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Automated Trans Membrane Pressure control is key to single pass Tangential Flow Filtration

A paper by Sanofi's Shashi Malladi and Michael Coolbaugh et al features Equilibar's Single Use back pressure regulator, which offers key advantages for Single Pass Tangential Flow Filtration.

Background

Tangential Flow Filtration (TFF) is a primary method of purifying and concentrating biomolecules in downstream processes of pharmaceutical manufacturing. During TFF, fluid passes across a membrane. A pressure differential is set up so that the larger molecules are retained while the smaller, selected solvents and molecules permeate the membrane. TFF decreases clogging problems compared to other filtration methods, which makes it well suited for continuous flow processes or single pass filtration. TFF can be used in concentration, diafiltration, or to remove unwanted larger particles.

Transmembrane pressure (TMP) is a critical variable that controls the permeate flux and influences the gelling on the membrane surface. Many TFF systems are designed to control the flow rate as a proxy for managing the TMP, either by using positive displacement pumps or flow control valves. Back pressure regulators with static set-points are also frequently utilized for TMP control based on the relationship curve between flux and TMP.

Batch TFF processes involve supply and receiver tanks with circulating pumps with flow or pressure regulating devices. These processes work similarly in both the traditional multi-use process systems as well as the newer single-use systems.

In recent years, new emphasis has been placed on continuous drug manufacturing, as opposed to batch manufacturing, for improved yield and productivity. Single pass TFF is a relevant innovation that provides for continuous separations while minimizing pump shear by eliminating unneeded and bulky pumps and tanks. One advantage of single pass TFF is reduced processing time.

Single pass TFF: a new control strategy

The Sanofi paper, published in The Journal of Membrane Science, focuses on single-pass ultrafiltration and diafiltration processes in three steps wherein the desired protein underwent successive steps of initial concentration to an intermediate value, buffer exchange, and final concentration.

Traditional multi-pass TFF processes typically use higher flux rates due to the multiple passes through the filter to concentrate and achieve complete buffer exchange. Design constraints for single pass TFF are more critical and typically require either multiple serial filter membranes or overall lower feed fluxes or their combinations to achieve the desired residence time within the filters. The Sanofi team found that unlike the traditional fixed TMP regime used in multi-pass TFF, SP-TFF requires real-time modulation of the TMP to achieve optimal control.

The Sanofi team used an Equilibar® back pressure regulator to test a novel feedback control system to maintain the retentate concentration at the desired target (grams/liter). The result was a stable six-day run that maintained stable permeate flux with minimal fouling and efficient buffer utilization. The data shows that over the 6-day trial, the TMP was maintained to within 0.4psi, a control window that is not achievable with other traditional technology available today.

In this system, an Equilibar® SDO single-use back pressure regulator was installed on the retentate stream of the two serial filter membranes to control the TMP for the SP-TFF operations. Unlike fixed set-point back pressure regulators, the dome-loaded SDO allowed for convenient and precise computer automation. The retentate concentration sensor signal was fed to the PID control algorithm in an Emerson Delta-V process controller, which output the required TMP pressure to the SDO's pilot regulator.

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By raising the TMP, the permeate flux increased, thereby increasing the retentate concentration when operated within the pressure-dependent regime of the permeate flux versus TMP curve.

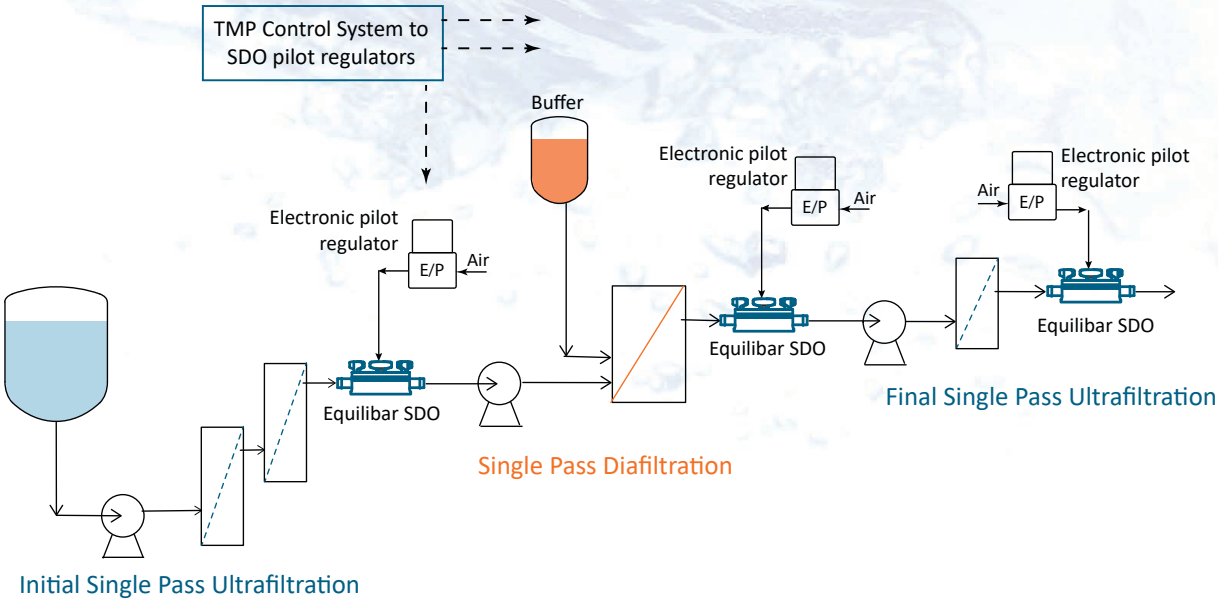

Figure 1: *The Equilibar SDO was used to control TMP in each of the three steps in this novel single pass process, as shown in this simplified illustration*

How Equilibar technology works

The Equilibar SDO is a dome-loaded multi-orifice valve that works by receiving a command signal from the process controller corresponding to the desired TMP. (Because the retentate pressure is typically near zero, the set-point to the SDO is effectively the TMP). The electronic pilot regulator converts the signal into an air pressure, and the SDO valve translates the air pressure to the permeate (TMP) pressure with high fidelity.

Inside the SDO, a thin and supple diaphragm covers a field of parallel orifices positioned between the main body and a reference cap. As fluids flow through the unit, the diaphragm lifts off the orifices to release pressure once the setpoint is reached. When flow is minimal, only a portion of one orifice will open to release the pressure. When flow is high, the diaphragm is pushed up to engage more orifices. The responsiveness and flexibility of the diaphragm engaging with the multiple orifices result in an extremely versatile flow rate range as well as millisecond response to disturbances, making this single use valve uniquely well suited for many sanitary applications.

Figure 2: *Equilibar SDO3 BPR was used in this research*

Reference

Shashi Malladi, Michael J. Coolbaugh, Crystal Thomas, Sushmitha Krishnan, Chad T. Varner, Jason Walther, Kevin P. Brower, Design of a process development workflow and control strategy for single-pass tangential flow filtration and implementation for integrated and continuous biomanufacturing, Journal of Membrane Science, Volume 677, 2023, 121633, ISSN 0376-7388, https://doi.org/10.1016/j.memsci.2023.121633 .

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