Solid-Liquid Separation
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BHS FILTRATION

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Abstract

In the manufacturing of this bulk active pharmaceutical ingredient (Bulk-API), the plant needed to increase production and to improve the washing efficiency of the process. The current process required two (2) inverting-basket centrifuges operating in parallel from one reactor to a downstream pelletizer.

Process testing was being conducted simultaneously in the laboratory and in the field to evaluate the BHS Pharma rotary pressure filter (Ph-RPF) as an alternative to the inverting-basket centrifuges. The lab testing used a BHS pressurized pocket leaf filter with 20 cm^2 of filter area while the fieldwork was conducted on a BHS rotary pressure filter with a filter area of 0.12 m^2.

The paper discusses test procedures, data collection, filter media selection and other process parameters. Equations are presented to scale-up the results to a full-scale production filter. Scale-up data includes process conditions, production rates and filtration, washing, drying and discharge times.

The results are then compared to the existing process to determine the cost-effectiveness of a process change to one (1) Ph-RPF from two (2) inverting-basket centrifuges. The operating savings from the Ph-RPF in terms of solvent consumption, energy consumption, number of units and maintenance costs as well as the capital costs for the equipment will yield a favorable rate of return on investment and an acceptable payback.

Keywords

Rotary Pressure Filter, Centrifuges, Inverting Basket Centrifuges, Solid-Liquid Slurry, Continuous, Thin-Cake, Pressure Filtration, Cake Washing, Drying, Filter Testing, Active Pharmaceutical Ingredients, Bulk Pharmaceutical and Chemical Production

Introduction

In the manufacturing of this Bulk-API, the plant was examining the process to determine the most cost-effective method to increase production and improve the product quality with increased washing efficiency. A study was undertaken, by plant engineering and development, to examine the use of a BHS Ph-RPF to improve the overall process operations for product quality and production rates.

BHS Rotary Pressure Filter

The Ph-RPF, shown in Figure 1, is a continuous pressure filter

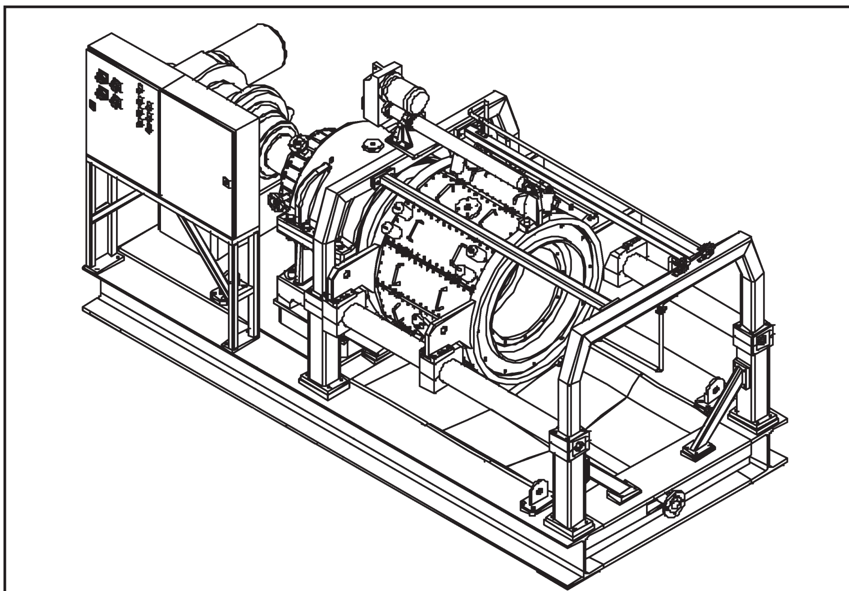

Figure 1. BHS Pharma Rotary Pressure Filter

designed for thin cake filtration with cake depths from 6 mm to 150 mm. The slowly rotating drum (6 - 60 rph) is divided into segments (called cells) each with their own filter media (synthetic cloth or single or multilayer metal) and outlet for filtrate or gas. The outlets are manifolded internally to a service/control head where each stream can be directed to a specific plant piping scheme or collection tank. In this way, the mother liquor can be kept separate from the subsequent washing filtrates and drying gases. This allows for better process control as well as reuse and recovery of solvents and the gases.

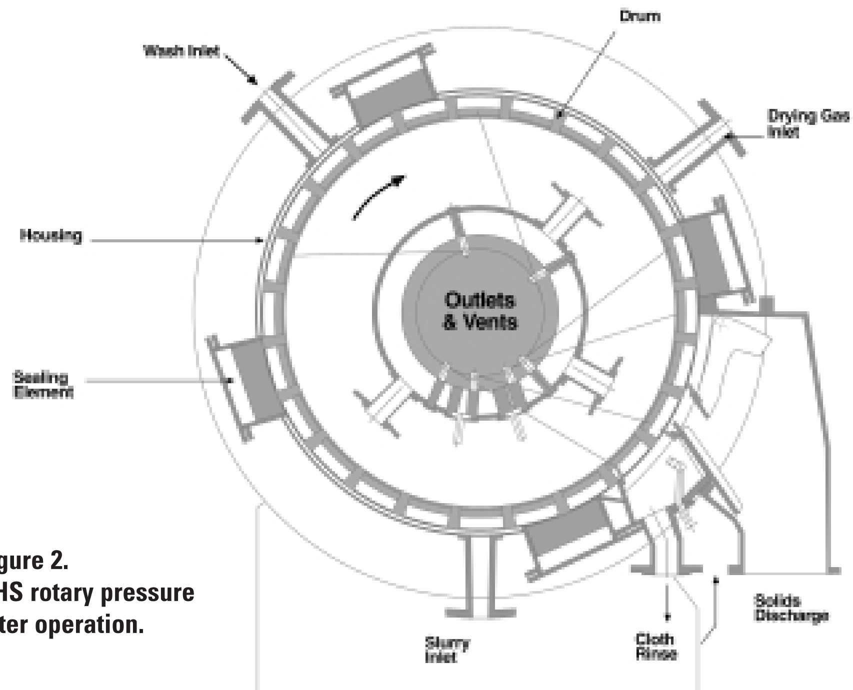

Figure 2. BHS rotary pressure filter operation.

The feed suspension enters each cell, under constant pressure, to form a filter cake. This is detailed in Figure 2. Internal divisions of the housing allow the cake to be processed in completely separate zones. Each zone can operate under different pressures depending upon the process requirements at each stage of filtration, washing and drying.

For example, pressure filtration is conducted up to a maximum differential pressure of 6 bar. Pressure filtration has the added benefit of eliminating post-precipitation of the solids if the process solvent is prone to flashing under vacuum filtration.

A second benefit of the slow-rotating pressure filtration is the reproducible cake depth and the ability to control the residence time (by the speed of the drum). The slow rotation also results in much lower maintenance and energy costs.

Positive displacement washing or counter-current washing follows filtration. The design of the pressure cells, such that they have no free-space and are completely filled, eliminates the possibility of cake cracking or bypass, providing maximum washing efficiency. Multiple washing steps can be accomplished along with solvent exchanges, steaming and extraction.

The cake then undergoes a drying step by blowing ambient

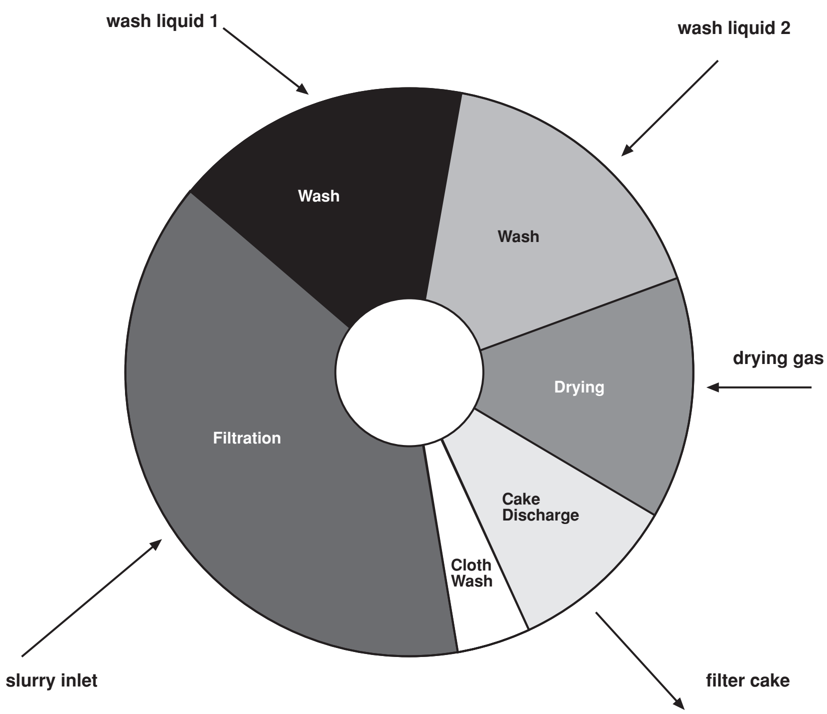

Figure 3. Typical flow showing process zones for a BHS filter.

temperature or hot gas through the cake. The control of this drying step is influenced by gas flow, pressure, temperature as well as the cake depth and residence time.

Finally, the pre-dried cake is continuously discharged. The cake is at atmospheric discharge, which allows it to be fed directly into the downstream equipment. The cake discharge is via a scraper knife and is assisted by a gas blowback.

After cake discharge, there is a cloth rinse step. This is controllable depending upon the product discharge, filter media and potential of cloth blinding. There are several options available for this step such as spray jets and gas blowback. The cloth wash can be done after each discharge or on an intermittent basis. With the drum rotating, after the cloth rinse step, the cells are ready to be filled for filtration. A typical process flow is shown graphically in Figure 3 (page 3).

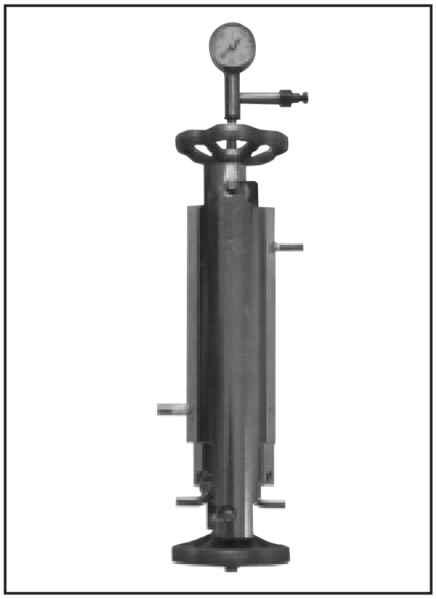

Figure 4. BHS Pocket-Leaf Filter for bench-top testing for filtration, washing and drying studies.

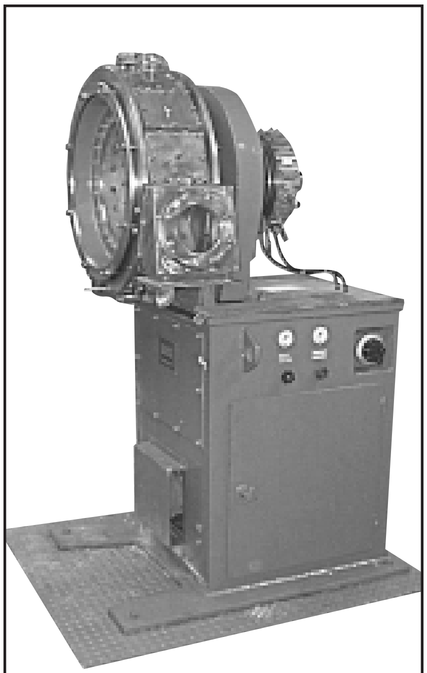

Figure 5. BHS 0.12 M^2 Pilot Filter

On-Site Process Testwork

Process testing was conducted at the site's laboratory and in the plant at the reactor. For the bench-top lab testing, the BHS pressurized pocket-leaf filter with 20 cm^2 of filter area was used. For the continuous pilot testing, a pilot BHS unit with 0.12 m^2 of filter area was installed.

The pocket-leaf filter and setup is described in Figure 4. The pilot unit is shown in Figure 5. The pocket-leaf filter was used to gather the basic filtration, washing and drying data. Once these operations were optimized, the tests were repeated with the actual slurry with the pilot unit.

The three objectives of these tests were as follows:

a. Achieve a final moisture content of less than 28 %
b. Reduce the wash ratios to below current operation
c. Maximize the production rates

Discussion of Pocket-Leaf Filter Laboratory Testwork

The pocket-leaf testing was conducted with the following slurry and process conditions:

Density of
the slurry ....1006 g/l

Temperatures
Filtration ....0°C
1st wash ....IPA 44% at 0°C
2nd wash ....IPA 88% at ambient temperature
Drying ....Air at ambient temperature

Pressures
Filtration, 1st and 2nd wash ......1 barg
Drying ....3 barg

Cake Thickness ......8-9 mm

Filter Media ....Polypropylene, 2.5 micron(um) removal efficiency

Filtration

The first optimization concerns 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.

In this application, several different cake depths were analyzed based upon the current operation. Filtration pressure and time were optimized for each depth of cake. The times were always between 5 - 8 seconds at 1 barg pressure for a cake depth of 8 - 9 mm.

Washing

Displacement washing tests are also performed in the pocket-leaf filter. A measured amount of wash liquid is added in a pre-determined wash ratio. Once again, pressure and time are measured.

In this application, multiple washing steps were undertaken with purified water, isopropyl alcohol (IPA) and methyl isobutyl ketone (MIBK) to determine which combination of washing techniques would meet the Karl Fischer (KF) moisture specification. After multiple tests with different combinations, it was found that with a 9 mm cake, using two displacement washes (44% IPA and 88% IPA), the KF specification could be met 100% of the time.

Drying

Product drying in the pocket-leaf filter is tested by blowing ambient-temperature or hot gas through the cake. 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 objective of less than 28% final moisture content.

Conclusion and Path Forward Steps from the Laboratory Testing with the Pocket Leaf Filter

Table 1 illustrates the scale-up to a production unit from the pocket leaf testwork. The results show that one rotary pressure filter, type K6, with of filter area of 1.08 m2 is sufficient to produce more than 1000 m-tons/year of the Bulk-API. Based upon this analysis, one K-6 unit would replace two (2 x 800mm) inverting basket centrifuges. The plant decided to continue the evaluation program and install a BHS 0.12 m^2 pilot scale filter for testing under actual plant conditions to confirm these results.

Table1: Pocket-Leaf Filter Laboratory Scale-up for the BHS Rotary Pressure Filter

The scale-up is based upon a cake thickness of 9 mm and 22 ml of IPA 44% for the 1st washing step and 9 ml IPA 88% for the 2nd washing step. With this amount of washing liquids, the lowest KF moistures were reached.

Cycle Times:	Seconds
Filtration:	8
IPA 44% wash:	15
IPA 88% wash:	5
Drying N2:	20
Total time:	**48 Seconds**

1. Specific filter performance: 145 kg/m^2/h
2. The selected filter is BHS K6 Rotary Pressure Filter with 1.08 m^2 of filter area, with an operation rate of 38.3 revolutions/hour. The unit will produce 1000 tons/year of the bulk-API.

Discussion of the BHS 0.12 M^2 Pilot-Scale Testwork

The BHS 0.12 m^2 pilot filter is configured for automatic-electric operation with a manual adjustment for drum speed control. It is connected directly to the reactor for continuous slurry feed. Washing liquids and drying and blowback gases are fed to the filter via the pilot plant headers and controlled by flow and/or pressure regulators. The BHS pilot unit allowed for testing under actual plant conditions. With the testing complete, the process scale-up and process guarantee can be finalized. The process scale-up is a combination of filtration theory and BHS experience along with the average of the testing times and selected cake depth in order to meet the production requirements.

Table 2 illustrates the production unit scale-up based upon the pilot filter. The conclusions are as follows:

- The filter performance from the lab tests (145 kg/m^{2}h) and the pilot tests (120 kg/m^{2}h) are approximately the same.
- The polypropylene filter cloth produced clear filtrates, eliminating product loses.
- The filter cloth did not blind during the trails.
- The wash ratios from the lab tests and the pilot tests are approximately the same.
- The KF drying results achieved the final dryness requirement.
- The BHS K-6 Filter is correctly sized to meet the annual production rate of 1000 tons
- The BHS K-6 can replace the two (2 x 800mm) inverting basket centrifuges.

Cost-Effectiveness Comparison of the BHS Pharma Rotary Pressure Filter to Inverting Basket Centrifuges

Table 3 illustrates the relative cost-effectiveness calculations that the plant used to examine the different technologies. The operating savings from the Ph-RPF included solvent consumption, energy consumption, number of units and maintenance costs as well as the capital costs for the equipment. The relative cost savings were on an order of 4-6 to 1 and would produce a favorable rate of return on investment and an acceptable payback.

Specification for the BHS Pharma Rotary Pressure Filter

Table 4 illustrates a typical specification for a BHS Pharma rotary pressure filter. The design eliminates product holdup and includes a CIP system. The result is a GMP installation with a dust-free discharge to the downstream equipment.

Summary

The process testwork demonstrated that the use of a BHS Pharma rotary pressure filter would significantly improve the process operations in several ways. First, product quality is improved through more efficient washing leading to maximum efficiency of the downstream pelletizer. Production can be increased with the use of only one piece of equipment rather than two inverting basket centrifuges. A side benefit to this is the significant amount of energy savings that can be realized along with solvent savings. Maximum containment of the solids and solvents is possible for operator safety along with the other process improvements of gas and solvent reuse. Finally, as compared with the inverting basket centrifuges, the Ph-RPF unit has high operating reliability due to its slow rotation (0.8 rpm) and 10 HP system-matched motor and variable frequency drive. The replacement of the current centrifugation equipment with the BHS Pharma Filter is recommended to meet the plant's quality, production, maintenance, and economic objectives.

Table 2: BHS 0.12 M^2 Pilot Filter Scale-up for the BHS Rotary Pressure Filter

		Run # 19
Filtration (3 Zones)		
Revolution	rph	20
Pressure	Kg/cm2	1.3
1st Wash (2 Zones)		
Wash Material		44% IPA
Pressure	Kg/cm2	1.8
Temperature	degrees C	5
Flow Rate of Filtrate	Kg/hr	23.0
Wash Ratio (kg wash/kg dry cake)		1.7
2nd Wash (2 Zones)		
Wash Material		88% IPA
Pressure	Kg/cm2	1.3
Temperature	degrees C	30
Flow Rate of Filtrate	Kg/hr	49.0
Wash Ratio (kg wash/kg dry cake)		3.6
N2 Drying (3 Zones)		
Pressure	Kg/cm2	1.4
Temperature	degrees C	30
Flow Rate	l/min	135
Cake Properties		
Thickness	mm	9
Rate of Wet Cake	Kg/hr	18.3
Rate of Dry Cake	Kg/hr	13.8
Residual Moisture by KF	%	16.4

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Table 3: Cost-Effectiveness Comparison of the BHS Pharma Rotary Pressure Filter to Inverting Basket Centrifuges

		Inverting Basket Centrifuges	BHS K-6 Pharma Filter
Assumptions			
Product		Bulk-API	Bulk-API
Total Rate of Dry Product per year	Tons	1000	1000
Number of Units Required		2 x 800mm	1
Total Filter Area Required	M^2	1.8	1.08
Motor Power of Units	HP	60 (each)	10
Rotational Speed	RPM	1600	0.3
Current Solvent Consumption			
First Wash Ratio for 44 % IPA	Relative gal/yr (1)	2.5	1.7
Second Wash Ratio for 88 % IPA	Relative gal/yr	5.0	3.6
Projected Utility Consumption			
Cost for Solvent Recovery by Distillation	Relative $/yr (2)	1.44	1
Energy Costs for Operating Motors	Relative $/yr	12	1
Energy Cost for Nitrogen Drying	Relative $/yr (3)	1	6
Maintenance Costs (4)		High	Average
Capital, Installation & Operating Costs	Relative $ (5)	4-6	1

NOTES:

(1) Relative gallons/year was calculated based upon the estimated solvent usage from the tests and actual solvent consumption from the current operation.

(2) Relative $/year was calculated based upon energy required to recovery the estimated solvent usage from the tests and actual energy usage for solvent recovery by distillation from the current operation.

(3) Energy costs for drying was calculated based upon the estimated gas usage for blowing for the BHS filter. The current operation does not require any gas usage as the inverting basket centrifuges meet the "lump-free product" specification with a final moisture content of 28% solely on the basis of "high-speed" rotation.

(4) Based upon the plant experience with the inverting-basket centrifuges as well as upon BHS conversations with users of the Ph-RPF and inverting-basket centrifuges.

(5) Relative $ is based upon the sum of the amortization of capital and installation costs of two inverting basket centrifuges versus one BHS pharma rotary pressure filter plus the estimated annual operating costs for each option.

Table 4: Pharmaceutical Design Considerations

The testwork led to a design of the BHS Ph-RPF K-6 rotary pressure filter to meet a moisture specification as well as to increase production. The final design for the Pharma rotary pressure filter is described below for a GMP installation.

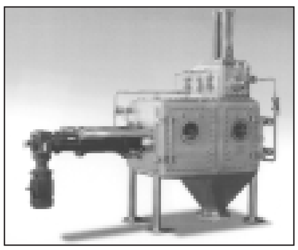
1. The rotating drum is sealed to the movable housing by a gas-inflated membrane, which eliminates all lubrication and packing and sources of impurities.
2. The housing is moved by an electric drive, which again eliminates all hydraulic operations.
3. Central drive coupled directly to a gear motor with double roller bearing ensures rotating stability.
4. The selected media is a 2 um sintered stainless steel that is welded to the cell inserts for a gap-free media installation.
5. All product-wetted and exterior parts are polished stainless steel with rounded corners to eliminate product holdup.
6. All seals are FDA-approved materials.
7. The entire unit is sealed in a liquid-tight enclosure with automatic CIP operation including pneumatically operated valves and orbital-welded piping.
8. Full containment of the bulk-API product and solvents that are used eliminates solids and solvents emissions.
9. Atmospheric discharge through a packing-head allows for dust-free and direct discharge to the downstream equipment.
10. Additional design features that allow the Ph-RPF unit to achieve maximum containment.
    a. Enclosed and pressurized control/service head and bearing shields. This will allow for containment of any potential solvent leakage through the control head.
    b. Planetary gearbox with roller bearings ensures a stable rotating drum with little or no changes in drum tolerances.
    c. Two recycle modes to further meet the containment objective.
        1. The cloth rinse solvent is used as the solvent for the first wash, which minimizes solvent usage and solvent emissions. In addition, residual solids that are not discharged are returned to the process without a loss of product yield.
        2. A gas compressor/condenser/reheater/solvent recovery system can be incorporated to reuse the nitrogen for cake drying, if possible, and to condense and recover the solvent from the nitrogen stream, depending upon the process details.

Specializing in Thin-Cake Filtration, Cake Washing & Drying Technologies

Test in the BHS Laboratory or at Your Plant for the Optimum Process Technology

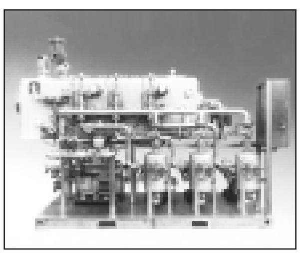
BHS Rotary Pressure Filter

- Continuous thin-cake (0.25-6 inches) production
- Filtration is conducted via pressure of up to 90 psig
- Positive displacement washing or counter-current washing
- Multiple washing steps as well as solvent exchanges, steaming and extraction
- Cake drying by blowing hot or ambient-temperature gas
- Atmospheric discharge from pressure operations for direct discharge to downstream equipment



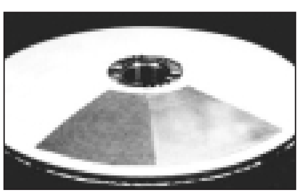
BHS-Autopress

- The Autopress is installed in potent compound and active pharmaceutical ingredient (API's) facilities as well as for specialty chemical applications
- Thin-cake, typically 0.25-1.0 inches, production
- Filter plates are contained in a pressurized filter housing for complete containment
- Batch pressure filtration and forward or reverse flow washing
- Vacuum or hot-gas drying or pre-drying without agitation or tumbling
- Mechanical compression to 600 psig to eliminate cake cracking
- Fully automatic, heel-free and contained product discharge
- CIP systems with documented performance based upon Riboflavin tests



BHS Belt Filter

- Continuous filtration, washing and drying
- Thin-cakes between 0.25-4 inches
- Multiple washing zones for forward or counter-current washing to 99.99% purity
- Drying to 0.1% moisture with heated trays and mechanical compression
- Materials include stainless steel, Hastelloy and synthetic materials
- Gas-tight and pressurized housings



BHS Pressure Plate Filter

- Horizontally designed for stable cakes
- Possible pre-coating of the media with activated carbon or diatomaceous earth
- Vibrating plates, along with gas-assist pulsing, provide for automatic discharge
- Effective solids discharge without spinning-plates
- No rotating or mechanical seals

BHS Candle Filter

- Pressure filtration, clarification and heel filtration
- Specialized candles with perforated metallic or synthetic cores
- Filter media to less than 1 micron
- Cake washing produces a uniform cake for drying
- Cake discharge via gas blowback
- Possible pre-coating of the media with activated carbon or diatomaceous earth

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