Organic Process Research & Development

ARTICLE

pubs.acs.org/OPRD

Lean Filtration: Approaches for the Estimation of Cake Properties

Saravanababu Murugesan,* Daniel M. Hallow, James P. Vernille, Jean W. Tom, and Jose E. Tabora*

Late Phase Chemical Development, Bristol-Myers Squibb Co., One Squibb Drive, New Brunswick, New Jersey 08903, United States

ABSTRACT: The majority of active pharmaceutical ingredients (APIs) and intermediates are isolated as solid products through crystallization, filtration, and drying. In some cases, filtration of APIs and intermediates exhibit long cycle times and may potentially become the bottleneck of the entire process train. Thus, early assessment of the cake properties is typically required to evaluate filtration performance prior to scale-up. This work presents two approaches to rapidly estimate the specific cake resistance through lab studies. Using the first approach, a first-order approximation of the specific cake resistance is estimated from data collected during a simple Buchner funnel filtration. The second approach provides a more accurate estimate from a more extensive filtration study incorporating dynamic pressure modulation (DPM, a single filtration with ascending pressures), improving the fidelity of filtration predictions. Results from several case studies demonstrate how a workflow combining these two approaches can be appropriately employed to assess the cake properties from laboratory filtrations for predictions of the pilot/manufacturing plant filtration performance.

INTRODUCTION

Active pharmaceutical ingredients (APIs) and intermediates manufactured by the pharmaceutical and specialty chemical industries are typically purified by crystallization and isolated from the mother liquor by filtration and drying to produce a stable, pure, and readily handled product. Pressure filtration is a popular approach due to its simplicity and ease of operation. Process development of pharmaceuticals is uniquely challenged by the need to develop a robust and efficient process for numerous chemical intermediates and APIs exhibiting widely different cake properties. Therefore, filtration time can vary from a few hours for a product to a few weeks for another product under similar operating conditions.

The properties of the slurry and the operating parameters of the isolation equipment dictate the filtration rate, and thereby the cycle time of this unit operation. Characterization of cake properties is therefore essential to assess potential risks in the isolation of the crystallized product, and appropriately direct process development efforts to achieve an optimal time-efficient process. Additionally, when material demands do not allow for process development to resolve filtration issues, this data may be used to aid the kilo lab in their choice of isolation equipment and operating conditions. Invariably, the process development of a filtration unit operation is initiated by establishing an estimate of the specific resistance of the cake. Multiple approaches of varying degrees of complexity have been implemented to characterize the cake.[1]

In this work, we describe two abbreviated approaches to obtain estimates of the specific cake resistance and enable prediction of the filtration cycle time at larger scales. The two procedures are (1) a first-order approximation of the specific cake resistance calculated from Buchner funnel filtration data and (2) a more accurate calculation of the specific cake resistance and compressibility index from a detailed filtration study incorporating dynamic pressure modulation (DPM, a single filtration with ascending pressures). Several case studies are presented that demonstrate the reliability of these two approaches. Finally, a workflow is proposed to minimize the experimental burden of the characterization of the filtration process, specifically the cake compressibility, by integrating the data collection to the natural experimental plans in the development process and performing fit-for-purpose risk assessment.

Filtration Theory. Numerous approaches have been developed to model pressure filtration incorporating different levels of detail in terms of local cake consolidation, settling, and pressure distribution. In the pharmaceutical industry, the expansion of Darcy's law[2] by Tiller[3] and Ruth[4] has been successful in its broad applicability, simplicity, and parameter economy. In this formalism, the cake filtration under constant pressure is modeled by the Ruth equation:

$$\frac{\mu\alpha C}{2A^2\Delta P}V^2 + \frac{\mu R_m}{\Delta P A}V - t = 0 \quad (1)$$

where, α is specific cake resistance (length/mass), R_m is medium resistance (1/length), μ is filtrate viscosity, C (= M/V) is solid mass (M) per volume of liquid (V) in the slurry, V is filtrate volume over time t, M is mass of cake collected over time t, A is filtration area and ΔP is the pressure drop across the cake.

The specific cake resistance (α) represents the resistance of the cake that provides a unit pressure drop per unit M/A and μ.[5] It is a key characteristic and intrinsic attribute which summarizes the properties of the cake during the process of consolidation. It is often approximated by a modified Almy−Lewis equation.[6]

$$\alpha = \alpha_0\left(\frac{\Delta P}{\Delta P_{ref}}\right)^n \quad (2)$$

where α_0 and n are empirical constants with n representing the compressibility index of the cake, and ΔP_{ref} is an arbitrary differential pressure under which the specific cake resistance corresponds to α_0.

Received: June 2, 2011
Published: November 01, 2011

dx.doi.org/10.1021/op2001468 | *Org. Process Res. Dev.* 2012, 16, 42–48

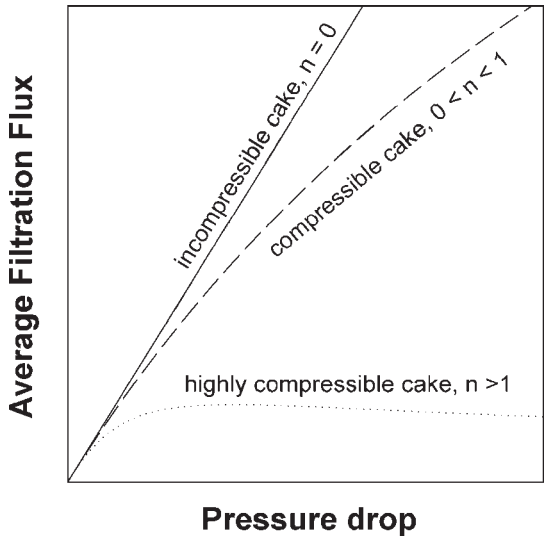

Figure 1. Profiles of filtrate flux as a function of pressure drop for cakes of different compressibility indices.

Equation 1 may be rearranged to obtain

$$\frac{V}{At} = \frac{\Delta P}{\mu}\left(\frac{1}{\frac{\alpha CV}{2A} + R_m}\right) \text{ or } \frac{At}{V} = \frac{\mu}{\Delta P}\left(\frac{\alpha CV}{2A} + R_m\right) \tag{3}$$

where the term V/At represents the average filtration flux ($\overline{u}$) and corresponds to the volume of the filtrate collected per unit area over a specific time, t. Note that the average filtration flux is an inverse function of the amount (M) of the cake collected:

$$\overline{u} = \frac{\Delta P}{\mu}\left(\frac{1}{\frac{\alpha}{2}\frac{M}{A} + R_m}\right) \tag{4}$$

Generally, filtration operations are evaluated for a given process stream for which the slurry density (C) and the viscosity (μ) are already defined. In this case, the filtration time as a function of M/A may be obtained by rearranging eq 4

$$t = \frac{\mu}{\Delta P}\frac{M}{CA}\left(\frac{\alpha}{2}\frac{M}{A} + R_m\right) \tag{5}$$

For incompressible cakes, the compressibility index (n) is 0, and α is independent of ΔP. If the cake is compressible (α is pressure dependent), then n is greater than 0. As per the authors' experience, typical pharmaceutical cakes have n in the range of 0−1. The average filtration flux profiles of the compressible and the incompressible cakes are illustrated in Figure 1 as a function of the pressure drop across the cake for various constant pressure filtrations.

In the case of the incompressible cakes ($n = 0$), an increase in the pressure drop results in a directly proportional increased filtrate flux, while in moderately compressible cakes ($0 < n < 1$), the filtrate flux monotonically increases but with decreasing slope, and in highly compressible cakes ($n > 1$) the flux reaches a maximum and may even decrease if the filtration is carried out at a sufficiently larger pressure drop.

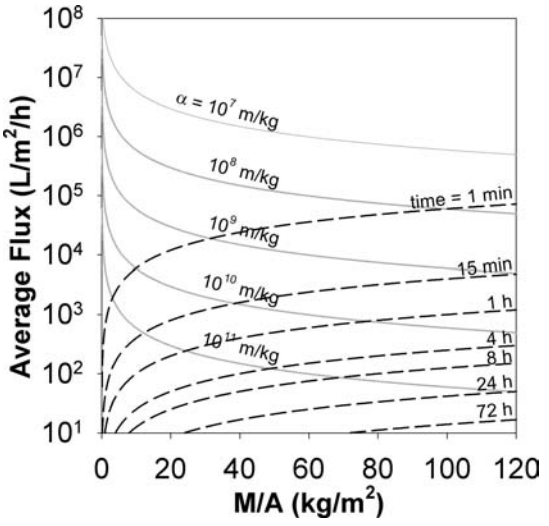

Figure 2. Correlation between average filtration flux (solid lines) and M/A as a function of α and comparison of the estimated filtration times (dashed lines) as a function of α.

In many cases, the development of the filtration process includes analysis of data from a laboratory filtration (e.g., leaf filter) to model or predict the filtration performance of larger batches in pilot or manufacturing plants. The traditional and the simplest approach of modeling the filtration unit operation is by performing multiple filtration experiments to collect t vs V data at multiple pressures; these profiles are linearized by plotting t/V vs V and obtaining the parameters α and R_m for each pressure. Subsequently each of these experiments are then linearized as a function of ΔP (plotting $\ln(\alpha)$ vs $\ln(\Delta P)$) to obtain the overall α_0 and n. These parameters are then used to predict the on-scale filtration performance. Even though this approach is widely accepted, resources (material, manpower, and time) are often limited, depending on the development stage of the particular project, and this analysis is not routinely performed.

For incompressible cakes, eqs 4 and 5 can be used to estimate the profiles of $\overline{u}$ as a function of α and M/A for a given ΔP, μ and R_m. For example, Figure 2 represents the plots of $\overline{u}$ as a function of α and M/A for a ΔP of 20 psi, μ of 1 cP and R_m 1×10^6 1/m. For any point in the graph, both the average filtration flux and the filtration time may be estimated for any specific cake resistance as a function of the selected M/A. For instance, a cake with $\alpha = 10^{10}$ m/kg will take approximately 15 min to filter with an M/A of 40 kg/m^2, and the average flux will be approximately 2000 L/m^{2}h. However the same cake will take 1 h if the M/A is increased to approximately 80 kg/m^2, and the average flux will decrease to 1000 L/m^2 h. Conversely, knowing an average filtration flux and M/A for a particular filtration would enable estimating α. Generally once a crystallization process has been defined, the parameters C, α_0, and n will be set. The scale and equipment-dependent parameters M/A and ΔP will determine the filtration time on scale. The maximum ΔP is normally set by equipment restrictions, and in the authors' experience pressure filtration ΔP is typically 20−60 psig in the pharmaceutical industry. The parameter M/A ranges from 60 to 120 in typical pilot and manufacturing equipment and is related through the density to the height (filter fill) of the filtered cake.

Figure 2 also illustrates that using $\overline{u}$ to compare the filtration performances of two different slurries could be misleading, as

dx.doi.org/10.1021/op2001468 |Org. Process Res. Dev. 2012, 16, 42–48

Table 1. α vs performance in a filtration equipment

α (m/kg)	filtration performance
$1 \times 10^7 - 1 \times 10^8$	fast filtering
$1 \times 10^8 - 1 \times 10^9$	moderately fast filtering
$1 \times 10^9 - 1 \times 10^{10}$	slow filtering
$>1 \times 10^{10}$	very slow filtering

those two streams could result in the same $\overline{u}$ but for different M/A. A comparison of performance using only $\overline{u}$ (e.g., from Buchner funnel filtration) is only applicable for similar values of M/A and ΔP.

Table 1 gives a general guidance of the filtration performance in terms of specific cake resistance. Generally, in the authors' experience, cakes having an $\alpha > 10^9$ m/kg have an increased likelihood of becoming process bottlenecks and are subjected to further characterization and optimization to enhance the filtration performance.

Filtration Modeling. To simplify and streamline the traditional approach, we introduce two different modeling alternatives. The first uses eqs 4 and 5 to correlate $\overline{u}$ and M/A obtained from a laboratory Buchner funnel filtration to estimate α which can then be used in the same equation along with the other parameters (such as M/A and ΔP) corresponding to the larger scale to predict $\overline{u}$ and the corresponding filtration time for the larger scale filtration. To automate this modeling approach, Microsoft Excel was used as the platform.

Generally, pharmaceutical solids are isolated as crystalline material, and cakes with low specific cake resistance have no or moderate compressibility index. Therefore, estimates of a very low specific cake resistance at moderate pressure drops typically used in laboratory bench scale (14 psi) are likely to be consistent at larger scale. Therefore, cakes with a low specific cake resistance pose a low risk in terms of the filtration performance and would not require more characterization beyond the first-order approximation. For cases in which a long cycle time is predicted through the first-order approximation, a more elaborate characterization of cake properties may be required to accurately model the scale-up and provide better estimates of filtration performance when assessing the risk of scale up. The dynamic pressure modulation (DPM) method enables the evaluation of α_0 and n by performing a single filtration experiment in a leaf filter at ascending pressures. For the DPM method, DynoChem was used as the modeling and parameter regression platform.

The advantages of using DynoChem include speed of data analysis and accuracy of regressions. It also offers the ability to easily simulate filtrations at larger scales to evaluate the cycle time and determine the optimum filter loading, filtration pressure, and equipment. Using a mathematical package that solves the ordinary differential equation and performs nonlinear parameter regression removes the requirement of performing two linearizations, one for α (eq 1) and one for α_0 and n (eq 2), and allows a global regression across multiple experiments to fit α_0 and n.

The cake parameters are traditionally estimated through conducting filtration experiments at several single pressures, and through correlating α and ΔP from linearization of eqs 1 and 2. In the DPM method, one regression is conducted for all the parameters over all the experiments, reducing the error associated with multiple regressions without requiring linearizations. For consistency, a value of 1×10^6 1/m was used for R_m unless otherwise noted. Based on previous measurements of the medium resistance for filter paper (Whatman), R_m is often an insignificant contribution to the total resistance.

Table 2. Details of the two batches isolated in the kilo lab (case study 1)

batch	filtrate volume (L)	mass of solids (kg)	average filtration flux (L/m^2h)	predicted filtration time (min)	actual filtration time (min)
1	26.1	2.2	1036	8.8	12.0
2	36.9	3.0	1040	16.9	16.0

EXPERIMENTAL SECTION

Buchner Funnel Filtration. Buchner funnel filtrations were conducted using a Buchner funnel, a Buchner flask, and Whatman filter paper. All the Buchner funnel filtrations conducted in this work used vacuum as the driving force with a ΔP of ~12 psi. The filter paper was initially wet with a few drops of the neat solvent (mostly the major solvent in the filtrate) to adhere the filter paper to the funnel, the slurry was then poured on the filter paper. Once there was enough slurry on the paper, vacuum was started, thereby initiating the filtration. The filtration time (t) was recorded as the time taken by the filtrate to go below the cake surface. The volume of the filtrate collected (V) over time (t) was measured using a graduate cylinder. The average filtration flux ($\overline{u}$) was then calculated as V/At. The wet cake was then dried in a conventional oven and then weighed (M). This methodology was followed in all the case studies for consistency.

Leaf Filtration (Traditional and DPM Methods). Laboratory leaf filtrations were conducted in a Lab Pocket Leaf Filter (BHS-Filtration Inc.) with Whatman filter paper as the filter medium and compressed N_2 as the pressure source. Traditional leaf filtration was conducted at a fixed pressure, and the filtrate mass was collected as a function of time using a scale connected to a computer with a data acquisition frequency of 0.5−1 Hz. The filtration was then repeated with fresh slurry at a different fixed pressure. The filtration time vs filtrate mass data sets collected at the different pressures were then used to fit α_0 and n.

DPM method used an equipment setup similar to that of the traditional leaf filtration except the pressure set point was increased at regular/irregular intervals of time during a single filtration. The instantaneous filtration time and filtrate mass collected as a function of ΔP from this single filtration was then used to fit α_0 and n.

RESULTS

This section provides various case studies where both methods were validated for their prediction accuracy. Case studies 1 and 2 evaluate the first-order approximation method, while case studies 3−5 evaluate the DPM method.

Case Study 1. In this case study, α was determined for compound A using the laboratory Buchner funnel filtration. A lab filtration was carried out by filtering 41 g of solids using a Buchner funnel (110 mm diam, filtration area 95 cm^2) with 12 psi ΔP (= 827 mbar, vacuum). Approximately 400 mL of filtrate was collected in 45 s. α was estimated to be 9.8×10^{10} m/kg, which was then used to predict filtration times for isolation in the kilo lab utilizing 1410 mbar ΔP on a 0.13 m^2 filter. Table 2 shows the isolation details for each batch. The actual and the predicted filtration times for the two batches match the expectations for the approximations applied in this approach.

dx.doi.org/10.1021/op2001468 |Org. Process Res. Dev. 2012, 16, 42–48

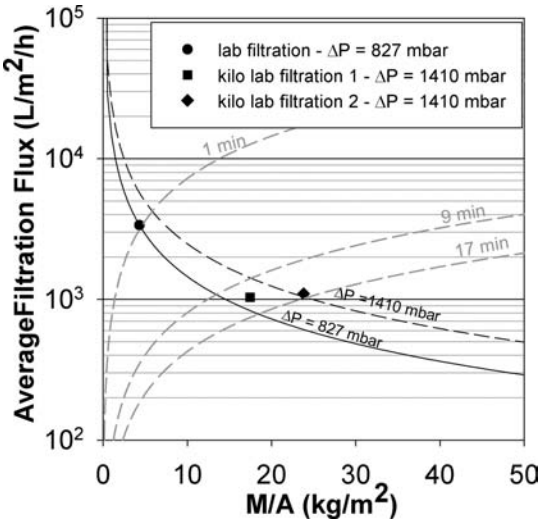

Figure 3. Projection of laboratory and pilot-plant average filtration fluxes on operating lines corresponding to the same average specific cake resistance (case study 1).

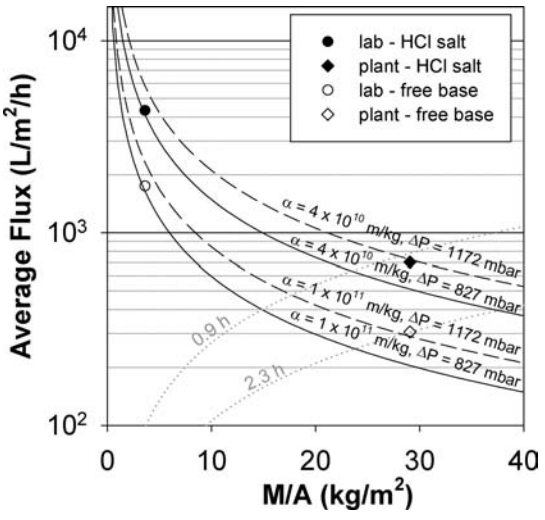

Figure 4. Projection of laboratory and pilot-plant average filtration fluxes on operating lines corresponding to the same average specific cake resistance (case study 2).

Figure 3 is shown to visually compare the values of the average filtration flux and specific cake resistance from the lab and the kilo lab as a function of M/A. The lab filtration (represented as a circle) is used to obtain the flux profile (solid curve) that corresponds to the estimated value of α (9.8×10^{10} m/kg). By using this estimated α value, the flux profile (dashed line) was calculated for kilo lab conditions (ΔP 1410 mbar).

Figure 3 also shows the constant filtration time lines for 1, 9, and 17 min, the time loci of points that correspond to combinations of average filtration flux and M/A, resulting in the same total filtration time. The 1 min line intersects the 1410 mbar filtration profile at a higher M/A value than the 827 mbar profile, indicating that a larger amount of material (higher M/A) can be filtered in 1 min at the higher ΔP, as expected. The average filtration fluxes of the two kilo-lab filtrations are close to the loci

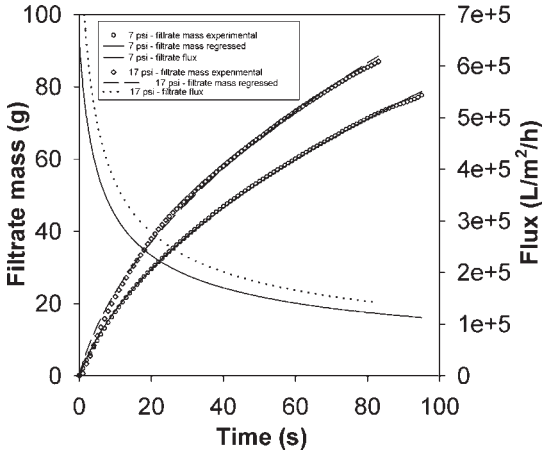

Figure 5. Comparison of regressed and measured data from the traditional leaf filtration of compound C (case study 3).

generated from the predicted filtration time and average filtration flux curves.

Case Study 2. For this case study, an HCl salt of compound B was crystallized and isolated. The isolated wet cake was then redissolved and crystallized to generate the free base of compound B. In the laboratory, the filtrations of the HCl salt and the free base were conducted using a Buchner funnel with 55 mm diameter (23 cm^2 filtration area) and ΔP of 827 mbar. Each filtration consisted of 240 mL of slurry containing 8.6 g dry cake. The filtration of the HCl salt took 1.4 min, whereas the filtration of the free base was significantly slower, taking 3.5 min. In the pilot plant, the corresponding filtrations were performed in a Nutsche filter with 0.75 m^2 filtration area, ΔP of 1172 mbar, 528 L of slurry, and 21.8 kg of dry cake. The predicted filtration times of the HCl salt and free base were 0.9 and 2.3 h, and the actual filtration times were 1.0 and 2.3 h, respectively. The observed average filtration fluxes of the two isolations from the laboratory and the plant were plotted against their M/A's to estimate the corresponding α values (Figure 4).

Solid lines represent the flux profiles for ΔP of 827 mbar (lab filtration), and the dashed lines correspond to the flux profiles for ΔP of 1172 mbar (plant filtration). Also shown are the predicted filtration times (dotted lines). It is apparent that the first-order estimation of α values of the laboratory resulted in accurate prediction of the pilot-plant filtration performance. The accuracy of this plant prediction at higher pressures suggested that the cakes were incompressible in this pressure range, deeming further evaluation of cake property through the DPM method unnecessary.

Case Study 3. In this case study, the filtration of a pharmaceutical intermediate (compound C) was used to demonstrate the reliability of the DPM method to estimate specific cake resistance and the compressibility index in a single filtration experiment as opposed to performing multiple single pressure filtrations to estimate the cake properties.

The slurry of compound C following the crystallization (concentration ~55 mg/mL) was divided into three portions. The first two portions (6.5 g dry cake basis) were filtered separately at constant pressures of 7 and 17 psig. The third portion (8.5 g dry cake basis) was filtered by applying pressure that was increased stepwise at regular intervals from 5 to 23 psi. The filtration area was 19.6 cm^2 for the filtrations in this case study. The single

dx.doi.org/10.1021/op2001468 |Org. Process Res. Dev. 2012, 16, 42–48

pressure experiments were fitted to obtain α_0, R_m, and n; Figure 5 shows the fitted plots of the filtrate mass and the instantaneous flux profiles when filtered at 7 and 17 psi ΔP's through the traditional approach. Equation 3 was used to predict the instantaneous flux values.

Filtration at higher ΔP resulted in a higher rate of filtration but not exactly proportional to the increase in applied pressure (Figure 5), indicating a compressible cake. The cake parameters fitted from the two procedures are given in the Table 3. In this case two profiles were sufficient to obtain adequate regressions of the three parameters.

Table 3. Comparison of the cake properties fitted from the traditional and the DPM methods (case study 3)

method	n	α ($\times 10^{-07}$) (m/kg)	R_m ($\times 10^{-08}$) (1/m)
traditional	0.72 ± 0.04	1.11 ± 0.01	2.90 ± 0.01
DPM	0.76 ± 0.02	1.24 ± 0.00	2.10 ± 0.00

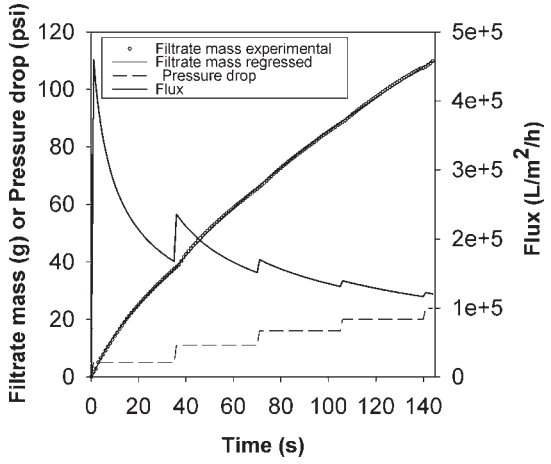

Figure 6. Comparison of regressed and measured data from the leaf filtration of compound C through the DPM method (case study 3).

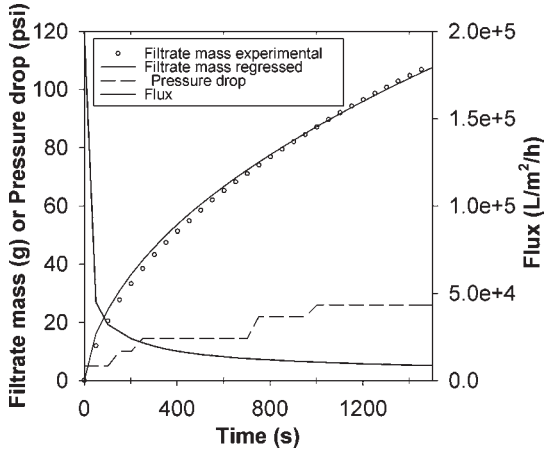

Figure 7. Comparison of regressed and measured data from the leaf filtration of compound D through the DPM method (case study 4, smaller PSD batch).

Figure 6 shows the profiles of the filtrate mass (experimental & regressed) and the instantaneous flux when filtered under a stepwise increase (dashed lines) in pressure (DPM Method).

For the purpose of comparison, α was calculated from α_0 and n for a ΔP of 30 psi (eq 2, ΔP_{ref} = 1 psi). The values of α, R_m, and n fitted from the traditional and the DPM methods were similar, suggesting that the DPM method is as adequate as multiple filtration experiments under constant (and different) applied pressure.

Thus, by using the DPM approach, a reasonable estimate of the cake properties was obtained with fewer resources. Comparing the values of n and α shown in Table 3, we observe approximately 5.6 and 11.7% error, respectively, between the two methods. A prior estimate of the specific cake resistance is desired in this procedure to appropriately stage the experiment and allow sufficient time/pressure profiles for a reliable estimate of the compressibility index. In our workflow, the estimate would be obtained from prior Buchner filtration data from the process.

Case Study 4. In another example of the DPM method, specific cake resistance and compressibility for a compound (compound D) were estimated for two different processes that produced different particle size distributions and therefore different filtration performances. Laboratory filtration experiments were carried out using the DPM method to determine the specific cake resistance and compressibility (Figure 7). As an example, only filtration data from the smaller PSD batch is provided. As expected, the slurry with the larger particle size had a lower specific cake resistance compared to the slurry with the smaller particle size (Table 4). Using the estimated parameters α_0 and n, the filtration time of the planned pilot-plant batches were predicted (Table 4). The actual filtration time was comparable to the predicted filtration time for each of the two batches.

Case Study 5. DPM filtration was carried out on slurries of compound E both in the laboratory and in the pilot-plant filters to assess the reliability of the DPM method at different scales. A slurry sample was obtained from a pilot-plant batch and filtered (0.0023 m^2) in the laboratory, implementing the DPM method with ΔP ranging from 5 to 35 psi with discrete increments of 5 psi per step. Figure 8 shows the comparison of the regressed and measured data from the laboratory DPM experiment.

The scaled-up DPM filtration carried out on the same batch was performed in a filter dryer (1 m^2) using pressures ranging from 15 to 25 psi. Figure 9 shows the comparison of the regressed and measured data from the plant DPM filtration. Cake parameters α_0, R_m, and n were determined for both laboratory and pilot-plant filtrations and are given in Table 5.

From this analysis, the estimated values of compressibility and cake resistance are in very close agreement between lab and plant. Regression of the pilot-plant filtration run failed to determine the value of R_m because no data were collected during the initial phase

Table 4. Comparison of the predicted and actual filtration times on scale (case study 4)

batch	particle size distribution	filtrate volume (L)	mass of solids (kg)	average filtration flux (L/m^2h)	specific cake resistance (m/kg)	n (−)	predicted filtration time (h)	actual filtration time (h)
1	large	117	4.5	64.3	1.0×10^{10}	1.06	7.2	6.5
2	small	160	6.9	18.17	2.4×10^{10}	1.00	35.3	32

dx.doi.org/10.1021/op2001468 |Org. Process Res. Dev. 2012, 16, 42–48

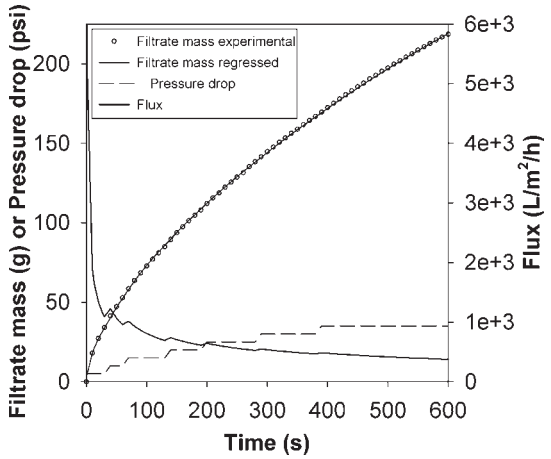

Figure 8. Comparison of regressed and measured data from the laboratory leaf filtration of compound E through the DPM method (case study 5).

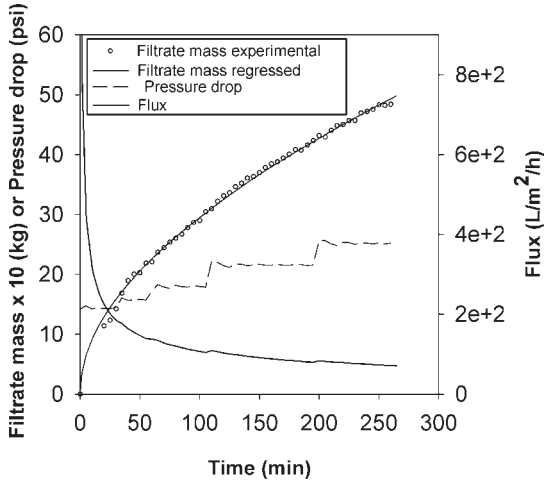

Figure 9. Comparison of regressed and measured data from the pilot-plant filtration of compound E through the DPM method (case study 5).

of filtration where the contribution from R_m would dominate the overall resistance. Since these data were gathered from the pilot plant using a level indicator, the data were not available for the first 25 min of the filtration as can be seen in Figure 9.

Sensitivity Analysis. In this work, eq 5 is the main instrument to predict the time required for filtration. To estimate the error in this prediction we considered the risk of using the experimental data and incorrectly underestimating the specific cake resistance and consequently underestimating the risk of a prohibitively long filtration time. Therefore, the error analysis was considered from those two perspectives. An underestimate of the specific cake resistance would be obtained if the values used in the abbreviated form of eq 5 aligned to provide a value lower than the "true" value. These conditions are summarized in eq 6.

$$\alpha_{max} = \frac{(t + \varepsilon_t^{\alpha})(\Delta P + \varepsilon_{\Delta P}^{\alpha})(C + \varepsilon_C^{\alpha})}{\mu - \varepsilon_{\mu}^{\alpha}} \left(\frac{A + \varepsilon_A^{\alpha}}{M - \varepsilon_M^{\alpha}}\right)^2 \quad (6)$$

All variables in eq 6 have their previous meanings, while ε_i^j denotes the measurement error of the variable i being used to estimate the quantity j. The range for α should then be in the range $(\alpha - \alpha_{max})$,

Table 5. Comparison of the cake properties between the lab and the pilot-plant filtrations (case study 5)

equipment	filtrate volume (L)	mass of solids (kg)	n	α_0 ($\times 10^{-11}$) (m/kg)	R_m ($\times 10^{10}$) (m/kg)
leaf filter	0.3244	0.0113	0.64	4.63	1.60
filter dryer	584.555	26.035	0.66	3.73	–

the maximum estimate for filtration time at a large scale t_s can then be obtained from eq 7.

$$t_{Smax} = \frac{\mu_S + \varepsilon_{\mu_S}^t}{2(\Delta P_S - \varepsilon_{\Delta P}^t)(C_S - \varepsilon_{C_S}^t)} \left(\frac{M_S + \varepsilon_{M_S}^t}{A_S - \varepsilon_{A_S}^t}\right)^2 (\alpha_{max}) \quad (7)$$

As a result, the projected range of the M/A and the estimated value of α will have a dominating impact on the maximum possible error of the predicted filtration time. Therefore, the larger the anticipated M/A for the scale-up and the estimated value of α, the more important it is to reduce the error in the α_0 and n estimates in order to improve the accuracy of the predicted filtration time.

The two case studies (1 and 2) presented in which the specific cake resistance was estimated from a single laboratory filtration measurement provided reasonable estimates of filtration times at the pilot scale. Table 6 summarizes the anticipated error expected from measurements in the laboratory filtrations for the two case studies. The errors in the parameters are forced to be in the direction which would provide the largest deviation of the estimate of α. The medium resistance is not included since even for unrealistic errors it had a minimal impact on the estimate of α.

In case studies 1 and 2, the maximum potential underestimation for α would be approximately 70%. By using this value the actual observed filtration time at scale-up (last column of Table 6) was within the predicted range.

Naturally, other sources of error are not accounted for in this formalism. For cases in which the operations at larger scale significantly alter the specific cake resistance, the predicted filtration performance will clearly not be representative. In addition, the properties of the cake may be such that the filtration model discussed here is not applicable. This may occur when phase separation, plasticization, or extensive polydispersion of the crystal size distribution may result in deviations from the model such that the cake is no longer adequately described by a specific cake resistance.[7] As discussed here, however, the formalism is reasonable in a number of cases.

Suggested Workflow for Data Collection. Typically, the cake resistance is not explicitly estimated in all small-scale filtrations. By using the overall filtration time, the M/A used, and an estimate of the pressure drop, the effort is significantly decreased while obtaining a reasonable estimate of the specific cake resistance. As the project approaches scale-up, the optimal implementation of the first method would generally involve obtaining more than one estimate of the cake properties through routine laboratory experiments.

In cases where the prediction would result in an unreasonably large time range, the DPM workflow provides a more data-rich and systematic estimate of α. The value of the DPM workflow is highlighted in case studies 3, 4, and 5.

Equations 4 and 5 were extensively used in modeling the two methods. MS Excel was used to automate the processing in the first method, while DynoChem was used to regress the filtration

dx.doi.org/10.1021/op2001468 |Org. Process Res. Dev. 2012, 16, 42–48

Table 6. Comparison of the actual time with the time predicted with the hypothetical maximum in the parameters

parameter	ΔP(mbar)	μ (cp)	time (s)	vol (mL)	M (g)	α (m/kg)	maximum under-estimate (%)	scale up M/A (kg/m^2)	estimated time (min)	actual time (min)
% error on measurement	20	−5	15	−5	−10					
					case study 1:					
estimate	827	0.42	45	400	41	9.76×10^{10}	**69.90**	**26.1**	**8.8**	**12.0**
potential worse case	992.4	0.40	51.8	380	36.9	1.66×10^{11}			**15.0**	
					case study 2 (free base):					
estimate	827	1	208	240	8.62	9.39×10^{10}	**62.51**	**29.1**	**2.3**	**2.3**
potential worse case	992.4	0.95	228.8	228	7.76	1.53×10^{11}			**3.7**	

time vs filtrate mass data obtained through the DPM method. This model can also be used in cases of traditional single pressure leaf filtration experiments. It is worth mentioning that, in the DPM method, it was found that the regression accuracy for a given cake was improved by fitting α_0 and n globally and fitting R_m separately for each filtration experiment. This was true even at small scales, where the cake resistance makes a significant contribution to the overall resistance. It was not uncommon to obtain R_m values that increased with increasing pressure, which is known to occur due to increased blinding of the filtration cloth with increasing pressures.[3]

Collectively, the procedures delineated in this paper suggest a workflow that would maximize the information gathered in the normal development strategy and provide a reasonable assessment of potential filtration issues as the synthetic process is increased in scale. In the initial stages a subset of experiments in which the cake is isolated in laboratory scale using Buchner funnel filtration would be used to obtain an estimate of the specific cake compressibility (from the average flux vs the M/A relationship). If these data suggest a high risk of filtration becoming a process bottleneck on the targeted scale-up equipment, a better estimate of the specific cake resistance and associated compressibility using a leaf filter with dynamic pressure modulation would be performed. At this stage the cake would be considered accurately characterized, and subsequent evaluation of the separation equipment or revision of the crystallization process to modify the specific cake resistance would be based on the assessment of the overall risk.

CONCLUSIONS

We presented in this work two simple modeling methodologies to efficiently estimate the cake properties of pharmaceutical intermediates and APIs by using less material and fewer experiments. By using the first method, data from laboratory Buchner funnel filtration can be used to estimate the specific cake resistance which can subsequently be used to predict the filtration performance on larger scales (kilo laboratories and pilot plants).

With the second and more complete filtration analysis, a single experiment can be performed in a leaf filter at stepwise increases in pressures at regular/irregular intervals of time, and the resulting dynamic flux data can be used to determine cake resistance, medium resistance, and compressibility index. The availability of ODE-solvers that can also perform nonlinear parameter regression significantly removes the restrictions placed by conventional filtration analysis (constant pressure, detailed V vs t profiles, and subsequent linearization) and allows for a more efficient and data-rich single filtration experiment. From this approach, the filtration performance on larger scales can be predicted more accurately.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: saravanababu.murugesan@bms.com, Telephone: (732) 227-7969; E-mail: jose.tabora@bms.com; Telephone: (732) 227-5099.

ACKNOWLEDGMENT

We thank our colleagues Michelle Mahoney, Jason Sweeney, Elizabeth Spiteri, Jason Zhu, Victor Hung, Maxime Soumeillant, Justin Burt, Shawn Brueggemeier, Mariano Massari, and Robert Martynuk for contributing to the case studies presented in this manuscript.

REFERENCES

(1) Tien, C., *Introduction to Cake Filtration: Analyses, Experiments and Applications*; Elsevier: Amsterdam, Netherlands, 2006.

(2) Darcy, H., *Les fontaines publiques de la ville de Dijon (The Public Fountains of the Town of Dijon)*; Dalmont: Paris, 1856.

(3) Tiller, F. M.; Crump, J. R. Solid-Liquid Separation: An Overview. *Chem. Eng. Prog.* **1977**, *73* (10), 65–75.

(4) Ruth, B. F.; Montillon, G. H.; Montonna, R. E. Studies in Filtration - I. Critical Analysis of Filtration Theory. *Ind. Eng. Chem.* **1933**, *25* (1), 76–82.

(5) McCabe, W. L.; Smith, J. C.; Harriott, P., *Unit Operations of Chemical Engineering*; McGraw-Hill: New York, 2005.

(6) Almy, C.; Lewis, W. K. Factors Determining the Capacity of a Filter Press. *J. Ind. Eng.Chem.* **1912**, *4* (7), 528–532.

(7) Tien, C.; Bai, R. An Assessment of the Conventional Cake Filtration Theory. *Chem. Eng. Sci.* **2003**, *58* (7), 1323–1336.