THIN-CAKE FILTRATION TECHNOLOGY TO MEET FULL CONTAINMENT FOR AIR-SENSITIVE AND TOXIC CHEMICAL & PHARMACEUTICAL PRODUCTION

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ABSTRACT & INTRODUCTION

In many chemical and pharmaceutical processes, solid-liquid separation, cake washing and drying steps directly impact the effectiveness of the production operation. Further complicating these operations is the nature of the process and especially if the process is air-sensitive or toxic. Process engineers devote much of their time to analyzing these steps.

The solid-liquid separation step can be by pressure, vacuum or centrifugation as well as in a batch or continuous mode. In this separation step, there is a further choice both of the type of filter media and the thickness of the cake or the cake depth during which the separation occurs. Cake washing generally follows and the choices are displacement or reslurry options. Finally, drying may be necessary and there are many possibilities including vacuum, convection, spray, steam and a combination of techniques.

This article discusses the choice of thin-cake (2 – 25 mm) pressure separation technology for full containment, no residual heel and their benefits to optimizing the effectiveness of the production process. For full containment, the paper then continues with a discussion of clean-in-place operations to meet current Good Manufacturing Practices (cGMP) guidelines including riboflavin test and validations. ANSI/ISA S88 (and IEC 61512-1 in the international arena) batch process control system standards are also examined. Finally, factory and site acceptance testing is described.

IMPORTANCE OF THIN-CAKE FILTRATION

Thin-cake solid-liquid separation can be defined as the formation of a cake in the 2-20 mm thickness range. In this range, cake compressibility becomes less important in the cake building stage of a separation process. Compressible cakes can be better handled at thinner cake depths and higher pressures. For example, an amorphous crystal that does not centrifuge well can be filtered at 45 psig with a cake thickness of 2 – 3 mm. Thin-cakes also lend themselves to more effective washing and drying as there is less of a chance of channeling and the mechanism of "plug-flow" of liquids or gases is enhanced.

THEORY OF THIN-CAKE FILTRATION

Filtration

During the initial mechanism of cake forming in the filtration step, the filter cloth acts just to initiate filtration by capturing the first particles. These first particles form bridges over the pores of the cloth (bridging). During this initial phase, smaller particles may pass through the filter cloth leading to turbid liquid (filtrate). As soon as a first layer of particles has accumulated on the filter medium, this cake will then act as the actual filter medium.

When plotting the amount of filtrate obtained at constant filtration pressure versus the filtration time, a filtration curve is developed, which represents a root function, V_F = Constant * $t_F{}^{0.5}$, as shown in Figure 1. .

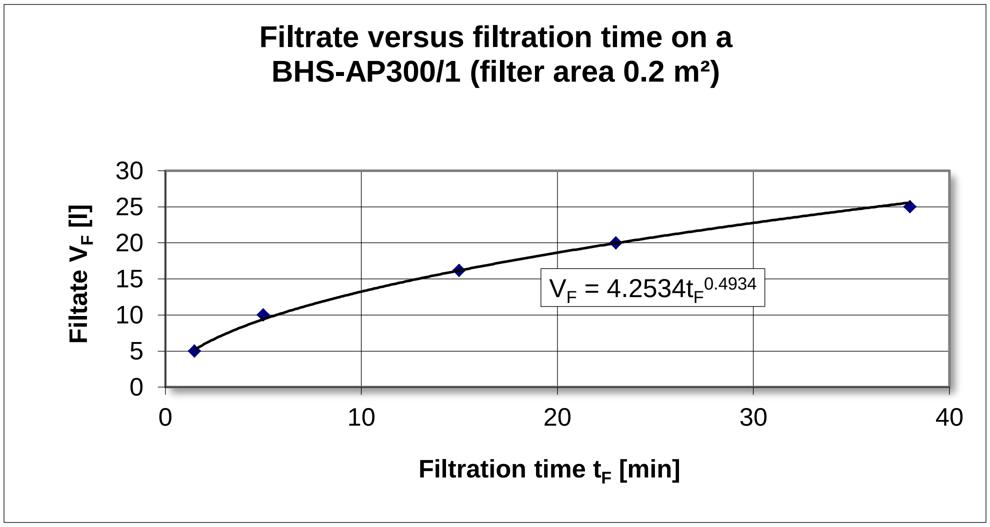


Figure 1: Example of a Typical Filtration Curve

The equation of the trend line for this specific chemical product was calculated by Excel. The exponent of 0.4934 almost exactly corresponds to the root function and the constant, in this case, equalled 4.2534. Accordingly, the filtrate flow rate is at its maximum in the beginning and then declines as a result of the constantly increasing filtration resistance (as the cake thickens).

The important question that follows is what is the optimum filtration time, i.e. when is the most efficient filtration performance obtained?

The filtration performance (P) is calculated using this formula:

$P = V_F / (A * t_{total})$, where $t_{total} = t_F + t_{side}$

The side time (t_{side}) includes the washing time, the drying time and the time for filter opening, cake discharge, closing, cleaning of the filter, if necessary, and other miscellaneous time. Every batch-operated filter has these side times, which are usually constant from process cycle to process cycle.

When plotting the filtration performance (P, in liters/m^2/hour), for example, and including a side time of 15 minutes (including washing and drying times), the result is as follows in Figure 2:

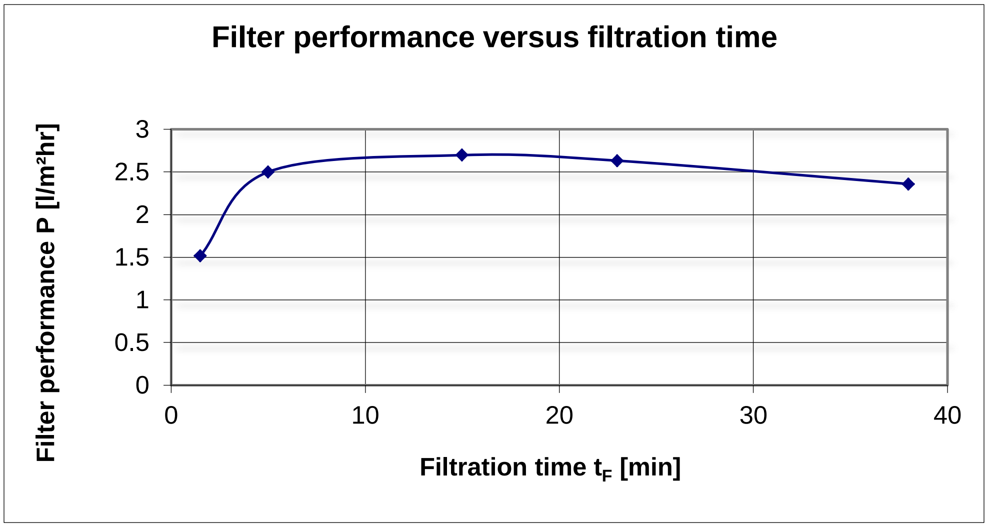


Figure 2: Filter Performance versus Filtration Time

From the curve, for this example, the maximum filter performance is obtained when the filtration time of 15 minutes equals the side time of 15 minutes. The mathematical formulas follow.

Mathematical Proofs for the Filter Performance (P)

Equation (1): $P = V_F / A * t_{total}$

Equation (2): $t_{total} = t_F + t_{side}$

Equation (3): $t_F / t_{F1} = V^2 / V_1^2$

By solving equation (1) with equations (2) and (3), the result is

$$P = (V_1^2 \, t_F / t_{F1})^{0.5} / A \, (t_F + t_{side})$$

From Figure 1, $(V_1^2 / t_{F1})^{0.5} / A$ = Constant, and therefore, Filter Performance (P) is

$$P = \text{Constant} * (t_F^{0.5} / (t_F + t_{side}))$$

The condition for the maximum filter performance is based upon the first derivative (d), where the ratio of derivatives of the Filter Performance (dP) to Filtration Time (dt_F) is equal to zero:

Equation (4): $dP / dt_F = 0$

And therefore: Equation (5): $(t_F^{0.5} / (t_F + t_{side}))' = 0$ (1^{st} derivative = 0)

By solving equation (5), the result is as follows:

$$0.5\ t_F^{-0.5}\ (t_F + t_{side}) - t_F^{0.5} / (t_F + t_{side})^2 = 0$$

and therefore, the result is

$$t_{side} = t_F$$

The conclusion is that the side times and the filtration times must be as short as possible and as equal as possible which leads to thin cake filtration. Of course, one has to ensure that the filter cake can still be discharged, as a thin cake.

Parameters that Influence Filtration Performance:

Filtration pressure

The higher the filtration pressure, the higher the filtration performance for a non-compressible cake. In case of a compressible solid matter, an increase of pressure will often not result in an increased performance because the filter cake gets more impermeable due to the compression. Finally, the filtration pressure may also impact the cake-forming layer, which could lead to a turbid filtrate, if there is a "fine particle tail" in the particle size distribution.

Temperature

The higher the temperature of the slurry, the lower its viscosity. The lower the viscosity, the higher the filtration performance. As a general rule, therefore, increasing the filtration temperature will result in an increase in the filtration performance.

Particle Size / Particle Size Distribution (PSD)

The particle size and particle size distribution are important parameters, which can influence the filtration performance. As the filter cake begins to form, channels (capillaries) are formed between the particles. The smaller the capillaries, the higher the capillary pressure and thus the resistance of the filter cake. Small particles and a wide particle size distribution result in a densely packed filter cake and reduced filtration performance. In cases such as these, a thinner cake will mitigate this impact and allow for successful filtration. Another alternative would be to use filter aid, either as a precoat or body feed, to increase the filtration performance.

Particle Shape

The type and shape of the particles also impact the filtration performance. Hard, spherical particles will form a permeable cake with increased void volume leading to high rates. Irregularly shaped crystals, platelet-type or flat crystals as well as needles and amorphous crystals can pack together and result is a dense and low-permeable cake. In cases such as these, once again, thin-cake filtration, low filtration pressures or filter aid mitigate the impacts of the particle shape.

Washing of the Filter Cake

When washing the filter cake, there are two mechanisms that occur: displacement washing and diffusional washing. With displacement washing, a large part of the void volume (which is still filled or saturated with mother liquor before washing starts) is replaced by the washing liquid.

Diffusional washing is the more important mechanism to remove bound or inner liquid. These liquids are removed by the diffusion washing, i.e. the liquid to be washed out diffuses into the washing liquid. The driving force is the concentration difference.

Depending upon the cake formation, there may be areas of the cake that have little or no permeability. These portions of the cake would not be efficiently washed by either mechanism. In cases such as these, there are generally two alternatives.

The first would be a reslurry wash. The cake would be discharged to a reslurry vessel or reslurried in-situ. The second alternative, which would require less wash liquid and less handling of solids, would be a thinner cake to minimize the impermeable areas. This would allow for a more “plug-flow effect” for the displacement washing. For the bound liquids, there would be a lower concentration of bound liquids, which would require less diffusional liquids and less contact time.

Finally, in terms of the parameters that impact washing, these would generally fall in the same category as the influences on filtration.

Drying of the Filter Cake

When dewatering the filter cake, the liquid remaining in the pores shall be replaced by gas (mechanical dewatering by blowing) with the objective of obtaining a residual moisture content as low as possible. During blow-out operation, the capillary pressure of the pores must be overcome. The smaller the capillaries, the higher the capillary pressure. As soon as the first capillaries are blown through, the gas consumption rises and reduction of the residual moisture becomes more ineffective. When this point occurs on the drying curve, there are two further approaches that are undertaken. First, the cake can be slowly compressed to allow for reduced gas consumption during this mechanical dewatering stage. Secondly, vacuum drying can be employed as well as thermal drying.

During the blowing phase, one of the most important factors for a low residual moisture is a high blow out pressure rather than gas flow. Depending upon the product characteristics, time, temperature and cake thickness will also impact the drying curve.

THIN-CAKE AUTOPRESS “PRESSURE FILTER” TECHNOLOGY

The AP Pressure Filter technology was investigated by the plant for filtration, cake washing and drying for full containment of operations in an inert environment. The AP consists of specially designed circular filter plates with synthetic or sintered metal filter media. These are shown in Figure 3 and Figure 4.

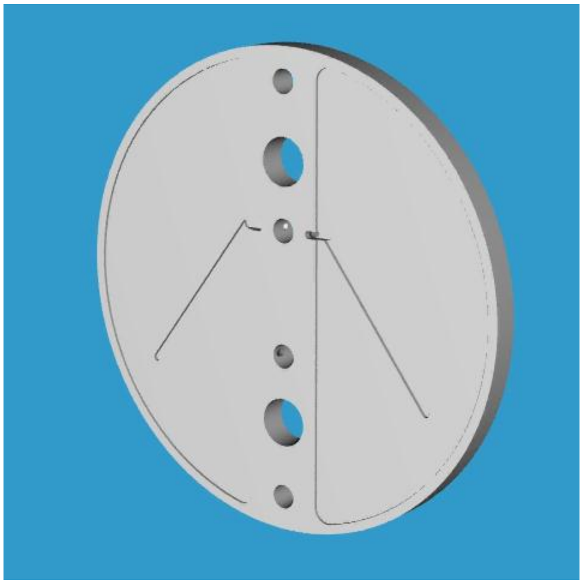


Figure 3: Filter Plate

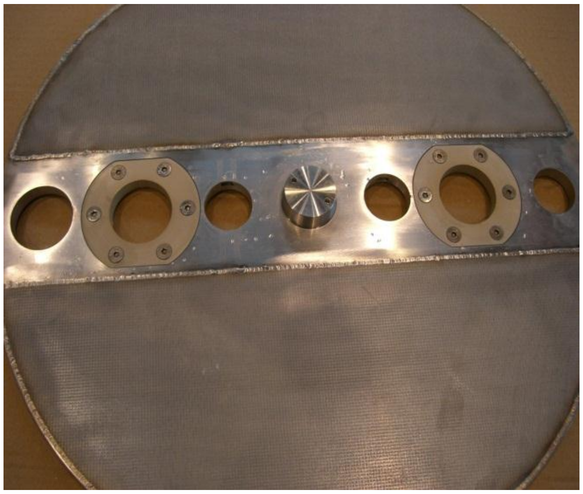


Figure 4: Metallic Filter Plate

The filter plates are sealed to each other by specially designed elastomers to eliminate solids, gas or liquid bypass. These are shown in Figure 5 and Figure 6.

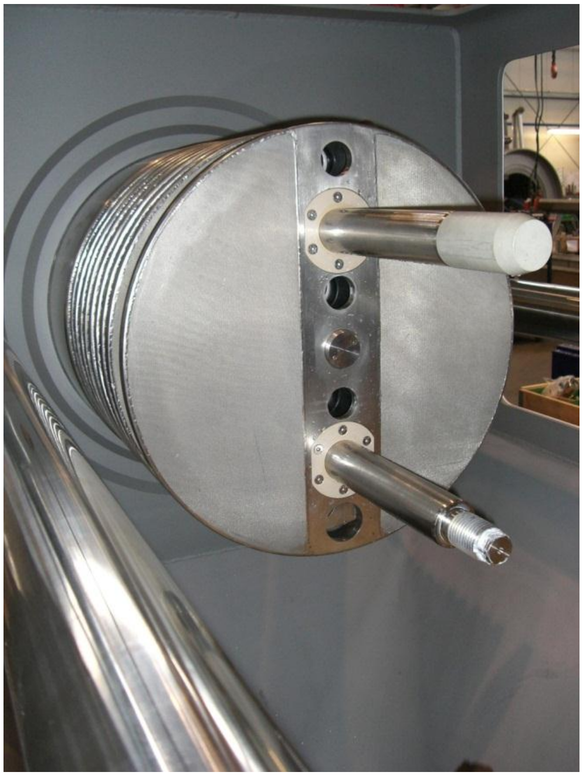


Figure 5: Filter Plate Stack

Figure 6: Elastomeric Spacer for Plate-to-Plate Sealing

The filter plates are contained in a pressurized filter housing where a gas-inflated membrane seals the annular space between the housing and the filter plates. All operations are contained from full vacuum to 150 psig. This is shown in Figure 7 and Figure 8.

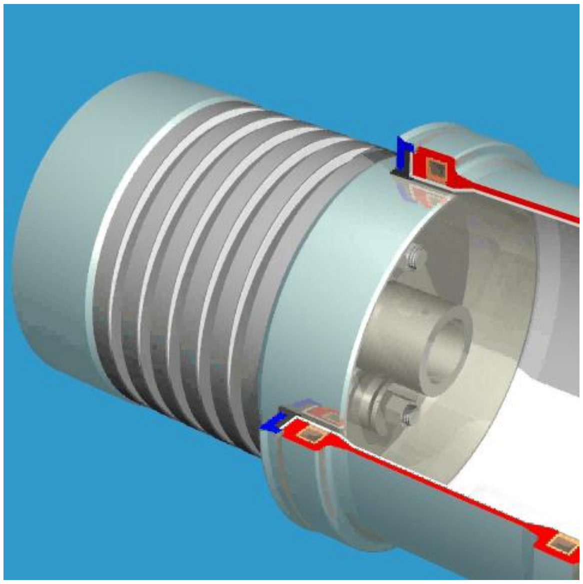


Figure 7: Plate Stack and Membrane (Shown in red)

Figure 8: Filter Plate Housing with Membrane (Shown in white)

The entire filter housing is then enclosed in a pressure-tight outer housing for complete product containment.

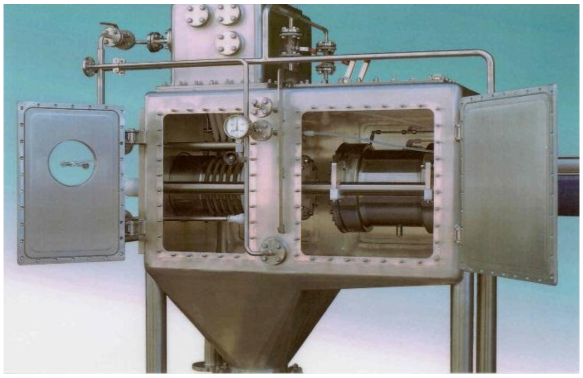


Figure 9: AP Internals with Plate Stack and Housing Opened in the Discharge Position

The operation of the AP Filter begins with slurry filling to form thin filter cakes of typically 5 – 25 mm thickness. Pressure filtration continues operating up to 8 barg. The cake can then be mechanically compressed to eliminate cracking to ensure maximum washing efficiency in the forward or reverse direction. Finally, the cake can be pre-dried or fully dried either by vacuum or blowing gas through the cake in either direction. Final moisture contents of less ten than (10%) have been achieved. This gentile drying without agitation or tumbling is important for fragile crystals and thixotropic cakes. Elastomeric knives sequentially and automatically discharge the circular cakes after which the filter begins a new cycle, shown in Figure 10.

Figure 10: Elastomeric knives sequentially and automatically discharge the circular cakes

AP FILTER PROCESS OPERATIONS

The AP process operations begin with filling and filtration. Filling is either via the bottom of the plates or top and bottom for high-settling products. Cake washing can then be in the forward or reverse direction. Cake pressing may be used to prevent cracks from developing in the cake. Cake drying is, as cake washing, in the forward or reverse directions and with or without cake squeezing. The cake is discharged and then depending upon the product requirements, a clean-in-place (CIP) operation can occur or the filling cycle can begin again. The six process modules can be run as a manual, semi-automatic or full automatic sequence. The PLC provides the choices to the operator with feedback to the plant distributed control system (DCS).

AP FILTER TESTWORK

In this application, an air-sensitive specialty chemical is tested. Appendix A shows the filtration, washing and drying graphs including scale-up. The filter media is a sintered-metal screen with a removal rating of rating of 2 – 5 microns (um).

The initial testwork is conducted using a pressurized pocket-leaf filter (PLF) with 20 cm^2 of filter area. These tests can be conducted in the customer's lab or in the BHS laboratory and is used to gather the basic filtration, washing and drying data. The PLF is shown in Figure 11.

Figure 11: BHS Pocket Leaf Filter (PLF)

Filtration

The first optimization concerns the cake depth versus the filtration rate. Filtration is conducted via pressure. A pre-measured amount of slurry is added from the top and the unit is pressurized. When the filtration begins, the amount of filtrate versus time is recorded at constant pressure. Other parameters that are varied sequentially include cake depth, filtration pressure and filter media. As stated earlier, cake depths can range between 5 – 25 mm.

Washing

Displacement washing tests are also performed in the pocket-leaf filter. For accurate testing, it is necessary to smooth out any cracks in the cake. This can be done in a number of ways either from the top with a long spatula or by carefully removing the bottom part. A measured about of methanol wash liquid is added in a pre-determined wash ratio. Once again, pressure and time are measured.

Drying

Product drying in the pocket-leaf filter is tested by blowing ambient-temperature or hot gas through the cake as well as with vacuum. The pressure is kept constant and gas throughput is measured versus time. After a pre-selected drying time, the cake is removed from the pocket-leaf filter, cake depth is determined and then it is weighed and analyzed for the moisture content. After several iterations, the drying times were optimized along with the gas pressure and flow rate to achieve the better than 20 percent final solvent content in the cake.

BENEFITS & CONCLUSION

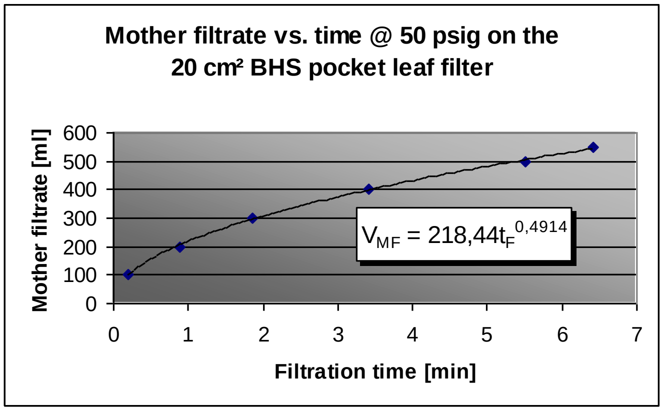
The Autopress AP Pressure Filter technology is able to conduct filtration, cake washing, pressure and vacuum drying all in a contained environment. Cake discharge is complete and there in no residual liquid or solid heel. This is an important benefit for air-sensitive and toxic products. .

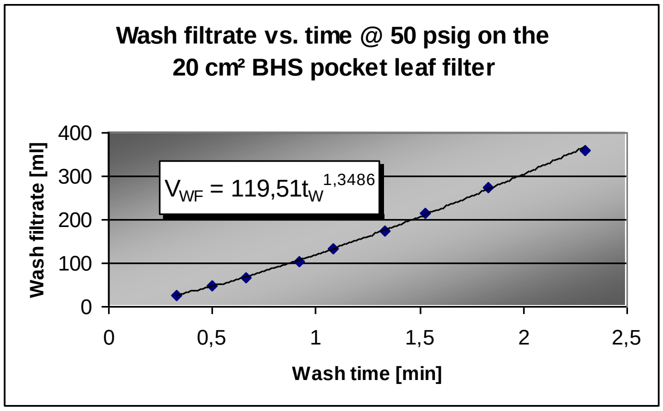
The materials of construction provided for all product wetted parts can be polished stainless steel or alloys with rounded corners to eliminate product holdup. The filter media can be metallic, synthetic or sintered stainless steel that is welded to the filter plates. All process and mechanical operations are either pneumatic or electric which allowed for a clean installation.

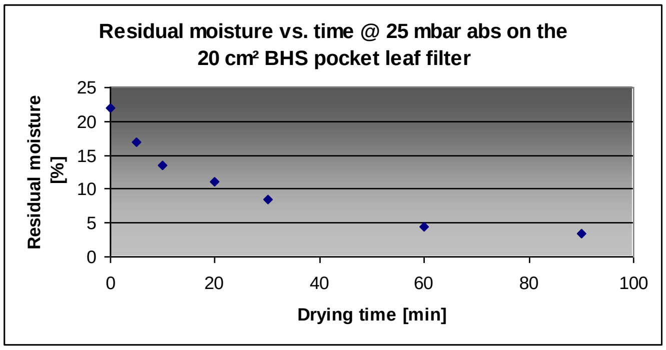
The PLC controls, Appendix B, and including the functional specification, Factory Acceptance Test (FAT) and Site Acceptance Test (SAT) all comply with Good Automated Manufacturing Practices (GAMP) guidelines. Finally, as part of the FAT and SAT, a Riboflavin CIP test, Appendix C, is conducted to demonstrate the ability of the AP Filter to be cleaned for batch-to-batch integrity or product-to-product campaigns.

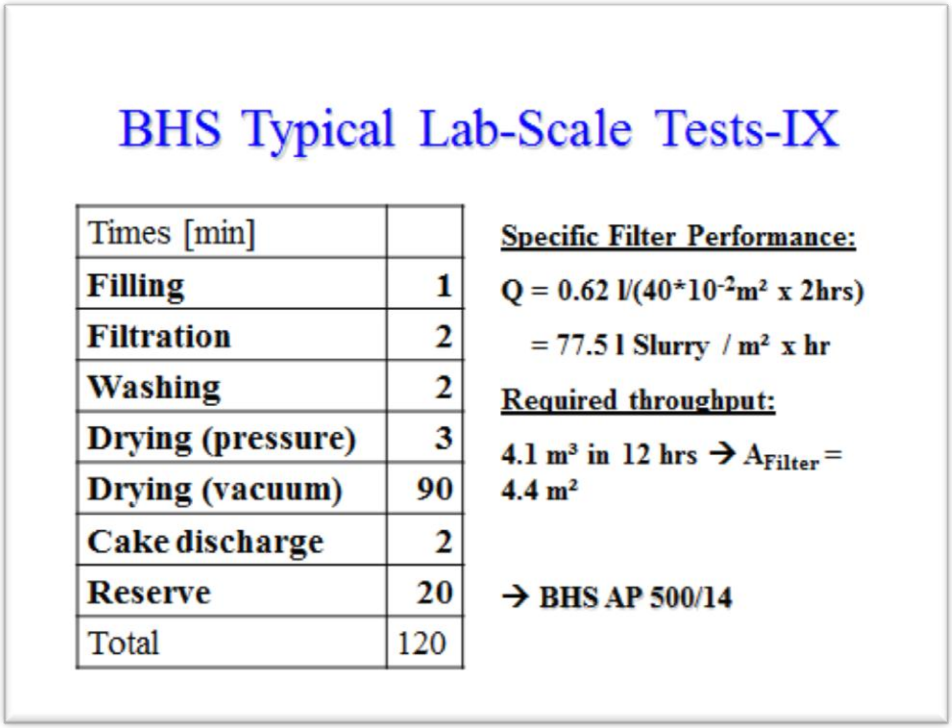
In summary, engineers must evaluate all outcomes to make an informed and successful decision. Technical evaluation, laboratory & pilot testing are critical for successful decisions and projects. The take-away is that close collaboration between the client and the vendor provides for creative problem-solving and process filtration solutions to achieve the production objectives.

APPENDIX A: FILTRATION, WASHING AND DRYING GRAPHS WITH SCALE-UP


Mother filtrate vs. time @ 50 psig on the 20 cm² BHS pocket leaf filter


Wash filtrate vs. time @ 50 psig on the 20 cm² BHS pocket leaf filter


Residual moisture vs. time @ 25 mbar abs on the 20 cm² BHS pocket leaf filter



BHS Typical Lab-Scale Tests-IX

Times [min]	
Filling	**1**
Filtration	**2**
Washing	**2**
Drying (pressure)	**3**
Drying (vacuum)	**90**
Cake discharge	**2**
Reserve	**20**
Total	120

Specific Filter Performance:

$Q = 0.62\ \mathrm{l}/(40 \cdot 10^{-2}\mathrm{m}^2 \times 2\mathrm{hrs})$

$= 77.5$ l Slurry / m² x hr

Required throughput:

4.1 m³ in 12 hrs → A_{Filter} = 4.4 m²

→ BHS AP 500/14

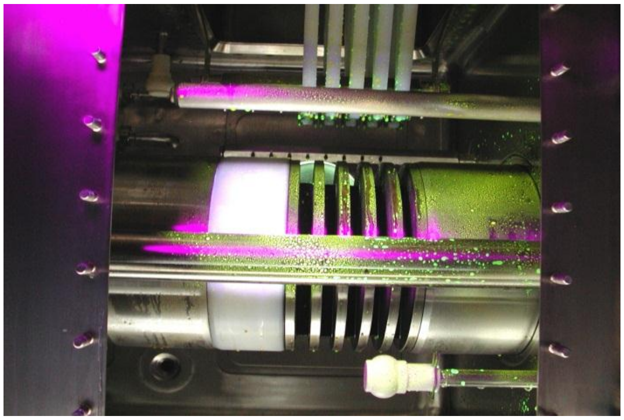
APPENDIX B: PLC CONTROL SYSTEMS WITH ANSI/ISA S88 BATCH PROCESS CONTROL SYSTEM STANDARDS

The final step of the process is controls and factory (FAT) and site acceptance (SAT) tests. The Batch-S88 standards allows for modular control system operation. It defines the process and cleaning operations in steps so that operators can perform certain tasks reliably and without variation to ensure a unit that is defined as clean. A typical sequence would be as follows:

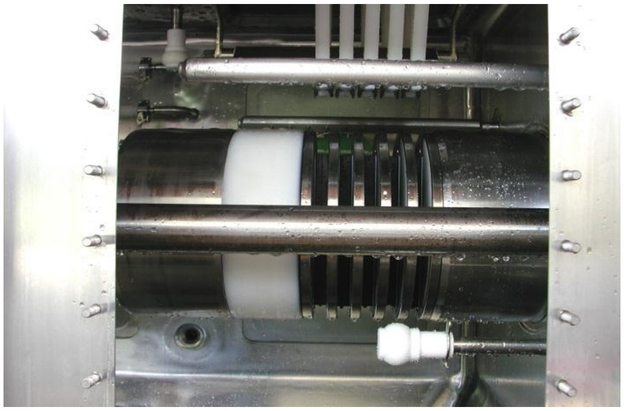
- IDLE – IN SEMI-AUTOMATIC/AUTOMATIC MODE SEQUENCE IS NOT RUNNING
- RUNNING – MAIN OPERATION IS RUNNING WITHOUT ANY ACTIVE SEQUENCES
  - PURGING – FAST PURGE SEQUENCE ACTIVE
  - SETUP – SETUP SEQUENCE ACTIVE
  - FILLING – FILLING SEQUENCE ACTIVE
  - WASH 1 – WASH 1 SEQUENCE ACTIVE
  - WASH 2 – WASH 2 SEQUENCE ACTIVE
  - BLOWING – BLOW SEQUENCE ACTIVE
  - DISCHARGING – DISCHARGE SEQUENCE ACTIVE
  - CLEAN-IN-PLACE
- COMPLETE – MAIN OPERATION SEQUENCE IS COMPLETE
- ABORTED – SEQUENCE ABORTED.
- HOLDING – HOLDING SEQUENCE ACTIVE
- HOLD – HOLDING SEQUENCE COMPLETED
- RESTARTING – SEQUENCE IS RESTARTING FROM HOLD STATE
- GROUNDING – GROUND SEQUENCE IS ACTIVE

APPENDIX C: RIBOFLAVIN TESTING FOR CLEAN-IN-PLACE (CIP) TESTING

Before Riboflavin Test
(Contaminated Areas shown in green /purple)



After CIP Cleaning



TYPICAL BATCH TO BATCH CIP OPERATION: ALLOWABLE TIME IS 2 HOURS

FOLLOWING PARTS ARE CLEANED WITH THE HOUSING OPENED:

SLURRY FEED PIPES, FILTRATE PIPES, PLATE STACK AND ENCLOSURE

CIP COMPONENTS:

2 NOZZLE BARS, 8 NOZZLES EACH, TO CLEAN THE FILTER PLATES
2 ROTATING TANK CLEANING NOZZLES AT THE TOP SIDE OF THE HOUSING
2 ROTATING TANK CLEANING NOZZLES AT THE CAKE DISCHARGE CHUTE
2 ROTATING TANK CLEANING NOZZLES IN THE OPEN HOUSING

LIQUID CONSUMPTION AT 3-4 BAR G

NOZZLES:	26 L/MIN
TANK CLEANING NOZZLES:	50 L/MIN PER NOZZLE

STEPS	**DURATION**	**CONSUMPTION**
I. PRE-CLEANING, COLD CITY WATER	30 MIN	3 M³
II. CLEANING, NAOH, 80 °C	60 MIN	6 M³ (*)
III. RE-WASH, CITY WATER, 80° C	20 MIN	2 M³
IV. RINSING, DI WATER, 80° C	10 MIN	1 M³
TOTAL	120 MIN	

(*) APPROXIMATELY 30 LITERS ARE RECIRCULATED