



Biotech

USD 3246a⁽¹⁾

Cadence[®] Virus Inactivation System



Single-Use Virus Inactivation System for Batch and Continuous Processing

The Cadence Virus Inactivation (VI) system is a fully automated system that provides the ability to perform low pH virus inactivation to an incoming elution stream continuously, with minimal operator involvement.

The system will collect the elution stream from a continuous chromatography system. However, it can easily process as standalone system or with a batch chromatography system.

The system automates sequentially: eluate collection, pH decrease, hold at low pH, pH neutralization, and the transfer to the next unit operation.

The system comprises of a control unit which attaches to one or two system specific Allegro[™] single-use mixers dependent on the application. The specification of the manifolds currently supports 24-hours continuous operation.

Filtration. Separation. Solution.SM

Benefits

- ▶ Designed for integrated unit operation
- ▶ Fully automated for true continuous processing
- ▶ Reduced risk of operator error
- ▶ Ability to operate in batch or continuous mode for flexible facility fit

Overview

Low pH virus inactivation has traditionally been a labor intensive task, involving a sequence of manual operations. The Cadence Virus Inactivation system takes this proven methodology and fully automates the process.

The progress toward unit operation integration and parallel continuous processing makes the adoption of an automated methodology necessary, with the added benefits of reduced operator error and more repeatable operations.

Software

The software represents the latest generation of the Pall automation philosophy, such that all interactions and workflows have been carefully designed and tested to minimize operator error and allow easy interaction with the system.

The program comes with inbuilt sequences for both batch and continuous operation, which can be fully configurable to meet all process requirements. The system is supplied with an Open Platform Communications (OPC) server to allow easy connection with other units and supervisory control and data acquisition (SCADA) systems.

Figure 1

A circular process status graphic shows system state at a glance

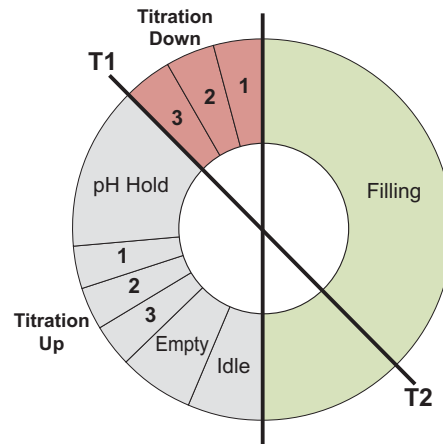


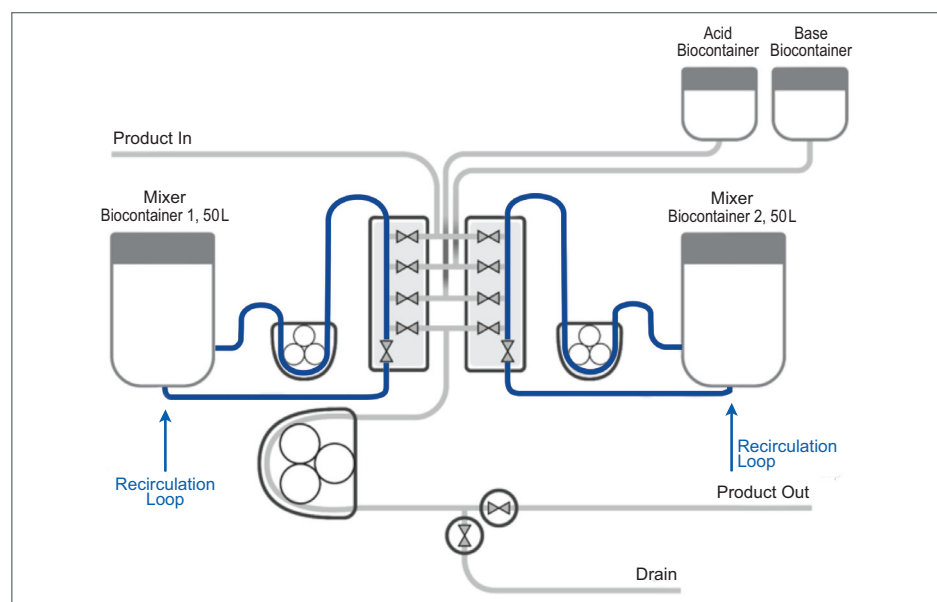
Figure 2

Home screen of the software



Figure 3

Schematic of the Cadence Virus Inactivation system



Mode of Operation

Recirculation Loop

The fluid flow into and out of the mixer is via the bottom of the unit, using the recirculation loop. The recirculation loop facilitates:

- ▶ Entry of externally pumped elutions into the mixer
- ▶ Addition of acid and base
- ▶ Transfer out of treated elution pool after processing
- ▶ Mixing of the elution pool during titrations and hold
- ▶ Sampling of elution pool

The gentle manner of liquid addition from the bottom of the mixer, combined with close control of the impeller by the control unit allows the transfer, titration and mixing of the elution pool without foaming and splash back – minimizing the risk of carry over between batches of elution.

Two Mixer Operation

The system mimics the traditional approach of manual low pH virus inactivation. The collection, low pH titration down, hold and high pH titration are all performed in the same mixer.

During continuous operation, when the system has reached steady state, the incoming elution flow is collected into one mixer, while the second mixer processes the collected elutions.

When mixer #2 has finished processing and has transferred out the current treated elution pool, it is then available for receiving elutions. Mixer #1 can then begin treating the next batch of elutions while the elution stream is directed to mixer #2. The diversion of the flow between mixers can be set to be switched when a certain fill level has been reached, or alternatively when connected to the continuous chromatography system at the end of the current elution after a certain minimum volume has been collected.

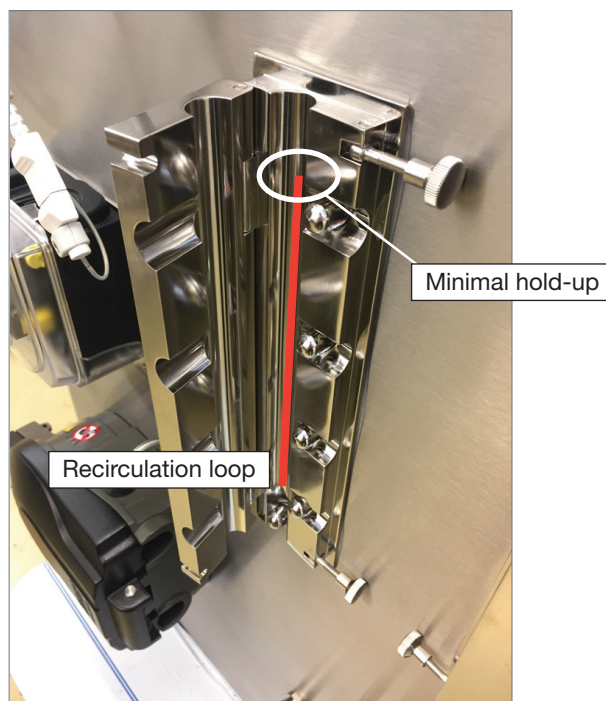
The valve block provides an effectively zero dead-leg valve configuration which ensures that the entire elution pool in the mixer and recirculation loop are effectively mixed and exposed to the inactivation cycle.

Single Mixer Operation

The system can operate with only one mixer attached, facilitating batch operations. A dedicated method template is included within the software to allow easy configuration.

Figure 4

One of the two valve blocks, opened, displaying the interior, into which the single-use liner is fitted



pH Titrations

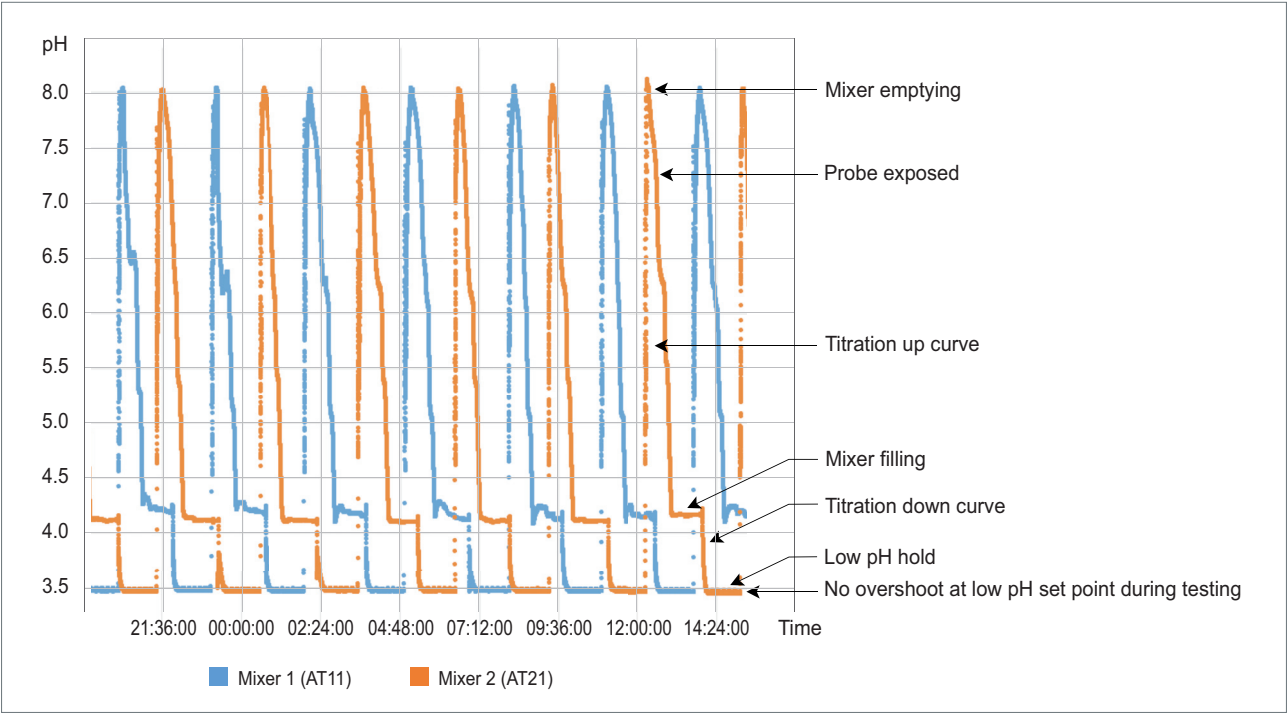
To ensure time efficient operation, the titrations are based on a decreasing dosing volume system. An initial large dose is added to make a quick step change in pH to get close to the desired set point, subsequently medium sized doses are added until an intermediate set point is reached. To obtain the final pH set point the titration process adds small doses, mixes and checks the pH until the final set point is reached.

The use of decreasing dose methodology ensures that the risk of overshoot is minimized, while processing in a timely manner.

For both acid and base additions, the titrations are fully configurable to ensure that the process can be optimized for a particular application.

Pall can supply onsite support with a subject matter expert to ensure that configuration and integration with your process is as easy as possible.

Figure 5
pH graph showing steady state titrations to low pH and high pH set points



Performance

The Cadence VI system can process elutions at a rate of up to approximately 30 L/h. The flow rate that the system can accommodate is dependent on titration behaviors, incubation time and other upstream process conditions.

To put this into context, for a typical monoclonal antibody (mAb) process, the table below shows a guideline operating envelope for the Cadence Virus Inactivation system with 50 L Allegro single-use mixers. Please contact Pall for help with detailed capacity determination.

Table 1
A guideline operating envelope for the Cadence virus inactivation system

	Titer 1 g/L				Titer 5 g/L				Titer 10 g/L			
	Bioreactor Size (L)											
	200	500	1000	2000	200	500	1000	2000	200	500	1000	2000
6 hours	In range	In range	In range	In range	In range	In range	Not in range	Not in range	In range	Not in range	Not in range	Not in range
24 hours	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	In range	Not in range

■ In range ■ Not in range

Manifold Installation

The manifolds are designed to be installed in less than 30 minutes, and are color-coded to ensure that the installation is right first time, every time. The operator is additionally lead by an onscreen installation guide. The entire process has been developed through user testing to ensure simple installation, resulting in time savings while minimizing operator error.

Specifications

Cadence Virus Inactivation System

Dimensions main control unit (w x d x h)	1100 x 900 x 2005 mm without warning light; 1100 x 900 x 2225 mm with warning light
Dimensions Allegro mixer (w x d x h)	964 x 654 x 1364 mm
Weight	350 kg (main control unit); 155 kg (Allegro mixer, full); 105 kg (Allegro mixer, empty)
Number of mixer positions	2 (2 required for continuous operation, 1 required for batch operation)
Maximum operating pressure	0.4 barg single-use assembly (atmospheric pressure only in mixer biocontainer)
Air supply	6 barg (main control unit feeds air to the mixers)
Electricity supply	Single phase

Cadence Virus Inactivation Single-Use (SU) Manifold

Item	Description
Hose and connectors	All tubing is silicone, with CPC connectors internally and sanitary clamp connectors to interface with upstream and downstream processes
Pressure	PendoTECH [®] pressure transmitter
Recirculation pump	Insert is standard silicone tubing-rated for 24 hours operation
Transfer pump	
Gamma irradiation dose	25 – 50 kGy
Tube size	¼ in., ⅜ in., ½ in.

Process Wetted Materials of Construction

Material*	Claims & Compliances
Silicone	USP <88> Class VI, USP <87>, 21CFR177, latex-, phthalate-, and melamine-free
Polypropylene (PP)	USP <88> Class VI, 21CFR177, latex-, phthalate-, and melamine-free
Polysulfone (PSU)	USP <88>. Class VI, ISO 10993, USP <661>, USP <381>, latex-, phthalate-, and melamine-free
Polycarbonate (PC)	USP <88> Class VI, ISO 10993, USP <661>, latex-, phthalate-, and melamine-free

**All components are either ADIF or EMA/410/01 compliant*

Continuous Operation and Expiry

Continuous operation	Specification of the manifolds supports 24 hours continuous operation
Expiry	Manifolds carry a minimum shelf life of 24 months

Ordering Information

Cadence Virus Inactivation System Hardware

Part Number	Description
CADVISYS1CE	VI - Control system complete with two pH probes (CE version)
CADVISYS1UL	VI - Control system complete with two pH probes (UL version)
CADVIMIX50LGRCE	VI - Allegro 50 L mixer VI specific (CE version)
CADVIMIX50LGRUL	VI - Allegro 50 L mixer VI specific (UL version)

Cadence Virus Inactivation Single-Use Manifold

The Cadence VI system comprises 4 separate manifolds:

- A manifold to interconnect with the upstream elution source
- The control panel manifold
- Two identical mixer biocontainer manifolds

The manifolds are supplied double-bagged and gamma-irradiated.

Part Number	Description
VICAD-CT-1	VI - Manifold for the control system (includes interconnection manifold and control system manifold), 1 required
VICAD-MX-50	VI - Allegro 50 L mixer biocontainer VI specific, no pH probe, 2 required to complete the system
LGRMX225PH	pH probe, 2 required per system, reusable probes. First set supplied with the control system
639-80N	pH probe installation bellows, 2 required per system



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