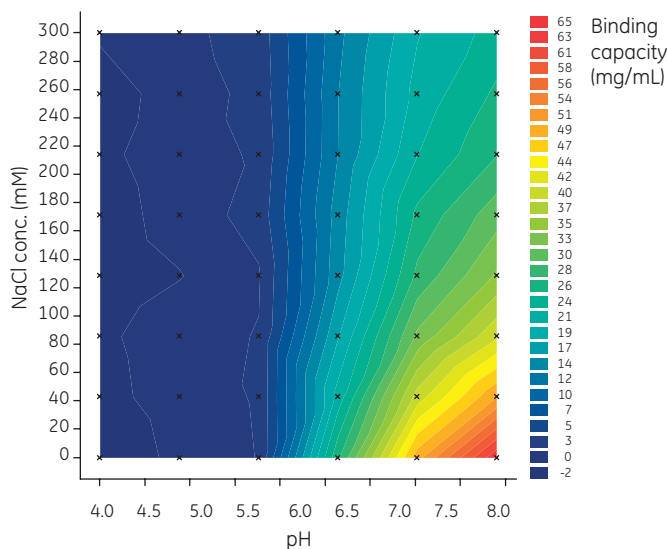


Fig 13. Contour plot from screening of SBC for MAb3 in PreDictor Capto adhere ImpRes 6 μ L.

Table 5. Results from the purification of MAb3 using Capto adhere ImpRes

	Yield (%)	Aggregates (%)	HCP reduction factor	Protein A (ppm)
Start	N/A	1.2	N/A	3
Elution pool	90	0.5	17	< 1
Strip pool	6	3.0	N/A	40

Column: Tricorn 5/50
 Sample load: 30 g MAb/L medium
 A-buffer: 25 mM phosphate, pH 8
 B-buffer: 25 mM phosphate, 25 mM citrate, 100 mM NaCl, pH 4

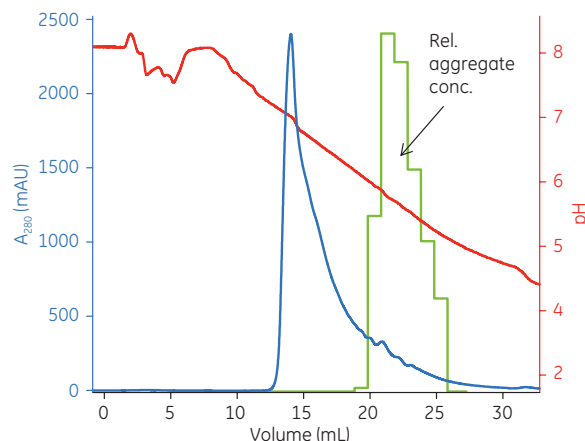


Fig 14. pH gradient elution of MAb3 on Capto adhere ImpRes.

Column: Tricorn 5/50
 Sample load: 30 g MAb/L medium
 A-buffer: 25 mM phosphate, 1.25 mM citrate, 5 mM NaCl, pH 7.8
 B-buffer: 25 mM phosphate, 11.25 mM citrate, 45 mM NaCl, pH 5.4
 Strip buffer: 25 mM phosphate, 25 citrate, 100 mM NaCl, pH 3.5

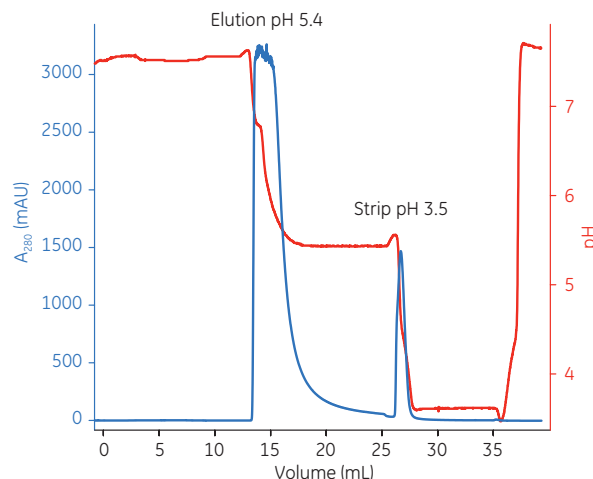


Fig 15. Step elution of MAb3 on Capto adhere ImpRes.

Virus clearance in both flow-through and bind-elute mode

Viral clearance in MAb polishing steps has been demonstrated with model viruses. In a study of Capto adhere run in flow-through mode at two different conductivities, the medium was shown to effectively remove both minute virus of mice (MVM) and murine leukemia virus (MuLV) at high conductivity (Table 5).

Table 5. Study of viral clearance using Capto adhere medium (flow-through mode)

Virus	Conductivity (mS/cm)	Log ₁₀ reduction factor ± 95% confidence limit
MVM	10	5.8 ± 0.3
MVM	30	5.9 ± 0.3
MuLV	10	4.5 ± 0.4
MuLV	30	3.6 ± 0.4

To evaluate virus clearance by using Capto adhere ImpRes in bind-elute mode, pooled fractions from a MAb capture step using MabSelect SuRe medium were used. The pool was spiked with stock solutions of MVM and MuLV. MAbs in the spiked sample were purified using the step-elution protocol described for MAb3 (Fig 15).

The elution pools were analyzed for virus titer by end-point titration. The results showed a 5 log reduction factor for both viruses. For MVM, residual infectivity was detected in the strip fraction, whereas for MuLV, residual infectivity was inactivated in the low-pH elution step.

Conclusions

A toolbox comprising modern chromatography media and membranes is useful in the development of effective purification platforms for MAbs. Protein A media, such as MabSelect SuRe LX, enables efficient purification of MAbs from high-titer harvested cell culture fluids to high purity and yield. The alkali-stabilized protein A ligand permits the use of NaOH for rigorous and cost-effective cleaning operations. The variable loading concept for MabSelect SuRe LX can improve productivity even further. High-resolution Capto ImpAct and Capto ImpRes chromatography media can be used in subsequent polishing steps. Chromatography membranes, such as the ReadyToProcess Adsorber Q, can be a cost-efficient alternative for MAb polishing when the scale is smaller or in a low-frequency manufacturing scenario.

Multiple examples of development of efficient MAb purification processes have been demonstrated in this white paper. Multimodal chromatography media such as Capto adhere and Capto adhere ImpRes offer the possibility of two-step purification processes. Ion exchangers such as Capto S ImpAct and Capto Q media can be combined for efficient removal of remaining impurities in tree-step processes. For more challenging purification tasks, alternative use of Capto adhere ImpRes can be applied.

For efficient process development, GE Healthcare's selection of chromatography media and membranes is available in a broad range of scalable formats for HTPD applications. Let our expertise and experience in the development of MAb processes guide you along your path to success.

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