In-line buffer conditioning for biopharmaceutical manufacturing

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Introduction

• Buffer preparation and handling is a major challenge in industrial biopharmaceutical production.

• There is a need to decrease costs in labor and space, this need can be met by formulating the buffers in-line using concentrated stock solutions and water for injection (WFI).

• In-line Conditioning (IC) is GE Healthcare’s newly introduced concept for buffer formulation combined with a purification step such as chromatography or filtration in large scale, based on the ÄKTApure™ platform with UNICORN™ control software.

• It is based on the combinations of various types of feedback control.
Introduction

Fig. 1. Flow diagram that allows buffer formulation according to different principles: flow feedback with recipe and pH feedback combined with flow feedback or conductivity feedback. WFI flow is constantly adjusted to ensure constant flow rate and maintain desired concentrations.
Introduction

Fig. 2. Photograph of the IC system used for buffer formulation in this work. This unit has a somewhat larger footprint than a standard ÄKTApure system and is equipped with 5 pumps, 5 flow meters, 4 conductivity meters and 4 pH meters. These instruments (or others like UV, IR, etc) can be used for control or continuous monitoring and release of the buffer based on various criteria such as pH, conductivity, flow rate (mass balance) or other.
Buffer formulation

- Concentrates of corresponding acid/base, and salt and WFI were used to formulate different buffers in sequence from the same set of concentrates (Fig. 3a).

- Algorithms considering stock concentration were used to determine the recipe to achieve correct pH and concentration using flow feedback (Fig. 3a and Fig. 4b).

- As alternative approaches, flow feedback was combined with pH feedback (Fig. 4a and Fig. 5a) and pH feedback was combined with conductivity feedback (Fig. 5b).

- The latter options allow larger variations in the stock concentrations.
1. **Equilibration buffer**: 20 mM Na phosphate, 50 mM NaCl, pH 7.2.
2. **Wash buffer #1**: 35 mM Na phosphate, 500 mM NaCl, pH 7.2.
3. **Wash buffer #2**: 20 mM Na phosphate, pH 7.2.
4. **Elution buffer**: 20 mM M Na citrate, pH 3.6. All buffers 1-3 formulated at 600 L/h from the same stock solutions 3.00 M NaH$_2$PO$_4$, 325 mM Na$_2$HPO$_4$ and 2.00 M NaCl and water for injection (WFI) using flow feedback.
Fig. 3b. Overlaid chromatograms (A280) from three cycles of a MabSelect SuRe™ antibody capture step with AxiChrom™ columns [Fig. 3 in GE Healthcare Application note 28-9403-48]. The numbers at the top denote the buffers used in each step as described in the previous figure.
Solution enabling significant cost reduction in production (up to 50%)

**Improved:**
- Scalability, flexibility & throughput
- Possibility to work with bags
- Consistency, documentation and traceability

**Reduced:**
- Number of steps, number and size of tanks, footprint, buffer preparation time
- QC testing for release of buffers, documentation lead time and resources needed
- Maintenance, WFI, CIP & waste costs
Process improvement and robustness

20 mM Citrate pH 3.5, 0-1M NaCl 400 L/h

**Fig. 4a.** Salt gradient using pH feedback for the base (flow rate shown in green) and the acid (grey) combined with flow feedback for the salt (light blue) and the WFI (orange).
Process improvement and robustness
20 mM Citrate pH 3.5, 0-1 M NaCl 300 L/h

Fig. 4b. Salt gradient using flow feedback with recipe for all the components, base (green), acid (grey), salt (light blue) and WFI (orange), where the recipe is continuously updated along the gradient. The total flow rate is shown in blue.
Process improvement and robustness

20 mM Citrate pH 3.5  385, 600, 385 L/h

Fig. 5a. pH feedback for the base (flow rate shown in green) and the acid (grey) combined with the constraint of constant buffer concentration through a step in total flow rate (blue).
Process improvement and robustness

20 mM Citrate pH 3.5-5.9 500 L/h

**Fig. 5b.** pH gradient using pH and conductivity feedback. The flow rate of the base is shown in green, and the acid in grey. The total flow rate is shown in blue.
Conclusion

- Buffer formulation at large scale from concentrated stock solutions employing In-line Conditioning feedback principles, allows simplification in biopharmaceutical manufacturing while being compatible with PAT for quality control.
Acknowledgments

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