GE Healthcare
Life Sciences

Application note 28-9845-64 AA

Process chromatography

High-throughput process development for design of cleaning-in-place protocols

Cleaning-in-place (CIP) of chromatography media (resins) is important for the integrity and safety of the final biopharmaceutical product. Efficient and media compatible cleaning procedures also increase the column lifetime and thereby contribute to cost effective processes. Here, a methodology is described where numerous cleaning agents and sequences of cleaning steps can be evaluated in parallel using PreDictor™ 96-well filter plates prefilled with chromatography media. The PreDictor plates were cycled repeatedly with feed and the cleaning efficiency of different chemicals and sequences of cleaning steps was evaluated by analyzing the residual amount of proteins on the beads after cleaning. This application describes screening of CIP conditions for MabSelect SuRe™ in a monoclonal antibody (MAb) process. However, the methodology is generic and can be applied to any combination of chromatography media and feed.

In the downstream purification of a biopharmaceutical process, CIP of the chromatography column is important for the integrity and safety of the final product. Depending on the source of the feed material, various types of impurities, if not removed, may be trapped in the chromatography medium and cause carryover from one cycle to the next. That carryover material may be product or product variants. Other potential carryover impurities are host cell proteins, nucleic acids, retroviral particles, process additives, and lipids (1).

Efficient column cleaning protocols also contribute to cost-effective processes. By preventing a gradual build-up of contaminants, the column lifetime can be increased. The decision to reuse or dispose of the column is driven by process economy and depends on a number of factors including the unit operation scale, cost of media, and media compatibility with cleaning agents. For example, a large protein A column typically warrants repeated use whereas a small ion-exchange column may not (2).

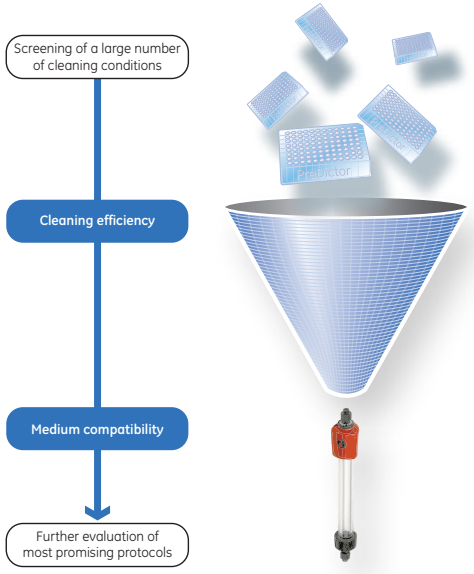

Fig 1. Screening of cleaning conditions using a high-throughput format. PreDictor plates were used for screening of CIP efficiency and medium compatibility with cleaning agents. The selected CIP protocol is verified in a traditional column lifetime study for assessment of the cleaning on performance after continued use.

Column cleaning conditions

Sodium hydroxide has become the gold standard for cleaning and sanitizing chromatography columns. However, some chromatography media are not compatible with sodium hydroxide. Examples of chromatography media sensitive to sodium hydroxide are: 1) chromatography media employing a protein ligand, and 2) chromatography media based on silica or glass. Recent technological development has to some extent alleviated these restrictions. MabSelect SuRe contains an alkali-stabilized, protein A-derived ligand, and provides greater stability than conventional protein A-based media in the alkaline conditions used in CIP protocols. MabSelect SuRe is also based on agarose, which is stable in alkaline conditions.

Traditional column lifetime studies are extremely time and material consuming. When using column chromatography only one cleaning condition study can be carried out at a time. Here a method is described where a large number of different CIP agents and sequences of cleaning steps can be evaluated in parallel for cleaning efficiency and media compatibility. PreDictor plates, 96-well filter plates prefilled with defined volumes of chromatography media, were used for screening of CIP conditions. The selected CIP protocol was then verified in a traditional column lifetime study for assessment of the cleaning on performance after continued use.

The focus of this study was to look at the cleaning efficiency for MabSelect SuRe in a MAb process. However, the method is generic and applicable for design of CIP protocols for any combination of feed and chromatography medium. The method was developed for evaluation of cleaning of protein impurities but could be extended to evaluation of cleaning efficiency of other impurities as well.

Materials and methods

Screening of cleaning conditions using PreDictor plates

The methodology consists of three parts. First the medium in the PreDictor plate is fouled by repeated load-elution of MAb feed without any cleaning. Secondly, different cleaning agents and concentrations of cleaning agents are added to the fouled medium in the wells. After incubation for a defined time, the cleaning agents are removed. The final step is to analyze the residual impurities remaining on the medium after cleaning. Identified CIP candidates can then be verified in a column lifetime study.

Fouling of media and screening of cleaning conditions can be done in a manual workflow using multi-pipettes and manual centrifugation or vacuum filtration. The procedure can also be implemented on an automated robotic system like Tecan™. Here, the procedure is described in general.

Fig 2. Manual or fully automated methods for high-throughput screening of CIP protocols. It is possible to do screening and optimization of CIP protocols manually, using multi-pipettes and manual centrifugation or vacuum filtration (left). The methodology can also be implemented on a fully automated system such as a Tecan robot (right).

Fouling of medium in PreDictor MabSelect SuRe

PreDictor MabSelect SuRe 20 µl was used. In order to resuspend any particles of medium sticking to the top seal, the PreDictor plate was inverted several times in a controlled way according to the instruction (3).

In each step below, the PreDictor plate was mixed briefly on a microplate shaker at 1100 rpm. The PreDictor plate was kept on a collection plate throughout the workflow to avoid direct contact between the PreDictor plate outlets (the drips on the bottom) and any surface. During mixing, the PreDictor plate and the collection plate were fixed to each other and secured to the microplate shaker. Removal of liquid from the PreDictor plates between each step below was done using centrifugation (500 × g for 1 min) or vacuum filtration (160 mbar for 30 s, followed by 300 mbar for 3 s). Before starting the cycling procedure, the storage solution (20% ethanol) was removed.

1. **Equilibration:** 200 µl PBS, pH 7.4 was added per well. This was done three times. After centrifugation or vacuum filtration in the last equilibration step, the bottom of the PreDictor plate was blotted on a soft paper tissue to remove any drops of equilibration buffer that may have accumulated on the bottom of the PreDictor plate*.
2. **Feed application:** 300 µl clarified CHO cell culture with MAb at a concentration of 1.1 g/L was added to the wells. Incubation was done for 30 min on a microplate shaker at 1100 rpm†, ‡.
3. **Wash:** 200 µl PBS, pH 7.4 was added per well
4. **Elution:** 200 µl 0.1 M sodium citrate, pH 3.5 was added per well§. This was done twice.

Steps 1 to 4 were repeated ten times corresponding to ten chromatography cycles and all liquid fractions were discarded. No cleaning was included in the cycling procedure. After elution in the last cycle, the PreDictor plate was re-equilibrated three times with 200 µl PBS per well and then washed once with 200 µl ultrapure water before storage in 200 µl ultrapure water until the screening procedure.

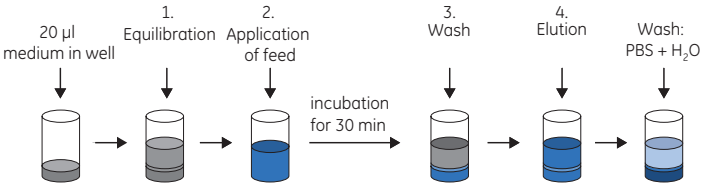

Fig 3. Fouling of media by repeated cycling of PreDictor plates with MAb feed. Steps 1 to 4 were repeated ten times, corresponding to ten chromatography cycles. In each step, mixing was done, and centrifugation or vacuum filtration was used for liquid removal. H_2O = ultrapure water.

* In the automated procedure the bottom of the PreDictor plate was blotted on a pad plate after each liquid removal. The pad plate is a 'holder filter paper', a dedicated Tecan accessory, with a filter in place.

† In the manual work flow, the top of the PreDictor plate was covered with microplate foil and secured on a collection plate on the microplate shaker using rubber bands.

‡ In the automated work flow, a 'Plate shaker PreDictor frame', which is a dedicated Tecan accessory, fixed the PreDictor plate on a collection plate on the shaker board.

§ The elution buffer/pH normally used in the process.

Screening of cleaning conditions

Thirty-two different cleaning protocols including one control (wash with PBS) were evaluated for cleaning efficiency. The CIP protocols contained sequences of 1 to 4 cleaning steps.

The first step was cleaning with an acidic buffer (0.1 M sodium citrate, pH 3.0 or pH 2.5). For the CIP protocols where no acidic step was included, the medium was washed with ultrapure water.

The second cleaning step included one of the following solutions:

- 50 or 100 mM 1-Thioglycerol or 100 mM DTT, pH 8.5
- 8 M urea, 0.1 M sodium citrate, pH 3.0
- 8 M urea, 1.0 M NaCl, 0.1 M sodium citrate, pH 3.0
- 0.1 M ascorbic acid
- 70% ethanol
- 30% isopropanol
- ultrapure water

The third cleaning step included cleaning with 6 M guanidine hydrochloride (Gua-HCl), or various concentrations of sodium hydroxide (0.1-0.5 M), or ultrapure water. MabSelect SuRe can be cleaned with 0.1 M sodium hydroxide, at a contact time of 15 min up to 200 cycles with constant capacity (> 90%). It is also possible to use 0.5 M sodium hydroxide up to 60 cycles (4).

The fourth cleaning step could include cleaning with 0.1 M sodium citrate, pH 3.0. For the CIP protocols where no final acidic step was included, the medium was washed with ultrapure water instead.

Before the screening experiment started, four deep well plates, one for each cleaning step, were prepared with cleaning solutions corresponding to the experimental set-up (Table 1). The different CIP protocols (1-32) were run in triplicates on the PreDictor plate (Fig 4).

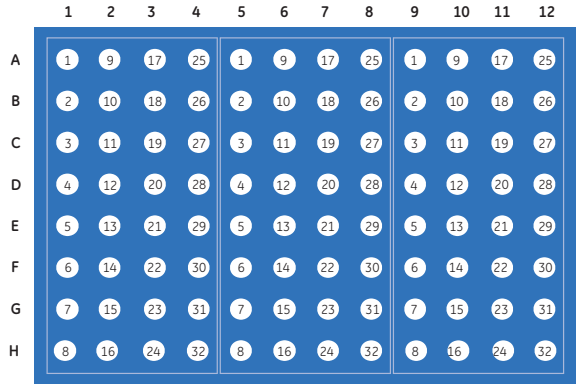

Fig 4. Distribution of the 32 different CIP protocols in the PreDictor plate.

Table 1. Thirty-two different cleaning protocols including one control (wash with PBS) were evaluated for cleaning efficiency. The composition of the reducing agent containing solutions were: 50 or 100 mM 1-Thioglycerol, 25 mM Tris, 0.15 M NaCl, 25 mM KCl, 1 mM EDTA (*without EDTA), pH 8.5, or 100 mM DTT, 25 mM Tris, 0.15 M NaCl, 25 mM KCl. For the CIP steps where no chemical is indicated, ultrapure water was added to the wells in the 96-well filter plate.

CIP protocol	CIP step 1	CIP step 2	CIP step 3	CIP step 4
1			PBS, pH 7.4 (Control)	
2	0.1 M citric acid pH 3.0			
3	0.1 M citric acid pH 2.5			
4			6 M Gua-HCl	
5		100 mM 1-Thioglycerol, pH 8.5		
6	0.1 M citric acid pH 3.0		6 M Gua-HCl	
7	0.1 M citric acid pH 3.0	100 mM 1-Thioglycerol, pH 8.5	6 M Gua-HCl	
8	0.1 M citric acid pH 3.0	100 mM 1-Thioglycerol, pH 8.5	6 M Gua-HCl	0.1 M citric acid pH 3.0
9		8 M urea, 0.1 M citric acid, pH 3.0		
10		8 M urea, 1 M NaCl, 0.1 M citric acid, pH 3.0		
11			100 mM NaOH	
12	0.1 M citric acid pH 3.0		100 mM NaOH	
13	0.1 M citric acid pH 2.5		100 mM NaOH	
14			100 mM NaOH	0.1 M citric acid pH 3.0
15	0.1 M citric acid pH 3.0		100 mM NaOH	0.1 M citric acid pH 3.0
16		8 M urea, 0.1 M citric acid, pH 3.0	100 mM NaOH	
17	8 M urea, 1 M NaCl, 0.1 M citric acid, pH 3.0	100 mM NaOH		
18		0.1 M ascorbic acid	100 mM NaOH	
19	0.1 M citric acid pH 3.0	70 % ethanol	100 mM NaOH	
20	0.1 M citric acid pH 3.0	30 % isopropanol	100 mM NaOH	
21			0.5 M NaOH	
22	0.1 M citric acid pH 3.0		0.5 M NaOH	
23	0.1 M citric acid pH 3.0		0.3 M NaOH	
24		100 mM 1-Thioglycerol, pH 8.5*	100 mM NaOH	
25		100 mM 1-Thioglycerol, pH 8.5	100 mM NaOH	
26		50 mM 1-Thioglycerol, pH 8.5	100 mM NaOH	
27		100 mM DTT, pH 8.5	100 mM NaOH	
28	0.1 M citric acid pH 3.0	100 mM 1-Thioglycerol, pH 8.5	100 mM NaOH	
29	0.1 M citric acid pH 3.0	100 mM 1-Thioglycerol, pH 8.5	100 mM NaOH	0.1 M citric acid pH 3.0
30		100 mM 1-Thioglycerol, pH 8.5	0.5 M NaOH	
31	0.1 M citric acid pH 3.0	100 mM 1-Thioglycerol, pH 8.5	0.5 M NaOH	
32		100 mM NaOH	100 mM 1-Thioglycerol, pH 8.5	

In each step below, the PreDictor plate was mixed briefly on a microplate shaker at 1100 rpm. The PreDictor plate was kept on a collection plate throughout the workflow to avoid direct contact between the PreDictor plate outlets (the drips on the bottom) and any surface. During mixing, the PreDictor plate and the collection plate were fixed to each other and secured to the microplate shaker. Liquid removal from the PreDictor plates between each wash (PBS, ultrapure water) and CIP step below was done using centrifugation (500 × g for 1 min) or vacuum filtration (160 mbar for 30 s, followed by 300 mbar for 3 s). Before starting the screening procedure, the ultrapure water was removed from the fouled PreDictor MabSelect SuRe. No tumbling of the plate was done since the plate had been stored horizontally, with the top up, after the fouling procedure.

1. **Wash:** 200 µl of ultrapure water was added per well. This was done twice. After centrifugation or vacuum filtration in the last wash step, the bottom of the PreDictor plate was blotted on a soft paper tissue to remove drops that may have accumulated on the bottom of the PreDictor plate*.
2. **CIP step 1:** 300 µl of cleaning solutions were transferred from column 1, 2, 3, 4 etc. in the deep-well plate 1, to column 1, 2, 3, 4, etc. in the PreDictor plate. Incubation was carried out for 15 min on a microplate shaker at 1100 rpm†, ‡.

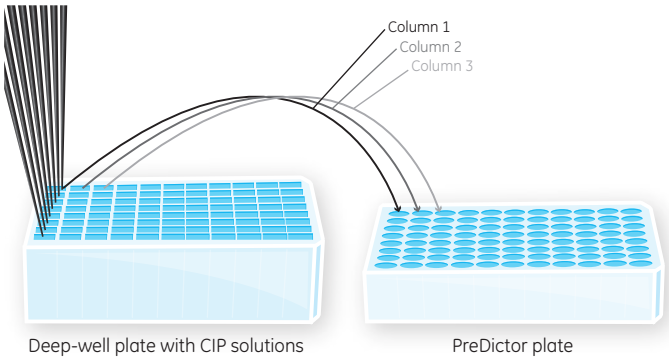

Fig 5. Transfer of cleaning solutions from the deep-well plate to PreDictor plate.

3. **Wash:** 300 µl PBS was added per well followed by wash with 300 µl ultrapure water. After centrifugation or vacuum filtration in the second wash step, the bottom of the PreDictor plate was blotted on a soft paper tissue to remove drops that may have accumulated on the bottom of the PreDictor plate*.
4. **CIP step 2:** 300 µl of cleaning solutions were transferred from column 1, 2, 3, 4 etc. in the deep-well plate 2, to column 1, 2, 3, 4, etc. in the PreDictor plate. Incubation was carried out for 15 min on a microplate shaker at 1100 rpm†, ‡.
5. **Wash:** 300 µl PBS was added per well followed by wash with 300 µl ultrapure water. After centrifugation or vacuum filtration in the second wash step, the bottom of the PreDictor plate was blotted on a soft paper tissue to remove drops that may have accumulated on the bottom of the PreDictor plate*.
6. **CIP step 3:** 300 µl of cleaning solutions were transferred from column 1, 2, 3, 4 etc. in the deep-well plate 3, to column 1, 2, 3, 4, etc. in the PreDictor plate. Incubation was carried out for 15 min on a microplate shaker at 1100 rpm†, ‡.
7. **Wash:** 300 µl PBS was added per well followed by wash with 300 µl ultrapure water. After centrifugation or vacuum filtration in the second wash step, the bottom of the PreDictor plate was blotted on a soft paper tissue to remove drops that may have accumulated on the bottom of the PreDictor plate*.
8. **CIP step 4:** 300 µl of cleaning solutions were transferred from column 1, 2, 3, 4 etc. in the deep-well plate 4, to column 1, 2, 3, 4, etc. in the PreDictor plate. Incubation was carried out for 15 min on a microplate shaker at 1100 rpm†, ‡.
9. **Wash with PBS:** 300 µl PBS was added per well and this step was repeated three times.
10. **Wash with ultrapure water:** 300 µl ultrapure water was added per well and this step was repeated three times.

All liquid fractions in the steps above were discarded.

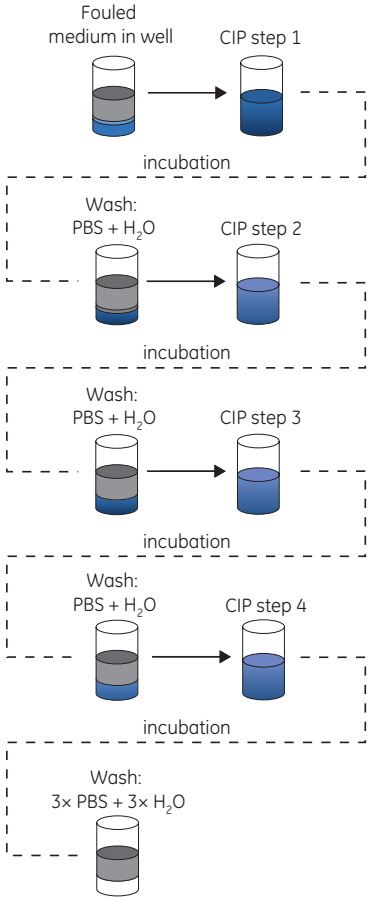

Fig 6. Screening of CIP agents. Different CIP chemicals and sequences of cleaning steps were applied to the fouled media in the wells. Incubation time in the plates was equal to the CIP contact time in a column (typically 15-20 min). Mixing was done in each step. H_2O = ultrapure water.

* In the automated procedure, the bottom of the PreDictor plate was blotted on a pad plate after each liquid removal. The pad plate is a 'holder filter paper', a dedicated Tecan accessory, with a filter in place.

† In the manual work flow, the top of the PreDictor plate was covered with microplate foil and secured on a collection plate on the microplate shaker using rubber bands.

‡ In the automated workflow, a shaker frame, which is a dedicated Tecan accessory, fixed the PreDictor plate on a collection plate on the shaker board.

Analysis of residual protein impurities on the medium after cleaning

Electrophoresis on a chip (HT Protein assay 100 on a Caliper LabChip™ 90 from Caliper Life Sciences) was used because of the automation and high throughput capability of the analytical method. With Caliper DataViewer software it is possible to generate semi-quantitative data, which are convenient when evaluating hundreds of data points. If no Caliper system is available, it is also possible to analyze the residual impurities using traditional SDS-PAGE.

In order to do sample preparation for analysis using chip electrophoresis, the drained media samples (gel plugs) were transferred from the PreDictor plate to an empty collection plate by placing a collection plate very precisely upside down on the filter plate. The two plates were secured with rubber bands. The plates were inverted and the media in the wells were transferred from the filter plate to the collection plate using centrifugation at 972 × g for 5 min.

Three grams of Tris was dissolved in 40 ml ultrapure water. The pH was adjusted to 7.5 with glacial acetic acid. The final volume was adjusted to 50 ml by adding ultrapure water. 0.5 g SDS was dissolved in 5 ml of the Tris buffer and the volume was adjusted to 50 ml by adding ultrapure water. The sample buffer was prepared by mixing 25 ml SDS buffer and 1.39 ml 1 M DTT and the volume was adjusted to 50 ml by adding ultrapure water.

Sample buffer (100 µl) was added to the medium in each well in the collection plate. The plate was covered with microplate foil and mixed briefly at 1100 rpm on a microplate shaker before heating the plate in a heating chamber or heating block at 104°C for 5 min. The collection plate was mixed again briefly at 1100 rpm before it was centrifuged at 500 × g for 2 min to spin down the chromatography medium. 40 µl of the supernatant, which now contained the protein impurities from the medium, was transferred to a PCR-plate for analysis by chip electrophoresis.

The Caliper HT Protein Express chip was prepared according to the HT Protein LabChip Kit User Guide (5). The HT Protein assay 100 high sensitivity was run on a Caliper LabChip™ 90 from Caliper Life Sciences and the data were evaluated using the Caliper software DataViewer.

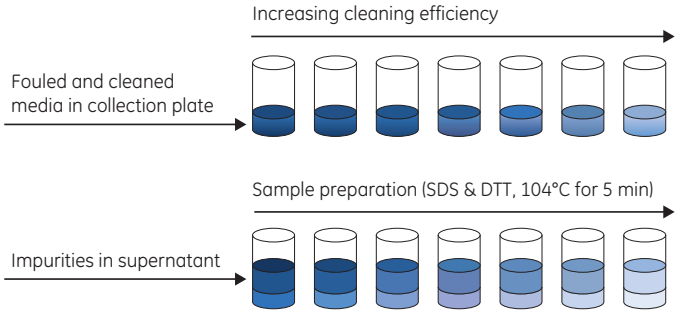

Fig 7. Sample preparation for analysis of residual impurities on the chromatography medium after cleaning. Sample preparation for chip electrophoresis was done by adding an SDS/DTT containing sample buffer and heating the collection plate in a heating chamber or heating block. The supernatant, which now contained the protein impurities from the medium, was removed and analyzed.

Column verification of selected cleaning condition

A selected CIP protocol was verified in a traditional column lifetime study. A Tricorn™ 5/50 column packed with MabSelect SuRe was used and the study was performed on an ÄKTAexplorer™ 10 system.

Clarified CHO cell culture with MAb was loaded to 28 mg MAb/ml MabSelect SuRe, which was 80% of the initial dynamic binding capacity at 10% breakthrough. After post-load wash, the MAb was eluted followed by CIP at a contact time of 15 minutes in each cycle. One hundred fifty cycles were performed. Every 10th cycle, a blank cycle (or "mock" run), where no feed was loaded, was performed. The mock eluate (i.e., the volume where elution peak was expected in a real cycle) was collected for analysis of carryover of target protein and host cell proteins.

Results

Screening of cleaning conditions using a high-throughput format

A MabSelect SuRe PreDictor plate 20 µl (a 96-well filter plate prefilled with MabSelect SuRe medium) was used for design of CIP protocols. The medium in the wells was fouled with MAb feed followed by incubation in various CIP agents. Thirty-two different CIP protocols, including up to four cleaning steps in sequence, were evaluated for cleaning of protein impurities. Chip electrophoresis was used for analysis of residual protein impurities on the medium after cleaning. Pure media samples corresponded to efficient cleaning procedures and vice versa (Figs 7 and 8). Semi-quantitative data generated by the Caliper software was used for evaluation of the cleaning efficiency of the various CIP protocols.

Efficient cleaning of MabSelect SuRe was obtained with 0.1 M sodium hydroxide (CIP protocol 11; Fig 9). No further improvement was seen when 0.1 M sodium hydroxide was combined with acidic steps, solvent, alcohol, or chaotropic agents (CIP protocols 12-20). Even more efficient cleaning was obtained with 0.3-0.5 M sodium hydroxide (CIP protocols 21-23) or with reducing agent (50-100 mM 1-Thioglycerol or 100 mM DTT) followed by sodium hydroxide (CIP protocols 24-31). No difference was observed between the samples that had been cleaned with 50 or 100 mM 1-Thioglycerol. After cleaning with 100 mM reducing agent, followed by 0.5 M sodium hydroxide, no trace of protein impurities could be detected on the medium (CIP 30 and 31). The reversed order of the two steps, 0.1 M sodium hydroxide followed by 100 mM 1-Thioglycerol (CIP protocol 32), did not show improved cleaning efficiency compared to 0.1 M sodium hydroxide alone. A sequence of 100 mM 1-Thioglycerol followed by 6 M guanidine hydrochloride also gave very efficient cleaning (CIP protocols 7 and 8)*. 1-Thioglycerol (100 mM) alone did not show any clearance of protein impurities (CIP protocol 5).

* US Patent 6972327 (Immunex Corporation)

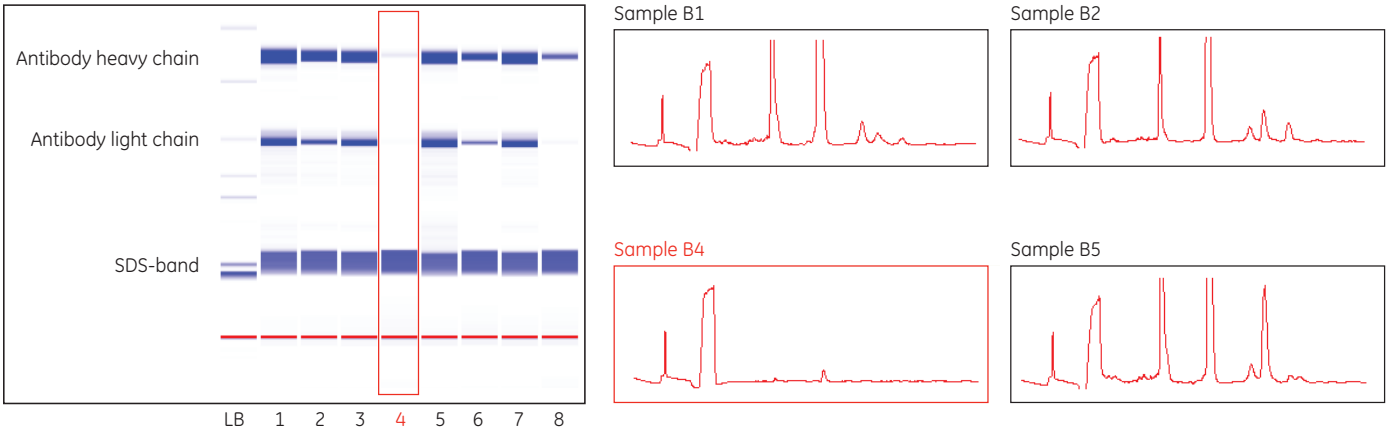

Fig 8. Chip electrophoresis analysis of residual impurities on the medium after cleaning. The Caliper software generates pseudo slab gels (left) and electropherograms (right). Low intensity lane in the slab gel, and corresponding electropherogram, representing the most efficient CIP protocol in this figure, are highlighted. The semi-quantitative data also generated by the Caliper software was used for evaluation of cleaning efficiency of the 32 CIP protocols.

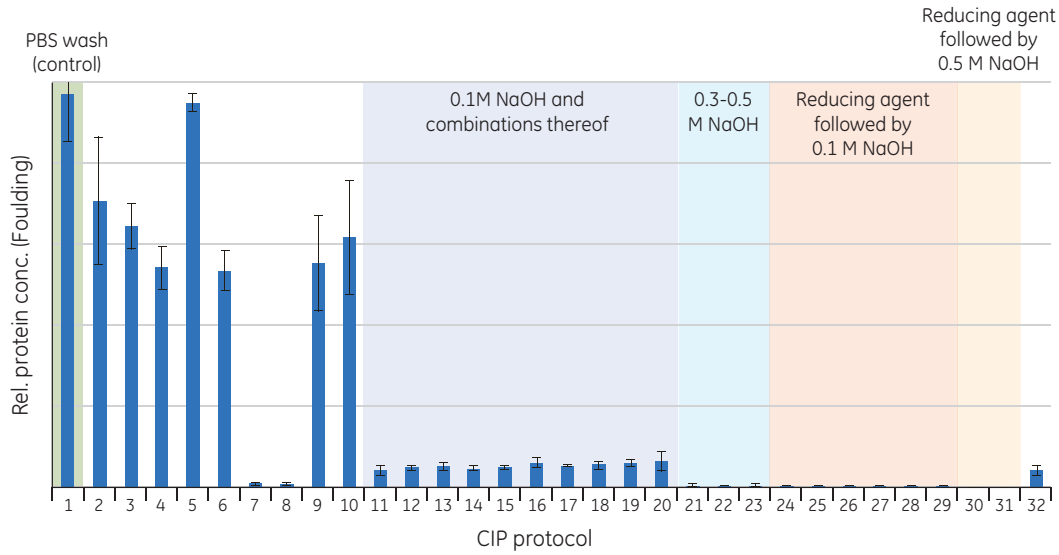

Fig 9. Remaining impurities on MabSelect SuRe after cleaning (n = 3, mean ± SD). Efficient cleaning was obtained with 0.1 M sodium hydroxide (CIP protocol 11). No further improvement was seen when 0.1 M sodium hydroxide was combined with acidic steps, solvent, alcohol or chaotropic agents (CIP protocols 12-20). Even more efficient cleaning was obtained with 0.3-0.5 M sodium hydroxide (CIP protocols 21-23) or with reducing agent (50-100 mM DTT or 1-Thioglycerol) followed by sodium hydroxide (CIP protocols 24-31). The reversed order, 0.1 M sodium hydroxide followed by 100 mM 1-Thioglycerol (CIP protocol 32), did not show improved cleaning efficiency compared to 0.1 M sodium hydroxide alone.

* US Patent 6972327 (Immunex Corporation)

Acidic cleaning alone (pH 3.0 CIP protocol 2, and pH 2.5 CIP protocol 3) gave slightly better cleaning compared with the control (CIP protocol 1), as did 6 M guanidine hydrochloride alone (CIP protocol 4) and 6 M guanidine hydrochloride in combination with an acidic step (CIP protocol 6). Urea (8 M) and 8 M urea in combination with 1.0 M NaCl at low pH (CIP protocol 9 and 10 respectively) also gave slightly better cleaning compared with the control.

Fouling of the plate with feed was done overnight using the robotic system. Working manually, the fouling is done in two working days. Screening of cleaning condition is done in half a day and so is analysis of residual impurities using chip electrophoresis.

Selection of CIP candidate for column verification

The selection of cleaning agent is not only dictated by cleaning effectiveness but also by media compatibility, cost, disposal issues, and experience (1). Two-step cleaning procedures with reducing agent followed by sodium hydroxide or reducing agent followed by guanidine hydrochloride resulted in the most efficient cleaning according to the screening. Nevertheless, a one-step cleaning procedure using 0.1 M sodium hydroxide was selected as the candidate to take further to column verification. Sodium hydroxide is an inexpensive chemical with no disposal issues. MabSelect SuRe is compatible with 0.1 M sodium hydroxide with maintained binding capacity after up to 200 cycles using a CIP contact time of 15 min in each cycle (4). Additionally, a one-step CIP will keep the column maintenance program as short as possible.

Column verification of selected cleaning condition

The result from the functional lifetime study running 150 cycles using a CIP with 0.1 M sodium hydroxide at a contact time of 15 min in each cycle was good. The yield was constant, within the range of 95% to 100% throughout the study. The product purity was consistent within the range 1000 to 1500 ppm HCP. There was no detectable carryover between cycles (< 10 ng/ml). The dynamic binding capacity was > 85% of initial value after 150 cycles. After completion of the study the column was dismantled. No discoloration or fouling of the used MabSelect SuRe medium was observed by visual inspection.

Conclusions

Sodium hydroxide (0.1-0.5 M) gives efficient cleaning of MabSelect SuRe in MAb processes. CIP protocols with reducing agent followed by 0.1-0.5 M sodium hydroxide can be an option for more challenging feedstocks. Reducing agent followed by lower sodium hydroxide concentrations (< 50 mM) or reducing agent followed by 6 M guanidine hydrochloride, are options for less alkali-tolerant affinity media like MabSelect, which is based on recombinant protein A. The method for CIP screening can be used in a manual workflow but it is also possible to implement the procedure on a Tecan robot. In this study, screening of cleaning conditions was done for MabSelect SuRe in a MAb process but the method is general and can be used for any combination of media and feedstock. Verification of selected CIP protocols showed that the correlation between the high-throughput format and columns is very good. Using the high-throughput method, hundreds of cleaning conditions can be screened in a couple of working days. With traditional columns, evaluation of hundreds of cleaning conditions is not feasible due to restriction to evaluation of one cleaning condition at a time.

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