Overcoming buffer challenges with in-line conditioning

cytiva.com

CY13812-25May20-AN

Overcoming buffer challenges with in-line conditioning

Preparation and storage of the large number of buffers required for biopharmaceutical production can be a challenge, particularly in large production scale. In this application note, we show how in-line conditioning (IC) can help reduce the number of hold tanks and floor space needed for buffer preparation and storage. With IC, buffers of desired formulations are prepared from small-volume single-component stock solutions at the time of need. Formulating buffers from single-component stock solutions eliminates the need of conductivity and pH post-adjustments and adds the flexibility of on-demand production of different buffer formulations from the same stock solutions, simplifying buffer preparation. Compared with using manually formulated 1× buffers, our results show that the total tank volume could be reduced up to 90% and the footprint by 40% using IC.

Introduction

For the production of one, single biopharmaceutical, multiple different buffer formulations are required. Traditionally, buffers are prepared manually according to specific recipes in the volumes needed. Due to the large quantities used, buffer management can become a bottleneck in the production line and, hence, will require careful planning. In addition to high labor cost, there is a risk of human error associated with such a time-intensive manual activity. Buffer variability can affect both quantity and quality of the final product. Also associated with a cost is the floor space required for the preparation and storage of such large buffer quantities.

In-line dilution (ILD) can be used to overcome this buffer challenge (Fig 1A). With ILD, floor space is reduced by the use of buffer concentrates that are diluted with water for injection (WFI)-grade water upon need. Using this approach, however, one buffer concentrate is required to produce one final buffer. As buffers are multi-component formulations, the common ion effect will limit concentration grade when preparing stock solutions. The least soluble ion will determine the maximum concentration of the stock solution. Furthermore, the subsequent dilution will cause pH and conductivity shifts that need to be taken into consideration in the final buffer formulation. ILD does not allow dynamic control and mass

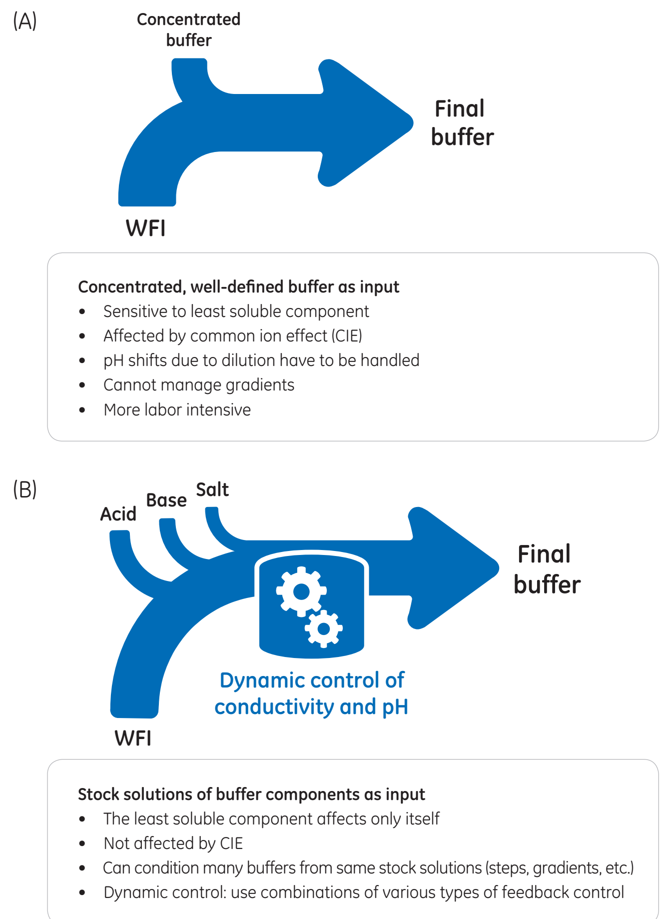

Fig 1. Two ways of addressing buffer challenges: (A) ILD and (B) IC.

balance is not taken into account. Concentrated buffers need to be precisely formulated as dilution will propagate any formulation error. Moreover, managing gradients is not possible with ILD.

IC is another, even more powerful, technique designed to overcome buffer challenges (Fig 1B). With IC, buffers are prepared in line from concentrated, single-component stock solutions of acid, base, salt, and WFI. Because IC uses single-component solutions, one single stock solution can be used to produce several buffers of different concentration, pH, or conductivity, in contrary to ILD where one concentrated solution can only produce one final buffer.

Another benefit of using single-stock components is that higher concentrations can be achieved. The common ion effect (CIE) is less of a limiting factor when each buffer component is concentrated in individual tanks or bags. As higher concentrations can be used, stock solutions of smaller volumes and typically longer shelf lives than neutral concentrated buffers can be used. Not only requiring less space than ILD, IC also addresses issues with buffer variability by allowing for feedback control of the buffer preparation process.

In this study, performance of the Inline conditioning system from GE Healthcare was investigated. The system features built-in dynamic control functionality to adapt to incoming variability and to produce consistent results. Dynamic control carefully monitors effects of ion activity as well as concentrations in stock solutions and final buffer so that buffer variability can be compensated for in line through adjustment of relative volumes to ensure quality control of the final buffer formulation. The dynamic control functionality of the Inline conditioning system uses feedback loops for pH and conductivity to ensure production of final buffer of the required strength and pH. Using equal acid and base single-component solutions, the study focused on evaluating robustness by producing the same buffer with identical critical quality attributes (pH and conductivity) starting with varying concentrations of single-component acid and base stock solutions. In addition, a process economy simulation was conducted, comparing traditional buffer preparation with buffer preparation using IC. The objective was to compare volume needed to formulate buffers, footprint required, and cumulative running costs of different approaches.

Materials and methods

Robustness testing

In this study, feedback control of pH and conductivity was used. Buffers of corresponding acid and base were formulated using the same method in the UNICORN™ system control software. Target pH was set to 4.5 and the conductivity target to 1.8 mS/cm. To probe robustness, three different concentrations of the single-component acid and base stock solutions were prepared. The concentrations ranged from 1.3 to 1.8 M for the base and from 1.5 to 2 M for the acid. Buffer of pH 4.5 and conductivity of 1.8 mS/cm was formulated seven times using different combinations of acid and base.

Process economy simulation

In this simulation, we compared process economy between producing buffers with IC with formulation of 1× buffers in the traditional manual way. Buffer preparations for a protein A chromatography capture step were used as model for the calculations, assuming processing of 30 batches per year.

The following cost categories were included in the simulation model:

- Vessel footprint and cost*
- System cost and maintenance
- Time for preparation of solutions
- Consumable and waste costs*
- Cleaning cost for stainless steel vessels*
- Costs for single-use bags up to 500 L
- Facility construction cost

The following general assumptions were made:

- Capital costs: includes investment cost for the system and tanks required for buffer/stock solution hold.
- Footprint: the floor space needed for the system and hold vessels for stock solutions and buffers. For cost, a factor of 0.15 was used to calculate the total footprint needed.
- Consumables: bags for buffer-hold, filters, and the waste cost for solids.
- Water costs: the water needed for cleaning of the stainless steel hold vessels. The water needed for buffer preparation was not included as it is assumed to be similar in both cases.
- Maintenance costs: the estimated service cost of the system and facility maintenance calculated from the footprint needed for the system and hold vessels and does not include the complete building.
- Labor costs: the labor needed for preparation of buffers and stock solutions, including filtration and cleaning of tanks.

* Data for cost of stainless steel vessels, facility construction, WFI, and waste handling were taken from BioSolve™ software (Biopharm Services Ltd).

Results

The Inline conditioning system can handle buffer preparation off line as well as in line as an integral part of a chromatography or filtration step (Fig 2). During buffer preparation, the system uses dynamic control for feedback regulation of the final buffer formulation. The dynamic control functionality tolerates flexibility in input parameters. Different concentrations of the stock solutions can be used to produce the same target buffer.

Three modes of feedback control can be used with the system: recipe and flow; pH and flow; and pH and conductivity (Fig 3). In recipe and flow feedback, a known buffer formulation is entered in the UNICORN software. The software adjusts the flow rates of the specified stock solutions to achieve desired formulation. This control mode is useful when the temperature is constant and the stock solutions are accurate. In pH and conductivity feedback, the user enters the target pH and conductivity and the software uses feedback from flow, conductivity, and pH sensors to adjust flow rates of the stock solutions to achieve desired conductivity and pH. In this control mode, both the temperature and the stock solution concentration can vary without affecting accuracy of final buffer formulation. In pH and flow feedback, the user enters target pH and the software adjusts the flow rates of the acid and base stock solutions to achieve desired pH in the final formulation.

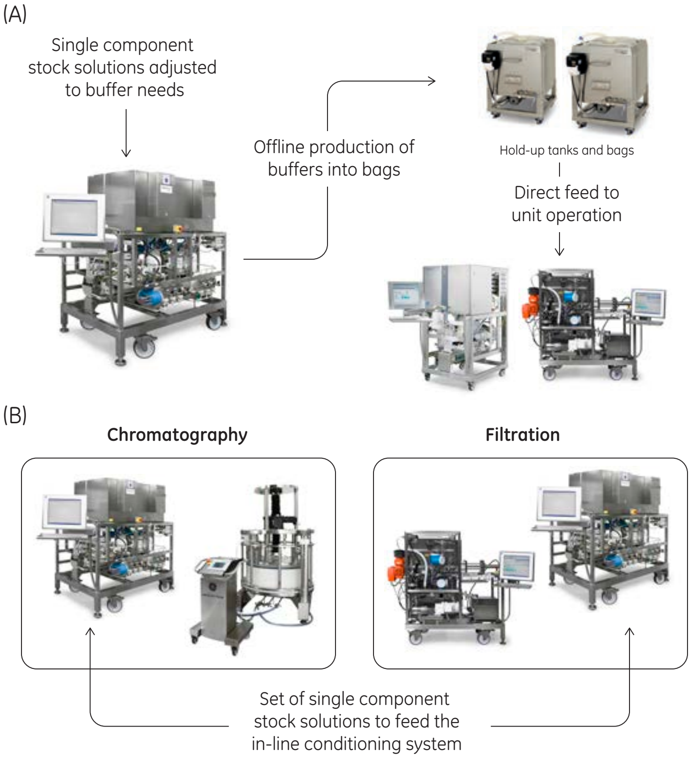

Fig 2. Inline conditioning system can be used as (A) central buffer preparation station or (B) as an integral part of a chromatography or filtration unit operation.

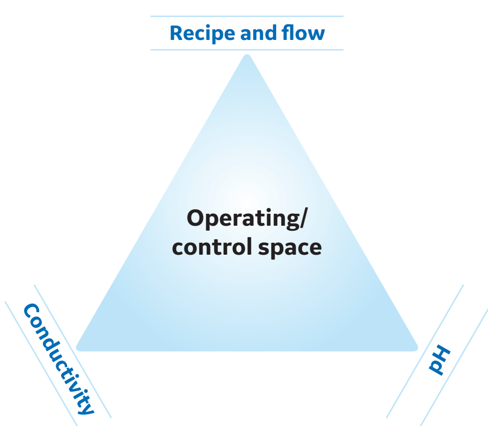

Fig 3. Feedback control modes of Inline conditioning system.

Robustness

Using pH and conductivity feedback control, buffer of desired formulation could be prepared even when stock solutions varied significantly in concentration (Fig 4). All studied combinations of stock solutions resulted in buffers with comparable final properties. All final buffer formulations were of specified pH and conductivity, pH 4.5 and 1.8 mS/cm, respectively (Fig 5). It should be noted that the curves in Figure 5 are not typical from all perspectives. The initial large deviation from target pH and conductivity is caused by setting the starting point for the pumps off target. This was done to challenge the system control and to show that final target will be reached independent of starting point. In a real situation, the starting point will most probably be more close to target and the time frame for reaching specified values much shorter.

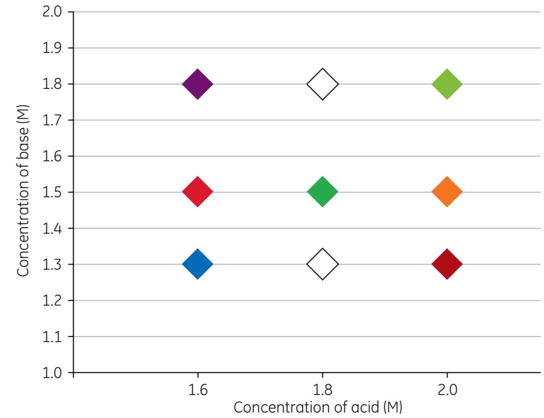

Fig 4. Chart illustrating the different combinations of acid and base stock solutions. The colors correspond to the curves in Figure 5.

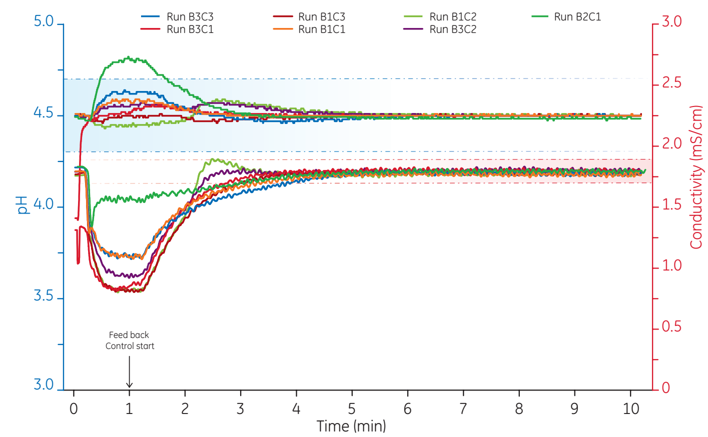

Fig 5. Conductivity and pH curves from seven of the nine runs using pH and conductivity feedback control. The pH and conductivity curves from the same run have the same color. The dotted lines indicate the specification range for pH and conductivity.

Process economy

Compared with the traditional manual way of preparing buffers, our results show that the volume of the buffer hold tanks can be reduced up to 90% for IC (Fig 6). In addition, the total footprint of tanks and system can be reduced by 40% (Fig 7).

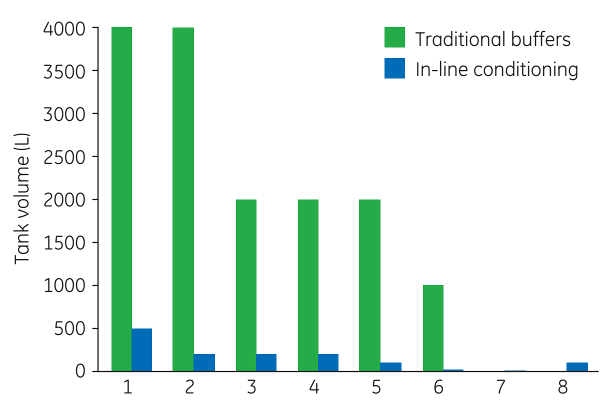

Fig 6. Comparison of tank volumes between traditionally prepared buffers and in-line conditioning.

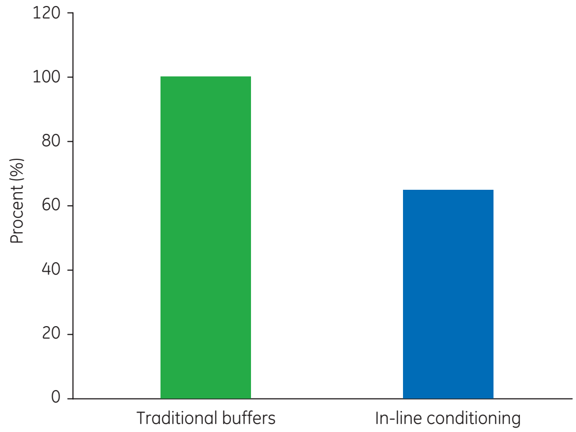

Fig 7. Comparison of footprint of system and tanks between traditionally prepared buffers and in-line conditioning.

Although the initial investment, including tanks and system, is larger for IC, the savings in operating costs are significant. Figure 8 illustrates the difference in cost between traditional buffer preparation and IC. As shown, the higher investment cost for IC can be recouped after only a few years of operation. Additionally, cost associated with waste of buffers that have become obsolete, for example, during delays in production, can be prevented using IC, as single-component stock solutions are highly concentrated solutions of acid, base, or salt, and hence, can exhibit longer shelf life than the final buffer formulation. Automated on-demand buffer preparation not only reduces human error and allows for a more consistent buffer preparation. By producing buffers when needed, the risk of buffers becoming obsolete can be avoided.

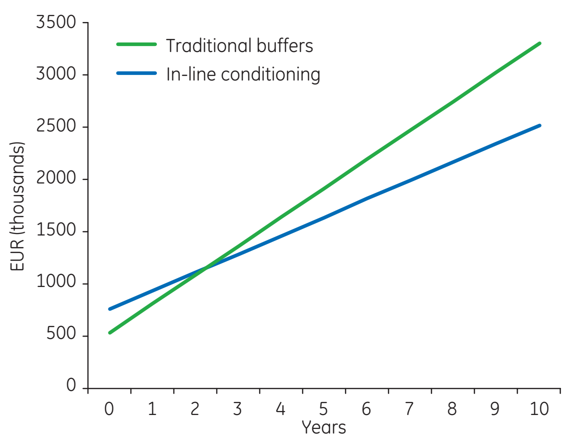

Fig 8. Comparing accumulative running cost between traditionally prepared buffers and in-line conditioning.

Conclusions

This application note demonstrates the performance of the Inline Conditioning system in buffer preparation. The ability of the dynamic control function of the system to adjust for variability in concentrations of stock solutions was demonstrated. Our results show that comparable final buffer formulations could be obtained even though single-component stock solutions varied in concentration.

Most often, buffers of varying pH and conductivity are used in consecutive production steps. As ion concentrations in both stock solutions and final buffer formulation are considered, the system allows the same single-component stock solutions to be used for preparation of buffers differing in ionic strength and pH. Ion concentrations are monitored in line, so that variability can be compensated for through adjustments of relative stock solution volumes.

The dynamic control functionality of the system supports process analytical technology (PAT) in accordance with the quality by design (QbD) initiative defined by the U.S Food and Drug Administration (FDA). Parameters for each buffer preparation are automatically logged for documentation. Automation also reduces manual interaction with the system to prevent risks of human error or contamination.

The process economy simulation reveals that operating costs can be significantly reduced with IC compared with traditional buffer preparation. Our results show that total tank volume can be reduced up to 90% and the footprint by 40% using IC. The small volume requirement for the stock solutions also enables the use of single-use bags.

gelifesciences.com/bioprocess

GE Healthcare UK Ltd., Amersham Place, Little Chalfont, Buckinghamshire, HP7 9NA, UK
GE Healthcare Europe GmbH, Munzinger Strasse 5, D-79111 Freiburg, Germany
GE Healthcare Bio-Sciences Corp., 100 Results Way, Marlborough, MA 01752, USA
GE Healthcare Dharmacon Inc., 2650 Crescent Dr, Lafayette, CO 80026, USA
HyClone Laboratories Inc., 925 W 1800 S, Logan, UT 84321, USA
GE Healthcare Japan Corp., Sanken Bldg., 3-25-1, Hyakunincho Shinjuku-ku, Tokyo 169-0073, Japan
For local office contact information, visit gelifesciences.com/contact.

29209677 AA 09/2016

GE Healthcare Bio-Sciences AB
Björkgatan 30
751 84 Uppsala
Sweden