Scale-up of Centrifugal Solid-Liquid Separation

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Many manufacturing processes for active pharmaceutical ingredients (APIs) and their manufacturing intermediates consist of reaction, post-processing, crystallization, filtration and drying operations. Particularly during filtration operations, we sometimes have operational troubles which can cause product quality deterioration and a large decrease in productivity and work efficiency. Therefore, it is important to stabilize filtration operation during API manufacturing processes.

In this paper, we would like to introduce several scale-up techniques from a small experimental scale to a commercial manufacturing scale by focusing mainly on operational condition setting of key parameters in centrifugal filtration processes.

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Introduction

Most of the processes for the manufacturing of active pharmaceutical ingredients and intermediates consist of a flow with reactions, post-processing, crystallization, filtration and drying operations. If problems occur in filtering operations, it often leads to reductions in product quality, large reductions in productivity and efficiency, and it is important to stabilize filtering processes in the manufacturing processes for pharmaceuticals.

Centrifugal separators, pressure filters and reduced pressure filters are typically used for this filtration, and among these many centrifugal separators have been introduced because of their large processing capacity and easy automation.

To minimize the trouble with centrifugal separators during manufacturing, we think that it is necessary to improve the techniques for measuring basic physical properties, testing techniques, techniques for increasing the scale and techniques for operating equipment for filtering in addition to stabilizing crystallization processes (grain diameter, etc.).

In this paper, we will introduce techniques for increasing the scale from a small experimental scale to manufacturing scale for setting (1) slurry mixture and filter cake rinsing parameters and (2) cake deliquoring operation parameters in filtering operations using a centrifugal separator (centrifugal filtering in the following).[1)]

Problems in Centrifugal Filtering

Table 1 gives the details of problems in centrifugal filtering and the causes for their occurrence. The causes of these problems can be divided into ones that arise in the processes before filtering and ones that arise during centrifugal filtering.

Operating Techniques for Centrifugal Separators

A single cycle for centrifugal filtering is slurry feed, deliquoring, rinsing, deliquoring, (shaking out), cake scraping and (detachment of filter bed), and several cycles are normally required for filtering all of the slurry. There is cake that is easy to compress and cake that is difficult to compress, and as will be discussed later, this greatly affects the filtering time.

Based on getting a grasp of the compressibility of the cake, it is possible to promote filtering rate stability, rinsability, deliquorability and improvements in cake separability. The operating pattern is shown in **Fig. 1**.

Table 1 Troubles in centrifugal filtration process

	troubles in filtration process	cause
reaction and crystallization	change in size/ size distribution of crystals	change in composition of reaction mixture
		change in crystallization conditions
crystallization slurry mixing/ feeding of slurry to filters	generation of finely-divided crystals	shear by slurry mixer and pump
	increase of residual impurities	time degradation of crystallization slurry
centrifugal filtration	imbalance of filtration cake	inappropriately-oriented slurry nozzle of filters
		small cake filtration resistance
	overflow of slurry or supernatant	too-fast feeding
		vibration of filter
	increase in filtration time	lower cake filterability
		clogging of filter medium
		masking of filter medium surface with fine crystals
	increase of residual impurities	imbalance of filtration cake
		inappropriately-oriented rinse nozzle of filters
		masking of cake surface with fine crystals
		nonuniformly-compressed cake
	poor cake removability	high liquid content of deliquored cake
		filter cake compression
		inappropriate cake remover

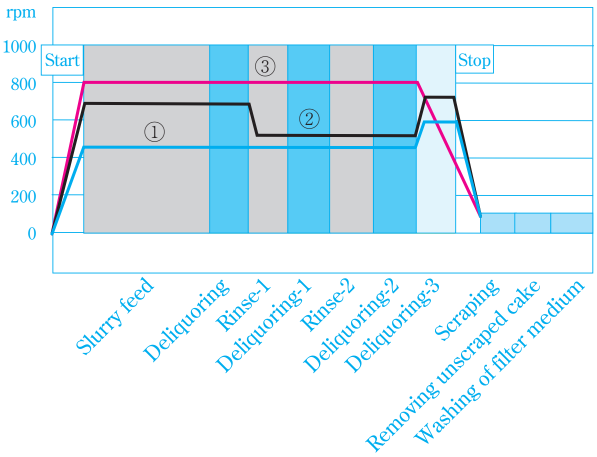

Fig. 1 Diagram of filtration, washing and deliquoring in centrifuge

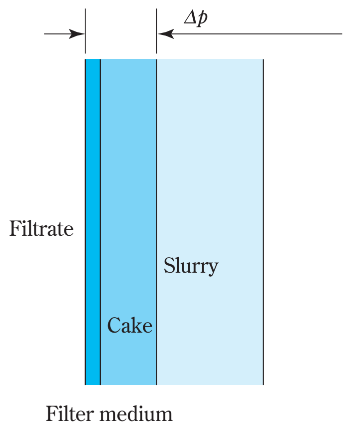

Fig. 2 Cross section drawing of filtration system

Increasing the Scale of Slurry Feed and Rinsing Operations

We will describe a technique for increasing the scale from small-scale experimental data to actual equipment using mean specific filtration resistance α_{av}, and the compression index n, which are basic physical properties of filtration.

1. Concept of increasing the scale

We will explain the basic theory of filtering using **Fig. 2**. The driving force for the filtrate passing through the filter medium and the cake is the difference in pressure Δp on the slurry side and the filter medium side. Centrifugal, pressure and reduced pressure filtering just have different operations that provide Δp, and can use the same filtering theory.

If the scale for centrifugal filtering is increased keeping the centrifugal effect Z ($= r_o\omega^2/g$, where ω is the angular velocity of rotation and g is gravitational acceleration) using the basket radius r_o, for the centrifugal separator, Δp ($= \rho_L\omega^2 (r_o - r_L)$, where ρ_L is the filter density and r_L is in the radius of the liquid membrane during filtering) increases from small centrifugal separators (6 inch, 15 inch, etc.) to actual equipment (48 inch, etc.) as is shown in **Fig. 3**, and if the cake has

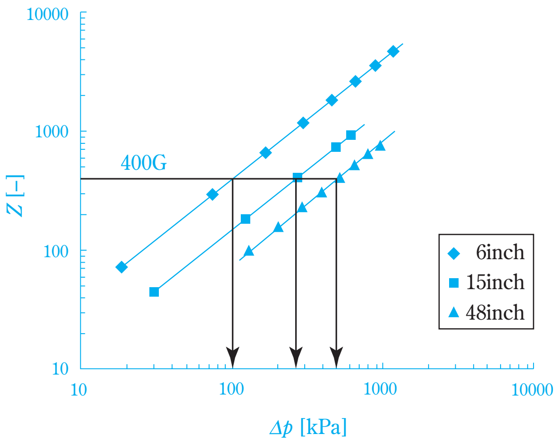

Fig. 3 Relationship between centrifugal effect and centrifugal filtration pressure

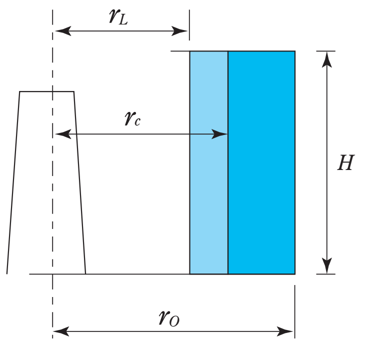

Fig. 4 Vertical cross section drawing of centrifuge

high compressibility (cake with a large n), it is compressed. Because of this there are problems such as reduction in filtration rate, reduction in rinsing efficiency and poor detachment of the filter bed.

Therefore, it is necessary to increase the scale of centrifugal filtration keeping Δp constant. **Fig. 4** shows a cross-section of a centrifugal separator for calculating Δp.

2. Estimating feed and rinsing time

It is possible to estimate the filtering time when the scale is increased by measuring α_{av} and n in small-scale experiments. Along with the slurry feed and cake rinsing liquid supply, various filtering times are calculated for the liquid supply time. This can be done with liquid supply time $\theta_1 = \mu_{L1} W V_1 \alpha_{av} / (2 \Delta p A^2)$ and rinsing time $\theta_2 = \mu_{L2} W V_2 \cdot \alpha_{av} / (2 \Delta p A^2)$ (where is the viscosity of the filtrate, W the cake mass, V the volume of the filtrate and A the area of the filter). Moreover, α_{av} can be expressed by a pressure function ($\alpha_{av} = \alpha_0 \Delta p^n$).

Table 2 Evaluation examples of average specific filtration resistance and compressibility of filtration cake

mean specific filtration resistance α_{av}	$< 5 \times 10^8$	very fast filtration/solid sedimentation
	$5 \times 10^8 \sim 2 \times 10^{10}$	best filterability
	$2 \times 10^{10} \sim 10^{11}$	not good
	$> 10^{11}$	bad
compressibility index n	> 1	serious compressibility; α_{av} increases seriously according to increase of Δp
	< 0.5	small compressibility e.g. typical APIs $n = 0.4 \sim 0.8$

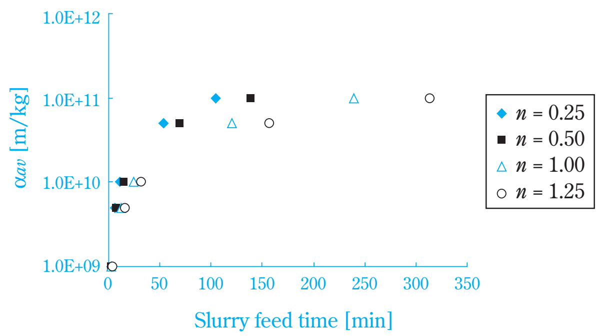

Fig. 5 Average specific filtration resistance plotted against slurry feed time

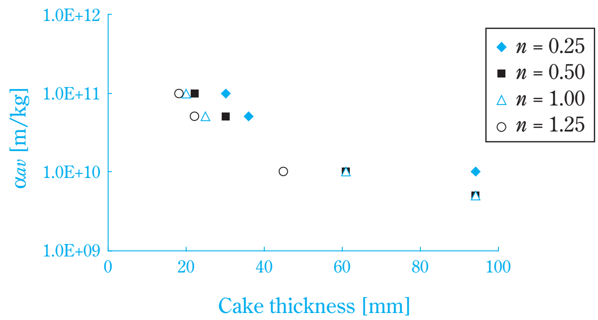

Fig. 6 Average specific filtration resistance plotted against cake thickness

3. Mean specific filtration resistance and compression index

Table 2 gives the criterion for α_{av} and n. Presuming filtration of α_0 particles with an upright centrifugal separator, **Fig. 5** is the results of calculations of the relationship between α_{av} and slurry feed time θ_1 for the case of the case of a fixed cake thickness of 94 mm. We see that when $\alpha_{av} \geq 10^{10}$ m/kg, θ_1 increases. **Fig. 6** is the result of calculations of the relationship between α_{av} and cake thickness when θ_1 is fixed at 10 minutes. We see that when $\alpha_{av} \geq 10^{10}$ m/kg, the cake thickness gets thinner, and that the thickness becomes one where it is difficult to scrape the cake with an upright centrifugal separator. Thus, we can see that any filtering using an upright centrifugal separator a criterion of $\alpha_{av} \leq 10^{10}$ m/kg is preferable for α_{av}.

4. Measurement of mean specific filtration resistance

The constant pressure filtration test equipment and the compression permeability test equipment shown in **Figs. 7** and **8** were used to measure α_{av} and n.

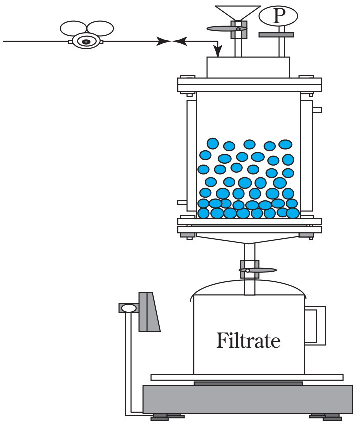

Fig. 7 Constant pressure filtration test equipment

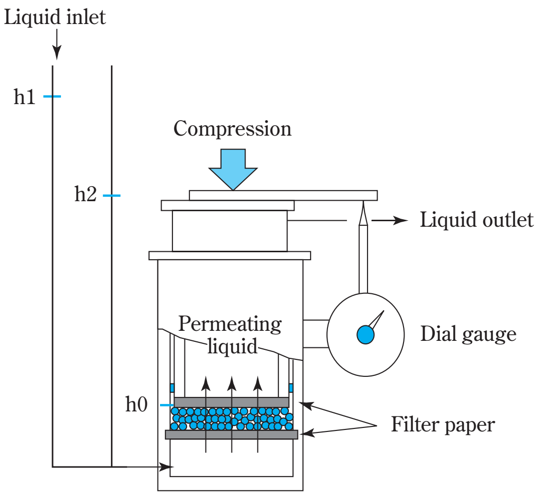

Fig. 8 Compression permeability test equipment

Table 3 compares the features of the constant pressure filter test equipment and the compression permeability test equipment. The compression permeability test equipment compresses the cake at the measurement pressure, forces a liquid to permeate it in that state and measures the partial specific resistance α_p,

Table 3 Comparison of constant pressure filtration test and compression permeability test

	constant pressure filter test	compression permeability test
purpose of measurement	α_{av} n	α_p n
accuracy of results	fair	very good
cost	low	high
equipment size	small	large
handling	very easy	easy
measurement time	short	long

and α_{av} is calculated. With this method, accurate results are obtained because a cake that corresponds to the measurement pressure is consolidated reliably.

The measurement method for the constant pressure filter test equipment sets the filter media to be used for increasing the scale, and after preparing the slurry, pressurizes it and measures the amount of liquid outflow along with time.

These results are analyzed using Ruth's filtration equation and α_{av}, n is calculated. Since it is difficult to consolidate a cake that corresponds to the pressure applied, the accuracy of the data from this method is somewhat inferior.

To measure α_{av} accurately using the constant pressure filter test equipment, the most important point is that the cake is compressed in a consolidated state corresponding to the filtration pressure. We have optimized the filtration test time so that the cake is formed in a reliable consolidated state. This has made accurate measurements of α_{av} possible using constant pressure filter test equipment.

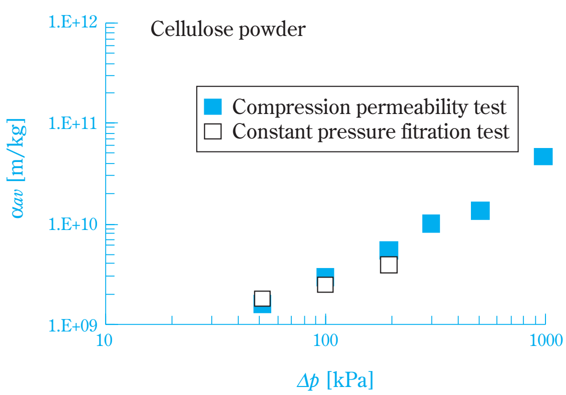

Fig. 9 Average specific filtration resistance measured in constant pressure filtration test and calculated from results of compression permeability test (cellulose powder)

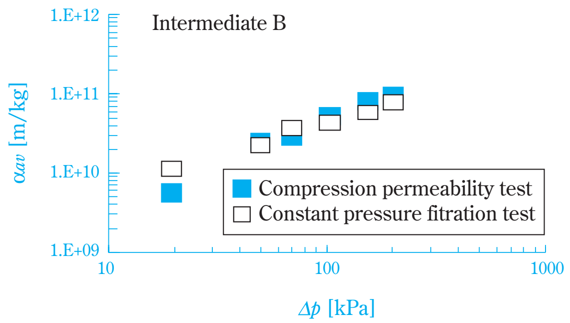

Fig. 10 Average specific filtration resistance measured in constant pressure filtration test and calculated from results of compression permeability test (intermediate B)

The measurement results for the constant pressure filter test equipment and the measurement results for the compression permeability test equipment are compared in **Figs. 9** and **10**.

5. Mean specific filtration resistance, compression index and solid content of filter cake

Fig. 11 shows the relationship between α_{av} measured using the constant pressure filtration test equipment and n. There is a tendency where n becomes larger (compression becomes easier) if α_{av} increases (filtering gets poorer).

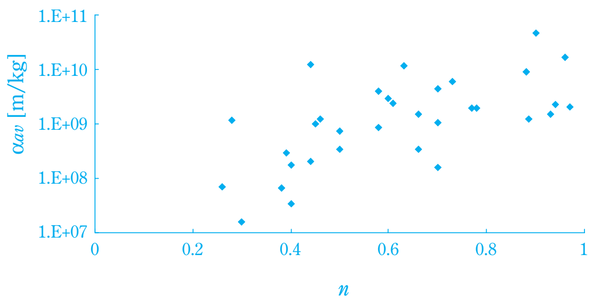

Fig. 11 Average specific filtration resistance measured in constant pressure filtration test plotted against compressibility index of cake

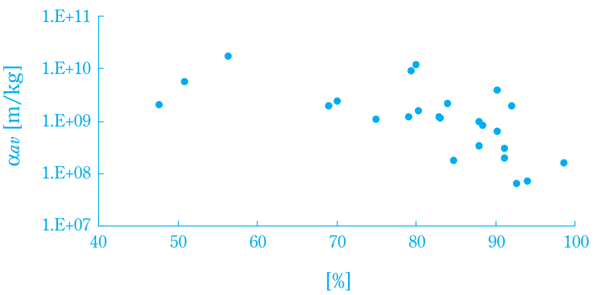

Fig. 12 Specific filtration resistance measured in centrifugal filtration test plotted against solid content of cake after centrifugal deliquoring

Fig. 12 shows the relationship between the solid content in a wet cake filtered by a centrifugal separator and α_{av}. One can see that there is a tendency for the solid content in the wet cake to become smaller if α_{av} increases.

Increasing the Scale of Deliquoring Operations[2)]

To estimate the deliquoring time using a centrifugal separator, the average liquid content of the cake after deliquoring has conventionally been found using a small centrifugal separator (6 inch) and a mid-sized centrifugal separator (15 inch diameter, etc.). As a result of examining methods for testing with a smaller sample, it has become possible to find the liquid content simply using a table tops interviews (**Fig. 13**).

Fig. 13 Table-top centrifuge

We will compare the measurement results for average liquid content with the small and mid-sized centrifugal separators and the tabletop centrifuge and introduce a test method for the tabletop centrifuge.

1. Average liquid content, average centrifugal effect and pressure for centrifugal deliquoring

Fig. 14 shows the relationship between the average liquid content of the cake and the centrifugal effect Z, and **Fig. 15** shows the relationship between the average liquid content and the apparent pressure $\Delta p'$ for centrifugal deliquoring. The small centrifugal separator has a diameter of 6 inches, and the mid-sized centrifugal separator has a diameter of 15 inches. When adjusted for Z, the two average liquid content scales did not agree, but then when adjusted for $\Delta p'$ as defined below

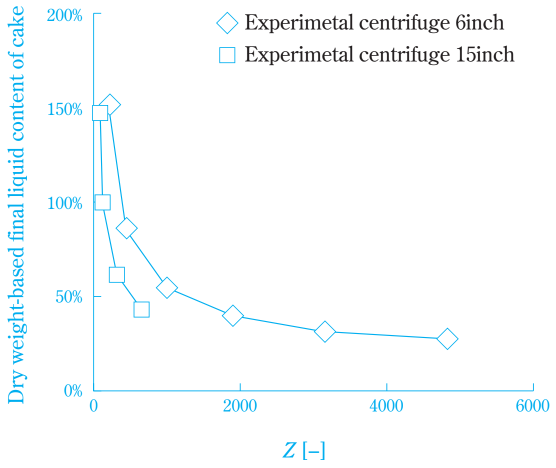

Fig. 14 Final liquid content of cake in centrifugal deliquoring plotted against centrifugal effect[2)]

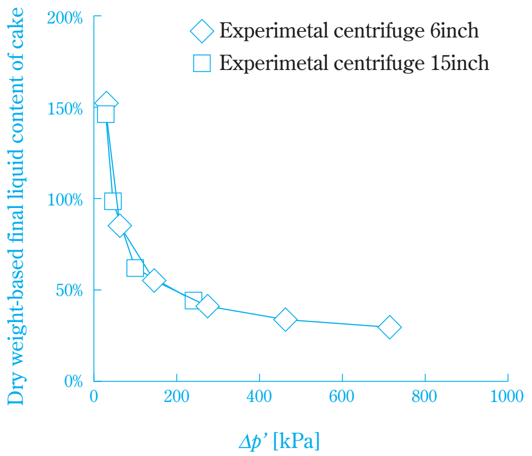

Fig. 15 Final liquid content of cake of low compressibility in centrifugal deliquoring by experimental centrifuges of different sizes plotted against apparent centrifugal deliqoring pressure[2)]

it, they agree well. Apparent pressure for centrifugal deliquoring $\Delta p' = (\rho_L \omega^2 (r_o^2 - r_c^2)$ is the calculated pressure when the liquid density ρ_L is substituted for the wet cake density.

2. Deliquoring test method using tabletop centrifuge

Fig. 16 shows the deliquoring experiment method using the tabletop centrifuge.

Paper is put into a filtering tube, and the wet cake is inserted. Next, the filter tube is put into the centrifugal sedimentation tube, and set into the tabletop centrifuge. The speed is set for a $\Delta p'$ close to the operating conditions for the increased scale, and the deliquoring time and change in weight of the filter tube are measured. By this means the relationship between the average liquid content and $\Delta p'$ is obtained.

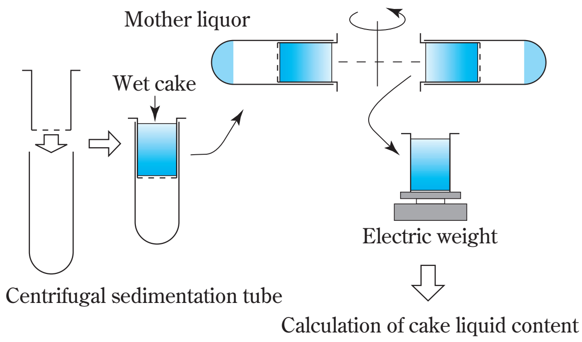

Fig. 16 Procedure of deliqoring experiment by table-top centrifuge

3. Cake compressibility and average liquid content

Fig. 17 shows the relationship between uncompressed cake and $\Delta p'$, and **Fig. 18** shows the relationship between the average liquid content of cake with compressibility and $\Delta p'$. The average liquid content for the cake with compressibility and the uncompressed cake agreed for the tabletop centrifuge and a small centrifugal separator used in the same manner. This shows that measurement of the average liquid content that has been carried out in small and mid-sized centrifugal separators can be carried out using a tabletop centrifuge.

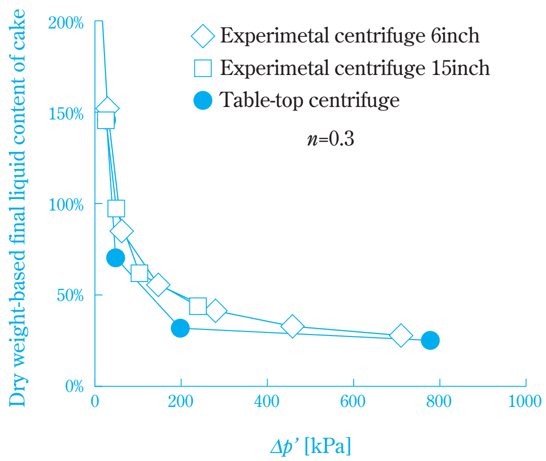

Fig. 17 Final liquid content of cake of low compressibility in centrifugal deliquoring plotted against apparent centrifugal deliqoring pressure; comparison of results of experimental centrifuges (open symbols) and those of table-top centrifuge (closed symbols)[2)]

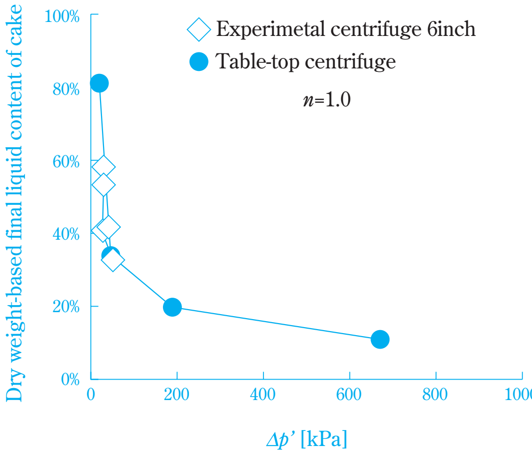

Fig. 18 Final liquid content of cake of high compressibility in centrifugal deliquoring plotted against apparent centrifugal deliqoring pressure; comparison of results of experimental centrifuge (open symbols) and those of table-top centrifuge (closed symbols)[2)]

Conclusion

In this paper, we have introduced the fact that it is possible to estimate the filtering time when increasing the scale in slurry feed and rinsing operations by obtaining α_{av} and n using constant pressure filtration test equipment as the technique for scaling up to production from small-scale experiments and that it is possible to estimate the deliquoring time and average liquid content by obtaining deliquoring data using a tabletop centrifuge. By making it possible to obtain the data for increasing the scale using small-scale experiments, it is possible to reduce the centrifugal separator tests at the middle scale for obtaining data for increasing the scale in solid-liquid separation operations using centrifugal separators and to increase efficiency of testing.

We would be happy to see the technique for increasing the scale introduced here used in industrialization research in the future.

Symbols Used

- A : filter area [m^2]
- g : gravitational acceleration [m/s^2]
- H : centrifugal separator basket height [m]
- n : compression index [–]
- Δp : filtration pressure [Pa]
- $\Delta p'$: apparent centrifugal deliquoring pressure [Pa]
- r_o : outside radius of the centrifugal separator basket [m]
- r_c : radius of cake inside surface [m]
- r_L : radius of liquid membrane during filtering [m]
- V : filtrate volume [m^3]
- W : cake mass [kg]
- Z : centrifugal effect [–]
- α_{av} : mean specific filtration resistance [m/kg]
- α_p : partial specific filtration resistance [m/kg]
- α_0 : $\alpha_{av} = \alpha_0 (\Delta p)^n$ [m/kg]
- θ : filtration time [s]
- ρ_L : filtrate density [kg/m^3]
- μ_L : filtrate viscosity [Pa · s]
- ω : angular velocity of rotation of centrifugal separation [rad/s]

References

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