Scaling in-line buffer preparation from process development to manufacturing

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Introduction

Preparing buffers for large-scale chromatography requires significant resources: time, money, and space to store large buffer volumes.

Inline conditioning (IC) is one possible way to address these challenges. A BioProcess™ IC System uses concentrated, single-component stock solutions of acid, base, salt, and water for injection (WFI), which reduces buffer volumes significantly, saving both floor space and tank volumes. In addition, different buffers can be prepared from the same set of concentrates, streamlining preparation work even further.

Process changes in biomanufacturing require downscaling models. The key tools, functions, and scale-down models that can be used to address these questions are presented here.

The IC approach to buffer manufacturing can also be applied in the lab-scale ÄKTA™ avant chromatography system by using the quaternary valve (Fig 1).

The valve has four inlets that can be used for acid, base, salt, and WFI, thus allowing for the replication of the BioProcess IC System in bench scale.

ÄKTA avant system

BioProcess IC System

To ensure accuracy in formulation and consistency between preparations, different feedback modes can be selected with the BioProcess IC System, while the ÄKTA avant system allows many explorative runs using lower volumes, fraction collector, and scouting.

(A) **ÄKTA avant quaternary valve**
Flow control mode

(B) **Inline conditioning**
Flow, pH, and conductivity control mode

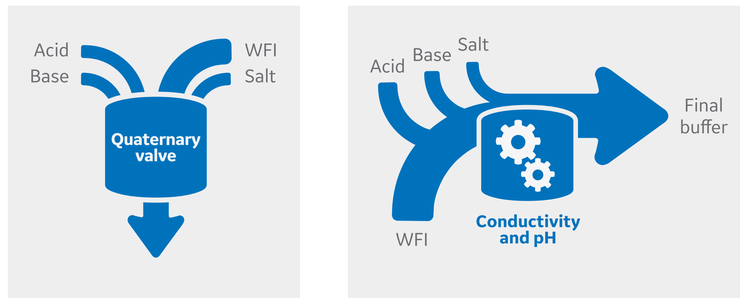


Fig 1. Illustration of mixing strategies used in ÄKTA avant system (A) and BioProcess IC System (B). ÄKTA avant quaternary valve with four inlets (water, acid base, and salt) uses defined amounts of each stock solution to prepare the final buffer. The BioProcess IC System mixes acid, base salt and water using the different feedback control modes pH, flow, and conductivity. The flow feedback corresponds to the quaternary valve function.

Tools

Buffer molar recipes are central for IC, as they are used for planning and optimizing the entire set of buffers needed for the process. Running the Bioprocess IC System in flow feedback mode during the whole run, or during the initial stages of pH and conductivity feedback mode, ensures robust and fast convergence.

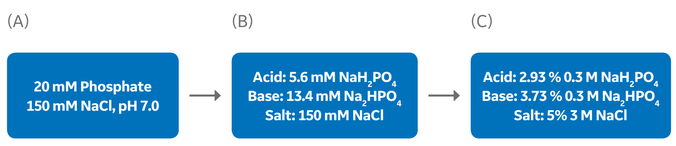
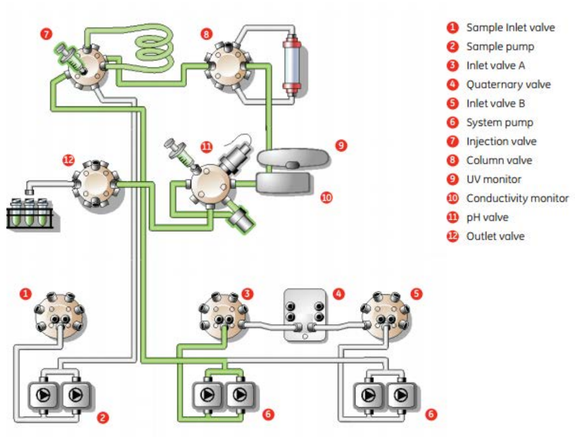


Fig 2. Going from buffer name (A), molar recipe (B) and UNICORN settings for ÄKTA avant quaternary valve, or buffer mix in BioProcess IC System (C).

Tool 1 – Software calculation: Molar recipes for many common buffers can be obtained with the "Explore proportions" functionality of the BufferPro tool in UNICORN™ 6 & 7 software.

(A)



(B)

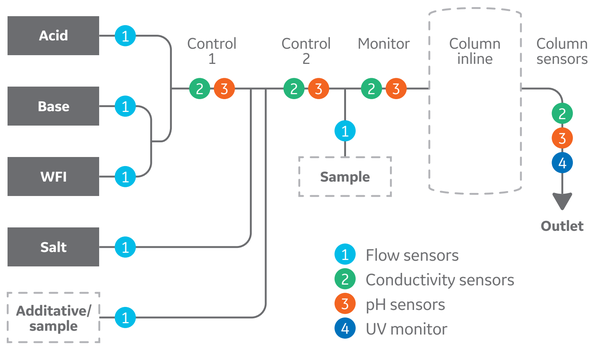


Fig 3. Flow diagrams of the two systems, ÄKTA avant system (A) and BioProcess IC System (B). The quaternary valve of ÄKTA avant simulates the four different pumps in the BioProcess IC System.

Tool 2 – ÄKTA avant quaternary valve: The valve is used in more complicated cases when tool 1 is not sufficient, e.g. for use of salts and additives. The molar recipes of any soluble buffer can be obtained by using the quaternary valve of ÄKTA avant system together with scouting. The flow diagrams above show the similarities between the systems.

Results of the scaled-down model

pH as function of the molar recipe obtained using the ÄKTA avant system: Buffer 20 mM Phosphate with 200 mM NaCl with pH 7.2, by reading the value on the x–axis at the desired pH the molar recipe can be determined (Fig 4).

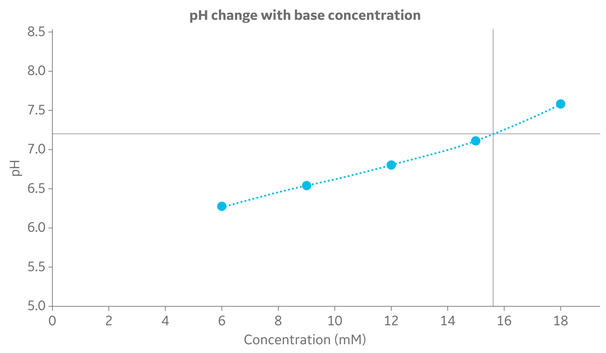


Fig 4. Titration curve to determine the base concentration at a specified pH. The example here is 20 mM Phosphate with 200 mM NaCl at pH 7.2 gives 15.6 mM of the base component (Na_2HPO_4).

To demonstrate that the ÄKTA avant system will give the same results as the BioProcess IC System, four common buffer types were run in systems using the same stock solutions and recipes. All runs gave comparable results (Fig 5). pH was also measured off line in the buffers made in lab-scale.

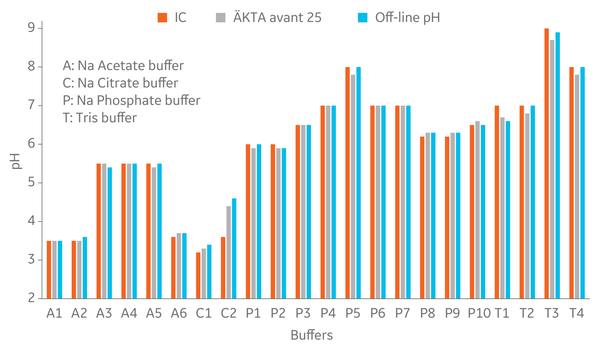


Fig 5. Chart comparing pH in different buffers, made with BioProcess IC System, ÄKTA avant system and off-line pH measurement. The pH value read from the two systems in built pH probes are compared with offline pH measurement of the buffer prepared in the ÄKTA avant system using a standalone pH meter.

The chromatograms in Figures 6 and 7 show how the same buffer is made using ÄKTA avant 25 system and an BioProcess IC System (10 mm; 600 L/h) with the same recipe and stock solutions, giving the same stable result.

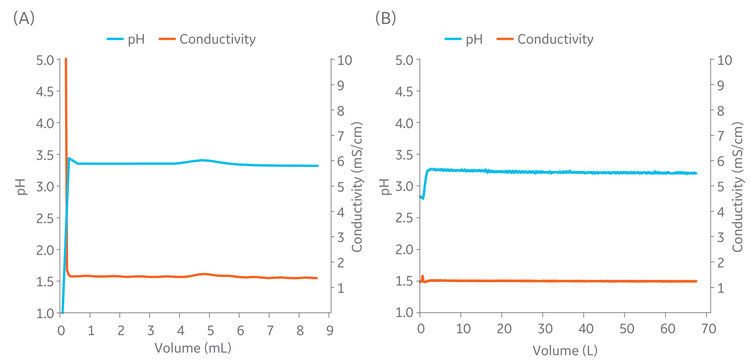


Fig 6. Example of a UNICORN run. 25 mM Na Citrate buffer at pH 3.2 from the ÄKTA avant 25 system (A) and the BioProcess IC System (B).

The X axis on the chromatograms show the required volumes in the different scales, 10 mL compared to 35–70 L per run, depending on the duration and flow rate of the two processes.

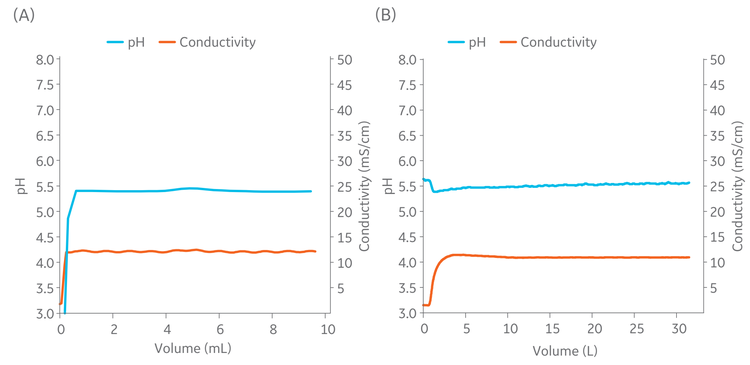


Fig 7. Example of a UNICORN run. 25 mM Na Acetate buffer, 100 mM NaCl at pH 5.5 from the ÄKTA avant system 25 (A) and the BioProcess IC System (B).

References

1. Carredano EN, Nordberg R, Westin S, Busson K, Karlsson TM, Blank TS, Sandegren H & Jagschies G. Simplification of Buffer Formulation and Improvement of Buffer Control with In-Line Conditioning (IC). Biopharmaceutical Processing: Development Design and Implementation of Manufacturing Processes. Amsterdam: Elsevier Ltd.; 2018. p 513–525.

Conclusion

ÄKTA avant system with quaternary valve can be used as a scaled-down model of an BioProcess IC System. With the model it is possible to:

- Determine molar recipes of buffers in an automated manner
- Reduce volumes when determining the buffer recipes
- Implement the IC approach to buffer manufacturing in small scale
- Verify that the IC concept will work with your buffers

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