This article discusses how the use of thin-cake vertical candle filters and horizontal pressure plate filters can efficiently remove activated carbon, metal catalysts, and trace insolubles from Active Pharmaceutical Ingredient (API) slurries.

Thin-Cake Filtration Technologies for Removing Activated Carbon, Catalysts, and other Trace Solids from Active Pharmaceutical Ingredient (API) Slurries

by Barry A. Perlmutter

Introduction

As the pharmaceutical industry has changed and grown since the mid-1980s, there are increasing concerns about the safe handling of Active Pharmaceutical Ingredients (APIs). To meet lower exposure limits of unknown compounds and to have batch-to-batch integrity with less operator interaction, the industry's need for new technologies has expanded.

In the chemical synthesis operations of a pharmaceutical plant, the components include reactors, separation equipment, drying equipment, containment systems, and other process systems and utilities. The reaction step generally includes hydrogenation catalysts, activated carbon, and other accelerators for the precipitation reaction. After this step, separation is required to remove these substances along with unreacted materials, process impurities and reaction by-products, and API residuals.

This article focuses on one area of importance, which is the efficient removal of activated carbon, metal catalysts, and trace insolubles, such as diatomaceous earth, from API slurries. Currently, most API slurries are clarified with the use of manual plate filters, filter presses, bag filters, cartridge filters, and other conventional filter equipment. All of these units require manual operations for cake discharge and cleaning between batches or campaigns, as well as suffer from high labor and maintenance costs, high disposal costs, and the exposure of the operators and the environment to toxic and hazardous solvents and solids in addition to used and contaminated filter cloth, bag filters, and filter cartridges.

Spinning disk filters also are commonly used for clarification. While these units over-

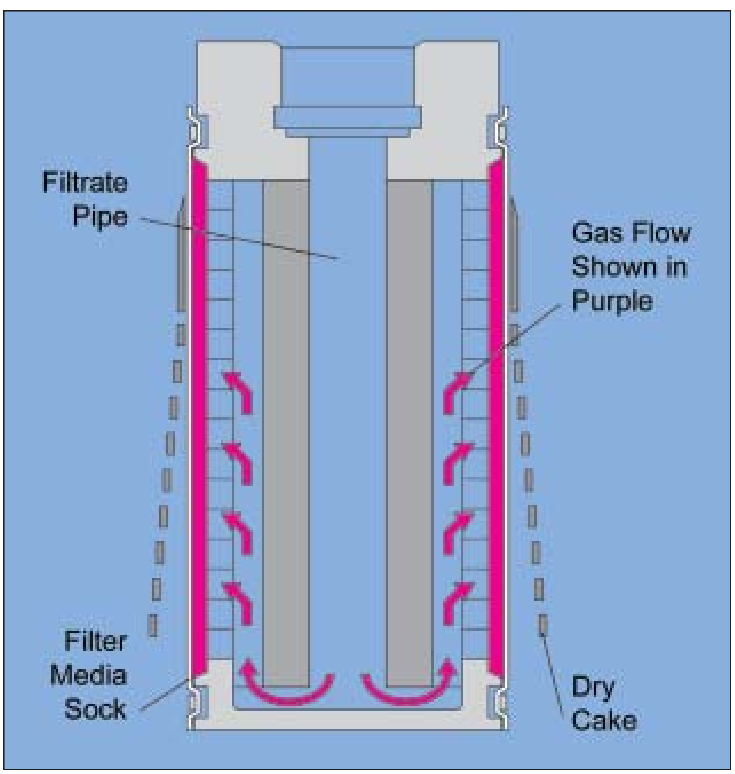

Figure 1. BHS candle showing gas flow to expand the filter media sock for cake discharge.

come some of the special handling requirements of manual filters, they add mechanical complexity to the process as well as special cleaning requirements. Spinning disk filters require drive motors, gear box assemblies (including gear box housing, gear reducers, bearings, shaft bearing arrangement, and bushings, torque loadings, etc.), mechanical seals (either single or double with special maintenance and cleaning), and unique installation concerns, such as center of gravity due to the spinning plates, static and dynamic balancing, and bearing lubrication and design to ensure no exposed threads and cleanability issues and overall maintenance of these components.

This article discusses the use of thin-cake vertical candle filters and horizontal pressure plate filters as alternatives to spining disk, manual, and conventional filter equipment. These new technologies are currently installed in many API applications and processes. The selection process as well as the technolgies are described in the article. The article includes test data and case histories and concludes with a discussion of clean-in-place operations and current Good Manufacturing Practices (cGMPs) guidelines. ANSI/ISA S88 (and IEC 61512-1 in the international arena) batch process control system standards also are examined for validation. Finally, factory and site acceptance testing is described.

Clarification of Slurries and Recovery of Solids

Candle filters and pressure plate filters are installed for clarification and recovery applications from liquids with low solids content. The candle filters are vertical candles, while the pressure plate filters are horizontal plates. The cake structure as well as the process parameters determine the optimum thin-cake technology.

Description and Operation of the Candle Filter

Candle filters provide for thin-cake pressure filtration, cake washing, drying, reslurry, and automatic discharge, as well as heel filtration in an enclosed, pressure vessel. Units are available from 0.17 m^2 up to 100 m^2 of filter area per vessel.

Filter Candles and Media

The filter candles (Figure 1) consist of three components: single-piece dip pipe for filtrates and gas, perforated core with outer support tie rods, and filter sock media. The filtrate pipe is the full length of the candle and ensures high liquid flow, as well as maximum distribution of the gas during cake discharge. The perforated core can be a synthetic material, stainless steel, or higher alloys and is designed for the full pressure of the vessel. The outer support tie rods provide for an annular space between the media and the core for a low pressure drop operation and efficient gas expansion of the filter media sock for cake discharge. Finally, the filter media is a synthetic type with a clean removal efficiency to less than one to three microns. As the cake builds up, removal efficiencies improve to less than one micron.

Filter Vessel and Candle Registers

The candle filter vessel is constructed of stainless steel or

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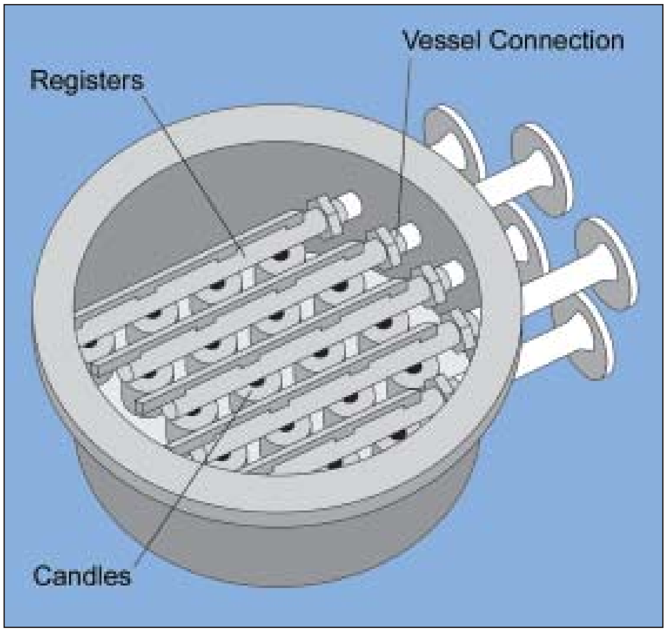

Figure 2. BHS candle filter.

higher alloys. Within the vessel are horizontal manifolds called candle registers. Each candle is connected to a register with a positive seal to prevent bypass. Each register may contain from one to 20 candles depending upon the filter size. The registers convey the liquid filtrate in the forward direction as well as the pressure gas in the reverse direction for filter media sock expansion. Each register is controlled with automated valves to ensure optimum flow in both directions. Figure 2 illustrates the candle filter vessel.

Automatic Process Cycles

Filling: The slurry feed enters the bottom of the filter vessel.

Filtration: The slurry is either pumped or pressurized from the reactor into the vessel. Cake will deposit on the outside of the candle; the separated filtrate will flow through the filtrate pipe and the registers. This process continues until one of the following conditions is achieved: maximum pressure drop, maximum cake thickness, minimum flow, or time.

Washing: Displacement washing or recirculation washing.

Drying: Blowing gas, steam, or "shock" drying.

Heel (Falling-Film) Filtration: The liquid remaining in the vessel cone after filtration or washing is completely filtered.

Cake Discharge: Gas flows sequentially through each of the candle registers, down each of the filtrate pipes, and then is distributed by the perforated core. The filter media sock gently expands by the gas flow and pressure allowing for cake discharge - *Figure 1*. Alternatively, the cake can be discharged as a slurry.

Description and Operation of the Pressure Plate Filter

The pressure plate filter has similar operating characteristics to the candle filter. The filter design is shown in Figure 3.

Automatic Process Cycles

Filling: The slurry feed enters the bottom of the filter vessel.

Filtration: The slurry is pumped under pressure into the vessel or via gas pressure through the reactor. Cake will deposit on the top of the plates. The separated filtrate will flow through the plates to the center main filtrate outlet. This process continues until one of the following conditions is achieved: maximum pressure drop, maximum cake thickness, minimum flow, or time.

Washing: Displacement washing or recirculation washing.

Drying: Blowing gas, steam, or "shock" drying.

Heel Filtration: The liquid remaining in the vessel cone after filtration or washing is completely filtered.

Cake Discharge: As shown in Figure 5 on page 72, the motors on the top of the filter operate at different frequencies and the plates gently vibrate for cake discharge. The plates vibrate in the vertical and horizontal planes and the solids are conveyed in an elliptical pattern to the outside of the vessel. Gas assist helps in the discharge process. There are no rotating plates, gears, or bushings and mechanical seals are not required.

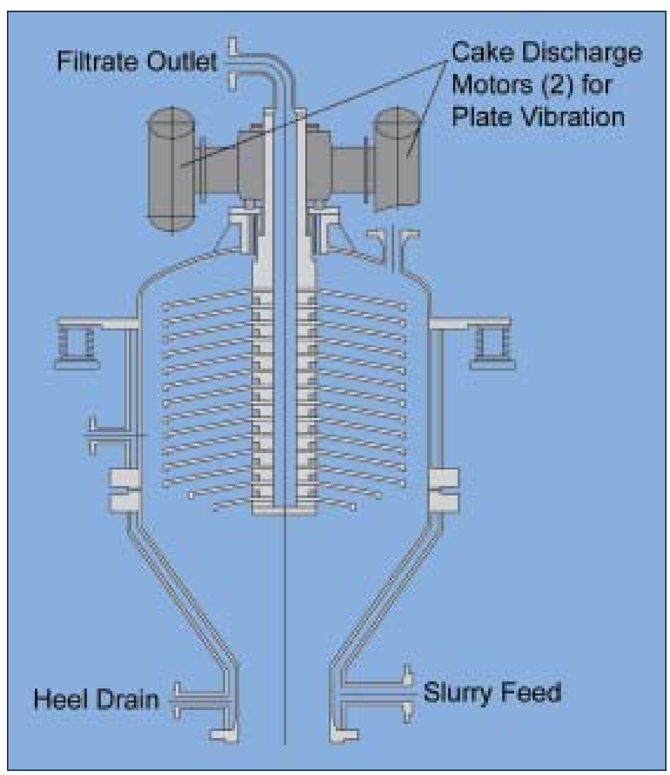

Figure 3. BHS pressure plate filter.

Selection of Candle versus Pressure Plate Filter Technologies: Cake Structure and Process Parameters

The major difference between the two technologies depends on the cake structure that is formed. Some cakes are better handled in the horizontal and some in the vertical.

Cake Thickness and Filtration: The candle filter is limited to cake structures that can be formed to about five-20 mm. The pressure plate filter can handle cakes up to 75 mm. Both units can conduct filtration up to 150 psig.

Filter Media: The candle filter uses only synthetic media with a clean removal efficiency from one to three micron range and finer down to 0.5 microns. The pressure plate filter also can use metal media. For the pressure plate filter, the clean micron range removal efficiency is also one to three microns and finer.

Cake Washing: If the process requires washing to remove the API from the solids, then generally the pressure plate filter is a better alternative. If washing is not as critical, then the candle filter may be the optimum technology for clarification and recovery.

Heel Filtration: The remaining liquid in the vessel (liquid heel) after filtration or washing can be removed from the candle filter or pressure plate filter by circulation, heel filter in the cone of the vessel, or additional heel filter plates in the pressure plate filter.

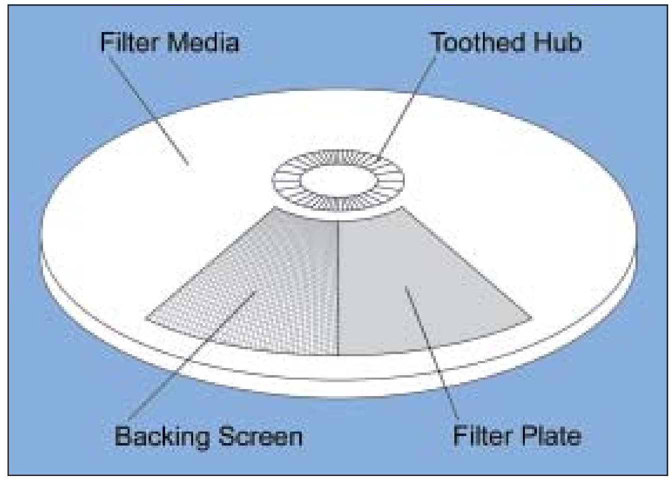

Figure 4. Filter plate.

Cake Drying: The candle filter can produce cakes with approximately 10% moisture. This moisture level depends upon the specific cake, but the moisture lower limit is that moisture just above the cake cracking point. The pressure plate filter can produce bone dry cakes.

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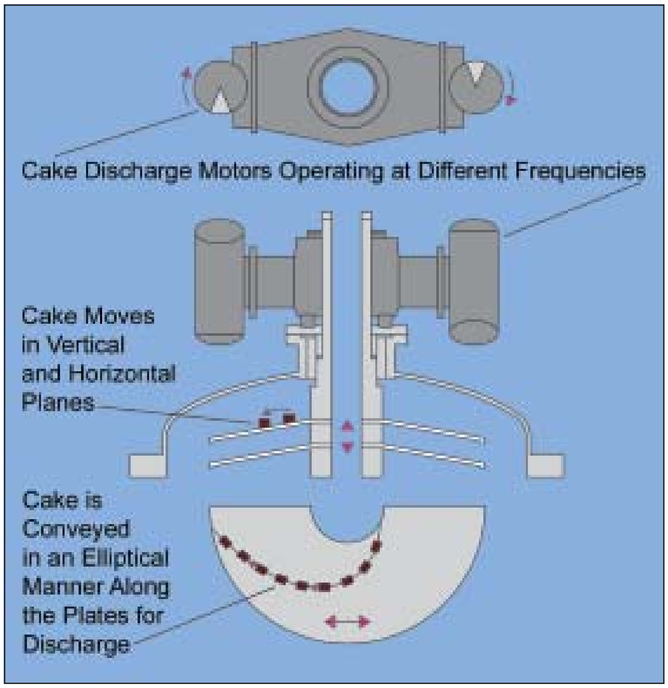

Figure 5. Cake discharge in the pressure plate filter.

Cake Discharge: Both designs can easily discharge most cakes equally with no residual heel.

Clean-In-Place (CIP)/Steam-In-Place (SIP): Both units conduct CIP/SIP operations in identical manners by filling and circulating cleaning fluids, while blowing gas in the reverse direction to the filtration direction, which creates a turbulent mixture or a quasi-ultrasonic cleaning effect. The pressure plate filter further enhances this operation with plate vibration.

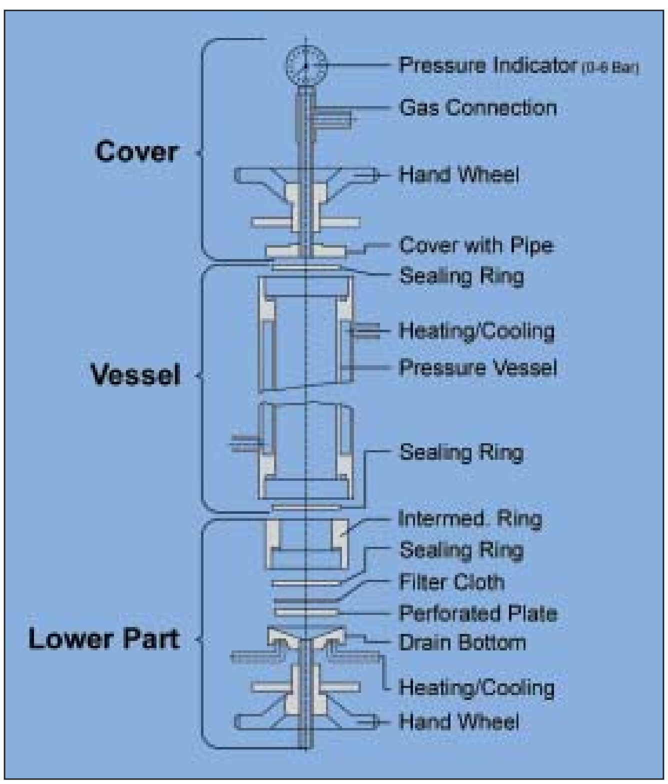

Figure 6. Pocket leaf filter.

Typical Testing to Determine the Optimum Filtration Technology of Vertical Candle Filter or Horizontal Plate Filter

Overview of Bench Top Testing

The bench top testing is conducted using a Pocket Leaf Filter (PLF) - *Figure 6*. The testing will analyze cake depths, operating pressures, filter media, washing and drying efficiencies, and cake discharge (qualitatively, based upon experience of the vendor). The PLF is used to gather the basic filtration, washing, and drying data.

Filtration: The first optimization concerns the cake depth versus the filtration rate. Other parameters that are varied sequentially include cake depth, filtration pressure, and filter media. Cake depths can range between six to 75 mm.

Washing: Displacement washing tests also are performed in the PLF. Washing pressure, time, and wash ratios are optimized to meet final quality specifications.

Drying: Product drying in the PLF is tested by blowing ambient-temperature or hot gas through the cake. The pressure is kept constant and gas throughput is measured versus time.

Example of a Typical Bench Top Testing Program

Bench top tests are conducted on an API/Solids Slurry using a PLF. The tests are conducted to demonstrate that the catalyst and impurities can be removed from the API by filtration. The tests demonstrate that the API can be easily filtered and that thin-cake pressure filtration using a candle filter or pressure plate filter would provide excellent results for this application.

The following filtration options are evaluated and are suitable for this application: candle filter and pressure plate filter.

Test Purposes

The purposes of this test were to:

- Determine if the catalyst and impurities can be separated from an API. The current filtration process is with disposable cartridge and bag filters:
  - A 12,000 liters batch of slurry is filtered in approximately six hours.
  - The slurry contains the catalyst and impurities and is a dark color. The filtrate is the product and should be a clear liquid.
  - The cake is washed and then discharged as a slurry for disposal.
- Determine which type of thin-cake filtration is suitable for this process: candle filter or pressure plate filter.
- Determine the required size for the production equipment.

Test Methods

The Pocket Leaf Filter was used to gather data and make observations on this product. The following information was gathered during this test:

- Filtrate Quality vs. Filter Media
- Filtration Time vs. Feed Volume (Cake Height) and Filtration Pressure
- Cake Height vs. Feed Volume
- Media Blinding vs. Number of Runs

Test Facilities

Tests were performed in a suitable laboratory with original slurry produced by the customer.

Test device: 400 ml Stainless Steel Pocket Leaf Filter with 12 cm^2 filter area

Filter cloths: FDA-Approved Polypropylene and Teflon cloths

Temperature:
- Ambient Slurry
- Ambient Pocket Leaf Filter
- Ambient Nitrogen for pressurizing the filter and drying

Test Data – Confidential

Test Results

- Filtrate Quality - The feed slurry is a dark color and the filtrate should be a clear liquid. An FDA-Approved Teflon media produced clear filtrate that contained no visible solids.

- Filtration Time

Filtration Time vs. Feed Volume

The filtration time increased with the square of the feed volume (or the cake height) as expected - *Figure 7*. The data clearly demonstrate that the filtration time for smaller feed volumes (i.e., thinner cakes) is the preferred filtration method.

The following equation can be used to predict the filtration time based on the data:

Equation 1: $t_F = a + b\,(V/A_F)^2$, where
t_F = the filtration time in minutes
a = a constant in minutes
b = a constant in minutes * m^4/m^6
V = the feed volume in m^3
A_F = the area of the filter in m^2

A least squares regression of the data yields the following constants for Runs 1, 2, 3, and 4:

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	a	b	R2
Run 1, 15 psi	0.32 minutes	27.16 minutes * m^4/m^6	0.982
Run 2, 15 psi	0.89 minutes	69.53 minutes * m^4/m^6	0.975
Run 3, 30 psi	1.34 minutes	15.75 minutes * m^4/m^6	0.983
Run 4, 45 psi	1.72 minutes	9.67 minutes * m^4/m^6	0.992

Filtration Time vs. Pressure

The filtration time varied with the inverse of the filtration pressure, indicating that the cake is non-compressible - *Figure 8*. This means that pressure filtration will result in the highest filtration rates and the smallest filter area. The following equation can be used to predict the filtration time for a given amount of feed vs. the filtration pressure:

Equation 2: $t_F = a' + b'/P$, where
t_F = the filtration time in minutes
a' = a constant in minutes
b' = a constant in minutes*psi
P = the filtration pressure in psi

A least squares regression of the data yields the following constants for the filtration time for 350 ml of feed slurry:

	a'	b'	R2
Runs 2, 3, 4	-0.0315 minutes	96.092 minutes * psi	0.992

Cloth Blinding

The same filter cloth was used for each trial and the time required for 400 ml of water to flow through the filter at 15 psi was recorded before the trials and after each run. The flow rate through the media slowed down after the first run, and then reached a steady rate. This indicates that a small and consistent amount of solids remains on the cloth after each run. This result is normal for a cloth media (unlike a cartridge, bag, or paper filter that tends to blind over time due to the particles being trapped in the depth of the filter) and demonstrates that the cloth did not blind during these trials.

Cake Discharge

The cake was discharged dry prior to drying on test Runs 1 to 5, after one minute of drying on Runs six to 10, and as a slurry on Runs 13 to 20. The cake discharge was excellent in each case. This allows the customer to choose the discharge method that is best for their particular situation.

Selection of Production Technologies and Scale-Up

The data indicates that thin-cake pressure filtration is the correct separation method for this product. The result of the tests indicate that either a candle filter or a pressure plate filter are suitable for this application. These filters are batch devices and the cycle time for a batch is the sum of the times for each step in the process.

The actual cycle time for a batch filter is the sum of:

t_{Fill}	= Filling Time	= 5 minutes
$t_{Turbid\ Filtration}$	= Turbid Filtration Time	= NA
t_F	= Filtration Time	= See Each Case Below
t_W	= Washing Time(s)	= 10 minutes
t_{Drain}	= Draining Time	= NA
t_{Drying}	= Drying Time	= NA
t_{Dis}	= Discharge Time	= 5 minutes
t_{Total}	= Total Cycle Time	= Filtration Time + 20 minutes

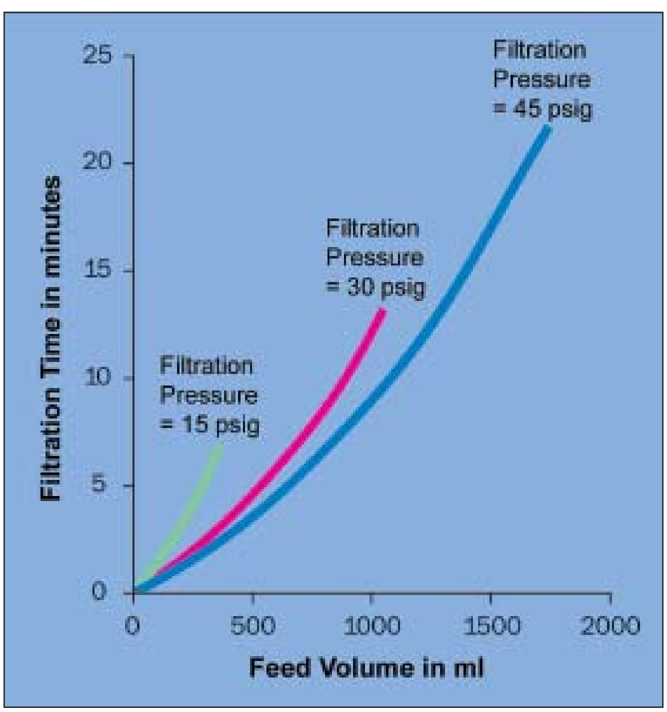

Figure 7. Filtration time versus feed volume.

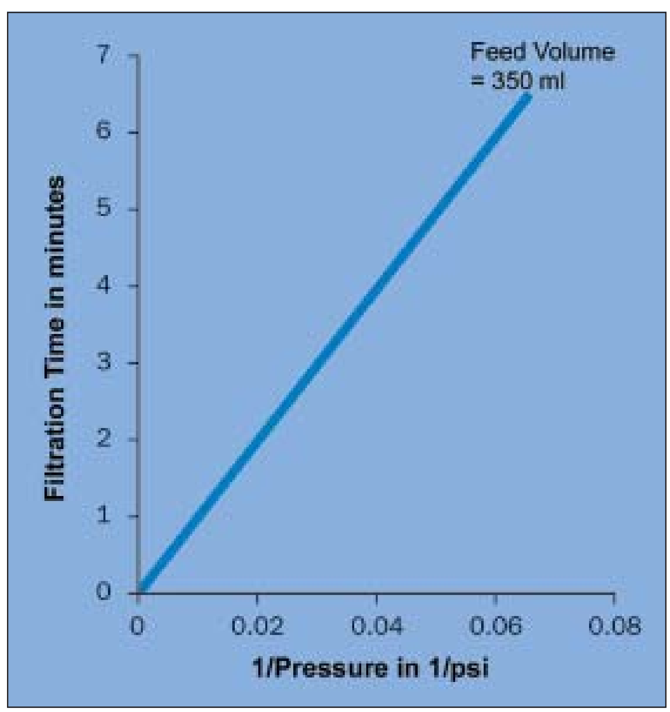

Figure 8. Filtration time versus 1/pressure.

Option 1: Process the Entire Reactor Batch in One Drop with a Candle Filter

The cycle time should not exceed six hours (240 minutes) so the allowable filtration time if the entire batch is processed in one batch is 240 minutes - 20 minutes = 220 minutes. The candle filter operates with a typical cake thickness of 10 mm, and Equation 3 can be rearranged to determine the required filtration area to process a 12,000 liter batch.

$A_F = b" * V/(h - a") = 12.846\ mm * m^2/m^3 * 12\ m^3/(10mm - 0.2436\ mm) = 15.8\ m^2$

A Candle Filter with an area of 18.8 m^2 is the inital choice for this option. We now use Equation 1 and the data from the specific run to confirm that the filtration time in this filter is acceptable:

$t_F = a + b\ (V/A_F)^2 = 1.72$ minutes + 9.67 minutes $* m^4/m^6 * (12\ m^3/18.8\ m^2)^2 = 5.7$ minutes.

This filtration time of 5.7 minutes is much less than the 220 minutes allowed, and this confirms that the candle filter is large enough for Option 1. A smaller filter with multiple drops is also possible, but the cGMP requirement is for one complete batch for batch-to-batch integrity.

Option 2: Process the Entire Reactor Batch in One Drop with a BHS Pressure Plate Filter

For this application, the pressure plate filter can operate with a cake thickness of 55 mm (maximum cake thickness = 75 mm) and Equation 3 can be rearranged to determine the required filtration area to process a 12,000 liter batch.

$A_F = b" * V/(h - a") = 12.846\ mm * m^2/m^3 * 12\ m^3/(55\ mm - 0.2436\ mm) = 2.82\ m^2$

A pressure plate filter with an area of 2.9 m^2 is the inital choice for this option. We now use Equation 1 and the data from the specific Run to confirm that the filtration time in this filter is acceptable:

$t_F = a + b\ (V/A_F\ )^2 = 1.72$ minutes + 9.67 minutes $* m^4/m^6 * (12\ m^3/2.9\ m^2)^2 = 167$ minutes.

This filtration time of 167 minutes is less than the 220 minutes allowed, and this confirms that the pressure plate filter is the correct size for Option 2.

Summary

The testing demonstrated that thin-cake pressure filtration technologies of candle or pressure plate filters with automatic operations can replace the bag and cartridge filters

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that are currently being used. The benefits include fully automatic operation, complete containment, no operator involvement, and low maintenance and operating costs. The candle filter requires 19 m^2 of filter area while the pressure plate filter requires 3 m^2 of filter area. Further discussion is required of the other process parameters to determine the appropriate choice of technology.

Typical Case Histories

The following are installation process details from candle and pressure plate API applications.

Application 1: Candle Filter with 6 m^2 of Filter Area

In a recent API installation, the customer installed two candle filters for removing activated carbon and diatomaceous earth from a 3000 kg API slurry. The details are as follows:

- Installation: Duplex candle filters, each with 6 m^2 of filter area
- Slurry has 25 kg of activated carbon + 15 kg of diatomaceous earth
- Batch size is 3000 kg of an API
- Filtration Pressure = 5 bar
- Drying with nitrogen to 5% final moisture
- Cycle Times:
  - 20 minutes of recirculation of the initial turbid filtrate containing solids. This recirculation was necessary for product clarity
  - 120 minutes of filtration for final production
  - 20 minutes for draining, drying, and cake discharge

Application 2: Candle Filter with 5 m^2 of Filter Area

- Installation: One candle filter with 5 m^2 of filter area for de-colorization of an API
- Slurry has 8 Kg activated carbon + 7 Kg of diatomaceous earth.
- Batch size is 4,000 liters of slurry.
- Filtration pressure is 2-6 bar.
- Cycle Times:
  - Filtration = 30 minutes with a cake depth of 20 millimeters
  - Drying = 5 minutes
  - Discharge = 10 minutes
- Process Details:
  - Production results are identical to pocket leaf filter tests of 1200 liters/m^2/hour
  - Cake discharge is 100%; no residual heel.

Application 3: Pressure Plate Filter

In this next application, a pressure plate filter was chosen rather than a candle filter. The API is bound to the activated carbon so intense washing is required. The benefit of the vibrating plates allowed the solvent and carbon to mix in the vessel and then reset the bed by filtration. The horizontal plates provided for a well-defined cake structure for cake washing and then bone-dry cake discharge. The details are as follows:

- Installation: Pressure plate filter with 10 m^2 of filter area
- Slurry has 100 kg of activated carbon.
- Batch size is 6500 kg of an API.
- Filtration Pressure = 3-5 bar.
- Drying with nitrogen to less than 10% final moisture.
- Cycle Times:
  - 4 minutes of recirculation of the initial turbid filtrate containing solids. This recirculation was necessary for product clarity
  - 120 minutes of filtration for final production
  - 20 minutes for draining, drying, and cake discharge

Typical Installation Drawings and P and IDs

Candle Filter

The question for API installations generally focuses on containment. Both the candle and pressure plate filters can be installed in a full glove box or only with a glove box at the cake discharge flange. Figure 9 illustrates a typical full glove box installation for a candle filter.

Pressure Plate Filter

Figure 10 on page 78 illustrates a typical installation where containment is not critical and the cake be discharged into open totes. The polishing filters produce "absolute-rated" final product quality for the downstream operations.

Process Controls and Testing

When evaluating an API application, bench top testing is the first step. After this step, the project continues through various stages until completion. The final step before the new

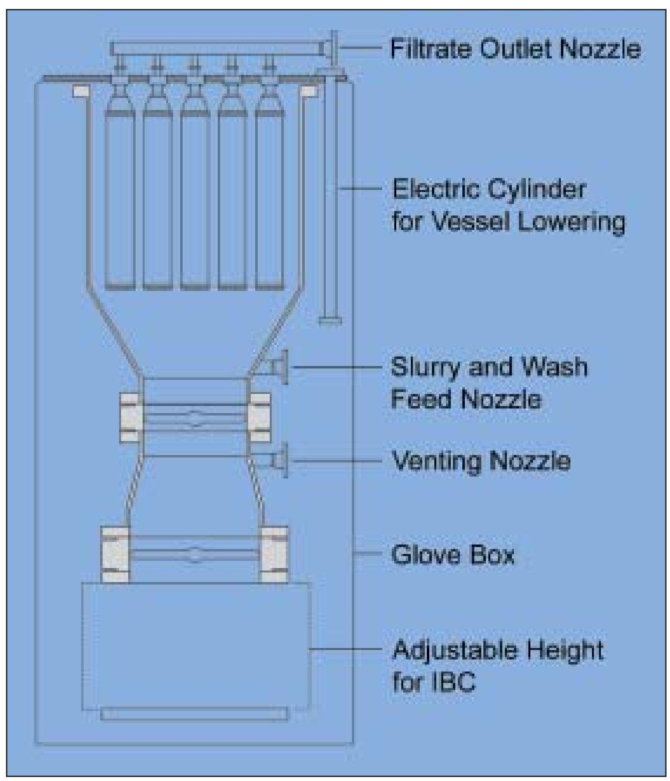

Figure 9. Candle filter with cGMP candles installed in a glove box (not all nozzles are shown; glove box designs require full customization).

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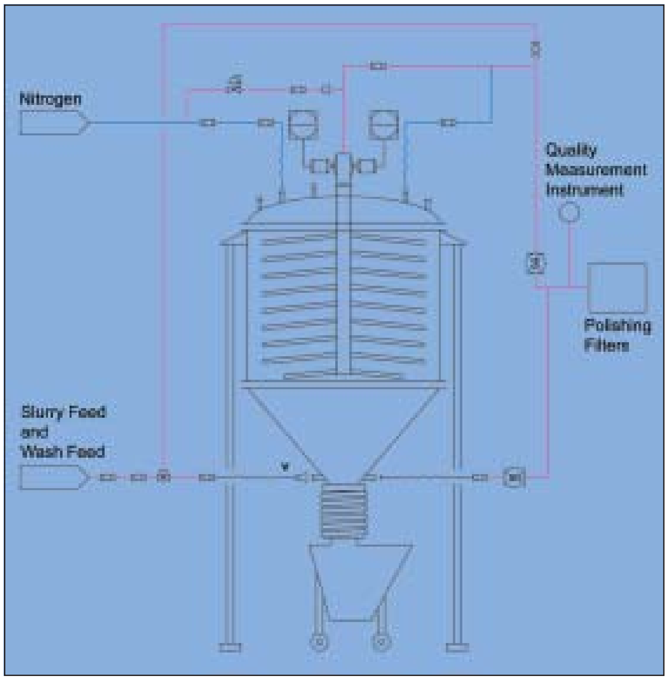

Figure 10. BHS pressure plate filter for cGMP production.

equipment and systems are sent to their final destination is the Factory Acceptance Test (FAT). The FAT may include PLC testing, CIP tests using riboflavin testing, swab tests, and other client specified tests.

Candle filters and pressure plate filters must be controlled either through a local Programmable Logic Controller (PLC) or a Distributed Control System (DCS). For PLC systems, the Batch-S88 standards allows for modular control system operation. It defines the process operations, including the cleaning operations in discrete and individual modules or steps so that operators can perform certain tasks reliably and without variation to ensure a unit that is operated correctly and produces reproducible batches as well as is defined "as clean." A typical PLC sequence would be as follows:

- Idle - in semi-automatic/automatic mode the sequence is not running
- Running - main operation is running without any active sequences
- Typical sequences of operation:
  - Nitrogen purging
  - setup
  - filling
  - wash 1
  - wash 2
  - blowing - drying
  - discharging
  - clean-in-place
- Typical batch outcomes:
  - cycle completed and the sequences begin again
  - aborted and corrective actions are required
  - holding in a sequence and waiting for an action
  - restarting a sequence from a Holding position
  - grounding to put the filter in its fail-safe position at the end of the reactor batch

After successful completion of the FAT, the unit can be shipped. Site acceptance tests as well as the IQ/OQ tests are then conducted using the S-88 standards and formats and repeating the procedures, as necessary.

Summary

Thin-cake filtration operations provide many benefits to the production/clarification process. By selecting the optimum thin-cake technology of candle filter or pressure plate filter, engineers can realize a more efficient process approach, including solids handling and cleaning of equipment with minimal operator involvement for improved safety and environmental concerns.

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About the Author

Barry A. Perlmutter is currently President and Managing Director of BHS-Filtration Inc., a subsidiary of BHS-Sonthofen GmbH. BHS is a manufacturer of thin-cake filtration, washing, and drying technologies. Perlmutter has more than 24 years of technical engineering and business marketing experience in the field of solid-liquid separation, including filtration and centrifugation and process drying. He has published and lectured extensively worldwide on the theory and applications for the chemical, pharmaceutical, and energy/environmental industries, and has been responsible for introducing many European companies and technologies into the marketplace. Perlmutter began his career with the US Environmental Protection Agency. He received a BS in chemistry from Albany State (NY) University, MS from the School of Engineering at Washington University, St. Louis, and an MBA from the University of Illinois. He serves on the Board of Directors of the American Filtration and Separations Society (AFS) and is a member of ISPE. He can be reached by e-mail at: barry.perlmutter@bhs-filtration.com.

BHS-Filtration Inc., 9123-115 Monroe Rd., Charlotte, North Carolina 28270.